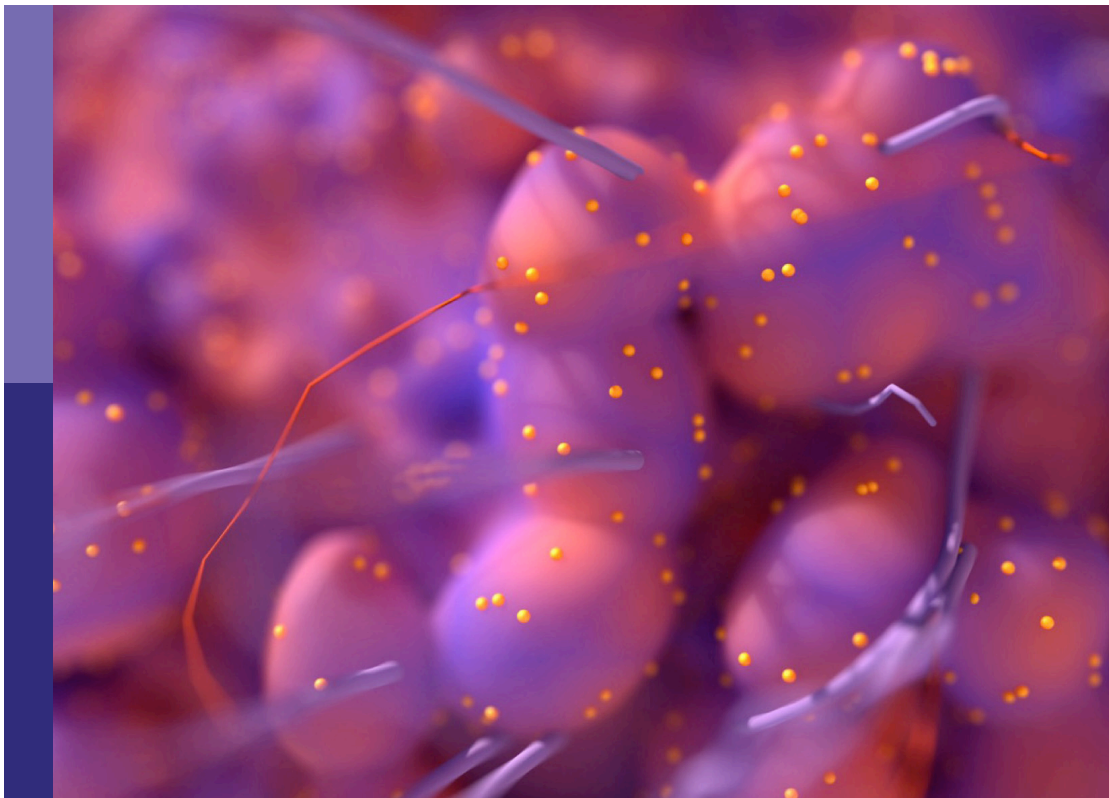
frontiers | Research Topics

Multimodality therapy for older cancer patients

Edited by
Nam Phong Nguyen, Vincent Vinh-Hung,
Mohammad Mohammadianpanah and Meritxell Arenas

Published in
Frontiers in Oncology



ISSN 1664-8714
ISBN 978-2-8325-5541-5
DOI 10.3389/978-2-8325-5541-5

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Multimodality therapy for older cancer patients

Topic editors

Nam Phong Nguyen — International Geriatric Radiotherapy Group, United States
Vincent Vinh-Hung — Centre Hospitalier Public du Cotentin, France
Mohammad Mohammadianpanah — Shiraz University of Medical Sciences, Iran
Meritxell Arenas — University of Rovira i Virgili, Spain

Citation

Nguyen, N. P., Vinh-Hung, V., Mohammadianpanah, M., Arenas, M., eds. (2024). *Multimodality therapy for older cancer patients*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5541-5

Table of contents

frontiers | Frontiers in Oncology

TYPE Editorial
PUBLISHED 30 September 2024
DOI 10.3389/fonc.2024.1487783

OPEN ACCESS

EDITED AND REVIEWED BY
Massimo Broggini,
Mario Negri Institute for Pharmacological Research (IRCCS), Italy

*CORRESPONDENCE
Nam P. Nguyen
NamPhong.Nguyen@yahoo.com

RECEIVED 28 August 2024
ACCEPTED 16 September 2024
PUBLISHED 30 September 2024

CITATION
Nguyen NP, Mohammadianpanah M, Arenas M and Vinh-Hung V (2024) Editorial: Multimodality therapy for older cancer patients.
Front. Oncol. 14:1487783.
doi: 10.3389/fonc.2024.1487783

Editorial: Multimodality therapy for older cancer patients

Nam P. Nguyen[1]*, Mohammad Mohammadianpanah[2], Meritxell Arenas[3] and Vincent Vinh-Hung[4]

[1]Department of Radiation Oncology, Howard University, Washington, DC, United States, [2]Colorectal Research Center, Department of Radiation Oncology, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran, [3]Department of Radiation Oncology, Sant Joan de Reus University, University of Rovira, I Virgili, Tarragona, Spain, [4]Department of Radiation Oncology, Centre Hospitalier Public du Contentin, Cherbourg-en-Contentin, France

KEYWORDS

older, immunotherapy, radiotherapy, synergy, multimodality

Editorial on the Research Topic
Multimodality therapy for older cancer patients

The management of locally advanced cancer frequently requires a multimodality approach due to high rates of loco-regional recurrences and/or distant metastases (1). Surgery, followed by postoperative radiation, concurrent chemotherapy and radiotherapy, and preoperative chemoradiation are standard approaches for these patients, depending on the anatomic site. However, older cancer patients with locally advanced disease are often not ideal candidates for surgical resection due to pre-existing comorbidities, a high risk of postoperative complications, and poor survival rates after treatment (2). Additionally, frail patients may not benefit from chemotherapy due to a high mortality rate and frequent hospitalizations during treatment (3). As a result, they are often denied curative treatment as clinicians are concerned about their ability to tolerate it.

Innovative therapies such as immunotherapy with immune checkpoint inhibitors (ICIs) may offer a curative option with minimal morbidity when combined with new radiotherapy techniques like image-guided radiotherapy. Immunotherapy is well -tolerated and has been reported to be effective for older cancer patients, comparable to its effectiveness in younger patients (4). It is most effective among patients with positive program death ligand 1 (PD-L1) expression, defined as 1% or above. However, patients who lack PD-L1 in their tumors may still benefit from immunotherapy if they receive radiotherapy first. Preclinical and preliminary clinical data suggest that radiotherapy may increase PD-L1 expression in tumors, as cancer cells produce an immune -suppressive environment to escape destruction by CD-8 T cells (5).

The best illustration of the synergy between radiotherapy and immunotherapy is reflected in the model of renal cell carcinoma, which is reported to be radio-resistant. This resistance often requires a high dose of radiation, which can potentially damage surrounding normal organs such as the liver and the small intestine. Additionally, there is a high rate of distant metastases in tumors with high risk features such as large size and poorly differentiated histology. Historically, patients who develop distant metastases had a very poor outcome due to the tumor resistance to chemotherapy. The survival of those

patients has significantly improved with ICIs. The combination of ICIs and radiotherapy is also very well tolerated and effective for patients with distant metastases. Thus, at least in theory, immunotherapy and modern radiotherapy techniques such as stereotactic body radiotherapy (SBRT), which delivers a high curative dose of radiation with minimal toxicity, should improve local control and survival for renal cancer patients with locally advanced disease (Nguyen et al.). In another example, the combination of ICIs with radiotherapy for locally advanced bladder cancer has produced an 81% biopsy proven complete response (CR), which is significantly higher than the responses reported after concurrent chemoradiation or neoadjuvant immunotherapy (Nguyen et al.). For selected patients with locally advanced rectal cancer, immunotherapy alone or combined with chemotherapy and radiotherapy may lead to organ preservation in a disease that traditionally require surgery for local control (6).

Therefore, the judicious sequencing of immunotherapy and radiotherapy may benefit most patients with locally advanced cancers, regardless of their PD-L1 status. Specific protocols need to be developed for each tumor type for older cancer patients, taking into account their frailty status to avoid unnecessary treatment toxicity (7). As an international organization dedicated to the care of older cancer patients, the International Geriatric Radiotherapy Group (http://www.igrg.org) is committed to conducting prospective trials combining radiotherapy and immunotherapy for this vulnerable population (8). The data obtained may allow us to optimize treatment strategies for older cancer patients, improving outcomes and quality of life for these individuals.

Author contributions

NN: Writing – original draft, Writing – review & editing. MM: Writing – original draft, Writing – review & editing. MA: Writing – original draft, Writing – review & editing. VV-H: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Zhou Y, Rassy E, Coutte A, Achkar S, Espenel S, Genespie C, et al. Current standards in the management of early and locally advanced cervical cancer: Update on the benefit of neoadjuvant/adjuvant strategies. *Cancers*. (2022) 14:2449. doi: 10.3390/cancers14102449

2. Lu C, Lee S, Liu K, Hung Y, Wang C, Lin Y, et al. Older age impact on survivaloutcome in patients receiving curative surgery for solid cancer. *Asian J Surg*. (2018) 41:333–40. doi: 10.1016/j.asjsur.2017.02.008

3. Ho Y, Tang W, Chen S, Lee S, Chen J, Hung Y, et al. Association of frailty and chemotherapy-related adverse outcomes in geriatric patients with cancer: a pilot observational study in Taiwan. *Aging*. (2021) 13:24192–2404. doi: 10.18632/aging.v13i21

4. Gomes F, Lorigan P, Woolley S, Foden P, Burns K, Yorke J, et al. A prospective study of the safety of checkpoint inhibitors in older cáncer patients-the ELDERS study. *Esmo Open*. (2021) 6:1–6. doi: 10.1016/j.esmoop.2020.100042

5. Patel KR, Martinez A, Stahl JM, Logan SJ, Perricone AJ, Ferris MJ, et al. Increase in PD-L1 expression after pre-operative radiotherapy for soft tissue sarcoma. *Oncoimmunology*. (2018) 7:e1442168. doi: 10.1080/2162402X.2018.1442168

6. Nguyen NP, Mohammadianpanah M, SunMyint A, Page BR, Vinh-Hung V, Gorobets O. et al: Immunotherapy and radiotherapy for older patients with locally advanced rectal cancer unfit for surgery or decline surgery: a practical proposal by the International Geriatric Radiotherapy Group. *Front Oncol*. (2024) 14:1325610. doi: 10.3389/fonc.2024.1325610

7. Nguyen NP, Page BR, Giap H, Dahbi Z, Vinh-Hung V, Gorobets O, et al. Immunotherapy and radiotherapy for older patients with locally advanced non-metastatic non-small cell lung cancer who are not candidates for or decline surgery and radiotherapy: a practical proposal by the International Geriatric Radiotherapy Group. *Cancers*. (2024) 16:3112. doi: 10.3390/cancers16173112

8. Nguyen NP, Baumert BG, Oboite E, Motta M, Appalanaido GK, Arenas M, et al. Immunotherapy and radiotherapy for older cáncer patients: proposed paradigm by the International Geriatric Radiotherapy Group. *Gerontology*. (2021) 67:379–85. doi: 10.1159/000514451

frontiers | Frontiers in Oncology

TYPE Clinical Trial
PUBLISHED 14 June 2023
DOI 10.3389/fonc.2023.1202544

OPEN ACCESS

EDITED BY
Nam Phong Nguyen,
International Geriatric Radiotherapy Group, United States

REVIEWED BY
Angel Montero,
HM Madrid Hospital, Spain
Eileen P Connolly,
Columbia University, United States

*CORRESPONDENCE
Paulo Henrique Costa Diniz
phdiniz@ufmg.br

RECEIVED 08 April 2023
ACCEPTED 30 May 2023
PUBLISHED 14 June 2023

CITATION
Gil GOB, de Andrade WP, Diniz PHC, Cantidio FS, Queiroz IN, Gil MLBV, Almeida CAM, Caldeira PPR, Regalin M and Silva-Filho AL (2023) A phase II randomized clinical trial to assess toxicity and quality of life of breast cancer patients with hypofractionated versus conventional fractionation radiotherapy with regional nodal irradiation in the context of COVID-19 crisis.
Front. Oncol. 13:1202544.
doi: 10.3389/fonc.2023.1202544

A phase II randomized clinical trial to assess toxicity and quality of life of breast cancer patients with hypofractionated versus conventional fractionation radiotherapy with regional nodal irradiation in the context of COVID-19 crisis

Gabriel Oliveira Bernardes Gil [1,2], Warne Pedro de Andrade [2,3], Paulo Henrique Costa Diniz [4,5]*, Farley Soares Cantidio [1], Izabella Nobre Queiroz [6], Maria Luísa Braga Vieira Gil [7], Conceição Aparecida Medeiros Almeida [6], Paola Palmer Reis Caldeira [6], Marcos Regalin [1] and Agnaldo Lopes Silva-Filho [2,7,8]

[1]Department of Radiation Oncology, Rede Mater Dei and Hospital da Baleia, Belo Horizonte, Minas Gerais, Brazil, [2]Gynecology Department, Universidade Estadual Paulista "Júlio de Mesquita Filho", Botucatu, São Paulo, Brazil, [3]ONCOBIO, Grupo Oncoclinicas, Department of Gynecology and Obstetrics of the School of Medicine of the Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil, [4]Department of Oncology, Rede Mater Dei, Belo Horizonte, Minas Gerais, Brazil, [5]Department of Internal Medicine, School of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil, [6]Department of Radiation Oncology, Hospital da Baleia, Belo Horizonte, Minas Gerais, Brazil, [7]Department of Radiation Oncology, Rede Mater Dei, Belo Horizonte, Minas Gerais, Brazil, [8]Department of Gynecology and Obstetrics of the School of Medicine of the Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

Purpose: This study, conducted during the COVID-19 crisis, primarily aimed to compare the acute toxicity between conventional fractionated radiation therapy (CF-RT) with hypofractionated radiation therapy (HF-RT) among patients who underwent breast-conserving surgery or mastectomy in whom breast or chest wall and regional nodal irradiation (RNI) were indicated. The secondary endpoints were both acute and subacute toxicity, cosmesis, quality of life, and lymphedema features.

Methods: In this open and non-inferiority randomized trial, patients (n = 86) were randomly allocated 2:1 in the CF-RT arm (n = 33; 50 Gy/25 fractions ± sequential boost [10 Gy/5 fractions]) versus the HF-RT arm (n = 53; 40 Gy/15 fractions ± concomitant boost [8 Gy/15 fractions]). Toxic effects and cosmesis evaluation used the Common Terminology Criteria for Adverse Events, version 4.03 (CTCAE) and the Harvard/National Surgical Adjuvant Breast and Bowel Project (NSABP)/Radiation Therapy Oncology Group (RTOG) scale. For the patient-reported quality of life (QoL), the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) and the breast cancer-specific supplementary questionnaire (QLQ-BR23) were used.

Lymphedema was assessed by comparing volume differences between the affected and contralateral arms using the Casley–Smith formula.

Results: Grade 2 and grade 3 dermatitis were lower with HF-RT than with CF-RT (28% *vs.* 52%, and 0% *vs.* 6%, respectively; p = 0.022). HF-RT had a lower rate of grade 2 hyperpigmentation (23% *vs.* 55%; p = 0.005), compared to CF-RT. No other differences in overall rates of physician-assessed grade 2 or higher and grade 3 or higher acute toxicity between HF-RT and CF-RT were registered. There was no statistical difference between groups regarding cosmesis, lymphedema rate (13% *vs.* 12% HF-RT *vs.* CF-RT; p = 1.000), and functional and symptom scales, during both the irradiation period and after 6 months of the end of treatment. The results revealed that the subset of patients up to 65 years or older did not show a statistical difference between both arm fractionation schedules (p > 0.05) regarding skin rash, fibrosis, and lymphedema.

Conclusion: HF-RT was non-inferior to CF-RT, and moderate hypofractionation showed lower rates of acute toxicity, with no changes in quality-of-life outcomes.

Clinical trial registration: ClinicalTrials.gov, identifier NCT 40155531.

KEYWORDS

breast cancer, radiation dose hypofractionation, toxicity, breast cancer lymphedema, quality of life

1 Introduction

Hypofractionated radiation therapy (HF-RT), in which irradiation may be delivered in dose fractions greater than 2 Gy/day, has emerged as an important tool in breast cancer radiation therapy (RT) (1). Previously, the standard RT dose consisted of 50 Gy in 25 fractions, 2 Gy per daily fraction, corresponding to conventional fractionated radiation therapy (CF-RT) (2, 3). However, after the publication of important phase 3 trials, such as START A and START B, the American Society for Radiation Oncology (ASTRO) endorsed this technique in the treatment of breast cancer (4–8) and extended its indication to patients of all ages, irrespective of chemotherapy receipt (9, 10). Nevertheless, despite the comparable long-term local control, equivalent or modestly improved toxicity outcomes, and additional benefits such as convenience and reduced costs, HF-RT incorporation in practice had been slow and varied worldwide (11).

The arguments against the routine adoption of HF-RT for breast cancer are often based on concerns about the underrepresentation of certain patient subgroups in major trials. Additional limiting use includes uncertainties regarding adverse effects of a higher daily fraction on the heart/lung/brachial plexus and paucity of data on the effects of hypofractionation in the regional nodal irradiation (RNI), post-mastectomy, and breast reconstruction setting (12). In 2019, addressing the representativeness of different patient populations, a phase 3 trial showed the non-inferiority of post-mastectomy RNI hypofractionation over the CF-RT schedule after surgery (12).

On March 11, 2020, the World Health Organization declared the COVID-19 outbreak a global pandemic. Public health officials mobilized communities to minimize transmission by self-isolation and social distancing (13). This scenario catalyzed the hypofractionation implementation broadly (14). In this context, we carried out a randomized phase 2 trial with the primary objective of comparing, in our population, the acute toxicity of HF-RT with CF-RT after breast-conserving surgery or mastectomy with RNI, including the internal mammary nodes (IMNs), when indicated. Then, acute and subacute toxicity, cosmesis, quality of life, and lymphedema features, at different times of the patient journey, were also investigated. The hypothesis established was the non-inferiority of the toxicity of the HF-RT arm compared to the CF-RT.

2 Methods

This phase II study was approved by the local research ethics committee under the number 51139715.0.0000.5123 and registered in 2019 on ClinicalTrials.gov (NCT04015531). The study was single-center, conducted on Hospital da Baleia, a Brazilian referral tertiary hospital, which performs radiation therapy among patients from Minas Gerais, the second-most populous state in Brazil. Written informed consent was obtained from each participant.

The study was conducted in accordance with the Declaration of Helsinki.

2.1 Enrollment

Patients were enrolled from November 2019 through May 2022 at Hospital da Baleia, a referral public oncology tertiary center in Belo Horizonte, Minas Gerais, Brazil. The inclusion criteria were female gender, 18 years or older, breast carcinoma, T1-4 with at least one positive lymph node (American Joint Committee on Cancer (AJCC) 8th) (15), mastectomy or breast-conserving surgery with the investigation of sentinel lymph node or axillary dissection. Adjuvant chemotherapy and hormone therapy were performed as local practice. Neoadjuvant chemotherapy and the use of breast implants were allowed in both study groups. Exclusion criteria were compromised margin, concomitant chemotherapy, internal mammary chain (IMC) or supraclavicular fossa lymph node involvement, previous chest RT, collagen disease, bilateral breast cancer, inflammatory carcinoma, concurrent skin treatment with irradiation, distant metastasis, and synchronic malignancy.

2.2 Randomization

Patients were randomly allocated to the control arm, CF-RT (50 Gy/25 fractions ± a sequential boost of 10 Gy/5 fractions, over 25–30 days), or the experimental arm, HF-RT (40 Gy/15 fractions ± a concomitant boost of 8 Gy/15 fractions, over 15 days) following breast surgery. The boost was realized in all cases of breast-conserving surgery. Randomization was planned and performed initially through a computer-generated 2:1 allocation (HF-RT *vs.* CF-RT) to preserve the safety, rights, and well-being of trial participants during the prolonged global public health crisis. Thus, we had more patients with a lower number of physician visits and fewer cross-transmission.

2.3 Treatment

Free-breathing computed tomography (CT) scans, with 5-mm slice thickness, in a supine position with arms raised over the head and supported by a ramp for immobilization were obtained for simulation. The organs at risk (OARs) and the target volumes were contoured according to the Radiation Therapy Oncology Group (RTOG) atlas (16–18). The planning target volume (PTV) was delineated with a 7-mm expansion from the clinical target volume (CTV) and 5 mm cropped from the skin, excluding the heart of the treatment volume (19). For women who underwent axillary dissection, the nodal irradiation included the ipsilateral axillary level III and supraclavicular nodes. For patients undergoing sentinel node surgery, nodal RT included the ipsilateral axillary level (I, II, and III) and supraclavicular nodes within the portals. Irradiation of the IMNs was performed based on the physician's discretion, including from the first to third intercostal space.

Three-dimensional conformal radiotherapy (3D-CRT) was performed using 6- to 10-MV photons. The dose fields were normalized in the same way as the three-field technique photon field. No axilla posterior field was permitted. If any part of the heart was included in the tangential fields, a multileaf collimator was used to shield it from the photon fields. The humeral head, larynx, and trachea were also shielded by the multileaf collimator. Dose constraints followed the RTOG 1005 protocol. At least 95% of each PTV was expected to receive >95% of the prescribed dose. The recommended maximum dose point was not greater than 110%.

2.4 Follow-up

All patients were evaluated at baseline, weekly during treatment, just at the end and 1, 2, and 6 months after treatment. The treating physician, a specialist in radiation therapy trained for the study procedures, assessed toxic effects and cosmesis using the Common Terminology Criteria for Adverse Events, version 4.03 (CTCAE v. 4.03). The Harvard/National Surgical Adjuvant Breast and Bowel Project (NSABP)/RTOG scale and pictures were taken at each moment (20–22). Patient-reported quality of life (QoL) was obtained at the first medical appointment, at the end of irradiation, and 1, 2, and 6 months after RT, using the Portuguese-validated versions of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-30 and the breast cancer-specific QLQ-BR23 applied questionnaires (20, 21, 23). The treating physician did not participate in the data analysis, which was performed by an independent committee.

2.5 Lymphedema evaluation

Lymphedema was evaluated by measuring the circumference of the affected and contralateral arm using the Casley–Smith volume formula (22, 24). The volume of each arm was estimated by the formula, corresponding to the distance from the wrist to the arm, which was divided by four segments of truncated cones separated every 10 cm, as exemplified by the calculation between segments C1 and C2 below:

$$V_2 = \frac{h \times (C_1^2 + (C_1 \times C_2) + C_2^2)}{12 \times \pi}, \; h = 100 \; mm$$

considering h = 100 mm a constant, the volume of each arm was estimated as the sum of the truncated cones (22).

The arm volume was the assessment at the first RT visit, during the discharge, and 6 months after the end of irradiation. After the measurement, the data were tabulated in a spreadsheet, with the formula already inserted for automatic calculations. Volume differences (VDs) between the affected arm and the contralateral were used to define lymphedema. VD >10% was classified as lymphedema (25, 26).

2.6 Statistical methods

The primary endpoint of this randomized phase II trial was the assessment of acute toxicity, considered from the baseline to the 3 months after RT, comparing the CF-RT regimen versus HF-RT. Acute toxicity fulfills clinical parameters, such as dermatitis, hyperpigmentation, and edema. Secondary outcomes included subacute toxicity, assessment of QoL, cosmesis, and lymphedema of patients treated with irradiation, presented at 6 months after treatment.

The trial was designed to enroll 80 evaluable patients, which yielded 80% power with a one-sided significance level of 0.05 to test the hypothesis that the probability of any grade ≥ 2 acute toxic effect Hyperfractionated whole breast irradiation (HF-WBI) is no more than 10% worse than the probability of CF-RT, assuming a prevalence of any grade ≥ 2 acute toxic outcome of 78% with CF-RT and 47% with HF-RT and a dropout rate of 15% (27).

Descriptive statistics were used to summarize the data. In the evaluation of the categorical variables, absolute and relative frequencies were determined. For the numerical variables, the absolute frequency, mean, and standard deviation were considered. The variables measured by the EORTC QLQ-C30 and QLQ BR23 were modified by linear transformation with scores from 0 to 100, whose high scores represented a high (better) level of functioning/symptoms or a low (worse) level. A normality test (Shapiro–Wilk) was performed for each continuous variable. The comparative analysis of categorical variables between the control and experimental groups was performed using the chi-square test and Fisher's exact test, while numerical variables were compared using the Mann–Whitney U test. The intergroup comparison of the EORTC QLQ-C30 was performed using the generalized estimating equation (GEE) method, known as an extension of generalized linear models. All analyses used two-sided $\alpha = 0.05$ and were performed using the R software version 4.1.2.

3 Results

Between November 2019 and February 2022, 128 patients were assessed for eligibility. A total of 86 women were allocated to the CF-RT (n = 53; 62%) or HF-RT arm (n = 33; 38%) (Figure 1). The mean age was 57 years (range, 25–91), and patients were self-declared white (30% × 41%), mixed ethnic group (37% × 44%), and black (33% × 15%) in the CF-RT and HF-RT arms. Regarding educational degrees, the majority of patients held a low schooling level (Supplementary Material). Most patients underwent breast-conserving surgery (CF-RT 73% *vs.* HF-RT 72%). Mean breast volume, measured using CTV volume, was greater than 1,100 cc (CF-RT 1196 cc *vs.* HF-RT 1,224 cc). Post-mastectomy breast reconstruction accounted for 17% and 12%, respectively, in the HF-RT and CF-RT groups. Of the patients, 56% underwent axillary dissection and 44% sentinel lymph node evaluation, with a mean of 10 lymph nodes removed and two positive lymph nodes. Almost two-thirds of patients had N1 staging, and the mean tumor size in this investigation was 3 cm, with 70% and 30% of staging II and III, respectively (Supplementary Material). Most of the women had invasive ductal carcinoma (IDC) and positive hormone receptors.

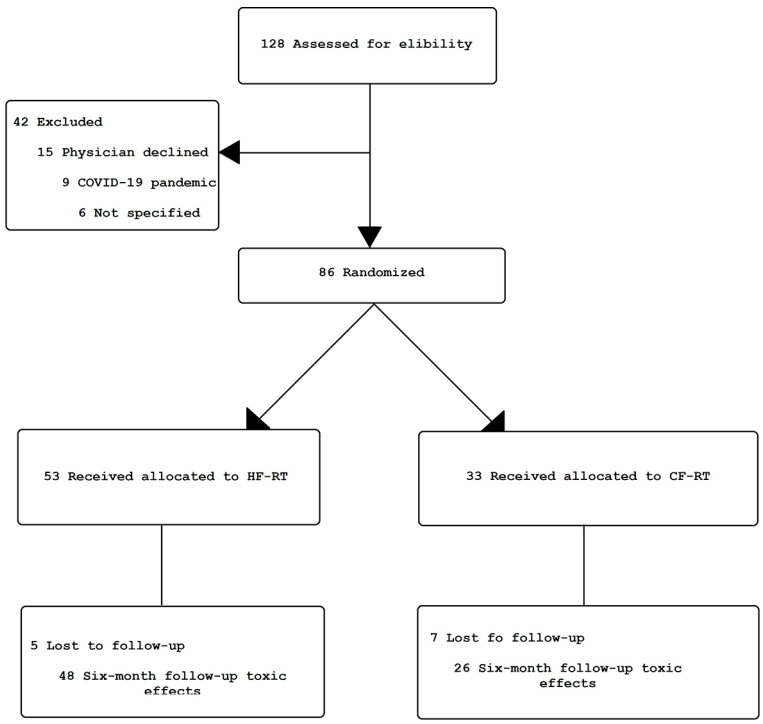


FIGURE 1
Clinical trial flowchart. HF-RT, hypofractionated radiation therapy; CF-RT, conventional fractionated radiation therapy.

In total, endocrine therapy was used in 67% of the women. Tamoxifen was the main drug, followed by anastrozole. More than two-thirds of patients received either neoadjuvant or adjuvant chemotherapy (CF-RT 72% *vs.* HF-RT 79%). IMC irradiation was performed in 14% (CF-RT 15% *vs.* HF-RT 13%) (Supplementary Material).

There were no differences in overall rates of any physician-assessed grade 2 or higher and grade 3 or higher acute toxicity between HF-RT and CF-RT. For specific acute toxicity effects, patients treated with HF-RT *vs.* CF-RT had a lower rate of grade 2 hyperpigmentation (23% *vs.* 55%; p = 0.005). The skin rash grade 2 and grade 3 dermatitis were lower with HF-RT than with CF-RT (28% *vs.* 52%, and 0% *vs.* 6%, respectively; p = 0.022). Most of the irradiated breasts showed no alteration compatible with fibrosis of the skin and subcutaneous tissue. There was no difference in acute grade 1 or higher for fibrosis and hypopigmentation. According to the esthetics assessment, most of the patients had excellent or good grades in both arms (CF-RT 40% *vs.* HF-RT 47%, and 27% CF-RT *vs.* 34% CF-RT, respectively; p = 0.288) (Table 1).

The comparative analysis of the physician-reported maximum global toxicity, including skin rash, fibrosis, and lymphedema, according to patients aged 65 years or older (Table 2), did not show a statistical difference between both arms (p > 0.05).

A total of 74 patients were evaluated for 6-month toxicity effects. There was no difference between arms regarding subacute toxicity, including the Harvard/NSABP/RTOG cosmesis scale (Table 3). There was no statistically significant difference in the rate of lymphedema after 6 months of treatment between the two RT fractionation groups (13% *vs.* 12% HF-RT *vs.* CF-RT, respectively; p = 1.000) (Figure 2). There were no reports of acute or subacute grade 4 toxicity, no symptomatic pulmonary toxicity, ischemic cardiac event, capsular contracture, rib fracture, brachial plexopathy, deaths, or distant metastases during the analyzed period. There was no statistical difference between the CF-RT and HF-RT arms from baseline to 6 months after treatment in functional and symptom scales of the QLQ-C30 questionnaire (Table 4). As detailed in Table 5, analysis of the QLQ-BR23 questionnaire showed no difference in symptom and functional scales between CF-RT and HF-RT groups.

4 Discussion

While breast HF-RT has been extensively studied, the use of HF in the setting of RNI and post-mastectomy remains more controversial (28). In this prospective, randomized trial, we evaluated the acute and subacute toxicity of HF-RT versus CF-RT after breast-conserving surgery or mastectomy with RNI. A particularly important finding of this study is the acute more favorable toxic outcome with the use of HF-RT in the RNI scenario. Specifically, the incidence of acute grade 2 hyperpigmentation was 32% lower in patients treated with HF-RT than with CF-RT. In addition, acute skin rash grade 2 and grade 3 dermatitis were significantly lower in the HF-RT arm. Both groups showed similar rates of other acute complications such as hypopigmentation and fibrosis of skin or subcutaneous tissue. We observed that HF-RT was similar to CF-RT concerning adverse physician-reported toxic effects 6 months after RT.

Based on long-term results from randomized trials, the evidence supports HF-RT for patients with early-stage, node-negative breast cancer aged >50 years after breast-conserving surgery (BCS). These patients should routinely receive HF-RT regimens of 40–42.6 Gy in 15–16 fractions (8–10, 29). The UK trials have been demonstrating that other even more abbreviated hypofractionated regimens for whole-breast radiation therapy (WBRT) can be delivered. The FAST trial found the dose of 28.5 Gy to be comparable to the 50-Gy arm and significantly milder in toxicity than the 30-Gy arm (30). Sequentially, in the FAST FORWARD trial, 26 Gy in five fractions over 1 week was non-inferior to the standard of 40 Gy in 15 fractions for local tumor control and is as safe in terms of normal tissue effects up to 5 years (31).

Consistent with our findings, 864 women who received locoregional radiotherapy in START trials showed no significant difference in acute toxicity between HF-RT and CF-RT groups (9, 32). Also, in the Chinese large-scale randomized trial directly comparing post-mastectomy with RNI, the HF-RT had less frequent grade 3 acute skin toxicity than the CF-RT arm, 3% *vs.* 8% p< 0.0001 (12). Furthermore, in the MD Anderson trial, maximum physician-reported acute dermatitis was lower in the HF-RT arm (36% *vs.* 69%; p< 0.001).

To our knowledge, this is the first Latin American randomized trial to report acute and subacute breast radiation toxicity between hypofractionation and conventional fractionation. Unlike the majority of the published trials, our population consisted predominantly of self-declared black or mixed ethnicity and had low educational levels (5, 29, 33).

Like other studies performed, we face great challenges due to the COVID-19 pandemic. Most of the time, we deal with the toughest moments of the pandemic. As it was impossible to postpone the treatment or to convert the physical appointment into video visits, we decide to adjust the allocation proportion to allocate a higher number of patients in the HF-RT, as reported above (34, 35). This shift followed the recommendations at that time, with emerging data suggesting no differences in efficacy or toxicity with HF-RT and CF-RT (36, 37).

Regarding the radiation fields, in the Royal Marsden Hospital (RMH) trial, START A, and START B, approximately 21%, 14%, and 7% of the patients received RNI, respectively (4, 38–41). Even though in the Chinese study all patients received level III and supraclavicular fossa nodal irradiation, there was no target volume for axilla and IMC (12). In our study, women with no axillary dissection received RT to levels I, II, and III and supraclavicular fossa, while in those who underwent the lymphadenectomy, the target volume included only the supraclavicular region and level III. IMC irradiation was performed in 15% of patients in the CF-RT arm versus 13% in the HF-RT arm. The randomized trials did not include the internal mammary chain in the target volumes. Despite some studies suggesting equivalent levels of acute and late toxicity, it is not possible to exclude the possibility of increased pulmonary, costal arch, and heart toxicity with hypofractionated radiotherapy (42). No pulmonary toxicity has been observed in patients with IMC irradiation, although we consider that a larger trial with long-term follow-up is required.

Breast reconstruction is performed to restore the breast shape after mastectomy and improves QoL (43). However, post-mastectomy radiation therapy (PMRT) can lead to increased complications of the

TABLE 1 Physician-reported maximum acute toxic effects.

Acute skin toxicity		CF-RT (N = 33)	HF-RT (N = 53)	p
Skin rash (radiotherapy-associated dermatitis)				
	Grade 0	1 (3%)	4 (8%)	**0.022**
	Grade 1	13 (39%)	34 (64%)	
	Grade 2	17 (52%)	15 (28%)	
	Grade 3	2 (6%)	0 (0%)	
Hyperpigmentation				
	Grade 0	0 (0%)	4 (8%)	**0.005**
	Grade 1	15 (45%)	37 (70%)	
	Grade 2	18 (55%)	12 (23%)	
Hypopigmentation				
	Grade 0	21 (64%)	32 (60%)	0.912
	Grade 1	11 (33%)	20 (38%)	
	Grade 2	1 (3%)	1 (2%)	
Induration/fibrosis of skin or subcutaneous tissue				
	Grade 0	21 (64%)	30 (57%)	0.854
	Grade 1	11 (33%)	18 (34%)	
	Grade 2	1 (3%)	4 (8%)	
	Grade 3	0 (0%)	1 (2%)	
Fibrosis/cosmetics				
	Grade 0	25 (76%)	34 (64%)	0.499
	Grade 1	4 (12%)	10 (19%)	
	Grade 2	4 (12%)	6 (11%)	
	Grade 3	0 (0%)	3 (6%)	
Deep connective tissue fibrosis				
	Grade 0	25 (76%)	34 (64%)	0.456
	Grade 1	6 (18%)	11 (21%)	
	Grade 2	2 (6%)	8 (15%)	
Any acute toxicity grade 2 or higher				
	No Yes	10 (30%) 23 (70%)	26 (49%) 27 (51%)	0.136
Any acute toxicity grade 3 or higher				
	No Yes	27 (82%) 6 (18%)	48 (91%) 5 (9%)	0.322
Harvard/NSABP/RTOG breast cosmesis grading scale				
	Poor Fair Good Excellent	5 (15%) 6 (18%) 13 (40%) 9 (27%)	2 (4%) 8 (15%) 25 (47%) 18 (34%)	0.288

As defined by the Harvard/NSABP/RTOG grading scale and CTCAE v. 4.03. Cosmesis and acute toxic effects were recorded on a weekly basis during radiation therapy using a structured template that specified these toxic effects and their definitions. Any subsequent toxic effect occurring within 60 days of treatment completion was also included in this analysis. Fisher's exact test was used for all values except for any grade 2 or higher toxic effect or any grade 3 or higher toxic effect (χ^2).

HF-RT, hypofractionated radiation therapy; CF-RT, conventional fractionated radiation therapy; NSABP, National Surgical Adjuvant Breast and Bowel Project; RTOG, Radiation Therapy Oncology Group; CTCAE, Common Terminology Criteria for Adverse Events.

Bold values means statistically significant.

TABLE 2 Physician-assessed maximum toxic effects at 6 months.

Subacute skin toxicity		CF-RT (N = 26)	HF-RT (N = 48)	p
Skin rash (radiotherapy-associated dermatitis)				
	Grade 0	26 (100%)	45 (94%)	0.548
	Grade 1	0 (0%)	3 (6%)	
Hyperpigmentation				
	Grade 0	7 (27%)	22 (46%)	0.125
	Grade 1	15 (58%)	24 (50%)	
	Grade 2	4 (15%)	2 (4%)	
Hypopigmentation				
	Grade 0	25 (96%)	46 (96%)	1.000
	Grade 1	1 (4%)	2 (4%)	
Induration/fibrosis of skin or subcutaneous tissue				
	Grade 0	21 (81%)	33 (69%)	0.792
	Grade 1	4 (15%)	11 (23%)	
	Grade 2	1 (4%)	3 (6%)	
	Grade 3	0 (0%)	1 (2%)	
Fibrosis/cosmetics				
	Grade 0	22 (84%)	37 (77%)	0.821
	Grade 1	2 (8%)	6 (13%)	
	Grade 2	2 (8%)	3 (6%)	
	Grade 3	0 (0%)	2 (4%)	
Deep connective tissue fibrosis				
	Grade 0	23 (88%)	39 (81%)	0.793
	Grade 1	2 (8%)	5 (11%)	
	Grade 2	1 (4%)	4 (8%)	
Harvard/NSABP/RTOG breast cosmesis grading scale				
	Poor Fair Good Excellent	0 (0%) 1 (4%) 10 (38%) 15 (58%)	1 (2%) 5 (10%) 11 (23%) 31 (65%)	0.432

HF-RT, hypofractionated radiation therapy; CF-RT, conventional fractionated radiation therapy; NSABP, National Surgical Adjuvant Breast and Bowel Project; RTOG, Radiation Therapy Oncology Group; CTCAE, Common Terminology Criteria for Adverse Events.
As defined by the Harvard/NSABP/RTOG grading scale and CTCAE v. 4.03. Cosmesis and acute toxic effects were recorded 6 months after radiation therapy using a structured template that specified these toxic effects and their definitions. Any subsequent toxic effect occurring 6 months after the treatment completion was also included in this analysis.
The Fisher's exact test was used for all values except for any grade 2 or higher toxic effect or any grade 3 or higher toxic effect (χ^2).

reconstructed breast (44). There is a paucity of data about how HF-RT affects breast-related complications after breast reconstruction. Kim and colleagues conducted a retrospective investigation of the impact of PMRT with conventional *vs.* hypofractionated settings and detected no difference in the occurrence of any or major breast-related complications between the two fractionations (45). In our trial, we had a small number of patients who underwent breast reconstruction, 12% and 17% in the CF-RT and HF-RT, respectively, and no difference was demonstrated between them. There was no implant failure reported. We look forward to a longer follow-up that could elucidate potential related complications. Current trials are evaluating HF-RT with reconstruction (Alliance221505/NCT03414970; FABREC Trial/NCT03422003).

The tumor bed boost dose was investigated in the EORTC boost trial. The results showed local control improvement, although there was an increased risk of fibrosis (46, 47). The use of a simultaneous integrated boost (SIB) during the whole-breast treatment has several theoretical dosimetric advantages and a more convenient treatment schedule. The dose can be reduced for the remaining breast as well as for OARs. The hypofractionated boost (HF-boost) has not been

10.3389/fonc.2023.1202544

TABLE 3 Mean baseline and 1-, 2-, and 6-month EORTC QLQ-C30 scale by randomization arm.

	CF-RT	HF-RT	
	Mean (SD)	Mean (SD)	p-Value
Baseline			
Fatigue	16 (26)	13 (19)	0.549
Nausea and vomiting	10 (22)	4 (12)	0.206
Pain	24 (31)	14 (23)	0.111
Dyspnea	12 (26)	8 (23)	0.467
Insomnia	28 (40)	16 (30)	0.117
Loss of appetite	13 (31)	11 (27)	0.706
Constipation	23 (35)	6 (20)	0.07
Diarrhea	3 (13)	3 (11)	0.847
Financial difficulties	23 (35)	16 (30)	0.298
One-month follow-up			
Fatigue	20 (29)	13 (20)	0.175
Nausea and vomiting	10 (24)	7 (13)	0.421
Pain	20 (30)	19 (23)	0.746
Dyspnea	18 (31)	9 (19)	0.096
Insomnia	26 (41)	19 (36)	0.394
Loss of appetite	15 (33)	10 (23)	0.392
Constipation	16 (30)	9 (26)	0.217
Diarrhea	6 (21)	3 (9)	0.367
Financial difficulties	23 (39)	21 (35)	0.778
Two-month follow-up			
Fatigue	15 (25)	15 (22)	0.976
Nausea and vomiting	3 (9)	5 (14)	0.329
Pain	23 (32)	19 (25)	0.544
Dyspnea	14 (31)	13 (29)	0.924
Insomnia	26 (40)	19 (36)	0.481
Loss of appetite	11 (28)	13 (28)	0.717
Constipation	14 (32)	10 (23)	0.558
Diarrhea	4 (19)	3 (14)	0.813
Financial difficulties	22 (38)	18 (34)	0.68
Six-month follow-up			
Fatigue	13 (21)	18 (27)	
Nausea and vomiting	4 (10)	10 (23)	
Pain	21 (31)	23 (30)	
Dyspnea	9 (24)	13 (26)	
Insomnia	26 (36)	30 (40)	
Loss of appetite	18 (32)	12 (25)	
Constipation	15 (34)	16 (32)	

(Continued)

TABLE 3 Continued

	CF-RT	HF-RT	
	Mean (SD)	Mean (SD)	p-Value
Diarrhea	4 (20)	6 (20)	
Financial difficulties	14 (29)	16 (31)	

HF-RT, hypofractionated radiation therapy; CF-RT, conventional fractionated radiation therapy; SD, standard deviation; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer quality of life questionnaire—core questionnaire/Portuguese (Brazil).
p-Value from Mann–Whitney test.

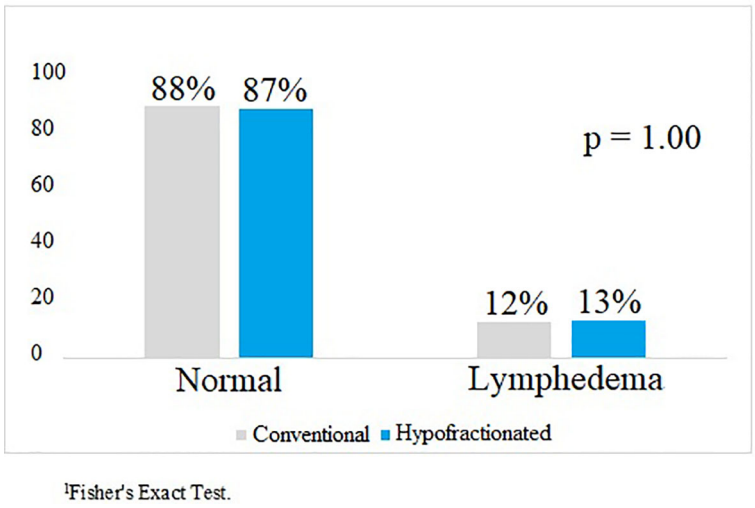


FIGURE 2
Comparison of lymphedema by randomization arm 6 months after treatment.

TABLE 4 Mean baseline and 1-, 2-, and 6-month EORTC QLQ-BR23 scale by randomization arm.

Index	CF-RT	HF-RT	p-Value
	Mean (SD)	Mean (SD)	
Baseline			
Functional scales			
Body image	76 (26)	77 (27)	0.808
Sexual functioning	74 (31)	79 (29)	0.45
Sexual pleasure	70 (35)	75 (29)	0.417
Future perspective	73 (36)	77 (29)	0.583
Symptom scales			
Side effects of systemic therapy	26 (22)	24 (16)	0.757
Breast symptoms	30 (29)	19 (26)	0.066
Arm symptoms	24 (26)	17 (21)	0.179
Upset by hair loss	14 (33)	17 (34)	0.699
One-month follow-up			
Functional scale			
Body image	76 (32)	75 (26)	0.941
Sexual functioning	78 (31)	73 (32)	0.526

(Continued)

TABLE 4 Continued

Index	CF-RT	HF-RT	p-Value
	Mean (SD)	Mean (SD)	
Sexual pleasure	62 (39)	75 (29)	0.087
Future perspective	76 (30)	76 (29)	0.855
Symptom scales			
Side effects of systemic therapy	24 (21)	20 (15)	0.343
Breast symptoms	20 (27)	16 (20)	0.399
Arm symptoms	20 (22)	15 (19)	0.307
Upset by hair loss	14 (33)	12 (29)	0.774
Two-month follow-up			
Functional scales			
Body image	73 (35)	76 (28)	0.811
Sexual functioning	78 (36)	80 (32)	0.878
Sexual pleasure	71 (36)	68 (36)	0.762
Future perspective	78 (35)	79 (32)	0.947
Symptom scales			
Side effects of systemic therapy	23 (21)	22 (19)	0.966
Breast symptoms	15 (21)	12 (20)	0.558
Arm symptoms	18 (24)	18 (24)	0.995
Upset by hair loss	16 (33)	15 (35)	0.855
Six-month follow-up			
Body image	79 (29)	82 (22)	0.676
Sexual functioning	78 (30)	76 (33)	0.608
Sexual pleasure	69 (39)	70 (35)	0.818
Future perspective	78 (31)	76 (35)	0.578
Symptom scales			
Side effects of systemic therapy	23 (25)	19 (20)	0.864
Breast symptoms	16 (25)	16 (25)	0.612
Arm symptoms	19 (25)	18 (22)	0.939
Upset by hair loss	12 (33)	3 (10)	0.353

HF-RT, hypofractionated radiation therapy; CF-RT, conventional fractionated radiation therapy; SD, standard deviation; EORTC QLQ-BR23, European Organisation for Research and Treatment of Cancer quality of life questionnaire—Breast Module/Portuguese (Brazil).
p-Value from Mann–Whitney test.

extensively investigated; however, emerging data suggested that it may be effective and safe. One Chinese study with 185 patients evaluated CF-RT with 50 Gy in 25 fractions followed by a sequential boost of 10 Gy in 5 fractions versus HF-RT with 42.56 Gy in 16 fractions with a SIB up to 48 Gy in 16 fractions. After 2 years, no difference in skin toxicity or cosmetic outcomes between the two arms was detected. Furthermore, the authors highlighted the possibility of hypofractionation with a concomitant boost as a valuable choice to recommend suitable candidates during the COVID-19 epidemic, as we did in our study (48). These findings were consistent with our study, in which all patients undergoing BCS received a boost (concurrent in the HF-RT arm versus sequential in the CF-RT arm), and there was no difference in acute toxicity, fibrosis, or worsening of cosmesis over the 6-month follow-up.

Axillary lymph node dissection and adjuvant radiotherapy are risk factors for lymphedema related to breast cancer (49, 50). The literature has investigated a wide variety of methods for evaluating limb volume when lymphedema is diagnosed. Options include bioelectrical impedance analysis (BIA), tape measurement, perometry, and water displacement. In our trial, lymphedema was evaluated by arm-treated volume measurement in comparison to the contralateral arm (51, 52). In the Indian randomized investigation with CF-RT versus HF-RT at a

TABLE 5 Physician-reported maximum global toxicity according to patients up to 65 years or older.

Global toxicity		<65 years old (N = 60)	≥65 years old (N = 26)	p
Skin rash (radiotherapy-associated dermatitis)				
	Grade 0	5 (8%)	0 (0%)	0.133
	Grade 1	31 (52%)	16 (62%)	
	Grade 2	22 (37%)	10 (38%)	
	Grade 3	2 (3%)	0 (0%)	
Hyperpigmentation				
	Grade 0	3 (5%)	1 (4%)	0.615
	Grade 1	34 (57%)	18 (69%)	
	Grade 2	23 (38%)	7 (27%)	
Hypopigmentation				
	Grade 0	33 (55%)	20 (77%)	0.054
	Grade 1	26 (43%)	5 (19%)	
	Grade 2	1 (2%)	1 (4%)	
Induration/fibrosis of skin or subcutaneous tissue				
	Grade 0	36 (60%)	15 (58%)	0.950
	Grade 1	20 (33%)	9 (34%)	
	Grade 2	3 (5%)	2 (8%)	
	Grade 3	1 (2%)	0 (0%)	
Fibrosis/cosmetics				
	Grade 0	42 (70%)	17 (66%)	0.649
	Grade 1	9 (15%)	5 (19%)	
	Grade 2	6 (10%)	4 (15%)	
	Grade 3	3 (5%)	0 (0%)	
Deep connective tissue fibrosis				
	Grade 0	43 (72%)	16 (62%)	0.581
	Grade 1	11 (18%)	6 (23%)	
	Grade 2	6 (10%)	4 (15%)	
Lymphedema				
	Lymphedema	7 (12%)	3 (12%)	1.000
	Normal	53 (88%)	23 (88%)	

Fisher's exact test.

median follow-up of 20 months, lymphedema was not observed at 88% in conventional irradiation and 86% in hypofractionation (53). A cohort of 1,640 breast cancer patients receiving post-mastectomy radiotherapy found lymphedema in four patients in CF-RT (1%) and four patients in HF-RT (1%), with no statistically significant difference between the schedules (54). Our lymphedema evaluation was performed from the baseline to 6 months after the treatment, and there was no statistically significant difference between arms. As lymphedema is considered a late toxicity effect of radiation therapy, a longer time of follow-up for our patients may be necessary.

Health-related quality of life is considered an important endpoint in cancer clinical trials (55, 56). There are scarce data available to describe patient-reported outcomes of hypofractionation in comparison to conventional fractionation. Jagsi and colleagues present a study with academic and community radiation oncology centers showing higher rates of fatigue 30% *vs.* 19%, p = 0.02, and self-reported moderate/severe pain, 41% *vs.* 24%, p = 0.003, respectively, to the CF-RT versus HF-RT (57). The MD Anderson trial reported less fatigue in patients randomized to the HF-RT group (0% *vs.* 6%; p = 0.01) and less lack of energy (23% *vs.* 39%; p< 0.001) *vs.* the CF-RT

group (27). The results of the abovementioned studies conflict with our trial. The QLC-C30 and QLC-BR23 scales were used to assess many factors. No difference was detected in all quality-of-life domains between arms. Nevertheless, it is important to mention that differences in the toxicity profile compared to our trial may be due to a limited number of patients enrolled in the present study, which might be unable and underpowered to detect smaller differences.

Our results revealed that even the subset of patients up to 65 years or older did not show a statistical difference between both arm fractionation schedules ($p > 0.05$) regarding skin rash, fibrosis, and lymphedema. Hypofractionation is more beneficial for frail and older patients because it reduces the need for transportation and increases their adherence, as verified by other studies (58, 59). Nevertheless, since there are a small number of elderly patients over 70 years old in our research, more studies should be conducted to investigate this finding.

This trial has some limitations. First, our study has a small sample size and a short-term follow-up period for late toxicity. Second, our study was carried out at a single center. Third, it was not double-blind. Fourth, overall survival data and local recurrence outcomes are absent. However, in this study, patients were selected by intention-to-treat analysis, and this analysis may stimulate more future research for these purposes. Additionally, our findings add to the evidence for HF-RT, which would help in therapeutic decisions even after the pandemic period.

5 Conclusions

In this randomized phase 2 study, HF-RT showed a lower frequency of skin rash and global acute and subacute toxicity when compared to CF-RT. There was a higher incidence of skin rash and hyperchromia in the control group. Due to the limitations of this analysis, more randomized phase 3 studies with a larger number of patients and a longer follow-up period are needed to better evaluate and compare toxicity.

Manuscript formatting

Headings

- Hypofractionated radiation therapy has irradiation dose fractions greater than 2 Gy/day.
- Conventional fractionation has daily radiation doses of 1.8–2 Gy.
- The primary endpoint of this randomized phase II trial was the assessment of acute toxicity.
- Secondary endpoints were subacute toxicity, assessment of QoL, cosmesis, and lymphedema.
- Skin rash grade 2 and grade 3 dermatitis were lower with HF-RT than with CF-RT.
- HF-RT was non-inferior with a lower frequency of skin rash and global acute and subacute toxicity when compared to CF-RT.

Equations

$$V_2 = \frac{h \times (C_1^2 + (C_1 \times C_2) + C_2^2)}{12 \times \pi}, \; h = 100 \; mm$$

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Ethics statement

The studies involving human participants were reviewed and approved by 5123 – Hospital da Baleia/Fundação Benjamin Guimarães. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

GOBG, PHCD, ALSF contributed to the study concept and design. All the authors performed the acquisition, analysis, and interpretation of data. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1202544/full#supplementary-material

References

1. Yarnold J. Changes in radiotherapy fractionation-breast cancer. *Br J Radiol* (2019) 92(1093):1–8. doi: 10.1259/bjr.20170849

2. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *New Engl J Med* (2002) 347(16):1233–41. doi: 10.1056/NEJMoa022152

3. Margenthaler JA, Dietz JR, Chatterjee A. The landmark series: breast conservation trials (including oncoplastic breast surgery). *Ann Surg Oncol* (2021) 28 (4):2120–7. doi: 10.1245/s10434-020-09534-y

4. Yarnold J, Ashton A, Bliss J, Homewood J, Harper C, Hanson J, et al. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. *Radiother Oncol* (2005) 75(1):9–17. doi: 10.1016/j.radonc.2005.01.005

5. Group TST. The UK standardisation of breast radiotherapy (START) trial a of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial, *Lancet Oncol* (2008) 9(4):331. doi: 10.1016/S1470-2045(08)70077-9

6. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *New Engl J Med* (2010) 362(6):513–20. doi: 10.1056/NEJMoa0906260

7. Smith BD, Bentzen SM, Correa CR, Hahn CA, Hardenbergh PH, Ibbott GS, et al. Fractionation for whole breast irradiation: an American society for radiation oncology (ASTRO) evidence-based guideline. *Int J Radiat Oncol Biol Phys* (2011) 81(1):59–68. doi: 10.1016/j.ijrobp.2010.04.042

8. Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, Bentzen SM, Bliss JM, et al. The UK standardisation of breast radiotherapy (START) trial b of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* (2008) 371(9618):1098. doi: 10.1016/S0140-6736(08)60348-7

9. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK standardisation of breast radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* (2013) 14(11):1086–94. doi: 10.1016/S1470-2045(13)70386-3

10. Smith BD, Bellon JR, Blitzblau R, Freedman G, Haffty B, Hahn C, et al. Radiation therapy for the whole breast: executive summary of an American society for radiation oncology (ASTRO) evidence-based guideline. *Pract Radiat Oncol* (2018) 8(3):145–52. doi: 10.1016/j.prro.2018.01.012

11. Wang EH, Mougalian SS, Soulos PR, Rutter CE, Evans SB, Haffty BG, et al. Adoption of hypofractionated whole-breast irradiation for early-stage breast cancer: a national cancer data base analysis. *Int J Radiat Oncol Biol Phys* (2014) 90(5):993–1000. doi: 10.1016/j.ijrobp.2014.06.038

12. Wang SL, Fang H, Song YW, Wang WH, Hu C, Liu YP, et al. Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial. *Lancet Oncol* (2019) 20(3):352–60. doi: 10.1016/S1470-2045(18)30813-1

13. Ferguson NM, Laydon D, Nedjati-Gilani G, Imai N, Ainslie K, Baguelin M, et al. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. *Imperial College COVID-19 Response Team* doi: 10.25561/77482

14. Al-Rashdan A, Roumeliotis M, Quirk S, Grendarova P, Phan T, Cao J, et al. Adapting radiation therapy treatments for patients with breast cancer during the COVID-19 pandemic: hypo-fractionation and accelerated partial breast irradiation to address world health organization recommendations. *Adv Radiat Oncol* (2020) 5 (4):575–6. doi: 10.1016/j.adro.2020.03.011

15. Giuliano AE, Edge SB, Hortobagyi GN. Eighth edition of the AJCC cancer staging manual: breast cancer. *Ann Surg Oncol* (2018) 25(7):1783–5. doi: 10.1245/s10434-018-6486-6

16. Breast Contouring RADCOMP Consortium. *RADCOMP breast atlas committee*. (2016). Available at: https://www.nrgoncology.org/About-Us/Center-for-Innovation-in-Radiation-Oncology/Breast-Cancer/RADCOMP-Breast-Atlas

17. Duane F, Aznar MC, Bartlett F, Cutter DJ, Darby SC, Jagsi R, et al. A cardiac contouring atlas for radiotherapy. *Radiother Oncol* (2017) 122(3):416–22. doi: 10.1016/j.radonc.2017.01.008

18. *RADCOMP breast atlas v.3 - bigreduced* (2023). Available at: https://www.nrgoncology.org/About-Us/Center-for-Innovation-in-Radiation-Oncology/Breast-Cancer/RADCOMP-Breast-Atlas

19. Vicini FA, Winter K, Freedman GM, Arthur DW, Hayman JA, Rosenstein BS, et al. RTOG 1005: A phase iii trial of hypo fractionated whole breast irradiation with concurrent boost vs. conventional whole breast irradiation plus sequential boost following lumpectomy for high risk early-stage breast cancer. *Int J Radiat Oncol Biol Phys* (2022) 114(3):S1. doi: 10.1016/j.ijrobp.2022.07.2320

20. Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, et al. The European organization for research and treatment of cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol* (1996) 14(10):2756–68. doi: 10.1200/JCO.1996.14.10.2756

21. M K MG, D M. Quality of life of Danish women: population-based norms of the EORTC QLQ-C30. *Qual Life Res* (1997) 6(1):27–34. doi: 10.1023/A:1026461310761

22. Casley-Smith JR. Measuring and representing peripheral oedema and its alterations. *Lymphology* (1994) 27(2):56–70.

23. Alessandra F, Michels S, Maria I, Dias De Oliveira R, Ii L, Do M, et al. Validity, reliability and understanding of the EORTC-C30 and EORTC-BR23, quality of life questionnaires specific for breast cancer. *Rev Bras Epidemiol* (2013) 16(2):352–63. doi: 10.1590/S1415-790X2013000200011

24. Tewari N, Gill PG, Bochner MA, Kollias J. Comparison of volume displacement versus circumferential arm measurements for lymphoedema: implications for the SNAC trial. *ANZ J Surg* (2008) 78(10):889–93. doi: 10.1111/j.1445-2197.2008.04686.x

25. Petrek JA, Pressman PI, Smith RA. Lymphedema: current issues in research and management. *CA Cancer J Clin* (2000) 50(5):292–307. doi: 10.3322/canjclin.50.5.292

26. National Cancer Institute. Lymphedema (PDQ): health professional version . Available at: https://www.cancer.gov/about-cancer/treatment/side-effects/lymphedema/lymphedema-hp-pdq. 2022.

27. Shaitelman SF, Schlembach PJ, Arzu I, Ballo M, Bloom ES, Buchholz D, et al. Acute and short-term toxic effects of conventionally fractionated vs hypofractionated whole-breast irradiation. *JAMA Oncol* (2015) 1(7):931. doi: 10.1001/jamaoncol.2015.2666

28. Vinh-Hung V, Nguyen NP, Verschraegen C. Hypofractionated nodal irradiation for breast cancer: a case for caution. *JAMA Oncol* (2019) 5(1):13–4. doi: 10.1001/jamaoncol.2018.5061

29. Whelan T, MacKenzie R, Julian J, Levine M, Shelley W, Grimard L, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Institute* (2002) 94(15):1143–50. doi: 10.1093/jnci/94.15.1143

30. Brunt AM, Haviland JS, Sydenham M, Agrawal RK, Algurafi H, Alhasso A, et al. Ten-year results of fast: a randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. *J Clin Oncol* (2020) 38(28):3261–72. doi: 10.1200/JCO.19.02750

31. Murray Brunt A, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet* (2020) 395 (10237):1613–26. doi: 10.1016/S0140-6736(20)30932-6

32. Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, Bentzen SM, Bliss JM, et al. The UK standardisation of breast radiotherapy (START) trial b of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial *Lancet* (2008) 371(9618):1098–107. doi: 10.1016/S0140-6736(08)60348-7

33. Shaitelman SF, Lei X, Thompson A, Schlembach P, Bloom ES, Arzu IY, et al. Three-year outcomes with hypofractionated versus conventionally fractionated whole-breast irradiation: results of a randomized, noninferiority clinical trial. *J Clin Oncol* (2018) 36(35):3495–503. doi: 10.1200/JCO.18.00317

34. Park JJH, Mogg R, Smith GE, Nakimuli-Mpungu E, Jehan F, Rayner CR, et al. How COVID-19 has fundamentally changed clinical research in global health. *Lancet Glob Health* (2021) 9(5):e711–20. doi: 10.1016/S2214-109X(20)30542-8

35. Orkin AM, Gill PJ, Ghersi D, Campbell L, Sugarman J, Emsley R, et al. Guidelines for reporting trial protocols and completed trials modified due to the COVID-19 pandemic and other extenuating circumstances: the CONSERVE 2021 statement. *JAMA* (2021) 326(3):257–65. doi: 10.1001/jama.2021.9941

36. Dietz JR, Moran MS, Isakoff SJ, Kurtzman SH, Willey SC, Burstein HJ, et al. Recommendations for prioritization, treatment, and triage of breast cancer patients during the COVID-19 pandemic. the COVID-19 pandemic breast cancer consortium. *Breast Cancer Res Treat* (2020) 181(3):487. doi: 10.1007/s10549-020-05644-z

37. Meattini I, Becherini C, Boersma L, Kaidar-Person O, Marta GN, Montero A, et al. European Society for radiotherapy and oncology advisory committee in radiation oncology practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. *Lancet Oncol* (2022) 23(1):e21–31. doi: 10.1016/S1470-2045(21)00539-8

38. Whelan TJ, Pignol J, Julian J, Grimard L, Bowen J, Perera F, et al. Long-term results of a randomized trial of accelerated hypofractionated whole breast irradiation following breast conserving surgery in women with node-negative breast cancer. *Int J Radiat OncologyBiologyPhysics.* (2008) 72(1):S28. doi: 10.1016/j.ijrobp.2008.06.829

39. Haffty BG. Long-term results of hypofractionated radiation therapy for breast cancer. *Yearbook Oncol* (2010) 2010:32–3. doi: 10.1016/S1040-1741(10)79575-0

40. Owen JR, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *Lancet Oncol* (2006) 7(6):467–71. doi: 10.1016/S1470-2045(06)70699-4

41. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, et al. The UK standardisation of breast radiotherapy (START) trial a of radiotherapy hypofractionation for treatment of early breast cancer: A randomised trial *Lancet Oncol* (2008) 9(4):331–41. doi: 10.1016/S1470-2045(08)70077-9

42. Freitas NMA, Rosa AA, Marta GN, Hanna SA, Hanriot R de M, Borges ABB, et al. Recommendations for hypofractionated whole-breast irradiation. *Rev Assoc Med Bras* (2018) 64(9):770–7. doi: 10.1590/1806-9282.64.09.770

43. Jagsi R, Li Y, Morrow M, Janz N, Alderman A, Graff J, et al. Patient-reported quality of life and satisfaction with cosmetic outcomes after breast conservation and mastectomy with and without reconstruction: results of a survey of breast cancer survivors. *Ann Surg* (2015) 261(6):1198–206. doi: 10.1097/SLA.0000000000000908

44. Jagsi R, Momoh AO, Qi J, Hamill JB, Billig J, Kim HM, et al. Impact of radiotherapy on complications and patient-reported outcomes after breast reconstruction. *J Natl Cancer Inst* (2018) 110(2):157–65. doi: 10.1093/jnci/djx148

45. Kim DY, Park E, Heo CY, Jin US, Kim EK, Han W, et al. Hypofractionated versus conventional fractionated radiotherapy for breast cancer in patients with reconstructed breast: toxicity analysis. *Breast* (2021) 55:37–44. doi: 10.1016/j.breast.2020.11.020

46. Bartelink H, Horiot JC, Poortmans P, Struikmans H, van den Bogaert W, Barillot I, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *New Engl J Med* (2001) 345 (19):1378–87. doi: 10.1056/NEJMoa010874

47. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol* (2015) 16(1):47–56. doi: 10.1016/S1470-2045(14)71156-8

48. Dong J, Yang Y, Han D, Zhao Q, Liu C, Sun H, et al. Hypofractionated simultaneous integrated boost radiotherapy versus conventional fractionation radiotherapy of early breast cancer after breast-conserving surgery: clinical observation and analysis. *Technol Cancer Res Treat* (2021) 20:153303382110647. doi: 10.1177/15330338211064719

49. Rockson SG. Precipitating factors in lymphedema: myths and realities. *Cancer* (1998) 83(12 Suppl American):2814–6. doi: 10.1002/(SICI)1097-0142(19981215)83:12B+<2814::AID-CNCR31>3.0.CO;2-E

50. McLaughlin SA, Staley AC, Vicini F, Thiruchelvam P, Hutchison NA, Mendez J, et al. Considerations for clinicians in the diagnosis, prevention, and treatment of breast cancer-related lymphedema: recommendations from a multidisciplinary expert ASBrS panel. *Ann Surg Oncol* (2017) 24(10):2818–26. doi: 10.1245/s10434-017-5982-4

51. Sayegh HE, Asdourian MS, Swaroop MN, Brunelle CL, Skolny MN, Salama L, et al. Diagnostic methods, risk factors, prevention, and management of breast cancer-related lymphedema: past, present, and future directions. *Curr Breast Cancer Rep* (2017) 9(2):111–21. doi: 10.1007/s12609-017-0237-8

52. Ridner SH, Montgomery LD, Hepworth JT, Stewart BR, Armer JM. Comparison of upper limb volume measurement techniques and arm symptoms between healthy volunteers and individuals with known lymphedema. *Lymphology* (2007) 40(1):35–46.

53. Rastogi K, Jain S, Bhatnagar AR, Bhaskar S, Gupta S, Sharma N. A comparative study of hypofractionated and conventional radiotherapy in postmastectomy breast cancer patients. *Asia Pac J Oncol Nurs* (2018) 5(1):107–13. doi: 10.4103/apjon.apjon_46_17

54. Chitapanarux I, Klunklin P, Pinitpatcharalert A, Sripan P, Tharavichitkul E, Nobnop W, et al. Conventional versus hypofractionated postmastectomy radiotherapy: a report on long-term outcomes and late toxicity. *Radiat Oncol* (2019) 14(1):175. doi: 10.1186/s13014-019-1378-x

55. Offersen BV, Alsner J, Nielsen HM, Jakobsen EH, Nielsen MH, Krause M, et al. Hypofractionated versus standard fractionated radiotherapy in patients with early breast cancer or ductal carcinoma *In situ* in a randomized phase III trial: the DBCG HYPO trial. *J Clin Oncol* (2020) 38(31):3615–25. doi: 10.1200/JCO.20.01363

56. Offersen BV, Alsner J, Nielsen HM, Jakobsen EH, Nielsen MH, Stenbygaard L, et al. Partial breast irradiation versus whole breast irradiation for early breast cancer patients in a randomized phase III trial: the Danish breast cancer group partial breast irradiation trial. *J Clin Oncol* (2022) 40(36):4189–97. doi: 10.1200/JCO.22.00451

57. Jagsi R, Griffith KA, Boike TP, Walker E, Nurushev T, Grills IS, et al. Differences in the acute toxic effects of breast radiotherapy by fractionation schedule: comparative analysis of physician-assessed and patient-reported outcomes in a Large multicenter cohort. *JAMA Oncol* (2015) 1(7):918–30. doi: 10.1001/jamaoncol.2015.2590

58. Kunkler I. The evolving role of whole breast hypofractionation in older patients with early breast cancer. *Semin Radiat Oncol* (2022) 32(2):155–8. doi: 10.1016/j.semradonc.2021.11.006

59. Pinzi V, Fariselli L, Jereczek-Fossa BA. Altered fractionation in radiation therapy for breast cancer in the elderly: are we moving forward? *Transl Cancer Res* (2020) 9(Suppl 1):S217–27. doi: 10.21037/tcr.2019.09.39

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 13 December 2023
DOI 10.3389/fonc.2023.1281432

OPEN ACCESS

EDITED BY
Nam Phong Nguyen,
International Geriatric Radiotherapy Group,
United States

REVIEWED BY
David Yang,
Dana–Farber Cancer Institute,
United States
Raphael Pfeffer,
Assuta Medical Center, Israel

*CORRESPONDENCE
Letizia Cavallini
letiziacavallini91@gmail.com

†These authors have contributed equally to this work and share first authorship

‡These authors have contributed equally to this work and share senior authorship

RECEIVED 22 August 2023
ACCEPTED 28 November 2023
PUBLISHED 13 December 2023

CITATION
Buwenge M, Macchia G, Cavallini L, Cortesi A, Malizia C, Bianchi L, Ntreta M, Arcelli A, Capocaccia I, Natoli E, Cilla S, Cellini F, Tagliaferri L, Strigari L, Cammelli S, Schiavina R, Brunocilla E, Morganti AG and Deodato F (2023) Unraveling the safety of adjuvant radiotherapy in prostate cancer: impact of older age and hypofractionated regimens on acute and late toxicity - a multicenter comprehensive analysis. *Front. Oncol.* 13:1281432. doi: 10.3389/fonc.2023.1281432

Unraveling the safety of adjuvant radiotherapy in prostate cancer: impact of older age and hypofractionated regimens on acute and late toxicity - a multicenter comprehensive analysis

Milly Buwenge[1†], Gabriella Macchia[2†], Letizia Cavallini[1,3*‡], Annalisa Cortesi[4], Claudio Malizia[5], Lorenzo Bianchi[1,6], Maria Ntreta[3], Alessandra Arcelli[3], Ilaria Capocaccia[1,3], Elena Natoli[1,3], Savino Cilla[7], Francesco Cellini[8,10], Luca Tagliaferri[8], Lidia Strigari[9], Silvia Cammelli[1,3], Riccardo Schiavina[1,6], Eugenio Brunocilla[1,6], Alessio Giuseppe Morganti[1,3‡] and Francesco Deodato[2,10‡]

[1]Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum University of Bologna, Bologna, Italy, [2]Radiation Oncology Unit, Gemelli Molise Hospital - Università Cattolica del Sacro Cuore, Campobasso, Italy, [3]Radiation Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [4]Radiotherapy Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy, [5]Nuclear Medicine, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [6]Division of Urology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [7]Medical Physics Unit, Gemelli Molise Hospital, Campobasso, Italy, [8]Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Rome, Italy, [9]Department of Medical Physics, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [10]Istituto di Radiologia, Università Cattolica del Sacro Cuore, Roma, Italy

Background: The objective of this study was to assess the impact of age and other patient and treatment characteristics on toxicity in prostate cancer patients receiving adjuvant radiotherapy (RT).

Materials and methods: This observational study (ICAROS-1) evaluated both acute (RTOG) and late (RTOG/EORTC) toxicity. Patient- (age; Charlson's comorbidity index) and treatment-related characteristics (nodal irradiation; previous TURP; use, type, and duration of ADT, RT fractionation and technique, image-guidance systems, EQD2 delivered to the prostate bed and pelvic nodes) were recorded and analyzed.

Results: A total of 381 patients were enrolled. The median EQD2 to the prostate bed (α/β=1.5) was 71.4 Gy. The majority of patients (75.4%) were treated with intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT). Acute G3 gastrointestinal (GI) and genitourinary (GU) toxicity rates were 0.5% and 1.3%, respectively. No patients experienced >G3 acute toxicity. The multivariable analysis of acute toxicity (binomial logistic regression)

showed a statistically significant association between older age (> 65) and decreased odds of G≥2 GI acute toxicity (OR: 0.569; 95%CI: 0.329-0.973; p: 0.040) and decreased odds of G≥2 GU acute toxicity (OR: 0.956; 95%CI: 0.918-0.996; p: 0.031). The 5-year late toxicity-free survival rates for G≥3 GI and GU toxicity were 98.1% and 94.5%, respectively. The only significant correlation found (Cox's regression model) was a reduced risk of late GI toxicity in patients undergoing hypofractionation (HR: 0.38; 95% CI: 0.18-0.78; p: 0.008).

Conclusions: The unexpected results of this analysis could be explained by a "response shift bias" concerning the protective effect of older age and by treatment in later periods (using IMRT/VMAT) concerning the favorable effect of hypofractionation. However, overall, the study suggests that age should not be a reason to avoid adjuvant RT and that the latter is well-tolerated even with moderately hypofractionated regimens.

KEYWORDS

prostate neoplasms, observational study, toxicity, predictive factors, radiotherapy, adjuvant therapy

Introduction

Prostate cancer (PCa) is a significant health concern, ranking second in terms of incidence and fifth in terms of mortality among male populations (1). Radical prostatectomy (RP) is a commonly employed treatment option for PCa. However, the five-year biochemical relapse-free survival (bRFS) rate after RP is approximately 50% of patients with high-risk features at pathological evaluation (2–4).

Postoperative radiotherapy (RT) has been investigated as an adjunctive treatment following RP, and the results of four randomized studies (2–5) have demonstrated improved bRFS rates (around 25% at five years) compared to RP alone. Moreover, one of these studies has shown a significantly reduced risk of metastasis and improved overall survival (OS) with postoperative RT (6).

Consequently, international guidelines, such as those from the European Association of Urology[1] (EAU 2022) and the National Comprehensive Cancer Network[2] (NCCN 2022), recommend postoperative RT as an adjuvant therapy for selected PCa patients. Specifically, EAU guidelines recommend adjuvant RT for high-risk patients (pN0) with at least two of the following high-risk features: International Society of Urological Pathology (ISUP) grade group 4–5, pT3 stage, and positive surgical margins.

Nevertheless, recent randomized trials (7–9) and a meta-analysis (10) have demonstrated that early salvage RT can achieve biochemical and clinical outcomes comparable to those of adjuvant RT, while significantly reducing the number of patients requiring pelvic RT and improving overall treatment tolerability. These findings highlight the importance of careful patient selection for adjuvant RT, considering the cost/benefit ratio.

In this regard, it is crucial to consider both factors that predict greater benefit from adjuvant RT, such as seminal vesicle involvement (11) and positive surgical margins (12) as well as factors that indicate a higher risk of side effects. However, the available evidence on the latter topic is limited and often derived from small studies that have analyzed only specific patient and/or treatment characteristics (13–17).

Therefore, the aim of this study is to analyze multiple patient- and treatment-related factors in a large multicenter series of PCa patients who underwent adjuvant RT, with the goal of identifying predictors of increased toxicity, and in particular to evaluate whether older age is associated with a greater risk of radiation-induced side effects.

Material and methods

Study design and endpoints

This sub-analysis is part of a multicenter observational study (311/2019/Oss/AOUBo, ICAROS-1 study) focusing specifically on patients with PCa who underwent postoperative adjuvant RT. The study endpoints encompass both acute and late gastrointestinal (GI) and genitourinary (GU) toxicities.

Inclusion criteria

The inclusion criteria were as follows: 1) patients diagnosed with PCa who underwent RP with negative or microscopically

1 https://uroweb.org/guidelines/prostate-cancer/chapter/treatment.

2 http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

positive margins (R0-1) and no distant metastases, and 2) RT delivered using external beam techniques with photon beams. Exclusion criteria were: 1) presence of macroscopic (R2) residual disease after RP, 2) postoperative PSA level exceeding 0.2 ng/ml, and 3) postoperative RT delivered more than one year after RP.

Evaluated parameters

The recorded and evaluated patient-related characteristics included age and Charlson's comorbidity index. Age was analyzed both as a continuous variable and as a dichotomous variable using a cut-off at the median value. The analyzed treatment characteristics encompassed the delivery of prophylactic lymph node irradiation (PNI), previous transurethral resection of the prostate (TURP), use and type of adjuvant androgen deprivation therapy (ADT) (LH-RH analogues or high-dose bicalutamide) and its duration, RT fractionation and technique (including the type of image-guidance systems employed), as well as the Equivalent Dose in 2 Gy per fraction (EQD2) delivered to the prostate bed and pelvic lymph nodes. Acute toxicity was monitored with weekly visits during treatment and with a follow-up visit 2 months after the end of treatment. Late toxicity was evaluated with a first follow-up visit 6 months after the end of treatment and then with further visits every 6 months up to 24 months after treatment, followed by annual assessments up to 10 years. Gastrointestinal toxicity was evaluated by patient interviews and proctoscopy, if necessary. Genitourinary toxicity was assessed through patient interviews and urine analysis during follow-up.

Statistical analysis

Statistical computations were performed using IBM SPSS Version 22.0 software package (IBM Corp, Armonk, NY, USA). A p-value less than 0.05 was considered statistically significant. Acute toxicity was evaluated using the RTOG scale, while late toxicity was assessed using the RTOG/EORTC scale (18). The chi-squared test with Yates' continuity correction and Fisher's exact test were employed in univariate logistic regression to examine the correlation between the analyzed variables and acute toxicity. Additionally, a binomial logistic stepwise regression was used to estimate the likelihood of acute toxicity based on the aforementioned variables. Late toxicity-free survival estimates were calculated using the Kaplan-Meier product-limit method (19) and compared using the log-rank test (20). Variables with a p-value less than 0.05 or showing a trend ($p < 0.1$) in the univariate analysis were included in a multivariate Cox regression model (21).

Ethical considerations

The study received approval from the local institutional review board, and participation in the analysis was limited to patients who provided written informed consent.

Results

Patients, tumors, and treatment characteristics

A total of 381 patients were included in this analysis, with a median age of 65 years (range: 43-79 years). Table 1 presents the patients, tumor, and treatment characteristics. The median delivered EQD2 to the prostate bed, calculated using α/β ratios of 1.5 Gy, 3 Gy, and 10 Gy, was 71.4 (range: 66.2-78.0), 68.7 (range: 67.0-78.0), and 68.2 (range: 65.1-78.0), respectively. Among the patients, 127 (33.3%) were treated with standard fractionation, while 254 (66.7%) received a hypofractionated regimen. $EQD2_{\alpha/\beta=3}$ was significantly higher in patients treated with hypofractionated regimens compared to standard fractionation

TABLE 1 Patients and treatment characteristics and results of univariate analysis on acute toxicity.

		n° of pts (%)	Gastrointestinal				Genitourinary			
			Grade ≥ 2 (%)	χ (Fisher's exact test)	Univariate logistic regression		Grade ≥ 2 (%)	χ (Fisher's exact test)	Univariate logistic regression	
				p-value	OR	p-value		p-value	OR	p-value
Age	≤ 65	174 (45.7)	23.5	**0.032**	ref.		20.1	0.424	ref.	
	> 65	207 (54.3)	14.5		0.55	**0.024**	16.4		0.78	0.352
	CV	381 (100)			0.97	0.078			0.96	**0.044**
Charlson's comorbidity index	0	309 (81.1)	19.4	0.161	ref.		18.1	0.971	ref.	
	1	57 (15.0)	17.5		0.88	0.741	19.3		1.08	0.833
	2	13 (3.4)	0		0.00	0.982	15.4		0.82	0.802
	3	2 (0.5)	50.0		4.15	0.317	0		0.00	0.983

(Continued)

10.3389/fonc.2023.1281432

TABLE 1 Continued

		n° of pts (%)	Gastrointestinal				Genitourinary			
			Grade ≥ 2 (%)	χ (Fisher's exact test)	Univariate logistic regression		Grade ≥ 2 (%)	χ (Fisher's exact test)	Univariate logistic regression	
				p-value	OR	p-value		p-value	OR	p-value
Age adjusted Charlson's comorbidity index	0	6 (1.6)	16.7	0.173	ref.		33.3	0.237	ref.	
	1	49 (12.9)	16.3		0.98	0.983	15.7		0.88	0.892
	2	178 (46.7)	24.7		1.64	0.655	16.8		0.37	0.268
	3	119 (31.2)	12.6		0.72	0.772	16.0		0.40	0.314
	4	25 (6.6)	12.0		0.68	0.761	0		0.38	0.346
	5	3 (0.8)	0		0.00	0.987	0		0.0	0.986
	6	1 (0.3)	0		0.00	0.992	0		0.0	0.992
PNI	No	84 (22)	13.1	0.187	ref.		10.7	0.053	ref.	
	Yes	297 (78)	20.2		1.68	0.143	20.2		2.11	0.050
Hypofractionation	No	127 (33.3)	15.7	0.376	ref.		15.7	0.480	ref.	
	Yes	254 (66.7)	20.1		1.34	0.307	19.3		1.28	0.398
Lymphadenectomy	No	94 (24.7)	21.3	0.288	ref.		19.1	0.706	ref.	
	< 15*	121 (31.8)	14.0		0.60	0.166	15.7		0.79	0.507
	≥ 15*	166 (43.8)	20.5		0.95	0.879	1.2		1.01	0.980
EQD_2 prostate bed α/β_{10} (Gy)	≤ 68.3	193 (50.7)	17.3	0.699	ref.		16.2	0.358	ref.	
	> 68.3	188 (49.3)	19.7		1.15	0.605	20.2		1.32	0.294
	CV	381 (100)			1.00	0.164			1.00	0.103
Radiotherapy Technique	3D-CRT	94 (24.7)	13.8	0.214	ref.		13.8	0.271	ref.	
	IMRT	273 (71.7)	20.9		1.64	0.136	20.1		1.57	0.177
	VMAT	14 (3.7)	7.1		0.48	0.496	7.1		0.48	0.496
Image guidance	EPID	351 (92.1)	18.8	1	ref.		18.8	0.480	ref.	
	CB-CT	30 (7.9)	16.7		0.86	0.773	10.0		0.48	0.239
ADT	No	127 (33.)	18.9	1	ref.		13.4	0.120	ref.	
	Yes	254 (66.7)	18.5		0.97	0.926	20.5		1.67	0.092
Type of ADT	None	127 (33.3)	18.9	0.381	ref.		13.4	0.108	ref.	
	LHRH	183 (48.0)	16.4		0.84	0.568	18.6		1.48	0.227
	HD-Bic	71 (18.6)	23.9		1.35	0.402	25.4		2.20	**0.036**
EQD_2 lymph nodes α/β_{10} (Gy)	≤ 44.3	280 (73.5)	18.2	0.839	ref.		16.4	0.204	ref.	
	> 44.3	101 (26.5)	19.8		1.11	0.725	22.8		1.5	0.158
	CV	381 (100)			1.00	0.126			1.0001	**0.035**

ADT, adjuvant deprivation therapy; CV, Continuous variable; PNI, prophylactic nodal irradiation.
Bold values means p-value less than 0.05.

protocols (mean: 71.3 Gy versus 69.7 Gy; p<0.001). RT was delivered using either 3D-conformal RT (94 patients, 24.7%) or modulated techniques such as intensity modulated arc therapy (IMRT) or volumetric modulated arc therapy (VMAT) (287 patients, 75.3%). The dose to the prostatic bed ranged between 65 and 78 Gy (median: 66 Gy). Moreover, of 254 patients treated with hypofractionation, the dose per fraction was 2.2 Gy in 100 patients, 2.5 Gy in 142 patients, and 2.6 Gy in 12 patients. Furthermore, of 127 patients treated with standard fractionation, the dose per fraction was 1.8 Gy in 42 patients and 2 Gy in 85 patients. Additionally, out of 254 patients treated with hypofractionation, 239 (94.1%) were treated with IMRT/VMAT and 15 (5.9%) with 3D-CRT. Finally, out of 297 patients receiving nodal irradiation, 250 (84.2%) were treated with IMRT/VMAT, while 47 (15.8%) were treated with 3D-CRT. Daily on-line set-up corrections were performed using an electronic portal imaging device (351 patients, 92.1%) or an on-board cone-beam CT (30 patients, 7.9%), as previously described (22).

Acute and late toxicity

Table 1 provides the results in terms of acute toxicity. None of the patients experienced acute toxicity greater than Grade 3, and the rates of Grade 3 gastrointestinal (GI) and genitourinary (GU) toxicity were 0.5% and 1.3%, respectively. The actuarial 5-year rates of Grade ≥ 2 GI and GU late toxicity-free survival were 90.4% and 83.5%, respectively. The actuarial 5-year rates of Grade ≥ 3 GI and GU late toxicity-free survival were 98.1% and 94.5%, respectively.

Univariate analysis

Univariate analysis revealed that acute Grade ≥ 3 GI and GU toxicity rates were not significantly correlated with any of the analyzed parameters. However, the delivery of PNI showed a trend for correlation with higher rates of Grade ≥ 2 acute GU toxicity (Table 1).

The actuarial 5-year late Grade ≥ 2 GI toxicity was significantly lower in patients treated with hypofractionation (dose per fraction > 2 Gy compared to ≤ 2 Gy; 93.6% vs 84.0%; p: 0.006), IMRT or VMAT techniques (compared to 3D-conformal therapy; 93.2-100.0% vs 82.6%; p: 0.027), and PNI (compared to irradiation of the prostate bed only; 92.9% vs 80.2%; p: 0.009). Moreover, actuarial 5-year late Grade ≥ 2 GU toxicity did not show any significant correlation with the analyzed parameters. Furthermore, actuarial 5-year late Grade ≥ 3 GI toxicity was significantly lower in patients treated with hypofractionation (dose per fraction > 2 Gy compared to ≤ 2 Gy; 99.2% vs 96.1%; p-value: 0.033) and IMRT or VMAT techniques (compared to 3D-conformal therapy; 100.0% vs 93.5%; p-value: 0.022). Late Grade ≥ 3 GU toxicity did not exhibit any significant correlation with the analyzed parameters (Table 2).

Multivariate analysis

The multivariable analysis of acute toxicity, conducted using binomial logistic regression, revealed a statistically significant association between older age and a reduced risk of Grade ≥ 2 GI acute toxicity (age analyzed as a dichotomous variable: OR: 0.569; 95% confidence interval [$_{95\%}$CI]: 0.329-0.973; p: 0.040). Apart from age, no other variable fitted in the multivariable logistic model for GI Grade ≥ 2 toxicity. Moreover, older age was significantly associated to a lower risk of Grade ≥ 2 GU acute toxicity (age analyzed as a continuous variable: OR: 0.956; $_{95\%}$CI: 0.918-0.996; p: 0.031). Regarding dichotomous variable GU Grade ≥ 2 acute toxicity, three variables were included in the multivariable model, including age as a continuous variable, ADT, and EQD2 α/β=10 to the prostate bed. While ADT and EQD2 enhanced the predictive model, they were not statistically significant (ADT: OR: 1.730, $_{95\%}$ CI: 0.966-3.234, p: 0.073; EQD2: OR: 1.0005, $_{95\%}$CI: 0.9999-1.0010, p = 0.075). In contrast, the age variable remained statistically significant, with age showing an inverse association with toxicity (OR: 0.956, 95% CI: 0.918-0.996, p: 0.031). The multivariable analysis of late toxicity confirmed only a lower risk of Grade ≥ 2 GI toxicity in patients undergoing hypofractionation (OR: 0.38; $_{95\%}$ CI: 0.18-0.78; p: 0.008). (Table 3).

Discussion

Adjuvant RT has been associated with an increased risk of side effects compared to surgery alone (4) and early salvage RT (7–9). However, it is important to note that, in selected high-risk PCa patients, adjuvant RT offers a higher chance of cure compared to surgery alone. Our multicenter observational study confirms that severe acute toxicity is rare in this setting. The rates of acute Grade ≥ 3 GI and GU toxicity were only 0.5% and 1.3%, respectively, and the 5-year actuarial cumulative incidence of late Grade ≥ 3 GI and GU toxicity rates were 1.9% and 5.5%, respectively.

Furthermore, our analysis demonstrated lower rates of GI acute toxicity in older patients. This unexpected result may arise from the fact that elderly patients may be more likely to have pre-existing symptoms or discomfort due to age-related health issues or comorbidities. As a result, they might be less inclined to report or attribute certain side effects to RT, especially if these side effects are mild or non-serious. The phenomenon of underreporting or downplaying side effects in elderly patients is known as “response shift” or “response shift bias” (23).

Other studies have reported an increased risk of GI early adverse effects in patients with higher mean rectal dose (16) or larger irradiated bowel volumes (24), those receiving PNI (25, 26), individuals with previous abdominal surgery (24), and those under anticoagulant or antiplatelet therapy (16). Additionally, Fiorino et al. observed reduced toxicity rates in patients receiving IMRT (24), although this effect was not observed in our cohort or in the study by Flores-Balcazar et al. (27).

Furthermore, our study demonstrated a reduced risk of GU acute toxicity in older patients, while Martinez-Arribas et al.

10.3389/fonc.2023.1281432

TABLE 2 Actuarial 5-year gastrointestinal and genitourinary late toxicity-free survival rates (Grade ≥ 2 and Grade ≥ 3; Kaplan-Meier) and results of univariate analysis (log-rank).

		No of pts (%)	Gastrointestinal				Genitourinary			
			G ≥ 2 (%)	P	G ≥ 3 (%)	p	G ≥ 2 (%)	P	G ≥ 3 (%)	P
Age	≤ 65 years	174 (45.7)	94.1	.065	100.0	**.037**	83.4	.909	94.3	.683
	> 65 years	207 (54.3)	87.2		96.5		83.7		94.6	
Charlson's comorbidity Index	0	309 (81.1)	91.5	.331	98.1	.900	82.6	.890	93.9	.688
	1	57 (15.0)	85.6		98.1		84.4		98.2	
	2	13 (3.4)	83.9		100.0		92.3		92.3	
	3	2 (0.5)	100.0		100.0		100.0		100	
Age adjusted Charlson's comorbidity index	0	6 (1.6)	100.0	.396	100.0	.811	75.0	.865	100.0	,651
	1	49 (12.9)	95.8		100.0		90.9		96.8	
	2	178 (46.7)	92.5		98.3		79.8		93.2	
	3	119 (31.2)	85.4		97.4		85.4		95.8	
	4	25 (6.6)	83.0		95.7		86.6		92.0	
	5	3 (0.8)	100.0		100.0		64.9		100.0	
	6	1 (0.3)	100.0		100.0		100.0		100.0	
Nodal irradiation	No	84 (22.0)	80.2	**.009**	96.8	.288	87.7	.139	98.0	.204
	Yes	297 (78.0)	92.9		98.4		82.4		93.5	
Hypofractionation	No	127 (33.3)	84.0	**.006**	96.1	**.033**	83.2	.764	93.2	.533
	Yes	254 (66.7)	93.6		99.2		83.6		95.2	
Lymphadenectomy	No	94 (24.7)	92.6	.098	98.6	.259	79.2	.464	95.9	.758
	< 15*	166 (43.6)	92.9		99.2		86.9		94.1	
	≥ 15*	121 (31.8)	84.4		96.0		83.0		93.9	
EQD_2 to the prostate bed α/β_3 (Gy)	≤ 68.3	226 (59.3)	91.1	.808	98.1	.973	84.2	.603	92.7	.120
	> 68.3	155 (40.7)	89.3		98.2		83.2		97.0	
Radiotherapy technique	3DCRT	94 (24.7)	82.6	**.027**	93.5	**.002**	83.4	.524	96.4	.692
	IMRT	273 (71.7)	93.2		100.0		83.1		93.2	
	VMAT	14 (3.7)	100.0		100.0		100.0		100.0	
Image guidance	EPID	351 (92.1)	90.0	.455	98.0	.556	82.4	.059	94.1	.319
	CB	30 (7.9)	96.6		100.0		100.0		100.0	
Previous abdominal or pelvic surgery	No	367 (96.3)	90.3	.914	98.1	.662	83.6	.718	94.3	.467
	Yes	14 (3.7)	90.0		100.0		84.4		100.0	
Adjuvant Hormone Therapy	No	127 (33.3)	89.2	.836	98.0	.829	85.9	.341	95.6	.267
	Yes	254 (66.3)	91.0		98.2		82.3		93.9	
EQD_2 to the lymph node α/β_3 (Gy)	No	84 (22.0)	80.2	**.033**	96.8	.329	87.7	.236	98.0	.121
	≤ 43.2	196 (51.4)	93.0		99.5		82.2		91.7	
	> 43.2	101 (26.5)	92.7		96.6		83.5		96.9	
Acute GI toxicity	G 0	162 (42.5)	91.3	.601	99.0	.442	NA	NA	NA	NA

(Continued)

10.3389/fonc.2023.1281432

TABLE 2 Continued

		No of pts (%)	Gastrointestinal				Genitourinary			
			G ≥ 2 (%)	P	G ≥ 3 (%)	p	G ≥ 2 (%)	P	G ≥ 3 (%)	P
	G 1	148 (38.8)	88.2		97.1		NA	NA	NA	NA
	G 2-3	71 (18.6)	92.5		98.3		NA	NA	NA	NA
Acute GU toxicity	G 0	150 (39.4)	NA	NA	NA	NA	90.7		95.3	
	G 1	162 (42.5)	NA	NA	NA	NA	85.5	**.000**	92.1	.390
	G 2-3	69 (18.1)	NA	NA	NA	NA	65.2		98.0	

3D-CRT, 3-dimensional conformal radiotherapy, CB, cone beam; EQD_2, Equivalent Dose in 2 Gy/fraction; EPID, Electronic portal imaging device; G, Grade; GI, gastrointestinal; GU, genitourinary; NA, not assessed; No, Number; Pts, patients; *number of resected lymph nodes.
Bold values means p<0.1.

reported higher GU acute toxicity rates in patients with urinary symptoms before RT. Additionally, similar to our findings, Flores-Balcazar et al. (27) and Deville et al. (26) did not observe a significant impact of IMRT/VMAT and PNI, respectively.

Moreover, our analysis revealed a reduced risk of GI late toxicity in patients treated with hypofractionated RT. Another study observed a higher risk of late GI adverse effects in subjects with higher body mass index values and those treated with higher RT doses (17). Furthermore, Flores-Balcazar et al. did not find a significant impact of IMRT/VMAT, in line with our findings, while Goenka et al. reported significantly reduced toxicity in patients treated with IMRT (28). Similarly, Deville et al. did not find different toxicity rates in subjects treated with PNI (26). **.

In our analysis, no parameter was significantly correlated with late GU toxicity. However, other studies have reported a significant correlation between higher toxicity rates and older age and receiving > 70 Gy to larger bladder volumes (17), hypofractionated RT (15), and Grade > 2 acute GU toxicity (13, 15). Interestingly, IMRT did not show an impact on late GU toxicity in two studies (27, 28), consistent with our analysis. Waldstein et al. reported increased toxicity rates in patients treated with PNI (25), while Deville et al. did not observe this correlation (26), similar to our series.

In conclusion, the results of available evidence conflict regarding: i) the impact of modulated RT techniques on acute GU toxicity and late GI side effects, and ii) the impact of PNI on late GU toxicity. Moreover, there is limited evidence available regarding parameters predicting acute GU side effects.

The use of hypofractionation in the adjuvant RT setting of PCa remains a controversial topic. Moderately hypofractionated regimens are considered preferable in patients undergoing exclusive RT (NCCN 2022) but not in the adjuvant setting. According to the NCCN guidelines, the recommended standard fractionation dose for adjuvant/salvage RT is 64-72 Gy (NCCN 2022). However, the data available on this topic are very heterogeneous. For instance, a systematic review on hypofractionated postoperative RT reported rates of Grade ≥ 2 late GU toxicity ranging between 0% and 66% (29).

The results of our analysis did not indicate a worse toxicity profile in patients undergoing hypofractionated RT. Furthermore, the multivariable analysis revealed a reduced rate of late GI toxicity after RT delivered with > 2 Gy per fraction. In contrast, Cozzarini et al. reported a significant increase in the rate of Grade ≥ 3 GU toxicity in patients receiving hypofractionated regimens compared to conventional fractionation (5-year risk: 18.1% versus 6.9%). This difference can be explained by comparing the equivalent doses delivered in our study and Cozzarini's et al. study. Assuming an α/β ratio of 3 Gy for late effects, patients undergoing hypofractionation in our study received a median dose of 68.7 Gy, while in Cozzarini's et al. study, the range was 68.4-80.8 Gy. Moreover, in Cozzarini's et al. study, the EQD2 was > 70 Gy in 79.8% of patients and > 79 Gy in 32.4% of subjects. Additionally, the EQD2 for PNI was 43.2 Gy in our series and 50.2 Gy in Cozzarini's et al. series. Even when using an α/β ratio of 5, as done by Cozzarini et al., our median EQD2 (67.0 Gy) was lower compared to their analysis (median: 70.4 Gy, IQR: 70.4-79.2 Gy).

Taken together, the results from the two studies suggest a possible association between dose and late urological toxicity in this setting, highlighting the need for further investigation. It is also worth noting that the safety of hypofractionation observed in our data is consistent with recent analyses (30–32). Probably, the lower incidence of late toxicity recorded in patients treated with hypofractionation in our study, despite a significantly higher $EQD2_{\alpha/\beta=3}$ value, may derive from the delivery of RT in more recent times, and therefore with more precise techniques.

The paradoxical result of our analysis, of reduced late gastrointestinal toxicity in patients undergoing PNI, remains to be explained. The only interpretation we can propose is that patients with better general conditions and fewer comorbidities (particularly at the intestinal level) were more frequently referred to PNI.

Our study has certain limitations. The scales used to score acute and late toxicity are outdated, and an assessment of the treatment impact on quality of life is lacking. Furthermore, despite efforts to include as many parameters as possible in the analysis, some were missing from our database. Among these, several factors have shown a significant impact on toxicity rates in previous studies, such as baseline symptoms (16) drug therapy during RT (16), planning dose/volume indices (14, 17), body mass index (17), and tobacco history (17).

On the other hand, the strengths of this study lie in the large number of cases analyzed and the comprehensive inclusion of

10.3389/fonc.2023.1281432

TABLE 3 Multivariable analysis of late gastrointestinal and genitourinary toxicity.

Gastrointestinal toxicity (Grade ≥ 2)				
Variable	*Value*	*Hazard Ratio*	*95%CI*	*p=*
Age	CV	1.036	0.976-1.107	0.232
Charlson's comorbidity index	0	Ref		
	> 0	1.678	0.953-2.955	0.073
Nodal irradiation	No	Ref		0.802
	Yes	0.974	0.593-1.498	
Hypofractionation	No	Ref		0.008
	Yes	0.381	0.184-0.783	
Lymphadenectomy	No/sampling	Ref		0.802
	Yes (>15)	0.942	0.589-1.505	
EQD_2 to the prostate bed α/β_3 (Gy)	CV	1.000	0.998-1.002	0.936
Radiotherapy technique	3D-CRT	Ref		0.929
	IMRT/VMAT	0.945	0.275-3.251	
Image guidance	EPID	Ref		0.267
	Cone-beam CT	0.561	0.202-1.557	
EQD2 to the lymph node α/β_3 (Gy)	CV	1.001	0.998-1.003	0.580
Genitourinary toxicity (Grade ≥ 2)				
Variable	*Value*	*Hazard Ratio*	*95%CI*	*p=*
Age	CV	0.991	0.945-1.040	0.710
Charlson's comorbidity index	0	Ref		0.468
	> 0	0.807	0.452-1.440	
Nodal irradiation	No	Ref		0.890
	Yes	0.744	0.110-4.894	
Hypofractionation	No	Ref		0.250
	Yes	0.544	0.193-1.534	
Lymphadenectomy	No/sampling	Ref		0.074
	Yes (>15*)	0.724	0.508-1.031	
EQD_2 to the prostate bed α/β_3 (Gy)	CV	1.001	0.998-1.003	0.120
Radiotherapy technique	3D-CRT	Ref		0.621
	IMRT/VMAT	0.767	0.269-2.191	
Image guidance	EPID	Ref		0.400
	Cone-beam CT	0.803	0.606-1.365	
EQD2 to the lymph node α/β_3 (Gy)	CV	1.000	0.999-1.001	0.972
Acute GU toxicity	Grade 0-1	Ref		0.059
	Grade 2-3	3.060	0.882-13.658	

3D-CRT,3-dimensional conformal radiotherapy; EQD2, Equivalent Dose in 2 Gy/fraction; EPID, Electronic portal imaging device; *number of resected lymph nodes.

numerous parameters related to both patients and treatments, as well as RT techniques in the analysis.

In conclusion, the results of our analysis demonstrate that although adjuvant RT significantly increases the overall rate of adverse events in PCa patients, the risk of severe toxicity is low. Additionally, acute toxicity rates were higher in younger patients, while a protective effect of hypofractionation was observed in terms of late GI toxicity.

To minimize the negative impact of adjuvant RT, further studies are warranted. These analyses should aim to: i) develop predictive models of toxicity combined with the risk of recurrence based on a comprehensive range of clinical, genetic-molecular, and treatment-related parameters, to guide the careful selection of patients for immediate adjuvant RT; ii) analyze toxicity rates in patients undergoing tailored/intensified adjuvant RT. For example, studies have shown that biochemical relapse-free survival can be improved by modulating postoperative RT, such as adjusting the dose based on surgical margin status, delivering PNI in selected cases, and administering ADT based on the risk of treatment failure (33–36); iii) clarify the impact of hypofractionation on late GU toxicity, given the conflicting evidence in the literature (29).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of IRCCS Azienda Ospedaliero-Universitaria di Bologna (311/2019/Oss/AOUBo, ICAROS-1 study). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MB: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. GM: Conceptualization, Writing – review & editing. LC: Data curation, Investigation, Writing – review & editing. AC: Data curation, Investigation, Writing – review & editing. CM: Formal analysis, Writing – review & editing. LB: Writing – review & editing. MN: Writing – review & editing. AA: Data curation, Formal analysis, Writing – review & editing. IC: Data curation, Investigation, Writing – review & editing. EN: Writing – review & editing. SCi: Formal analysis, Writing – review & editing. FC: Writing – review & editing. LT: Writing – review & editing. LS: Writing – review & editing. SCa: Data curation, Writing – review & editing. RS: Writing – review & editing. EB: Writing – review & editing. AGM: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. FD: Conceptualization, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We would like to thank Cinzia Giacometti for her invaluable help in data management.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* (2018) 68(6):394–424. doi: 10.3322/caac.21492

2. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA* (2006) 296(19):2329–35. doi: 10.1001/jama.296.19.2329

3. Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* (2009) 27(18):2924–30. doi: 10.1200/JCO.2008.18.9563

4. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* (2012) 380(9858):2018–27. doi: 10.1016/S0140-6736(12)61253-7

5. Hackman G, Taari K, Tammela TL, Matikainen M, Kouri M, Joensuu T, et al. Randomised trial of adjuvant radiotherapy following radical prostatectomy versus radical prostatectomy alone in prostate cancer patients with positive margins or extracapsular extension. *Eur Urol* (2019) 76(5):586–95. doi: 10.1016/j.eururo.2019.07.001

6. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* (2009) 181(3):956–62. doi: 10.1016/j.juro.2008.11.032

7. Parker CC, Clarke NW, Cook AD, Kynaston HG, Petersen PM, Catton C, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. *Lancet* (2020) 396(10260):1413–21. doi: 10.1016/S0140-6736(20)31553-1

8. Sargos P, Chabaud S, Latorzeff I, Magné N, Benyoucef A, Supiot S, et al. Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. *Lancet Oncol* (2020) 21(10):1341–52. doi: 10.1016 S1470-2045(20)30454-X

9. Kneebone A, Fraser-Browne C, Duchesne GM, Fisher R, Frydenberg M, Herschtal A, et al. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. *Lancet Oncol* (2020) 21(10):1331–40. doi: 10.1016/S1470-2045(20) 30456-3

10. Vale CL, Fisher D, Kneebone A, Parker C, Pearse M, Richaud P, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. *Lancet* (2020) 396(10260):1422–31. doi: 10.1016/S0140-6736(20) 31952-8

11. Swanson GP, Goldman B, Tangen CM, Chin J, Messing E, Canby-Hagino E, et al. The prognostic impact of seminal vesicle involvement found at prostatectomy and the effects of adjuvant radiation: data from Southwest Oncology Group 8794. *J Urol* (2008) 180(6):2453–7; discussion 2458. doi: 10.1016/j.juro.2008.08.037

12. Van der Kwast TH, Bolla M, Van Poppel H, Van Cangh P, Vekemans K, Da Pozzo L, et al. Identification of patients with prostate cancer who benefit from immediate postoperative radiotherapy: EORTC 22911. *J Clin Oncol* (2007) 25 (27):4178–86. doi: 10.1200/JCO.2006.10.4067

13. Choo R, Pearse M, Danjoux C, Gardner S, Morton G, Szumacher E, et al. Analysis of gastrointestinal and genitourinary morbidity of postoperative radiotherapy for pathologic T3 disease or positive surgical margins after radical prostatectomy using national cancer institute expanded common toxicity criteria. *Int J Radiat Oncol Biol Phys* (2008) 72(4):989–95. doi: 10.1016/j.ijrobp.2008.02.044

14. Perna L, Alongi F, Fiorino C, Broggi S, Cattaneo Giovanni M, Cozzarini C, et al. Predictors of acute bowel toxicity in patients treated with IMRT whole pelvis irradiation after prostatectomy. *Radiother Oncol* (2010) 97(1):71–5. doi: 10.1016/ j.radonc.2010.02.025

15. Cozzarini C, Fiorino C, Deantoni C, Briganti A, Fodor A, La Macchia M, et al. Higher-than-expected severe (Grade 3-4) late urinary toxicity after postprostatectomy hypofractionated radiotherapy: a single-institution analysis of 1176 patients. *Eur Urol* (2014) 66(6):1024–30. doi: 10.1016/j.eururo.2014.06.012

16. Martínez-Arribas CM, González-San Segundo C, Cuesta-Álvaro P, Calvo-Manuel FA. Predictors of urinary and rectal toxicity after external conformed radiation therapy in prostate cancer: Correlation between clinical, tumour and dosimetric parameters and radical and postoperative radiation therapy. *Actas Urol Esp.* (2017) 41(10):615–23. doi: 10.1016/j.acuro.2017.03.010

17. Akthar AS, Liao C, Eggener SE, Liauw SL. Patient-reported outcomes and late toxicity after postprostatectomy intensity-modulated radiation therapy. *Eur Urol* (2019) 76(5):686–92. doi: 10.1016/j.eururo.2019.05.011

18. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the european organization for research and treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys* (1995) 31(5):1341–6. doi: 10.1016/0360-3016 (95)00060-C

19. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. In: Kotz S, Johnson NL, editors. *Breakthroughs in Statistics: Methodology and Distribution*. New York, NY: Springer (1992). p. 319–37. doi: 10.1007/978-1-4612-4380-9_25

20. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc Ser A (General)* (1972) 135(2):185–207. doi: 10.2307/2344317

21. Cox DR. Regression models and life-tables. *J R Stat Soc Ser B (Methodological)* (1972) 34(2):187–220. doi: 10.1111/j.2517-6161.1972.tb00899.x

22. Deodato F, Cilla S, Massaccesi M, Macchia G, Ippolito E, Caravatta L, et al. Daily on-line set-up correction in 3D-conformal radiotherapy: is it feasible? *Tumori* (2012) 98(4):441–4. doi: 10.1177/030089161209800407

23. Ilie G, Bradfield J, Moodie L, Lawen T, Ilie A, Lawen Z, et al. The role of response-shift in studies assessing quality of life outcomes among cancer patients: A systematic review. *Front Oncol* (2019) 9:783. doi: 10.3389/fonc.2019.00783

24. Fiorino C, Alongi F, Perna L, Broggi S, Cattaneo GM, Cozzarini C, et al. Dose–volume relationships for acute bowel toxicity in patients treated with pelvic nodal irradiation for prostate cancer. *Int J Radiat OncologyBiologyPhysics* (2009) 75(1):29–35. doi: 10.1016/j.ijrobp.2008.10.086

25. Waldstein C, Dörr W, Pötter R, Widder J, Goldner G. Postoperative radiotherapy for prostate cancer: Morbidity of local-only or local-plus-pelvic radiotherapy. *Strahlenther Onkol* (2018) 194(1):23–30. doi: 10.1007/s00066-017-1215-9

26. Deville C, Vapiwala N, Hwang WT, Lin H, Ad VB, Tochner Z, et al. Comparative toxicity and dosimetric profile of whole-pelvis versus prostate bed-only intensity-modulated radiation therapy after prostatectomy. *Int J Radiat Oncol Biol Phys* (2012) 82(4):1389–96. doi: 10.1016/j.ijrobp.2011.04.041

27. Flores-Balcázar CH, Urías-Arce DM, Bourlon MT, Gabilondo-Navarro F, Pérez-Álvarez SI, Ramos-Prudencio R, et al. Transitioning from conformal radiotherapy to intensity-modulated radiotherapy after radical prostatectomy: Clinical benefit, oncologic outcomes and incidence of gastrointestinal and urinary toxicities. *Rep Pract Oncol Radiother* (2020) 25(4):568–73. doi: 10.1016/j.rpor.2020.04.018

28. Goenka A, Magsanoc JM, Pei X, Schechter M, Kollmeier M, Cox B, et al. Improved toxicity profile following high-dose postprostatectomy salvage radiation therapy with intensity-modulated radiation therapy. *Eur Urol* (2011) 60(6):1142–8. doi: 10.1016/j.eururo.2011.08.006

29. Siepe G, Buwenge M, Nguyen NP, Macchia G, Deodato F, Cilla S, et al. Postoperative hypofractionated radiation therapy in prostate carcinoma: A systematic review. *Anticancer Res* (2018) 38(3):1221–30. doi: 10.21873/ anticanres.12343

30. Tramacere F, Arcangeli S, Pignatelli A, Bracci S, Vinella M, Portaluri M. Postoperative hypofractionated radiotherapy for prostate cancer. *Anticancer Res* (2018) 38(5):2951–6. doi: 10.21873/anticanres.12544

31. Mahase S, Nagar H. Hypofractionated postoperative radiotherapy for prostate cancer: is the field ready yet? *Eur Urol Open Sci* (2020) 22:9–16. doi: 10.1016/ j.euros.2020.10.001

32. Moll M, D'Andrea D, Zaharie A, Grubmüller B, Paschen C, Zehetmayer S, et al. Comparative effectiveness of moderate hypofractionation with volumetric modulated arc therapy versus conventional 3D-radiotherapy after radical prostatectomy. *Strahlenther Onkol* (2022) 198(8):719–26. doi: 10.1007/s00066-022-01909-2

33. Mantini G, Siepe G, Alitto AR, Buwenge M, Nguyen NP, Farioli A, et al. Tailored postoperative treatment of prostate cancer: final results of a phase I/II trial. *Prostate Cancer Prostatic Dis* (2018) 21(4):564–72. doi: 10.1038/s41391-018-0064-7

34. Cozzarini C, Montorsi F, Fiorino C, Alongi F, Bolognesi A, Da Pozzo LF, et al. Need for high radiation dose (>or=70 gy) in early postoperative irradiation after radical prostatectomy: a single-institution analysis of 334 high-risk, node-negative patients. *Int J Radiat Oncol Biol Phys* (2009) 75(4):966–74. doi: 10.1016/j.ijrobp.2008.12.059

35. Ost P, Cozzarini C, De Meerleer G, Fiorino C, De Potter B, Briganti A, et al. High-dose adjuvant radiotherapy after radical prostatectomy with or without androgen deprivation therapy. *Int J Radiat Oncol Biol Phys* (2012) 83(3):960–5. doi: 10.1016/ j.ijrobp.2011.09.007

36. Katayama S, Habl G, Kessel K, Edler L, Debus J, Herfarth K, et al. Helical intensity-modulated radiotherapy of the pelvic lymph nodes with integrated boost to the prostate bed - initial results of the PLATIN 3 Trial. *BMC Cancer* (2014) 14:20. doi: 10.1186/1471-2407-14-20

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 01 February 2024
DOI 10.3389/fonc.2024.1302001

OPEN ACCESS

EDITED BY
Benyi Li,
University of Kansas Medical Center,
United States

REVIEWED BY
Siyuan Cheng,
Louisiana State University Health Shreveport,
United States
Francesco Cuccia,
ARNAS Ospedali Civico Di Cristina Benfratelli,
Italy

*CORRESPONDENCE
Youssef Slama
youssef.slama@clinifutur.net

RECEIVED 25 September 2023
ACCEPTED 17 January 2024
PUBLISHED 01 February 2024

CITATION
Slama Y, Baumont G, Arcambal A, Begue M, Maillot O, Sayah R, Castanet R, Caboche R, Liberati P, Slaoui H, Bouaziz M, Borson O, Nguyen NP and Dutheil F (2024) Retrospective study on the toxicity induced by stereotactic body radiotherapy: overview of the reunion experience on prostate cancer in elderly patients.
Front. Oncol. 14:1302001.
doi: 10.3389/fonc.2024.1302001

Retrospective study on the toxicity induced by stereotactic body radiotherapy: overview of the reunion experience on prostate cancer in elderly patients

Youssef Slama[1]*, Gilles Baumont[1], Angelique Arcambal[1], Mickael Begue[1], Olivier Maillot[1], Rima Sayah[1], Romain Castanet[1], Raoul Caboche[2], Pedro Liberati[2], Hakim Slaoui[2], Medi Bouaziz[2], Olivier Borson[3], Nam P. Nguyen[4] and Fabien Dutheil[1]

[1]Clinique Sainte-Clotilde, Department of Radiotherapy, Groupe Clinifutur, Saint-Denis, La Réunion, France, [2]Clinique Sainte-Clotilde, Department of Urology, Groupe Clinifutur, Saint-Denis, La Réunion, France, [3]Cabinet de Radiologie Les Alizés, Saint-Denis, La Réunion, France, [4]Department of Radiation Oncology, Howard University, College of Medicine, Washington, DC, United States

Introduction: Prostate cancer is the fourth most commonly diagnosed cancer among men worldwide. Various tools are used to manage disease such as conventional radiotherapy. However, it has been demonstrated that large prostate volumes were often associated with higher rates of genitourinary and gastrointestinal toxicities. Currently, the improvements in radiotherapy technology have led to the development of stereotactic body radiotherapy, which delivers higher and much more accurate radiation doses. In order to *complete literature data about short-term outcome and short-term toxic effects of* stereotactic body radiotherapy*, we aimed to share our experience about gastrointestinal and genitourinary toxicities associated with* stereotactic body radiotherapy *in prostate cancer in patients over 70 years old.*

Methods: We retrospectively reviewed the medical records of elderly patients with prostate cancer treated between 2021 and 2022. The elderly patients were treated with a non-coplanar robotic stereotactic body radiotherapy platform using real-time tracking of implanted fiducials. The prostate, with or without part of the seminal vesicles, was treated with a total dose of 36.25 Gy delivered in five fractions, each fraction being administered every other day.

Results: We analyzed a total of 80 elderly patients, comprising 38 low-, 37 intermediate- and 5 high-risk patients. The median follow-up duration was 12 months. We did not observe biochemical/clinical recurrence, distant metastasis, or death. Grade 2 acute genitourinary toxicity was observed in 9 patients (11.25%) and Grade 2 acute gastrointestinal toxicity in 4 patients (5.0%). We did not observe any grade 3 or more acute or late toxicities.

Conclusion: Over the follow-up period, we noted a low frequency of gastrointestinal and genitourinary toxicities induced by stereotactic body radiotherapy in the context of prostate cancer in elderly patients. Therefore, stereotactic body radiotherapy seems to represent a promising treatment option for elderly patients, with acceptable acute toxicity.

KEYWORDS

prostate cancer, elderly patients, stereotactic body radiotherapy, gastrointestinal toxicity, genitourinary toxicity

Introduction

Based on prostate cancer (PCa) statistics, PCa is the 2nd most commonly occurring cancer in men and the 4th most common cancer overall. There were more than 1.4 million new cases of prostate cancer in 2020 (1). Nowadays, the clinical localization of the disease determines the risk level of the disease through the National Comprehensive Cancer Network (NCCN) guidelines. As per these guidelines, most patients diagnosed for PCa have low-risk or intermediate-risk disease (2). The 5-year survival rate for people diagnosed with PCa is 84% for those with local- or regional-stage PCa. However, this rate drops to 31% for those diagnosed with distant-stage *disease* (3, 4). Despite an overall 10-year survival rate of 98% across all stages, which is attributed to the high cure rate of the disease in the United States, PCa treatment is still associated with a risk of disability and co-morbidities (5). Various disease management strategies can be considered for the treatment of PCa, including definitive external beam radiotherapy (EBRT) delivered in conventional fractions of 1.8 to 2.0 Gy for 8 or 9 weeks. Given that prostate cancer exhibits a high sensitivity to higher doses per fraction due to a low α to β ratio compared to organs at risk, hypofractionated treatment with a higher dose per fraction seems to be more appropriate and more effective. Over the past 25 years, radiotherapy procedures have significantly advanced, resulting in improved precision for locating and tracking the tumor, and decreased positioning error rates in the treatments (6). This improvement has led to the emergence of Stereotactic Body Radiation Therapy (SBRT) or extreme hypofractionation. In fact, the combination of multiple fields with image guidance and SBRT allows to deliver higher and more accurate radiation doses than in the past (7–13).

Nevertheless, hypofractionation may not be beneficial for all types of tumors. In case of PCa, it could help to balance the benefits and risks by improving cure rates and reducing risks of gastrointestinal and genitourinary toxicities (14–17).

Aging affects the individual's tolerance to ionizing radiation due to physiological changes and comorbid illnesses. Indeed, geriatric conditions can influence the normal tissue response to radiation and affect the ability of patients to complete radiation treatment and tolerate radiotherapy-related side effects (18). Of note, radiation-induced toxicities are not directly proportional to age but are more associated with the severity of the comorbidities of patients (19). Moreover, it is well established that the probability of developing PCa increases with age and that men aged 70 and older may especially experience radiation-induced toxicities (4).

Even if over the past decade, SBRT technology has been extensively used worldwide and the data collected has proved that its effectiveness and acceptability are constantly increasing, there is a lack of literature data regarding elderly patients and the short-term outcomes of SBRT, particularly potential short-term toxic effects.

The aim of this study is to share our experience regarding the short-term outcomes of SBRT in elderly patients (70 years old and older) including acute toxicity associated with the treatment in a cohort of 80 patients with various PCa risk levels (low to high-risk) treated between 2021 and 2022.

Materials and methods

Patient selection and characteristics

Elderly patients with PCa, for whom radiation therapy was selected as the preferred treatment in a multidisciplinary consultation meeting and who opted for SBRT over EBRT, were included in this study. The 80 patients were exclusively treated with SBRT at La Clinique Sainte-Clotilde (Reunion Island, France) for the first time and all toxicity data were collected. To enable tracking of the prostate and improve the accuracy of the dose delivery during SBRT, 3 or 4 gold seeds were inserted into the prostate transperineally or transrectally. In case of transrectal insertion, prophylactic antibiotics were administrated to the patient before and after the procedure. The fiducial markers inserted were gold

Abbreviations: CGA, comprehensive geriatric assessment; CTCAE, Common Terminology Criteria for Adverse Events; CTV, Clinical Target Volume; EBRT, External Beam Radiation Therapy; NCCN, National Comprehensive Cancer Network; OAR, Organ at risk; PCa, Prostate Cancer; PSA, Prostate Specific Antigen; PTV, Planning Target Volume; QoL, Quality of Life; RTOG, Radiation Therapy Oncology Group; SBRT, Stereotactic Body Radiation Therapy.

anchor (0.4x10 mm) delivered through a thin needle (G22) (20, 21). Patients underwent planning computed tomography with a slice thickness of 1.5 mm at least 7 days after fiducial markers insertion. The computed tomography scan extended at least 15 cm above and below the prostate to ensure the inclusion of the testicles in the scanned volume. Additionally, a magnetic resonance imaging of the prostate was performed, specifically to delineate the urethra (22, 23). For low-risk patients, the clinical target volume (CTV) included only the prostate. However, for intermediate or high-risk patients, the CTV included the prostate and a proximal 1 cm of the seminal vesicles (24). The organs at risk (OAR) were delineated according to the recommendations of the Radiation Therapy Oncology Group (RTOG) (25). The bladder was contoured as a solid organ from base to dome. The rectum was contoured from recto-sigmoid flexure to anal verge. and the urethra from bladder to 2 cm below the prostatic apex. The bowel was countered as a "bowel bag" i.e in the space within the peritoneal cavity that could contain the bowel.

The following instructions were given to all patients to ensure an appropriate bladder and rectum preparation:

- Empty the bladder one hour before the dosimetric scanner and the radiotherapy sessions then drink 50 cl of water and avoid urinating.
- Low residue diet during the treatment phase (from the medical consultation).
- Prescription of daily laxative (from the medical consultation).
- Fasting 4 hours before the dosimetric scanner and the treatment sessions.
- Prescription of Enema 2 hours before the dosimetric scanner and the treatment sessions.

TABLE 1 Organ at risk (OAR) dose constraints.

Organ at risk	Volume	Dose
Rectum	Maximum point dose (0.03 cc)	≤38.06Gy (105% of the prescription dose)
	Less than 3 cc	<34.4Gy (95% of the prescription dose)
	10% rectum	≤32.625Gy (90% of the prescription dose)
	20% rectum	≤29Gy (80% of the prescription dose)
	50% rectum	≤18.125Gy (50% of the prescription dose)
Bladder	Maximum point dose (0.03 cc)	≤38.06Gy (105% of the prescription dose)
	10% bladder	≤32.625Gy (90% of the prescription dose)
	50% bladder	≤18.125Gy (50% of the prescription dose)
Penil bulb	Maximum point dose	<100% of the prescription dose
	Less than 3 cc	20Gy (54% of the prescription dose)
Femoral heads	Less than 10 cc accrued (right-left)	20Gy (54% of the prescription dose)
	Maximum point dose	30Gy (81% of the prescription dose)
Bowel (GETUG 14)	D5 cc	<18.1Gy
	D1 cc	<30Gy
Urethra	Maximum dose	≤38.78Gy (107% of the prescription dose)

cc = cubic centimetre.

Radiation treatment

Planning

The radiotherapy planning target volume (PTV) is created by adding appropriate margins to the CTV. To create the PTV, the CTV is expanded by 5 mm in all directions, except 3 mm posteriorly. This volume likely includes 1-2 mm of microscopic extracapsular spread, which helps mitigate delineation uncertainties and treatment delivery inaccuracies as reported in literature trials (26, 27). However, optimal margins for high-risk patients needed to be defined. The primary planning objective was to deliver 36.25 Gy in 5 fractions to the PTV. The plans were normalized such that 95% of the PTV volume receives at least 36.25 Gy. The dosimetric objectives to the OAR are summarized in Table 1.

Treatment

All patient were treated with a non-isocentric robotic radiation therapy platform (CyberKnife; Accuray, Sunnyvale, CA) capable of producing rapid fall-off dose gradients with submillimeter accuracy in dose delivery (28, 29). Three or four prostate fiducials were tracked in real time, with automatic correction for translational and rotational target motion. Treatment was completed over a period of 10 to 14 days. Retrospective assessment of genitourinary and gastrointestinal functions was performed using the CTCAE V.5 scale systems at regular intervals during the first 12 months following the beginning of the treatment (end of treatment, 1, 3, 6 month and 1 year).

Prostate-specific antigen level quantification

The blood prostate specific antigen (PSA) levels were measured before SBRT treatment and after the completion of SBRT. The PSA bounce was defined as a PSA circulating level increase of 0.2 ng/mL from the previous level measured, followed by an important decrease.

Statistical analysis

Results were expressed as median ± standard deviation (SD), mean ± SD or median ± interquartile range when appropriate. One-way analysis of variance (ANOVA) followed by Sidak tests was

assessed. Multiple comparison between groups was performed using Graph-Pad Prism 8 program (GraphPad Software, Inc.). A p values ≤ 0.05 was considered statistically significant.

Results

Distribution of patients according to tumor characteristics

Eighty elderly patients were treated between September 2021 and December 2022 with SBRT. All characteristics of patients and tumors are listed in Table 2. The majority of elderly patients had a prostate cancer classified as T2a and T2b stages and 72.5% of them had a Gleason score established at 3 + 3 and 3 + 4. Furthermore, this study included a majority of low and intermediate-risk patients with 5 patients considered as being at high-risk disease and 15% of patients with a PSA>20 ng/mL. It is worth noting that 58.8% of patients underwent a hormone therapy.

TABLE 2 Distribution of patients according to their PCa characteristics and their treatments.

Parameters	Score/Value	Number of patients (%)
Stage	T1a	0 (0)
	T1b	2 (2.50)
	T1c	3 (3.75)
	T2a	35 (43.75)
	T2b	33 (41.25)
	T2c	6 (7.50)
	ND	1 (1.25)
Gleason score	3 + 3	30 (37.5)
	3 + 4	28 (35.0)
	4 + 3	15 (18.75)
	3 + 5	1 (1.25)
	4 + 4	1 (1.25)
	4 + 5	2 (2.50)
	5 + 5	1 (1.25)
	ND	2 (2.50)
Initial PSA levels (ng/mL)	<10 ng/mL	44 (55.0)
	10 – 20 ng/mL	24 (30.0)
	>20 ng/mL	12 (15.0)
NCCN Risk grouping	Low	38 (47.5)
	Intermediate	37 (46.3)
	High	5 (6.2)
Hormone therapy	Yes	47 (58.75)
	Short	1 (1.25)
	No	32 (40.0)
Age (Mean ± SD)	76.21 ± 5.18	
Number of patients (N)	80	

NCCN, National Comprehensive cancer Network; ND, not disclosed; PSA, Prostate-specific antigen.

Radiation dosimetric data

Dosimetric data were collected and listed in Table 3. Results show selected dose-volume histogram parameters for the rectum, the bladder and target volumes. This table also indicates the CTV volume.

The typical dose distribution for radiotherapy treatment of prostate patients are represented in Figure 1 with the axial (Figure 1A), sagittal (Figure 1B) and coronal (Figure 1C) views. The typical Dose-Volume Histogram is represented on Figure 1D as well as the corresponding dosimetric validation table (Figure 1E).

Genitourinary and gastrointestinal toxicities reported over time

Toxicity induced by SBRT was assessed by gathering patients' feedback (Figure 2). The reported toxicity, as measured on the CTCAE V.5 scale, was low; the gastrointestinal and the genitourinary grade 2 toxicity occurrence after treatment was 5% (Figure 2A) and 11.25%, respectively (Figure 2B). Data indicated that genitourinary toxicity became more significant over time than gastrointestinal toxicity. Moreover, two patients reported a grade 3 genitourinary toxicity at the vesical globe level.

Correlation between reported toxicities and dose-volume parameters

The genitourinary toxicity grades were determined by gathering patients' feedback over time following SBRT treatment. As shown in Figure 2, most of the toxicities reported by the patients were genitourinary. Therefore, we analyzed the dose-volume data to investigate whether these toxicities could be predicted and correlated with CTV, PTV, and bladder volume, as well as the doses received by the bladder (Figure 3). No difference was observed between groups of grades 0, 1 or 2 regarding the prostate CTV, PTV (Figures 3A, B) and bladder volume (Figure 3C), one week after the end of SBRT.

On this cohort, we did not observe any correlation between the toxicity recorded 1 week after the end of SBRT and the doses received by the bladder (Figures 3D-F).

Prostate-specific antigen analysis

All elderly patients selected for the present study were included in the post-treatment analysis of prostate specific antigen. The data presented in Table 2 shows that 58.8% of patients had concomitant

TABLE 3 Dose-volume parameters for stereotactic body radiotherapy plans.

	Parameters	Median ± SD (n=80)
CTV	Prostate CTV volume	32.64 ± 13.86 cc
PTV	Volume of PTV receiving the prescription dose	95 ± 1.02%
	PTV volume	70.83 ± 20.99
	PTV_{max} dose	40.94 ± 1.07 Gy
	PTV_{min} dose	32.69 ± 2.28 Gy
Bladder	Bladder maximal dose (0.035 cc)	37.43 ± 0.46 Gy
	10% dose for the bladder	28.89 ± 5.99 Gy
	50% dose for the bladder	11.57 ± 3.51 Gy
Rectum	Rectum maximal dose (0.035 cc)	37.14 ± 0.56 Gy
	3 cc dose for the rectum	33.66 ± 2.12 Gy
	10% dose for the rectum	29.93 ± 2.66 Gy
	20% dose for the rectum	22.27 ± 3.07 Gy
	50% dose for the rectum	10.43 ± 3.89 Gy

cc, cubic centimeter; CTV, clinical target volume; PTV, planning target volume.

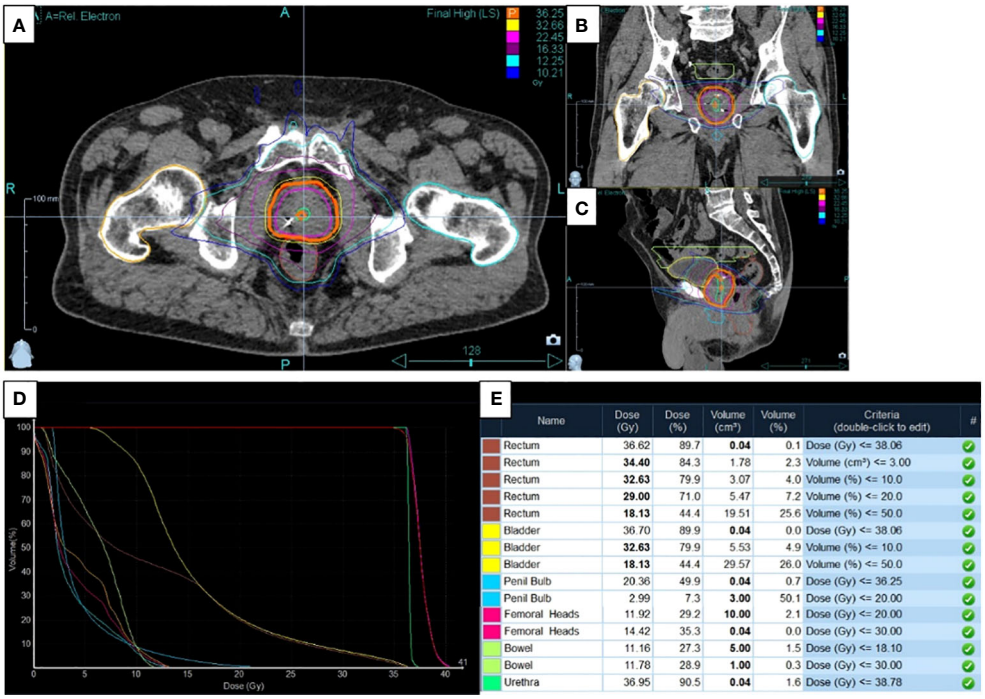
androgen deprivation therapy. The PSA levels quantified before the start of treatment were 19.03 ± 39.69 within a range of [0.230 – 266.00] for 80 patients.

The median follow-up time was 12 months and we observed a gradual decline of the median PSA level over time (Figure 4). Indeed, the 6 months post-treatment median PSA has dropped to 0.33 ng/ml. At 6 months after treatment, 20% of patients exhibited a temporary rise in PSA levels, followed by a subsequent decrease to the previous levels. However, PSA outcomes with such a short follow-up period should be interpreted with caution and will need to be reassessed when the median follow-up period approaches 5 years.

Discussion

The aim of this retrospective study was to report the toxicity data collected from 80 elderly patients with PCa and treated with the SBRT technique using the Cyberknife system. No instances of biochemical or clinical recurrence, distant metastasis occurrence or death were observed during the follow-up period. Acute gastrointestinal and genitourinary toxicities observed in this study were not correlated with the calculated dose levels received by the bladder or the rectum. Two patients experienced grade 3 toxicity level during the SBRT treatment, which led to the interruption of their treatment.

Importantly, geriatric conditions may affect response to radiation and studies reported that comprehensive geriatric assessment (CGA) can help to predict the occurrence of acute radiation-induced toxicities for patients treated for PCa or Head and neck cancers (30–32).



Name	Dose (Gy)	Dose (%)	Volume (cm³)	Volume (%)	Criteria (double-click to edit)	#
Rectum	36.62	89.7	**0.04**	0.1	Dose (Gy) <= 38.06	✓
Rectum	**34.40**	84.3	1.78	2.3	Volume (cm³) <= 3.00	✓
Rectum	**32.63**	79.9	3.07	4.0	Volume (%) <= 10.0	✓
Rectum	**29.00**	71.0	5.47	7.2	Volume (%) <= 20.0	✓
Rectum	**18.13**	44.4	19.51	25.6	Volume (%) <= 50.0	✓
Bladder	36.70	89.9	**0.04**	0.0	Dose (Gy) <= 38.06	✓
Bladder	**32.63**	79.9	5.53	4.9	Volume (%) <= 10.0	✓
Bladder	**18.13**	44.4	29.57	26.0	Volume (%) <= 50.0	✓
Penil Bulb	20.36	49.9	**0.04**	0.7	Dose (Gy) <= 36.25	✓
Penil Bulb	2.99	7.3	**3.00**	50.1	Dose (Gy) <= 20.00	✓
Femoral Heads	11.92	29.2	**10.00**	2.1	Dose (Gy) <= 20.00	✓
Femoral Heads	14.42	35.3	**0.04**	0.0	Dose (Gy) <= 30.00	✓
Bowel	11.16	27.3	**5.00**	1.5	Dose (Gy) <= 18.10	✓
Bowel	11.78	28.9	**1.00**	0.3	Dose (Gy) <= 30.00	✓
Urethra	36.95	90.5	**0.04**	1.6	Dose (Gy) <= 38.78	✓

FIGURE 1
Typical dose distribution, dose-volume and dosimetric data for application of radiotherapy treatment on prostate cancer. **(A)** The axial, **(B)** sagittal and **(C)** coronal views were presented concerning dose distribution as well as **(D)** the dose-Volume Histogram and **(E)** the corresponding dosimetric validation table.

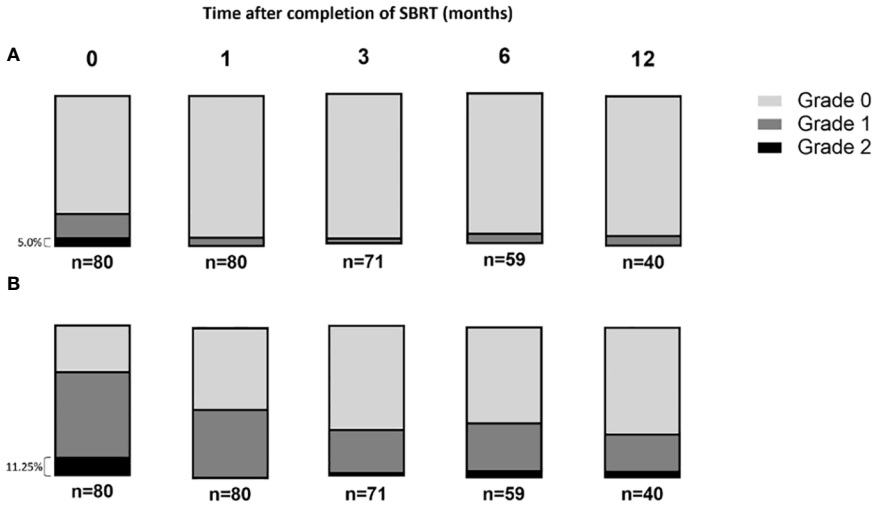


FIGURE 2
The rate of acute gastrointestinal and genitourinary toxicities after prostate stereotactic body radiotherapy scored following Radiation Therapy Oncology Group score. **(A)** The gastrointestinal and **(B)** genitourinary toxicities were presented overtime after the completion of SBRT protocol.

In the present study, we did not perform a CGA before SBRT, which represents a limitation of our study. Recently, studies tried to predict tolerance of radiotherapy by proceeding to CGA to identify predictors of reduced Quality of Life (QoL) and occurrence of toxicities. Nevertheless, some studies on cohorts of prostate cancer elderly patients using conventional or hypofractionated radiotherapy demonstrated the lack of sensitivity of CGA outcome and did not find predictive factors to determine toxicities or impaired QoL following radiotherapy (33–35). Indeed, screening tools need to be more experienced.

PCa incidence risk increases with age and it seems crucial to pay attention to acute and or late radiation-induced toxicities for elderly patients after the completion of their radiotherapy protocol. However, literature data about the side effects of radiotherapy are more associated with protocols using EBRT than those using SBRT and the level of evidence in older patients is limited. Thus, we chose to focus on SBRT-induced toxicities.

Currently, SBRT technology is a new technique that presents a significant benefit for PCa treatment. As demonstrated in literature,

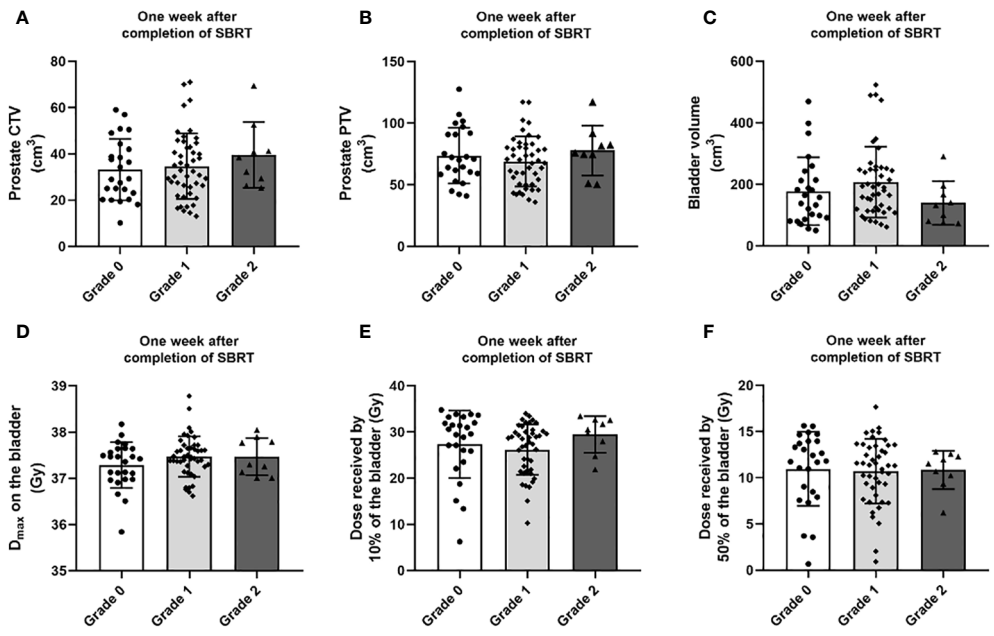


FIGURE 3
Distribution of **(A)** CTV, **(B)** PTV, **(C)** bladder volume, **(D)** maximum dose (dose in a volume of 0.035 cc) to the bladder, **(E)** the dose received by 10% of the bladder volume and **(F)** the dose received by 50% of the bladder volume by genitourinary toxicity grade occurring one week after the end of the SBRT treatment. Data are expressed as mean ± SD.

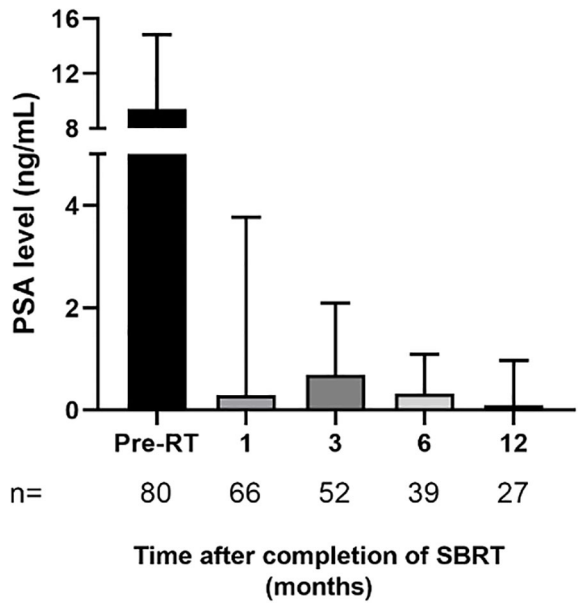


FIGURE 4
Patient level of prostate-specific antigen (PSA) after completion of prostate stereotactic body radiotherapy. Data are expressed as median ± interquartile range. The number of patients corresponding to PSA levels quantified at each period is specified on figure histogram. *Abbreviations:* ***pre-RT*** = *pre-radiotherapy.*.

results of SBRT are encouraging, supporting its use for PCa treatment (36, 37).

In fact, several phase III randomized non-inferiority trials have mentioned that SBRT allowed tumor control without providing serious toxicities (13, 38). Our study demonstrated that SBRT was well tolerated in elderly patients; however, a longer follow-up period would be necessary to assess the real effect of the treatment. Acute grade 2 genitourinary toxicity was reported for 21 patients (13.6%). The frequency of acute genitourinary toxicity reported in previous Phase II or III studies was within a range of 20.2 to 35.3%. Thus, the frequency of these toxicities found out in our study may seem low compared to literature data (13, 38, 39). This difference could be explained by our strict adherence to the bladder dose constraints recommended by RTOG, in our treatment plans. Similarly, our study found a lower incidence of gastrointestinal toxicities compared to the levels commonly reported in the literature for prostate cancer patients undergoing SBRT. In fact, the 1-year cumulative incidence rate of grade 2 gastrointestinal toxicities reached 4% compared to 14% in other studies (40–42).

Interestingly, it has been demonstrated that moderate hypofractionated RT by helical tomotherapy used to treat patients aged ≥ 75 years with localized prostate cancer, induced acceptable acute and late toxicity. As observed in our study using extreme hypofractionated RT, Cuccia et al. did not observe a significant difference in urinary and bowel function of patients being treated by moderate hypofractionated RT (43).

Moreover, we did not observe any post-treatment grade 3 toxicity in our patients, unlike other studies which reported a toxicity of grade ≥ 3 for 1 to 2% of patients (37, 44). This low frequency of gastrointestinal toxicities could be also explained by the strict compliance with the dose constraints to the organs at risk. The low levels of toxicity in our study may be also attributed to other factors. First of all, several publications have demonstrated that image guided radiotherapy is associated with a lower level of genitourinary and gastrointestinal toxicities compared to non-image-guided radiotherapy. This may be attributed to the smaller positioning errors, thereby avoiding unnecessary irradiation of the healthy surrounding organs. Moreover, the image guidance allows for the reduction of radiotherapy planning margins, resulting in delivering lower doses to the normal tissue (45–47). In addition, the dose fall-off resulting from the use of multiple noncoplanar beams produced by the Cyberknife is sharper than in conventional techniques. Besides, the difference in the alpha/beta ratios between prostate and rectum may have helped to improve the therapeutic balance in our favor. In fact, we may be able to achieve the same cure rates with lower toxicity to the rectum which has a lower fractionation sensitivity compared to prostate cancer cells.

Biochemical response rates for prostate SBRT have been published in several trials, the largest being a trial with a cohort of 1100 patients treated within eight independent US institutions using similar protocols with doses ranging from 35 to 40 Gy delivered in 5 fractions (40).

The biochemical response rate at 5-year follow-up was 95.2% for low risk and 84.1% for intermediate risk patients (including Gleason 4 + 3) and 86% of patients did not receive androgen deprivation therapy. The authors noted that out of a total cohort of 49 patients who met the criteria for biochemical failure, 9 patients experienced a mild PSA rebound but remained biochemically controlled. A PSA rebound is a recognized but poorly understood phenomenon occurring after prostate irradiation, and is observed in 20% of the patients in our study. It can persist for several years after SBRT treatment (48).

In this context, it is important for radiation oncologists to be aware of this phenomenon to avoid subjecting patients to unnecessary examinations.

Our study was also limited by its retrospective design and low sampling. Few patients had associated comorbidities, such as diabetes or a history of cardiovascular disease requiring supplemental medication. So, we could not include the confounding factors in our study. It should be noted that this study only presents preliminary results. In particular, an important aspect to consider would be the evaluation of late toxicities, such as hematuria and rectal hemorrhage which are commonly observed within 2 years following SBRT treatment. Therefore, the short-term findings reported in our study should be interpreted with caution. A longer follow-up is necessary, especially to assess treatment effectiveness and late toxicities.

Conclusion

The retrospective results obtained from this cohort showed that SBRT treatment for PCa in elderly patients is well tolerated and provides an early biochemical response and good efficacy over a period of one year for patients from Reunion Island. This is in line with the data from randomized trials such as PACE B and HYPO-

RT trials, which showed the benefit of SBRT for men with low- and intermediate-risk prostate cancer. Although the treatment is generally well-tolerated by the patients, the occurrence of gastrointestinal and genitourinary toxicities remains a significant problem.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This retrospective clinical study was evaluated and approved bythe Ethics Committee of Research at the University of Montpellier on 09 May 2023 (UM 2023-013). All data collected were obtained during routine clinical practice and all authors conducted this study by respecting the ethical standards of their respective institutions as laid down in the 1964 Declaration of Helsinki. All patients were informed about the use of their individual personal data and gave their consent to participate in the present study.

Author contributions

YS: Writing – original draft, Data curation, Methodology, Supervision. GB: Validation, Writing – review & editing. AA: Methodology, Writing – original draft, Formal analysis, Resources. MiB: Methodology, Writing – original draft. OM: Validation, Writing – review & editing. RS: Methodology, Writing – review & editing. RoC: Conceptualization, Writing – original draft. RaC: Data curation, Writing – review & editing. PL: Writing – original draft, Data curation. HS: Methodology, Writing – review & editing. MeB: Data curation, Writing – review & editing. OB: Data curation, Writing – original draft. NN: Writing – original draft. FD: Writing – original draft, Data curation, Methodology, Supervision.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* (2021) 71:209–49. doi: 10.3322/caac.21660

2. Mohler JL, Higano CS, Pugh TJ. Prostate Cancer, Version 4.2019, NCCN Clinical Practice Guidelines in Oncology. *NCCN* (2019). Available at: https://www.nccn.org.

3. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* (2022) 72:7–33. doi: 10.3322/caac.21708

4. American Cancer Society. Cancer Facts & Figures 2022. Atlanta: American Cancer Society. (2022).

5. Howlader N, Noone A, Krapcho M, Miller D, Brest A, Yu M, et al. SEER cancer statistics review, 1975-2018. *Natl Cancer Inst* (2021).

6. P. Weiner J, Schwartz D, Shao M, Osborn V, Choi K, Schreiber D. Stereotactic radiotherapy of the prostate: fractionation and utilization in the United States. *Radiat Oncol J* (2017) 35:137–43. doi: 10.3857/roj.2017.02026

7. Kole TP, Tong M, Wu B, Lei S, Obayomi-Davies O, Chen LN, et al. Late urinary toxicity modeling after stereotactic body radiotherapy (SBRT) in the definitive treatment of localized prostate cancer. *Acta Oncol* (2016) 55:52–8. doi: 10.3109/0284186X.2015.1037011

8. Helou J, D'Alimonte L, Quon H, Deabreu A, Commisso K, Cheung P, et al. Stereotactic ablative radiotherapy in the treatment of low and intermediate risk prostate cancer: Is there an optimal dose? *Radiother Oncol* (2017) 123:478–82. doi: 10.1016/j.radonc.2017.03.006

9. Zhang L, Johnson J, Gottschalk AR, Chang AJ, Hsu I-C, Roach M, et al. Receiver operating curves and dose-volume analysis of late toxicity with stereotactic body radiation therapy for prostate cancer. *Pract Radiat Oncol* (2017) 7:e109–16. doi: 10.1016/j.prro.2016.07.004

10. Jackson WC, Silva J, Hartman HE, Dess RT, Kishan AU, Beeler WH, et al. Stereotactic body radiation therapy for localized prostate cancer: A systematic review and meta-analysis of over 6,000 patients treated on prospective studies. *Int J Radiat Oncol* (2019) 104:778–89. doi: 10.1016/j.ijrobp.2019.03.051

11. Miszczyk L, Napieralska A, Namysł-Kaletka A, Głowacki G, Grabińska K, Woźniak G, et al. CyberKnife-based prostate cancer patient radioablation – early results of irradiation in 200 patients. *Cent Eur J Urol* (2015) 68:289–95. doi: 10.5173/ceju.2015.582

12. Ito M, Yoshioka Y, Takase Y, Suzuki J, Matsunaga T, Takahashi H, et al. Stereotactic body radiation therapy for Japanese patients with localized prostate cancer: 2-year results and predictive factors for acute genitourinary toxicities. *Jpn J Clin Oncol* (2021) 51:1253–60. doi: 10.1093/jjco/hyab094

13. Tree AC, Ostler P, van der Voet H, Chu W, Loblaw A, Ford D, et al. Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol* (2022) 23:1308–20. doi: 10.1016/S1470-2045(22)00517-4

14. Proust-Lima C, Taylor JMG, Sécher S, Sandler H, Kestin L, Pickles T, et al. Confirmation of a low α/β Ratio for prostate cancer treated by external beam radiation therapy alone using a post-treatment repeated-measures model for PSA dynamics. *Int J Radiat Oncol* (2011) 79:195–201. doi: 10.1016/j.ijrobp.2009.10.008

15. Miralbell R, Roberts SA, Zubizarreta E, Hendry JH. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: α/β = 1.4 (0.9–2.2) gy. *Int J Radiat Oncol* (2012) 82:e17–24. doi: 10.1016/j.ijrobp.2010.10.075

16. Dasu A, Toma-Dasu I. Prostate alpha/beta revisited – an analysis of clinical results from 14 168 patients. *Acta Oncol* (2012) 51:963–74. doi: 10.3109/0284186X.2012.719635

17. Cosset J-M, Chargari C, Créhange G. Quel rapport alpha/bêta pour le cancer prostatique en 2019? *Cancer/Radiothérapie* (2019) 23:342–5. doi: 10.1016/j.canrad.2019.01.004

18. Gomez-Millan J. Radiation therapy in the elderly: More side effects and complications? *Crit Rev Oncol Hematol* (2009) 71:70–8. doi: 10.1016/j.critrevonc.2008.11.004

19. Pragnahitha N, Rao AS. Radiation tolerance in geriatric patients: A retrospective observational study. *J Radiat Cancer Res* (2023) 14:76. doi: 10.4103/jrcr.jrcr_92_22

20. Suzuki T, Saito M, Onishi H, Mochizuki K, Satani K, Yamazaki A, et al. Comparison of CT artifacts and image recognition of various fiducial markers including two types of thinner fiducial markers for CyberKnife treatment. *Rep Pract Oncol Radiother* (2020) 25:117–24. doi: 10.1016/j.rpor.2019.12.005

21. Marsico M, Gabbani T, Livi L, Biagini MR, Galli A. Therapeutic usability of two different fiducial gold markers for robotic stereotactic radiosurgery of liver Malignancies: A pilot study. *World J Hepatol* (2016) 8:731. doi: 10.4254/wjh.v8.i17.731

22. Zakian KL, Wibmer A, Vargas HA, Alberts E, Kadbi M, Mychalczak B, et al. Comparison of motion-insensitive T2-weighted MRI pulse sequences for visualization of the prostatic urethra during MR simulation. *Pract Radiat Oncol* (2019) 9:e534–40. doi: 10.1016/j.prro.2019.06.009

23. Kataria T, Gupta D, Goyal S, Bisht SS, Chaudhary R, Narang K, et al. Simple diagrammatic method to delineate male urethra in prostate cancer radiotherapy: an MRI based approach. *Br J Radiol* (2016) 89:20160348. doi: 10.1259/bjr.20160348

24. Salembier C, Villeirs G, De Bari B, Hoskin P, Pieters BR, Van Vulpen M, et al. ESTRO ACROP consensus guideline on CT- and MRI-based target volume delineation for primary radiation therapy of localized prostate cancer. *Radiother Oncol* (2018) 127:49–61. doi: 10.1016/j.radonc.2018.01.014

25. Gay HA, Barthold HJ, O'Meara E, Bosch WR, El Naqa I, Al-Lozi R, et al. Pelvic normal tissue contouring guidelines for radiation therapy: A radiation therapy oncology group consensus panel atlas. *Int J Radiat Oncol* (2012) 83:e353–62. doi: 10.1016/j.ijrobp.2012.01.023

26. Song C, Kang T, Lee M, Ro JY, Lee SE, Lee E, et al. Clinico-pathological characteristics of prostate cancer in korean men and nomograms for the prediction of the pathological stage of the clinically localized prostate cancer: A multi-institutional update. *Korean J Urol* (2007) 48:125. doi: 10.4111/kju.2007.48.2.125

27. Goldsmith C, Green MM, Middleton B, Cowley I, Robinson A, Plowman NP, et al. Evaluation of cyberKnife® Fiducial tracking limitations to assist targeting accuracy: A phantom study with fiducial displacement. *Cureus* (2018) 10:e3523. doi: 10.7759/cureus.3523

28. Xie Y, Djajaputra D, King CR, Hossain S, Ma L, Xing L. Intrafractional motion of the prostate during hypofractionated radiotherapy. *Int J Radiat Oncol* (2008) 72:236–46. doi: 10.1016/j.ijrobp.2008.04.051

29. Gao J, Xu B, Lin Y, Xu Z, Huang M, Li X, et al. Stereotactic body radiotherapy boost with the cyberKnife for locally advanced cervical cancer: dosimetric analysis and potential clinical benefits. *Cancers* (2022) 14:5166. doi: 10.3390/cancers14205166

30. Paal K, Stranz B, Thurner E-M, Langsenlehner U, Renner W, Brunner TB, et al. Comprehensive geriatric assessment predicts radiation-induced acute toxicity in prostate cancer patients. *Strahlenther Onkol* (2023). doi: 10.1007/s00066-023-02132-3

31. de Vries J, Poelman A, Sidorenkov G, Festen S, de Bock GH, Langendijk JA, et al. The association of frailty and outcomes of geriatric assessment with acute radiation-induced toxicity in patients with head and neck cancer. *Oral Oncol* (2022) 130:105933. doi: 10.1016/j.oraloncology.2022.105933

32. VanderWalde NA, Deal AM, Comitz E, Stravers L, Muss H, Reeve B, et al. Comprehensive geriatric assessment as a predictor of tolerance, quality of life, and toxicity in older patients receiving radiation. *Int J Radiat Oncol Biol Phys* (2016) 94:885. doi: 10.1016/j.ijrobp.2015.12.070

33. Osborne GEC, Appleyard SA, Gilbert DC, Jones CI, Lorimer C, Villanueva M, et al. Comprehensive geriatric assessment in men aged 70 years or older with localised prostate cancer undergoing radical radiotherapy. *Clin Oncol* (2017) 29:609–16. doi: 10.1016/j.clon.2017.05.003

34. Goineau A, Campion L, Commer J-M, Vié B, Ghesquière A, Béra G, et al. Can comprehensive geriatric assessment predict tolerance of radiotherapy for localized prostate cancer in men aged 75 years or older? *Cancers* (2020) 12:635. doi: 10.3390/cancers12030635

35. Goineau A, Campion L, d'Aillières B, Vié B, Ghesquière A, Béra G, et al. Comprehensive Geriatric Assessment and quality of life after localized prostate cancer radiotherapy in elderly patients. *PloS One* (2018) 13:e0194173. doi: 10.1371/journal.pone.0194173

36. King CR, Brooks JD, Gill H, Presti JC. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *Int J Radiat Oncol* (2012) 82:877–82. doi: 10.1016/j.ijrobp.2010.11.054

37. Kishan AU, Dang A, Katz AJ, Mantz CA, Collins SP, Aghdam N, et al. Long-term outcomes of stereotactic body radiotherapy for low-risk and intermediate-risk prostate cancer. *JAMA Netw Open* (2019) 2:e188006. doi: 10.1001/jamanetworkopen.2018.8006

38. Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet* (2019) 394:385–95. doi: 10.1016/S0140-6736(19)31131-6

39. Fuller DB, Falchook AD, Crabtree T, Kane BL, Medbery CA, Underhill K, et al. Phase 2 multicenter trial of heterogeneous-dosing stereotactic body radiotherapy for low- and intermediate-risk prostate cancer: 5-year outcomes. *Eur Urol Oncol* (2018) 1:540–7. doi: 10.1016/j.euo.2018.06.013

40. King CR, Freeman D, Kaplan I, Fuller D, Bolzicco G, Collins S, et al. Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol* (2013) 109:217–21. doi: 10.1016/j.radonc.2013.08.030

41. Thomas TO, Hasan S, Small W, Herman JM, Lock M, Kim EY, et al. The tolerance of gastrointestinal organs to stereotactic body radiation therapy: what do we know so far? *J Gastrointest Oncol* (2014) 5:236–46. doi: 10.3978/j.issn.2078-6891.2014.024

42. Tree AC, Ostler P, Hoskin P, Dankulchai P, Nariyangadu P, Hughes RJ, et al. Prostate stereotactic body radiotherapy — First UK experience. *Clin Oncol* (2014) 26:757–61. doi: 10.1016/j.clon.2014.08.007

43. Cuccia F, Fiorentino A, Corrao S, Mortellaro G, Valenti V, Tripoli A, et al. Moderate hypofractionated helical tomotherapy for prostate cancer in a cohort of older patients: a mono-institutional report of toxicity and clinical outcomes. *Aging Clin Exp Res* (2020) 32:747–53. doi: 10.1007/s40520-019-01243-1

44. Musunuru HB, Quon H, Davidson M, Cheung P, Zhang L, D'Alimonte L, et al. Dose-escalation of five-fraction SABR in prostate cancer: Toxicity comparison of two prospective trials. *Radiother Oncol* (2016) 118:112–7. doi: 10.1016/j.radonc.2015.12.020

45. Zelefsky MJ, Kollmeier M, Cox B, Fidaleo A, Sperling D, Pei X, et al. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. *Int J Radiat Oncol* (2012) 84:125–9. doi: 10.1016/j.ijrobp.2011.11.047

46. Park SS, Yan D, McGrath S, Dilworth JT, Liang J, Ye H, et al. Adaptive image-guided radiotherapy (IGRT) eliminates the risk of biochemical failure caused by the bias of rectal distension in prostate cancer treatment planning: clinical evidence. *Int J Radiat Oncol* (2012) 83:947–52. doi: 10.1016/j.ijrobp.2011.08.025

47. Kok D, Gill S, Bressel M, Byrne K, Kron T, Fox C, et al. Late toxicity and biochemical control in 554 prostate cancer patients treated with and without dose escalated image guided radiotherapy. *Radiother Oncol* (2013) 107:140–6. doi: 10.1016/j.radonc.2013.04.007

48. Jiang NY, Dang AT, Yuan Y, Chu F-I, Shabsovich D, King CR, et al. Multi-institutional analysis of prostate-specific antigen kinetics after stereotactic body radiation therapy. *Int J Radiat Oncol* (2019) 105:628–36. doi: 10.1016/j.ijrobp.2019.06.2539

frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 22 March 2024
DOI 10.3389/fonc.2023.1307434

OPEN ACCESS

EDITED BY
Nam Phong Nguyen,
International Geriatric Radiotherapy Group, United States

REVIEWED BY
Zach Dovey,
Icahn School of Medicine at Mount Sinai, United States
Luciana Da Mata,
Federal University of Minas Gerais, Brazil
Pier Paolo Avolio,
Humanitas Research Hospital, Italy

*CORRESPONDENCE
Ji Lu
lu_ji@jlu.edu.cn

RECEIVED 04 October 2023
ACCEPTED 27 December 2023
PUBLISHED 22 March 2024

CITATION
Yu K, Bu F, Jian T, Liu Z, Hu R, Chen S and Lu J (2024) Urinary incontinence rehabilitation of after radical prostatectomy: a systematic review and network meta-analysis. *Front. Oncol.* 13:1307434.
doi: 10.3389/fonc.2023.1307434

Urinary incontinence rehabilitation of after radical prostatectomy: a systematic review and network meta-analysis

Kai Yu[1], Fan Bu[2], Tengteng Jian[1], Zejun Liu[1], Rui Hu[1], Sunmeng Chen[1] and Ji Lu[1]*

[1]Department of Urology, The First Hospital of Jilin University, Changchun, China, [2]Department of Plastic and Aesthetic Surgery, The First Affiliated Hospital of Jilin University, Changchun, China

Purpose: The aim of this study is to provide treatment for patients with urinary incontinence at different periods after radical prostatectomy.

Methods: The PubMed, Embase, Cochrane, and Web of Science were searched for all literature on the effectiveness on urinary control after radical prostate cancer between the date of database creation and 15 November 2023 and performed a quality assessment. A network meta-analysis was performed using RevMan 5.3 and Stata 17.0 software and evaluated using the surface under the cumulative ranking curve.

Results: The results of the network meta-analysis showed that pelvic floor muscle therapy including biofeedback with professional therapist–guided treatment demonstrated better results at 1 month to 6 months; electrical stimulation, biofeedback, and professional therapist guidance may be more effective at 3 months of treatment; professional therapist–guided recovery may be less effective at 6 months of treatment; and combined therapy demonstrated better results at 1 year of treatment. During the course of treatment, biofeedback with professional therapist–guided treatment may have significant therapeutic effects in the short term after surgery, but, in the long term, the combination of multiple treatments (pelvic floor muscle training+ routine care + biofeedback + professional therapist–guided treatment + electrical nerve stimulation therapy) may address cases of urinary incontinence that remain unrecovered long after surgery.

Conclusion: In general, all treatment methods improve the different stages of functional recovery of the pelvic floor muscles. However, in the long term, there are no significant differences between the treatments. Given the cost-effectiveness, pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + electrical nerve stimulation therapy within 3 months and pelvic floor muscle + routine care after 3 months may be a more economical option to treat urinary incontinence.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=331797, identifier CRD42022331797.

KEYWORDS

radical prostatectomy, pelvic floor muscle, urinary incontinence, network meta-analysis, rehabilitation

1 Introduction

Prostate cancer, one of the most serious diseases affecting older men, has been increasing in incidence year by year in recent years and is now the most common malignancy of the male urological system and related malignancies (1). Prostate cancer may show great heterogeneity among different patients. Active detection is usually adopted for some low- to medium-risk tumors with slow growth, weak invasiveness, and localized prostate cancer. For these tumors that will not develop in a long period of time, radical surgery may bring about great side effects (2). For advanced prostate cancer that progresses rapidly and is highly aggressive, radical prostate cancer surgery is usually used. The most used surgical procedures for radical prostate cancer include standard open retropubic radical prostatectomy, therapeutic laparoscopic radical prostatectomy, and robot-assisted radical prostatectomy. In a radical prostatectomy, a patient's pelvic floor muscles and the nerves that innervate them may be destroyed, resulting in certain complications, the most common of which is urinary incontinence in patients after radical prostatectomy (3). In the realm of surgical approaches, robot-assisted radical prostatectomy has demonstrated superior outcomes in postoperative urinary control. The research by Sehgal et al. indicates that robot-assisted radical prostatectomy exhibits better results in urinary continence 3 months postoperatively compared with open radical prostatectomy (4). In the assessment of postoperative urinary continence, robot-assisted radical prostatectomy surpasses the outcomes of laparoscopic radical prostatectomy. Regarding the surgical approach, the study by Tuğcu et al. (5) suggests that the perineal approach for radical prostatectomy yields superior results in terms of urinary continence compared with the abdominal approach.

Urinary incontinence often has a negative impact on the patient's physical and mental health, increasing the patient's psychological burden and prolonging the postoperative recovery time. Thus, finding more effective and convenient methods is the primary issue in this area. Modern studies have documented that pelvic floor muscle training after radical prostate cancer surgery can improve incontinence, but they have been based on conventional randomized controlled trials and traditional meta-analyses, with no direct-evidence–based medical evidence for the effectiveness of combining many modalities in the treatment of incontinence. In summary, this study used a network meta-analysis to compare the efficacy of many incontinence prevention measures on urinary incontinence. This method allows for a simultaneous comparison of the clinical efficacy of many prevention measures on urinary incontinence prevention, ranked according to the different treatment effects, and thus provides good-evidence–based medical evidence for clinical urologists in preventing urinary incontinence after radical prostate cancer surgery.

2 Methods

2.1 Study design

The study protocol was registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42022331797). This study followed the updated Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guideline and its extension for network meta-analysis (6).

2.2 Literature search

We searched PubMed, Embase, and Cochrane CENTRAL databases to identify reports published by 15 November 2023, on training for recovery from urinary incontinence after radical prostate cancer surgery. The trial included treatment related to pelvic floor muscle therapy after radical prostate cancer surgery. A number of subject terms and free words related to prostate cancer, radical surgery, multiple pelvic floor muscle training, and randomized controlled trials were used. A detailed database search strategy is given in Figure 1.

2.3 Inclusion and exclusion criteria

A trial was included in the systematic review if: ① The study type is randomized controlled trial (RCT). ② Languages are limited to English. ③ Disease diagnostic criteria are authoritative and have been published in the literature in professional journals. ④ The data presented in the literature are more standard data. The interventions were pelvic floor training with a physiotherapist or routine care and more. ⑤ The outcome indicator was the number of

No.	Search Strategy	Number
#1	"prostatic neoplasms"[MeSH Terms] OR "prostatic neoplasms"[All Fields] OR "tumor of prostate"[All Fields] OR " PCa"[All Fields] OR "prostate cancer"[All Fields] OR "prostat*"[All Fields]	322,020
#2	("prostate"[MeSH Terms] OR "prostatitis"[MeSH Terms] OR "prostatitis"[All Fields]) AND ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields] OR "carcinomas"[All Fields])	6,096
#3	#1 OR #2	322,020
#4	"uracratia"[All Fields] OR "urinary incontinence"[MeSH Terms] OR ("urinary"[All Fields] AND "incontinence"[All Fields]) OR "urinary incontinence"[All Fields]	51,034
#5	("urinary tract"[MeSH Terms] OR "urinary incontinence"[MeSH Terms] OR "urinary incontinence" [All Fields]) OR ("uracratia"[All Fields] OR "urinary incontinence"[MeSH Terms] OR ("urinary"[All Fields] AND "incontinence"[All Fields]) OR "urinar*"[All Fields])	847,070
#6	#4 OR #5	847,070
#7	"pelvic floor muscle" [All Fields] OR "pelvic floor muscle training"[All Fields] OR "pelvic*"[All Fields] OR "PFME"[All Fields] OR "PFMT"[All Fields]	153,692
#8	"Randomized Controlled Trial"[All Fields] OR "rando*"[All Fields]	1,704,325
#9	#3 OR #6 OR #7 OR #8	423

FIGURE 1
PubMed search strategy.

people recovering from incontinence at 1 month, 3 months, 6 months, and 12 months after pelvic floor training. ⑥ Patients were excluded if they had medical history of urethral, vesical, or prostatic surgery; overactive bladder; and neurogenic lower urinary tract dysfunction. ⑦ Incontinence was controlled by the following criteria: 24-h urine pad <2 g or 5.5 g and 8 g; use 1 or fewer pee pads per day and ICIQ-SF score of 0.

A trial was exclusion in the systematic review if: ① The literature has a high degree of similarity or is a duplicate report. ② The study design in the literature has more obvious flaws. ③ The data included in the literature is incomplete or too much is missing. ④ Animal studies and research. ⑤ Data in the literature were displayed in icon format and data could not be extracted after attempts or data were not available.

Preliminary screening initial screening of ineligible reports was performed on the basis of the title and abstract of the article. Potentially relevant reports were reviewed in the full text of the article, and their relevance was confirmed after data extraction. The screening of titles and abstracts and the screening of full text were done independently by two investigators (ZL and TJ), disagreements were resolved by consensus among the co-authors (KY), and consensus was reached among the authors.

2.4 Data collection

Two researchers (FB and RH) independently gleaned the following details from the included articles: the primary author's name, year of publication, surgical approach, age of the experimental and control groups, criteria for assessing urinary incontinence resolution in each article, total postoperative treatment duration, specific treatment methods and their durations, sample size of the experimental and control groups, as well as the number of patients who achieved urinary continence recovery at 1 month, 3 months, 6 months, and 12 months. Any disparities in data extraction were resolved through consensus among all authors.

2.5 Quality evaluation

After undergoing systematic training, the two researchers (FB and RH) independently carried out literature screening and cross-referenced the data extraction in accordance with pre-defined inclusion and exclusion criteria and data extraction forms. If an agreement could not be reached, then a third researcher involved in the study was consulted for mediation. The assessment of bias risk and the quality of the literature was conducted using RevMan 5.3, utilizing the risk of bias assessment criteria outlined in the Cochrane Collaboration Network. The assessment involved evaluating whether: 1) random allocation methods were employed; 2) there was concealment of the allocation scheme; 3) patients and physicians involved were blinded; 4) researchers recording the results were blinded; 5) outcome data were complete; 6) study results were selectively reported; and 7) there were other sources of bias. All literature was independently evaluated by two researchers, and any discrepancies were either further discussed or resolved through consultation with a third researcher co-investigating the study. Funnel plots were employed to ascertain the presence of a small sample effect, with statistical significance set at $p < 0.05$.

2.6 Statistical analysis

Stata 17.0 software was applied for data analysis in this paper. Odds ratios (ORs) and 95% confidence intervals (CI) were used as effect size indicators for the dichotomous outcome indicators. The results of direct comparisons were compared with the results of indirect comparisons using the nodal analysis model in the software to see if the results were consistent. Inconsistency tests were performed on the closed loop formed by the direct and indirect evidence to produce an inconsistency factor (IF). The surface area under the cumulative ranking curve (SUCRA) was used to estimate the probability of treatment for each outcome (7), using the SUCRA to reflect the ranking of the intervention; the closer to 100%, the higher the probability that the intervention is most effective.

3 Results

3.1 Literature screening process and results

A total of 732 titles were obtained from the initial screening, including 423 titles from PubMed, 207 titles from EMBASE, 79 titles from Cochrane, 23 titles from other databases, and some conference papers. A total of 246 titles were obtained after de-duplication into Endnote literature management software, and 42 titles were included after initial screening and rescreening (Figure 2).

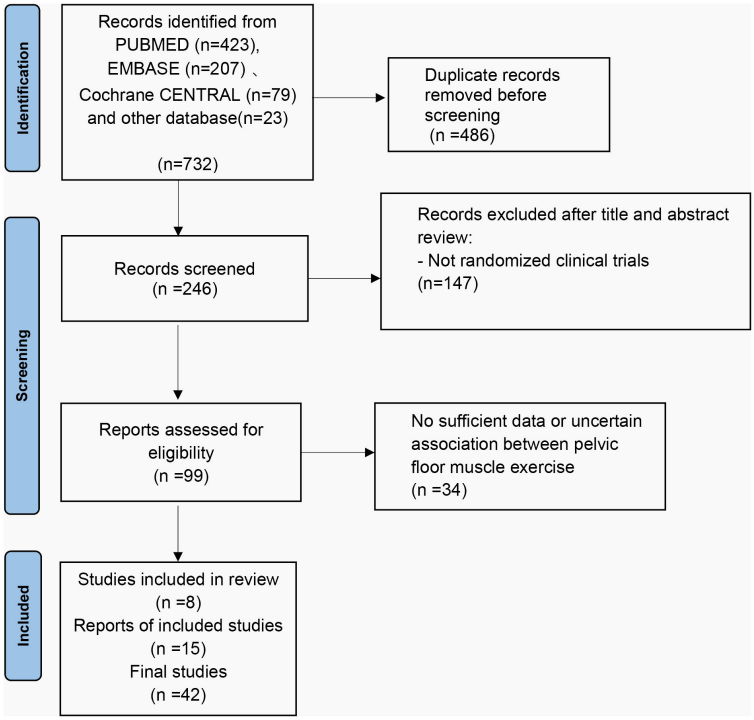


FIGURE 2
Literature screening process and results.

3.2 Basic characteristics of the included studies: risk of bias evaluation

A total of 4,256 subjects, 2,216 in the experimental group and 2,040 in the control group, were included in the 42 (8–49) RCTs included in this network meta-analysis, as shown in Supplementary Table 1. Among the interventions in the experimental group were Kegel exercises guided by a professional such as a physical instructor or nurse, bioelectric therapy, pharmacotherapy, biofeedback, and one or a combination of one or more of conventional pelvic floor muscle therapy, and, in the control group a combination of conventional care, one or more of conventional pelvic floor muscle training and electrotherapy. Conventional care includes conventional care of patients' urethral orifice, change of urinary tube, and cleaning of perineum. Professional therapists and nurses include those with experience in pelvic floor exercises. The observed outcome indicators broadly describe the recovery of urinary control in patients after the different treatment modalities interventions and after different time periods in 1 month, 3 months, 6 months, and 12 months.

3.3 Risk of bias evaluation

This network meta-analysis was conducted using the Cochrane risk-of-bias assessment tool to assess the quality of the 42 included papers (see Figures 3, 4, where red dots indicate a high risk of bias for each bias criterion, yellow states a moderate risk, and green indicates a low risk of bias). In a blinded assessment, if both the experimental and control groups had another form of training in addition to routine care, in both experimenter exchanges, patients may perceive themselves as better able to cooperate with treatment for the experimental group because of the additional training for both, and it has less psychological impact on patients, at which point such cases are identified as low risk of bias in the blinded bias assessment and, conversely, high risk of bias. Thirty-four studies specified a specific randomization scheme, with the generation of the randomized sequence being not specified in eight studies and with a high risk of bias being grouped in two studies. Of the publication bias, four studies were considered to be at high risk of bias, possibly due to their association with novel device development. Other sources of bias were judged to be unclear except for one study that may have a potential link to a medical device company or a company related to a novel treatment. One study clarified the absence of corporate sponsorship (Figures 3, 4).

3.4 Results of the network meta-analysis

3.4.1 The web of relationships

According to the order of the various treatment methods, the 17 treatment methods were classified as follows: routine care (1), routine care + pelvic floor muscle training (2), pelvic floor muscle training + routine care + biofeedback (3), routine care + pelvic floor muscle training + professional therapist–guided treatment (4), pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment (5), pelvic floor muscle training + electrical nerve stimulation therapy + routine care (6),

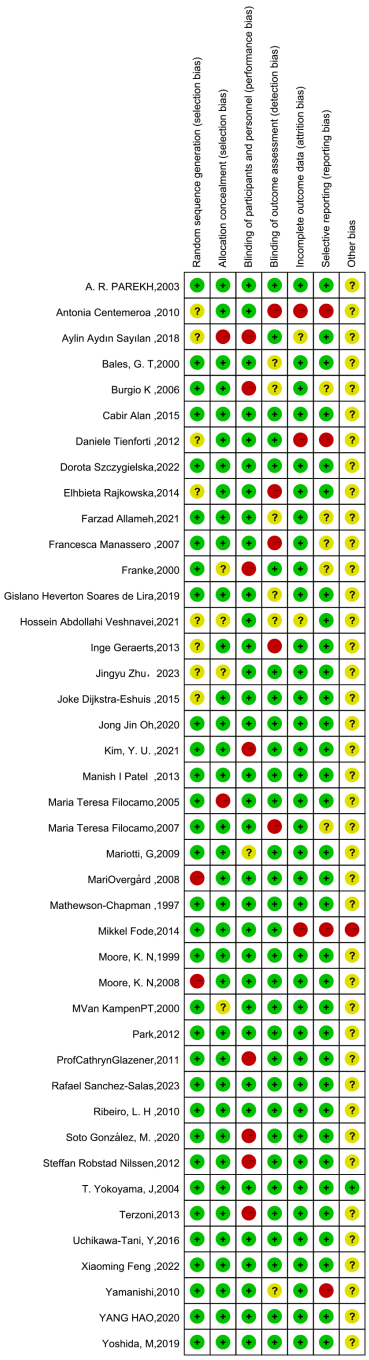


FIGURE 3
Literature bias evaluation results.

special medical instruments (penile vibratory stimulation (PVS) units) + routine care + pelvic floor muscle training (7), routine care + pelvic floor muscle training + drug treatment (duloxetine) (8), pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + electrical nerve stimulation therapy (9), routine care + electrical nerve stimulation therapy + professional therapist–guided treatment + pelvic floor muscle training (10), electrical nerve stimulation therapy + biofeedback + pelvic floor muscle training + routine care floor muscle training + routine care (11), pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + preoperative pelvic floor muscle training + routine care (12), pelvic floor muscle training and routine care + pelvic floor muscle training + advanced pelvic floor exercises (13), routine care + preoperative pelvic floor muscle training + biofeedback + professional therapist–guided (14), routine care + preoperative pelvic floor muscle training (15), routine care + drug treatment (duloxetine) (16), routine care + drug treatment (duloxetine) + pelvic floor muscle training + biofeedback + professional therapist–guided treatment (17), as shown in Table 1 and Figure 5.

The network relationships for the treatments used to restore postoperative incontinence in patients undergoing radical prostatectomy are shown in Figures 6A–D. The network diagram represents the number of studies, with the thicker the line segment, the more studies are included; the circular area in the network diagram represents the sample size of the population using the measure, with the larger the circle, the larger the population included in the study. The line segments between the dots represent studies for which they are directly comparable.

3.4.2 Inconsistency test

3.4.2.1 Overall inconsistency test

The results of the overall inconsistency analysis showed that the overall effective rate was greater than 0.05, indicating that the results of direct and indirect comparisons were consistent across treatment modalities.

3.4.2.2 Ring inconsistency test

The lower 95% CI for all closed-loop IFs involved in the indicator did not reach 0, suggesting that the loop inconsistency was statistically significant, whereas the rest of the loops were not statistically significant.

3.4.3 Results of the network meta-analysis

3.4.3.1 Total clinical effectiveness in 1 month

We used network meta-analysis of different pelvic floor muscle treatment measures to assess the recovery of urinary incontinence in patients at 1 month after radical prostate cancer surgery. Treatment 9 (pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + electrical nerve) demonstrated better outcomes compared with treatment 1 (routine care) and treatment 2 (routine care + pelvic floor muscle training) at 1 month (OR: 5.65, 95% Confidence Range Interval (Crl): 1.18–26.96; OR: 3.26, 95% CrI: 1.01–10.50). Treatment 13 showed better results compared with treatment 1 at 1 month postoperatively (OR: 13.50, 95% CrI: 1.25–146.11), as shown in Figure 7A. The SUCRA values for the various treatments are shown in Figure 7B.

In Figure 7B, we can see that treatment 14 (routine care + preoperative pelvic floor muscle training + biofeedback + professional therapist–guided treatment), treatment 9 (pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + electrical nerve), and treatment 8 (routine care + pelvic floor muscle training + drug treatment (duloxetine) are ranked as the top three in terms of efficacy. In

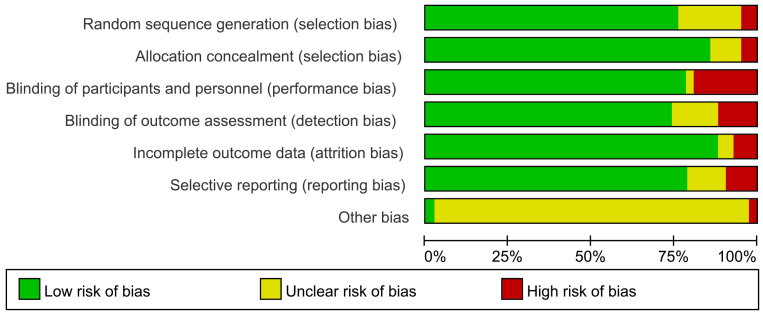


FIGURE 4
Results of literature bias evaluation.

TABLE 1 Pelvic floor muscle treatment methods and corresponding numbers.

Treatment 1	Routine care
Treatment 2	Routine care + pelvic floor muscle training
Treatment 3	Pelvic floor muscle training + routine care + biofeedback
Treatment 4	Routine care + pelvic floor muscle training + professional therapist guided treatment
Treatment 5	Pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment
Treatment 6	Pelvic floor muscle training + electrical nerve stimulation therapy + routine care
Treatment 7	Special medical instruments (PVS units) + routine care + pelvic floor muscle training
Treatment 8	Routine care + pelvic floor muscle training + drug treatment (duloxetine)
Treatment 9	Pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + electrical nerve stimulation therapy
Treatment 10	Routine care + electrical nerve stimulation therapy + professional therapist–guided treatment + pelvic floor muscle training
Treatment 11	Electrical nerve stimulation therapy + biofeedback + pelvic floor muscle training + routine care
Treatment 12	Pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + preoperative pelvic floor muscle training
Treatment 13	Routine care + pelvic floor muscle training + advanced pelvic floor exercises
Treatment 14	Routine care + preoperative pelvic floor muscle training + biofeedback + professional therapist–guided treatment
Treatment 15	Routine care + preoperative pelvic floor muscle training
Treatment 16	Routine care + drug treatment (duloxetine)
Treatment 17	Routine care + drug treatment (duloxetine) + pelvic floor muscle training + biofeedback + professional therapist–guided treatment

the network meta-analysis ladder table of urinary incontinence recovered within 1 month after surgery, we found that biofeedback therapy under professional guidance had a better therapeutic effect, and the drug duloxetine also had a better adjunctive effect on the recovery of postoperative incontinence in patients.

In the recovery of urinary incontinence after radical prostate cancer surgery, in Table 2 we found the role of biofeedback therapy under professional guidance is evident during the first month of treatment, whereas drug treatment also plays a significant role in postoperative recovery. This means that, for a rapid recovery or improved control of incontinence, professionally supervised biofeedback pelvic floor muscle training supplemented with medication is required.

3.4.3.2 Total clinical effectiveness in 3 months

We used a network meta-analysis of different pelvic floor muscle treatment measures to assess the recovery of urinary incontinence in patients at 3 months after radical prostate cancer surgery.

Treatment 6 (pelvic floor muscle training + electrical nerve stimulation therapy + routine care) showed better results at 3 months compared with treatment 1 (routine care), treatment 2 (routine care + pelvic floor muscle training), treatment 4 (routine care + pelvic floor muscle training + professional therapist–guided treatment), treatment 5 (pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment), treatment 7 [special medical instruments (PVS units) + routine care + pelvic floor muscle training], treatment 12 (pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + preoperative pelvic), treatment 16 [routine care + drug treatment (duloxetine)], and treatment 17 [routine care + drug treatment (duloxetine) + pelvic floor muscle training + biofeedback + professional therapist–guided treatment] at 3 months postoperatively (OR: 18.06, 95% CrI: 3.00–108.71; OR: 16.40, 95% CrI: 3.22–83.57; OR: 10.81, 95% CrI: 1.83–63.97; OR: 9.35, 95% CrI: 1.47–59.38; OR: 14.05, 95% CrI: 1.24–159.37; OR: 11.76, 95% CrI: 1.85–74.73; OR: 18.85, 95% CrI: 1.85–192.29; OR: 34.02, 95% CrI: 3.07–377.25). Treatment 9 (pelvic floor muscle training + routine care + biofeedback + professional therapist–

10.3389/fonc.2023.1307434

TABLE 2 Network meta-analysis ladder table of postoperative urinary incontinence recovered in 1 month.

Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	Treatment 6	Treatment 8	Treatment 9	Treatment 10	Treatment 12	Treatment 14	Treatment 15
0.58 (0.21, 1.62)											
0.28 (0.07, 1.22)	0.49 (0.16, 1.50)										
0.34 (0.12, 1.00)	0.60 (0.27, 1.29)	1.21 (0.37, 3.91)									
0.34 (0.10, 1.16)	0.58 (0.23, 1.47)	1.18 (0.28, 4.95)	0.98 (0.31, 3.13)								
0.66 (0.10, 4.28)	1.14 (0.25, 5.22)	2.32 (0.36, 15.03)	1.92 (0.36, 10.36)	1.97 (0.33, 11.61)							
0.16 (0.02, 1.20)	0.28 (0.05, 1.57)	0.56 (0.07, 4.42)	0.47 (0.07, 3.12)	0.48 (0.07, 3.41)	0.24 (0.02, 2.43)						
0.18 (0.04, 0.84)	0.31 (0.10, 0.99)	0.62 (0.12, 3.12)	0.52 (0.13, 2.09)	0.53 (0.12, 2.34)	0.27 (0.04, 1.81)	1.11 (0.14, 8.97)					
0.43 (0.08, 2.31)	0.74 (0.10, 5.37)	1.51 (0.16, 13.99)	1.25 (0.17, 9.18)	1.28 (0.16, 10.34)	0.65 (0.05, 8.05)	2.69 (0.19, 37.27)	2.43 (0.24, 24.15)				
0.34 (0.09, 1.34)	0.59 (0.24, 1.45)	1.20 (0.29, 5.00)	1.00 (0.31, 3.24)	1.02 (0.28, 3.69)	0.52 (0.09, 3.00)	2.14 (0.30, 15.06)	1.93 (0.44, 8.41)	0.80 (0.09, 6.97)			
0.07 (0.01, 0.80)	0.13 (0.01, 1.40)	0.26 (0.02, 3.56)	0.22 (0.02, 2.51)	0.22 (0.02, 2.26)	0.11 (0.01, 1.91)	0.46 (0.02, 8.89)	0.42 (0.03, 5.99)	0.17 (0.01, 3.19)	0.22 (0.02, 2.78)		
0.16 (0.03, 1.03)	0.28 (0.04, 1.81)	0.57 (0.07, 4.88)	0.48 (0.07, 3.30)	0.49 (0.08, 2.86)	0.25 (0.02, 2.73)	1.02 (0.08, 12.98)	0.92 (0.10, 8.28)	0.38 (0.03, 4.63)	0.48 (0.06, 3.75)	2.21 (0.49, 9.95)	

guided treatment + electrical nerve) showed better results compared with treatment 1 (routine care), treatment 2 (routine care + pelvic floor muscle training), treatment 4 (routine care + pelvic floor muscle training + professional therapist–guided treatment), treatment 12 (pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + preoperative pelvic), treatment 16 [routine care + drug treatment (duloxetine)], and treatment 17 [routine care + drug treatment (duloxetine) + pelvic floor muscle training + biofeedback + professional therapist–guided treatment] (OR: 7.89, 95% CrI: 1.89–32.96; OR: 7.16, 95% CrI: 2.13–24.12; OR: 4.72, 95% CrI: 1.16–19.31; OR: 5.14, 95% CrI: 1.15–22.96). Treatment 11 (electrical nerve stimulation therapy + biofeedback + pelvic floor muscle training + routine care) showed better results compared with treatment 17 [routine care + drug treatment (duloxetine) + pelvic floor muscle training + biofeedback + professional therapist–guided treatment] (OR: 13.76, 95% CrI: 1.17–161.77).

Treatment 3 (pelvic floor muscle training + routine care + biofeedback) showed better results compared with treatment 2 (routine care + pelvic floor muscle training) (OR: 2.71, 95% CrI: 1.03–7.14). Treatment 10 (routine care + electrical nerve stimulation therapy + professional therapist–guided treatment + pelvic floor muscle) showed better results compared with treatment 1 (routine care) (OR: 3.80, 95% CrI: 1.01–14.26). Treatment 11 (electrical nerve stimulation therapy + biofeedback + pelvic floor muscle training + routine care) showed better results compared with treatment 1 (routine care) and treatment 2 (routine care + pelvic floor muscle training) (OR: 7.32, 95% CrI: 1.12–47.80; OR: 6.65, 95% CrI: 1.20–36.97) at 3 months postoperatively, as shown in Figure 8A. The SUCRA values for the various treatments are shown in Figure 8B.

In Figure 8B, we can see that treatment 6 (pelvic floor muscle training + electrical nerve stimulation therapy + routine care), treatment 9 (pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + electrical nerve), and treatment 15 (routine care + preoperative pelvic floor muscle training) are in the top three in terms of effectiveness. In the network meta-analysis ladder table of postoperative urinary incontinence recovered in 3 months, we could find that treatment 6 (pelvic floor muscle training + electrical nerve stimulation therapy + routine care) was better than most of the treatments at 3 months.

In the short to medium term, in Table 3 we found electrostimulation has been shown to have a significant effect on the recovery of urinaryincontinence, and this has led to the need for more electrical stimulation of the relevant pelvic floor nerves. Similarly, biofeedback is also useful in the short to medium term. In Table 4, we found that preoperative pelvic floor muscle exercise may affect the effectiveness of electrotherapy for postoperative urinary incontinence in patients and that preoperative pelvic floor muscle training is not a good option for patients who want to treat urinary incontinence with electrotherapy after radical prostate cancer surgery.

3.4.3.3 Total clinical effectiveness in 6 months

We used a network meta-analysis of different pelvic floor muscle treatment measures to assess the recovery of urinary

TABLE 3 Network meta-analysis ladder table of postoperative urinary incontinence recovered in 6 months.

Treatment 1													
1.85 (0.57, 6.00)	Treatment 2												
0.03 (0.00, 0.94)	0.01 (0.00, 0.42)	Treatment 3											
0.64 (0.16, 2.48)	0.34 (0.12, 0.96)	23.61 (0.71, 790.05)	Treatment 4										
1.26 (0.43, 3.65)	0.68 (0.23, 2.02)	46.62 (1.37, 1587.93)	1.97 (0.49, 7.91)	Treatment 5									
0.48 (0.04, 5.24)	0.26 (0.03, 2.08)	17.72 (0.34, 922.15)	0.75 (0.07, 7.72)	0.38 (0.04, 4.02)	Treatment 6								
4.33 (0.32, 58.80)	2.33 (0.23, 23.99)	160.68 (2.70, 9548.99)	6.81 (0.53, 87.11)	3.45 (0.26, 45.21)	9.07 (0.40, 207.32)	Treatment 7							
0.34 (0.03, 3.78)	0.18 (0.02, 1.50)	12.52 (0.24, 660.18)	0.53 (0.05, 5.58)	0.27 (0.02, 2.90)	0.71 (0.04, 13.80)	0.08 (0.00, 1.81)	Treatment 8						
0.34 (0.05, 2.18)	0.18 (0.04, 0.78)	12.58 (0.33, 485.49)	0.53 (0.09, 3.18)	0.27 (0.04, 1.66)	0.71 (0.06, 9.01)	0.08 (0.01, 1.22)	1.00 (0.08, 13.01)	Treatment 9					
0.23 (0.03, 2.00)	0.12 (0.01, 1.45)	8.57 (0.13, 548.00)	0.36 (0.03, 4.66)	0.18 (0.02, 2.04)	0.48 (0.02, 12.16)	0.05 (0.00, 1.58)	0.68 (0.03, 17.48)	0.68 (0.04, 11.79)	Treatment 10				
1.85 (0.16, 22.05)	1.00 (0.11, 8.84)	68.87 (1.26, 3762.83)	2.92 (0.26, 32.56)	1.48 (0.13, 16.92)	3.89 (0.19, 79.56)	0.43 (0.02, 10.42)	5.50 (0.26, 114.53)	5.48 (0.40, 74.91)	8.03 (0.30, 214.38)	Treatment 12			
0.50 (0.03, 8.17)	0.27 (0.01, 5.16)	18.67 (0.21, 1622.82)	0.79 (0.04, 16.70)	0.40 (0.02, 6.92)	1.05 (0.03, 39.01)	0.12 (0.00, 4.97)	1.49 (0.04, 56.01)	1.48 (0.06, 39.47)	2.18 (0.06, 73.99)	0.27 (0.01, 10.59)	Treatment 15		
1.48 (0.25, 8.64)	0.80 (0.11, 5.65)	54.95 (1.13, 2671.06)	2.33 (0.28, 19.11)	1.18 (0.20, 6.88)	3.10 (0.18, 54.27)	0.34 (0.02, 7.17)	4.39 (0.25, 78.20)	4.37 (0.38, 49.83)	6.41 (0.39, 104.11)	0.80 (0.04, 14.93)	2.94 (0.12, 75.03)	Treatment 16	
2.27 (0.38, 13.46)	1.22 (0.17, 8.78)	84.19 (1.72, 4123.43)	3.57 (0.43, 29.69)	1.81 (0.30, 10.72)	4.75 (0.27, 84.00)	0.52 (0.02, 11.09)	6.72 (0.37, 121.03)	6.69 (0.58, 77.26)	9.82 (0.60, 161.19)	1.22 (0.06, 23.11)	4.51 (0.18, 115.99)	1.53 (0.22, 10.84)	Treatment 17

10.3389/fonc.2023.1307434

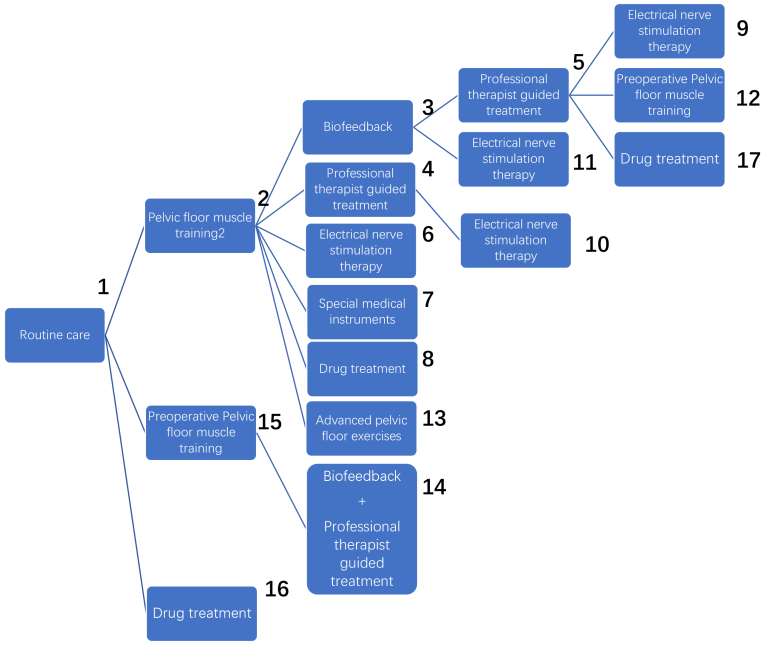


FIGURE 5
Treatment methods.

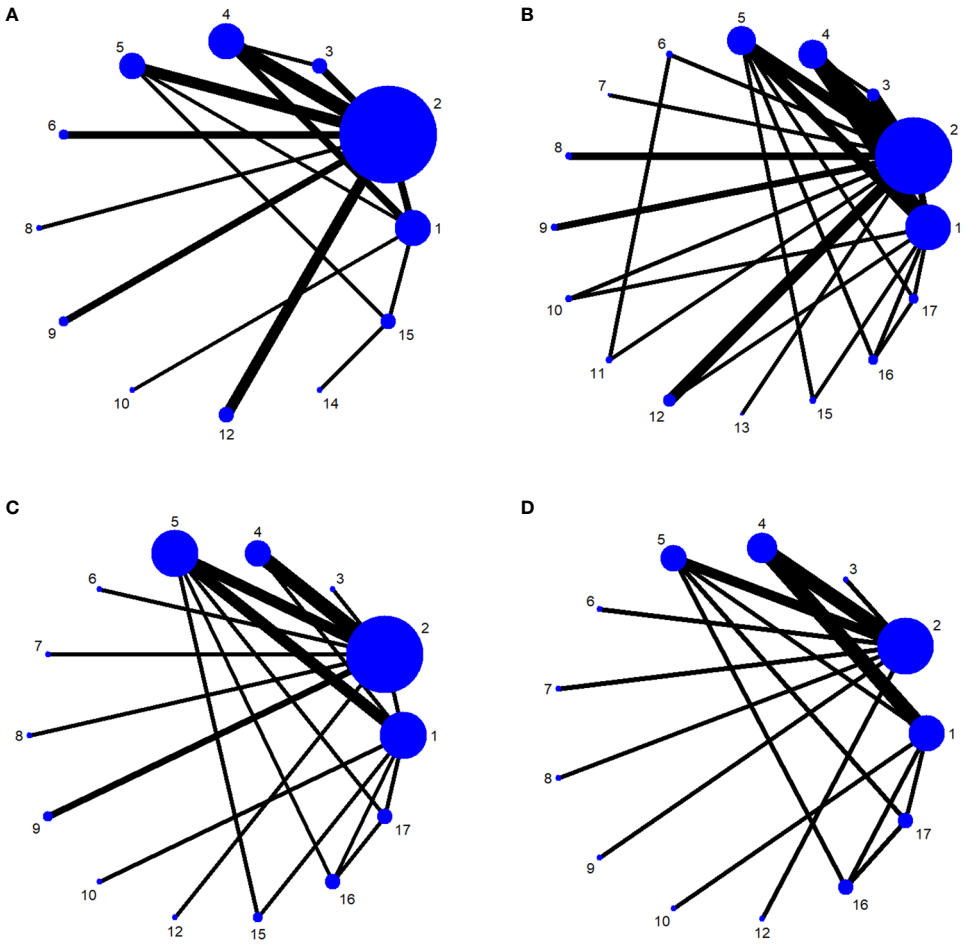


FIGURE 6
(A) One-month network chart. **(B)** Three-month network chart. **(C)** Six-month network chart. **(D)** Twelve-month network chart.

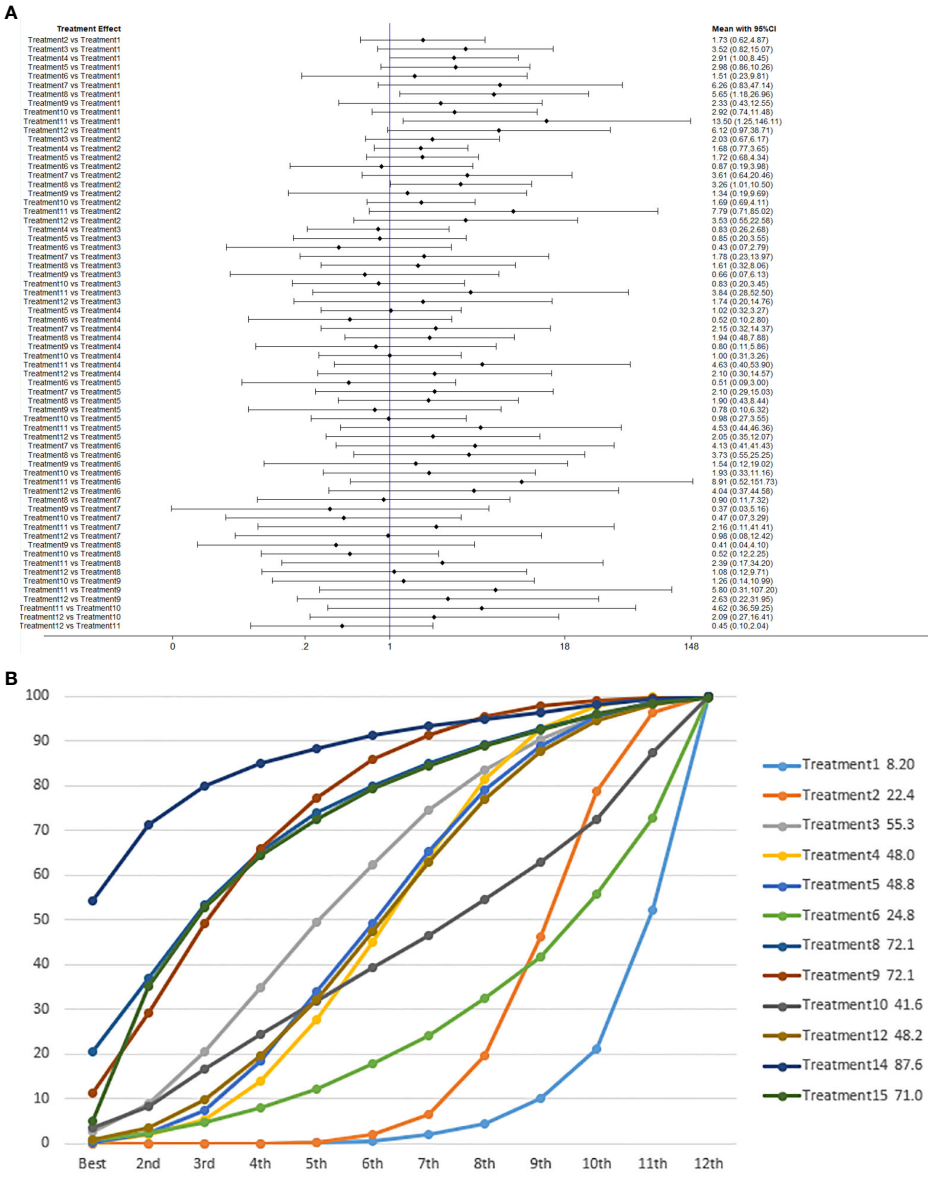


FIGURE 7
(A) The forest plot represents the OR and 95% CrI for a two-by-two comparison of multiple treatment modalities for urinary incontinence at 1 month after radical prostatectomy. **(B)** Cumulative probability graph of postoperative urinary incontinence recovered in 1 month.

incontinence in patients at 6 months after radical prostate cancer surgery.

Treatment 3 (pelvic floor muscle training + routine care + biofeedback) showed better results compared with treatment 1 (routine care), treatment 2 (routine care + pelvic floor muscle training), treatment 5 (pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment), treatment 7 [special medical instruments (PVS units) + routine care + pelvic floor muscle training], treatment 12 (pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + preoperative pelvic floor muscle training), treatment 16 [routine care + drug treatment (duloxetine), and treatment 17 [routine care + drug treatment (duloxetine) + pelvic floor muscle training + biofeedback + professional therapist–guided treatment] (OR: 43.43, 95% CrI: 1.15–1,642.47; OR: 68.87, 95% CrI: 2.30–2,060.60; OR: 46.62, 95% CrI: 1.37–1,587.93; OR: 160.68, 95% CrI: 2.70–9,548.99; OR: 68.87, 95% CrI: 1.26–3,762.83; OR: 54.95, 95% CrI: 1.13–2,671.06; OR: 84.19, 95% CrI: 1.13–2,671.06). Treatment 2 (routine care + pelvic floor muscle training) showed worse results compared with treatment 4 (routine care + pelvic floor muscle training + professional therapist–guided treatment) and treatment 9 (pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + electrical nerve) (OR: 0.34, 95% CrI: 0.12–0.96; OR: 0.18, 95% CrI: 0.04–0.78) at 6 months postoperatively, as shown in Figure 9A. The SUCRA values for the various treatments are shown in Figure 9B.

In Figure 9B, we can see that treatment 3 (pelvic floor muscle training + routine care + biofeedback), treatment 10 (routine care + electrical nerve stimulation therapy + professional therapist–guided

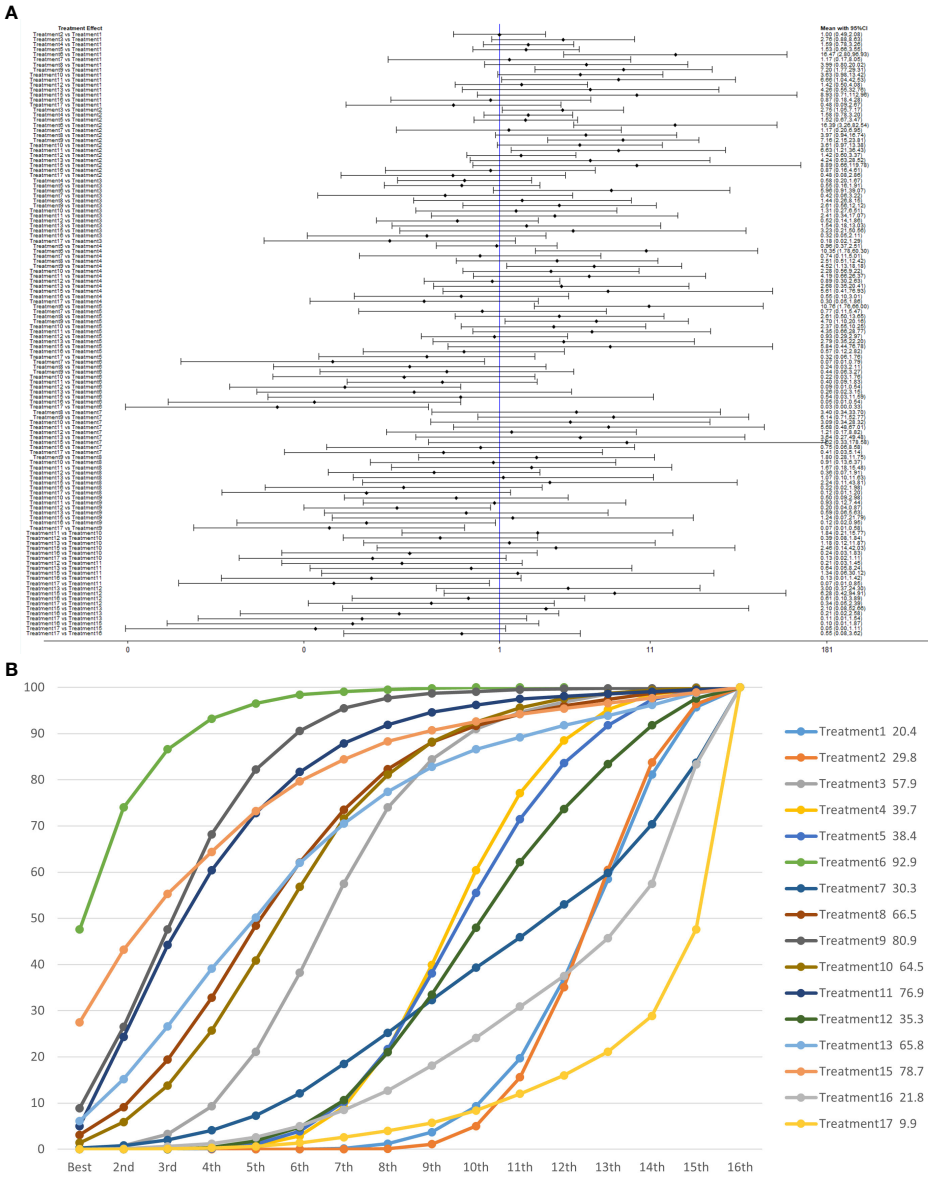


FIGURE 8
(A) The forest plot represents the OR and 95% CrI for a two-by-two comparison of multiple treatment modalities for urinary incontinence at 3 months after radical prostatectomy. **(B)** Cumulative probability graph of postoperative urinary incontinence recovered in 3 months.

treatment + pelvic floor muscle), and treatment 9 (pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + electrical nerve) are in the top three in terms of effectiveness. In the network meta-analysis ladder table of postoperative urinary incontinence recovered in 6 months, we could find that treatment 3 (pelvic floor muscle training + routine care + biofeedback) was better than treatment 5 (pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment) and treatment 12 (pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + preoperative pelvic).

In Table 5, we found that electrical stimulation and biofeedback therapy remained effective during the 6-month interim treatment period. At the 6-month interim treatment, preoperative pelvic floor muscle training still had a detrimental effect on the postoperative electrical stimulation treatment and, unexpectedly, on the guided treatment by the specialist therapist, which may be related to the level of the specialist therapist.

3.5 Total clinical effectiveness at 12 months

We used a network meta-analysis of different pelvic floor muscle treatment measures to assess the recovery of urinary incontinence in patients at 12 months after radical prostate cancer surgery. Treatment 2 (routine care + pelvic floor muscle training) showed better results compared with treatment 9 (pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + electrical nerve) (OR: 0.10, 95% CrI: 0.01–0.86) at 12 months postoperatively, as shown in Figure 10A.

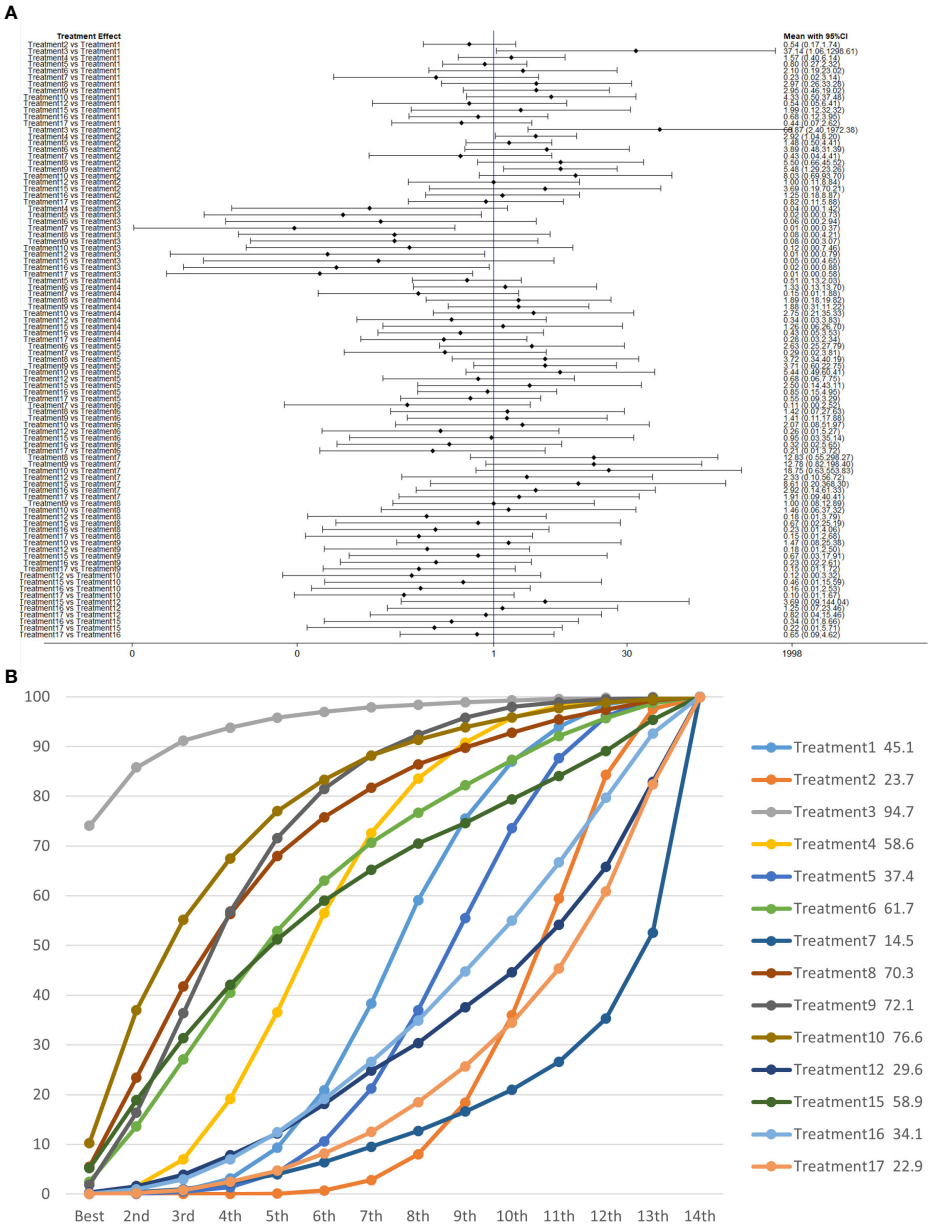


FIGURE 9
(A) The forest plot represents the OR and 95% CrI for a two-by-two comparison of multiple treatment modalities for urinary incontinence at 6 months after radical prostatectomy. **(B)** Cumulative probability graph of postoperative urinary incontinence recovered in 6 months.

The SUCRA values for the various treatments are shown in Figure 10B.

In Figure 10B, we can see that treatment 9, treatment 10, and treatment 3 are in the top three in terms of effectiveness. In the long term, comprehensive treatment remains at the top of the treatment effectiveness scale, whereas the rest of the treatment modalities do not produce significant changes, which may be consistent with previous research that various treatments help control incontinence in the short term, but have similar effects in the long term.

In general, biofeedback and pelvic floor training can be used to treat incontinence in the early post-operative period in order to maintain a better recovery, and, where possible, specialist treatment is also required. Professional treatment can also have a significant effect on the first and middle post-operative period, and it is advisable to also offer bioelectric stimulation in the post-operative period. In the longer term, there is no significant difference between the treatments, and, for those who are not financially able to do so, we can use general pelvic floor training, which is slightly less effective in the early stages of treatment, but, in the long term, the two treatments are similar. At the same time, we can also start to develop more advanced medical devices for the treatment.

3.5.1 Small sample effect estimation

Funnel plots were drawn for the total effective outcome indicator to test for publication bias. The results showed that all studies were generally symmetrically distributed around the X = 0

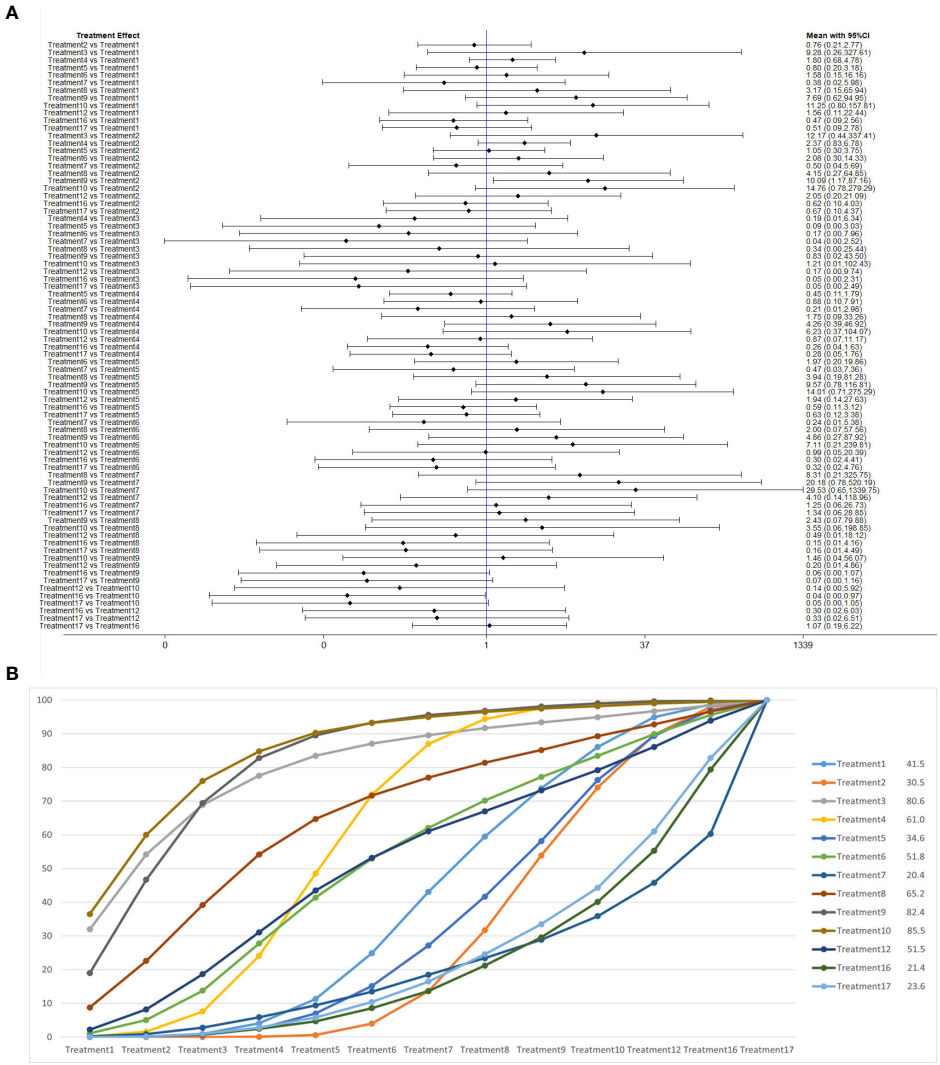


FIGURE 10
(A) The forest plot represents the OR and 95% CrI for a two-by-two comparison of multiple treatment modalities for urinary incontinence at 12 months after radical prostatectomy. **(B)** Cumulative probability graph of postoperative urinary incontinence recovered in 12 months.

vertical line, and most studies fell inside the funnel, whereas some fell at the bottom, suggesting a possible small sample effect (Figures 11A–D).

There are some limitations in this study: all of the naive studies were in English, and most of them were of high quality in terms of allocation concealment and blinded implementation, but there may still be some bias. This suggests that future studies should pay attention to the reporting of safety.

This study has considerable merit in that the quality of the literature is relatively high and the included literature has a low publication bias. This network meta-analysis did not require a high level of gender, age, and basic physical fitness of the patients studied, and the relatively small amount of relevant foreign language literature retrieved so far could be used to increase the amount of data collected later in the study to better define the findings.

In summary, the results of this study showed that pelvic floor muscle training combined with biofeedback and guidance from professional therapists had a better recovery effect on urinary incontinence about 1 month after surgery than conventional care and pelvic floor muscle training. Bioelectrical stimulation combined with pelvic floor muscle exercise has a good recovery effect at 3 months; biofeedback treatment is more conducive to the recovery of urinary incontinence at 6 months after surgery; at 12 months, combined with biofeedback and electrical stimulation, therapist-guided pelvic floor muscle training is better than traditional pelvic floor muscle training.

4 Discussion

Urinary incontinence in individuals with radical prostate cancer primarily arises from structural or functional irregularities in the urethral sphincter. This can encompass damage to both the external urethral sphincter and associated nerves, as well as an inadequate length of the functional urethra. These issues subsequently induce

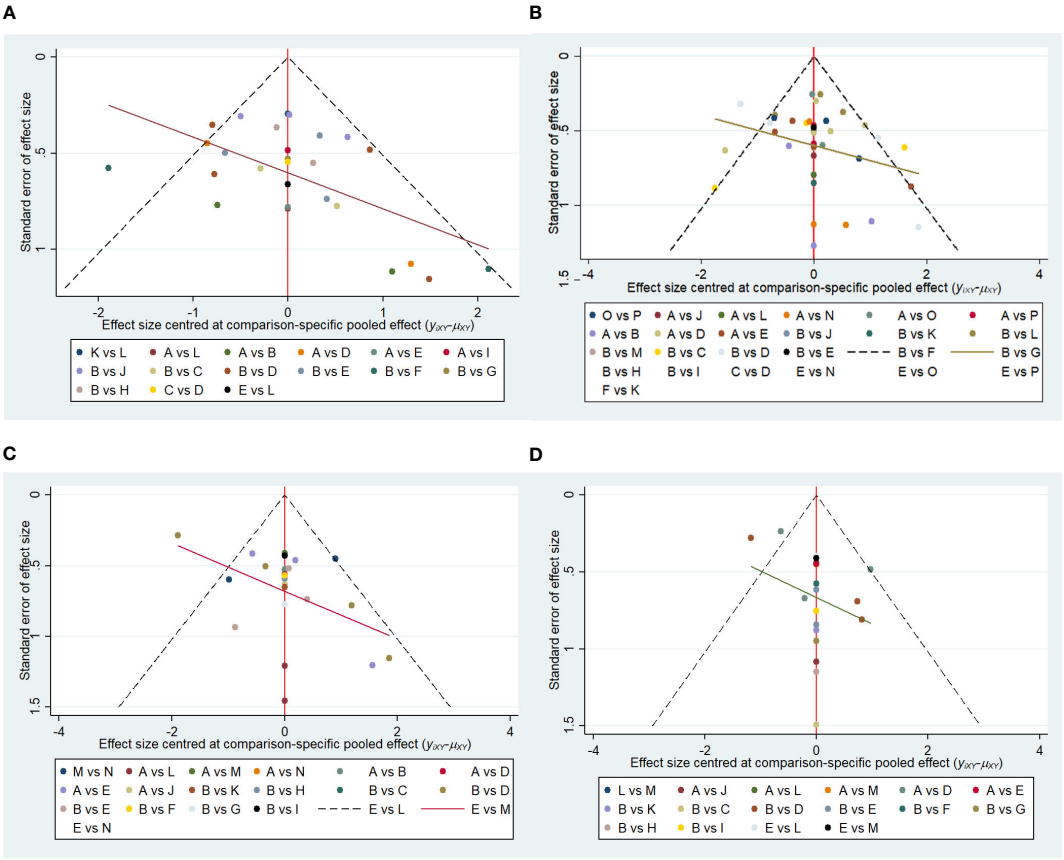


FIGURE 11
(A) Funnel plot of references cited in 1 month. **(B)** Funnel plot of references cited in 3 months. **(C)** Funnel plot of references cited in 6 months. **(D)** Funnel plot of references cited in 12 months.

alterations in the anatomy and function of the bladder and its outlet. Consequently, some patients may encounter urinary incontinence, attributed to diverse factors, including damage to the detrusor muscle, the duration of the extraction procedure, and individual variations in physical condition (50, 51).

"No pad" after radical prostatectomy is currently considered to have the best effect in assessing the effect of other factors on urinary incontinence (52). The baseline level (surgical method, degree of urinary incontinence, and other physical indicators) of patients after radical prostatectomy also has a certain impact on the treatment effect of patients. In terms of surgical methods, patients with robot-assisted radical prostatectomy recover the fastest after surgery (53); in surgical approach, perineal radical resection of prostate cancer is more effective than peritoneal radical resection; in surgical procedure, retention of lateral prostatic fascia (54), anterior and posterior fascia (55), nerve (56), and distal urethral sphincter complex (57) can accelerate the occurrence of postoperative urinary incontinence. In terms of physical indicators, younger patients (58), less weight (body mass index < 30) and frequent physical exercise (1 h or more per week) (59), and patients with longer preoperative membranous urethral length (60) showed faster recovery of postoperative urinary incontinence. However, the baseline level only had an impact on the early urinary incontinence back-resuscitation after radical prostatectomy, and there was no significant difference in the recovery of long-term urinary incontinence.

The common clinical treatment modalities include surgical treatment, and non-surgical treatment includes 1. pelvic floor muscle training (preoperative, postoperative, and ultrasound-guided), 2. electrical stimulation (electrical nerve stimulation - perineum, and electrotherapy - anal electrical stimulation), 3. lifestyle modification, 4. external penile compression devices, 5. conservative treatment (reducing coffee intake and weight loss), 6. medication (duloxetine, etc.), 7. endoscopic treatment, 8. urethral fillers (collagen injections), 9. specialist therapist supervision, 10. bladder training and surgical treatment, 11. sling surgery, and 12. the implantation of an artificial sphincter.

In our studies, we have found that the treatment or prevention of urinary incontinence through preoperative or postoperative measures has a significant effect on the development of complications of urinary incontinence in the short term but not in the long term. This does not mean that this range of therapeutic measures is not sufficiently effective, provided that we can reduce the duration of the effects of complications in a proactive way to bring about an improvement in the quality of life of patients after surgery and also to reduce the burden of disease on patients and health institutions (61). In terms of economic effects, biofeedback and professional therapist–guided treatment have similar treatment

TABLE 4 Network meta-analysis ladder table of postoperative urinary incontinence recovered in 3 months.

Treatment 1															
1.00 (0.48, 2.06)	Treatment 2														
0.36 (0.12, 1.13)	0.36 (0.14, 0.95)	Treatment 3													
0.63 (0.31, 1.29)	0.63 (0.31, 1.27)	1.74 (0.60, 5.02)	Treatment 4												
0.65 (0.28, 1.52)	0.66 (0.29, 1.50)	1.80 (0.52, 6.22)	1.04 (0.40, 2.72)	Treatment 5											
0.06 (0.01, 0.36)	0.06 (0.01, 0.31)	0.17 (0.03, 1.10)	0.10 (0.02, 0.56)	0.09 (0.02, 0.57)	Treatment 6										
0.85 (0.12, 5.86)	0.86 (0.14, 5.11)	2.36 (0.31, 17.87)	1.36 (0.20, 9.24)	1.31 (0.18, 9.32)	14.05 (1.26, 156.12)	Treatment 7									
0.25 (0.05, 1.26)	0.25 (0.06, 1.06)	0.69 (0.12, 3.91)	0.40 (0.08, 1.97)	0.38 (0.07, 2.01)	4.13 (0.47, 35.93)	0.29 (0.03, 2.91)	Treatment 8								
0.14 (0.03, 0.57)	0.14 (0.04, 0.46)	0.38 (0.08, 1.79)	0.22 (0.06, 0.89)	0.21 (0.05, 0.91)	2.29 (0.31, 17.15)	0.16 (0.02, 1.40)	0.55 (0.09, 3.61)	Treatment 9							
0.28 (0.07, 1.02)	0.28 (0.07, 1.03)	0.76 (0.15, 3.77)	0.44 (0.11, 1.78)	0.42 (0.10, 1.82)	4.54 (0.57, 36.38)	0.32 (0.04, 2.96)	1.10 (0.16, 7.70)	1.98 (0.34, 11.74)	Treatment 10						
0.15 (0.02, 0.96)	0.15 (0.03, 0.83)	0.41 (0.06, 2.93)	0.24 (0.04, 1.50)	0.23 (0.03, 1.52)	2.47 (0.55, 11.20)	0.18 (0.01, 2.07)	0.60 (0.06, 5.55)	1.08 (0.13, 8.68)	0.54 (0.06, 4.67)	Treatment 11					
0.70 (0.25, 2.01)	0.71 (0.30, 1.68)	1.94 (0.54, 7.00)	1.12 (0.38, 3.29)	1.08 (0.34, 3.44)	11.58 (1.85, 72.47)	0.82 (0.11, 5.99)	2.80 (0.52, 15.05)	5.06 (1.15, 22.25)	2.55 (0.54, 11.93)	4.68 (0.69, 31.70)	Treatment 12				
0.23 (0.03, 1.80)	0.24 (0.04, 1.58)	0.65 (0.08, 5.47)	0.37 (0.05, 2.84)	0.36 (0.05, 2.86)	3.86 (0.32, 47.01)	0.28 (0.02, 3.74)	0.94 (0.09, 10.19)	1.69 (0.18, 16.06)	0.85 (0.08, 8.59)	1.56 (0.12, 20.14)	0.33 (0.04, 2.71)	Treatment 13			
0.11 (0.01, 1.42)	0.11 (0.01, 1.52)	0.31 (0.02, 4.83)	0.18 (0.01, 2.44)	0.17 (0.01, 2.25)	1.84 (0.09, 39.42)	0.13 (0.01, 3.08)	0.45 (0.02, 8.74)	0.81 (0.05, 14.14)	0.41 (0.02, 6.93)	0.75 (0.03, 16.75)	0.16 (0.01, 2.41)	0.48 (0.02, 11.99)	Treatment 15		
1.14 (0.23, 5.61)	1.15 (0.22, 6.10)	3.16 (0.47, 21.03)	1.82 (0.33, 9.98)	1.75 (0.36, 8.63)	18.85 (1.85, 192.29)	1.34 (0.12, 15.43)	4.57 (0.50, 41.30)	8.24 (1.05, 64.31)	4.15 (0.55, 31.46)	7.62 (0.70, 82.63)	1.63 (0.26, 10.31)	4.88 (0.39, 61.38)	10.22 (0.53, 195.83)	Treatment 16	
2.07 (0.37, 11.41)	2.08 (0.35, 12.33)	5.70 (0.77, 42.01)	3.29 (0.54, 20.15)	3.16 (0.57, 17.55)	34.02 (3.07, 377.25)	2.42 (0.19, 30.16)	8.24 (0.83, 81.37)	14.86 (1.73, 127.49)	7.49 (0.90, 62.45)	13.76 (1.17, 161.77)	2.94 (0.42, 20.65)	8.80 (0.65, 119.61)	18.45 (0.90, 377.58)	1.80 (0.28, 11.80)	Treatment 17

10.3389/fonc.2023.1307434

TABLE 5 Network meta-analysis ladder table of postoperative urinary incontinence recovered in 12 months.

Treatment 1												
1.31 (0.36, 4.78)	Treatment 2											
0.11 (0.00, 3.81)	0.08 (0.00, 2.28)	Treatment 3										
0.55 (0.21, 1.47)	0.42 (0.15, 1.21)	5.14 (0.16, 167.61)	Treatment 4									
1.24 (0.31, 4.93)	0.95 (0.27, 3.37)	11.55 (0.33, 404.45)	2.25 (0.56, 9.06)	Treatment 5								
0.63 (0.06, 6.46)	0.48 (0.07, 3.33)	5.86 (0.13, 273.67)	1.14 (0.13, 10.29)	0.51 (0.05, 5.12)	Treatment 6							
2.62 (0.17, 41.18)	2.00 (0.18, 22.74)	24.35 (0.40, 1493.55)	4.74 (0.34, 66.95)	2.11 (0.14, 32.71)	4.15 (0.19, 92.62)	Treatment 7						
0.32 (0.02, 6.58)	0.24 (0.02, 3.76)	2.93 (0.04, 218.45)	0.57 (0.03, 10.81)	0.25 (0.01, 5.23)	0.50 (0.02, 14.37)	0.12 (0.00, 4.72)	Treatment 8					
0.13 (0.01, 1.61)	0.10 (0.01, 0.86)	1.21 (0.02, 63.31)	0.23 (0.02, 2.58)	0.10 (0.01, 1.27)	0.21 (0.01, 3.72)	0.05 (0.00, 1.28)	0.41 (0.01, 13.54)	Treatment 9				
0.09 (0.01, 1.25)	0.07 (0.00, 1.28)	0.82 (0.01, 69.64)	0.16 (0.01, 2.68)	0.07 (0.00, 1.40)	0.14 (0.00, 4.74)	0.03 (0.00, 1.54)	0.28 (0.01, 15.74)	0.68 (0.02, 26.19)	Treatment 10			
0.64 (0.04, 9.20)	0.49 (0.05, 5.02)	5.94 (0.10, 343.82)	1.16 (0.09, 14.91)	0.51 (0.04, 7.31)	1.01 (0.05, 20.91)	0.24 (0.01, 7.08)	2.03 (0.06, 74.45)	4.92 (0.21, 117.87)	7.20 (0.17, 306.99)	Treatment 12		
2.11 (0.39, 11.38)	1.61 (0.25, 10.41)	19.55 (0.43, 884.00)	3.80 (0.61, 23.56)	1.69 (0.32, 8.93)	3.33 (0.23, 48.99)	0.80 (0.04, 17.23)	6.67 (0.24, 185.09)	16.20 (0.93, 281.04)	23.71 (1.03, 544.32)	3.29 (0.17, 65.30)	Treatment 16	
1.96 (0.36, 10.71)	1.50 (0.23, 9.78)	18.21 (0.40, 827.30)	3.54 (0.57, 22.16)	1.58 (0.30, 8.40)	3.11 (0.21, 45.93)	0.75 (0.03, 16.14)	6.21 (0.22, 173.33)	15.10 (0.87, 263.41)	22.09 (0.96, 509.90)	3.07 (0.15, 61.18)	0.93 (0.16, 5.39)	Treatment 17

10.3389/fonc.2023.1307434

prices (62), and electrical nerve stimulation therapy is often more expensive than conventional care in the treatment of patients (63). Pelvic floor muscle therapy alone and usual care are more cost-effective than other forms of treatment. Taking into account quality adjusted life year, we point out that treatment for only severe life-affecting incontinence is likely to be cost-effective. We also state that, when severe urinary incontinence occurs after surgery, pelvic floor muscle exercise therapy such as biofeedback, electrical stimulation, and personal guidance can effectively increase the recovery of urinary incontinence in the first 3 months. When urinary incontinence does not have a great impact on life, conservative treatment and ordinary pelvic floor muscle exercise may be more cost-effective.

During pelvic floor exercises, which are difficult to assess and often have an impact on the management of pelvic floor exercises, relying on professional guidance and biofeedback can be burdensome to treatment. If the patient can be given this training preoperatively, it may be possible to reduce the cost and time and effort of treatment by allowing the patient to complete this modified version of the pelvic floor exercise, and, more fortunately, a new device has been investigated by Hodges and others, and we will soon see the results of the device (64, 65).

Validity testing of the stopwatch may be a valid assessment tool when determining the strength of the pelvic floor muscles exercised after radical prostate cancer surgery, in a simple test that can determine the degree of strength of the patient's pelvic floor muscles, which may be a better option compared with complex electrophysiological activity tests.

In a study by Tantawy and others (66), whole-body vibration training has been shown to be effective as an alternative to traditional treatment for patients with post-radical prostate cancer incontinence (66). In a study by Centemero et al., pelvic floor training prior to surgery in the perioperative period for radical prostate cancer improved postoperative urinary incontinence (22).

When patients have different degrees of post-operative incontinence, different treatment modalities should be used. Conservative treatment including Endo urethral injection can be used for mild incontinence that has only a minor impact on life, whereas surgical treatment is more effective when the incontinence has reached a level that seriously affects the patient's quality of life (67).

In a study of related drug treatments, it was found that, in addition to duloxetine, proviverrine hydrochloride, and vardenafil and tadalafil as phosphodiesterase type 5 inhibitors (PDE5-I), solifenacin as M-type choline receptor antagonist, solifenacin, is also effective in early postoperative urinary incontinence (68–71).

The use of PDE5-I improves the quality of life of patients after surgery and is associated with its ability to relieve urinary incontinence (72). Solifenacin's effect is mainly to reduce the probability of postoperative complications by improving detrusor overactivity (DO) and cytometric capacity (73).

Non-surgical management of incontinence after radical prostate cancer surgery can also be managed by bladder training, penciled clamps, endoscopic therapy, injections, and lifestyle modifications such as improving lifestyle, reducing coffee, and weight loss, but little research has been reported on these modalities. It is hoped that more research will be conducted on these approaches in future studies (74). Moreover, families with high medical burdens can wait for the natural recovery of incontinence instead of using more costly alternative treatments. As more relevant trials are conducted, in the future, we may propose postoperative staged treatment options for patients with postoperative urinary incontinence after radical prostate cancer surgery. Researchers have also found acupuncture to be more effective for pelvic floor muscle treatment (75), pending further development of the database in the future experimental results in different languages can be cross-referenced, and future researchers may add to this paper for acupuncture treatment, future researchers may add a comparison of the effects of acupuncture treatment to this paper.

The majority of randomized controlled trials that are currently available in clinical practice have been entered in this study, but there may still be some omissions or errors in the analysis. Most of the clinical data in this paper are usually published in professional journals and magazines. For conference papers, due to the difficulty of finding the original text, the data extracted from other journals may be inaccurate, and only some of the conference papers where the original text can be found are used in this paper. As some of the experiments may have different conditions, there may be some contradictions between experiments, we have reduced the influence of potential influencing factors on the analysis results after a more formal and reasonable method.

In this study, we mainly discussed the effect evaluation of various treatment methods for urinary incontinence after radical prostate cancer surgery. The baseline level of urinary incontinence patients is also a confounding factor affecting postoperative urinary incontinence, which mainly affects the evaluation of treatment effect alone, whereas the baseline level of urinary incontinence has little impact on the comparison of multiple treatment methods. There is still a large scope for research in this area of clinical research, and there are gaps in the study of many treatment modalities that need to be investigated in more depth.

5 Conclusion

In this network meta-analysis, we compared the efficacy of pelvic floor muscle training-based pelvic floor therapy measures in patients with postoperative urinary incontinence after radical prostate cancer surgery. We observed that biofeedback + professional therapist–guided treatment demonstrated superior therapeutic efficacy at 1 month to 6 months for early recovery of incontinence, and electrical nerve stimulation therapy demonstrated superior efficacy at about 3 months postoperatively for recovery of incontinence in the middle of the postoperative period. In December postoperatively, no significant difference was observed in the rest of the modalities, except for electrotherapy + biofeedback + professional guidance. Thus, we can conclude that electrostimulation and biofeedback have a better effect in the early and middle postoperative period, and if they are not effective, pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + electrical nerve stimulation therapy is

still an effective measure to recover incontinence in the longer postoperative period of about 1 year. In 12 months, the various modalities do not show much variation. In the cost-effectiveness of treatment, pelvic floor muscle training + routine care + biofeedback + professional therapist–guided treatment + electrical nerve stimulation therapy within 3 months can quickly restore urine control, improve patients' quality of life and the cost of follow-up daily care. After 3 months, pelvic floor muscle + routine care may be a more economical option to treat urinary incontinence.

It can greatly reduce the cost of treatment. However, with this type of treatment, patients may experience a decrease in quality of life and may increase the cost of care during urine-controlled recovery time.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

KY: Writing – original draft. FB: Data curation, Formal analysis, Writing – original draft. TJ: Investigation, Methodology, Writing – review & editing. ZL: Supervision, Validation, Writing – review & editing. RH: Data curation, Formal analysis, Supervision, Writing – original draft. SC: Writing – review & editing, Methodology, Supervision. JL: Conceptualization, Formal analysis, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by Jilin Scientific and Technological Development Program (20200201315JC), Jilin Province Tianhua Health Foundation (J2023JKJ017) and Bethune Urological Oncology Special Grant, Beijing Bethune Charity Foundation (mnzl202022).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1307434/full#supplementary-material

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2018) 68:394–424. doi: 10.3322/caac.21492

2. Avolio PP, Polascik TJ, Rastinehad A, de la Rosette J, Sanchez-Salas R. Focal therapy for prostate cancer: evolutionary parallels to breast cancer treatment. *Letter. J Urol*. (2023) 209:848–9. doi: 10.1097/JU.0000000000003423

3. Rahnama'i MS, Marcelissen T, Geavlete B, Tutolo M, Hüsch T. Current management of post-radical prostatectomy urinary incontinence. *Front Surg*. (2021) 8:647656. doi: 10.3389/fsurg.2021.647656

4. Sehgal A, Baverstock R, Wright I, Frey C, Crump T, Carlson K. A comparative analysis of physiotherapy for stress urinary incontinence after open or robotic-assisted radical prostatectomy. *Physiother Can*. (2019) 71:207–12. doi: 10.3138/ptc.2017-90

5. Tuğcu V, Akça O, Şimşek A, Yiğitbaşı İ, Şahin S, Yenice MG, et al. Robotic-assisted perineal versus transperitoneal radical prostatectomy: A matched-pair analysis. *Turk J Urol*. (2019) 45:265–72. doi: 10.5152/tud.2019.98254

6. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. (2015) 162:777–84. doi: 10.7326/M14-2385

7. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods*. (2012) 3:80–97. doi: 10.1002/jrsm.1037

8. Mathewson-Chapman M. Pelvic muscle exercise/biofeedback for urinary incontinence after prostatectomy: an education program. *J Cancer Educ*. (1997) 12:218–23. doi: 10.1080/08858199709528492

9. Moore KN, Griffiths D, Hughton A. Urinary incontinence after radical prostatectomy: a randomized controlled trial comparing pelvic muscle exercises with or without electrical stimulation. *BJU Int*. (1999) 83:57–65. doi: 10.1046/j.1464-410x.1999.00894.x

10. Bales GT, Gerber GS, Minor TX, Mhoon DA, McFarland JM, Kim HL, et al. Effect of preoperative biofeedback/pelvic floor training on continence in men undergoing radical prostatectomy. *Urology*. (2000) 56:627–30. doi: 10.1016/S0090-4295(00)00687-7

11. Franke JJ, Gilbert WB, Grier J, Koch MO, Shyr Y, Smith JA Jr. Early post-prostatectomy pelvic floor biofeedback. *J Urol*. (2000) 163:191–3. doi: 10.1016/S0022-5347(05)68002-0

12. Van Kampen M, De Weerdt W, Van Poppel H, De Ridder D, Feys H, Baert L. Effect of pelvic-floor re-education on duration and degree of incontinence after radical prostatectomy: a randomised controlled trial. *Lancet*. (2000) 355:98–102. doi: 10.1016/S0140-6736(99)03473-X

13. Parekh AR, Feng MI, Kirages D, Bremner H, Kaswick J, Aboseif S. The role of pelvic floor exercises on post-prostatectomy incontinence. *J Urol*. (2003) 170:130–3. doi: 10.1097/01.ju.0000072900.82131.6f

14. Yokoyama T, Nishiguchi J, Watanabe T, Nose H, Nozaki K, Fujita O, et al. Comparative study of effects of extracorporeal magnetic innervation versus electrical stimulation for urinary incontinence after radical prostatectomy. *Urology*. (2004) 63:264–7. doi: 10.1016/j.urology.2003.09.024

15. Filocamo MT, Li Marzi V, Del Popolo G, Cecconi F, Marzocco M, Tosto A, et al. Effectiveness of early pelvic floor rehabilitation treatment for post-prostatectomy incontinence. *Eur Urol*. (2005) 48:734–8. doi: 10.1016/j.eururo.2005.06.004

16. Burgio KL, Goode PS, Urban DA, Umlauf MG, Locher JL, Bueschen A, et al. Preoperative biofeedback assisted behavioral training to decrease post-prostatectomy incontinence: a randomized, controlled trial. *J Urol*. (2006) 175:196–201. doi: 10.1016/S0022-5347(05)00047-9

17. Filocamo MT, Li Marzi V, Del Popolo G, Cecconi F, Villari D, Marzocco M, et al. Pharmacologic treatment in postprostatectomy stress urinary incontinence. *Eur Urol*. (2007) 51:1559–64. doi: 10.1016/j.eururo.2006.08.005

18. Manassero F, Traversi C, Ales V, Pistolesi D, Panicucci E, Valent F, et al. Contribution of early intensive prolonged pelvic floor exercises on urinary continence recovery after bladder neck-sparing radical prostatectomy: results of a prospective controlled randomized trial. *Neurourol Urodyn*. (2007) 26:985–9. doi: 10.1002/nau.20442

19. Moore KN, Valiquette L, Chetner MP, Byrniak S, Herbison GP. Return to continence after radical retropubic prostatectomy: a randomized trial of verbal and written instructions versus therapist-directed pelvic floor muscle therapy. *Urology*. (2008) 72:1280–6. doi: 10.1016/j.urology.2007.12.034

20. Overgård M, Angelsen A, Lydersen S, Mørkved S. Does physiotherapist-guided pelvic floor muscle training reduce urinary incontinence after radical prostatectomy? A randomised controlled trial. *Eur Urol*. (2008) 54:438–48. doi: 10.1016/j.eururo.2008.04.021

21. Mariotti G, Sciarra A, Gentilucci A, Salciccia S, Alfarone A, Di Pierro G, et al. Early recovery of urinary continence after radical prostatectomy using early pelvic floor electrical stimulation and biofeedback associated treatment. *J Urol*. (2009) 181:1788–93. doi: 10.1016/j.juro.2008.11.104

22. Centemero A, Rigatti L, Giraudo D, Lazzeri M, Lughezzani G, Zugna D, et al. Preoperative pelvic floor muscle exercise for early continence after radical prostatectomy: a randomised controlled study. *Eur Urol*. (2010) 57:1039–43. doi: 10.1016/j.eururo.2010.02.028

23. Ribeiro LH, Prota C, Gomes CM, de Bessa J Jr., Boldarine MP, Dall'Oglio MF, et al. Long-term effect of early postoperative pelvic floor biofeedback on continence in men undergoing radical prostatectomy: a prospective, randomized, controlled trial. *J Urol*. (2010) 184:1034–9. doi: 10.1016/j.juro.2010.05.040

24. Yamanishi T, Mizuno T, Watanabe M, Honda M, Yoshida K. Randomized, placebo controlled study of electrical stimulation with pelvic floor muscle training for severe urinary incontinence after radical prostatectomy. *J Urol*. (2010) 184:2007–12. doi: 10.1016/j.juro.2010.06.103

25. Glazener C, Boachie C, Buckley B, Cochran C, Dorey G, Grant A, et al. Urinary incontinence in men after formal one-to-one pelvic-floor muscle training following radical prostatectomy or transurethral resection of the prostate (MAPS): two parallel randomised controlled trials. *Lancet*. (2011) 378:328–37. doi: 10.1016/S0140-6736(11)60751-4

26. Nilssen SR, Mørkved S, Overgård M, Lydersen S, Angelsen A. Does physiotherapist-guided pelvic floor muscle training increase the quality of life in patients after radical prostatectomy? A randomized clinical study. *Scand J Urol Nephrol*. (2012) 46:397–404. doi: 10.3109/00365599.2012.694117

27. Park SW, Kim TN, Nam JK, Ha HK, Shin DG, Lee W, et al. Recovery of overall exercise ability, quality of life, and continence after 12-week combined exercise intervention in elderly patients who underwent radical prostatectomy: a randomized controlled study. *Urology*. (2012) 80:299–305. doi: 10.1016/j.urology.2011.12.060

28. Tienforti D, Sacco E, Marangi F, D'Addessi A, Racioppi M, Gulino G, et al. Efficacy of an assisted low-intensity programme of perioperative pelvic floor muscle training in improving the recovery of continence after radical prostatectomy: a randomized controlled trial. *BJU Int*. (2012) 110:1004–10. doi: 10.1111/j.1464-410X.2012.10948.x

29. Geraerts I, Van Poppel H, Devoogdt N, Joniau S, Van Cleynenbreugel B, De Groef A, et al. Influence of preoperative and postoperative pelvic floor muscle training (PFMT) compared with postoperative PFMT on urinary incontinence after radical prostatectomy: a randomized controlled trial. *Eur Urol*. (2013) 64:766–72. doi: 10.1016/j.eururo.2013.01.013

30. Patel MI, Yao J, Hirschhorn AD, Mungovan SF. Preoperative pelvic floor physiotherapy improves continence after radical retropubic prostatectomy. *Int J Urol*. (2013) 20:986–92. doi: 10.1111/iju.12099

31. Terzoni S, Montanari E, Mora C, Ricci C, Destrebecq A. Reducing urine leakage after radical retropubic prostatectomy: pelvic floor exercises, magnetic innervation or no treatment? A quasi-experimental study. *Rehabil Nurs*. (2013) 38:153–60. doi: 10.1002/rnj.72

32. Fode M, Borre M, Ohl DA, Lichtbach J, Sønksen J. Penile vibratory stimulation in the recovery of urinary continence and erectile function after nerve-sparing radical prostatectomy: a randomized, controlled trial. *BJU Int*. (2014) 114:111–7. doi: 10.1111/bju.12501

33. Rajkowska-Labon E, Bakuła S, Kucharzewski M, Sliwiński Z. Efficacy of physiotherapy for urinary incontinence following prostate cancer surgery. *BioMed Res Int*. (2014) 2014:785263. doi: 10.1155/2014/785263

34. Alan C, Eren AE, Ersay AR, Kocoglu H, Basturk G, Demirci E. Efficacy of duloxetine in the early management of urinary continence after radical prostatectomy. *Curr Urol*. (2015) 8:43–8. doi: 10.1159/000365688

35. Dijkstra-Eshuis J, Van den Bos TW, Splinter R, Bevers RF, Zonneveld WC, Putter H, et al. Effect of preoperative pelvic floor muscle therapy with biofeedback versus standard care on stress urinary incontinence and quality of life in men undergoing laparoscopic radical prostatectomy: a randomised control trial. *Neurourol Urodyn*. (2015) 34:144–50. doi: 10.1002/nau.22523

36. Uchikawa-Tani Y, Yazawa M, Sakuma H, Hikosaka M, Takayama M, Kishi K. Reconstruction of the urethral sphincter with dynamic graciloplasty in a male rabbit model. *Urol Int*. (2016) 96:217–22. doi: 10.1159/000442474

37. Aydın Sayılan A, Özbaş A. The effect of pelvic floor muscle training on incontinence problems after radical prostatectomy. *Am J Mens Health*. (2018) 12:1007–15. doi: 10.1177/1557988318757242

38. de Lira GHS, Fornari A, Cardoso LF, Aranchipe M, Kretiska C, Rhoden EL. Effects of perioperative pelvic floor muscle training on early recovery of urinary continence and erectile function in men undergoing radical prostatectomy: a randomized clinical trial. *Int Braz J Urol*. (2019) 45:1196–203. doi: 10.1590/s1677-5538.ibju.2019.0238

39. Yoshida M, Matsunaga A, Igawa Y, Fujimura T, Shinoda Y, Aizawa N, et al. May perioperative ultrasound-guided pelvic floor muscle training promote early recovery of urinary continence after robot-assisted radical prostatectomy? *Neurourol Urodyn*. (2019) 38:158–64. doi: 10.1002/nau.23811

40. Oh JJ, Kim JK, Lee H, Lee S, Jin Jeong S, Kyu Hong S, et al. Effect of personalized extracorporeal biofeedback device for pelvic floor muscle training on urinary incontinence after robot-assisted radical prostatectomy: A randomized controlled trial. *Neurourol Urodyn*. (2020) 39:674–81. doi: 10.1002/nau.24247

41. Soto González M, Da Cuña Carrera I, Gutiérrez Nieto M, López García S, Ojea Calvo A, Lantarón Caeiro EM. Early 3-month treatment with comprehensive physical therapy program restores continence in urinary incontinence patients after radical prostatectomy: A randomized controlled trial. *Neurourol Urodyn*. (2020) 39:1529–37. doi: 10.1002/nau.24389

42. Yang H, TT L, L X, Yao LJ, L JW. Electroacupuncture stimulation of the pudendal nerve for urinary incontinence after radical prostatectomy. *Zhonghua Nan Ke Xue*. (2020) 26:1119–23.

43. Kim YU, Lee DG, Ko YH. Pelvic floor muscle exercise with biofeedback helps regain urinary continence after robot-assisted radical prostatectomy. *Yeungnam Univ J Med*. (2021) 38:39–46. doi: 10.12701/yujm.2020.00276

44. Feng X, Lv J, Li M, Lv T, Wang S. Short-term efficacy and mechanism of electrical pudendal nerve stimulation versus pelvic floor muscle training plus transanal electrical stimulation in treating post-radical prostatectomy urinary incontinence. *Urology*. (2022) 160:168–75. doi: 10.1016/j.urology.2021.04.069

45. Szczygielska D, Knapik A, Pop T, Rottermund J, Saulicz E. The effectiveness of pelvic floor muscle training in men after radical prostatectomy measured with the insert test. *Int J Environ Res Public Health*. (2022) 19(5):2890. doi: 10.3390/ijerph19052890

46. Veshnavei HA. Urinary incontinency after radical prostatectomy and effects of 1 month pre-operative biofeedback training. *Am J Clin Exp Urol*. (2021) 9:489–96.

47. Allameh F, Rayegani SM, Razzaghi M, Abedi AR, Rahavian A, Javadi A, et al. Comparison of the effect of the pelvic floor muscle biofeedback prior or postradical prostatectomy on urinary incontinence: A randomized controlled trial. *Turk J Urol*. (2021) 47:436–41. doi: 10.5152/tud.2021.21096

48. Zhu J, Gao F, He H, Li S, Zhang S, Jiang Y, et al. The effect of low-frequency electrical stimulation combined with anus lifting training on urinary incontinence after radical prostatectomy in a chinese cohort. *Am J Mens Health*. (2023) 17:15579883231183770. doi: 10.1177/15579883231183770

49. Sanchez-Salas R, Tourinho-Barbosa R, Sivaraman A, Borges RC, Candela L, Cathala N, et al. Assessing the efficacy of pelvic floor muscle training and duloxetine on urinary continence recovery following radical prostatectomy: A randomized clinical trial. *Prostate*. (2023) 84(2):158–165. doi: 10.1002/pros.24634

50. Chung DE, Dillon B, Kurta J, Maschino A, Cronin A, Sandhu JS. Detrusor underactivity is prevalent after radical prostatectomy: A urodynamic study including risk factors. *Can Urol Assoc J*. (2013) 7:E33–7. doi: 10.5489/cuaj.192

51. Jeong IG, You D, Yoon JH, Hong S, Lim JH, Hong JH, et al. Impact of tamsulosin on urinary retention following early catheter removal after robot-assisted laparoscopic radical prostatectomy: a prospective randomized controlled trial. *Int J Urol*. (2014) 21:164–8. doi: 10.1111/iju.12225

52. Moretti TBC, Magna LA, Reis LO. Continence criteria of 193 618 patients after open, laparoscopic, and robot-assisted radical prostatectomy. *BJU Int*. (2023). doi: 10.1111/bju.16180

53. Haney CM, Kowalewski KF, Westhoff N, Holze S, Checcuci E, Neuberger M, et al. Robot-assisted versus conventional laparoscopic radical prostatectomy: A systematic review and meta-analysis of randomised controlled trials. *Eur Urol Focus*. (2023) 9:930–7. doi: 10.1016/j.euf.2023.05.007

54. Choi WW, Freire MP, Soukup JR, Yin L, Lipsitz SR, Carvas F, et al. Nerve-sparing technique and urinary control after robot-assisted laparoscopic prostatectomy. *World J Urol*. (2011) 29:21–7. doi: 10.1007/s00345-010-0601-z

55. Sessa F, Nicoletti R, Pecoraro A, Polverino P, Rivetti A, Conte FL, et al. Urinary Continence Recovery after Robotic Radical Prostatectomy without Anterior or Posterior Reconstruction: Experience from a Tertiary Referral Center. *J Clin Med*. (2023) 12(4):1358. doi: 10.3390/jcm12041358

56. van der Slot MA, Remmers S, van Leenders G, Busstra MB, Gan M, Klaver S, et al. Urinary incontinence and sexual function after the introduction of neuroSAFE in radical prostatectomy for prostate cancer. *Eur Urol Focus*. (2023) 9:824–31. doi: 10.1016/j.euf.2023.03.021

57. Liu A, Gao Y, Huang H, Yang X, Lin W, Chen L, et al. A combined technology to protect the anatomic integrity of distal urethral sphincter complex in radical prostatectomy improves early urinary continence recovery without sacrifice of oncological outcomes. *Front Oncol*. (2021) 11:711093. doi: 10.3389/fonc.2021.711093

58. Mendiola FP, Zorn KC, Mikhail AA, Lin S, Orvieto MA, Zagaja GP, et al. Urinary and sexual function outcomes among different age groups after robot-assisted laparoscopic prostatectomy. *J Endourol*. (2008) 22:519–24. doi: 10.1089/end.2006.9845

59. Wolin KY, Luly J, Sutcliffe S, Andriole GL, Kibel AS. Risk of urinary incontinence following prostatectomy: the role of physical activity and obesity. *J Urol*. (2010) 183:629–33. doi: 10.1016/j.juro.2009.09.082

60. Mac Curtain BM, Sugrue DD, Qian W, O'Callaghan M, Davis NF. Membranous urethral length and urinary incontinence following robot-assisted radical prostatectomy: a systematic review and meta-analysis. *BJU Int*. (2023). doi: 10.1111/bju.16170

61. Turner DA, Shaw C, McGrother CW, Dallosso HM, Cooper NJ. The cost of clinically significant urinary storage symptoms for community dwelling adults in the UK. *BJU Int*. (2004) 93:1246–52. doi: 10.1111/j.1464-410x.2004.04806.x

62. Hagen S, Elders A, Stratton S, Sergenson N, Bugge C, Dean S, et al. Effectiveness of pelvic floor muscle training with and without electromyographic biofeedback for urinary incontinence in women: multicentre randomised controlled trial. *Bmj*. (2020) 371:m3719. doi: 10.1136/bmj.m3719

63. Leroi AM, Lenne X, Dervaux B, Chartier-Kastler E, Mauroy B, Normand LL, et al. Outcome and cost analysis of sacral nerve modulation for treating urinary and/or fecal incontinence. *Ann Surg*. (2011) 253:720–32. doi: 10.1097/SLA.0b013e318210f1f4

64. Doorbar-Baptist S, Adams R, Rebbeck T. Ultrasound-based motor control training for the pelvic floor pre- and post-prostatectomy: Scoring reliability and skill acquisition. *Physiother Theory Pract*. (2017) 33:296–302. doi: 10.1080/09593985.2017.1290171

65. Hodges P, Stafford R, Coughlin GD, Kasza J, Ashton-Miller J, Cameron AP, et al. Efficacy of a personalised pelvic floor muscle training programme on urinary incontinence after radical prostatectomy (MaTchUP): protocol for a randomised controlled trial. *BMJ Open*. (2019) 9:e028288. doi: 10.1136/bmjopen-2018-028288

66. Tantawy SA, Elgohary HMI, Abdelbasset WK, Kamel DM. Effect of 4 weeks of whole-body vibration training in treating stress urinary incontinence after prostate cancer surgery: a randomised controlled trial. *Physiotherapy*. (2019) 105:338–45. doi: 10.1016/j.physio.2018.07.013

67. Imamoglu MA, Tuygun C, Bakirtas H, Yiğitbasi O, Kiper A. The comparison of artificial urinary sphincter implantation and endourethral macroplastique injection for the treatment of postprostatectomy incontinence. *Eur Urol*. (2005) 47:209–13. doi: 10.1016/j.eururo.2004.08.019

68. Ohba K, Miyata Y, Mukae Y, Mitsunari K, Matsuo T, Sakai H. Efficacy of propiverine hydrochloride for urinary incontinence after robot-assisted or laparoscopic radical prostatectomy. *Can J Urol*. (2021) 28:10706–12.

69. Gacci M, Ierardi A, Rose AD, Tazzioli S, Scapaticci E, Filippi S, et al. Vardenafil can improve continence recovery after bilateral nerve sparing prostatectomy: results of a randomized, double blind, placebo-controlled pilot study. *J Sex Med*. (2010) 7:234–43. doi: 10.1111/j.1743-6109.2009.01471.x

70. Liss MA, Morales B, Skarecky D, Ahlering TE. Phase 1 clinical trial of Vesicare™ (solifenacin) in the treatment of urinary incontinence after radical prostatectomy. *J Endourol*. (2014) 28:1241–5. doi: 10.1089/end.2014.0342

71. Bianco FJ, Albala DM, Belkoff LH, Miles BJ, Peabody JO, He W, et al. A randomized, double-blind, solifenacin succinate versus placebo control, phase 4, multicenter study evaluating urinary continence after robotic assisted radical prostatectomy. *J Urol*. (2015) 193:1305–10. doi: 10.1016/j.juro.2014.09.106

72. Patel HR, Ilo D, Shah N, Cuzin B, Chadwick D, Andrianne R, et al. Effects of tadalafil treatment after bilateral nerve-sparing radical prostatectomy: quality of life, psychosocial outcomes, and treatment satisfaction results from a randomized, placebo-controlled phase IV study. *BMC Urol*. (2015) 15:31. doi: 10.1186/s12894-015-0022-9

73. Yang R, Liu L, Li G, Yu J. Efficacy of solifenacin in the prevention of short-term complications after laparoscopic radical prostatectomy. *J Int Med Res*. (2017) 45:2119–27. doi: 10.1177/0300060517713405

74. Shim M, Kim J, Park S, Choi SK, Lee SM, Huh KO, et al. The therapeutic effect of solifenacin succinate on the recovery from voiding dysfunction after radical prostatectomy in men with clinically localized prostate cancer: a prospective, randomized, controlled study. *Urology*. (2015) 85:1123–9. doi: 10.1016/j.urology.2015.01.022

75. Bernardes M, Mata L, Azevedo C, Izidoro LCR, Oliveira CMC, Chianca TCM. Effectiveness of systemic acupuncture in the control of urinary incontinence following radical prostatectomy: a randomized clinical trial. *Rev Esc Enferm USP*. (2022) 56:e20220135. doi: 10.1590/1980-220x-reeusp-2022-0135pt

frontiers | Frontiers in Oncology

TYPE Perspective
PUBLISHED 24 May 2024
DOI 10.3389/fonc.2024.1391464

OPEN ACCESS

EDITED BY
Liyuan Zhang,
Second Affiliated Hospital of Soochow University, China

REVIEWED BY
Francolini Giulio,
University of Florence, Italy

*CORRESPONDENCE
Nam P. Nguyen
NamPhong.Nguyen@yahoo.com

RECEIVED 25 February 2024
ACCEPTED 15 April 2024
PUBLISHED 24 May 2024

CITATION
Nguyen NP, Chirila M-E, Page BR, Vinh-Hung V, Gorobets O, Mohammadianpanah M, Giap H, Arenas M, Bonet M, Lara PC, Kim L, Dutheil F, Lehrman D, Montes LZ, Tlili G, Dahbi Z, Loganadane G, Blanco SC, Bose S, Natoli E, Li E, Mallum A and Morganti AG (2024) Immunotherapy and stereotactic body radiotherapy for older patients with non-metastatic renal cancer unfit for surgery or decline nephrectomy: practical proposal by the International Geriatric Radiotherapy Group. *Front. Oncol.* 14:1391464. doi: 10.3389/fonc.2024.1391464

Immunotherapy and stereotactic body radiotherapy for older patients with non-metastatic renal cancer unfit for surgery or decline nephrectomy: practical proposal by the International Geriatric Radiotherapy Group

Nam P. Nguyen[1*], Monica-Emilia Chirila[2,3], Brandi R. Page[4], Vincent Vinh-Hung[5], Olena Gorobets[6], Mohammad Mohammadianpanah[7], Huan Giap[8], Meritxell Arenas[9], Marta Bonet[10], Pedro Carlos Lara[11], Lyndon Kim[12], Fabien Dutheil[13], David Lehrman[14], Luis Zegarra Montes[15], Ghassen Tlili[16], Zineb Dahbi[17], Gokoulakrichenane Loganadane[18], Sergio Calleja Blanco[19], Satya Bose[1], Elena Natoli[20,21], Eric Li[22], Abba Mallum[23] and Alessio G. Morganti[20,21]

[1]Department of Radiation Oncology, Howard University, Washington, DC, United States, [2]Department of Clinical Development, MVision AI, Helsinki, Finland, [3]Department of Radiation Oncology, Amethyst Radiotherapy Centre, Cluj-Napoca, Romania, [4]Department of Radiation Oncology, Johns Hopkins University, Baltimore, MD, United States, [5]Department of Radiation Oncology, Centre Hospitalier Public du Contentin, Cherbourg-en-Contentin, France, [6]Department of Oral Surgery, University Hospital of Martinique, Fort-de-France, France, [7]Colorectal Research Center, Department of Radiation Oncology, Shiraz University of Medical Sciences, Shiraz, Iran, [8]Department of Radiation Oncology, Medical University of South Carolina, Charleston, SC, United States, [9]Department of Radiation Oncology, Sant Joan de Reus University Hospital, University of Rovira, I Virgili, Tarragona, Spain, [10]Department of Radiation Oncology, Arnau de Vilanova University Hospital, Lleida, Spain, [11]Department of Radiation Oncology, Fernando Pessoria Canarias Las Palmas University, Las Palmas, Spain, [12]Division of Neuro-Oncology, Mount Sinai Hospital, New York, NY, United States, [13]Department of Radiation Oncology, Clinique Sainte Clotilde, Saint-Denis, Reunion Island, France, [14]Department of Radiation Oncology, International Geriatric Radiotherapy Group, Washington, DC, United States, [15]Department of Urology, University of Peruana, Lima, Peru, [16]Department of Urology, Sahloul University Hospital, Sousse, Tunisia, [17]Department of Radiation Oncology, Mohammed VI University of Health Sciences, Casablanca, Morocco, [18]Department of Radiation Oncology, Institut Curie, Paris, France, [19]Department of Oral Maxillofacial Surgery, Howard University, Washington, DC, United States, [20]Department of Radiation Oncology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Azienda Ospedaliera-Universitaria di Bologna, Bologna, Italy, [21]Radiation Oncology, Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studorium, Bologna University, Bologna, Italy, [22]Department of Pathology, Howard University, Washington, DC, United States, [23]Department of Radiation Oncology, University of KwaZulu Natal, Durban, South Africa

The standard of care for non-metastatic renal cancer is surgical resection followed by adjuvant therapy for those at high risk for recurrences. However, for older patients, surgery may not be an option due to the high risk of complications which may result in death. In the past renal cancer was considered to be radio-resistant, and required a higher dose of radiation leading to excessive complications secondary to damage of the normal organs

surrounding the cancer. Advances in radiotherapy technique such as stereotactic body radiotherapy (SBRT) has led to the delivery of a tumoricidal dose of radiation with minimal damage to the normal tissue. Excellent local control and survival have been reported for selective patients with small tumors following SBRT. However, for patients with poor prognostic factors such as large tumor size and aggressive histology, there was a higher rate of loco-regional recurrences and distant metastases. Those tumors frequently carry program death ligand 1 (PD-L1) which makes them an ideal target for immunotherapy with check point inhibitors (CPI). Given the synergy between radiotherapy and immunotherapy, we propose an algorithm combining CPI and SBRT for older patients with non-metastatic renal cancer who are not candidates for surgical resection or decline nephrectomy.

KEYWORDS

older, renal cancer, CPI, SBRT, protocol

Introduction

The management of renal cancer remains a challenge for older patients. Surgical resection is the standard treatment for non-metastatic renal cancer. However, due to the presence of co-morbidities, older patients may not benefit from surgery. In a study of 537 patients aged 75 or above with localized renal cancer 7 cm in size or less, nephrectomy has led to a poor survival as patients died from cardiovascular disease and deterioration of renal function in the remaining kidney (1). Compared to radical nephrectomy, a partial nephrectomy for localized renal cancer may better preserve renal function but did not improved survival among patients aged 65 or older (2). Regardless of age or type of surgery, frail patients with renal cancer are at increased risk for major complications and poor survival after the procedure (3, 4). Preserving renal function is imperative for averting the necessity of dialysis, mitigating chronic kidney disease, and reducing mortality associated with cardiac events (5). Thus, older and frail renal cancer patients may not be candidates for surgery and need an alternative for curative treatment when diagnosed at an early stage.

In the past, renal cancer was considered to be radio-resistant and required a higher dose per fraction (hypofractionation) in order to overcome the tumor cell ability to repair radiation damage (6). However, the delivery of a high radiation dose may also lead to serious complications due to damage to the normal organs at risk (OAR) surrounding the cancer with older radiotherapy techniques. The introduction of stereotactic body radiotherapy (SBRT) in the treatment of early stage non-small cell lung cancer (NSCLL) has led to its successful application for non-metastatic renal cancer in patients who are not surgical candidates due to their age and pre-existing comorbidities (7). Preliminary studies are very promising with excellent local control and survival in selected patients with small tumors and low grade histology (8, 9). As a local treatment similar to surgery, SBRT for renal cancer may not be effective for tumors with high risk for loco-regional recurrences and distant metastases due to their size and aggressive histology. Those tumors often carry program death ligand 1 (PD-L1) which allow them to evade immune surveillance and make them an ideal target for immunotherapy with checkpoint inhibitors (CPI) (10, 11). As high dose radiotherapy has a synergistic effect with CPI, this combination may be ideal for the treatment of older cancer patients with non-metastatic renal cell cancer (12).

The International Geriatric Radiotherapy Group (http://www.igrg.org) is an organization devoted to the care of older cancer patients, minorities, and women who are frequently excluded from clinical trials (13). Based on currently published literature, members of the genitourinary cancers subgroup propose in this article a practical protocol for older patients with non-metastatic renal cancer who are too frail to undergo surgery or who decline nephrectomy. Radiotherapy and immunotherapy may induce long-term remission and potential cure for those patients.

Rationale for using immunotherapy in renal cancer

Renal cancer immune environment

Renal cell cancer has a very complex tumor immune microenvironment (TIME) which depends on the tumor histology and evolves over the course of treatment, thus defying any simple classification (14–17). Most studies have focused on clear cell renal (CCR) carcinoma which comprises the majority (up to 80%) of the tumor subtypes. Other non-CCR carcinoma such as the sarcomatoid subtype may have a more aggressive biology behavior and a different TIME (18). In general, renal cell TIME is characterized by an

overwhelming abundance of immunosuppression which allows cancer cells to evade immune surveillance and cause disease progression. A preponderance of immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor beta (TGF-β) promotes the differentiation of regulatory T cells (Treg) which in turn inhibit CD8+ T cells from tumor killing (19–25). In addition, tumor cells may also express PD-L1 which binds with the programmed cell death protein 1 (PD-1) on CD8+ T cells to neutralize its tumoricidal function (10, 11). Hypoxia is also another contributing factor to the tumor immune resistance (26, 27). Thus, any effective treatment should target all of the elements that contribute to the tumor ability to evade immunosurveillance. Even though PD-L1 is not a perfect biomarker, increase in PD-L1 expression has been reported to be correlated with a poor prognosis. Among 346 patients with renal cell carcinoma who had long-term follow-up, high PD-L1 expression was correlated with increased tumor size, high nucleolar grade, lymph nodes invasion, tumor recurrence, and cancer specific death, and sarcomatoid subtype (28, 29). The adverse histopathological features linked to PD-L1 expression has been corroborated in other studies for clear cell and non-clear cell renal carcinoma (30, 31). In another study of 381 patients with renal cell carcinoma who underwent nephrectomy, 120 patients (31.4%) had PD-L1 in the surgical specimen. Compared to patients who were PD-L1 negative, those with positive biomarker had shorter time to recurrence and decreased survival (32). Two meta-analysis also corroborated the poor prognosis conferred by PD-L1 expression in renal cell carcinoma for early disease stage and for patients with distant metastases (10, 33). Conversely, PD-L1 expression is also associated with an excellent response to immunotherapy with CPI (34). Thus, any induced increase in PD-L1 expression in renal cell carcinoma may lead to an improved response to immunotherapy and potentially better survival.

Alteration of renal cancer immune environment with radiotherapy

Radiotherapy produces a significant alteration of the renal TIME which is dose dependent and not fully understood. At high dose level, hypofractionated radiotherapy predominantly produces a pro-immunogenic tumor environment through endothelial cell apoptosis induced by activation of ceramide which in turn initiates the release of mitochondrial cytochrome c (35–37). As renal cell cancer is a hypervascular tumor, this may account for tumor shrinkage following SBRT (38, 39). In addition, there is significant infiltration of CD8+T cells in the tumor microenvironment after an ablative dose of radiation leading to eradication of the primary tumor (40). The role of T cells-induced by radiation is highlighted in a study of early stage renal cancer treated with SBRT to a total dose of 15 Gy followed by nephrectomy four weeks later. A significant infiltration of T cells was observed not only in the surgical specimen but also in the bloodstream of patients receiving preoperative radiotherapy compared to the ones who had surgery alone (41). Increased of T cells in the tumor microenvironment is postulated through the production of interferon gamma (IFNγ) by inflammatory cells (T helper 1, natural killer, and natural killer T cells) following radiation (34). However, increased in IFNγ production may also lead to an increase in PD-L1 expression by the tumor cells which may attenuate the immune response as the cancer cells may escape killing by CD8+T cells (42–44). The dual role of IFNγ may explain the upregulation of PD-L1 expression in many solid tumors following radiotherapy and confers resistance to the immune effect of radiotherapy. The increase in PD-L1 expression may also serve as a strategy for clinicians to combine radiotherapy and CPI to improve survival of patients with renal cancer (45, 46).

Effectiveness of immunotherapy for renal cancer

The role of CPI for resectable renal cancer

Even though surgical resection remains the treatment of choice for early stage renal cancer, up to 30% of the patients may develop loco-regional recurrence and/or distant metastases following the procedure. Many algorithms have been proposed to assess the recurrence risk for those patients based on tumor size, histologic grade, histology subtype such as sarcomatoid histology, and pathological stage (47–49). Thus, an attempt is made to use neoadjuvant immunotherapy to reduce recurrence risks for high risk renal cancer patients. The rationale for neoadjuvant immunotherapy relies on its theoretical ability to improve immune surveillance, thus reducing the risk of micrometastases.

Preliminary experience for neoadjuvant immunotherapy has been promising with minimal serious side-effects during the neoadjuvant phase and acceptable surgical complications (50–55). Three studies investigated the response of non-metastatic renal carcinoma to nivolumab after three to four cycles. There was an intense infiltration of CD8+ T cells in the surgical specimen even although the tumor size remained mostly stable (50–52). Two other studies included patients with metastatic disease who underwent nephrectomy following neoadjuvant immunotherapy with a combination of CPI and other biologic agents (53, 54). Interestingly, 13% of the patients achieved a complete pathologic response in the primary renal cancer (53). However, only one study had PD-L1 investigated in the initial biopsy (7% positivity rate) (54). Thus, the correlation between PD-L1 positivity and response rate to CPI remains to be investigated in future studies. Patients who had a high CD8+T cells in the biopsy specimen may have a better response and improved survival. Those studies are limited by the small number of patients and a short follow-up. However, they illustrated that CPI are well tolerated and do not impair the surgical outcome. Table 1 summarizes relevant studies on the use of neoadjuvant immunotherapy for renal cell cancer.

Among patients at high risk for recurrence after nephrectomy for renal cancer, pembrolizumab given every three weeks up to one year has been reported to improve recurrence rates and disease-free survival (DFS) compared to patients who received placebo (55). Recurrence rates were 22% and 33% for pembrolizumab and placebo, respectively. Corresponding distant metastases rates were 22.7% and 31.2%, respectively. At 30 months follow-up, DFS was 70.6% and 64.8% for pembrolizumab and placebo, respectively. In the third interim analysis, there was also a 38% reduction of death with adjuvant pembrolizumab

TABLE 1 Relevant studies on the use of neoadjuvant immunotherapy for renal cell carcinoma.

Study	Patient No.	Biologic agent	Response rate	Recurrence	Survival	Complications
Gorin et al. (50)	17	Nivo	Stable	11.7%	85.7% (3-year)	11.8% gr.3
Carlo et al. (51)	18	Nivo	15%	18%	NS	11% gr.3
						11% postoperative complications
Singla et al. (52)	15	Nivo	Stable	NS	NS	NS
Panian et al. (53)	52	Various	42%	36.3%	NS	None
Alex et al. (54)	40	Avelumab	30%	32%	NS	20% gr 3
		Axitinib				

Nivo, Nivolumab; Gr, grade; NS, not specified.

compared to placebo at a follow-up of 48 months (56). There was no difference in outcome between patients who were PD-L1 positive or negative. However, there was a surprisingly high proportion of PD-L1 positive patients in both groups, 74% and 77% for pembrolizumab and placebo, respectively, which may have accounted for the benefit of pembrolizumab in the adjuvant setting. The positive outcome of immunotherapy for high risk renal cancer after nephrectomy has not been corroborated in two other trials with atezolizumab and nizolumab combined with ipilimumab (57, 58). In the adjuvant atezolizumab trial, 778 renal cancer patients with high risk of recurrence after surgery was randomized between atezolizumab (n=390) every three weeks for one year or placebo (n=388). T. Median DFS was 57.2 months and 47.9 months for patients receiving atezolizumab and placebo, respectively (57). Thus, atezolizumab did not improve the clinical outcome. However, compared to the study with adjuvant pembrolizumab, the proportion of patients with PD-L1 expression was lower and may have accounted for the survival difference. The proportion with positive PD-L1 was 59% and 61% for the atezolizumab and placebo arms, respectively. In the study comparing the combination of nivolumab and ipilimumab to placebo, 816 patients was randomized to both CPI (n=405) or placebo (n=411) after surgery for renal cell carcinoma with high risk features. There was no difference in DFS between these two groups (58). However, PD-L1 was not investigated as a biomarker, thus, many questions remain unanswered about the efficacy of CPI for patients at high risk for recurrence after nephrectomy for renal cancer. It is clear that the influence of PD-L1 as a biomarker for CPI efficacy should be investigated in future prospective studies of renal cell cancer.

Recently, a novel and potent immune indicator for predicting immunotherapy response and oncology outcomes has been proposed for solid tumors. Immunoscore is based on immunohistochemistry and quantitative measurement of the density of CD3+ and CD8+ cytotoxic T cells in two different locations of the tumor center and the margin of tumor invasion. Intermediate and high immunoscore predict favorable response to immunotherapy and good prognosis (59). Preliminary studies suggest a powerful predicting and prognostic role for this scoring system in renal cell carcinoma (60, 61). Thus, immunoscore could be part of a protocol study on immunotherapy for renal cell cancer.

The role of CPI for advanced or metastatic renal cancer

In contrast to the controversy surrounding immunotherapy for resectable cancer at risk for recurrence after nephrectomy, the combination of CPIs or a CPI with an anti-vascular endothelial growth factor (VEGF) antibody or tyrosine kinase inhibitor (TKI) has become the standard of care for metastatic renal cancer (62).

Nivolumab and ipililumab have been reported to have superior survival and DFS compared to sunitinib for advanced renal carcinoma with a clear cell component (63). The 4-year survival was 53.4% and 43.3% for nivolumab and ipililumab, and sunitinib, respectively. In another study with a similar population of renal cancer patients, avelumab (PD-L1 antibody) and axitinib, an anti-VEGF TKI also demonstrated superior progression-free survival (PFS) compared to sunitinib. The median PFS at 13 months was 13.3 and 8 months for avelumab and axitinib and sunitinib, respectively (64). Corresponding numbers for patients with positive PD-L1 tumors, was 13.8 and 7 months for the combination group, and sunitinib, respectively. Thus, patients who had PD-L1 expression had a better outcome when treated with CPI. Another anti PD-1 agent, pembrolizumab was also effective when combined with axitinib for the treatment of advanced clear cell carcinoma (65, 66). At a median follow-up of 42 months, the survival rate was 57.5% and 48.5%, for the combination arm, and sunitinib, respectively (65). Other studies also demonstrated the superiority of combining immunotherapy and an anti-VEGF agent compared to sunitinib: Nivolumab and cabozantinib, pembrolizumab and lenvatinib (67, 68). However, it is unclear which combination is most effective for those patients even though the highest complete response (CR) rate (16%) has been reported with the lenvatinib combination (68).

Taken together, given the complex immune micro-environment of renal cancer, a combination treatment with immunotherapy and another agent may be more effective than immunotherapy alone to overcome the tumor ability to evade killing by the immune system. Radiotherapy may potentially further improve survival and loco-regional control for those patients due to its synergy with immunotherapy, if excessive irradiation to the normal organs could be avoided.

Efficacy of immunotherapy among older cancer patients with renal cancer

A meta-analysis of studies using immunotherapy alone or combined with other anti-VEGF agents as first-line of treatment demonstrated that older patients with renal cancer defined as 65 years of age or older had improved survival compared to the ones receiving sunitinib (69). Again, the combination of lenvatinib and pembrolizumab seems to be most promising but needs to be confirmed in future prospective studies (69). There was no difference in survival among patients 75 years of age or older compared to other younger age groups who received immunotherapy for metastatic renal cancer (70). However, they may be more prone for dose reduction to minimize treatment toxicity due to their frailty status (70). Thus, older renal cancer patients receiving immunotherapy should be monitored closely by a team familiar with geriatric care. Other studies also corroborated the safety profile of immunotherapy for older patients with other solid tumors such as bladder cancer (71–74).

The role of SBRT in the management of non-metastatic renal cancer

The combination of intensity-modulated radiotherapy with precision image-guidance has brought a new era in the treatment of cancer thought to be radio-resistant such as renal cell cancer and melanoma. Daily imaging before treatment allows delivery of a high dose of radiation to the target while minimizing damage to the OAR, thus improving local control and potential cure for localized disease. Serious side effects and complications are significantly reduced to allow frail patients who are not candidates for surgical resection to have an alternate treatment option with curative intent. As an illustration, older NSCLC patients with early disease stage had an excellent local control and survival following SBRT (7).

Even though other non-surgical treatment modalities for renal cancer are available such as cryotherapy or microwave ablation, they are limited by the size of the tumor, the proximity of the ureters and the large vessels in patients who may also require anticoagulants due to the tumor thrombus (75). Excellent local control may be achieved with large renal cancers (median 4.9 cm) treated with SBRT even though those tumors frequently develop distant metastases after treatment and may be candidates for systemic therapy (76). The tumor shrinks slowly over time after SBRT and the irradiated kidney develops atrophy proportional to the radiation dose (77). However, even though the ipsilateral kidney function deteriorated over time after treatment, the spared contralateral kidney function may improve and allow a better renal function preservation (78). In a prospective pilot study, Kirste et al. (79) applied SBRT using five fractions of 10 Gy or eight fractions of 7.5 Gy for the treatment of seven patients with renal cancer who were affected with the Von Hippel-Lindau disease. The patient tolerated SBRT well and no patient experienced acute or chronic grade 2 or more toxicity. After a median follow-up of 43 months, the 2-year locol control and cancer-specific survival were 100% with long-term renal preservation. As older patients renal function usually decreases over time, SBRT may be the best suited treatment option for those patients with unresectable or medically inoperable cancer (80). In addition, compared to other non-surgical procedures such as radiofrequency ablation (RFA), it is technically much easier to perform SBRT. As an illustration, in a trial which was initially designed to compare the efficacy between SBRT and RFA for small size renal cancer, 24 patients were recruited with the intent to have 12 patients in each arm. However, after randomization, only 7 was assigned to RFA due to the technical difficulty to perform the procedure. Two other patients was reassigned to SBRT, and three refused any procedure. Even though there was an imbalance between the two arms, there was no difference in survival between the two groups which highlights the effectiveness of SBRT for renal cancers (81).

Even though SBRT is a safe procedure with preliminary excellent outcome, many questions remain unanswered as each institution has different protocols for the dose fractionation and techniques of irradiation. In addition, a national survey of stage I renal cell carcinoma treated with different modalities, suggests that SBRT may have an inferior survival outcome compared to partial nephrectomy or thermal ablation (82). However, SBRT was performed in non-academic centers which may have less experience in treating renal carcinoma. Survey of centers with SBRT expertise in treating a large number of renal cancers reported excellent local control and survival.

Siva et al. (83) reported a prospective non-randomized trial of 70 patients from eight institutions with biopsy proven renal carcinoma and a median size of 4.6 cm (range 3.7 to 5.5 cm) treated with SBRT (FASTRACT II trial). The dose ranged from 26 Gy single fraction (<4 cm) or 14 Gy times three (>4 cm). At a median follow-up of 42 months, local control and survival was 100%. Only 10% developed grade 3 complications. Thus, in a well-designed multi-institution study with selected patients and strict protocol enforcement, SBRT is safe and effective. Other studies also corroborated the excellent local control achieved with SBRT for small tumors (4 cm or less) with minimal complications ranging from 0 to 10% depending from the length of follow-up (84–86). For example, in a meta-analysis of 190 patients treated with SBRT for renal carcinoma with either single or multiple fractions from the IROCK (the International Radiosurgery Consortium of the Kidney), local control was 94.5% at 5 years (86). However, similar to reports from surgical studies for non-metastatic renal carcinoma, size of the tumor remains a poor prognostic factor. The maximum size of tumor is a significant predicting factor of death linked to the development of distant metastases (76, 85). Thus, a treatment strategy needs to be developed for those patients to improve their survival. In addition, other poor prognostic factors such as tumor grade and sarcomatoid subtype need to be investigated in future prospective SBRT studies.

Preliminary report suggests that patients with renal cell carcinoma may enjoy a good quality of life (QOL) following SBRT despite the fact that many are old and have co-morbidity factors that preclude them from having surgery. Swaminath et al. (87) reported the QOL of 28 patients who underwent SBRT for renal cell carcinoma with the Functional Assessment of Cancer Therapy-Kidney Symptoms Index-19 (FACT FKSI-19) and the

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-15 Palliative (EORTC-QLQ-C15-PAL). There was little change of QOL over time from the baseline prior to treatment and six months after SBRT. Interestingly, emotional score improves over time likely related to the significant decrease of pain produced by the reduction in size of the tumor mass. As kidney cancer becomes atrophic and shrinks over time, it is anticipated that their QOL may further improve with long-term follow-up (77). However, further studies should be performed to verify this hypothesis.

There is still a debate about the optimum dose selection for the treatment of renal cancer with SBRT. Small tumors (4 cm or less) tend to be treated with a single fraction which may be more convenient for older patients with transportation difficulty. Larger tumors are frequently treated with multiple fractions ranging from three to ten. However, most institutions use a protocol of three to five fractions for patient and staff convenience. Many institutions have performed phase I dose escalation study to assess what is the maximum dose that may be achieved without having excessive toxicity (88, 89). An alternative question would be about the biologic equivalent dose (BED) necessary to control tumors of different sizes. Kurban et al. (90) reported the pathology of 323 nephrectomies for renal mass with tumor size ranging from 4 cm or less (small), 4 to 7 cm (intermediate), and greater than 7 cm (large). Ninety percent of the small tumors were localized to the kidney and were of low histologic grade. Large tumors often invaded adjacent tissues, and presented with aggressive features such as high grade, necrosis, and sarcomatoid changes. Thus, it would be easy to eradicate a small tumor with a single fraction of 26 Gy for example. Hypoxia and necrosis associated with larger tumors often confer radio-resistance and may require a higher BED to overcome their resistance. Even though there is still debate on the value of the α/β value for renal cancer, Tran et al. (91) using an α/β ratio of 3 to review the literature on SBRT for renal cancer suggests that a BED3 of 225 or more which corresponds to 48 to 60 Gy in 3 fractions or 48 Gy in 4 fractions may be associated with a better survival.

Thus, for large tumors either a high BED or combining SBRT with a radiosensitizing agent such as CPI may improve local control and/or survival. The combination of immunotherapy and SBRT may be more attractive due to the potential to eradicate micrometastases and survival. As a local therapy like nephrectomy, SBRT would not impact the development of distant metastases in tumors with high risk features for recurrence.

Safety profile of immunotherapy and hypofractionated radiotherapy for advanced or metastatic renal carcinoma

Due to the synergy between immunotherapy and radiotherapy for renal cancer, and in particular the potential beneficial effect of the radiotherapy-induced abscopal effect, many institutions have conducted trials to assess the feasibility of SBRT or radiosurgery with immunotherapy for metastatic disease (34, 92–98).

Preliminary results are very promising. The combination of hypofractionated radiotherapy and immunotherapy is safe. There is no reported treatment related death (34, 92–97). Grade 3–4 toxicity ranged from 5.6 to 30%. Selected studies suggest a survival advantage combining radiotherapy and immunotherapy versus immunotherapy alone for metastatic renal cancer.

Piening et al. (96) reported the survival outcome of 644 patients with metastatic renal cancer who received hypofractionated radiotherapy combined with CPI (n=63) or CPI alone (n=581). The 2-year survival for patients with brain metastases was significantly improved for the combined therapy, and was 70.8% and 51.4% for the radiotherapy with CPI arm and CPI alone, respectively. Timing of immunotherapy before or after radiotherapy had no impact on survival. Even though that was a retrospective study, the benefit of adding radiotherapy to CPI is also corroborated in other trials (94, 97, 98). For example, Li et al. (98) reported in a randomized study the benefit of adding a split course of radiotherapy to nivolumab (n=22) compared to nivolumab alone (n=22). Even though the patient number is small, median PFS was 28.1 and 21.5 months for the combined modality and nivolumab alone, respectively. Patients with oligometastases seem to benefit the most from the combined treatment.

Siva et al. (97) treated 30 renal cancer patients with one to five metastatic sites with a single course of 20 Gy SBRT or 30 Gy in 10 fractions to all metastatic sites followed by pembrolizumab 200 mg administered every three weeks for eight cycles. At a median follow-up of 28 months, 2 year survival and disease control rate was 74% and 83%, respectively. In another study, Li et al. (98) reported the outcome of 44 patients with renal oligo metastases randomized to immunotherapy alone (n=22) or combined with radiotherapy (n=22) at a dose of 50 Gy in 5 fractions. The objective response rate was 59% and 27% for the combined treatment and immunotherapy alone, respectively. Corresponding numbers for progression-free survival was 28.1 and 21.5 months respectively. There was no difference in adverse events between those two groups. Thus, immunotherapy is safe and may be effective in selected patients when combined with high dose radiation. However, the caveat of those studies is the lack of biomarkers such as PD-L1 to assess response rate and survival. They did highlight the fact that immunotherapy can be safely integrated in a protocol using SBRT for non-metastatic renal carcinoma in patients with high risk features for recurrences.

Evaluation of frailty in older patients with renal cell carcinoma

Before enrolling any older cancer patients (defined as 65 years old or above) in any protocol, frailty needs to be assessed due to its impact on the treatment. Frailty is defined as a state of increased vulnerability resulting from aging associated decline in reserve and function across multiple physiologic systems (99). Even though there are many questionnaires to assess frailty in older patients. the

G-8 questionnaire is simple to administer in a busy clinic, thus practical to implement in clinical trials (100). Those with a score of 15 or above are defined as fit. Those with a score of 14 or less will undergo a complete geriatric assessment with the comprehensive geriatric assessment (CGA) survey (101). Thus, any impact of frailty on patient tolerance to treatment could be recorded and be used to develop future treatment protocols on the combination of immunotherapy and radiotherapy for renal cancers. In addition, to achieve optimal technical outcome in older cancer patients who may have mental issue in collaborating with immobilization protocols such as 3D exhale breath-hold technique, cognitive assessment questionnaire such as Mini-Mental Status Exam (MMSE) or Montreal Cognitive Assessment (MoCA) may be useful to assess their suitability for collaboration (102).

Proposed IGRG algorithm for older patients with non-metastatic renal cancer who are not candidates for surgery or decline surgery

All tumor biopsy specimen should undergo next generation sequencing (NGS) if feasible which includes PD-L1 and other potential biomarkers for immune response. However, if NGS is not feasible, PD-L1 status should be confirmed with immunohistochemistry. All patients should be assessed for frailty prior to their enrollment to investigate its impact on the combined treatment. Patients with small (4 cm or less) cancers of low grade histology and non-aggressive subtypes should undergo SBRT alone to a dose of 26 Gy single fraction as they are likely to have excellent local control and survival. Immunotherapy is unlikely to add any benefit for those patients but could be used for salvage therapy in case of recurrence. Patients with large tumors (more than 4 cm) and/or associated with high risk for recurrences such as high grade histology or aggressive subtypes should be stratified based on their PD-L1 status. Those with PD-L1 with 1% or more should undergo immunotherapy first for four cycles before radiotherapy as they are likely to respond to CPI. They should undergo fractionated SBRT to achieve a BED3 of 225 Gy (91). Immunotherapy should be resumed for four cycles after SBRT unless the patient developed significant toxicity to CPI during the induction phase to achieve a total of eight cycles (97).

Those with PD-L1 less than 1% should receive SBRT first with the same fractionation and BED to induce upregulation of PD-L1 followed by eight cycles of immunotherapy unless they develop undue toxicity to CPI. We postulate that the combination of immunotherapy and SBRT may improve survival for those patients as it may decrease the risk of micrometastases and improve local control in large tumors which are often necrotic and hypoxic.

The conclusions based on prospectively collected data may improve the design of future clinical trials targeting older patients treated with immunotherapy and SBRT for renal cancer. Figure 1 summarizes the proposed algorithm.

With a network of 1282 cancer institutions across the world and a large number of patients from all ethnicities, the IGRG is committed to conduct those studies when funding becomes available (103, 104).

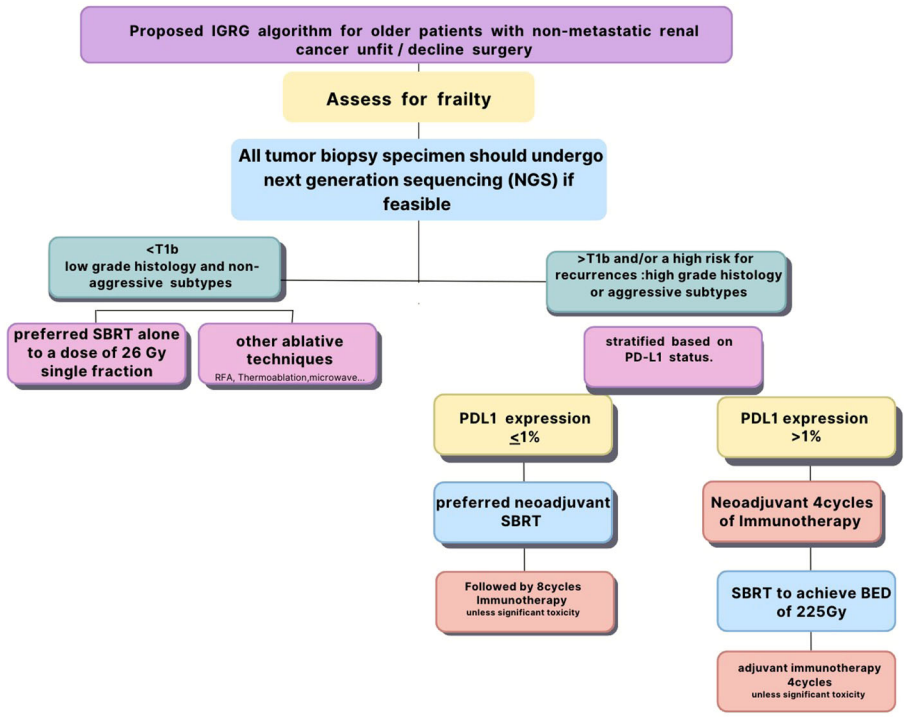


FIGURE 1
International Geriatric Radiotherapy protocol for non-metastatic renal cancer.

Conclusion

The combination of SBRT and immunotherapy may be beneficial for older patients with non-metastatic renal cancer who are not candidates for surgical resection or decline nephrectomy. Prospective studies should be conducted to verify this hypothesis.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

NN: Writing – original draft, Writing – review & editing. M-EC: Writing – original draft, Writing – review & editing. BP: Writing – original draft, Writing – review & editing. VV-H: Writing – original draft, Writing – review & editing. OG: Writing – original draft, Writing – review & editing. MM: Writing – original draft, Writing – review & editing. HG: Writing – original draft, Writing – review & editing. MA: Writing – original draft, Writing – review & editing. MB: Writing – original draft, Writing – review & editing. PL: Writing – original draft, Writing – review & editing. LK: Writing – original draft, Writing – review & editing. FD: Writing – original draft, Writing – review & editing. DL: Writing – original draft, Writing – review & editing. LM: Writing – original draft, Writing – review & editing. GT: Writing – original draft, Writing – review & editing. ZD: Writing – original draft, Writing – review & editing. GL: Writing – original draft, Writing – review & editing. SCB: Writing – original draft, Writing – review & editing. SRB: Writing – original draft, Writing – review & editing. EN: Writing – original draft, Writing – review & editing. EL: Writing – original draft, Writing – review & editing. AAM: Writing – original draft, Writing – review & editing. AGM: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

The authors would like to thank Donna M Alexander for her help in the writing of this manuscript.

Conflict of interest

Author ME-C was employed by company MVision AI.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Lane BR, Abouassaly R, Gao T, Weight CJ, Hernandez AV, Larson BT, et al. Active treatment of localized renal tumors may not impact survival in patients aged 75 or older. *Cancer*. (2010) 116:3119–26. doi: 10.1002/cncr.25184

2. Chung JS, Son NH, Lee SE, Hong SK, Lee SC, Kwak C, et al. Overall survival and renal function after partial and radical nephrectomy among older patients with localized renal cancer: A propensity-matched multicenter study. *Eur J Cancer*. (2015) 51:489–497. doi: 10.1016/j.ejca.2014.12.012

3. Campi R, Berni A, Amparore D, Bertolo R, Capitanio U, Carbonara U, et al. Impact of frailty on perioperative and oncologic outcomes in patients undergoing surgery or ablation for renal cancer. *Minerva Urol Nephrol*. (2022) 74:146–60. doi: 10.23736/S2724-6051.21.04583-3

4. Rosielo G, Re C, Larcher A, Fallara G, Sorce G, Baiamonte G, et al. The effect of frailty on post-operative outcomes and health care expenditures in patients treated with partial nephrectomy. *Eur J Surg Oncol*. (2022) 48:1840–7. doi: 10.1016/j.ejso.2022.01.001

5. Parker D, Kutirov A, Uzzo RG, Smaldone MC. Understanding chronic kidney disease of surgical versus medical origin: The missing link to the partial versus radical nephrectomy debate? *Eur Urol*. (2015) 68:1004–6. doi: 10.1016/j.eururo.2015.06.001

6. Spyropoulou D, Tsiganos P, Dimitrakopoulos F, Tolia M, Koutras A, Velissaris D, et al. Radiotherapy and renal cell carcinoma: A continuing saga. *In Vivo*. (2021) 35:1365–77. doi: 10.21873/invivo.12389

7. Nguyen NP, Godinez J, Wei S, Vinh-Hung V, Gorobets H, Thariat J, et al. Is surgery indicated for elderly patients with early stage nonsmall cell lung cancer, in the era of stereotactic body radiotherapy. *Medicine*. (2016) 95:e5212. doi: 10.1097/MD.0000000000005212

8. Funayama S, Onishi H, Kuriyama K, Komiyama T, Marino K, Araya M, et al. Renal cancer is not radioresistant: Slowly but continuing shrinkage of the tumor after stereotactic body radiotherapy. *Tech Cancer Res Treat*. (2018) 18:1–8. doi: 10.1177/1533033818822329

9. Siva S, Bressel M, Sidhom M, Sridharan S, Vanneste B, Davey R, et al. TROG 15.03/ANZUP international multicenter phase II trial of focal ablative stereotactic radiotherapy for cancers of the kidney (FASTRACT II). *Int J Radiother Oncol Biol Phys*. (2023) 117:5. doi: 10.1016/j.ijrobp.2023.06.208

10. Wang Z, Peng S, Xie H, Guo L, Cai Q, Shang Z, et al. Prognostic and clinicopathological significance of PD-L1 in patients with renal cell carcinoma: A meta-analysis based on 1863 individuals. *Clin Exp Med*. (2018) 18:165–75. doi: 10.1007/s10238-018-0488-3

11. Roviello G, Corona SP, Nesi G, Mini E. Results from a meta-analysis of immune check point inhibitors in first-line renal cancer patients: does PD-L1 matter? *Ther Adv Med Oncol*. (2019) 11:1–8. doi: 10.1177/1758835919861905

12. Buttigliero C, Allis S, Tucci M, Zichi C, Leone G, Di Stephano RF, et al. Role of radiotherapy in improving activity of immune-modulating drugs in advanced renal

cancer: Biologic rationale and clinical evidences. *Cancer Treat Rev*. (2018) 69:215–23. doi: 10.1016/j.ctrv.2018.07.010

13. Nguyen NP, Baumert BG, Oboite E, Motta M, Appalanaido GK, Arenas M, et al. Immunotherapy and radiotherapy for older cáncer patients: proposed paradigm by the International Geriatric Radiotherapy Group. *Gerontology*. (2021) 67:379–85. doi: 10.1159/000514451

14. Monjaras-Avila CU, Lorenzo-Leal AC, Luque-Badillo AC, D'Costa N, Chavez-Munoz C, Bach H. The tumor microenvironment in clear cell renal cacinoma. *Int J Mol Sci*. (2023) 24:7946. doi: 10.3390/ijms24097946

15. Kammerer-Jacquet S, Deleuze A, Saout J, Mathieu R, Laguerre B, Verhoest G, et al. Targeting the PD-1/PD-L1 pathway in renal cell carcinoma. *Int J Mol Sci*. (2019) 20:1692. doi: 10.3390/ijms20071692

16. Lin E, Liu X, Liu Y, Zhang Z, Xie L, Tian K, et al. Roles of the dynamic tumor immune microenvironment in the individualized treatment of advanced clear cell carcinoma. *Front Immunol*. (2021) 12:6533358. doi: 10.3389/fimmu.2021.653358

17. Shapiro DD, Dolan B, Laklouk IA, Rassi S, Lozar T, Emamekhoo H, et al. Understanding the tumor microenvironment in renal cell carcinoma. *Cancers*. (2023) 15:2500. doi: 10.3390/cancers15092500

18. Kato R, Obara W. Anti-PD-1/PD-L1 therapy for renal cell carcinoma: challenge in the development of predictive biomarkers. *Exp Rev Cancer Ther*. (2022) 22:667–9. doi: 10.1080/14737140.2022.2087631

19. Kim Y, Yang H, Lee WK, Cheon J, Sang YB, Kang B, et al. High levels of baseline serum IL-10 are associated with reduced benefit from first-line immune checkpoint inhibitor therapy in advanced renal cell carcinoma. *J Cancer*. (2023) 14:935–42. doi: 10.7150/jca.81384

20. Menetrier-Caux C, Bain C, Favrot MC, Duc A, Blay JY. Renal cell carcinoma induces interleukin 10 and prostagnadin E2 production by monocytes. *Br J Cancer*. (1999) 79:119–30. doi: 10.1038/sj.bjc.6690021

21. Bao J, Dang Q, Lin C, Lo U, Feldkoren B, Dang A, et al. SPARC is a key mediator of TGR-beta-induced renal cáncer metastasis. *J Cell Phys*. (2021) 236:1926–38. doi: 10.1002/jcp.29975

22. Bostrom A, Lindgren D, Johannson ME, Axelson H. Effects of TGF-beta signaling in clear cell renal cell carcinoma cells. *Biochem Biophys Res Comm*. (2013) 435:126–133. doi: 10.1016/j.bbrc.2013.04.054

23. Griffiths RW, Elkord E, Gilham DE, Ramani V, Clarke N, Stern PL, et al. Frequency of regulatory T cells in renal cell carcinoma patients and investigation and correlation with survival. *Cancer Immunol Immunother*. (2007) 56:1743–53. doi: 10.1007/s00262-007-0318-z

24. Ning H, Shao Q, Ding K, Gao D, Lu Q, Cao Q, et al. Tumor-infiltrating regulatory T cells are positively correlated with angiogenic status in renal cell carcinoma. *Chin Med J*. (2012) 125:2120–5. doi: 10.3760/cma.j.issn.0366-6999.2012.12.008

25. Zhu G, Pei L, Yin H, Lin F, Li X, Zhu X, et al. Profiles of tumor- infiltrating tumor cells in renal cell carcinoma and their clinical implications. *Oncol Lett*. (2019) 18:5235–42. doi: 10.3892/ol

26. Liu T, Liang W, Chen Z, Wang G, Cao R, Zhou F, et al. Hypoxia-induced PLOD2 promotes clear cell renal cell carcinoma progression via modulating EGFR-dependent AKT pathway activation. *Cell Death Dis*. (2023) 14:774. doi: 10.1038/s41419-023-06298-7

27. Zhang Z, Li Q, Wang F, Ma B, Meng Y, Zhang Q. Identifying hypoxia characteristics to stratify prognosis and assess the tumor microenvironment in renal cell carcinoma. *Front Genet*. (2021) 12:606816. doi: 10.3389/fgene.2021.606816

28. Carlsson J, Sundvist P, Kosuta V, Falt A, Giunchi F, Florentino M, et al. PD- L1 expression is associated with poor prognosis in renal cell carcinoma. *App Immunohistochem Mol Morphol*. (2020) 28:213–20. doi: 10.1097/PAI.0000000000000766

29. Ueda K, Suekane S, Kurose H, Chikui K, Nakiri M, Nishihara K, et al. Prognostic value of PD-1 and PD-L1 expression in patients with metastatic clear cell renal carcinoma. *Urologic Oncol*. (2018) 499:e9–e16. doi: 10.1016/j.urolonc.2018.07.003

30. Choueri TK, Fay AP, Gray KP, Caella M, Ho TH, Albiges L, et al. PD-L1 expression in non-clear renal cell carcinoma. *Ann Oncol*. (2014) 25:2178–84. doi: 10.1093/annonc/mdu445

31. Leite KRM, Reis ST, Junior JP, Zerati M, de Oliveira Gomes D, Camara-Lopes LH, et al. PD-L1 expression in renal cell carcinoma clear cell type is related to unfavorable prognosis. *Diagn Pathol*. (2015) 10:189. doi: 10.1186/s13000-015-0414-x

32. Tamada S, Nozawa M, Ohba K, Mizuno R, Takamoto A, Ohe C, et al. Prognostic value of PD-L1 expression in recurrent renal cell carcinoma after nephrectomy: a secondary analysis of the ARCHERY study. *Int J Clin Oncol*. (2023) 28:289–98. doi: 10.1007/s10147-022-02256-z

33. Iacovelli R, Nole F, Verri E, Renne G, Paglino C, Santoni M, et al. Prognostic role of PD-L1 expression in renal cell carcinoma. A systemic review and meta-analysis. *Target Oncol*. (2016) 11:143–8. doi: 10.1007/s11523-015-0392-7

34. de Wolf K, Vermaelen K, de Meerleer G, Lambrecht BN, Ost P. The potential of radiotherapy to enhance the efficacy of renal cell carcinoma therapy. *Oncoinmmunology*. (2015) 4:e1042198. doi: 10.1080/2162402X.2015.1042198

35. Kolesnik R, Fuks Z. Radiation and ceramide-induced apoptosis. *Oncogene*. (2003) 22:5897–906. doi: 10.1038/sj.onc.1206702

36. Zhu H, Deng K, Zhao Y, Wang X, Shen Y, Liu T, et al. The effect of ASMase mediated endothelial cell apoptosis in multiple hypofractionated irradiation in CT26 bearing mice. *Asian Pac J Cancer Prev*. (2015) 16:4543–8. doi: 10.7314/APJCP.2015.16.11.4543

37. Dubois N, Rio E, Ripoche N, Ferchaud-Roucher V, Gaugler M, Campion L, et al. Plasma ceramide, a real time predictive marker of pulmonary and hepatic metastases response to stereotactic body radiation therapy combined with irinotecan. *Radiother Oncol*. (2016) 119:229–35. doi: 10.1016/j.radonc.2016.03.014

38. Takahashi A, Sasaki H, Kim SJ, Tobisu K, Kakizoe T, Tsukamoto T, et al. Markedly increased amount of messenger RNAs for vascular endothelial growth factor and placenta growth factor in renal cell carcinoma associated with angiogénesis. *Cancer Res*. (1994) 54:4233–7.

39. Funayama S, Onishi H, Kuriyama K, Komiyama T, Marino K, Araya M, et al. Renal cancer is not radioresistant: slowly but continuing shrinkage of the tumor after stereotactic body radiotherapy. *Technol Cancer Res Treat*. (2019) 18:1–8. doi: 10.1177/1533033818822329

40. Lee Y, Auh SL, Wang Y, Burnette B, Wang Y, Meng Y, et al. Therapeutic effect of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. *Blood*. (2009) 114:589–95. doi: 10.1182/blood-2009-02-206870

41. Chow J, Hoffend NC, Abrams SI, Schwaab T, Singh K, Muhitch JB. Radiation induces dynamic change to the T cell repertoire in renal cell carcinoma patients. *Blood*. (2009) 114:589–95. doi: 10.1073/pnas.2001933117

42. Chen J, Cao Y, Markelc B, Kaeppler J, Vermeer JAF, Muschel RJ. Type I IFN protects cáncer cells from CD8+T cells mediated cytotoxicity after radiation. *J Clin Invest*. (2019) 129:4224–38. doi: 10.1172/JCI127458

43. Mandai M, Hamanishi J, Abiko K, Marsumura N, Baba T, Konishi A. Dual face of IFNgamma in cáncer progression: A role of PD-L1 induction in the determination of pro- and antitumor activity. *Clin Cancer Res*. (2016) 22:2229–334. doi: 10.1158/1078-0432.CCR-16-0224

44. Imai Y, Chiba T, Kondo T, Kanzaki H, Kanayama K, Ao J, et al. Interferon-gamma induced PD-L1 expression and soluble PD-L1 expression in gastric cancer. *Oncol Lett*. (2020) 20:2161–8. doi: 10.3892/ol

45. Wang N, Lei Z, Yang H, Tang Z, Yang M, Wang Y, et al. Radiation- induced PD-L1 expression in tumor and its microenvironment faciltates cancer-Immune escape: A narrative review. *Ann Transl Med*. (2022) 10:1406. doi: 10.21037/atm

46. Stenzel PJ, Schindeldecker M, Tagscherer KE, Foersch S, Herpel E, Hohenfellner M, et al. Prognostic and predictive value of tumor-infiltrating leucocytes and of immunomolecules PD1 and PDL1 in clear cell renal carcinoma. *Trans Oncol*. (2020) 13:336–45. doi: 10.1016/j.tranon.2019.11.002

47. Kattan MW, Reuter V, Motzer RJ, Katz J, Russo P. A postoperative prognosis for renal cancer. *J Urol*. (2001) 166:63–7. doi: 10.1016/S0022-5347(05)66077-6

48. Jamil ML, Keeley J, Sood A, Dalela D, Arora S, Peabody O, et al. Long-term risk of recurrence in surgically treated renal cell carcinoma: a posthoc analysis of the Eastern Cooperative Oncology Group. *Eur Urol*. (2020) 77:277–81. doi: 10.1016/j.eururo.2019.10.028

49. Usher-Smith JA, Li L, Roberts L, Harrison H, Rossi SH, Sharp SJ, et al. Risk models for recurrence and survival after kidney cancer: a systemic review. *BJU Int*. (2022) 130:562–79. doi: 10.1111/bju.15673

50. Gorin AM, Patel HD, Rowe SP, Hahn NM, Hammers HJ, Pons A, et al. Neoadjuvant nivolumab in patients with high risk nonmetastatic renal carcinoma. *Eur Urol Oncol*. (2022) 5:113–7. doi: 10.1016/j.euo.2021.04.002

51. Carlo MI, Attalla K, Mazaheri Y, Gupta S, Yildirim O, Murray SJ, et al. Phase II study of nivolumab in patients with locally asvanced renal cancer undergoing nephrectomy. *Eur Urol*. (2022) 81:570–3. doi: 10.1016/j.eururo.2022.01.043

52. Singla N, Nirschl TR, Obradovic A, Shenderov E, Lombardo K, Liu X, et al. Immunomodulary response to neoadjuvant nivolumab in non-metastatic renal cell carcinoma. *Scient Rep*. (2024) 14:1458. doi: 10.1038/s41598-024-51889-9

53. Panian J, Saidian A, Hakimi K, Ajmera A, Anderson WJ, Barata P, et al. Pathological outcomes of patients with advanced renal carcinoma who receive nephrectomy following immunotherapy. *Oncologist*. (2023). doi: 10.1093/oncolo/oyad166

54. Bex A, Abu-Ghanem Y, Van Thienen JV, Grafland N, Lagerveld B, Zondervan P, et al. Efficacy, safety, and biomarker analysis of neoadjuvant avelumab/axitinib in patients with localized renal cell carcinoma who are high risk of relapse after nephrectomy. *J Clin Oncol*. (2022) 40:6. doi: 10.1200/JCO.2022.40.6_suppl.289

55. Powles T, Tomczak P, Park SH, Venugopal B, Ferguson T, Syomenides SN, et al. Pembrolizumab versus placebo as postnephrectomy adjuvant therapy for clear cell renal carcinoma: 30-month follow-up of a multicentre, randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet*. (2022) 23:1133–44. doi: 10.1016/S1470-2045(22)00487-9

56. Choueiri TK, Tomczak P, Park SH. Overall survival results from the phase 3 KEYNOTE-564 study of adjuvant pembrolizumab versus placebo for the treatment of clear cell renal carcinoma (ccRCC). *J Clin Oncol*. (2024) 42:LBA359. doi: 10.1200/JCO.2024.42.4_suppl.LBA359

57. Pal SK, Uzzo R, Karam JA, Master JA, Donskow F, Suarez C, et al. Adjuvant atezolizumab versus placebo for renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase III trial. *Lancet*. (2022) 400:1103–16. doi: 10.1016/S0140-6736(22)01658-0

58. Motzer RJ, Russo P, Grunwald V, Tomita Y, Zurawski B, Parikh O, et al. Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase III trial. *Lancet*. (2023) 401:821–32. doi: 10.1016/S0140-6736(22)02574-0

59. Marliot F, Lafontaine L, Galon J. Immunoscore assay for the immune classification of solid tumors: Technical aspects, improvements and clinical perspectives. *Methods Enzymol*. (2020) 636:109–28. doi: 10.1016/bs.mie.2019.07.018

60. Guo C, Zhao H, Wang Y, Bai S, Yang Z, Wei F, et al. Prognostic value of the neo-immunoscore in renal cell carcinoma. *Front Oncol*. (2019) 9:439. doi: 10.3389/fonc.2019.00439

61. Selvi I, Demirci U, Bozdogan N, Basar H. The prognostic effect of immunoscore in patients with clear cell renal carcinoma: preliminary results. *Int Urol Nephrol*. (2020) 52:21–34. doi: 10.1007/s11255-019-02285-0

62. Kathuria-Prakash N, Drolen C, Hannigan CA, Drakari A. Immunotherapy and metastatic renal cell carcinoma: A review of new treatment approaches. *Life*. (2022) 12:24. doi: 10.3390/life12010024

63. Albiges L, Tannir NM, Burotto M, McDermott D, Plimack ER, Barthelemy P, et al. Nivolimab plus ipililumab versus sunitinib for first-line treatment of advanced renal carcinoma: extended 4-year follow-up of the phase III CheckMate 214 Trial. *ESMO Open*. (2020) 5:e001079. doi: 10.1136/esmoopen-2020-001079

64. Choueiri TK, Motzer RJ, Rini BI, Haanen J, Campbell MT, Venugopal B, et al. Updated efficacy results from the JAVELIN Renal 101 trial: fist-line avelumab plus axitinib versus sunitinib in patients with advanced renal cáncer. *Ann Oncol*. (2020) 31:1030–9. doi: 10.1016/j.annonc.2020.04.010

65. Rini BI, Plimack ER, Stus V, Waddell T, Gafanov R, Pouliot F, et al. Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for advanced clear cell renal carcinoma: Results from 42-month follow-up of KEYNOTE-426. *J Clin Oncol*. (2021) 39:15. doi: 10.1200/JCO.2021.39.15_suppl.4500

66. Powles T, Plimack ER, Soulieres D, Waddell T, Stus V, Gafanov R, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol*. (2020) 21:1563–73. doi: 10.1016/S1470-2045(20)30436-8

67. Choueiri TK, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Eng J Med*. (2021) 384:829–41. doi: 10.1056/NEJMoa2026982

68. Motzer R, Alekseev B, Rha S, Porta C, Eto M, Powles T, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Eng J Med*. (2021) 384:1289–300. doi: 10.1056/NEJMoa2035716

69. Fujiwara Y, Miyashita H, Liaw BC. First-line therapy for elderly patients with advanced renal cell carcinoma in the immunology oncology era: a network meta-analysis. *Cancer Immnunol Immunother*. (2023) 72:1355–64. doi: 10.1007/s00262-022-03341-y

70. Hermansen CK, Donskov F. Outcomes based on age in patients with metastatic renal cell carcinoma treated with first-line targeted therapy or checkpoint immunotherapy: Older patients more prone to toxicity. *J Geriatr Oncol*. (2021) 12:827–33. doi: 10.1016/j.jgo.2020.12.008

71. Nishiyama N, Kobayashi T, Narita S, Hikada Y, Ito K, Maruyama S, et al. Efficacy and safety of pembrolizumab for older patients with chemoresistant urothelial carcinoma assessed using propensity score matching. *J Geriat Oncol*. (2022) 13:88–93. doi: 10.1016/j.jgo.2021.07.002

72. Schulz B, Rodler S, Szabados B, Graser A, Buchner A, Stief C, et al. Safety, efficacy, and prognostic impact of checkpoint inhibitors in older patients with genitourinary cáncer. *J Geriat Oncol*. (2020) 11:1061–6. doi: 10.1016/j.jgo.2020.06.012

73. Herin H, Aspeslagh S, Castanon E, Dyevre V, Marabelle A, Varga A, et al. Immunotherapy phase I trials in patients older than 70 years with advanced solid tumors. *Eur J Cancer*. (2018) 95:68–74. doi: 10.1016/j.ejca.2018.03.002

74. Gomes F, Lorigan P, Woolley S, Foden P, Burns K, Yorke J, et al. A propective study of the safety of checkpoint inhibitors in older cáncer patients-the ELDERS study. *Esmo Open*. (2021) 6:1–6. doi: 10.1016/j.esmoop.2020.100042

75. De la Pinta C, Latorre RG, Fuentes R. SBRT in localized renal carcinoma: a review of the literatura. *Anticancer Res*. (2022) 42:667–74. doi: 10.21873/anticanres.15525

76. Siva S, Staeler M, Correa RJM, Warner A, Ellis RJ, Gandhisavan S, et al. Stereotactic body radiotherapy for large primary renal cell carcinoma: A report from the International Radiosurgery Consortium. *Int J Radiat Oncol Biol Phys*. (2019) 105:2592. doi: 10.1016/j.ijrobp.2020.06.014

77. Yamamoto T, Kadoya N, Takeda K, Matsushita H, Umezawa R, Sato K, et al. Renal atrophy after stereotactic body radiotherapy for renal cell carcinoma. *Radiat Oncol*. (2016) 11:72. doi: 10.1186/s13014-016-0651-5

78. Glicksman RM, Cheung P, Korol R, Niglas M, Nusrat H, Erler D, et al. Stereotactic body radiotherapy for renal cell carcinoma: Oncological and renal functional outcome. *Clin Oncol*. (2023) 35:20–8. doi: 10.1016/j.clon.2022.06.007

79. Kirste S, Ruhle A, Zschiedrich S, Schultze-Seeman W, Jilg CA, Neumann-Haefelin E, et al. Stereotactic body radiotherapy for renal cell carcinoma in patients with Von Hippel-Lindau disease-Results of a prospective trial. *Cancers*. (2022) 14:5069. doi: 10.3390/cancers14205069

80. Denic A, Glassock RJ, Rule AD. The kidney in normal aging. A comparison with chronic kidney disease. *CJASN*. (2022) 17:137–9. doi: 10.2215/CJN.10580821

81. Swaminath A, Cassim R, Millan B, Mironov O, Ahir P, Tajzler C, et al. Final results from a prospective randomized trial of stereotactic body radiotherapy vs radiofrequency ablation for the management of small renal masses. *Int J Radiat Oncol Biol Phys*. (2023) 117:S82. doi: 10.1016/j.ijrobp.2023.06.402

82. Uhlig A, Uhlig J, Trojan L, Kim HS. Stereotactactic body radiotherapy for stage I renal cell carcinoma: National treatment trends and outcomes compared to partial nephrectomy and thermal ablation. *J Vasc Interv Radiol*. (2020) 31:564–71. doi: 10.1016/j.jvir.2019.11.009

83. Siva S, Bressel M, Sidhom M, Sridhahan S, Vanneste B, Davey R, et al. TROG 15.03/ANZUP international multicenter phase II trial of focal ablative stereotactic radiotherapy for cancers of the kidney. *Int J Radiat Oncol Biol Phys*. (2023) 117:5. doi: 10.1016/j.ijrobp.2023.06.208

84. Hannan R, McLaughlin MF, Pop LM, Pedrosa I, Kapur P, Garant A, et al. Phase 2 trial of stereotactic ablative radiotherapy for patients with primary renal cancer. *Eur Urol*. (2023) 84:275–86. doi: 10.1016/j.eururo.2023.02.016

85. Siva S, Louie AV, Warner A, Muacevic A, Gandhihasan S, Ponsky L, et al. Pooled analysis of stereotactic ablative radiotherapy for primary renal carcinoma: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). *Cancer*. (2018) 124:934–42. doi: 10.1002/cncr.31156

86. Siva S, Ali M, Correa RJM, Muacevic A, Ponsky L, Ellis RJ, et al. 5-year outcomes after stereotactic ablative body radiotherapy for primary renal cell carcinoma: an individual patient data meta-analysis from IROCK. *Lancet Oncol*. (2022) 23:1508–16. doi: 10.1016/S1470-2045(22)00656-8

87. Swaminath A, Cheung P, Glicksman RM, Donovan EK, Niglas M, Vesprini D, et al. Patient- reported quality of life following stereotactic body radiotherapy for primary kidney cancer-Results from a prospective cohort study. *Clin Oncol*. (2021) 33:468–75. doi: 10.1016/j.clon.2021.03.002

88. Grubb W, Ponsky L, Lo SS, Traughber BJ, Zhang Y, Liu Y, et al. Dose escalation to 60 Gy in 3 fractions with stereotactic body radiation therapy (SBRT) for poor surgical candidates with localized renal carcinoma: Expansion of a phase I study. *Int J Radiat Oncol Biol Phys*. (2018) 102:E91. doi: 10.1016/j.ijrobp.2018.07.360

89. Lapierre A, Badet L, Rouviere O, Crehange G, Berthiller J, Paparel P, et al. Safety and efficacy of stereotactic ablative radiation therapy for renal cancer: 24- months results of the RSR1 phase 1 dose escalation. *Pract Radiat Oncol*. (2023) 13:e73–79. doi: 10.1016/j.prro.2022.06.012

90. Kurban LAS, Vosough A, Jacob P, Prasad D, Lam T, Scott N, et al. Pathological nature of renal tumors-does size matter? *Urol Ann*. (2017) 9:330–4. doi: 10.4103/UA.UA_17_17

91. Tran KT, Chevli NC, Messer JA, Haque W, Farach AM, Satkunasivam R, et al. Prognostic impact of biologically equivalent dose in stereotactic body radiotherapy for renal cancer. *Clin Translat Oncol*. (2023) 39:10592. doi: 10.1016/j.ctro.2023.100592

92. Masini C, Iotti C, De Georgi U, Bellia RS, Buti S, Salaroli F, et al. Nivolumab in combination with stereotactic body radiotherapy in pretreated patients with metastatic renal cell carcinoma. Results of the phase II Nives study. *Eur Urol*. (2022) 81:274–82. doi: 10.1016/j.eururo.2021.09.016

93. Kroeze SGC, Fritz C, Schaule J, Siva S, Kahl KH, Sundahl N, et al. Stereotactic radiotherapy combined with immunotherapy or targeted therapy for metastatic renal carcinoma. *BJU Int*. (2021) 127:703–11. doi: 10.1111/bju.15284

94. Yomo S, Oda K, Oguchi K. Effectiveness of immune checkpoint inhibitors in combination with stereotactic radiosurgery with brain metastases from renal cell carcinoma: inverse probability of treatment weighing using propensity scores. *J Neurosurg*. (2023) 138:1591–9. doi: 10.3171/2022.9.JNS221215

95. Lin J, Song AJ, Hoffman-Censits J, Leiby BE, Tuluc M, Shaw C, et al. A pilot study of radiation therapy in combination with pembrolizumab in patients with metastatic renal cell cancer. *Am J Clin Oncol*. (2020) 43:82–6. doi: 10.1097/COC.0000000000000636

96. Piening A, Al-Hammadi N, Dombrowski J, Hamilton Z, Teague RM, Swaminath A, et al. Survival in metastatic renal cell carcinoma treated with immunotherapy alone: A national cancer database analysis. *Adv Radiat Oncol*. (2023) 8:101238. doi: 10.1016/j.adro.2023.101238

97. Siva S, Bressel M, Wood ST, Shaw MG, Loi S, Sandhu SK, et al. Stereotactic radiotherapy and short-course pembrolizumab for oligometastatic renal cell carcinoma-The PAPPORT trial. *Eur Urol*. (2022) 81:364–72. doi: 10.1016/j.eururo.2021.12.006

98. Li W, Cao Z, Chang P, Zhang B, Li F, Chang D. Clinical efficacy of PD-1 inhibitor plus split-course radiotherapy in the first-line treatment of advanced kidney cancer: A randomized control trial. *J Oncol*. (2022) 8100323:1–6. doi: 10.1155/2022/8100323

99. Xue Q. The frailty syndrome: Definition and natural history. *Clin Geriatr Med*. (2011) 27:1–15. doi: 10.1016/j.cger.2010.08.009

100. Takahashi M, Takahashi M, Komine K, Yamada H, Kasahara Y, Chikamatsu S, et al. The G8 screening tool enhances prognostic value to ECOG performance status in elderly cancer patients: a retrospective, single institution study. *PloS One*. (2017) 12:e0179694. doi: 10.1371/journal.pone.0179694

101. Bellera CA, Rainfray M, Mathoulin-Pelissier S, Mertens C, Delva F, Fonck A, et al. Screening older cancer patients: first evaluation of the G8 screening tool. *Ann Oncol*. (2012) 23:2166–72. doi: 10.1093/annonc/mdr587

102. Ranjit E, Sapra A, Bhandari P, Albers CE, Ajmeri MS. Cognitive assessment of geriatric patients in primary care settings. *Cureus*. (2020) 12:e1044. doi: 10.7759/cureus.10443

103. Popescu T, Karlsson U, Vinh-Hung V, Trigo L, Thariat J, Vuong T, et al. Challenges facing radiation oncologists in the management of older cancer patients: Consensus of the International Geriatric Radiotherapy Group. *Cancers*. (2019) 11:271. doi: 10.3390/cancers11030371

104. Nguyen NP, Vinh-Hung V, Baumert B, Zamagni A, Arenas M, Motta M, et al. Older cancer patients during the COVID-19 epidemic: practice proposal of the International Geriatric Radiotherapy Group. *Cancers*. (2020) 12:1287. doi: 10.3390/cancers12051287

frontiers | Frontiers in Oncology

TYPE Perspective
PUBLISHED 04 July 2024
DOI 10.3389/fonc.2024.1371752

OPEN ACCESS

EDITED BY
Zhiwei Hu,
The Ohio State University, United States

REVIEWED BY
Patrizia Giannatempo,
Fondazione Istituto Nazionale dei Tumori, Italy

*CORRESPONDENCE
Nam Phong Nguyen
namphong.nguyen@yahoo.com

RECEIVED 16 January 2024
ACCEPTED 03 June 2024
PUBLISHED 04 July 2024

CITATION
Nguyen NP, Karlsson UL, Page BR, Chirila M-E, Vinh-Hung V, Gorobets O, Arenas M, Mohammadianpanah M, Javadinia SA, Giap H, Kim L, Dutheil F, Murthy V, Mallum AA, Tlili G, Dahbi Z, Loganadane G, Blanco SC, Bose S, Natoli E, Li E and Morganti AG (2024) Immunotherapy and radiotherapy for older patients with invasive bladder cancer unfit for surgery or chemotherapy: practical proposal by the international geriatric radiotherapy group. *Front. Oncol.* 14:1371752. doi: 10.3389/fonc.2024.1371752

Immunotherapy and radiotherapy for older patients with invasive bladder cancer unfit for surgery or chemotherapy: practical proposal by the international geriatric radiotherapy group

Nam Phong Nguyen[1*], Ulf Lennart Karlsson[2], Brandi R. Page[3], Monica-Emilia Chirila[4,5], Vincent Vinh-Hung[6], Olena Gorobets[7], Meritxell Arenas[8], Mohammad Mohammadianpanah[9], Seyed Alireza Javadinia[10], Huan Giap[11], Lyndon Kim[12], Fabien Dutheil[13], Vedang Murthy[14], Abba Aji Mallum[15], Ghassen Tlili[16], Zineb Dahbi[17], Gokoulakrichenane Loganadane[18], Sergio Calleja Blanco[19], Satya Bose[1], Elena Natoli[20,21], Eric Li[22] and Alessio G. Morganti[20,21]

[1]Department of Radiation Oncology, Howard University, Washington, DC, United States, [2]Department of Radiation Oncology, International Geriatric Radiotherapy Group, Washington, DC, United States, [3]Department of Radiation Oncology, Johns Hopkins University, Baltimore, MD, United States, [4]Department of Clinical Development, MVision AI, Helsinki, Finland, [5]Department of Radiation Oncology, Amethyst Radiotherapy Centre, Cluj-Napoca, Romania, [6]Department of Radiation Oncology, Centre Hospitalier Public du Contentin, Cherbour-en-Contentin, France, [7]Department of Oral Surgery, University Hospital of Martinique, Fort-de-France, France, [8]Department of Radiation Oncology, Sant Joan de Reus University Hospital, University of Rovira, I Virgili, Tarragona, Spain, [9]Colorectal Research Center, Department of Radiation Oncology, Shiraz University of Medical Sciences, Shiraz, Iran, [10]Non-Communicable Diseases Research Center, Sabzevar University of Medical Sciences, Sabzevar, Iran, [11]Department of Radiation Oncology, Medical University of South Carolina, Charleston, SC, United States, [12]Division of Neuro-Oncology, Mount Sinai Hospital, New York, NY, United States, [13]Department of Radiation Oncology, Clinique Sainte Clotilde, Saint Denis, Reunion, France, [14]Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India, [15]Department of Radiation Oncology, University of KwaZulu Natal, Durban, South Africa, [16]Department of Urology, University Hospital Center, Sousse, Tunisia, [17]Department of Radiation Oncology, Mohammed VI University of Health Sciences, Casablanca, Morocco, [18]Department of Radiation Oncology, Institut Curie, Paris, France, [19]Department of Oral Maxillofacial Surgery, Howard University, Washington, DC, United States, [20]Department of Radiation Oncology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [21]Radiation Oncology, DIMEC, Bologna University, Bologna, Italy, [22]Department of Pathology, Howard University, Washington, DC, United States

The standard of care for non-metastatic muscle invasive bladder cancer is either radical cystectomy or bladder preservation therapy, which consists of maximal transurethral bladder resection of the tumor followed by concurrent chemoradiation with a cisplatin-based regimen. However, for older cancer patients who are too frail for surgical resection or have decreased renal function, radiotherapy alone may offer palliation. Recently, immunotherapy with immune checkpoint inhibitors (ICI) has emerged as a promising treatment

when combined with radiotherapy due to the synergy of those two modalities. Transitional carcinoma of the bladder is traditionally a model for immunotherapy with an excellent response to Bacille Calmette-Guerin (BCG) in early disease stages, and with avelumab and atezolizumab for metastatic disease. Thus, we propose an algorithm combining immunotherapy and radiotherapy for older patients with locally advanced muscle-invasive bladder cancer who are not candidates for cisplatin-based chemotherapy and surgery.

KEYWORDS

older, bladder cancer, invasive, ICI, radiotherapy

Introduction

Bladder cancer prevalence increases significantly with age. Old age is also associated with a high risk of death, likely due to pre-existing comorbidities (1). Currently, the standard approach for eligible patients with non-metastatic muscle-invasive bladder cancer (MIBC) consists of neoadjuvant chemotherapy followed by radical cystectomy, pelvic lymph node dissection, and urinary neobladder reconstruction. In radical cystectomy, genitourinary organs including the bladder, prostate, and seminal vesicle in male patients, and the bladder, uterus, ovaries, fallopian tubes, and anterior vaginal wall in female patients, should be resected (2). Radical cystectomy is a highly morbid surgical procedure that significantly compromises patients' quality of life. In addition, less than half of older patients with MIBC receive definitive therapy either with surgical resection or transurethral resection of a bladder tumor (TURBT) followed by chemoradiation (3). Among patients with invasive bladder cancer who underwent radical cystectomy. the mortality rate was significantly higher in older patients one year after the procedure (4). Frailty prior to surgical resection is often prognostic of a high mortality rate after treatment (5). Thus, older and frail patients are not ideal candidates for surgery. Bladder preservation therapy with chemotherapy following maximal TURBT and radiation is often offered as an alternative for those patients.

A dose-dense MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) regimen is the most effective combined chemotherapy in urothelial carcinoma; however, due to its toxicity, only a minority of patients can tolerate this protocol (6). An alternative less toxic cisplatin-based chemotherapy regimen frequently used is gemcitabine and cisplatin (GC). For patients who are not candidates for cisplatin due to reduced kidney function, mitomycin and 5-fluorouracil (5-FU) may be offered as another alternative, even though this regimen may be more toxic (7). The National Comprehensive Cancer Network (NCCN) guidelines also recommend cisplatin alone, low-dose gemcitabine, or 5-FU and mitomycin as preferred radiation sensitizers. However, older patients are infrequent candidates for cisplatin-based chemotherapy due to the high prevalence of chronic renal failure (CRF). It is estimated that 39.4% of Americans over the age of 60 would develop CRF (8). Those who are 75 years or older are at higher risk of end-stage renal failure requiring dialysis (9). Frailty, which significantly increases with age, is also associated with an adverse outcome following chemotherapy or chemoradiation (10, 11). Thus, older and frail patients with MIBC pose a treatment challenge to clinicians, as radiotherapy alone is less effective compared to concurrent chemoradiation for local control and survival (12).

Recent advances in immunotherapy have shed some light on how immune checkpoint inhibitors (ICI) may confer a survival advantage when combined with radiotherapy for MIBC due the synergy between those two modalities (13). Immunotherapy has been reported to be effective for local control in patients with non-muscle-invasive bladder cancer unresponsive to Bacille Calmette-Guerin (BCG) vaccine (14, 15). In addition, for locally advanced bladder cancer, neoadjuvant immunotherapy has been reported to induce a high rate of pathological response, and potentially improve survival through the reduction of occult distant metastases (16). Even though the data is still preliminary, it suggests that combining immunotherapy with a local therapy which may be synergistic with immunotherapy such as radiotherapy may further improve the response rate and increase the rate of anatomic bladder preservation (17).

The International Geriatric Radiotherapy Group (http://www.igrg.org) is an organization devoted to the care of older cancer patients, minorities, and women who are frequently excluded from clinical trials. Based on currently published literature, members of the genitourinary cancers subgroup propose in this article a practical protocol for older patients with MIBC who are too frail to undergo surgery or who are not candidates for chemotherapy (17). Radiotherapy and immunotherapy may induce long-term remission and potential cure for those patients.

Rationale for using immunotherapy in bladder cancer

Bladder cancer immune environment

Among many anatomic tumor types, bladder cancer has a unique tumor microenvironment which make it an ideal target for ICI.

Tumor mutation burden is a quantitative genomic biomarker that measures the number of mutations within a tumor (18). Higher expression of neoantigens by tumor cells leads to an increased accumulation of tumor-infiltrating lymphocytes (TIL) in the tumor microenvironment. These infiltrating lymphocytes come from the blood stream (B cells, T cells, natural killer cells, macrophages, dendritic cells etc. in various proportions) and adhere to tumor cells to kill them. There is a positive correlation between high TMB expression and TIL. TMB is measured by mutations per megabase of the cancel cell genomic (mut/Mb). Cancer cells that express 10mut/Mb or more are defined to have a high TMB (TMB-H). Among patients with bladder cancers, TMB-H tumor is associated with a better survival and disease-free survival (18–21). It is postulated that a high concentration of CD8 T cells, CD4 memory T cells, and NK cells in the tumor produces a better immune response (19). The correlation between high TIL in the tumor microenvironment and survival was corroborated in another study (22). A combination of TMB-H and a high concentration of TIL, defined as immune cell infiltration (ICI-H) in the tumor, provides the best prognosis for patients with MIBC (23). In addition, the frequency of mutations in mismatch repair (MMR) genes producing microsatellite instability is also significantly higher in TMB-H tumor, leading to a better response to immunotherapy (20).

Correlation between TMB-H and good prognosis for MIBC has been corroborated by other MIBC studies as those tumors are likely to respond to immunotherapy with ICI resulting in longer survival compared the ones with a low TMB (TMB-L) (24–26). A metaanalysis of 6,131 cancer patients treated with ICI reported a significant improvement in survival and progression-free survival for those with TMB-H (25). However, a higher cutoff value of 20 mut/Mb or more was correlated with a better survival, as it was a compilation of many cancers with different anatomic sites and different tumor microenvironments. For cancers with traditionally high TMB such as melanoma, colorectal, bladder, and non-small cell lung cancer, a cutoff value of 13 mut/Mb was reported (26). Thus, TMB value should be incorporated in any prospective study for MIBC.

In addition to TMB, program death ligand-1 (PD-L1) is another biomarker which has been reported to be associated with a poor prognosis and a better immune response to ICI in bladder cancer. Overexpression of PD-L1 by bladder tumor is frequently associated with a high tumor grade, poor response to BCG vaccine, stage progression and poor survival (27, 28). The role of PD-L1 is to help the tumor cells escape killing by the immune system. Binding to PD-L1 to the program cell dead-1 (PD-1) present on T cells leads to inhibition of their activation. The mechanism of T cell inhibition is complex and ranges from apoptosis to T cell exhaustion (29). An increase in PD-L1 expression has been reported in non-invasive bladder cancer after BCG treatment, suggesting that this biomarker confers resistance to intravesical bladder vaccination and subsequent disease progression (30). Depending on the cutoff value, the prevalence of PD-L1 ranges from 26% to 58% in bladder tumor specimens (31–33). High expression of PD-L1 is correlated with a poor response to chemotherapy (33). Radiotherapy significantly increases PD-L1 expression of bladder cancer cells in both *in vitro* and *in vivo* experiments, as the tumor produces an immunosuppressive environment through inhibition of CD-8 T cells to escape radiation killing (32). Conversely, high PD-L1 expression confers an excellent response to immunotherapy with ICI (34, 35). Thus, combining both TMB and PD-L1 expression may be advantageous to predict the response to immunotherapy for MIBC (36).

Effectiveness of immunotherapy for bladder cancer

The role of ICI for non-muscle invasive bladder cancer

Radical cystectomy is the treatment of choice following BCG-unresponsive high grade non-muscle-invasive bladder cancer (NMIBC). However, many patients are unfit for surgery due to their age and co-existing morbidity. For those patients, a phase II study with atezolizumab every three weeks for one year has reported a biopsy-proven 26% complete response (CR) at six month (37). Treatment toxicity is acceptable, with 9 out of 73 patients (12.3%) developing grade 3–5 toxicity. One death was reported. Another report of 96 patients with NMIBC unresponsive to BCG also corroborated the efficacy and low toxicity of pembrolizumab (14). At a median follow-up of 36.4 months, 39 patients (41%) had CR. There was no treatment-related death. Eight patients (8%) developed grade 3–4 complications. Those two studies illustrated the proof of concept that ICI is effective for NMIBC *in vivo* due to the high PD-L1 expression of tumor cells (38).

The role of ICI for non-metastatic MIBC

Complete pathologic response (pCR) following neoadjuvant chemotherapy for bladder cancer is predictive of an excellent prognosis. Induction chemotherapy may decrease the rate of occult distant metastases and confer better survival for those patients. Indeed, a meta-analysis of 13 studies using neoadjuvant cisplatin-based chemotherapy reported excellent survival and relapse-free survival for patient who achieved pCR compared to those with residual disease in the surgical specimen (39). In addition, compared to patients undergoing radical cystectomy alone for invasive bladder cancer, induction chemotherapy has been reported to improve survival likely due to a reduction of distant metastases with systemic therapy (40).

Thus, investigations have been performed to assess whether neoadjuvant immunotherapy can achieve the same role as chemotherapy either for all chemotherapy naïve patients or for those who cannot receive cisplatin due to reduced kidney function. Immunotherapy with various ICI for two to three cycles before radical cystectomy was performed to assess pCR and survival for patients with locally advanced bladder cancer (41–50). The impact of biomarkers on response rate has also been investigated in selective studies.

Bandini et al. (41) reported 112 patients clinical stage T2-T4N0 who underwent neoadjuvant pembrolizumab for three cycles before radical cystectomy. The pCR rate was 37.5%. There was a positive correlation between TMB value and PD-L1 expression with pCR rate. However, on multivariate analysis, only PD-L1 expression was

correlated with a high pCR rate. In a follow-up study of 155 patients, both TMB and PD-L1 have been reported to be associated with excellent event-free survival (EFS). The 3-year EFS was 87.3% and 89.8% for high TMB and PD-L1, respectively (43). Thus, the study highlighted the importance of those biomarkers to predict a good response to immunotherapy and survival. Correlation between high PD-L1 and TMB rate and high pCR rate was also reported after pembrolizumab among 34 patients with non-clear cell histology. The pCR was 37% (45).

Powles et al. (42) reported a 31% pCR following two cycles of atezolizumab and cystectomy for 95 patients with locally advanced bladder cancer. The pCR rate for PD-L1 positive patients was 37%. It was unclear what the PCR rate for PD-L1 negative patients was, but the difference did not achieve statistical significance. On the other hand, high CD8 level within the tumor was associated with a high pCR rate. The pCR rate was 40% and 20% for patients with high and low CD8 levels, respectively.

Nivolumab alone or in combination with another agent was investigated for neoadjuvant locally advanced bladder cancer in two studies. The pCR rate for nivolumab alone was 17% (47). It was unclear whether this lower pCR rate was attributed to the administration of the drug schedule, as patients only received two cycles before surgery. However, when combined with ipililumab with the same treatment schedule, there was a significant increase in the pCR rate. The PCR rate was 42.9% independent of CD8 level (48). The study suggests that combining immunotherapy with another biologic agent or another treatment modality such as radiotherapy may enhance the effectiveness of immunotherapy, leading to a better survival and potential bladder preservation.

Real-world data and other studies also support the use of neoadjuvant immunotherapy for bladder cancer. Using a propensity score matching method, Grassauer et al. (49) reported the survival and outcome of 840 patients who had surgery alone (n=280), neoadjuvant chemotherapy (n-=280), and neoadjuvant immunotherapy (n=280) for their locally advanced bladder cancer. The pCR rate was 26.4% and 22.5% for the neoadjuvant chemotherapy and immunotherapy, respectively. Survival rate was similar for both chemotherapy and immunotherapy and was significantly superior compared to the surgery-alone group. Table 1 summarizes relevant neoadjuvant immunotherapy for bladder cancer.

Taken together, these studies suggest that neoadjuvant immunotherapy may be a viable option for patients who are not candidates for chemotherapy due to a high pCR rate and may also serve as a template for patients for desire anatomic bladder preservation, such as radiotherapy. Biomarkers such as PD-L1 and TMB should be included in any prospective studies for locally advanced MIBC, as they may be predictive of the response rate to ICI.

TABLE 1 Neoajuvant immunotherapy for non-metastatic invasive bladder cancer.

Studies	Patient No	Immuno therapy	PCR	Biomarkers correlation
Bandini et al (41)	112	pembrolizumab 3 cycles	37.5%	PD-L1
Powles et al (42)	95	atezolizumab 2 cycles	31%	CD8+ expression
Basile et al (43)	155	pembrolizumab 3 cycles	36.8%	PD-L1, TMB>11.5
Hu et al (44)	48	tislelizumab	14.6%	NS
Necchi et al (45)	34	pembrolizumab 3 cycles	37%	PD-L1, TMB>11.5%
Li et al (46)	39	pembrolizumab 3 cycles	32.1%	NS
Grivas et al (47)	13	nivolumab 2 cycles	17%	NS
Van Dijk et al (48)	24	nivolumab +ipilumomab 2 cycles	46%	Independent
Grassauer et al (49)	280	NS	22.5%	NS

PCR, pathologic complete response; TMB, tumor mutation burden; NS, not specified.

The role of ICI for metastatic MIBC

The effectiveness of immunotherapy alone and standard chemotherapy has been tested in a randomized study for metastatic bladder carcinoma in the first-line setting. The median survival was 15.7 and 13.1 month, for atezolizumab and chemotherapy, respectively. However, serious adverse events resulting in withdrawal of the medication was significant less among patients who had ICI, at 6% and 34%, respectively (51). In a previous study, the response rate to atezolizumab was correlated with PD-L1 expression on tumor-infiltrating immune cells (52). In another study testing atezolizumab against chemotherapy in the second line setting for patients with metastatic bladder cancer refractory to platinum-based chemotherapy, there was no survival advantage for immunotherapy, but the response duration was longer and the adverse events were reduced compared to chemotherapy (52) Another anti-PD-L1 agent, durvalumab, did not improve survival in the first-line setting for metastatic bladder cancer patients. However, among patients with PD-L1 positive cancer, median survival was significantly longer compared to those receiving chemotherapy (53). These studies emphasized that selection of patients for immunotherapy was the key for its success.

Another PD-1 inhibitor, pembrolizumab, has been reported to improve survival compared to salvage chemotherapy among patients who relapsed following cisplatin-based chemotherapy. The 2-year survival was 26.9% and 14.3% for pembrolizumab and chemotherapy, respectively. Grade 3 or more side effects were also significant less with immunotherapy, at 16.5% and 50.2%, respectively (54). Pembrolizumab also conferred significant survival as first-line treatment for patients with locally advanced or metastatic urothelial cancer who were not eligible for cisplatin chemotherapy, especially among those with significant PD-L1 expression (55).

A comprehensive Cochrane systemic review and meta-analysis evaluated the effectiveness and safety of immunotherapy and chemotherapy in patients with locally advanced and metastatic bladder urothelial carcinoma. Immunotherapy was reported to be superior to chemotherapy in terms of high grade adverse events,

patients' compliance, and quality of life in both first-line and second-line therapy for those patients (56). Furthermore, most current guidelines recommend avelumab as first line maintenance therapy after platinum-based chemotherapy as the new standard for patients with locally advanced or metastatic urothelial carcinoma. In a phase III study of 700 patients with advanced or metastatic urothelial carcinoma who did not have disease progression following first-line chemotherapy, avelumab significantly improved survival compared to the patients who only had supportive care (57). The 1-year survival was 71.3% and 60.4% for the avelumab group and supportive care group, respectively. Thus, patients who respond to the induction chemotherapy can be offered avelumab first-line maintenance therapy until disease progression or unacceptable adverse events (58, 59).

However, in contrast to studies using immunotherapy for locally advanced bladder MIBC, there are still controversies about the role of biomarkers in patients with metastatic bladder cancer, as patients with low PD-L1 expression may also have similar survival after immunotherapy compared to those with higher expression (60). We postulate that the difference in tumor response may have been related to the tumor microenvironment of the distant metastases, which have been reported to differ from the primary sites in different tumors (61–64). Biopsies of the primary tumor and their metastases demonstrated a discordance between PD-L1 expression and a tumor microenvironment which is less responsive to immunotherapy (61, 62). However, more investigations need to be done as most clinicians assume that the tumor microenvironment is similar between the primary tumor and the distant metastatic sites. Thus, biopsy of the distant metastases is frequently not performed, and treatment decision of stage four disease relies on the biomarkers of the primary site (65).

Effectiveness of radiotherapy to enhance tumor killing by ICI

In vivo experiments have demonstrated the effectiveness of high-dose radiotherapy to improve survival among animals who were inoculated with bladder cancer cells. Compared to placebo, mice who developed bladder cancer had significantly improved survival when treated with radiotherapy alone, ICI alone, and ICI combined with radiotherapy. The group who received the combined treatment had the best survival (66). Part of the survival improvement was due to the abscopal effect of radiotherapy as the chemokine C-X-C motif ligand 9 (CXCL) was upregulated of the combined treatment group, leading to an increase of CD8+ T cells and natural killer (NK) cells in the tumor (66). Timing of the radiation before, during, or after ICI did not affect survival for those receiving radiotherapy and ICI (67). Thus adding radiotherapy to immunotherapy was the key for survival benefit. In patients with low PD-L1 expression (<1%), radiotherapy upfront may be advantageous as it upregulates PD-L1 expression of tumor cells, thus making them more sensitive to ICI (32).

The induction of PD-L1 formation following radiotherapy is not specific to bladder cancer as it has been reported among many tumors with different histology both in the laboratory and in clinical studies.

Using immunofluorescence and three-dimensional structured illumination spectroscopy, Permata et al. (68) demonstrated a substantial increase in PD-L1 expression following irradiation of osteosarcoma cells lines with various doses of carbon-ion and X-ray irradiation. The increase in PD-L1 expression was greater with carbon-ion suggesting that high linear-energy transfer particles irradiation may be more effective compared to photons. Prostate cancer allografts also experienced delayed growth and an increase in PD-L1 expression following three fractions of 5 Gy seven days after irradiation (69). In another study using immunoPET/CT imaging by Zr-89-labeled anti-PD-L1 monoclonal antibody, Kikuchi et al. (70), reported a significant elevation of PD-L1 of head and neck and melanoma cancer implanted in mice after radiotherapy with two fractions of 2 Gy times 4 or 10 fractions. The increase in PD-L1 expression is dose-dependent among tumors which have little baseline PD-L1 expression such as esophageal adenocarcinoma (71). These *in vitro* and *in vivo* experiments supported the role of irradiation in the upregulation of PD-L1 expression.

Clinical studies also corroborate the impact of radiotherapy on the expression of PD-L1 in tumor cells. Even among tumors that do not express PD-L1 at diagnosis, radiotherapy administration may turn them PD-L1 positive. Among 46 patients with extremities sarcoma who were PD-L1 negative on initial biopsy, following preoperative radiotherapy to a dose ranging from 45 Gy to 50 Gy, 10.6% became positive after irradiation (72). In other studies preoperative radiotherapy or chemoradiation enhanced PD-L1 expression. Boustani et al. (73) reported the PD-L1 expression in 74 patients who underwent preoperative radiotherapy or chemoradiation for locally advanced rectal cancer. PD-L1 expression was 15% and 50% before and after irradiation, respectively. Corresponding figures for 75 patients who underwent chemoradiation for cervical cancer were 5% and 52%, respectively (74). In patients with non-small cell lung cancer, not only PD-L1 expression in the biopsy specimen increased from 1% to 48% after chemoradiation, but there was also a significant increase in PD-L1 expression in circulating tumor cells (CTC) during treatment, suggesting a natural response of tumor cells to escape the immune response induced by radiotherapy (75, 76).

Upregulation of PD-L1 in tumor cells and in the tumor microenvironment by radiotherapy is a complex mechanism and thought to be through four pathways: Interferon γ signaling, epidermal growth factor receptor pathway, DNA damage signaling pathway, and cGAS-STING pathway (77). Increase in PD-L1 expression allows the tumor cells to escape killing by CD-8+ T cells, which are attracted to the tumor microenvironment after radiation through binding of T cells program death 1 (PD-1) receptor (78). Thus, clinicians can formulate a policy to combine immunotherapy with radiotherapy to improve local control and survival not only for bladder cancer but also other tumor types such as non-malanoma skin cancer (79).

Preliminary studies suggest that the combination of immunotherapy and radiotherapy may be feasible with acceptable toxicity. Among 32 patients with clinical stage T2–4aN0M0 who were not eligible for surgery or declined cystectomy, TURBT was

performed followed by immunotherapy with durvalumab and tremelimumab every four weeks for three doses. Radiotherapy was initiated two weeks after immunotherapy to a total dose of 64 Gy to 66 Gy and 46 Gy to the bladder and pelvic lymph nodes, respectively. 26 patients (81%) achieved a biopsy proven CR after treatment which was significantly higher than the ones reported after neoadjuvant immunotherapy ranging from 14% to 46% (Table 1). Grade 3–4 toxicity was 34% (80). Another study corroborated the efficacy of pembrolizumab as a second-line treatment for locally advanced bladder cancer in combination with radiotherapy. Among 12 patients treated with curative intent, median survival was 27.7 months. There was no difference in grade 3–4 toxicity compared to a group of patients who was treated with pembrolizumab alone (81). Thus, given the synergy between immunotherapy and radiotherapy, further prospective studies are needed to select patients who are most likely to benefit from the combined treatment while minimizing treatment toxicity.

Efficacy of immunotherapy among older cancer patients with bladder cancer

Preliminary studies suggest that ICI, and in particular pembrolizumab, are well tolerated and effective among older patients with bladder cancer and a poor performance status. Among advanced bladder cancer patients who were ineligible for cisplatin due to their age and poor performance status (Eastern Cooperative Oncology Group performance status score 2), pembrolizumab was administered as first-line therapy every three weeks until disease progression, intolerable toxicity, or 24 months of therapy. There was no difference in response rate, survival, and toxicity between patients aged 65 or older (n=302) and 75 or older (n=179) (82). Another study using real-world data corroborated the efficacy and safety of pembrolizumab for older patients with advanced bladder cancer who progressed after chemotherapy. There was no difference in survival or grade 3–4 toxicity between patients less than 75-year-old (n=215) or 75-year-old or older (n=215) (83). Other ICI are also well tolerated in older patients with urothelial carcinoma (84). These studies emphasized the safety profile of ICI for the treatment of other solid tumors in older patients (85–88).

Image-guided radiotherapy for the treatment of locally advanced MIBC.

Radiotherapy has been an effective treatment for locally advanced bladder cancer either alone or combined with chemotherapy. However, radiotherapy planning is difficult due to the distensibility of the bladder, leading to potential marginal miss and/or serious toxicity from excessive irradiation of the normal organs surrounding the target (89). It is also very difficult to deliver a high dose to the gross tumor volume (GTV) as it is not well delineated on the planning CT scan. An ideal radiotherapy technique would deliver a very high dose to the GTV while minimizing dose to the organs at risk (OAR) to decrease the risk of complications.

Fiducial markers are critical to delineate the bladder GTV for accurate radiotherapy delivery (90). Two fiducial markers, gold seeds and Lipiodol, are available to outline the GTV. Even though they are equally effective, the advantage of Lipiodol is the relative technical ease for injection and the absence of risk linked to seed migration after its insertion (90). Thus, for practical purpose, Lipiodol may be the preferred fiducial method for clinical studies involving multiple institutions (91).

Following TURBT, a soluble iodinated radiocontrast agent, Lipiodol, is injected through flexible cystoscopy into the bladder submucosa circumferentially 2–3 mm from the margin of resection or the visible GTV. The contrast agent remains visible during the conventional seven-weeks course of radiotherapy. Many studies have investigated the safety and visibility of Lipiodol on planning CT scan and cone beam CT scan during radiotherapy (92–95). As an illustration, Nakamura et al. (95) emphasized the feasibility of partial bladder tumor boost with Lipiodol toward the end of the treatment with IGRT, which decreased the risk of long-term cystitis while allowing long-term local control.

Advancements in radiotherapy techniques like intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) have allowed clinicians to accurately deliver a high tumor dose while minimizing OAR's dose, thus improving local control and reducing serious complications in older patients with locally advanced MIBC (96).

A review of the literature on locally advanced MIBC treated with IGRT alone or combined with chemotherapy corroborates that the normal organs sparing of this technique translates into improved tolerance to radiotherapy for older cancer patients. Acute grade 3–4 toxicity ranged from 2.3% to 30.3%. Long-term toxicity was low and ranged from 0 to 11.5% (97–104). Local control ranges from 56% to 78% depending on the length of the follow-up. However, there was no consensus on the dose and target volume delineation. For frail and old cancer patients, an ultra-weekly hypofractionation of 6 Gy times 6 to the bladder was well tolerated (99, 102, 104). Chemotherapy is omitted for those patients due to their frailty status. Other studies used an integrated boost technique to deliver a higher dose to the GTV concurrently with chemotherapy to minimize toxicity for patients with a better performance status, as the pelvic lymph nodes and bladder received a lower dose (90, 91). Overall, hypofractionated radiotherapy was well tolerated and might be best suited for older cancer patients to decrease their need for transportation. Table 2 summarizes the studies on IGRT for locally advanced MIBC.

Evaluation of frailty in older patients with locally advanced MIBC

Evaluation of frailty in older patients (defined as 65 years old or above) with locally advanced MIIBC is crucial before enrolling them in any protocol, given its impact on treatment outcomes. Frailty is defined as a state of increased vulnerability resulting from aging

associated decline in reserve and function across multiple physiologic systems (105). As a result, the body's ability to deal with stress is altered. In frail cancer patients, there is an increase mortality risk with surgery and chemotherapy (10, 106). There are several questionnaires to assess frailty in older patient, with the G-8 questionnaire being practical to implement in clinical trials due to its simplicity (107). Patients with a score of 15 or above are defined as fit while those with a score of 14 or less undergo a complete geriatric assessment with the comprehensive geriatric assessment (CGA) survey (108). We propose a protocol using patient fitness and biomarkers to stratify treatment of older patients with locally advanced MIBC who are not candidates for cisplatin chemotherapy and surgery.

Proposed IGRG algorithm for older patients with locally advanced MIBC

All tumor biopsy specimen should undergo next generation sequencing (NGS), if feasible, which includes PD-L1 and TMB status.

Patients with PD-L1 with 1% or more and/or TMB equal or more than 13 mut/MB should undergo immunotherapy as the first-line of treatment for four cycles before radiotherapy as they are likely to respond to ICI. Four cycles of immunotherapy are proposed instead of the two to three cycles reported for neoadjuvant immunotherapy, with the hypothesis that it may further improve the pCR rate. Notably, the pCR was higher for three cycles compared to two cycles with single agent ICI (Table 1). Thus, adding one cycle, similar to the protocol for patients who underwent neoadjuvant immunotherapy for locally advanced squamous cell carcinoma of the skin, may be beneficial (99, 109). Gross et al. (109) reported a pCR rate of 51% for those patients.

For frail patients, we propose a regimen of 6 Gy weekly for six weeks to the bladder with IGRT two weeks following immunotherapy as this regimen is well tolerated for older patients. We believe that sequential treatment works best to minimize treatment toxicity, as significant toxicity was reported with concurrent immunotherapy and weekly radiotherapy for bladder cancer. In a phase I study of five patients with bladder cancer who underwent concurrent immunotherapy and concurrent immunotherapy, four patients developed grade 3–4 toxicity (110).

Fit patients should receive a hypofractionated regimen, which includes treating the pelvic lymph nodes, bladder, and GTV to a total dose of 44 Gy in 2.2 Gy/fraction, 50 Gy in 2.5 Gy/fraction and 55 Gy in 2.75 Gy/fraction, respectively, with the simultaneous integrated boost technique to minimize treatment toxicity. Corresponding biologic equivalent dose (BED) would be 45.22, 62.5, and 70.1 Gy, respectively.

For patients with PD-L1 less than 1% and TMB less than 13 mut/MB, radiotherapy should be administered first to induce upregulation of PD-L1, followed by four cycles of immunotherapy. The radiotherapy dose and fractionation are identical for frail and fit patients.

External beam pelvic irradiation should be performed with IMRT and IGRT to minimize complication rates. The GTV should be outlined with Lipiodol or another fiducial marker depending on the institution's expertise. Patients who respond to the combination of radiotherapy and immunotherapy may be offered avelumab maintenance therapy until disease progression or unacceptable adverse events occur, at the discretion of the investigator.

Conclusions based on prospectively collected data would improve the design of future clinical trials targeting older patients treated with immunotherapy and radiotherapy for bladder cancer.

Figure 1 summarizes the proposed algorithm.

The IGRG is committed to conducting such studies when funding becomes available, leveraging its network of cancer institutions worldwide (n=1282) and diverse patient population (111, 112).

Conclusion

The combination of radiotherapy and immunotherapy may be beneficial for older patients with locally advanced MIBC who are

TABLE 2 Image-guided radiotherapy for locally advanced muscle invasive bladder cancer.

Study	Patient	Radiation	dose		Chemotherapy	Local control	Complications	
	No	Pelvis	Bladder	GTV			Acute	Late
Murthy et al (97)	44	55 Gy	64 Gy	68 Gy	Yes	78% (3 year)	11% gr 3	4% gr 3
Kang et al (98)	26	45 Gy	45 Gy	62.5 Gy	Yes	86% (2 year)	3.8% gr 4	11.5% gr. 3
Huddart et al (99)	33		36 Gy		No	71.7% (1 year)	30.3% gr 3-4	11.5% gr 2-4
Navarro et al (100)	117	NS	55-60Gy		Yes	56% (5 year)	4% gr 3-4	4% gr 3-4
Remonde et al (101)	300	NS	59.4 Gy		Yes	71.7 (5 year)	NS	NS
Zygogianni et al (102)	43		36 Gy		No	NS	2.3%	O%
Hsieh et al (103)	10	NS	57.6 Gy		Yes	83.3% (2 year)	10% gr 3	NS
Hafeez et al (104)	55		36 Gy		No	83% (2 year)	22% gr 3	4.3% gr 3

No, number; NS, non specified; gr, grade; Gy, gray; GTV, gross tumor volume.

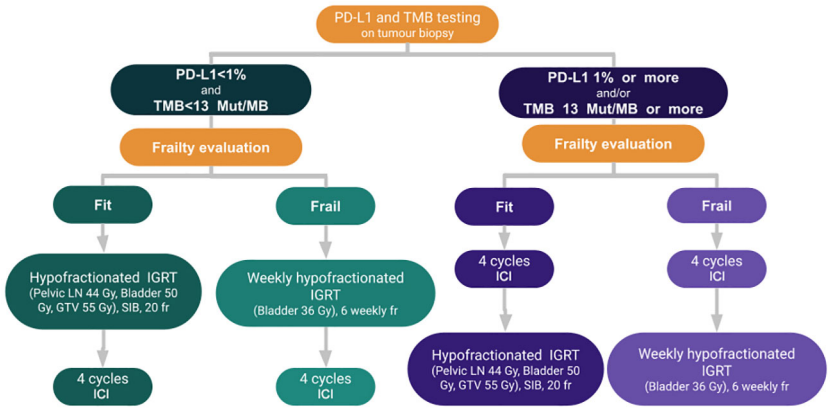


FIGURE 1
Treatment algorithm for muscle invasive bladder cancer.

not eligible for cisplatin chemotherapy and are not candidates or decline cystectomy. Prospective studies should be conducted to verify this hypothesis.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author/s.

Author contributions

NN: Formal analysis, Writing – original draft, Writing – review & editing. UK: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. BP: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. M-EC: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. VV-H: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. OG: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. MA: Conceptualization, Writing – original draft, Writing – review & editing. MM: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. SJ: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. HG: Conceptualization, Formal analysis, Writing – original draft. LK: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. FD: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. VM: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. AMa: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. GT: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. ZD: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. GL: Conceptualization, Writing – original draft, Writing – review & editing. SeB: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. SaB: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. EN: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. EL: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. AMo: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

The authors would like to thank Donna M. Alexander for her assistance in writing this manuscript.

Conflict of interest

VV-H declares stock ownerships in Affluent Medical. Author ME-C was employed by company MVision AI.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

References

1. Lin W, Pan X, Zhang C, Ye B, Song J. Impact of age on diagnosis of bladder cancer on survival: A surveillance, epidemiology, and end results-based study 2004-2015. *Cancer Control*. (2023) 30:1–4. doi: 10.1177/10732748231152322

2. Milowsky MI, Rumble RB, Booth CM, Gilligan T, Eapen LJ, Hauke RJ, et al. Guideline on muscle-invasive and metastatic bladder cancer (Eurpean Association of Urology guideline): American Society of Clinical Oncology clinical practice guideline endorsements. *J Clin Oncol*. (2016) 34:1945–52. doi: 10.1200/JCO.2015.65.9797

3. Skinner EC. Treatment of muscle invasive bladder cancer in older patients. *Am Soc Clin Educ Book*. (2016) 36:e228–3. doi: 10.14694/EDBK_158974

4. Leminski A, Kaczmarek K, Golab A, Kotfis K, Skonieczna-Zydecka K, Stozewski M. Muscle invasive bladder cancer: a retrospective observational comparative study. *Clin Interv Aging*. (2022) 17:255–63.

5. Stamatakos PV, Moschotzopoulos D, Glykas I, Fragkoulis C, Kostakopoulos N, Papapoulos G, et al. Outcomes of radical cystectomy in pT4 bladder cancer frail patients: A high volume single center study. *JFSF*. (2022) 7:147–50. doi: 10.22540/JFSF-07-147

6. Choueiri TK, Jacobus S, Bellmunt J, Qu A, Appleman LJ, Tretter C, et al. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarkers correlates. *J Clin Oncol*. (2014) 32:1889–94. doi: 10.1200/JCO.2013.52.4785

7. de Haar-Hollerman A, van Hoogstraten LMC, Hulshof MCCM, Tascilar M, Bruck K, Meijer RP, et al. Chemoradiation for muscle invasive bladder cancer using 5-fluorouracil versus capecitabine: A nationwide cohort study. *Radiother Oncol*. (2023) 183:109584. doi: 10.1016/j.radonc.2023.109584

8. Mallappallil M, Friedman EA, Delano BG, McFarlane SI, Salifu MO. Chronic kidney failure in the elderly. *Clin Pract*. (2014) 11:525–35. doi: 10.2217/cpr.14.46

9. Rosansky SJ, Schell J, Shega J, Scherer J, Jacobs L, Couchoud C, et al. Treatment decisions for older adults with advanced chronic kidney disease. *BMC Nephrol*. (2017) 18:200. doi: 10.1186/s12882-017-0617-3

10. Ho Y, Tang W, Chen S, Lee S, Chen J, Hung Y, et al. Association of frailty and chemotherapy-related adverse outcomes in geriatric patients with cáncer: a pilot observational study in Taiwan. *Aging*. (2021) 13:24192–204. doi: 10.18632/aging.v13i21

11. Chou W, Lai C, Hung C, Hsueh S, Yeh K, Lu C, et al. Clinical significance of frailty on treatment outcome in non-geriatric patients with head and neck cáncer and esophageal cáncer undergoing curative intent concurrent chemoradiotherapy. *Cancer Control*. (2022) 29:1–10. doi: 10.1177/10732748211045276

12. James ND, Hussain SA, Hall E, Jenkins P, Tremlett J, Rawlings C, et al. Radiotherapy with or without chemotherapy for muscle invasive bladder cáncer. *N Engl J Med*. (2012) 366:1477–88. doi: 10.1056/NEJMoa1106106

13. Rompre-Brodeur A, Shinde-Jadhav S, Ayoub M, Piccirillo CA, Seuntjens J, Brimo F, et al. PD-1/PD-L1 check point inhibition with radiation in bladder cáncer: in *situ* and abscopal effects. *Mol Cancer Thera*. (2020) 19:211–20. doi: 10.1097/01.JU.0000556624.17353.4f

14. Balar AV, Kamat AM, Kulkarni GS, Uchio EM, Boormans JL, Roumiguie W, et al. Pembrolizumab monotherapy for the treatment of high risk non muscle invasive bladder cáncer unresponsive to BCG (Keynote-057): an open label, single arm, multicentre, phase 2 study. *Lancet Oncol*. (2021) 22:919–30. doi: 10.1016/S1470-2045(21)00147-9

15. Black PC, Tangen C, Singh P, McConkey DJ, Lucia S, Lawrance WT, et al. Phase II trial of atezolizumab in BCG-unresponsive non-muscle invasive bladder cáncer: SWOG S1605 (NCT02844816). *J Clin Oncol*. (2021) 39:4541. doi: 10.1200/JCO.2021.39.15_suppl.4541

16. Peyrottes A, Ouzaid I, Califano G, Hermieu J, Xylinas E. Neoadjuvant immunotherapy for bladder cáncer. *Medicina*. (2021) 57:769. doi: 10.3390/medicina57080769

17. Nguyen NP, Baumert BG, Oboite E, Motta M, Appalanaido GK, Arenas M, et al. Immunotherapy and radiotherapy for older cáncer patients: proposed paradigm by the International Geriatric Radiotherapy Group. *Gerontology*. (2021) 67:379–85. doi: 10.1159/000514451

18. Xu H, Clemenceau JR, Park S, Choi J, Lee SH, Hwang TH. Spatial heterogeneity and organization of tumor mutation burden with immune infiltrates within tumors based on whole slide images correlated with patient survival in bladder cáncer. *J Pathol Inf*. (2022) 13:100105. doi: 10.1016/j.jpi.2022.100105

19. Wu Z, Wang M, Liu Q, Zhu K, Chen L, Guo H, et al. Identification of gene expression profiles and immune cells infiftration signatures between low and high tumor mutation burden groups in bladder cáncer. *Int J Med Sci*. (2020) 17:89–96. doi: 10.7150/ijms.39056

20. Voutsadakis IA. Urothelial bladder carcinoma with a high tumor mutation burden have a better prognosis and targetable molecular defects beyond immunotherapy. *Curr Oncol*. (2022) 19:1390–407. doi: 10.3390/curroncol29030117

21. Lu J, Zhu Y, Ji A, Zhang Q, Liao G. Mining TCGA database for tumor mutation burden and their clinical significance in bladder cáncer. *Biosci Rep*. (2020) 40:1–12. doi: 10.1042/BSR20193421

22. Pfannstiel C, Strissel PL, Chiapinelli KB, Sikic D, Wach S, Wirtz RM, et al. The tumor microimmune environment drives a prognostic relevance that correlates with bladder cáncer subtypes. *Cancer Immunol Res*. (2019) 7:923–38. doi: 10.1158/2326-6066.CIR-18-0758

23. Zhang Y, Wang Y, Wang J, Zhang K. The immune cell infiltration and patterns and characterization score in bladder cáncer to identify the diagnosis. *Front Genet*. (2022) 13:852708. doi: 10.3389/fgene.2022.852708

24. Wang Z, Zhu L, Stebbing J, Wang Z, Peng L. Identification of an immune gene-associated prognostic signature in patients with bladder cáncer. *Cancer Gene Ther*. (2022) 29:494–504. doi: 10.1038/s41417-022-00438-5

25. Huang T, Chen X, Zhang H, Liang Y, Li L, Wei H, et al. Prognostic role of tumor mutation burden in cáncer patients treated with immune check point inhibitors. *Front Oncol*. (2021) 11:706652. doi: 10.3389/fonc.2021.706652

26. Zheng M. Tumor mutation for predicting immune check point blockade response: the more the better. *J Imunother Cancer*. (2022) 10:e003087. doi: 10.1136/jitc-2021-003087

27. Tawahara T, Ishiguro Y, Ohtake S, Kato I, Ito Y, Ito H, et al. PD-1 and PD-L1 are more highly expressed in high grade bladder cáncer than in low grade cases: PD-L1 might function as a mediator of stage progression in bladder cáncer. *BMC Urol*. (2018) 18:97. doi: 10.1186/s12894-018-0400-1

28. Toren P, Brisson H, Simonyan D, Hovington H, Lacombe L, Bergeron A, et al. Androgen receptor and immune cell PD-L1 expression in bladder tumors predict disease recurrence and survival. *World J Urol*. (2021) 39:1549–58. doi: 10.1007/s00345-020-03358-x

29. Chen L, Han X. Anti-PD1/PD-L1 therapy of human cáncer. *J Clin Invest*. (2015) 9:3384–91. doi: 10.1172/JCI80011

30. Hashizume A, Umemoto S, Yokose T, Nakamura Y, Yoshihara M, Shoji K, et al. Enhanced expression of PD-L1 in non-muscle-invasive bladder cáncer after treatment with Bacillus Calmette-Guerin. *Oncotarget*. (2018) 9:34066–78. doi: 10.18632/oncotarget.v9i75

31. Zavalishina L, Tsimafeyeu I, Povilaitite P, Raskin G, Andreeva Y, Petrov A, et al. RUSSCO-RSP comparative study of immunohistochemistry diagnostic assays for PD-L1 expression in urothelial bladder cáncer. *Virchows Archiv*. (2018) 473:719–24. doi: 10.1007/s00428-018-2453-7

32. Wu T, Chen W, Chang Y, Lin W, Chen M. The role of PD-L1 in the radiation response clinical outcome for bladder cáncer. *Sci Rep*. (2016) 6:1974. doi: 10.1038/srep19740

33. Pichler R, Heidegger I, Fritz J, Danzl M, Sprung S, Zelger B, et al. PD-L1 expression in bladder cáncer and metástasis and its influence on oncologic outcome after cystectomy. *Oncotarget*. (2017) 8:66849–64. doi: 10.18632/oncotarget.v8i40

34. Inman BA, Longo TA, Ramalingam S, Harrison MR. Atezolizumab: A PD-L1 blocking antibody for bladder cáncer. *Clin Cancer Res*. (2017) 23:1886–90. doi: 10.1158/1078-0432.CCR-16-1417

35. Rouanne M, Radulescu C, Adam J, Allory Y. PD-L1 testing in urothelial bladder cáncer: essentials of clinical practice. *World J Urol*. (2021) 39:1345–55. doi: 10.1007/s00345-020-03498-0

36. Liu C, Liu Z, Jin K, Zeng H, Shao F, Chang Y, et al. Integrative tumor burden with CD39 and PD-L1 for the prediction of response to PD-L1 blockade and adjuvant chemotherapy in muscle-invasive bladder cáncer patients. *Br J Cancer*. (2022) 127:1718–25. doi: 10.1038/s41416-022-01943-y

37. Black PC, Tangen C, Singh P, McConkey DJ, Lucia S, Lowrance WT. Phase II trial of atezolumab in BCG-unresponsive non-muscle invasive bladder cáncer: SWOG S1605. *J Clin Oncol*. (2021) 39:4541. doi: 10.1200/JCO.2021.39.15_suppl.4541

38. Vandeveer AJ, Fallon JK, Tughe R, Sabvezari H, Schlom J, Greiner JW. Systemic therapy of non-muscle invasive mouse bladder cáncer with avelumab, an anti-PD-L1 immune checkpoint inhibitor. *Cancer Immunol Res*. (2016) 4:452–62. doi: 10.1158/2326-6066.CIR-15-0176

39. Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Vavassori I, Barni S. Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cáncer treated with cystectomy: A meta-analysis. *Eur Urol*. (2014) 65:350–7. doi: 10.1016/j.eururo.2013.06.049

40. Hamid ARAH, Ridwan FR, Parikesit D, Widia F, Mochtar CA, Umbas R. Meta-analysis of neoadjuvant chemotherapy compared to radical cystectomy alone in improving overall survival of muscle-invasive bladder cáncer patients. *BMC Urol*. (2020) 20:158. doi: 10.1186/s12894-020-00733-z

41. Bandini M, Ross JS, Raggi D, Gallina A, Colecchia M, Luciano R, et al. Predicting the complete pathologic response after neoadjuvant pembrolizumab in muscle invasive bladder cáncer. *J Natl Cancer Inst*. (2021) 113:48–53. doi: 10.1093/jnci/djaa076

42. Powles T, Kockx M, Rodriguez-Vida A, Duran I, Crabb SJ, van der Heijden MS, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. *Nat Med*. (2019) 25:1706–14. doi: 10.1038/s41591-019-0628-7

43. Basile G, Bandini M, Gibb EA, Ross JS, Raggi D, Marandino L, et al. Neoadjuvant pembrolizumab and radical cystectomy in patients with muscle invasive bladder cáncer: 3-year-median follow-up of the update of PURE-01 trial. *Clin Cancer Res*. (2022) 28:5108–14. doi: 10.1158/1078-0432.CCR-22-2158

44. Hu J, Chen J, Ou Z, Chen H, Liu Z, Chen M, et al. Neoadjuvant immunotherapy, chemotherapy, and combination therapy in muscle-invasive bladder cáncer: a multi-

center real-world retrospective study. *Cells Rep Med*. (2022) 3:100785. doi: 10.1016/j.xcrm.2022.100785

45. Necchi A, Raggi D, Gallina A, Madison R, Colecchia M, Luciano R, et al. Updated results of PURE-01 with preliminary activity of neoadjuvant pembrolizumab in patients with muscle-invasive bladder carcinoma with variant histologies. *Eur Urol*. (2020) 77:439–46. doi: 10.1016/j.eururo.2019.10.026

46. Li R, Nocera L, Rose KM, Raggi D, Naidu S, Mercinelli C, et al. Comparative effectiveness of neoadjuvant pembrolizumab versus cisplatin-based chemotherapy or upfront radical cystectomy in patients with muscle-invasive urothelial bladder cáncer. *Eur Urol Oncol*. (2024) 7. doi: 10.1016/j.euo.2023.12.008

47. Grivas P, Koshkin VS, Chu X, Cole S, Jain RK, Dreicer R, et al. PrECOG PrE0807: A phase I feasibility trial of neoadjuvant nivolumab without and with Lirilumab in patients with muscle-invasive bladder cáncer ineligible for or refusing cisplatin-based neoadjuvant chemotherapy. *Eur Urol Oncol*. (2023). doi: 10.1016/j.euo.2023.11.022

48. van Dijk N, Gil-Jimenez A, Silina K, Hendriksen K, Smith LA, de Feijter JM, et al. Preoperative ipilimumab plus nivolumab in locoregionally advanced urothelial cáncer: the NABUCCO trial. *Nat Med*. (2020) 26:1839–44. doi: 10.1038/s41591-020-1085-z

49. Grassauer J, Schmidt J, Cowan A, Gilbert SM, Chakiryan MH. Downstaging and survival associated with neoadjuvant immunotherapy before radical cystectomy for muscle-invasive bladder cáncer. *Eur Urol Oncol*. (2024) 7:139–46. doi: 10.1016/j.euo.2023.06.005

50. Galsky MD, Arija JAA, Bamias A, Davis ID, de Santis M, Kikuchi E, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cáncer: a multicenter, randomised, placebo controlled trial. *Lancet*. (2020) 395:1547–57. doi: 10.1016/S0140-6736(20)30230-0

51. Rosenberg JE, Hoffman-Censits J, Pawles T, van den Heijden MS, Balar AJ, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial cancercinoma who have progressed following treatment with platinum-based chemotherapy: a single arm multicenter, phase II trial. *Lancet*. (2016) 387:1909–20. doi: 10.1016/S0140-6736(16)00561-4

52. Powles T, Duran I, van der Heijden MS, Loriot Y, Vogelzang NJ, De Georgi U, et al. Atezolizumab versus chemotherapy in patients with platinum treated locally advanced or metastatic urothelial carcinoma: a multicentre, open-label, randomized trial. *Lancet*. (2018) 391:748–57. doi: 10.1016/S0140-6736(17)33297-X

53. Powles T, van der Heijden MS, Castellano D, Galsky MD, Loriot Y, Petrylak DP, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma: a randomized, open-label, multicentre, phase 3 trial. *Lancet Oncol*. (2020) 21:1574–88. doi: 10.1016/S1470-2045(20)30541-6

54. Fradet Y, Bellmunt J, Vaughn DJ, Lee JL, Fong L, Vogeljang NJ, et al. Randomized phase III Keynote-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cáncer: results of >2 years follow-up. *Ann Oncol*. (2019) 30:970–6. doi: 10.1093/annonc/mdz127

55. Vuky J, Balar AV, Castellano D, O'Donnell PH, Grivas P, Bellmunt J, et al. Long-term outcomes in KEYNOTE-052: phase II study investigating first-line pembrolizumab in cisplatin ineligible patients with locally advanced or metastatic urothelial cáncer. *J Clin Oncol*. (2020) 38:2658–66. doi: 10.1200/JCO.19.01213

56. Maisch P, Hwang EC, Kim K, Naravan VM, Bakker C, Kunath F, et al. Immmunotherapy for advanced or metastatic urothelial carcinoma. *Cochrane Database Syst Rev*. (2023) 10:CD013774. doi: 10.1002/14651858.CD013774.pub2

57. Powles T, Park SH, Voog E, Cacerta C, Valderrama BP, Gurney H, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *New Engl J Med*. (2020) 383:1218–30. doi: 10.1056/NEJMoa2002788

58. Mansinho A, Cruz A, Marconi L, Pinto C, Augusto I. Avelumab as first line maintenance treatment in locally advanced or metastatic urothelial carcinoma. *Adv Ther*. (2023) 40:4134–50. doi: 10.1007/s12325-023-02624-9

59. Sridhar SS, Powles T, Climent Durant MA, Park SH, Massari F, Thiery-Vuillemin A, et al. Avelumab first line maintenance for advanced urothelial carcinoma: Analysis from Javelin Bladder 100 by duration of first line chemotherapy and interval before maintenance. *Eur Urol*. (2023) 85.

60. Aggen DH, Drake CG. Biomarkers for immunotherapy in bladder cáncer: A moving target. *J Immunother Cancer*. (2017) 5:94. doi: 10.1186/s40425-017-0299-1

61. Szekely B, Bossuyt V, Li X, Wali VB, Patwardhan GA, Frederick C, et al. Immunological difference between primary and metastatic breast cáncer. *Ann Oncol*. (2018) 29:2232–9. doi: 10.1093/annonc/mdy399

62. Song SG, Kim S, Koh J, Yim J, Han B, Kim JA, et al. Comparative analysis of the tumor microenvironment of primary and brain metastases of non-small cell lung cáncer reveals organ-specific and EGFR mutation-dependent unique immune landscape. *Cancer Immunol Immunother*. (2021) 70:2035–48. doi: 10.1007/s00262-020-02840-0

63. Callea M, Albiges L, Gupta M, Cheng S, Genega EM, Fay AP, et al. Differential expression of PD-L1 between primary and metastatic sites in clear cell renal carcinoma. *Cancer Immunol Res*. (2015) 10:1158–64. doi: 10.1158/2326-6066.CIR-15-0043

64. Chen X, Chen H, He D, Cheng Y, Zhu Y, Xiao M, et al. Analysis of tumor microenvironment characteristics in bladder cancer. *Front Immunol*. (2021) 12:672158. doi: 10.3389/fimmu.2021.672158

65. Khasraw M, Brogi E, Seidman AD. The need to examine metastatic tissue at the time of progression of breast cáncer: Is re-biopsy a necessary or a luxury. *Curr Oncol Rep*. (2011) 13:17–25. doi: 10.1007/s11912-010-0137-9

66. Rompre-Brodeur A, Shinde-Jadhav S, Ayoub M, Piccirillo CA, Seuntjens J, Brimo F, et al. PD-1/PD-L1 immune check point inhibition with radiation in bladder cáncer: *In situ* and abscopal effect. *Mol Cancer Ther*. (2020) 19:211–20. doi: 10.1158/1535-7163.MCT-19-0503

67. Tholomier C, Marcq G, Shinde-Jadhav S, Yahoub M, Huang JM, Kool R, et al. Optimizing sequence of PD-L1 immune checkpoint inhibitors and radiation therapy in bladder Cáncer. *Bladder cáncer*. (2020) 6:295–302. doi: 10.3233/BLC-200315

68. Permata TBM, Sato H, Gu W, Kakoti S, Uchihara Y, Yoshimatsu Y, et al. High linear energy transfer carbón-irradiation upregulates PD-L1 expression more significantly than X-rays in human osteosarcoma U2OS cells. *J Radiat Res*. (2021) 62:773–81. doi: 10.1093/jrr/rrab050

69. Philippou Y, Sjoberg HT, Murphy E, Alyacoubi S, Jones KI, Gordon-Weeks AN, et al. Impact of combining anti PD-L1 immunotherapy and radiotherapy on the tumor micro-environment in a murine prostate cáncer model. *Br J Cancer*. (2020) 123:1089–100. doi: 10.1038/s41416-020-0956-x

70. Kikuchi M, Clump DA, Srivasta RM, Sun L, Zeng D, Diaz-Perez, et al. Preclinical immunoPET/CT imaging usinf Zr-89-labeled anti-PD-L1 antibody for assessing radiation-induced PD-L1 upregulation in head and neck cáncer and melanoma. *Oncoimmunology*. (2017) 19:e1329071. doi: 10.1080/2162402X.2017.1329071

71. Kelly R, Zaidi A, Smith M, Omstead A, Kosovec J, Matsui D, et al. The dynamic and transient immune microenvironment in locally advanced adenocarcinoma post chemoradiation. *Ann Surg*. (2018) 268:992–9. doi: 10.1097/SLA.0000000000002410

72. Patel KR, Martinez A, Stahl JA, Logan SJ, Perricone AJ, Ferris MJ, et al. Increase in PD-L1 expression after pre-operative radiotherapy for soft tissue sarcoma. *Oncoimmunology*. (2018) 7:e1442168. doi: 10.1080/2162402X.2018.1442168

73. Boustani J, Derangere V, Bertaut A, Adotevi O, Morgand V, Charron-Barra C, et al. Radiotherapy scheme effect on PD-L1 expression for locally advanced rectal cancer. *Cells*. (2020) 9:2071. doi: 10.3390/cells9092071

74. Mori Y, Sato H, Kumazawa T, Permata TBM, Yoshimoto Y, Murata K, et al. Analysis of radiotherapy-induced alteration of CD8+ and PD-L1 expression in patients with uterine cervical carcinoma. *Oncol Lett*. (2021) 21:446. doi: 10.3892/ol

75. Yoneta K, Kuwata T, Kanayama M, Mori M, Kawanami T, Yatera K, et al. Alteration in tumoural PD-L1 expression and stromal CD8-positive tumor-infiltrating lymphocytes after concurrent chemo-radiotherapy for non-small cell lung cancer. *Br J Cancer*. (2019) 121:490–6. doi: 10.1038/s41416-019-0522-5

76. Wang Y, Kim TH, Fouladdel S, Zhang Z, Soni P, Qin Y, et al. PD-L1 expression in circulating tumor cells increases during radio(chemo)therapy and indicates poor prognosis in non-small cell lung cáncer. *Sci Rep*. (2018) 9:566. doi: 10.1038/s41598-018-36652-2

77. Sato H, Okonogi N, Yoshimoto Y, Tamaki T, Suzuki Y. Radiotherapy and PD-L1 expression. *Cancer Chemother*. (2019) 46:845–9.

78. Wu M, Huang Q, Xie Y, Wu X, Ma H, Zhang Y, et al. Improvement of the anticancer efficacy of PD-1/PD-L1 blockade via combination therapy and PD-L1 regulation. *J Hematol Oncol*. (2022) 15:24. doi: 10.1186/s13045-022-01242-2

79. Nguyen NP, Thariat J, Gorobets O, Vinh-Hung V, Kim L, Blanco SC, et al. Immunotherapy and hypofractionated radiotherapy in older patients with locally advanced cutaneous squamous cell carcinoma of the head and neck: A proposed paradigm by the International Geriatric Radiotherapy Group. *Cancers*. (2023) 14:4981. doi: 10.3390/cancers15204981

80. del Muro XG, Valderrama BP, Medina A, Cuellar MA, Etxaniz O, Sarrio RG, et al. Phase II trial of durvalumab plus tremelimumab with concurrent radiotherapy in patients with localized muscle invasive bladder cáncer treated with a selective bladder preservation approach. *J Clin Oncol*. (2021) 39:4505. doi: 10.1200/JCO.2021.39.15_suppl.4505

81. Sano T, Aizawa R, Ito K, Nakamura K, Ogata T, Takeda M, et al. Efficacy and tolerability of second line pembrolizumab with radiation therapy in advanced urothelial carcinoma. *Anticancer Res*. (2023) 43:2119–26. doi: 10.21873/anticanres.16373

82. Grivas P, Plimack ER, Balar AV, Castellano D, O'Donnell PH, Bellmunt J, et al. Pembrolizumab as first-line therapy in cisplatin-ineligible advanced urothelial cancer (KEYNOTE-052): Outcomes in older patients by age and performance status. *Eur Urol Oncol*. (2020) 3:351–9. doi: 10.1016/j.euo.2020.02.009

83. Nishiyama N, Kobayashi T, Narita S, Hikada Y, Ito K, Maruyama S, et al. Efficacy and safety of pembrolizumab for older patients with chemoresistant urothelial carcinoma assessed using propensity score matching. *J Geriat Oncol*. (2022) 13:88–93. doi: 10.1016/j.jgo.2021.07.002

84. Schulz B, Rodler S, Szabados B, Graser A, Buchner A, Stief C, et al. Safety, efficacy, and prognostic impact of checkpoint inhibitors in older patients with genitourinary cáncer. *J Geriat Oncol*. (2020) 11:1061–6. doi: 10.1016/j.jgo.2020.06.012

85. Herin H, Aspeslagh S, Castanon E, Dyevre V, Marabelle A, Varga A, et al. Immunotherapy phase I trials in patients older than 70 years with advanced solid tumors. *Eur J Cancer*. (2018) 95:68–74. doi: 10.1016/j.ejca.2018.03.002

86. Gomes F, Lorigan P, Woolley S, Foden P, Burns K, Yorke J, et al. A propective study of the safety of checkpoint inhibitors in older cáncer patients-the ELDERS study. *Esmo Open*. (2021) 6:1–6. doi: 10.1016/j.esmoop.2020.100042

87. Wu Q, Wang Q, Tang X, Xu R, Zhang L, Chen X, et al. Correlation between patients' age and cáncer immunotherapy efficacy. *Oncoimmunology*. (2019) 8: e1568810. doi: 10.1080/2162402X.2018.1568810

88. Corbaux P, Maillet D, Boespflug A, Locatelli-Sanchez M, Periez-Muzet M, Duruisseaux M, et al. Older and younger patients treated with immune checkpoint inhibitors have similar outcomes in real life setting. *Eur J Cancer*. (2019) 1212:192–201. doi: 10.1016/j.ejca.2019.08.027

89. Fokdal L, Honore H, Hoyer M, Meldgaard P, Fode K, von der Maase H. Impact of changes in bladder and rectal filling volume on organ motion and dose distribution of the bladder in radiotherapy for urinary bladder cáncer. *Int J Radiat Oncol Biol Phys*. (2004) 59:436–44. doi: 10.1016/j.ijrobp.2003.10.039

90. Della Bianca C, Yorke ED, Mechalakos JG, Kollmeier MA. Comparison of setup by bony anatomy and by fiducial marker registration in image-guided radiotherapy for bladder cáncer. *Int J Radiat Oncol Biol Phys*. (2009) 75:S649.

91. Nolan CP, Forde EJ. A review of the use of fiducial markers for image-guided radiotherapy. *Acta Oncol*. (2016) 55:533–8. doi: 10.3109/0284186X.2015.1110250

92. Baumgarten AS, Emtage JB, Wilder RB, Biagioli MC, Gupta S, Spiess PE. Intravesical lipiodol injection technique for image-guided radiation therapy for bladder cáncer. *Urology*. (2014) 83:946–50. doi: 10.1016/j.urology.2013.09.058

93. Chai X, van Herk M, van de Kamer JB, Remeijer P, Bex A, Betgen A, et al. Behavior of lipiodol markers during image-guided radiotherapy of bladder cáncer. *Int J Radiat Oncol Biol Phys*. (2010) 77:309–14. doi: 10.1016/j.ijrobp.2009.08.019

94. Pos F, Bex A, Dees-Ribbers HM, Betjen A, van Herk M, Remeijer P. Lipiodol injection for target volume delineation and image guidance during radiotherapy for bladder cáncer. *Radiother Oncol*. (2009) 93:364–7. doi: 10.1016/j.radonc.2009.09.003

95. Nakamura R, Kakuhara H, Kikuchi K, Segawa T, Oikawa H, Iwasaki K, et al. Partial bladder boost using lipiodol marking during image-guided radiotherapy for bladder cáncer. *Anticancer Res*. (2018) 38:4827–31. doi: 10.21873/anticanres.12793

96. Frick MA, Ogunkeye J, Oladipo ED, Prado K, Bagshaw HP. Radiotherapy vs cystectomy for treatment of muscle invasive bladder cáncer in very elderly patients. *Int J Radiat Oncol Biol Phys*. (2023) 117:2839. doi: 10.1016/j.ijrobp.2023.06.2498

97. Murthy V, Masodkar R, Kalyani N, Mahantshetty U, Bakshi G, Prakash G, et al. Clinical outcomes with dose escalated adaptive radiation therapy for urinary bladder cáncer: a prospective study. *Int J Radiat Oncol Biol Phys*. (2016) 94:60–6. doi: 10.1016/j.ijrobp.2015.09.010

98. Kang JJ, Steinberg M, Kupelian P, Alexander S, King CR. Whole versus partial bladder irradiation. *Am J Clin Oncol*. (2018) 41:107–14. doi: 10.1097/COC.0000000000000237

99. Huddart R, Hafeez S, Lewis R, McNair H, Syndicus I, Henry A, et al. Clinical outcomes of a randomised trial of adaptive plan of the day treatment in patients receiving ultra-hypofractionated weekly radiation therapy for bladder cáncer. *Int J Radiat Oncol Biol Phys*. (2021) 110:411–24. doi: 10.1016/j.ijrobp.2020.11.068

100. Navarro-Domenech I, Arulanantham S, Liu ZA, Tjong M, Kong V, Malkov V, et al. Clinical and dosimetric outcomes of image-guided, dose-painted radiotherapy in muscle invasive bladder cáncer. *Radiat Oncol*. (2023) 18:154. doi: 10.1186/s13014-023-02338-w

101. Remonde D, Saenz D, Zhang J, Kaushik D, Rasmussen K, Galvan E, et al. Outcome of bladder preservation with combined modality treatment in the modern era of radiation therapy for muscle invasive bladder cáncer: A single tertiary cáncer center experience. *Int J Radiat Oncol Biol Phys*. (2020) 108:E918. doi: 10.1016/j.ijrobp.2020.07.557

102. Zygogianni A, Kouloulias V, Armpilia C, Antypas C, Kantzou I, Balafouta M, et al. A weekly hypofractionated radiotherapeutic schedule for bladder carcinoma in elderly patients: local response, acute and late toxicity, dosimetric parameters and pain relief. *JBUON*. (2013) 18:407–12.

103. Hsieh C, Chung S, Chan P, Lai S, Chang H, Hsiao C, et al. Intensity modulated radiotherapy for elderly bladder cáncer patients. *Radiat Oncol*. (2011) 6:75. doi: 10.1186/1748-717X-6-75

104. Hafeez S, McDonald F, Lalondrelle S, McNair H, Warren-Oseni K, Jones K, et al. Clinical outcomes of image guided adaptive hypofractionated weekly radiotherapy for bladder cáncer in patients unsuited for treatment. *Int J Radiat Oncol Phys Biol*. (2017) 98:115–22. doi: 10.1016/j.ijrobp.2017.02.223

105. Xue Q. The frailty síndrome: Definition and natural history. *Clin Geriatr Med*. (2011) 27:1–15. doi: 10.1016/j.cger.2010.08.009

106. Ethun CG, Bilen MA, Jani AB, Maithel SK, Ogan K, Master VA. Frailty and cáncer: implication for oncology surgery, medical oncology, and radiation oncology. *CA Cancer J Clin*. (2017) 67:362–77. doi: 10.3322/caac.21406

107. Takahashi M, Takahashi M, Komine K, Yamada H, Kasahara Y, Chikamatsu S, et al. The G8 screening tool enhances prognostic value to ECOG performance status in elderly cáncer patients: a retrospective, single institution study. *PloS One*. (2017) 12: e0179694. doi: 10.1371/journal.pone.0179694

108. Bellera CA, Rainfray M, Mathoulin-Pelissier S, Mertens C, Delva F, Fonck A, et al. Screening older cáncer patients: first evaluation of the G8 screening tool. *Ann Oncol*. (2012) 23:2166–72. doi: 10.1093/annonc/mdr587

109. Gross ND, Miller DM, Khushalani NI, Divi V, Ruiz ES, Lipson EJ, et al. Neoadjuvant cimiplimab for stage II-IV cutaneous squamous cell carcinoma. *N Engl J Med*. (2022) 387:1557–68. doi: 10.1056/NEJMoa2118823

110. Tree AC, Jones K, Hafeez S, Sharabiani MTA, Harrington KJ, Lalondrelle S, et al. Dose-limiting urinary toxicity with pembrolizumab combined with weekly hypofractionated radiation therapy in bladder cáncer. *Int J Radiat Oncol Biol Phys*. (2018) 101:1168–71. doi: 10.1016/j.ijrobp.2018.04.070

111. Popescu T, Karlsson U, Vinh-Hung V, Trigo L, Thariat J, Vuong T, et al. Challenges facing radiation oncologists in the management of older cancer patients: Consensus of the International Geriatric Radiotherapy Group. *Cancers*. (2019) 11:271. doi: 10.3390/cancers11030371

112. Nguyen NP, Vinh-Hung V, Baumert B, Zamagni A, Arenas M, Motta M, et al. Older cancer patients during the COVID-19 epidemic: practice proposal of the International Geriatric Radiotherapy Group. *Cancers*. (2020) 12:1287. doi: 10.3390/cancers12051287

frontiers | Frontiers in Oncology

TYPE Review
PUBLISHED 16 July 2024
DOI 10.3389/fonc.2024.1384906

OPEN ACCESS

EDITED BY
Mohammad Mohammadianpanah,
Shiraz University of Medical Sciences, Iran

REVIEWED BY
Elisa Roca,
Casa di cura Pederzoli, Italy
Savvas Lampridis,
Imperial College London, United Kingdom

*CORRESPONDENCE
Li Zhang
zzzzbear2023@163.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 11 February 2024
ACCEPTED 02 July 2024
PUBLISHED 16 July 2024

CITATION
Chen Q, Ying S, Qin J and Zhang L (2024) Optimization of treatment strategies for elderly patients with advanced non-small cell lung cancer.
Front. Oncol. 14:1384906.
doi: 10.3389/fonc.2024.1384906

Optimization of treatment strategies for elderly patients with advanced non-small cell lung cancer

Qiang Chen[1†], Shuo Ying[2†], Jianwen Qin[1] and Li Zhang[1*]

[1]Department of Respiratory and Critical Care Medicine, Tianjin Chest Hospital, Tianjin, China, [2]Department of Cardiology, Tianjin Chest Hospital, Tianjin, China

Lung cancer stands as a malignant neoplasm bearing the highest burden of morbidity and mortality within the elderly population on a global scale. Among the lung cancer subtypes, non-small cell lung cancer (NSCLC) prevails as the most prevalent. As age advances, elderly patients often present with an increased prevalence of comorbidities, diminished organ reserve function, and alterations in drug pharmacokinetics, including absorption, distribution, metabolism, and clearance. These factors collectively contribute to a reduction in their capacity to tolerate therapeutic interventions. Regrettably, there exists a paucity of research data and evidence regarding the management of elderly patients afflicted by advanced lung cancer. This article endeavors to compile and elucidate strategies for the enhancement of treatment approaches, with the aim of aiding clinical decision-making. Prior to the selection of clinical treatment modalities for elderly patients with advanced NSCLC, a comprehensive assessment should be conducted, taking into account various facets, including tumor characteristics, patient age, physiological status, and the presence of comorbidities. The treatment strategy should be implemented in a tiered fashion, thereby affording the opportunity for the tailoring of individualized therapeutic approaches for elderly patients afflicted by advanced NSCLC. The demographic of elderly patients confronting advanced NSCLC presents a complex landscape marked by intricate underlying conditions, necessitating the imperative optimization of treatment strategies.

KEYWORDS

advanced non-small cell lung cancer (NSCLC), elderly, lack of clinical evidence, assessment tools, optimized treatment

1 Introduction

In 2020, lung cancer ranked as the second most frequently diagnosed malignancy and claimed the top spot as the leading cause of cancer-related mortality. It constituted roughly 11.4% of all newly diagnosed cancer cases and accounted for a staggering 18.0% of cancer-related deaths (1). In the year 2023, it is projected that approximately 350 individuals will

succumb to lung cancer daily in the United States, firmly maintaining its status as the foremost cause of cancer fatality (2). This ailment predominantly affects the elderly population, with the median age at the time of diagnosis hovering around 70 years (3). Among the various forms of lung cancer, non-small cell lung cancer (NSCLC) prevails as the most prevalent, comprising approximately 85% of cases (4).

Elderly patients grappling with this disease often present with an array of underlying health conditions, utilize numerous concomitant medications, experience a decline in organ function, and undergo alterations in pharmacokinetics and pharmacodynamics. Paradoxically, this patient demographic is frequently underrepresented in clinical trials. Conventional lung cancer treatments may exacerbate the incidence of increasingly severe adverse events (AEs) in this context. The burgeoning field of geriatric oncology has witnessed significant advancements in recent years, advocating for a comprehensive evaluation of elderly individuals both before and during their cancer treatment, aiming to deliver more precise therapeutic interventions (5). The primary objective of this article is to consolidate and elucidate the concept of geriatric assessment and the optimization of treatment strategies for elderly patients with advanced NSCLC, with the aspiration of furnishing a valuable reference for clinical practice.

1.1 Definition of old age

The definition of 'old age' lacks a universally accepted standard due to its subjective nature, reliant upon social, economic, and health-related variables. In most industrialized societies, old age is conventionally defined at the age of 70, whereas in less affluent regions, age 65, 60, or even 55 might serve as the demarcation point (6). The National Comprehensive Cancer Network (NCCN) Geriatric Oncology Guidelines delineate the elderly as individuals aged 65 and above, further subdividing them into three categories: those aged 65 to 75 categorized as young elderly, those between 76 and 85 as elderly, and those over 85 as advanced aged (7).

2 Optimization strategy

2.1 Strategy 1: utilize appropriate tools for pre-treatment assessment

The elderly population exhibits a considerable degree of heterogeneity, with age alone unable to adequately capture the extent of aging. In the realm of geriatric oncology, treatment strategies for patients should pivot primarily on functional status rather than age, allowing for a balanced consideration of the benefits and risks associated with treatment. Therefore, a comprehensive assessment of the patient's overall condition before initiating treatment is imperative to maximize organ function preservation during the therapeutic process (6).

Several assessment tools are currently employed to evaluate the health status of cancer patients, predict treatment efficacy, and assess tolerance. Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) scores are widely used to evaluate the functional status of cancer patients. However, these methods fall short in capturing the overall status of elderly cancer patients and accurately predicting adverse outcomes of chemotherapy, thereby having limitations in guiding treatment (8). Consequently, the International Society of Geriatric Oncology (SIOG) and the American Society of Clinical Oncology (ASCO) strongly advocate for the incorporation of comprehensive geriatric assessment (CGA) into the management plans for these patients. CGA encompasses multiple dimensions beyond conventional medical assessment, including functional status, fatigue, comorbidities, cognitive function, mental health, social support, nutrition, and geriatric syndromes (9, 10). A systematic review conducted by Hamaker et al. (11) revealed that 28% of patients modified their oncology treatment plans, with the majority receiving fewer intensive regimens, while a median of 72% of patients opted for non-oncological interventions. 75% of the studies in this review demonstrated that the geriatric assessment group exhibited higher treatment completion rates, with 55% of the studies indicating lower treatment-related toxicities or complications. Quite a few real-world studies use ECOG PS as an assessment tool, which limits the ability to generalize data and compare it with other case series from different institutions. Current studies suggest that age and PS scores do not fully reflect the physical condition of elderly patients, and that CGA should be conducted according to the guidelines to avoid overtreatment or undertreatment (12–16). It is inferred that geriatric assessment can enhance treatment tolerance and completion in elderly cancer patients.

2.1.1 Chemotherapy risk assessment tools: cancer aging research group (CARG) and chemotherapy risk assessment scale for high-age patients (CRASH)

The primary tools recommended for assessing chemotherapy risk in elderly patients encompass the following: CARG chemotherapy risk assessment scale (17), CRASH (18), instrumental activities of daily living (IADL), activities of daily living (ADL), Charlson comorbidity index (CCI), cumulative illness rating scale-geriatric (CIRS-G), mini-mental state examination (MMSE), geriatric depression scale (GDS), geriatric screening tool-8 (G-8) and vulnerable elders survey-13 (VES-13), among others (8).

Of particular clinical significance, CARG and CRASH exhibit comprehensive coverage and robust clinical applicability. Moreover, they exhibit comparable predictive performance for chemotherapy resistance (19), positioning them as the most promising tools for optimizing chemotherapy regimens (6). Hurria et al. (17) initially introduced the CARG scale in a prospective cohort study involving 500 cancer patients aged 65 and older, with 29% diagnosed with lung cancer. The study found that patients classified as low risk, medium risk, or high risk based on the CARG scale had proportions of grade three to five chemotherapy-related AEs of 30%, 52%, and 83%, respectively ($P < 0.001$). Conversely, when risk grouping was based on KPS scores, no significant difference in the incidence of chemotherapy-related AEs was observed in each group ($P = 0.19$). Subsequent analysis involved calculating the area under the receiver operating

characteristic (ROC) curve, revealing that the CARG outperformed KPS in predicting chemotherapy-related AEs (0.72 vs. 0.53). This has led to the speculation that the CARG scale possesses predictive capabilities regarding chemotherapy tolerance in elderly patients, a hypothesis substantiated by subsequent research (20). In 2012, Extermann et al. (18) proposed the CRASH scale for the first time. The scale was based on a introduced the CRASH scale, based on a prospective cohort study encompassing 562 cancer patients, including 518 evaluable cases, with an average age of 70 years or older (20% of whom were lung cancer patients). The study demonstrated that the CRASH scale could predict the incidence of hematological and non-hematological toxicity induced by chemotherapy drugs, suggesting its potential to forecast chemotherapy tolerance in elderly patients. CARG and CRASH are shown in Tables 1–3, respectively.

2.1.2 Targeting and immunotherapy evaluation tools: G-8 and VES-13

The utility of CGA in guiding targeted and immunotherapy for elderly patients with advanced NSCLC remains an evolving field with no established assessment tool. A prospective observational cohort study by Gomes et al. (21) involved 140 elderly patients with cancer, of which 55% were diagnosed with NSCLC. The study categorized patients into elderly and young groups based on a 1:1 age ratio, with median ages of 75 and 62 years, respectively. The G-8 assessment was conducted before treatment in the elderly group, with a score of less than 15 indicating a positive result. Single-drug immune checkpoint inhibitors (ICIs) were administered as treatment. The study revealed that elderly patients with a positive G-8 assessment exhibited higher mortality and readmission rates, suggesting the G-8 score may play a role in predicting severe adverse events in frail elderly NSCLC patients. A recent review of screening assessment tools for elderly cancer patients (22) highlighted G-8 and VES-13 as the most commonly used assessment tools. G-8 demonstrated higher sensitivity, whereas VES-13 exhibited higher specificity, and both can be employed individually or in combination. However, it should be noted that these two assessment tools lack specificity for NSCLC, and there remains a dearth of high-quality research to validate their use.

However, CGA often requires multidisciplinary collaboration to accurately assess patients and is therefore very time-consuming, posing a significant barrier to its adoption in clinical practice (23). In the future, two approaches could be explored: First, the design of a more convenient evaluation tool, followed by large-scale prospective clinical trials to verify its effectiveness; second, the development of a calculator based on the current evaluation tool to facilitate the calculation of scores and assist in assessing pre-treatment risk.

2.2 Strategy 2: mitigate drug interactions

Elderly lung cancer patients often find themselves taking multiple medications to manage various comorbid conditions. Some studies (24, 25) have reported that the median number of concomitant medications for elderly cancer patients ranges from five to nine, with approximately 35% of patients experiencing significant drug interactions. A concise listing of common NSCLC treatment drugs and the potential effects of concurrent medications is provided for reference in Table 4 (8).

TABLE 1 CARG chemotherapy risk assessment scale.

Predictors		Points
Age (year)	65 to <72	0
	≥72	2
Cancer type	Other	0
	GI or GU	2
Chemotherapy dosing	Reduced	0
	Standard	2
No. of chemotherapy agents	Monochemotherapy	0
	Polychemotherapy	2
Hemoglobin (g/dL)	≥11 (male), ≥10 (female)	0
	<11 (male), <10 (female)	3
Creatinine clearance (mL/min)	≥34	0
	<34	3
Hearing	good	0
	fair or worse	2
No. of falls in last 6 months	None	0
	≥1	3
Medication intake	No assistance	0
	with some help/unable	1
Limited in walking 1 block	Not limited at all	0
	Somewhat limited/ limited a lot	2
Decreased social activity because of health/ emotional problems	A little, or none of the time	0
	Some, most, all of the time	1

CARG, Cancer and Aging Research Group; GI, gastrointestinal; GU, genitourinary; Low risk: 0-5 points, medium risk: 6-9 points, high risk: ≥10 points

2.3 Strategy 3: tailor drug dosages based on liver and kidney function

Hepatic and renal insufficiency is prevalent among elderly lung cancer patients. Consequently, when administering anti-tumor drugs subject to hepatic and renal metabolism, it is imperative to make appropriate adjustments to the dosage to mitigate adverse effects. A succinct compendium of common NSCLC treatment drugs necessitating dosage adjustments is provided for reference in Table 5 (8).

TABLE 2 CRASH score.

Predictors	Points			Risks	
	0	1	2	Single	combined
Hematologic score*				Low: 0-1 points	Low: 0-3 points
Diastolic BP	≤72	>72		Med low: 2-3 points	Med low: 4-6 points
IADL	26-29	10-25		Med high: 4-5 points	Med high: 7-9 points
LDH (if ULN 618 U/L; otherwise, 0.74/L*ULN)	0-459		>459	High: 6-8 points	High: ≥10 points
Chemotox[&]	0-0.44	0.45- 0.57	>0.57		
Nonhematologic score*				Low: 0-2 points	
ECOG PS	0	1-2	3-4	Med low: 3-4 points	
MMS	30		<30	Med high: 5-6 points	
MNA	28-30		<28	High: 7-8 points	
Chemotox[&]	0-0.44	0.45-0.57	>0.57		

CRASH, the chemotherapy risk assessment scale for high-age patients; BP, blood pressure; Chemotox, toxicity of the chemotherapy regimen; ECOG PS, Eastern Cooperative Oncology Group performance status; IALD, instrumental activities of daily living; LDH, lactate dehydrogenase; MMS, Mini Mental Health Status; MNA, Mini Nutritional Assessment; ULN, upper limit of normal.

* For the combined risks, add the points from the hematologic and nonhematologic score, counting Chemotox only once.

[&] For examples of Chemotox values for specific regimens, see Table 3.

2.4 Strategy 4: selecting the optimal treatment option

Clinical trials provide a critical foundation for formulating guidelines and guiding treatment. However, current clinical trial results cannot be generalized to elderly patients with advanced NSCLC. Subgroup analyses of older patients were conducted retrospectively, and those who participated in clinical trials were generally healthier than those treated in routine practice, resulting in a lack of real-world evidence. Additionally, traditional cancer clinical trials are often time-consuming and expensive, and they frequently produce results with limited real-world applicability, posing challenges for patient participation.

Real-world data studies offer a promising solution to fill evidence gaps and provide essential information about the effects of cancer treatments in real-world settings. However, the quality of real-world data can affect the reliability of real-world evidence. Therefore, combining traditional clinical trials with real-world data studies can provide a stronger foundation for treatment decisions in elderly patients with advanced NSCLC (26).

2.4.1 Preferred treatment for patients with positive driver mutations: targeted Therapy

The driver gene profiles of elderly patients exhibit certain characteristics, which, however, are not significantly different from those of younger patients. Targeted therapy offers distinct advantages, including minimal side effects, good tolerance, enhanced quality of life, and potential improvements in prognosis. Consequently, it is recommended that patients with non-squamous NSCLC and certain squamous cell carcinomas undergo routine screening for specific driver gene mutations, such as epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) fusion genes, ROS1 fusion genes, RET fusion genes, BRAF gene V600E mutation, MET gene exon 14 skipping mutation, and other pertinent driver genes. Targeted therapy is the primary treatment choice for elderly patients with advanced NSCLC who test positive for these driver mutations (8, 27).

2.4.1.1 EGFR - tyrosine kinase inhibitors: third generation > second generation > first generation

In China, EGFR-TKIs approved for first-line treatment are categorized into three generations: the first generation includes gefitinib, erlotinib, and icotinib; the second generation comprises afatinib and dacomitinib, while the third generation features osimertinib and ametinib. A meta-analysis conducted by Greenhalgh et al. (28) revealed that when compared to chemotherapy, EGFR-TKIs demonstrate superior outcomes, including a better tumor response rate, extended progression-free survival (PFS), fewer AEs, and an enhanced health-related quality of life. However, it is noteworthy that limited research has indicated whether EGFR-TKIs contribute to longer overall survival (OS).

Meta-analyses have underscored the advantages of EGFR-TKIs in the treatment of elderly patients with advanced NSCLC. However, these studies have not delved into the therapeutic distinctions among various EGFR-TKIs. A retrospective observational cohort study comparing first- and second-generation EGFR-TKIs (29) among patients aged 60 years and older, it was found that the median OS was 19.1 months for gefitinib, 22.9 months for erlotinib, and an impressive 35.6 months for afatinib. The OS of the afatinib group not only exceeded that of the gefitinib group (P= 0.009) but also outperformed the gefitinib combined with erlotinib group (35.5 vs. 21.4 months, P=0.016). Remarkably, there was no statistically significant difference in PFS among these three groups. This suggests that the longer OS observed in the afatinib group might

TABLE 3 Example of chemotox values for various chemotherapy regimens.

Points[#]		
0	1	2
Capecitabine 2g	Capecitabine 2.5 g	5-FU/LV (Roswell-Park)
Cisplatin/pemetrexed	Carboplatin/gemcitabine AUC 4-6/1 g d1, d8	5-FU/LV (Mayo)
Dacarbazine	Carboplatin/pemetrexed	5-FU/LV and bevacizumab
Docetaxel weekly	Carboplatin/ paclitaxel q3w	CAF
FOLFIRI	Cisplatin/gemcitabine d1, d8	Carboplatin/ docetaxel q3w
Gemcitabine 1 g 3/4 wk	ECF	CHOP
Gemcitabine 1.25 g 3/ 4 wk	Fludarabine	Cisplatin/docetaxel 75/75
Paclitaxel weekly	FOLFOX 85 mg	Cisplatin/etoposide
Pemetrexed	Gemcitabine 7/8 wk then 3/4 wk	Cisplatin/gemcitabine d1, d8, d15
	Gemcitabine/irinotecan	Cisplatin/paclitaxel 135-24 h q3w
	PEG doxorubicin 50 mg q4w	CMF classic
	Topotecan weekly	Doxorubicin q3w
	XELOX	FOLFOX 100-130 mg
		Gemcitabine/ pemetrexed d8
		Irinotecan q3w
		Paclitaxel q3w
		Docetaxel q3w
		Topotecan monthly

5-FU, 5-fluorouracil; AUC, area under the concentration-time curve; CAF, cyclophosphamide, doxorubicin,and 5-fluorouracil; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; ECF, epirubicin, cisplatin and 5-fluorouracil; FOLFIRI, irinotecan, leucovorin, and 5-fluorouracil; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; LV, leucovorin; PEG, pegylated; q3w, every 3 weeks; q4w, every 4 weeks; XELOX, capecitabine and oxaliplatin
[#]Unless specified otherwise, the doses are per meter squared. If no dose is specified, then this means that the various common doses used for this regimen all fall into the same category.

be attributed to different resistance mechanisms that manifest during treatment. Subgroup analysis from the successive ARCHER1050 studies (30, 31) demonstrated that dacomitinib can significantly prolong PFS compared with gefitinib in patients aged 65 years and older (Hazard Ratio (HR)= 0.69, 95% confidence interval (CI): 0.48-0.99), though there was no significant OS benefit (HR=0.987, 95% CI: 0.687-1.419).

It's important to note that the selected population of these studies excluded individuals who had developed central nervous system (CNS) metastasis, a condition associated with shorter survival. Among NSCLC patients with EGFR mutations, roughly 25% present with CNS metastasis at the time of diagnosis, and approximately 50% develop CNS metastasis within three years of diagnosis (32).

Moreover, most NSCLC patients with EGFR mutations experience disease progression after nine to thirteen months, with over half attributed to the EGFR exon 20 T790M mutation (33). As a third-generation EGFR-TKI, osimertinib can selectively inhibit EGFR-TKI sensitizing mutations and T790M resistance mutations, while also exhibiting activity within the CNS. The FLAURA study (34, 35) confirmed that the use of osimertinib in patients aged 65 years and older could significantly extend PFS compared to first-generation EGFR-TKIs (HR=0.49, 95% CI: 0.35-0.67). However, the OS benefit was not statistically significant (HR=0.87, 95% CI: 0.63-1.22).

In the last five years, real-world studies have shown that although EGFR-TKIs are effective and safe for older adults, and their PFS in patients is generally consistent with the results of clinical trials, the improvement in OS is limited (3, 36, 37). One study found that older individuals treated with osimertinib had longer PFS than those treated with first-generation EGFR-TKIs. However, it cannot be ignored that osimertinib has a higher risk of pneumonia compared to first-generation EGFR-TKI therapy (38).

2.4.1.2 ALK-TKIs: Alectinib as the preferred choice

ALK fusion gene positivity is a relatively rare occurrence in NSCLC, accounting for approximately 3 to 5% of cases. It is more prevalent among younger individuals, those with adenocarcinoma, and never-smokers. ALK-TKIs approved for use in China are categorized into two generations: the first generation, represented by crizotinib, and the second generation, which includes alectinib, ceritinib, and ensartinib. A subgroup analysis of the PROFILE 1014 study (39) revealed that elderly patients aged 65 years or older treated with crizotinib experienced longer PFS when compared to chemotherapy (HR=0.37, 95% CI: 0.17-0.77). However, the clinical application of crizotinib is limited due to the high incidence of secondary mutations in the ALK gene during its treatment. The ASCEND-4 study (40) demonstrated the potential of ceritinib to prolong median PFS in various subgroups, including elderly patients aged 65 years or older (HR=0.45, 95% CI: 0.24-0.86), when compared to chemotherapy. While second-generation ALK-TKIs have shown promising response rates and survival benefits (41), studies focused on elderly patients remain scarce, with most results arising from subgroup analyses. A multicenter, randomized, open-label phase III study (42) found that ensartinib significantly extended the median PFS compared to crizotinib, though no significant difference was observed in the PFS subgroup analysis of elderly patients aged 65 years or older. The ALEX study (43) demonstrated that the use of alectinib in elderly patients aged 65 years or older, when compared to crizotinib, significantly prolonged PFS (HR= 0.45, 95% CI: 0.24-0.87). A real-world retrospective study (44) encompassing 53 patients with ALK fusion gene-positive advanced NSCLC categorized into two age groups (<65 and ≥65 years) and treated with crizotinib, ceritinib, and alectinib respectively, found that age did not significantly impact PFS and OS in either group. Patients treated with alectinib exhibited the lowest incidence of AEs, with ceritinib showing the highest, and

TABLE 4 Common NSCLC treatment drugs have related effects with other drugs.

medicine	other drugs	result
Carboplatin, etoposide, gemcitabine, paclitaxel, and gefitinib	Warfarin	Increase the blood concentration of warfarin and the risk of bleeding
Cisplatin	Phenytoin	Reduce the blood concentration of phenytoin, which is not conducive to epilepsy control
First- and third-generation EGFR-TKIs	carbamazepine, phenytoin	Reduce the plasma concentration of first- and third-generation EGFR-TKIs and affect the efficacy
First-generation EGFR-TKIs	itraconazole	Increase the plasma concentration of first-generation EGFR-TKIs and increase adverse drug reactions
First-generation EGFR-TKIs	PPIs	Reduce the absorption of first-generation EGFR-TKIs and increase the risk of death
ICIs	PPIs	Affect the efficacy of ICIs and increase the risk of poor prognosis

NSCLC, non-small cell lung cancer; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors; PPIs, proton pump inhibitors; ICIs, immune checkpoint inhibitors.

crizotinib falling in between. This suggests that in elderly advanced NSCLC patients with ALK fusion gene positivity, crizotinib, ceritinib, and alectinib offer similar efficacy but varying safety profiles. Alectinib stands out with a lower incidence of serious AEs and a reduced rate of treatment discontinuation, making it a promising first-line treatment option for elderly NSCLC patients with positive ALK fusion genes (8).

2.4.1.3 Other genetic mutations

fFor other gene mutations with lower incidence rates, we will provide concise recommendations. Savolitinib is a suitable option for elderly patients who have progressed after platinum-based chemotherapy with MET exon 14 skipping mutation or those who cannot tolerate platinum-based chemotherapy (45). Crizotinib is an effective choice for elderly patients with a ROS1 fusion-positive gene (46). The combination of dabrafenib and trametinib is recommended for elderly patients with a BRAF V600E mutation (47). Platinib is a viable treatment for elderly patients with a positive RET fusion gene (48).

TABLE 5 Common therapeutic drugs for NSCLC requiring dose adjustment.

Reason for adjustment	Representative medicine
Dosage needs to be adjusted based on renal function	Cisplatin, carboplatin, pemetrexed, etoposide, and crizotinib
Mild to moderate hepatic insufficiency requires to adjust dose	Docetaxel, paclitaxel, nab-paclitaxel, gemcitabine, gefitinib, erlotinib, crizotinib, and brigatinib
Severe hepatic impairment requires dose adjustment	Alectinib, ceritinib, osimertinib, pemetrexed, etoposide, and vinorelbine

2.4.2 ICIs: pembrolizumab single agent is preferred

ICIs have ushered in groundbreaking advancements in the treatment of advanced lung cancer, making them a focal point in the realm of lung cancer treatment. Subgroup analysis of KEYNOTE-024 study (49) revealed that among elderly patients with advanced NSCLC exhibiting high expression of programmed cell death ligand 1 (PD-L1) (TPS ≥50%) and lacking EGFR/ALK mutations, pembrolizumab was consistent with the overall population in extending OS and significantly outperformed chemotherapy (HR=0.64, 95% CI: 0.42-0.98). In a subgroup analysis of the EMPOWER Lung-01 study (50), elderly patients with advanced NSCLC and high PD-L1 expression experienced significant extensions in both OS and PFS when treated with cemiplimab compared to chemotherapy. A real-world study (51) involving 2049 patients who received ICIs demonstrated that elderly patients aged ≥75 years, after undergoing immune monotherapy, exhibited no significant difference in OS compared to patients aged 50-75 or <50 years. Both non-elderly and elderly patients benefited from PFS when platinum-based chemotherapy was combined with pembrolizumab in the Keynote-189 (52) and Keynote-407 (53), though the benefit was somewhat lower in elderly patients. In the IMpower 150 study (54), elderly patients aged ≥75 years did not experience a significant PFS benefit with atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (ABCP) compared to the bevacizumab plus carboplatin plus paclitaxel (BCP) group, while non-elderly patients showed significant benefits in a subgroup (65-75 years old: 9.7 vs 6.9 months, P<0.05; <65 years old: 8.0 vs 6.8 months, P<0.05). In the phase III randomized CheckMate-227 trial (55), nivolumab combined with ipilimumab offered a modest OS benefit to patients aged ≥75 and 65-74 years old compared to chemotherapy, but this benefit was less pronounced than in patients under 65. In the Check-Mate 9LA study (56), patients aged ≥75 years did not derive an OS benefit, while those under 75 experienced significant OS benefits. These results suggest that the diminished OS benefit in elderly patients under intensive combination therapy may be associated with lower tolerability. According to the FDA's retrospective summary analysis (57), when PD-L1 expression is ≥50%, there is no difference in survival between chemotherapy combined with ICIs and ICIs alone in patients aged 65-74 years. Patients aged ≥75 years exhibited better survival outcomes with ICIs than with chemotherapy combined with ICIs. For patients with PD-L1 expression of 1-49%, chemotherapy combined with ICIs was superior to ICIs alone in patients under 75 years old, but there was no difference in survival between these two treatment strategies in patients aged ≥75 years.

A meta-analysis (58) of patients receiving nivolumab for advanced renal cell carcinoma, melanoma, and NSCLC demonstrated that the incidence of all-grade AEs was similar in elderly and non-elderly patients, but elderly patients had a higher incidence of ≥grade three AEs (71.7% vs. 58.4%). Conversely, in a

pooled analysis (59) encompassing the CheckMate-057, KEYNOTE-010, OAK, and POPLAR studies, the incidence of grade three to four immune-related AEs in individuals aged ≥75 years was lower than in each age group under 75 years (23% vs. 47%, 49%), and the incidence of AEs leading to treatment discontinuation was similar (5% vs. 7%, 7%). These findings suggest that older age does not increase the number of immune-related AEs leading to treatment termination and may even reduce it.

Although the real-world study included a heterogeneous population of patients treated with different types of PD-(L)1 inhibitors, these patients received different treatment regimens (60), and direct comparisons between the study results and clinical trials are not reasonable (61). However, real-world studies have reached conclusions similar to clinical studies, namely that old age is not a substitute for clinical frailty, nor is age a limiting condition for immunotherapy (12, 13, 23, 60, 62–75). Many studies have shown that older patients exhibit similar efficacy and safety in immunotherapy as the general population. A real-world study comparing the effectiveness of pembrolizumab, nivolumab, and atezolizumab found objective response rates (ORR) and disease control rates (DCR) of 22.4%, 8.2%, and 4.3% (p = 0.004) and 59.2%, 55.7%, and 30.0% (p = 0.001), respectively. Although there was no difference in OS between the three groups (12.6 months vs. 8.4 months vs. 7.7 months, p = 0.334), pembrolizumab had the longest OS. In the PD-L1 ≥ 50% subgroup, pembrolizumab showed a statistically significant OS advantage compared to atezolizumab (pembrolizumab vs. atezolizumab, p = 0.023; nivolumab vs. atezolizumab, p = 0.153; pembrolizumab vs. nivolumab, p = 0.406) (61).

In conclusion, it is recommended that elderly patients with advanced NSCLC who exhibit high PD-L1 expression should be treated with ICIs monotherapy as the first-line approach. While ICIs combination therapy demonstrates a beneficial trend in patients under 75 years old, there is insufficient evidence to support its use in patients aged ≥75 years.

2.4.3 Chemotherapy: preferential use of single-agent regimen with third-generation non-platinum chemotherapy drugs for patients lacking driver genes or exhibiting low PD-L1 expression in NSCLC

The third generation of non-platinum chemotherapy drugs comprises agents such as vinorelbine, gemcitabine, paclitaxel, docetaxel, and pemetrexed. Previous studies have extensively examined the survival outcomes and safety profile of chemotherapy in elderly lung cancer patients. For elderly patients with advanced NSCLC who lack targeted driver gene mutations and exhibit low PD-L1 expression, platinum-containing doublet combination therapy is the recommended first-line treatment option for those who are suitable (76). However, this approach can be associated with greater AEs, making it unsuitable for elderly patients or individuals in poor health. The ELVIS study (77) investigated 191 elderly patients aged 70 years and above with advanced NSCLC. Results revealed that, when compared to the best supportive care (BSC) group alone, the vinorelbine combined with BSC group significantly prolonged the median survival time (MST) (28 weeks vs. 21 weeks), improved the 1-year survival rate (32% vs. 14%), and enhanced the quality of life (QOL). A meta-analysis (78) that included data from 10 studies involving a total of 2,510 elderly patients with advanced NSCLC demonstrated that the response and survival rates were superior in the platinum-containing doublet chemotherapy group compared to single-agent therapy. However, it's worth noting that the incidence of grade 3/4 adverse events such as anemia, thrombocytopenia, and neurological toxicity was higher in the doublet chemotherapy group.

A real-world study involving 474 consecutive elderly patients (≥70 years of age) diagnosed with stage IIIB-IV NSCLC found that a platinum-based dual-drug regimen (OR 2.23, 95% CI 1.02-4.87, p<0.04) was an independent risk factor for hospitalization. The use of a platinum-based dual-drug regimen was associated with a higher risk of hospitalization and conferred no survival benefit compared to a third-generation single-drug chemotherapeutic regimen (79).

In summary, when considering treatment options for elderly patients, it is crucial to conduct a comprehensive assessment of their overall health and ability to tolerate double-drug chemotherapy. This approach is recommended as the first-line treatment for elderly patients without driver gene mutations and with low PD-L1 expression.

2.4.4 Anti-angiogenic drugs: consistency in therapeutic dosage and safety across the patient population

Anti-angiogenic therapeutic drugs, whether administered alone or in combination with chemotherapy, EGFR-TKIs, or immune checkpoint inhibitors, have demonstrated significant efficacy (8). The ALTER0303 study (80) revealed that anlotinib exhibited notable benefits for elderly patients, exhibiting superior PFS (HR=0.22, 95% CI: 0.07-0.64) and OS (HR=0.34, 95% CI: 0.12-0.94), particularly among those aged ≥70 years. Conversely, the POINTBREAK study (81) showed that while the combination of chemotherapy with anti-angiogenic drugs extended PFS compared to chemotherapy alone (6.0 months vs. 5.6 months), there was no significant difference in OS. The ARIES study (82) reported that combining bevacizumab with chemotherapy in elderly patients did not result in different PFS and adverse event profiles when compared to their non-elderly counterparts, although OS was slightly shorter. In the NEJ026 study (83), elderly patients with EGFR fusion gene-positive NSCLC, both those < 75 and ≥75 years old, experienced PFS benefits from erlotinib combined with bevacizumab. Similarly, the ACTIVE study (84) demonstrated improved PFS in the elderly subgroup when apatinib was combined with gefitinib (HR=0.9 vs. 0.67). Studies like those referenced (82, 85, 86) indicate that the adverse event grading for bevacizumab combined with chemotherapy mostly remained below grade two, with no statistical difference in the incidence of grade three and higher adverse events between elderly and non-elderly patients. This suggests that the safety profile of anti-angiogenic treatment is comparable for both elderly and non-elderly lung cancer patients.

In a real-world study that retrospectively collected electronic medical records of NSCLC patients receiving Endostar combined with chemotherapy, 554 and 571 patients were assigned to ≤60 years of non-elderly patients and >60 years of elderly patients, respectively, and performed propensity score matching. Results showed no significant difference in efficacy between the two groups, and the adverse reactions were tolerable (87). Another study retrospectively enrolled 83 elderly patients (>65 years of age) with NSCLC who had previously received at least two lines of systemic therapy and whose disease had progressed. The ORR was 7.2% (95% CI = 2.7-15.1%) and the DCR was 78.3% (95% CI = 67.9-86.6%), consistent with the ALTER0303 clinical trial. This study found that the third-line efficacy of anlotinib monotherapy in the treatment of elderly patients with advanced NSCLC was satisfactory, and the safety was tolerable (88).

It is important to note that elderly patients often present with underlying cardiovascular and cerebrovascular conditions, and the risk of these conditions may increase with the use of anti-angiogenic drugs. Therefore, treatment decisions should not be based solely on age and should be approached with caution and vigilant monitoring.

2.4.5 Radiotherapy - dearth of robust evidence presently

For patients with unresectable stage III NSCLC, the guidelines recommend concurrent chemoradiotherapy (cCRT) with subsequent durvalumab treatment for one year (76). Subgroup analysis of the PACIFIC study (89, 90) compared patients who received cCRT followed by durvalumab with those who received cCRT followed by a placebo. In the elderly subgroup aged ≥65 years, there was a prolonged PFS (HR=0.74, 95% CI: 0.54-1.01) and a 5-year OS (HR=0.79, 95% CI: 0.60-1.05), although the differences were not statistically significant. A retrospective study conducted using real-world data from the Netherlands (91) involved 2,942 patients with stage III NSCLC who underwent radical chemoradiotherapy (CRT). The study categorized patients into two groups: cCRT and sequential chemoradiotherapy (seqCRT). The median ages for these groups were 66 and 69 years, respectively. The study found that age itself was not a risk factor for acute toxicity or 3-month mortality after a three-month follow-up. However, it was noted that patients treated with cCRT, those with a higher TNM stage (IIIC) and poorer baseline health status had significantly higher three-month toxicity.

A retrospective analysis was conducted in patients with unresectable lung cancer who received treatment. Although older patients who received synchronous CRT had better OS (median OS: 40.9 months vs. 24.4 months), this difference was not statistically significant in the multivariate analysis (P = 0.09), suggesting that the treatment outcome in the elderly remained unsatisfactory and that the effect of multimodal therapy on elderly patients was limited (92). Two other studies found no association between age 70 and factors such as grade 3-4 CRT or Durvalumab toxicity, reduced chemotherapy dose, delay or cessation of treatment, progression, or death. These findings reinforce the current guideline recommendation that cCRT is associated with optimal outcomes in unresectable locally advanced NSCLC, even in older patients (93, 94).

In summary, there is currently insufficient evidence to make strong recommendations regarding the use of radiotherapy and chemotherapy in elderly patients with stage III NSCLC.

2.4.6 Surgical interventions: current lack of sufficient evidence

The current guidelines (76) do not provide a surgical strategy for elderly patients with advanced NSCLC, and the suitability of surgical interventions for such patients remains undetermined. Kirk et al. (95) conducted a retrospective study to investigate the safety of lobectomy in NSCLC patients aged 80 years or older. They found that surgical morbidity and mortality were not increased in this age group; however, it's important to note that the proportion of patients in this age category was low (4.9%). Additionally, these patients underwent rigorous screening and had low rates of smoking and pre-existing respiratory, cardiovascular, and neurological diseases. These factors could potentially introduce biases into the conclusions. As a result, more prospective research evidence is necessary to establish whether elderly patients with advanced NSCLC can benefit from surgical interventions.

3 Conclusions

the incidence of lung cancer in the elderly is on the rise, and these patients often present complex underlying health conditions. The available clinical evidence for guiding treatment decisions is notably limited, making the precise treatment of elderly patients a significant challenge. While some assessment tools for elderly patients are currently used in clinical practice, their results and simplicity are not ideal. These tools are primarily geared towards making chemotherapy decisions, and there remains a notable absence of tools designed for targeted therapies and immunotherapies.

For elderly patients with advanced NSCLC who possess driver genes, targeted therapy is the preferred treatment, though its efficacy might be reduced in patients with an ECOG PS score of two or higher. The G-8 and VES-13 scales are useful for pre-treatment evaluation. When chemotherapy is the chosen treatment for elderly patients with advanced NSCLC, the CARG or CRASH scale can be employed to assess their chemotherapy tolerance before initiating treatment. Elderly patients with advanced NSCLC and high PD-L1 expression can receive immune monotherapy, but combination therapy is not recommended for those aged 75 and older. Anti-angiogenic drugs can be used either alone or in combination and have demonstrated effectiveness in elderly patients with advanced NSCLC, but a thorough assessment of the risks related to blood and cerebrovascular diseases is essential.

Furthermore, elderly patients face numerous unfavorable factors when it comes to treatment, and distinguishing whether their death is due to cancer or other causes can be challenging. Therefore, the primary focus should be on preserving or enhancing

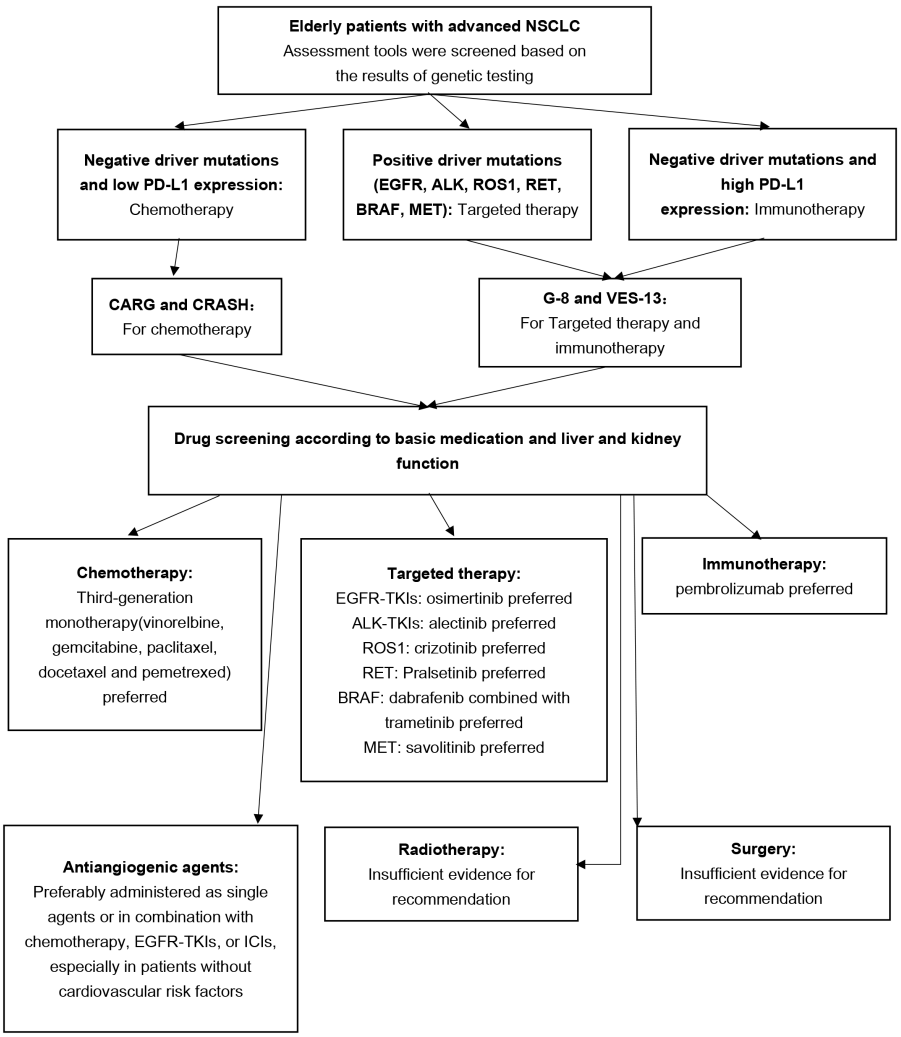


FIGURE 1
Flowchart for treating advanced non-small cell lung cancer in the elderly.

their quality of life and functional status, with extending overall survival being a secondary objective.

In the future, it is imperative to develop more straightforward and accurate assessment tools and include a greater number of elderly patients in prospective clinical studies. This will provide stronger evidence support for future treatment options and help address the unique challenges associated with treating elderly patients with lung cancer (Figure 1).

Author contributions

QC: Formal analysis, Methodology, Visualization, Writing – original draft. SY: Data curation, Investigation, Writing – original draft. JQ: Validation, Visualization, Writing – original draft. LZ: Conceptualization, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The study was funded by National Clinical Key Specialty Construction Project, Tianjin Key Medical Discipline (Specialty) Construction Project [TJYXZDXK-049A] and Tianjin Health Science and Technology Project [TJWJ2023QN063].

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. (2021) 71:209–49. doi: 10.3322/caac.21660

2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. (2023) 73:17–48. doi: 10.3322/caac.21763

3. Fukushima T, Oyamada Y, Ikemura S, Nukaga S, Inoue T, Arai D, et al. Real-world clinical practice for advanced non-small-cell lung cancer in the very elderly: A retrospective multicenter analysis. *Clin Lung Cancer*. (2022) 23:532–41. doi: 10.1016/j.cllc.2022.05.003

4. Thai AA, Solomon BJ, Sequist LV, Gainor JF, Heist RS. Lung cancer. *Lancet*. (2021) 398:535–54. doi: 10.1016/s0140-6736(21)00312-3

5. Couderc AL, Tomasini P, Rey D, Nouguerède E, Correard F, Barlesi F, et al. Octogenarians treated for thoracic and lung cancers: Impact of comprehensive geriatric assessment. *J Geriatr Oncol*. (2021) 12:402–09. doi: 10.1016/j.jgo.2020.10.005

6. Almodovar T, Teixeira E, Barroso A, Soares M, Queiroga HJ, Cavaco-Silva J, et al. Elderly patients with advanced NSCLC: The value of geriatric evaluation and the feasibility of CGA alternatives in predicting chemotherapy toxicity. *Pulmonology*. (2019) 25:40–50. doi: 10.1016/j.pulmoe.2018.07.004

7. Balducci L. Management of cancer in the elderly. *Oncol (Williston Park)*. (2006) 20:135–43.

8. Chinese Geriatric Health Care Association Lung Cancer Professional Committee, Beijing Oncology Society Lung Cancer Professional Committee. Chinese Expert Consensus on the Internal Medicine Treatment of Late-Stage Lung Cancer in the Elderly (2022 edition). *J Chin J Lung Cancer*. (2022) 25:363–84. doi: 10.3779/j.issn.1009-3419.2022.101.25

9. Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations†. *Ann Oncol*. (2015) 26:288–300. doi: 10.1093/annonc/mdu210

10. Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. *J Clin Oncol*. (2018) 36:2326–47. doi: 10.1200/jco.2018.78.8687

11. Hamaker ME, Te Molder M, Thielen N, van Munster BC, Schiphorst AH, van Huis LH. The effect of a geriatric evaluation on treatment decisions and outcome for older cancer patients - A systematic review. *J Geriatr Oncol*. (2018) 9:430–40. doi: 10.1016/j.jgo.2018.03.014

12. Yu M, Gao X, Fu S, Zhang H, Qin N, Hao X, et al. [Analysis of the efficacy of immunotherapy in elderly patients with lung cancer]. *Zhongguo Fei Ai Za Zhi*. (2022) 25:401–08. doi: 10.3779/j.issn.1009-3419.2022.102.16

13. Galli G, De Toma A, Pagani F, Randon G, Trevisan B, Prelaj A, et al. Efficacy and safety of immunotherapy in elderly patients with non-small cell lung cancer. *Lung Cancer*. (2019) 137:38–42. doi: 10.1016/j.lungcan.2019.08.030

14. Vinod S, Khoo A, Berry M, Bell K, Ahmed E, Campisi J, et al. Implementation and evaluation of a geriatric-oncology model of care for older adults with lung cancer. *J Geriatr Oncol*. (2023) 14:101578. doi: 10.1016/j.jgo.2023.101578

15. Stevens S, Nindra U, Shahnam A, Wei J, Bray V, Pal A, et al. Real world efficacy and toxicity of consolidation durvalumab following chemoradiotherapy in older Australian patients with unresectable stage III non-small cell lung cancer. *J Geriatr Oncol*. (2024) 15:101705. doi: 10.1016/j.jgo.2024.101705

16. Friedlaender A, Banna GL, Buffoni L, Addeo A. Poor-performance status assessment of patients with non-small cell lung cancer remains vague and blurred in the immunotherapy era. *Curr Oncol Rep*. (2019) 21:107. doi: 10.1007/s11912-019-0852-9

17. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol*. (2011) 29:3457–65. doi: 10.1200/jco.2011.34.7625

18. Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer*. (2012) 118:3377–86. doi: 10.1002/cncr.26646

19. Ortland I, Mendel Ott M, Kowar M, Sippel C, Jaehde U, Jacobs AH, et al. Comparing the performance of the CARG and the CRASH score for predicting toxicity in older patients with cancer. *J Geriatr Oncol*. (2020) 11:997–1005. doi: 10.1016/j.jgo.2019.12.016

20. Hurria A, Mohile S, Gajra A, Klepin H, Muss H, Chapman A, et al. Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. *J Clin Oncol*. (2016) 34:2366–71. doi: 10.1200/jco.2015.65.4327

21. Gomes F, Lorigan P, Woolley S, Foden P, Burns K, Yorke J, et al. A prospective cohort study on the safety of checkpoint inhibitors in older cancer patients - the ELDERS study. *ESMO Open*. (2021) 6:100042. doi: 10.1016/j.esmoop.2020.100042

22. Garcia MV, Agar MR, Soo WK, To T, Phillips JL. Screening tools for identifying older adults with cancer who may benefit from a geriatric assessment: A systematic review. *JAMA Oncol*. (2021) 7:616–27. doi: 10.1001/jamaoncol.2020.6736

23. Gomes F, Wong M, Battisti NML, Kordbacheh T, Kiderlen M, Greystoke A, et al. Immunotherapy in older patients with non-small cell lung cancer: Young International Society of Geriatric Oncology position paper. *Br J Cancer*. (2020) 123:874–84. doi: 10.1038/s41416-020-0986-4

24. Lees J, Chan A. Polypharmacy in elderly patients with cancer: clinical implications and management. *Lancet Oncol*. (2011) 12:1249–57. doi: 10.1016/s1470-2045(11)70040-7

25. Alkan A, Yaşar A, Karcı E, Köksoy EB, Ürün M, Şenler F, et al. Severe drug interactions and potentially inappropriate medication usage in elderly cancer patients. *Support Care Cancer*. (2017) 25:229–36. doi: 10.1007/s00520-016-3409-6

26. Kokkotou E, Anagnostakis M, Evangelou G, Syrigos NK, Gkiozos I. Real-world data and evidence in lung cancer: A review of recent developments. *Cancers (Basel)*. (2024) 16:1414. doi: 10.3390/cancers16071414

27. Health Commission Of The People's Republic Of China N. National guidelines for diagnosis and treatment of lung cancer 2022 in China (English version). *Chin J Cancer Res*. (2022) 34:176–206. doi: 10.21147/j.issn.1000-9604.2022.03.03

28. Greenhalgh J, Boland A, Bates V, Vecchio F, Dundar Y, Chaplin M, et al. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. *Cochrane Database Syst Rev*. (2021) 3:Cd010383. doi: 10.1002/14651858.CD010383.pub3

29. Ng WW, Lin CC, Cheng CY, Jiang JS, Kao SJ, Yeh DY. Real-world outcomes of first- and second-generation tyrosine kinase inhibitors first-line in patients with epidermal growth factor receptor mutation-positive non-small cell lung cancer: A retrospective observational cohort study. *PloS One*. (2021) 16:e0253335. doi: 10.1371/journal.pone.0253335

30. Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol*. (2017) 18:1454–66. doi: 10.1016/s1470-2045(17)30608-3

31. Mok TS, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, et al. Updated overall survival in a randomized study comparing dacomitinib with gefitinib as first-line treatment in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. *Drugs*. (2021) 81:257–66. doi: 10.1007/s40265-020-01441-6

32. Rangachari D, Yamaguchi N, VanderLaan PA, Folch E, Mahadevan A, Floyd SR, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. *Lung Cancer*. (2015) 88:108–11. doi: 10.1016/j.lungcan.2015.01.020

33. Decoster L, Schallier D. Treatment of older patients with advanced non-small cell lung cancer: A challenge. *J Geriatr Oncol*. (2019) 10:528–33. doi: 10.1016/j.jgo.2018.09.008

34. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. (2018) 378:113–25. doi: 10.1056/NEJMoa1713137

35. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med*. (2020) 382:41–50. doi: 10.1056/NEJMoa1913662

36. FranChina T, Russo A, Ricciardi G, FranChina V, Adamo V. P2.16-38 efficacy and safety of target therapy and immunotherapy in advanced NSCLC in elderly: A systematic review of real world studies. *J Thorac Oncol*. (2019) 14:S880–S81. doi: 10.1016/j.jtho.2019.08.1905

37. Cheng WC, Lin CC, Liao WC, Lin YC, Chen CH, Chen HJ, et al. The difference between dacomitinib and afatinib in effectiveness and safety in first-line treatment of patients with advanced EGFR-mutant non-small cell lung cancer: a real-world observational study. *BMC Cancer*. (2024) 24:228. doi: 10.1186/s12885-024-11956-w

38. Sakata Y, Saito G, Sakata S, Oya Y, Tamiya M, Suzuki H, et al. Osimertinib as first-line treatment for elderly patients with advanced EGFR mutation-positive non-small cell lung cancer in a real-world setting (OSI-FACT-EP). *Lung Cancer*. (2023) 186:107426. doi: 10.1016/j.lungcan.2023.107426

39. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. (2014) 371:2167–77. doi: 10.1056/NEJMoa1408440

40. Soria JC, Tan DSW, Chiari R, Wu YL, Paz-Ares L, Wolf J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet*. (2017) 389:917–29. doi: 10.1016/s0140-6736(17)30123-x

41. Chuang CH, Chen HL, Chang HM, Tsai YC, Wu KL, Chen IH, et al. Systematic review and network meta-analysis of anaplastic lymphoma kinase (ALK) inhibitors for treatment-naïve ALK-positive lung cancer. *Cancers (Basel)*. (2021) 13:1966. doi: 10.3390/cancers13081966

42. Horn L, Wang Z, Wu G, Poddubskaya E, Mok T, Reck M, et al. Ensartinib vs crizotinib for patients with anaplastic lymphoma kinase-positive non-small cell lung cancer: A randomized clinical trial. *JAMA Oncol*. (2021) 7:1617–25. doi: 10.1001/jamaoncol.2021.3523

43. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. (2017) 377:829–38. doi: 10.1056/NEJMoa1704795

44. Bedas A, Peled N, Maimon Rabinovich N, Mishaeli M, Shochat T, Zer A, et al. Efficacy and safety of ALK tyrosine kinase inhibitors in elderly patients with advanced ALK-positive non-small cell lung cancer: findings from the real-life cohort. *Oncol Res Treat*. (2019) 42:275–82. doi: 10.1159/000499086

45. Lu S, Fang J, Li X, Cao L, Zhou J, Guo Q, et al. Once-daily savolitinib in Chinese patients with pulmonary sarcomatoid carcinomas and other non-small-cell lung cancers harbouring MET exon 14 skipping alterations: a multicentre, single-arm, open-label, phase 2 study. *Lancet Respir Med*. (2021) 9:1154–64. doi: 10.1016/s2213-2600(21)00084-9

46. Dziadziuszko R, Krebs MG, De Braud F, Siena S, Drilon A, Doebele RC, et al. Updated integrated analysis of the efficacy and safety of entrectinib in locally advanced or metastatic ROS1 fusion-positive non-small-cell lung cancer. *J Clin Oncol*. (2021) 39:1253–63. doi: 10.1200/jco.20.03025

47. Planchard D, Besse B, Groen HJM, Hashemi SMS, Mazieres J, Kim TM, et al. Phase 2 study of dabrafenib plus trametinib in patients with BRAF V600E-mutant metastatic NSCLC: updated 5-year survival rates and genomic analysis. *J Thorac Oncol*. (2022) 17:103–15. doi: 10.1016/j.jtho.2021.08.011

48. Gainor JF, Curigliano G, Kim DW, Lee DH, Besse B, Baik CS, et al. Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study. *Lancet Oncol*. (2021) 22:959–69. doi: 10.1016/s1470-2045(21)00247-3

49. Brahmer JR, Rodriguez-Abreu D, Robinson AG, Hui R, Csszi T, Fülp A, et al. LBA51 KEYNOTE-024 5-year OS update: First-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumour proportion score (TPS) ≥50%. (2020) 31:.

50. Sezer A, Kilickap S, Gümüş M, Bondarenko I, Özgüroğlu M, Gogishvili M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *Lancet*. (2021) 397:592–604. doi: 10.1016/s0140-6736(21)00228-2

51. Olsson-Brown AC, Baxter M, Dobeson C, Feeney L, Lee R, Maynard A, et al. Real-world outcomes in older adults treated with immunotherapy: A United Kingdom multicenter series of 2,049 patients. *J Clin Oncol*. (2021) 39:15. doi: 10.1200/JCO.2021.39.15_suppl.12026

52. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. (2018) 378:2078–92. doi: 10.1056/NEJMoa1801005

53. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. (2018) 379:2040–51. doi: 10.1056/NEJMoa1810865

54. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. (2018) 378:2288–301. doi: 10.1056/NEJMoa1716948

55. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. (2019) 381:2020–31. doi: 10.1056/NEJMoa1910231

56. Paz-Ares L, Ciuleanu TE, Cobo M, Schenker M, Zurawski B, Menezes J, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. (2021) 22:198–211. doi: 10.1016/s1470-2045(20)30641-0

57. Akinboro O, Vallejo JJ, Nakajima EC, Ren Y, Mishra-Kalyani PS, Larkins EA, et al. Outcomes of anti–PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non–small cell lung cancer (NSCLC) with PD-L1 score ≥ 50%: FDA pooled analysis. (2022) 40(16_suppl):9000–00. doi: 10.1200/JCO.2022.40.16_suppl.9000

58. Singh H, Kim G, Maher VE, Beaver JA, Pai-Scherf LH, Balasubramaniam S, et al. FDA subset analysis of the safety of nivolumab in elderly patients with advanced cancers. (2016) 34(15_suppl):10010–10. doi: 10.1200/JCO.2016.34.15_suppl.10010

59. Marur S, Singh H, Mishra-Kalyani P, Larkins E, Keegan P, Sridhara R, et al. FDA analyses of survival in older adults with metastatic non-small cell lung cancer in controlled trials of PD-1/PD-L1 blocking antibodies. *Semin Oncol*. (2018) 45:220–25. doi: 10.1053/j.seminoncol.2018.08.007

60. Abedian Kalkhoran H, Zwaveling J, Storm BN, van Laar SA, Portielje JE, Codrington H, et al. A text-mining approach to study the real-world effectiveness and potentially fatal immune-related adverse events of PD-1 and PD-L1 inhibitors in older patients with stage III/IV non-small cell lung cancer. (2023) 23(1):247.

61. Ham A, Lee Y, Kim HS, Lim T. Real-world outcomes of nivolumab, pembrolizumab, and atezolizumab treatment efficacy in Korean veterans with stage IV non-small-cell lung cancer. *Cancers (Basel)*. (2023) 15:4198. doi: 10.3390/cancers15164198

62. Morinaga D, Asahina H, Ito S, Honjo O, Tanaka H, Honda R, et al. Real-world data on the efficacy and safety of immune-checkpoint inhibitors in elderly patients with non-small cell lung cancer. *Cancer Med*. (2023) 12:11525–41. doi: 10.1002/cam4.5889

63. Elkrief A, Richard C, Malo J, Cvetkovic L, Florescu M, Blais N, et al. Efficacy of immune checkpoint inhibitors in older patients with non-small cell lung cancer: Real-world data from multicentric cohorts in Canada and France. *J Geriatr Oncol*. (2020) 11:802–06. doi: 10.1016/j.jgo.2020.01.002

64. Lim SM, Kim SW, Cho BC, Kang JH, Ahn MJ, Kim DW, et al. Real-world experience of nivolumab in non-small cell lung cancer in Korea. *Cancer Res Treat*. (2020) 52:1112–19. doi: 10.4143/crt.2020.245

65. Okishio K, Morita R, Shimizu J, Saito H, Sakai H, Kim YH, et al. Nivolumab treatment of elderly Japanese patients with non-small cell lung cancer: subanalysis of a real-world retrospective observational study (CA209-9CR). *ESMO Open*. (2020) 5:e000656. doi: 10.1136/esmoopen-2019-000656

66. Li L, Xu C, Wang W, Zhang Q. Efficacy and safety of PD-1/PD-L1 inhibitors in elderly patients with advanced non-small cell lung cancer. *Clin Respir J*. (2024) 18:e13763. doi: 10.1111/crj.13763

67. Takamori S, Shimokawa M, Komiya T. Prognostic impact of chronological age on efficacy of immune checkpoint inhibitors in non-small-cell lung cancer: Real-world data from 86 173 patients. *Thorac Cancer*. (2021) 12:2943–48. doi: 10.1111/1759-7714.14178

68. Grossi F, Genova C, Crinò L, Delmonte A, Turci D, Signorelli D, et al. Real-life results from the overall population and key subgroups within the Italian cohort of nivolumab expanded access program in non-squamous non-small cell lung cancer. *Eur J Cancer*. (2019) 123:72–80. doi: 10.1016/j.ejca.2019.09.011

69. Markovic F, Jovanovic MK, Janzic UJEO. 94P Efficacy of first-line pembrolizumab in elderly patients with advanced non-small cell lung cancer with high PD-L1 expression. (2024) 9:. doi: 10.1016/j.esmoop.2024.102673

70. van Veelen A, Veerman GDM, Verschueren MV, Gulikers JL, Steendam CMJ, Brouns A, et al. Exploring the impact of patient-specific clinical features on osimertinib effectiveness in a real-world cohort of patients with EGFR mutated non-small cell lung cancer. *Int J Cancer*. (2024) 154:332–42. doi: 10.1002/ijc.34742

71. Yu J, Wu X, Ma J, Chen X, Li L. [Clinical observation of immunotherapy efficacy and adverse effects in Chinese patients with lung squamous cell carcinoma]. *Zhongguo Fei Ai Za Zhi*. (2022) 25:546–54. doi: 10.3779/j.issn.1009-3419.2022.101.36

72. Zhang W, Zhang Y, Zhao Q, Liu X, Chen L, Pan H, et al. Long-term safety of icotinib in patients with non-small cell lung cancer: a retrospective, real-world study. *J Thorac Dis*. (2020) 12:639–50. doi: 10.21037/jtd.2019.12.115

73. Sánchez-Cousido L, Piedra MR, Flores ML, Sillero ID, González AL, Castañón C, et al. P2.16-43 immunotherapy in elderlies. *Real World data*. (2019) 14:S882–S83.

74. Song P, Zhang J, Shang C, Zhang LJSR. Real-world evidence and clinical observations of the treatment of advanced non-small cell lung cancer with PD-1/PD-L1 inhibitors. (2019) 9(1):4278. doi: 10.1038/s41598-019-40748-7

75. Muchnik E, Loh KP, Strawderman M, Magnuson A, Mohile SG, Estrah V, et al. Immune checkpoint inhibitors in real-world treatment of older adults with non–small cell lung cancer. (2019) 67(5):905–12. doi: 10.1111/jgs.15750

76. The National Health Committee General Office. Guidelines for the diagnosis and treatment of primary lung cancer (2022 edition). *J Med J Peking Union Med Coll Hosp*. (2022) 13:549–70. doi: 10.12290/xhyxzz.2022-0352

77. Gridelli C. The ELVIS trial: a phase III study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer. *Elderly Lung Cancer Vinorelbine Ital Study Oncologist*. (2001) 6 Suppl 1:4–7. doi: 10.1634/theoncologist.6-suppl_1-4

78. Qi WX, Tang LN, He AN, Shen Z, Lin F, Yao Y. Doublet versus single cytotoxic agent as first-line treatment for elderly patients with advanced non-small-cell lung cancer: a systematic review and meta-analysis. *Lung*. (2012) 190:477–85. doi: 10.1007/s00408-012-9399-3

79. Pelizzari G, Cortiula F, Giavarra M, Bartoletti M, Lisanti C, Buoro V, et al. Platinum-based chemotherapy in older patients with non-small cell lung cancer: what to expect in the real world. *Drugs Aging*. (2020) 37:677–89. doi: 10.1007/s40266-020-00785-8

80. Han B, Li K, Wang Q, Zhang L, Shi J, Wang Z, et al. Effect of anlotinib as a third-line or further treatment on overall survival of patients with advanced non-small cell lung cancer: the ALTER 0303 phase 3 randomized clinical trial. *JAMA Oncol*. (2018) 4:1569–75. doi: 10.1001/jamaoncol.2018.3039

81. Langer CJ, Socinski MA, Patel JD, Sandler A, Schiller JH, Leon L, et al. MO06.12 Efficacy and safety of paclitaxel and carboplatin with bevacizumab for the first-line treatment of patients with nonsquamous non-small cell lung cancer (NSCLC): analyses

based on age in the phase 3 PointBreak and E4599 trials. *Clin Adv Hematol Oncol*. (2014) 12:4–6. doi: 10.1200/jco.2013.31.15_suppl.8073

82. Wozniak AJ, Kosty MP, Jahanzeb M, Brahmer JR, Spigel DR, Leon L, et al. Clinical outcomes in elderly patients with advanced non-small cell lung cancer: results from ARIES, a bevacizumab observational cohort study. *Clin Oncol (R Coll Radiol)*. (2015) 27:187–96. doi: 10.1016/j.clon.2014.12.002

83. Saito H, Fukuhara T, Furuya N, Watanabe K, Sugawara S, Iwasawa S, et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Oncol*. (2019) 20:625–35. doi: 10.1016/s1470-2045(19)30035-x

84. Zhao H, Yao W, Min X, Gu K, Yu G, Zhang Z, et al. Apatinib plus gefitinib as first-line treatment in advanced EGFR-mutant NSCLC: the phase III ACTIVE study (CTONG1706). *J Thorac Oncol*. (2021) 16:1533–46. doi: 10.1016/j.jtho.2021.05.006

85. Leighl NB, Zatloukal P, Mezger J, Ramlau R, Moore N, Reck M, et al. Efficacy and safety of bevacizumab-based therapy in elderly patients with advanced or recurrent nonsquamous non-small cell lung cancer in the phase III BO17704 study (AVAiL). *J Thorac Oncol*. (2010) 5:1970–6. doi: 10.1097/JTO.0b013e3181f49c22

86. Laskin J, Crinò L, Felip E, Franke F, Gorbunova V, Groen H, et al. Safety and efficacy of first-line bevacizumab plus chemotherapy in elderly patients with advanced or recurrent nonsquamous non-small cell lung cancer: safety of avastin in lung trial (MO19390). *J Thorac Oncol*. (2012) 7:203–11. doi: 10.1097/JTO.0b013e3182370e02

87. Jiang W, Liang J, Sun W, Li W, Gao J, Wang H, et al. Effectiveness and safety of Endostar combined with chemotherapy in treating advanced NSCLC patients with different ages. (2023) 4(1):41–7. doi: 10.1002/aac2.12062

88. Jiang HT, Li W, Zhang B, Gong Q, Qie HL. Efficacy and safety of anlotinib monotherapy as third-line therapy for elderly patients with non-small cell lung cancer: a real-world exploratory study. *Int J Gen Med*. (2021) 14:7625–37. doi: 10.2147/ijgm.S334436

89. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. (2017) 377:1919–29. doi: 10.1056/NEJMoa1709937

90. Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *J Clin Oncol*. (2022) 40:1301–11. doi: 10.1200/jco.21.01308

91. Dieleman E, van der Woude L, van Os R, van Bockel L, Coremans I, van Es C, et al. The dutch lung cancer audit-radiotherapy (DLCA-R): real-world data on stage III non-small cell lung cancer patients treated with curative chemoradiation. *Clin Lung Cancer*. (2023) 24:130–36. doi: 10.1016/j.cllc.2022.11.008

92. Chan J, Chowdhury A, Tan WC, Ang MK, Tan D, Tan A, et al. The impact of multi-modality treatment in geriatric patients with unresectable Stage 3 NSCLC. *J Geriatric Oncol*. (2023) 14:S18. doi: 10.1016/S1879-4068(23)00293-X

93. Stevens S, Nindra U, Shahnam A, Bray V, Pal A, Yip P, et al. 965P Real-world toxicity of consolidation durvalumab following chemoradiotherapy (CRT) in elderly and comorbid patients (pts) with unresectable stage III NSCLC: A multi-centre, Australian experience. (2022) 33:S989. doi: 10.1016/j.annonc.2022.07.1091

94. Gibson A, D'silva A, Dean M, Tudor R, Elegbede A, Otsuka S, et al. P2. 16-12 treatment uptake and outcomes of elderly stage III NSCLC patients: a 15-year retrospective real-world study. (2019) 14(10):S869–S70.

95. Kirk F, Chang S, Yong MS, He C, Hughes I, Yadav S, et al. Thoracic surgery and the elderly; is lobectomy safe in octogenarians? *Heart Lung Circ*. (2023) 32:755–62. doi: 10.1016/j.hlc.2023.03.005

frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 25 July 2024
DOI 10.3389/fonc.2024.1399021

OPEN ACCESS

EDITED BY
Nam Phong Nguyen,
International Geriatric Radiotherapy Group, United States

REVIEWED BY
Hironari Tamiya,
Osaka International Cancer Institute, Japan
Yong Zhou,
Sichuan University, China

*CORRESPONDENCE
Xiuchun Yu
13969132190@163.com

RECEIVED 11 March 2024
ACCEPTED 10 July 2024
PUBLISHED 25 July 2024

CITATION
Chen Q, Cui H, Zheng K, Xu M and Yu X (2024) Denosumab combined with chemotherapy followed by anlotinib in the treatment of multiple metastases of malignant peripheral nerve sheath tumor: a case report and literature review. *Front. Oncol.* 14:1399021. doi: 10.3389/fonc.2024.1399021

Denosumab combined with chemotherapy followed by anlotinib in the treatment of multiple metastases of malignant peripheral nerve sheath tumor: a case report and literature review

Qian Chen, Haocheng Cui, Kai Zheng, Ming Xu and Xiuchun Yu*

Department of Orthopedics, The 960th Hospital of the People's Liberation Army, Jinan, Shandong, China

Primary intraosseous malignant peripheral nerve sheath tumors (MPNSTs) are rare yet highly aggressive neoplasms originating from peripheral nerves. Typically manifesting as soft tissue masses accompanied by pain or functional impairment, these tumors pose significant challenges in management. Surgical intervention remains the cornerstone of treatment for patients with MPNST lacking distant metastasis, with generally modest success rates. In cases of recurrence and metastasis, the pursuit of effective systemic therapies has been a focus of clinical investigation. Herein, we present a case study involving an elderly female patient with refractory MPNST. In light of surgical limitations, a multimodal therapeutic approach combining chemotherapy, denosumab, and subsequent administration of anlotinib was pursued following collaborative consultation. This regimen yielded noteworthy clinical benefits, exemplifying a promising avenue in the management of challenging MPNST cases.

KEYWORDS

malignant peripheral nerve sheath tumor, anlotinib, denosumab, adjuvant chemotherapy, case report

Introduction

Malignant peripheral nerve sheath tumor (MPNST) represents a highly aggressive sarcoma arising from neuroectodermal cells of peripheral or cranial nerves, comprising approximately 4%–5% of all soft tissue sarcoma (STS) and contributing to an estimated 1,500 new cases annually in the European Union (1). In 2002, the WHO classification of

nervous system tumors adopted MPNSTs to supplant the perplexing nomenclature encompassing malignant Schwann cell tumors, malignant schwannoma, neurosarcoma, and neurofibrosarcoma (2). With an annual incidence of one in a million and a male-to-female ratio of 2.5:1, MPNST predominately afflicts adults aged 20–50 years, with a prevalence of 10%–20% before 20 years old (3). Predominantly localized along peripheral nerves of the trunk, extremities, head and neck regions, and spine, MPNSTs exhibit histological hallmarks such as heightened cellularity, frequent mitoses, anaplasia, necrosis, infiltrative growth patterns, pleomorphism, and elevated proliferative activity (4). Metastases are identified in 40%–70% of patients, commonly affecting the lungs, liver, or bones (5). The data of Akshintala et al. have established a baseline progression-free survival (PFS) of 1.77 months in patients with recurrent or unresectable/metastatic MPNST (6).

The management of MPNST poses formidable challenges owing to its propensity for recurrence and metastasis, coupled with its limited responsiveness to systemic therapies. Complete surgical excision with wide negative margins stands as the sole curative modality for MPNST; however, its feasibility is often impeded by tumor size, location, or metastatic dissemination, leaving patients with unresectable, metastatic, or recurrent disease devoid of curative options (7). Hence, there arises an urgent imperative to delineate effective therapeutic paradigms for MPNST.

We herein present the case of a 68-year-old woman with primary MPNST devoid of neurofibromatosis-1 (NF-1). At the time of initial diagnosis, the patient presented with distant metastases, underscoring the imperative for aggressive multimodal local therapies in patients with localized MPNST for optimal disease control.

Case report

A 68-year-old female patient presented at our hospital on 28 May 2023, with a chief complaint of "low back pain with left lower limb pain for 2 weeks." Upon specialized physical examination, she exhibited a normal gait upon entering the ward. The patients reported left lumbar back pressure pain without radiation to the lower limb. Examination of the lumbar spine indicated normal flexion and extension activity, with left quadriceps muscle strength graded at level IV. Sensation in the lower limbs and saddle area was intact, alongside normal muscle tension. Bilateral heel–knee tendon reflexes were within normal limits, with no pathological signs detected. Normal skin temperature and color were normal in the right axilla. Palpitation revealed soft masses approximately 5 cm × 3 cm in depth, with indistinct boundaries, absence of tenderness, and immobility. Subsequent lumbar spine X-ray depicted slight flattening of the lumbar vertebra 4 (L4) vertebral body (Figure 1A). Computed tomographic (CT) imaging of the lumbar spine revealed flattening of the L4 vertebral body, thin and discontinuous bone cortex, and osteolytic bone destruction on the left side of the vertebra, measuring approximately 3.0 cm × 2.0 cm × 2.2 cm (Figure 1B). No compression of the dural sac or significant abnormalities in the surrounding soft tissue were noted. Lung CT revealed distinctive insect-like patterns of local bone destruction affecting thoracic vertebra 4 (T4) and the right first rib, with irregular soft tissue density shadows observed in the right armpit (Figure 2B). Lumbar magnetic resonance imaging (MRI) displayed an uneven bone damage signal in the L4 vertebral body (Figure 1E). Ultrasonography detected a low-echo mass measuring approximately 32 mm × 26 mm, featuring clear boundaries and an irregular shape, exhibiting uneven internal echoes and the

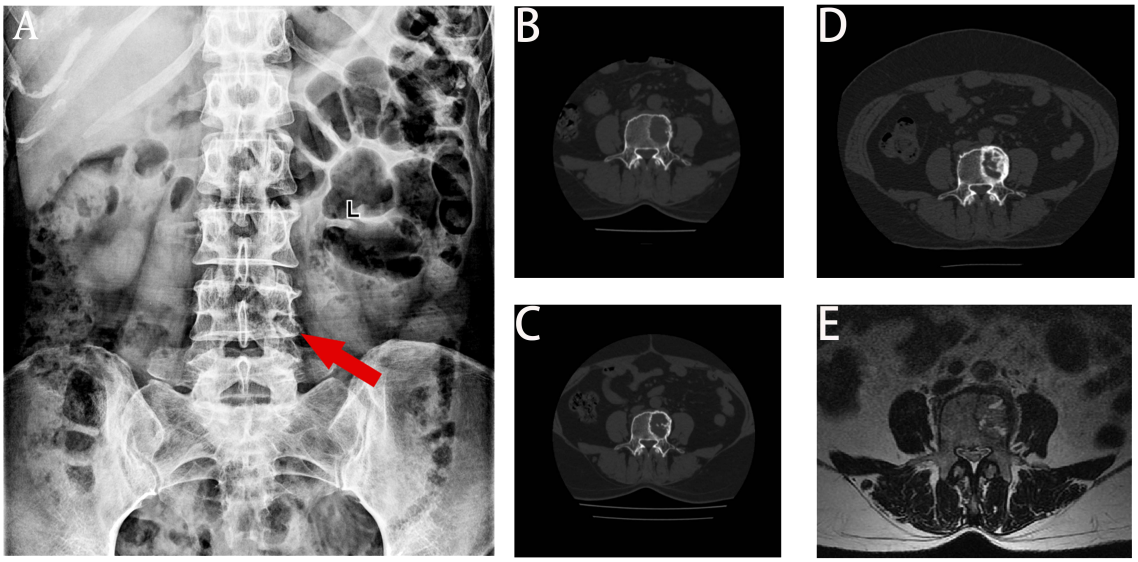


FIGURE 1
X-ray, CT, and MRI images. Panel **(A)** displays the flattening of the L4 left vertebral body height. Panel **(B)** displays the bone destruction of L4 before chemotherapy, with a moderately circular low-density shadow with a range of 3.4 cm × 2.0 cm × 2.2 cm. Panel **(C)** displays a decrease in lytic bone destruction and an increase in the cortical bone density in posterior L4 after six cycles of chemotherapy. Panel **(D)** displays obvious calcification in the bone destruction area of the L4 vertebra at the last review. Panel **(E)** displays that the left side of the L4 vertebra is slightly flattened, with patchy long T1 equal length T2 signals and high T2 pressure lipid images.

characteristic "rat tail sign" at both ends in the right axilla (Figure 2A). Emission computed tomography (ECT) scans revealed multiple abnormal focal nuclide concentrations in the right first rib, L4 vertebral body, and right iliac bone, consistent with bone metastases (Figure 3). To determine the nature and origin of the tumors, a CT-guided puncture biopsy of the right iliac bone tumor was conducted on 29 May 2023, revealing a short spindle-cell malignant mesenchymal tumor suggestive of MPNST upon immunohistochemistry and staining (Figure 4A). Subsequently, on 6 June 2023, an ultrasound-guided puncture biopsy of the right axillary soft tissue tumor confirmed MPNST (Figure 4B). The final diagnosis was MPNST with multiple metastases.

Following thorough departmental deliberation, initiation of a chemotherapy regimen combining cisplatin with doxorubicin was decided upon. Given the predominant imaging findings of osteolytic bone destruction, denosumab, FDA-approved for preventing skeletal-related events in patients with bone metastasis from solid tumors, was adjunctively administered to inhibit osteolysis. The treatment protocol combined chemotherapy (AP regimen cisplatin (DDP) 120mg/m^2/day ×1 day + pegylated liposomal doxorubicin (PLD) 40 mg/m^2/day × 1 day, once every 21 days) with denosumab (120 mg, subcutaneous injection, once/4 weeks), supplemented with Vitamin D3 (600 μg daily). Throughout the treatment course, the patient experienced significant alleviation of pain symptoms compared to admission, improved sleep without medication assistance, and absence of drug-related adverse reactions. Regular imaging assessments performed before each admission facilitated the evaluation of the combination therapy's efficacy. Following the completion of six cycles of chemotherapy, pulmonary CT scans evidenced a gradual reduction in the maximum diameter of the irregular soft tissue mass under the right axilla (Figure 2C), while lumbar spine CT exhibited thickening and densification of the bone cortex surrounding the L4 vertebral body, accompanied by evident bone formation and scattered calcification shadows in the area of osteolytic bone destruction (Figure 1C).

On 18 October 2023, the patient completed six cycles of chemotherapy combined with denosumab treatment, with lung CT indicating an absence of lung metastasis. Evaluation of the soft tissue mass in the right armpit, designated as the target lesion according to RECIST 1.1 criteria, revealed stable disease. To inhibit disease progression post-cessation of intensive chemotherapy cycles, the patient was prescribed the oral targeted drug anlotinib (12 mg/day, taken for 2 weeks followed by a 1-week break) to enhance chemotherapy sensitization and prevent disease progression. Denosumab (120 mg, subcutaneous injection, once

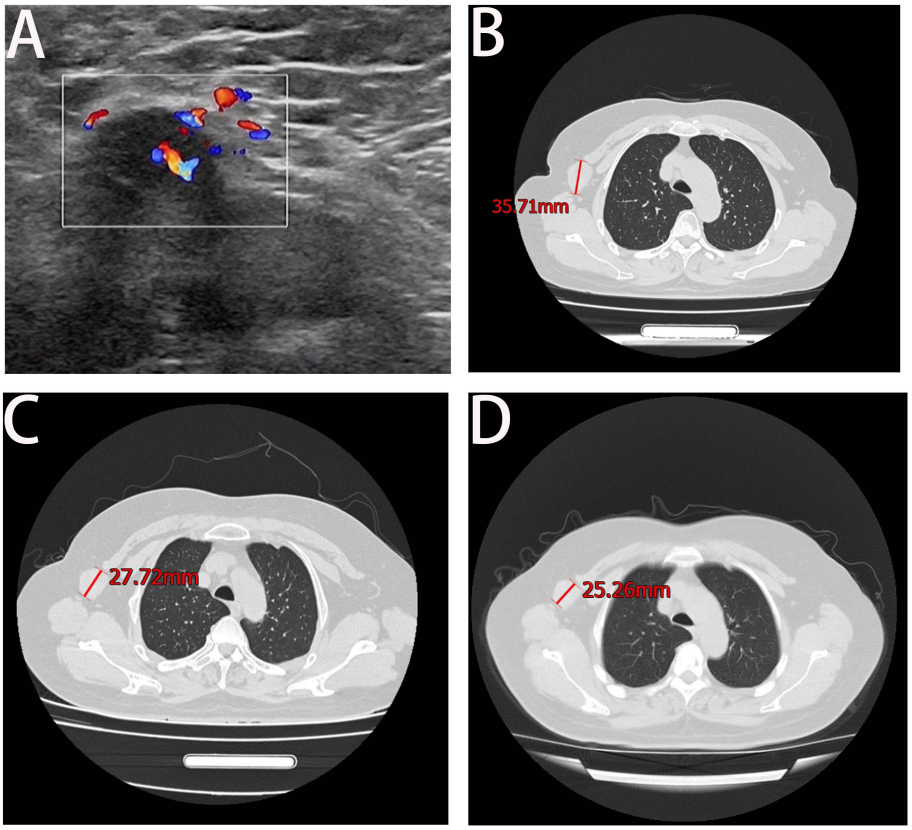


FIGURE 2
Axillary ultrasound and lung CT. Panel **(A)** shows the right axillary probe and irregularly shaped hypoechoic mass, measuring approximately 32 mm × 26 mm. Panel **(B)** shows the maximum axillary mass diameter at the time of initial admission. Panel **(C)** shows a significant reduction in the maximum diameter of the irregular soft tissue mass under the right axilla at the end of the entire chemotherapy cycle. Panel **(D)** displays the result of the February 2024 review, which indicated a decrease of approximately 2 cm in the maximum tumor diameter from the previous review.

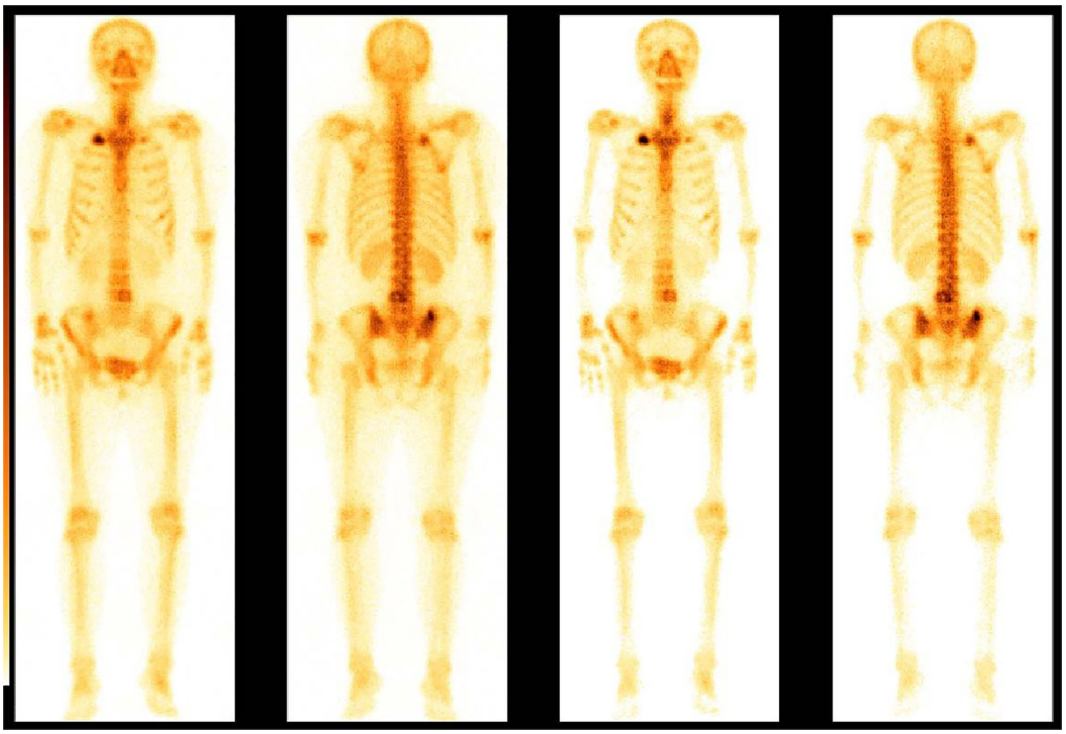


FIGURE 3
Bone scan nuclide concentration results. ECT revealed sparse radioactivity on the left side of the T4 and multiple abnormal focal nuclide concentrations on the right first rib, the L4, and the right iliac bone.

every 4 weeks) was continued to enhance bone strength. Presently, the patient has endured the tumor for 10 months. Regular follow-up visits every 3 months for lung and lumbar CT scans were advised to monitor therapeutic efficacy and adjust the medication regimen as necessary. On 20 February 2024, a re-examination CT revealed prominent calcification in the area of bone destruction in the L4 vertebral body (Figure 1D), with no significant alteration in the maximum diameter of the axillary mass compared to the previous scan (Figure 2D).

Discussion

Intraosseous MPNSTs represent a rare manifestation of cancer, often arising from secondary invasion from adjacent soft tissues (8). Published studies have documented only a handful of cases of primary intraosseous MPNST, with the mandible being the most common sure (approximately 50%), followed by the maxilla, spine, and, occasionally, the appendicular skeleton. In cases affecting the appendicular skeleton, intraosseous MPNSTs predominately occur in bones of the upper extremity (humerus, ulna, metacarpal, and phalanx), with involvement of the lower extremity bones being uncommon (9). The etiology and pathogenesis of primary intraosseous MPNST remain elusive. Unlike MPNST of the soft tissues, most often, primary intraosseous MPNST is not associated with NF-1. While soft tissue MPNSTs typically manifest as fusiform or eccentric masses originating from major nerves, presenting initially as painless enlarging masses, primary intraosseous MPNSTs typically present with pain, with swelling often developing later in the disease course. MPNSTs arising from major nerves commonly result in sensorimotor symptoms corresponding to the distribution of the affected nerve, with variable pain presentation (10). Results from phase II trials have indicated a median PFS of 1.77 months for relapsed refractory MPNST, with PFS rates at 2 months and 4 months being 0.42 and 0.15, respectively (6). In such cases, curative treatment is typically unattainable, and palliative systemic therapy serves as the primary approach to enhance patients' survival and quality of life.

The challenge in cases like this lies in the complexity of achieving complete wide resection due to multiple vertebral and iliac metastases. Simple excision of the soft tissue mass under the armpit does not improve the patient's survival and may entail the additional risk of significant functional loss. Following consultation with the patient and family, a conservative treatment approach was deemed appropriate.

Systemic treatment strategies for MPNST generally align with the general guidelines for other STS algorithms and predominantly rely on genotoxic chemotherapy, primarily serving a palliative role in the setting of metastatic diseases (11). The SARC006 phase II trial conducted by the Sarcoma Alliance for Research (SARC) suggests that NF1-associated disease predicts inferior responses to chemotherapy compared with sporadic disease (12). Although chemotherapy can mitigate tumor recurrence and distant metastasis rates, and improve patient's quality of life of patients, it typically does not extend overall survival. While several agents have exhibited some efficacy against MPNST, including

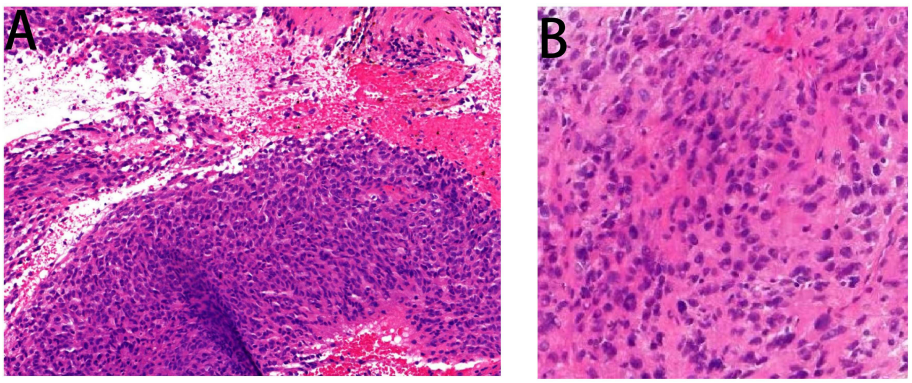


FIGURE 4
Pathology images. Panel **(A)** displays the pathological image of the right iliac bone tumor taken by a light microscope at ×200 magnification, wherein some heterotypic cell components were detected. Panel **(B)** is a pathological image of an axillary puncture captured by light microscopy under a ×200 magnifying glass. Malignant tumor cells were detected in the image.

gemcitabine, docetaxel, carboplatin, etoposide, dactinomycin, cisplatinum, vincristine, cyclophosphamide, imidazole carboxamide, doxorubicin, and ifosfamide, their clinical benefits have been inconsistent (13). Until 2010, high doses of ifosfamide were commonly used; however, recent research and clinical trials have favored doxorubicin-based treatment, reflecting evolving insights into MPNST biology and affirming the superiority of such regimens (14). Notably, liposomal formulations of doxorubicin have demonstrated enhanced efficacy and reduced toxicity in MPNST xenograft models (15). Despite pathological confirmation of MPNST with multiple systemic involvement, identifying the primary lesion remains challenging. Presently, combination regimens such as anthracyclines with isocyclic phosphamide and etoposide (ICE) have emerged as a focus of clinical research (16), although their toxicity is relatively high. Considering the patient's age, extensive bone destruction, and the primary origin of the malignant tumor from bone, we have opted for a chemotherapy regimen typically employed in osteosarcoma cases. Specifically, cisplatin has been chosen over ifosfamide due to its status as a first-line preferred treatment when combined with doxorubicin.

Upon admission, imaging studies revealed extensive osteolytic bone destruction involving multiple vertebrae and the right ilium, a condition that could not be adequately managed through chemotherapy alone and posed a risk of vertebral fractures and other adverse complications if left unchecked. Drawing from the pivotal Fracture Reduction Evaluation of Denosumab in Osteoporosis (FREEDOM) trial, which demonstrated a significant reduction in fracture risk by 68% and hip fractures by 40% over 3 years with denosumab (17), the decision was made to incorporate denosumab into the treatment regimen. Denosumab, a human monoclonal antibody that inhibits bone resorption, promotes new bone formation and delays tumor progression by binding to the receptor activator of nuclear factor-κB ligand (RANKL) and preventing its interaction with RANK, thus mimicking the action of osteoprotegerin (OPG) (18). Additionally, denosumab has been cleared by the FDA for use in various conditions, including osteoporosis and bone metastases (19). However, discontinuing denosumab poses challenges, as rapid reversal after discontinuation can lead to a rebound in bone turnover, potentially resulting in complications such as hypercalcemia and vertebral compression fractures (20). Therefore, a careful and deliberate strategy is essential when discontinuing denosumab (21). Limited evidence suggests that transitioning to a short course of bisphosphonate therapy with close monitoring of BMD and BTMs may mitigate bone loss and reduce multiple vertebral fracture risk (22). The medication cycle can be appropriately adjusted according to the patient's situation, potentially extending from once every month, in the beginning, to once every 1.5 months to once every 2 months, with continued medication to prevent adverse events after withdrawal.

Anlotinib is a novel orally administered TKI targeting vascular endothelial growth factor receptor-1/2/3, PDGFR α/β, fibroblast growth factor receptor-1/2/3/4, c-Kit, and Ret (23), which demonstrates antitumor activity in patients with refractory metastatic STS, with a median PFS of 5.6 months (24). In China, anlotinib has been approved for the treatment of advanced STS based on the results of phase II and phase IIb studies (ALTER0203). Common adverse events associated with anlotinib therapy, mostly grade 1/2, include triglyceride elevation, hypertension, hand–foot skin reaction, oral mucositis, and fatigue. Zhang et al. (25) reported that switching maintenance therapy to anlotinib after chemotherapy has been significantly associated with longer median PFS and OS. Such associations may be attributed to achieving an objective response or stable disease after chemotherapy, which may select patients with good prognoses, and the delayed effects of chemotherapy may contribute to anlotinib maintenance therapy. Certain studies suggest that anlotinib with DDP significantly reduces tumor size and may reverse multidrug resistance to doxorubicin, thus enhancing chemotherapy sensitization (26). In the present case, the patient exhibited a significant reduction in axillary tumor volume at the end of the chemotherapy plus anlotinib regimen, demonstrating good short-term clinical efficacy with no serious adverse reactions. Nonetheless, further large-scale studies are warranted to confirm its effectiveness and safety.

Conclusion

The management of MPNST remains challenging due to the lack of high-quality evidence regarding the efficacy of systemic treatments for this particular sarcoma type (27). The complexity of MPNST treatment stems not only from its high rates of local recurrence (40%–65%) and metastasis (40%–80%) but also from its poor response to conventional therapies and therapeutic options. Future research avenues may include identifying molecular markers to predict the efficacy of targeted therapy, exploring novel targeted therapy agents, investigating multi-target combination therapies, and assessing the potential synergistic effects of targeted drugs with traditional treatments. While our center has only conducted a preliminary trial of combined drug regimens, further comprehensive investigations through multi-center, large-scale studies offer the promise of uncovering effective treatments for metastatic MPNST, thereby providing renewed hope for patients with this challenging malignancy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Department of Medical Ethics, 960th Hospital, Joint Logistic Support Force, People's Liberation Army. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

QC: Formal analysis, Investigation, Writing – original draft. HC: Data curation, Formal analysis, Supervision, Writing – review & editing. KZ: Data curation, Formal analysis, Supervision, Writing – review & editing. MX: Data curation, Formal analysis, Supervision, Writing – review & editing. XY: Data curation, Formal analysis, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Iqbal F, Jamaluddin M, Bukhari F, Islam OS. Malignant peripheral nerve sheath tumours in a patient with Neurofibromatosis-1. *J Pak Med Assoc*. (2023) 73:393–5. doi: 10.47391/JPMA.4612

2. Bradford D, Kim A. Current treatment options for Malignant peripheral nerve sheath tumors. *Curr Treat Options Oncol*. (2015) 16:328. doi: 10.1007/s11864-015-0328-6

3. Somatilaka BN, Sadek A, McKay RM, Le LQ. Malignant peripheral nerve sheath tumor: models, biology, and translation. *Oncogene*. (2022) 41:2405–21. doi: 10.1038/s41388-022-02290-1

4. Ortiz WJ, Salazar MS, Eager JJ, Sajid S, Cervantes M. Primary intraosseous Malignant peripheral nerve sheath tumor of the humerus: report of a rare case. *Cureus*. (2022) 14:e33178. doi: 10.7759/cureus.33178

5. Gupta G, Maniker A. Malignant peripheral nerve sheath tumors. *Neurosurg Focus*. (2007) 22:E12. doi: 10.3171/foc.2007.22.6.13

6. Akshintala S, Mallory NC, Lu Y, Ballman KV, Schuetze SM, Chugh R, et al. Outcome of patients with Malignant peripheral nerve sheath tumors enrolled on sarcoma alliance for research through collaboration (SARC) phase II trials. *Oncologist*. (2023) 28:453–9. doi: 10.1093/oncolo/oyac272

7. Millesi E, Rechberger JS, Wang H, Mardini S, Spinner RJ, Daniels DJ. Advancements in therapeutic approaches for Malignant peripheral nerve sheath tumor. *Ther Deliv*. (2023) 14:385–9. doi: 10.4155/tde-2023-0014

8. Liu W, Zhang S, Liu J, Shao Z. Intraosseous Malignant peripheral nerve sheath tumor of 2 consecutive lumbar vertebrae: A case report and literature review. *World Neurosurg*. (2019) 130:459–66. doi: 10.1016/j.wneu.2019.07.117

9. Muthusamy S, Conway SA, Pitcher JD, Temple HT. Primary intraosseous Malignant peripheral nerve sheath tumor of the medial cuneiform: A case report and review of the literature. *J Foot Ankle Surg*. (2017) 56:129–34. doi: 10.1053/j.jfas.2016.05.013

10. Kendi TK, Erakar A, Yildiz HY, Saglik Y, Erekul S. Intraosseous Malignant peripheral nerve sheath tumor with local recurrence, lung metastases and death. *Skeletal Radiol*. (2004) 33:223–5. doi: 10.1007/s00256-003-0678-1

11. Karakousis CP, Perez RP. Soft tissue sarcomas in adults. *CA Cancer J Clin*. (1994) 44:200–10. doi: 10.3322/canjclin.44.4.200

12. Farid M, Demicco EG, Garcia R, Ahn L, Merola PR, Cioffi A, et al. Malignant peripheral nerve sheath tumors. *Oncologist*. (2014) 19:193–201. doi: 10.1634/theoncologist.2013-0328

13. Moretti VM, Crawford EA, Staddon AP, Lackman RD, Ogilvie CM. Early outcomes for Malignant peripheral nerve sheath tumor treated with chemotherapy. *Am J Clin Oncol*. (2011) 34:417–21. doi: 10.1097/COC.0b013e3181e9c08a

14. Grimer R, Judson I, Peake D, Seddon B. Guidelines for the management of soft tissue sarcomas. *Sarcoma*. (2010) 2010:506182. doi: 10.1155/2010/506182

15. Madhankumar AB, Mrowczynski OD, Slagle-Webb B, Ravi V, Bourcier AJ, Payne R, et al. Tumor targeted delivery of doxorubicin in Malignant peripheral nerve sheath tumors. *PloS One*. (2018) 13:e0181529. doi: 10.1371/journal.pone.0181529

16. Wang Y, Katagiri H, Murata H, Wasa J, Miyagi M, Kakuda Y, et al. Metastatic Malignant peripheral nerve sheath tumor with NF1 successfully treated with 'Gradual subtraction' ICE chemotherapy. *Anticancer Res*. (2020) 40:1619–24. doi: 10.21873/anticanres.14110

17. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. (2009) 361:756–65. doi: 10.1056/NEJMx090058

18. Boyce AM. Denosumab: an emerging therapy in pediatric bone disorders. *Curr Osteoporos Rep*. (2017) 15:283–92. doi: 10.1007/s11914-017-0380-1

19. Visgauss JD, Lazarides A, Dickson B, Cardona D, Sheth M, DeWitt SB, et al. Treatment of chondroblastoma with denosumab: A case report with a correlative analysis of effect on the RANK signaling pathway. *JBJS Case Connect*. (2021) 11: e20.00178. doi: 10.2106/JBJS.CC.20.00178

20. Pan KS, Boyce AM. Denosumab treatment for giant cell tumors, aneurysmal bone cysts, and fibrous dysplasia-risks and benefits. *Curr Osteoporos Rep*. (2021) 19:141–50. doi: 10.1007/s11914-021-00657-

21. Tay WL, Tay D. Discontinuing denosumab: can it be done safely? A review of the literature. *Endocrinol Metab (Seoul)*. (2022) 37:183–94. doi: 10.3803/EnM.2021.1369

22. Sølling AS, Tsourdi E, Harsløf T, Langdahl BL. Denosumab discontinuation. *Curr Osteoporos Rep*. (2023) 21:95–103. doi: 10.1007/s11914-022-00771-6

23. Liu J, Deng YT, Jiang Y. Switch maintenance therapy with anlotinib after chemotherapy in unresectable or metastatic soft tissue sarcoma: a single-center retrospective study. *Invest New Drugs*. (2021) 39:330–6. doi: 10.1007/s10637-020-01015-z

24. Chi Y, Fang Z, Hong X, Yao Y, Sun P, Wang G, et al. Safety and efficacy of anlotinib, a multikinase angiogenesis inhibitor, in patients with refractory metastatic soft-tissue sarcoma. *Clin Cancer Res*. (2018) 24:5233–8. doi: 10.1158/1078-0432.CCR-17-3766

25. Zhang RS, Liu J, Deng YT, Wu X, Jiang Y. The real-world clinical outcomes and treatment patterns of patients with unresectable locally advanced or metastatic soft tissue sarcoma treated with anlotinib in the post-ALTER0203 trial era. *Cancer Med*. (2022) 11:2271–83. doi: 10.1002/cam4.4613

26. Cai M, Zhu J, Zhou G. Efficacy and safety of treating refractory bone and soft tissue sarcoma with anlotinib in different treatment patterns. *Comput Math Methods Med*. (2022) 2022:3287961. doi: 10.1155/2022/3287961

27. Sobczuk P, Teterycz P, Czarnecka AM, Świtaj T, Koseła-Paterczyk H, Kozak K, et al. Systemic treatment for advanced and metastatic Malignant peripheral nerve sheath tumors-A sarcoma reference center experience. *J Clin Med*. (2020) 9(10):3157. doi: 10.3390/jcm9103157

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 25 July 2024
DOI 10.3389/fonc.2024.1437732

OPEN ACCESS

EDITED BY
Mohammad Mohammadianpanah,
Shiraz University of Medical Sciences, Iran

REVIEWED BY
Elise Nassif,
University of Texas MD Anderson Cancer Center, United States
Alessandro De Vita,
Scientific Institute of Romagna for the Study and Treatment of Tumors (IRCCS), Italy

*CORRESPONDENCE
Giuseppe Corona
giuseppe.corona@cro.it

RECEIVED 24 May 2024
ACCEPTED 08 July 2024
PUBLISHED 25 July 2024

CITATION
Miolo G, Buonadonna A, Lombardi D, Scalone S, Lauretta A, Della Puppa L and Corona G (2024) Trabectedin may be a valuable treatment option for elderly patients with metastatic soft tissue sarcomas. *Front. Oncol.* 14:1437732. doi: 10.3389/fonc.2024.1437732

Trabectedin may be a valuable treatment option for elderly patients with metastatic soft tissue sarcomas

Gianmaria Miolo[1], Angela Buonadonna[1], Davide Lombardi[1], Simona Scalone[1], Andrea Lauretta[2], Lara Della Puppa[3] and Giuseppe Corona[4]*

[1]Medical Oncology and Cancer Prevention Unit, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy, [2]Unit of General Oncologic Surgery, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy, [3]Oncogenetics and Functional Oncogenomics Unit, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy, [4]Immunopathology and Cancer Biomarkers Unit, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy

Background: In the landscape of metastatic soft tissue sarcoma (mSTS) treatment, anthracyclines have shown efficacy; however, their associated toxicity imposes significant limitations, especially in frail elderly patients with mSTS who are highly susceptible to severe adverse effects. In this context, trabectedin, due to its distinct pharmacological profile and safety profile, may represent an interesting alternative being demonstrated to be active in treating mSTS. These features hold particular significance for elderly and unfit patients with mSTS, where balancing treatment benefits with potential adverse effects represents the pivotal objective.

Methods: The investigation was focused on a specific group of 11 elderly patients with mSTS aged ≥70, all undergoing first-line treatment with trabectedin, and it was supported by comprehensive pharmacokinetic and pharmacodynamic studies. Among these patients, 9 out of 11 started the treatment at a dose of 1.5 mg/m^2.

Results: The primary objective of this investigation is to highlight trabectedin as a valuable first-line treatment option for elderly and unfit patients with mSTS. Additionally, this investigation seeks to explore whether higher administered doses of trabectedin can enhance clinical outcomes while maintaining the same toxicity profiles. The median progression-free survival (PFS) was 77 days (95% CI, 53–89), the median overall survival (OS) was 397 days (95% CI, 66–2,102), while the overall toxicity of grade 3–4 severity amounted to 43%.

Conclusion: These findings provide new insights into the clinical outcomes and toxicity associated with trabectedin in an elderly patient population, enhancing our understanding of better treatment approaches for a specific population of patients with mSTS.

KEYWORDS

cancer, trabectedin, elderly, sarcoma, first-line treatment, pharmacokinetics

1 Introduction

The choice of the most suitable treatment options for patients with locally advanced or metastatic soft tissue sarcoma (mSTS) is a complex task that requires a comprehensive understanding of both the tumor histological–molecular characteristics and the clinical conditions of the patient. This challenge is significantly heightened for the elderly mSTS population where common age-related dysfunctions as well as the frequent presence of comorbidities, which are important signals of a fragile health status, pose a significant obstacle in tailoring an effective healthcare approach (1–4). The natural aging process contributes to a decline in essential organ functions, particularly the liver and kidneys wherein altering the clearance drugs can have a detrimental effect on their safety profile (5, 6). In this context, considering the elevated risk of toxicity linked to traditional cytotoxic agents (7–9), there is a pressing need to explore innovative treatments capable of ensuring in elderly population active treatments with favorable safety profiles.

A subgroup analysis of patients over 65 years revealed that single-agent doxorubicin yielded an overall survival (OS) of 9.8 months (95% CI, 7.4–11.5), which was comparable to the OS of 9.9 months (95% CI, 5.9–11.8) for those treated with epirubicin over a 24-month follow-up while trabectedin demonstrated an OS of 17.3 months (95% CI, 9.4–17.3) despite a shorter 6.7-month follow-up (10). In a different study involving a large cohort of 361 elderly patients with mSTS, anthracycline-based regimens achieved a median OS of 10.9 months, but 32% of patients experienced severe hematological toxicities that required treatment discontinuation in 16% of them (7). Analogously, in a phase II study involving 40 elderly patients with mSTS aged 60 to 84 years (median age, 70.5 years) treated with doxorubicin, the OS was 9.8 months (95% CI, 6.7–11.6), alongside a notable severe side effect rate of 59% (11).

When extending the age threshold to ≥70 years, the anthracycline-based chemotherapy conferred survival advantage over best supportive care but did not demonstrate a survival advantage compared to other treatments. Moreover, it led to a significant grade 3–4 toxicity rate (ranging from 33% to 58%), further underscoring the challenges in managing these patients (9).

Trabectedin is an antineoplastic agent primarily indicated for the treatment of patients with mSTS following the failure of anthracycline-based regimens that presents a multifaceted mechanism of action such as targeting DNA interactions, transcriptional processes, and DNA repair mechanisms (12–16). One of the distinct advantages of trabectedin is its well-tolerated safety profile characterized by adverse events that are generally reversible and noncumulative (17–20). Thus, these pharmacological features may make it a valuable choice in the population of elderly and unfit patients with mSTS, especially where the primary objective is a viable treatment option preserving an acceptable quality of life (21). A previous clinical exploration performed on elderly patients with mSTS seems to indicate promising outcomes for this drug when utilized as first-line treatment, showing a median progression-free survival (PFS) of 4 months and an OS of 12 months, respectively (22). Recently, a multicentric study aimed at evaluating the feasibility and prognostic value of comprehensive geriatric assessment investigated 69 patients with STS, 56 of whom were aged ≥70 years, obtaining a PFS of 2.5 months and an OS of 11.2 months (23). Especially for the leiomyosarcoma histotype, it was observed that frontline treatment based on the combination of doxorubicin and trabectedin could lead to a doubling of PFS compared to doxorubicin alone (12.2 months vs. 6.2 months) (24).

While these results are promising, they require further confirmation to ascertain the possible alternative option of trabectedin as a first-line treatment in an elderly population of patients with mSTS.

The objective of the current study is to advance existing research by investigating the use of trabectedin as a first-line treatment for elderly patients with mSTS, aiming to determine whether higher administered doses of trabectedin can enhance clinical outcomes while maintaining the same toxicity profiles.

This is achieved by presenting a monocentric experience, detailing a comprehensive pharmacokinetic and pharmacodynamic investigation conducted on a specific group of 11 elderly patients with mSTS aged ≥70, all undergoing first-line treatment with trabectedin. This clinical pharmacology exploration provides further valuable insights into the clinical outcomes and toxicity associated to trabectedin in this specific demographic, thereby enhancing our understanding of treatment strategies for elderly patients with mSTS.

2 Materials and methods

2.1 Clinical population

All patients with a histological diagnosis of locally advanced or mSTS (25) who met the following criteria were consecutively enrolled in a clinical trial aimed at identifying pre-dose plasma metabolomics signatures potentially associated with individual variations in trabectedin pharmacokinetics: normal hematological, renal (≤1.6 mg/dL), liver, and cardiac functions; a performance status (PS) ≤ 2; no CNS metastases; or no history of previous cancer. All patients aged 70 or older who were considered unsuitable for standard first-line treatment with anthracycline-based regimens and underwent first-line treatment with trabectedin were evaluated. This prospective, monocentric clinical investigation focused on 11 consecutive elderly patients. Among these, 4 had received neoadjuvant radiotherapy and 7 had undergone surgical treatment. Only two patients received adjuvant treatments consisting of radiotherapy or chemotherapy, respectively. The surgical interventions resulted in no residual disease (R0) in three cases, microscopic residual disease (R1) in three cases, and macroscopic residual disease (R2) in the remaining case.

Trabectedin was administered to the patients at a dosage ranging from 1.1 to 1.5 mg/m^2 with a maximum of dose of 2.6 mg per cycle, infused over 24 h every 3 weeks via a central venous catheter.

A baseline CT scan was conducted at the onset of treatment, followed by another scan after 12 weeks. In patients showing no progression, tumor imaging assessments were continued every 3 months for an additional year, and then reduced to once every 6 months.

10.3389/fonc.2024.1437732

Treatment continued until disease progression or development of intolerable adverse events that required treatment discontinuation. Dexamethasone premedication at 4 mg twice a day, beginning the day before trabectedin administration and continuing for two consecutive days after with 4 mg a day, was administered to all patients. Response assessment was conducted in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 while the toxicity was reported according to CTCAE version 3. Each patient provided informed consent for participation in the investigation. This clinical investigation adhered to the principles outlined in the Declaration of Helsinki and followed the Good Clinical Practice Guidelines of the International Conference on Harmonization. The study protocol was subjected to review and approval by the institutional review board.

2.2 Pharmacokinetics study

For the pharmacokinetics analysis, blood samples were systematically collected at various time points during the trabectedin infusion and its elimination phases over 48 h. The sampling schedule included pre-dose (before administration) and during infusion at 2, 8, and 24 h (end of infusion), whereas post-infusion samples were obtained at 0.5, 1, 4, 8, and 24 h. Plasma concentration of trabectedin at these time points was measured by the high-performance liquid chromatography with tandem mass spectrometry (LC/MS/MS) method (26). The lower limit of quantification for this method was 0.01 ng/mL, providing a reliable range for detecting and measuring trabectedin concentrations in the collected samples. Pharmacokinetic parameters were calculated from the drug plasma concentration vs. time profiles using a non-compartmental model (27). The area under the curve up to 48 h (AUC0–48) was calculated using the trapezoidal method, the area under the moment curve (AUMC0–48) was calculated as the (concentration • time) time data plot, the mean resident time (MRT) was calculated as the AUC0–48/AUMC0–48 ratio, $t_{1/2}$ was calculated from 0.693/k where k is the slope of the late phase of the logC vs. time curve, while the drug clearance was estimated by dose/AUC0–48. The C_{max} and C_{last} were derived from the pharmacokinetics profile and corresponded to the concentration of trabectedin at the end of the 24-h infusion and at 48 h from the start of infusion.

2.3 Statistical methods

Survival curves were generated using the Kaplan–Meier method, and data analyses were carried out using MedCalc Statistical Software for Windows, version 19.4 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2020).

3 Results

The median age of the patients at study entry was 76 years [interquartile range (IQR), 75–79 years; minimum–maximum range of 70–90 years]. The Eastern Cooperative Oncology Group (ECOG) performance status reflected as 0 in five patients, 1 in five patients, and 2 in the remaining patient. Predominantly, leiomyosarcoma and liposarcoma constituted the most frequent histological subtypes (55%) followed by pleomorphic sarcoma (18%). High-grade tumors were prevailing, representing 82% (9 out of 11) of the cases (Table 1).

In the overall population, the median number of trabectedin courses administered was 3 (IQR, 3–6), with four patients (29%) receiving six or more cycles. Specifically, patients with L-sarcoma received a median of 4.5 courses (range, 1–21), while patients with Other-sarcoma received a median of 3 courses (range, 3–6). The starting dose of trabectedin was set at 1.5 mg/m² for nine patients, while in two cases, the dose administered was 1.1 mg/m², chosen by a physician based on frailty characteristics, including performance status and multiple comorbidities. Treatment discontinuation primarily occurred due to disease progression (PD), followed by medical decision. One patient died 33 days after treatment initiation

TABLE 1 Characteristics of the enrolled patients and their tumors.

Age	Mean (SD)	78	5.5
	Median (IQR)	76	75–79
Sex	Female	3	73%
	Male	8	27%
ECOG	0	5	45%
	1	5	45%
	2	1	10%
BMI	Mean (SD)	27	4.0
	Median (IQR)	27	23.1–31.4
Grade	2	2	18%
	≥3	9	82%
Histotype	Leiomyosarcoma^	3	27%
	Liposarcoma*	3	27%
	Others°	5	46%
Primary site of disease	Retroperitoneum	4	36%
	Gluteus	3	27%
	Trunk	3	27%
	Forearm	1	10%
Metastases			
	Lung	6	55%
	Extra-lung	5	45%
Median trabectedin courses (IQR)		3	3–6

^ One pleomorphic leiomyosarcoma (PLMS) and two leiomyosarcoma NAS.
* One well-differentiated liposarcoma (WDLS), one dedifferentiated liposarcoma (DDLS), and one myxoid liposarcoma (MLS).
° Three undifferentiated pleomorphic sarcoma (UPS), one myxofibrosarcoma, and one sarcoma NAS.

and was subsequently excluded from the response assessment. After the third cycle, PD was observed in six patients (60%), while four patients (40%) demonstrated disease stability (SD). Among the histological subtypes responsive to treatment, four were from the L-sarcoma group, while the remaining responsive case belonged to the Other-sarcoma group, specifically a pleomorphic sarcoma.

The median PFS was 77 days (95% CI, 53–89) (Figure 1), while the median OS was 397 days (95% CI, 66–2,102) (Figure 2). The median follow-up was 2.11 years, ranging from 0.1 to 7.66.

A total of 14 adverse events were documented, with six of them (43%) classified as grade 3–4. Specifically, hematological toxicity of grade 3–4 was observed in 29%, while non-hematological grade 3 toxicity accounted for 14%. Among hematological toxicities, neutropenia was the most prevalent, followed by leukopenia, while among non-hematological toxicities, emesis emerged as the most frequent (Table 2). Overall, five patients (55%) required a reduction in their initial treatment dose. Among them, two patients underwent dose reduction starting from the second cycle, while the remaining three, including one who initially started with a reduced dose, began the reduction from the fourth cycle onwards (Table 2).

Overall, 6 of these 11 patients received a second-line treatment consisting of gemcitabine plus dacarbazine (4), eribulin (1), and doxorubicin single-agent regimen (1). Only three of these patients, previously treated with the combination regimen, received a third-line treatment with pazopanib (2) and eribulin (1).

Pharmacokinetic assessments were conducted during the first cycle of treatment for all patients. The mean dose of trabectedin administered was 1.32 mg/m^2 (SD ± 0.15). Table 3 shows the characteristics of each enrolled patient, and Figure 3 summarizes the plasma pharmacokinetics profile of trabectedin in all patients investigated. At approximately 8 h of infusion and up to the end of the 24-h infusion, trabectedin reached and maintained steady-state concentration, followed by a rapid decline within 6 h from the end of infusion according to multiphase elimination steps. At 24 h from the end of the infusion, trabectedin was still measurable in all patients, and the mean concentration at 48 h (C_{last}) was 0.2 ng/mL (IQR, 0.2–0.3; minimum–maximum range, 0.1–0.4). The other mean pharmacokinetics parameters of trabectedin were as follows: the drug concentration evaluated at the end of 24 h of infusion, expressed as C_{max}, is 1.1 ng/mL (IQR, 0.8–1.4; minimum–maximum range, 0.4–1.6); the trabectedin exposure expressed as AUC0–48h is 30.6 ng/mL*h (IQR, 21.2–37.9; minimum–maximum range 12.7–47.7); estimated clearance = 48.6 L/h/m^2 (IQR, 36.6–60.2; minimum–maximum range, 27.2–87.7), and the mean residence time (MRT) = 18.1 h (IQR, 17.5–18.7; minimum–maximum range 16.9–19.3) (Table 4). These parameters did not differ significantly from those observed in a group of 31 patients with age ≤65 years undergoing second-line treatment and are superimposable with those observed in previously pharmacokinetic investigations (Supplementary Table 1).

4 Discussion

While anthracyclines have proven to be effective in mSTS treatment, their notable toxicity poses challenges in administering this class of drugs to frail elderly patients with cancer who are more susceptible to adverse events (7, 9–11). Trabectedin emerged as a compelling therapeutic alternative for this specific patient population due to its favorable safety profile, characterized by a reduced incidence of both non-hematological and hematological toxicity (28, 29).

Recent studies have emphasized the potential role of systemic inflammatory indices, such as the lower lymphocyte/monocyte ratio, in predicting trabectedin efficacy in frail elderly patients with STS, further highlighting the importance of these biomarkers in treatment planning (30–33) of elderly patients. Thus, the tumor-related systemic inflammation, coupled with its favorable toxicity, make trabectedin a possible alternative to anthracyclines in elderly patients with mSTS. In this context, our monocentric study aims to assess the effectiveness of trabectedin as tailored frontline treatment in a cohort of elderly patients with mSTS aged ≥70 years.

This age threshold exceeds the conventional definition of elderly patients, typically set at 65 years, but the extension of this age threshold acknowledges the evolving landscape of cancer patient

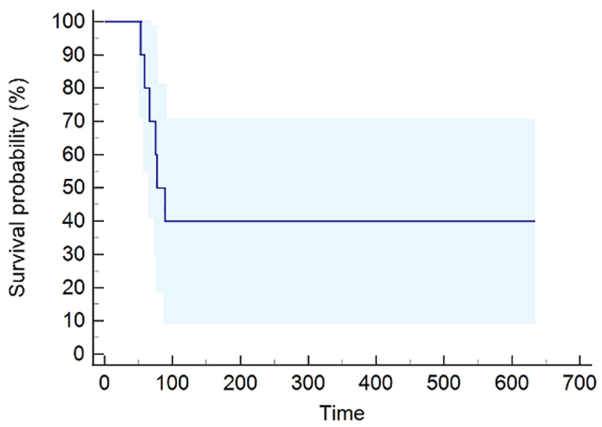


FIGURE 1
Progression-free survival (PFS) curve calculated using the Kaplan–Meier method.

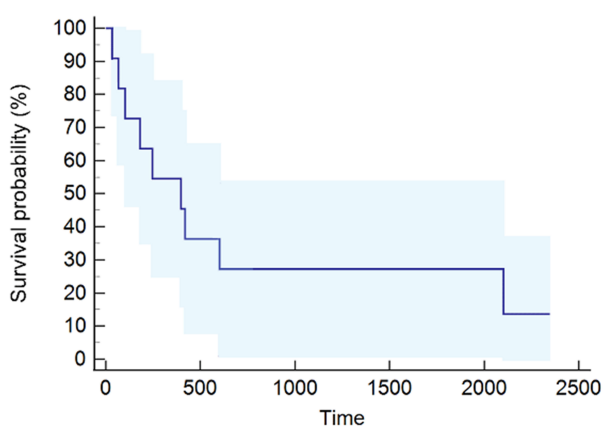


FIGURE 2
Overall survival (OS) curve calculated using the Kaplan–Meier method.

10.3389/fonc.2024.1437732

TABLE 2 Hematological and non-hematological toxicities.

n	Dose*	Toxicity NE		Toxicity E		First reduction	Second reduction
		G1–G2	G3–G4	G1–G2	G3–G4		
1	2.6	–	G3	–	G3	From fourth cycle to 1.9 mg	
2	2.6	–	–	–	G4		
3	2.6	–	–	G1	–		
4	2.6	G1	–	–	–	From second cycle to 1.6 mg	
5	2.6	–	–	–	G4		
6	2.4	–	–	G2	–		
7	1.8	G2	–	G2	–		
8	2.6	G2	–	G2	–	From fourth cycle to 2.5 mg	From fifth cycle to 2.3 mg
9	2.6	–	G3	–	G3	From second cycle to 2.2 mg	From third cycle to 1.9 mg
10	2.0	G2	–	–	–	From fourth cycle to 1.9 mg	
11	2.6	–	–	–	–		
		4/11 (36%)	2/11 (18%)	4/11 (36%)	4/11 (36%)		

*Total dose (mg).

demographics, thus providing a more accurate representation of the elderly population observed in clinical practice.

In order to provide key information on the optimal drug dosage, administration frequency, and potential dose adjustments, pharmacokinetic investigations have been performed in all patients enrolled in the study. The mean clearance of trabectedin was 48.6 L/h/m^2 (SD ±18.78), slightly higher than values reported in other studies (34–38), although not significantly different from the value of 39.98 L/h/m^2 (SD ±14.08) reported in a study conducted in a highly selected population of patients with mSTS aged ≥65 years (22). These results appear in contrast with the diminished organ functionality, gradual decline in liver volume, and altered expression profile of CYP3A4, typically observed in older patients and potentially leading to a reduction in the metabolic clearance of trabectedin (6, 39–41). However, it is worth noting that in managing elderly patients with mSTS, a concurrent administration of dexamethasone is employed to achieve an optimal balance between drug metabolism, efficacy, and adverse events (42). Dexamethasone is known to act as a CYP3A4 concentration-dependent inducer playing a pivotal role in increasing the metabolic clearance of trabectedin and reducing drug-induced hepatotoxicity and myelosuppression (43). Interestingly, no significant alteration in the main drug metabolism emerged in our selected

TABLE 3 Physical and biochemical characteristics of each enrolled patient.

PTS (*n*)	Sex	Age (years)	Weight (k)	Height (cm)	BSA (m^2)	Serum creatinine (mg/dL)	Creatinine clearance (mL/min)*	BT (mg/dL)	BD (mg/dL)	AST (U/L)	ALT (U/L)	Hb (g/dL)
1	M	75	74	165	1.8	0.82	81.5	1.54	0.78	16	11	13.7
2	M	71	96	173	2.1	1.59	57.9	0.63	0.27	25	20	13.8
3	M	90	83	173	2.0	1.00	57.6	0.34	0.14	11	9	11.9
4	M	77	59	167	1.7	1.32	39.1	1.47	0.15	19	17	14.1
5	F	79	75	168	1.9	0.73	74.0	0.69	0.52	33	26	13.2
6	F	75	73	146	1.6	1.00	56.0	0.28	0.30	17	11	10.5
7	F	88	60	165	1.7	0.79	46.6	0.30	0.14	11	8	11.1
8	M	76	79	170	1.9	0.80	87.8	0.59	0.11	20	12	11.2
9	M	75	83	163	1.9	0.96	78.1	0.40	0.20	17	22	13.,1
10	M	79	75	180	1.9	1.04	61.1	0.50	0.21	9	6	12.2
11	M	75	82	183	2.0	1.07	69.2	0.50	0.20	24	24	14.8

* The creatinine clearance was calculated using the Cockroft–Gauilt equation.

10.3389/fonc.2024.1437732

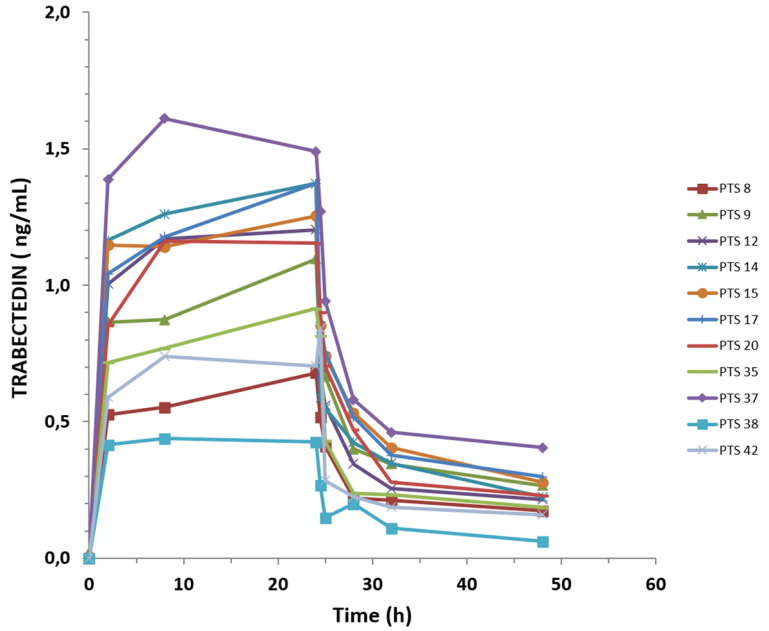


FIGURE 3
Plasma concentration–time profile of trabectedin detected in the 11 analyzed patients.

patients, despite the fact that reduced CYP3A4 expression has been observed and dexamethasone has a decreased capacity to induce CYP3A4 in the elderly population (6, 44, 45). The pharmacokinetic findings emphasize that elderly patients receiving 1.5 mg/m^2 of trabectedin, along with dexamethasone premedication, maintain an effective trabectedin clearance comparable to younger patients who received trabectedin as a second-line treatment. Indeed, the inter-patient variability of AUC0–48h, which is a surrogate of total drug exposure for elderly patients, was similar to that observed in a group of 31 patients with mSTS aged ≤70 years undergoing second-line treatment (Supplementary Table 1). AUC0–48h was found to be not correlated with toxicity, indicating that pharmacokinetic profiles are more comprehensively influenced by a combination of multiple factors including individual genetics, specific physio-pathological conditions, and environmental variables rather than being solely determined by age (46).

Beyond a favorable toxicity safety profile, this exploratory assessment revealed a notable clinical benefit of 40%, indicating trabectedin as an interesting treatment choice for this group of patients who often has limited therapeutic alternatives. Although the overall clinical benefit was 50% lower than that reported by Grosso et al. (22), it is worth noting that the latter included fewer cases with unfavorable prognosis. Indeed, our elderly population was characterized by 45% of cases with Other-sarcoma, while in the previous study, where a clinical benefit that is twofold higher was achieved, only 20% of the patients were classified as Other-sarcoma, with a net predominance of L-sarcoma. Thus, the different percentages of L-sarcoma that, according to the literature, represent the histological subtypes most responsive to trabectedin treatment can be partially responsible for this apparent incongruity observed between the two studies. Despite this heterogeneity, median PFS and OS were found to be approximately 3 and 12 months, respectively, suggesting that trabectedin, when used as a first-line treatment in a population of elderly patients with mSTS, has no negligible clinical impact in view of the fact that such clinical outcomes were reached using a starting dose of 1.3 mg/m^2 of trabectedin. Overall, the clinical outcomes observed in

TABLE 4 Pharmacokinetic parameters of trabectedin.

	C_{max} (ng/mL)	AUC_{0-48} (ng/mL*h)	MRT (h)	CL (L/h/m^2)	$C_{last(48h)}$ (ng/mL)
Mean	1.1	30.6	18.1	48.6	0.2
SD	0.3	10.2	0.8	18.7	0.1
Median	1.2	33.6	18.1	44.0	0.2
Min	0.4	12.7	16.9	27.2	0.1
Max	1.6	47.7	19.3	87.7	0.4
n	11	11	11	11	11

this investigation, as well as in the previous study of Grosso et al. (22), did not significantly differ from those previously reported in patients with mSTS aged 60 years or older who were randomized to receive pazopanib or doxorubicin as first-line treatment (47), with the PFS ranging between 4.4 and 5.3 months across treatment arms and the OS ranging between 12.3 and 14.3 months, while the adverse events of grade 3–4 severity amounted to 85.6%.

Although the small number of patients limits the ability to draw definitive conclusions, the results of this investigation provide valuable confirmation of previous findings (22, 23) contributing to establishing a more solid foundation for the use of trabectedin treatment in elderly patients with mSTS.

5 Conclusion

Optimizing the management of STS in elderly patients is a significant clinical challenge, particularly because this demographic represents a substantial and growing proportion of the cancer population due to increasing life expectancy. The findings of this study seem to confirm that 1.3 mg/m^2 dose of trabectedin represents a valuable first-line pharmacological option for treating elderly patients with mSTS, given its favorable balance between clinical efficacy and lower toxicity profile that directly affects quality of life.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Institutional Review Board of CRO Aviano. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

GM: Conceptualization, Writing – original draft, Writing – review & editing. AB: Writing – review & editing. DL: Writing – review & editing. SS: Writing – review & editing. AL: Writing – review & editing. LDP: Writing – review & editing. GC: Conceptualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was funded by the Italian Ministry of Health-Ricerca Corrente.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1437732/full#supplementary-material

References

1. Goede V. Frailty and cancer: current perspectives on assessment and monitoring. *Clin Interv Aging*. (2023) 18:505–21. doi: 10.2147/CIA.S365494

2. Scotté F, Bossi P, Carola E, Cudennec T, Dielenseger P, Gomes F, et al. Addressing the quality of life needs of older patients with cancer: a SIOG consensus paper and practical guide. *Ann Oncol*. (2018) 29:1718–26. doi: 10.1093/annonc/mdy228

3. Di Capua B, Bellieni A, Fusco D, Gambacorta MA, Tagliaferri L, Villani ER, et al. Perspectives and limits of cancer treatment in an oldest old population. *Aging Clin Exp Res*. (2021) 33:2831–7. doi: 10.1007/s40520-021-01821-2

4. Malaguarnera M, Frazzetto PM, Erdogan O, Cappellani A, Cataudella E, Berretta M. Geriatric evaluation of oncological elderly patients. *Anticancer Agents Med Chem*. (2013) 13:1300–9. doi: 10.2174/18715206113136660343

5. Klotz U. Pharmacokinetics and drug metabolism in the elderly. *Drug Metab Rev*. (2009) 41:67–76. doi: 10.1080/03602530902722679

6. Konstandi M, Johnson EO. Age-related modifications in CYP-dependent drug metabolism: role of stress. *Front Endocrinol (Lausanne)*. (2023) 14:1143835. doi: 10.3389/fendo.2023.1143835

7. Garbay D, Maki RG, Blay JY, Isambert N, Piperno Neumann S, Blay C, et al. Advanced soft-tissue sarcoma in elderly patients: patterns of care and survival. *Ann Oncol*. (2013) 24:1924–30. doi: 10.1093/annonc/mdt059

8. Repetto L. Greater risks of chemotherapy toxicity in elderly patients with cancer. *J Support Oncol*. (2003) 1:18–24.

9. Chiusole B, Tortorelli I, Galiano A, Murtas F, Ahcene-Djaballah S, Tierno G, et al. Management and outcomes of older patients (Age ≥ 70 years) with advanced soft tissue sarcoma and role of geriatric assessment and oncological multidimensional prognostic index (Onco-MPI) in a real-world setting. *Cancers (Basel)*. (2023) 15:1043. doi: 10.3390/cancers15041043

10. Younger E, Litière S, Le Cesne A, Mir O, Gelderblom H, Italiano A, et al. Outcomes of elderly patients with advanced soft tissue sarcoma treated with first-line chemotherapy: A pooled analysis of 12 EORTC soft tissue and bone sarcoma group trials. *Oncologist*. (2018) 23:1250–9. doi: 10.1634/theoncologist.2017-0598

11. Hartmann JT, Kopp HG, Gruenwald V, Piperno-Neumann S, Kunitz A, Hofheinz R, et al. German Sarcoma Group within the Working Group Medical Oncology (AIO) of the German Cancer Society/AIO-STS-002, Arbeitsgemeinschaft Internistische Onkologie der Deutschen Krebsgesellschaft e.V. Randomised phase II trial of trofosfamide vs. doxorubicin in elderly patients with untreated metastatic soft-tissue sarcoma. *Eur J Cancer*. (2020) 124:152–60. doi: 10.1016/j.ejca.2019.10.016

12. D'Incalci M. Trabectedin mechanism of action: what's new? *Future Oncol*. (2013) 9:5–10. doi: 10.2217/fon.13.207

13. David-Cordonnier MH, Gajate C, Olmea O, Laine W, de la Iglesia-Vicente J, Perez C, et al. DNA and non-DNA targets in the mechanism of action of the antitumor drug trabectedin. *Chem Biol*. (2005) 12:1201–10. doi: 10.1016/j.chembiol.2005.08.009

14. Herrero AB, Martín-Castellanos C, Marco E, Gago F, Moreno S. Cross-talk between nucleotide excision and homologous recombination DNA repair pathways in the mechanism of action of antitumor trabectedin. *Cancer Res*. (2006) 66:8155–62. doi: 10.1158/0008-5472.CAN-06-0179

15. Larsen AK, Galmarini CM, D'Incalci M. Unique features of trabectedin mechanism of action. *Cancer Chemother Pharmacol*. (2016) 77:663–71. doi: 10.1007/s00280-015-2918-1

16. Laroche A, Chaire V, Le Loarer F, Algéo MP, Rey C, Tran K, et al. Activity of trabectedin and the PARP inhibitor rucaparib in soft-tissue sarcomas. *J Hematol Oncol*. (2017) 10:84. doi: 10.1186/s13045-017-0451-x

17. Schöffski P, Cornillie J, Wozniak A, Li H, Hompes D. Soft tissue sarcoma: an update on systemic treatment options for patients with advanced disease. *Oncol Res Treat*. (2014) 37:355–62. doi: 10.1159/000362631

18. Gajdos C, Elias A. Trabectedin: safety and efficacy in the treatment of advanced sarcoma. *Clin Med Insights Oncol*. (2011) 5:35–43. doi: 10.4137/CMO.S4907

19. Le Cesne A, Ray-Coquard I, Duffaud F, Chevreau C, Penel N, Bui Nguyen B, et al. Trabectedin in patients with advanced soft tissue sarcoma: a retrospective national analysis of the French Sarcoma Group. *Eur J Cancer*. (2015) 51:742–50. doi: 10.1016/j.ejca.2015.01.006

20. Grignani G, Le Cesne A, Martín-Broto J. Trabectedin as second-line treatment in advanced soft tissue sarcoma: quality of life and safety outcomes. *Future Oncol*. (2022) 18:13–22. doi: 10.2217/fon-2022-0518

21. Jones RL, Le Cesne A, Ibrahim T, Garcia Del Muro X, Menge F. Preserving quality of life as a key treatment goal in advanced soft tissue sarcomas. *Expert Rev Anticancer Ther*. (2018) 18:1241–8. doi: 10.1080/14737140.2018.1524298

22. Grosso F, D'Ambrosio L, Zucchetti M, Ibrahim T, Tamberi S, Matteo C, et al. Pharmacokinetics, safety, and activity of trabectedin as first-line treatment in elderly patients who are affected by advanced sarcoma and are unfit to receive standard chemotherapy: A phase 2 study (TR1US study) from the Italian Sarcoma Group. *Cancer*. (2020) 126:4726–34. doi: 10.1002/cncr.33120

23. Kasper B, Pink D, Rothermundt C, Richter S, Augustin M, Kollar A, et al. Geriatric assessment of older patients receiving trabectedin in first-line treatment for advanced soft tissue sarcomas: the E-TRAB study from the german interdisciplinary sarcoma group (GISG-13). *Cancers (Basel)*. (2024) 16:558. doi: 10.3390/cancers16030558

24. Pautier P, Italiano A, Piperno-Neumann S, Chevreau C, Penel N, Firmin N, et al. Doxorubicin alone versus doxorubicin with trabectedin followed by trabectedin alone as first-line therapy for metastatic or unresectable leiomyosarcoma (LMS-04): a randomised, multicentre, open-label phase 3 trial. *Lancet Oncol*. (2022) 23:1044–54. doi: 10.1016/S1470-2045(22)00380-1

25. WHO Classification of Tumours Editorial Board. *Soft tissue and bone tumours. Lyon (France): International Agency for Research on Cancer* (2020). Available online at: https://publications.Iarc.fr/588.

26. Di Gregorio E, Miolo G, Steffan A, Corona G. Novel method for fast trabectedin quantification using hydrophilic interaction liquid chromatography and tandem mass spectrometry for human pharmacokinetic studies. *J Pharm BioMed Anal*. (2020) 185:113261. doi: 10.1016/j.jpba.2020.113261

27. Gabrielsson J, Weiner D. Non-compartmental analysis. *Methods Mol Biol*. (2012) 929:377–89. doi: 10.1007/978-1-62703-050-2_16

28. Jordan K, Jahn F, Jordan B, Kegel T, Müller-Tidow C, Rüssel J. Trabectedin: Supportive care strategies and safety profile. *Crit Rev Oncol Hematol*. (2015) 94:279–90. doi: 10.1016/j.critrevonc.2015.02.012

29. Samuels BL, Chawla S, Patel S, von Mehren M, Hamm J, Kaiser PE, et al. Clinical outcomes and safety with trabectedin therapy in patients with advanced soft tissue sarcomas following failure of prior chemotherapy: results of a worldwide expanded access program study. *Ann Oncol*. (2013) 24:1703–9. doi: 10.1093/annonc/mds659

30. Fausti V, De Vita A, Vanni S, Ghini V, Gurrieri L, Riva N, et al. Systemic inflammatory indices in second-line soft tissue sarcoma patients: focus on lymphocyte/monocyte ratio and trabectedin. *Cancers (Basel)*. (2023) 15:1080. doi: 10.3390/cancers15041080

31. Imai T, Kojima Y, Shimoi T, Aiba H, Okuma HS, Saito A, et al. Predicting trabectedin efficacy in soft tissue sarcoma: inflammatory biomarker analysis. *Anticancer Res*. (2024) 44:2125–32. doi: 10.21873/anticanres.17018

32. Tanaka K, Ozaki T. Management of elderly patients with bone and soft tissue sarcomas: JCOG Bone and Soft Tissue Tumor Study Group. *Jpn J Clin Oncol*. (2022) 52:526–30. doi: 10.1093/jjco/hyac027

33. De Vita A, Recine F, Miserocchi G, Pieri F, Spadazzi C, Cocchi C, et al. The potential role of the extracellular matrix in the activity of trabectedin in UPS and L-sarcoma: evidences from a patient-derived primary culture case series in tridimensional and zebrafish models. *J Exp Clin Cancer Res*. (2021) 40:165. doi: 10.1186/s13046-021-01963-1

34. Garcia-Carbonero R, Supko JG, Manola J, Seiden MV, Harmon D, Ryan DP, et al. Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy. *J Clin Oncol*. (2004) 22:1480–90. doi: 10.1200/JCO.2004.02.098

35. Garcia-Carbonero R, Supko JG, Maki RG, Manola J, Ryan DP, Harmon D, et al. Ecteinascidin-743 (ET-743) for chemotherapy-naive patients with advanced soft tissue sarcomas: multicenter phase II and pharmacokinetic study. *J Clin Oncol*. (2005) 23:5484–92. doi: 10.1200/JCO.2005.05.028

36. Perez-Ruixo JJ, Zannikos P, Hirankarn S, Stuyckens K, Ludwig EA, Soto-Matos A, et al. Population pharmacokinetic meta-analysis of trabectedin (ET-743, Yondelis) in cancer patients. *Clin Pharmacokinet*. (2007) 46:867–84. doi: 10.2165/00003088-200746100-00005

37. Taamma A, Misset JL, Riofrio M, Guzman C, Brain E, Lopez Lazaro L, et al. Phase I and pharmacokinetic study of ecteinascidin-743, a new marine compound, administered as a 24-hour continuous infusion in patients with solid tumors. *J Clin Oncol*. (2001) 19:1256–65. doi: 10.1200/JCO.2001.19.5.1256

38. Puchalski TA, Ryan DP, Garcia-Carbonero R, Demetri GD, Butkiewicz L, Harmon D, et al. Pharmacokinetics of ecteinascidin 743 administered as a 24-h continuous intravenous infusion to adult patients with soft tissue sarcomas: associations with clinical characteristics, pathophysiological variables and toxicity. *Cancer Chemother Pharmacol*. (2002) 50:309–19. doi: 10.1007/s00280-002-0498-3

39. Wauthier V, Verbeeck RK, Calderon PB. The effect of ageing on cytochrome p450 enzymes: consequences for drug biotransformation in the elderly. *Curr Med Chem*. (2007) 14:745–57. doi: 10.2174/092986707780090981

40. George J, Byth K, Farrell GC. Age but not gender selectively affects expression of individual cytochrome P450 proteins in human liver. *Biochem Pharmacol*. (1995) 50:727–30. doi: 10.1016/0006-2952(95)00192-3

41. McLachlan AJ, Pont LG. Drug metabolism in older people–a key consideration in achieving optimal outcomes with medicines. *J Gerontol A Biol Sci Med Sci*. (2012) 67:175–80. doi: 10.1093/gerona/glr118

42. Grosso F, Dileo P, Sanfilippo R, Stacchiotti S, Bertulli R, Piovesan C, et al. Steroid premedication markedly reduces liver and bone marrow toxicity of trabectedin in advanced sarcoma. *Eur J Cancer*. (2006) 42:1484–90. doi: 10.1016/j.ejca.2006.02.010

43. Paz-Ares L, López-Pousa A, Poveda A, Balañá C, Ciruelos E, Bellmunt J, et al. Trabectedin in pre-treated patients with advanced or metastatic soft tissue sarcoma: a phase II study evaluating co-treatment with dexamethasone. *Invest New Drugs*. (2012) 30:729–40. doi: 10.1007/s10637-010-9561-9

44. McCune JS, Hawke RL, LeCluyse EL, Gillenwater HH, Hamilton G, Ritchie J, et al. *In vivo* and in *vitro* induction of human cytochrome P4503A4 by dexamethasone. *Clin Pharmacol Ther*. (2000) 68:356–66. doi: 10.1067/mcp.2000.110215

45. Schmucker DL, Wang RK. Age-dependent alterations in rat liver microsomal NADPH-cytochrome c (P-450) reductase: a qualitative and quantitative analysis. *Mech Ageing Dev*. (1983) 21:137–56. doi: 10.1016/0047-6374(83)90070-2

46. Corona G, Di Gregorio E, Buonadonna A, Lombardi D, Scalone S, Steffan A, et al. Pharmacometabolomics of trabectedin in metastatic soft tissue sarcoma patients. *Front Pharmacol*. (2023) 14:1212634. doi: 10.3389/fphar.2023.1212634

47. Grünwald V, Karch A, Schuler M, Schöffski P, Kopp HG, Bauer S, et al. Randomized comparison of pazopanib and doxorubicin as first-line treatment in patients with metastatic soft tissue sarcoma age 60 years or older: results of a german intergroup study. *J Clin Oncol*. (2020) 38:3555–64. doi: 10.1200/JCO.20.00714

Frontiers in Oncology

Advances knowledge of carcinogenesis and tumor progression for better treatment and management

The third most-cited oncology journal, which highlights research in carcinogenesis and tumor progression, bridging the gap between basic research and applications to imrpove diagnosis, therapeutics and management strategies.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact