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Advancing patient-centric oncology: non-operative management and surgical de-escalation in cancer care

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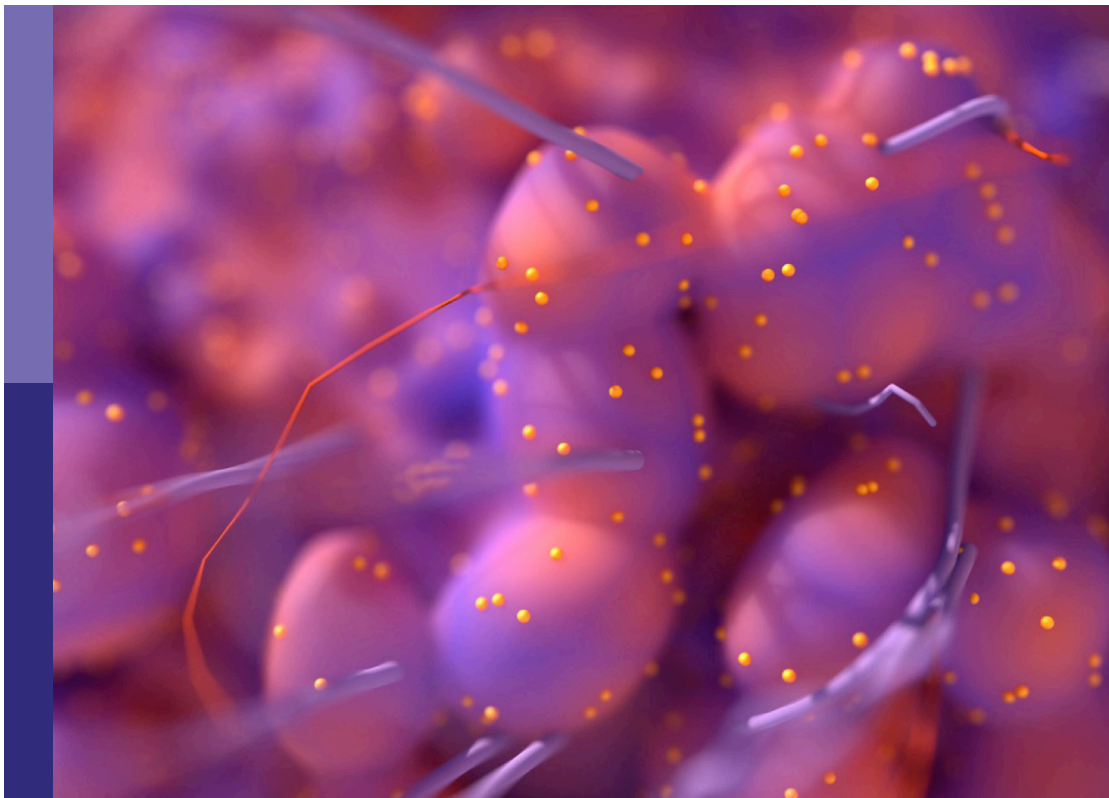

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Advancing patient-centric oncology: non-operative management and surgical de-escalation in cancer care

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One more rep! The case for resistance training in young cancer survivors

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Resistance training is now seen as a powerful tool to improve the health and functionality of cancer survivors. Literature shows that it can be implemented both during and after cancer treatment, with the intent of preserving muscle mass in the former and increasing muscle mass in the latter case. However, currently available data on this matter are predominantly derived from adult cancer survivors (ACS), and it is questionable whether the exact same raining regimen should be implemented in young cancer survivors (YCS) given the unique challenges they experience throughout their disease trajectory. Therefore, the goal of this work is to distill the existing evidence on resistance training (RT) interventions in ACS and facilitate discussion on whether the same patterns of RT can be applied in YCS.

KEYWORDS

cancer, resistance training, strength training, exercise oncology, muscle tissue

1 Introduction

Over the last several decades, evidence has shown us that resistance training (RT) is not just about feeling bulky and looking good but that there is more beyond aesthetics. The main target of RT, skeletal muscle, is now seen as an essential element of the complex network between hormonal, metabolic, and inflammatory pathways in addition to its

innate function in the neuromuscular system (1, 2). Indeed, it is unsurprising then that the health benefits of RT are numerous and include reduced all-cause mortality and cardiovascular disease incidence, improved quality of life, improved mental health and physical functioning, and prevention of sarcopenia (3–8). In addition, the risks associated with regular RT are negligible compared to the benefits associated with this type of training (3). Likewise, novel studies indicate many benefits of RT in adult cancer survivors (ACS) (9), but it seems that ACS are rather sedentary both before (10) and after cancer treatment (11, 12). It is estimated that more than 70% of ACS are obese or overweight (13). Nevertheless, the most recent findings suggest that ACS can improve physical fitness through regular exercise (including RT) similar to adults unaffected by cancer (14). In addition, a recent meta-analysis showed that RT increases muscle strength independent of the cancer treatment type (15).

Despite exercise therapy, including RT, being appraised as the most effective adjunct therapy to prevent and treat a spectrum of late effects of cancer and therapy in young cancer survivors (YCS), there is stunningly poor evidence supporting the benefits of exercise based on YCS-focused research (16). Young cancer survivors are those who develop cancer between the ages of 15 and 39 and are recognized as a distinct population in the oncology community given the unique challenges they experience throughout their disease trajectory (17).

However, despite the accumulating data on RT in ACS, there is an ongoing debate about whether the same RT guidelines should be followed in the YCS RT regimen. Thus, the goal of this manuscript is to distill the existing evidence on RT interventions in ACS, describe employed patterns of RT used in the intervention studies, outline key benefits and potential pitfalls, and facilitate discussion on whether the same RT patterns can be applied in YCS.

2 RT design

As safety always comes first, it is important to outline that there is a consensus that under initial supervision and proper guidance, RT is safe in ACS (14). This has been shown in a plethora of studies, but it is very important to take into account whether RT is conducted during or after cancer therapy, as treatment-associated fatigue can be a limiting factor when performing RT, especially during treatment (18). Likewise, age, severity (stage) of cancer, and previous experience in RT need to be taken into account when considering RT design (19). Ideally, RT would be tailored to fit the needs of every patient with cancer, but in reality, this is often not the case, as many cannot afford personal trainers and are usually part of larger groups that follow identical protocols regardless of the previously mentioned factors. However, the social component of group training can be a potent tool in helping patients with cancer adhere to the RT protocol that was initiated during the intervention (20). In contrast, in case ACS or YCS want to perform training at home or any other setting of their choice, there are many zero-cost phone apps that offer audio-visual guidance on how to perform RT.

Despite growing data on RT in ACS, some authors claim that current approaches to RT prescription in this population can be seen as "basic and potentially underdeveloped" (21). Indeed, many randomized controlled trials (RCTs) dealing with cancer survivors still fail to report essential aspects of RT such as modes of progression, duration of RT sessions, and baseline fitness levels of subjects (21, 22). Thereby, caution should be taken when a certain study reports that RT was ineffective in a specific domain of interest, as this might be due to inadequate RT design rather than lack of efficacy of the RT itself (21).

However, certain common traits can be detected among higher-quality randomized control trials that have conducted RT in ACS (13, 14, 21). When designing RT for this population, it is advised to involve major muscle groups via six to eight exercises in a single session (on non-consecutive days). These exercises should be performed in one to three sets, 8–12 repetitions per set. To accustom novel exercisers, RT can be initially performed on machines and later by free weights, as the latter stimulates muscle tissue to a greater degree than machine-based exercises (23, 24). In addition, resistance bands or bodyweight exercises may be considered when a lack of resources or deconditioning may preclude exercise participation. Intensity should be matched to 60%–70% of 1 repetition maximum (1RM), whereby RT would be challenging but not exhausting. Progression can be carried out by increasing the weight or resistance in a given exercise, increasing the number of repetitions per set or the number of sets in total, reducing the break between the sets, or all of the above. However, progression should also be adjusted according to the subjective perception of RT; hence, tools like the Borg scale can be very useful to ensure that RT is challenging but not overwhelming.

2.1 Current recommendations for young cancer survivors

As RT studies on YCS are rather scarce, it seems widely accepted that this group should follow the guidelines from RT studies performed in ACS. In the following paragraphs, we will outline key components of RT implemented in ACS in the existing literature.

Using the appropriate individualization, RT may be used to target specific cancer and therapy symptoms. The current American College of Sports Medicine (ACSM) guidelines affirm that RT alone may be a valuable strategy to improve the health of ACS, although suggesting in the first place a combined moderate-intensity aerobic protocol (3 times/week for a minimum of 30 minutes) with the inclusion of 2 RT days (60% of 1RM, 2–3 sets of 8–15 repetitions per muscle group) (25). The Exercise & Sports Science Australia (ESSA) guidelines, supporting the benefits of exercise for ACS, emphasize the need to individualize multimodal moderate- to high-intensity exercise interventions (which is consistent with ACSM guidelines' final considerations) (26).

In addition, the American Society of Clinical Oncology (ASCO) guidelines for ACS undergoing treatments indicate aerobic and RT

as a strategy to dampen treatment side effects (27). Interestingly, these guidelines (including diet and weight management indications) highlighted the paucity of evidence supporting weight loss interventions (or weight gain avoidance) to improve patients' health (27). Therefore, the anabolic potential of RT could be, however, supported to avoid cachexia, which is diagnosed in approximately 50% of patients with cancer (15), and deconditioning. This indication may also be extremely relevant for older patients who may have faced muscle mass loss before diagnosis and therapies and present higher cachexia levels than YCS (28, 29).

Until more data on studies specifically designed for YCS are available, it is reasonable to follow RT guidelines for ACS while being cautious of unique needs and barriers that this population might face. Engaging in RT and other forms of exercise is particularly important for YCS given their higher 5-year survival rates (82.5%) and the greater potential for years of productive life lost per individual than people diagnosed after the fourth decade (16).

3 Future perspectives

RT and its anabolic effect may be a strategy not only to avoid muscle mass loss (particularly in the older cancer population) but also to maintain higher adherence, which should be promoted through individualization. Tailoring the intervention is extremely relevant when considering the difference between those who are undergoing therapy and those who completed treatments with curative intent. In the first population, RT strategies should be implemented to avoid excessive muscle mass loss and deconditioning, aiming to maintain patients' physical function, rather than improving it. For those who completed all treatments, RT could be essential not only to recover from therapeutic side effects but, once recovery is completed, also to improve physical fitness levels, similar to what is conducted for healthy individuals.

Although individualization could be the key to exercise prescription on cancer populations, it is also worth noting that certain types of cancer have been understudied in the exercise oncology field and that guidelines commonly refer to randomized controlled trials on commonly and less detrimental cancer types (e.g., breast, colorectal, and prostate cancers). Exercise specialists should tailor RT intervention for patients with cancer after oncologist approval and know the risks that exercise may cause along with the safety procedures to avoid those risks. As the exercise was recently adopted as a standard of cancer care in Australia and will likely be adopted in the USA and Canada (30), thorough guidelines on implementing RT in YCS are imperative.

4 Discussion

Although the literature on exercise oncology has grown immensely in recent years, there are certain issues in this field that need to be addressed. As stated previously, precise reporting on the details of the RT interventions is lacking in many instances. To provide valid and reliable RCTs that can be replicated in various settings, methodological quality, i.e., detailed study design description, should be mandatory and requested by the reviewers and editors of journals. Vague descriptions of RT patterns employed in RCTs can lead to inaccurate conclusions and inappropriate delivery in clinical and community settings. To prevent this, scientists have developed a standardized method for reporting exercise programs that require a thorough description of essential aspects of exercise interventions (31). This tool can markedly improve the ability to accurately analyze and replicate RT interventions.

In keeping with this theme, the heterogeneity of the existing RCTs needs to be discussed. Indeed, studies lasting 12–52 weeks of an intensity of 40%–80% 1RM and different progression modes (if reported) are likely to yield vastly different results in the outcomes measured (15). In addition, adherence to RT protocols is either poorly reported or not reported at all in currently available studies (32). Likewise, there are also major issues with the standardization of procedures for body composition assessment in ACS, making it unclear to delineate the exact effects of RT on body composition as opposed to errors in methodology or assumption (32). Moreover, we accounted that available literature on RT and its effects on muscle mass in ACS rarely if ever included reporting on dietary patterns of cancer survivors despite muscle mass commonly being the most important outcome observed. Data on muscle wasting and diet are still in their infancy, and certainly, more studies need to be conducted in this field. Finally, data on the follow-up after RT interventions are rather scarce, making it unclear whether cancer survivors adhere to their RT regimen after the intervention.

Future studies should investigate the hypertrophic potential of young cancer survivors (33). Based on the data available from the healthy population, age might be a limiting factor when it comes to muscle gains as a result of RT (34). Thus, it would be interesting to see the differences in RT-caused muscle gains in young versus older cancer survivors under standardized conditions. Furthermore, researchers should consider reporting male and female data separately, as men commonly have a significantly greater absolute increase in muscle volume compared to women following RT (35).

On a broader scale, medical staff might be a key figure in RT adherence, as patients reported a higher amount of physical activity (PA) at 2–3 years post-diagnosis in patients with cancer who recalled receiving physical activity advice from a health care professional after diagnosis compared to those who did not recall receiving the same advice (36). Indeed, data show that only 51% of health professionals reported giving PA advice to their patients, while 36% declared to be unaware of any lifestyle guidelines for cancer survivors, and approximately half (49%) were aware of PA guidelines (37).

We acknowledge that other forms of exercise induce numerous health benefits in ACS and YCS, but the focal point of this manuscript was RT and muscle tissue, which seems to be the tissue most aggravated by cancer and cancer treatments. To our

knowledge, RT is by far the most effective way to preserve and increase muscle mass in ACS, and thus RCTs on the effects of RT on YCS are urgently needed.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: Data will be provided upon reasonable request.

Author contributions

NL: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. SF: Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. SO: Conceptualization, Supervision, Writing – review & editing. DJ: Conceptualization, Investigation, Writing – review & editing. ZA: Methodology, Supervision, Writing – review & editing. AV: Methodology, Supervision, Writing – review & editing. PT: Funding acquisition, Project administration, Writing – review & editing. VV: Funding acquisition, Project administration, Writing – review & editing. JT: Funding acquisition, Resources, Writing – review & editing. SP: Funding acquisition, Resources, Writing – review & editing. MK: Formal Analysis, Project administration, Writing – review & editing. FG: Supervision, Validation, Writing – review & editing. AP: Conceptualization, Writing – original draft, Writing – review & editing. AB: Data curation, Investigation, Writing – original draft, Writing – review & editing.

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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.

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Personalized medicine for locally advanced rectal cancer: five years of complete clinical response after neoadjuvant radiochemotherapy—a case report with a literature review

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We present a case report of a 73-year-old male patient with a complete clinical response following neoadjuvant radiochemotherapy of mid-rectal adenocarcinoma. The patient was initially diagnosed with stage IIIB microsatellite stable mid-rectal adenocarcinoma in February 2017. During restaging in June 2017, which included rectoscopy, endosonography, computed tomography and magnetic resonance imaging, a complete clinical response was observed. After appropriate consultation, a watch-and-wait strategy was chosen. During stringent follow-up every 3 months for the first 3 years and thereafter every 6 months, no recurrence or regrowth was observed. After the fifth year of complete clinical response, we recommended an annual follow-up. As of November 2023, the patient has no signs of recurrence or late toxicity after radiochemotherapy. The omission of resection in patients with locally advanced rectal cancer and the establishment of a watch-and-wait strategy are currently under discussion as possible treatment courses in patients with complete clinical response. Long-term data on watch-and-wait strategies for patients with a complete clinical response in locally advanced rectal cancer are rare. A clear national and international accepted standardization of follow-up programs for patients managed by a watch-and-wait strategy in the long-term is missing. Here, we report the case of a patient who had undergone a follow-up program for more than five years and discuss the current literature. Our case report and literature review highlights that a watch-and-wait strategy does not seem to increase the risk of systemic disease or compromise survival outcomes in selected locally advanced rectal cancer patients. Thus, our case contributes to the growing body of knowledge on personalized and precision medicine for rectal cancer.

KEYWORDS

rectal cancer, neoadjuvant radiochemotherapy (nRCT), complete clinical response (cCR), non-operative management (NOM), watch-and-wait (W&W) strategy, personalized medicine, case report

Abbreviations

LARC, locally advanced rectal cancer; NOM, non-operative management; W&W, watch and wait; cCR, complete clinical response; pCR, pathologic complete response; nRCT, neoadjuvant radiochemotherapy; CT, computed tomography; MRI, magnetic resonance imaging; TME, total mesorectal excision; CEA, carcinoembryonic antigen; UICC, Union for International Cancer Control; TNT, total neoadjuvant therapy; IGF2, insulin-like growth factor 2; L1CAM, L1 cell adhesion molecule.

Introduction

The standard therapy for patients with locally advanced rectal cancer (LARC) is neoadjuvant radiochemotherapy (nRCT) followed by total mesorectal excision (TME), with or without postoperative chemotherapy (1–3). Up to one-third of the patients receiving nRCT for LARC achieve a complete clinical response (cCR) and/or a pathologic complete remission (pCR) (4–6). Habr-Gama and colleagues reported several series in which the cCR rate ranged from 26% to 38% (7–10). Thus, the acceptance of non-operative management (NOM) or organ preservation for LARC patients via the watch-and-wait (W&W) strategy (4, 6, 7, 9) is increasing. Owing to the fact that the TME is associated with a risk of surgery-related complications, morbidities and mortality (11, 12), there are quite a number of patients who decline abdominoperineal resection, or a Hartmann procedure with permanent colostomy or even low anterior rectal resection without creation of protective ileostomy or colostomy. Compared with the TME, the W&W strategy achieves similar overall survival and better preservation of organ anatomy and physiological function. Meta-analyses studying the W&W strategy vs. the TME indicate that the W&W group has a greater local recurrence rate than the TME group does, but the overall survival and rate of distant metastasis are similar between the two groups (13–15). Furthermore, Zhang et al. showed that elevated carcinoembryonic antigen (CEA) levels ≥5 ng/ml after chemoradiotherapy is negatively associated with tumor response to total neoadjuvant therapy (TNT) (16). Therefore, through consistent and standardized follow-up examinations, NOM with the W&W strategy can achieve equivalent results in patients with cCR compared to those with TME. Recommendations for a stringent course of investigation during follow-up with regard to the method and time point never existed at the first presentation in 2017 in many national guidelines.

Here, we present a case of cCR in a patient with LARC in the midrectum after nRCT with more than 5 years surveillance via the W&W strategy and provide recommendations for follow-up management in patients with cCR after nRCT in LARC, as this approach is feasible and safe for appropriately selected patients. This highlights the need for precision personalized medicine in rectal cancer patients.

Case presentation

A 79-year-old male German patient (i.e., 73 years old at first presentation) was diagnosed with microsatellite stable mid-rectaladenocarcinoma during a screening colonoscopy without any clinical symptoms in February 2017 (see also Table 1). The patient had no relevant comorbidities and was in good clinical condition. Colonoscopy revealed a semicircular and exophytic tumor with a size of 50 mm in the rectum 8 cm from the anal verge (Figure 1). Pathology of a biopsy specimen revealed moderately differentiated adenocarcinoma of the colorectal type. Abdominopelvic computed tomography (CT; Figure 2) and pelvic magnetic resonance imaging (MRI) showed concentric growing rectal carcinoma with locoregional lymph node metastasis in the mesorectum as well as circumferential wall thickening with perirectal fat infiltration (Figure 3A). No distant metastases were found. Endoscopy revealed a tumor with a maximum thickness of 13 mm in the midrectum that broadly exceeded the muscularis, as well as suspicious regional lymph nodes. The tumor marker carcinoembryonic antigen (CEA) level was within the normal range. The clinical stage was determined to be uT3uN1cM0; stage IIIB according to the Union for International Cancer Control (UICC) staging manual (7th edition).

TABLE 1 Timeline.

February 2017	Incidental diagnosis by screening colonoscopy
	Rectoscopy, abdominopelvic CT, MRI, CT scan of the chest endosonography, CEA
February 2017	Discussion in tumor board and recommendation of nRCT
March 2017	Start of neoadjuvant therapy with up to 50.4 Gy radiotherapy and simultaneous chemotherapy with capecitabine 825 mg/m^2
May 2017	End of neoadjuvant therapy
June 2017	Restaging including digital rectal examination, rectoscopy, abdominopelvic CT, MRI, endosonography with biopsy showing only a fibrotic mass with no viable tumor cells
September 2017–June 2022	Stringent follow-up including digital rectal examination, rectoscopy, measurement of tumor markers CEA, chest radiology, abdominopelvic sonography and MRI

The case was then discussed by our multidisciplinary tumor board, for which nRCT with up to 50.4 Gy radiotherapy and simultaneous chemotherapy with capecitabine 825 mg/m^2 twice daily were recommended. Neoadjuvant therapy started in March 2017, and was given for six weeks without interruption or absence of any severe complications. Briefly, the total dose of preoperative radiotherapy was 50.4 Gy, which was given in a fractionated manner over a period of 6 weeks (1.8 Gy × 28 fr over 6 weeks) in the supine position. The clinical target volumes included the gross mural tumor, regional lymph nodes in the mesorectum and presacral space and the internal iliac and distal common iliac lymphatics. The oral concurrent chemotherapy with capecitabine (825 mg/m^2) was administered twice daily.

A reevaluation of the nRCT response and simultaneous planning of the TME and a protective ileostomy were scheduled approximately 8 weeks after nRCT completion. On presentation in June 2017, no tumor mass or stenosis was palpable during a digital rectal examination. A slight bluish venous dilatation with negligible ulceration was evident on rectoscopy. On endosonography no tumor or lymph nodes were observed. A wall thickening of the rectum was described. MRI revealed no definite mass lesion but mucosal thickening of the rectum after nRCT and no evidence of metastatic lymph nodes. These findings were discussed in detail with the patient and his relatives. We explained the extent of surgical therapy with TME and the possibility of protective ileostomy. The patient refused to undergo surgery. Therefore, we proposed a follow-up regimen for the patient, including digital rectal examination combined with rectoscopy (through an experienced colorectal surgeon), CEA measurement, chest radiology, abdominal ultrasound and pelvic

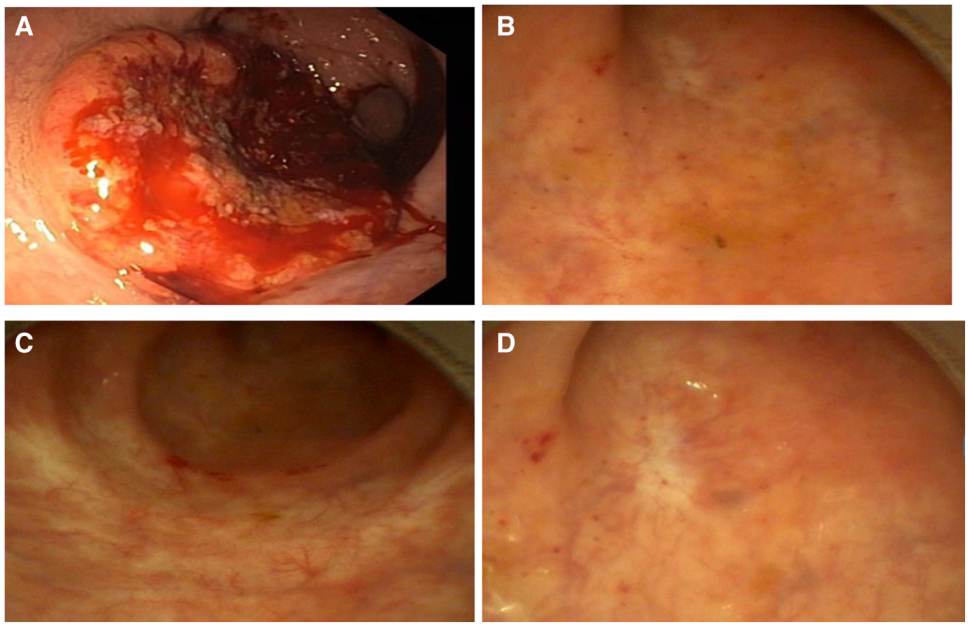

FIGURE 1
Colonoscopy/rectoscopy images; (A) February 2017, (B) May 2019, (C) May 2021 and (D) November 2023.

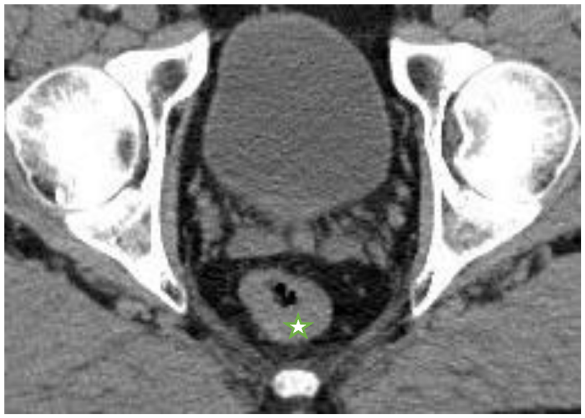

FIGURE 2
Computed tomography (February 2017) showing wall thickening of the rectum, marked with a star.

MRI every 3 months. The advantages and disadvantages of these methods were discussed in depth. A written informed consent was obtained from the patient.

At the end of August 2017, there was no tumor seen during rectoscopy, and the bluish venous dilatation with negligible ulceration had disappeared. A wall thickening was suspected at 8 cm from the anal verge. This was confirmed by endosonography. We opted to carry out a biopsy at the suspected area. The final histological findings showed only a fibrotic mass without tumor cells. All other examinations, including pelvic MRI, abdominal ultrasound and chest radiology, showed no evidence of local or lymph node recurrence or distant tumor manifestation. The tumor marker CEA was also within the normal range. Follow-up evaluations were performed every three months for the first three years until March 2020, and no regrowth or evidence of lymph node recurrence or distant tumor manifestation was observed. No further thickening of the rectum was observed 12 months after the nRCT. Thereafter, we extended the time interval between follow-up appointments to 6 months. To date, after more than 5 years of follow-up, no evidence of regrowth or recurrence has been observed. We recommended an annual follow-up examination as well as a colonoscopy to rule out a second carcinoma.

Discussion

With this case report, we are able to provide additional evidence that NOM via the W&W strategy can be feasible and safe. Furthermore, surgery can be possibly avoided for patients with cCR after nRCT in locally advanced rectal cancer when a structured follow-up evaluation is implemented. NOM with the W&W strategy has gained popularity for patients with cCR after nRCT following LARC. This forces us, as the involved physicians, to resort to recommendations that the national guidelines do not provide. On the other hand, the increasing interest in NOM with the W&W strategy requires reliable methods to identify patients with cCR (17). We defined cCR as follows: endoscopy showing only a white scar with or without telangiectasia; moreover, no abnormalities were palpable on the rectum wall, and no residual tumor or suspicious lymph nodes could be observed on MRI. A wall thickening of the rectum alone was not considered pathological.

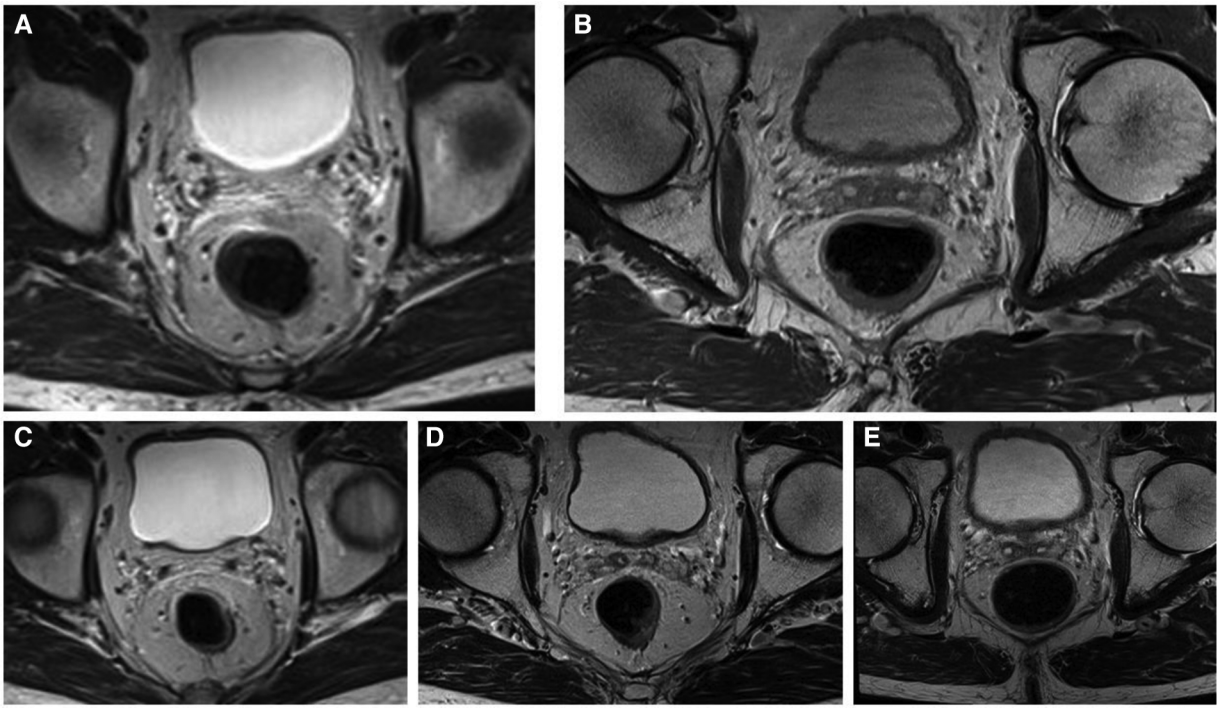

FIGURE 3
Dotarem-enhanced T2 magnetic resonance (MR) images of the patient during the W&W follow-up visit with no signs of local regrowth or lymph node metastasis; (A) June 2017, (B) June 2018, (C) May 2019, (D) June 2020, and (E) May 2021.

TME is still the standard procedure for treating LARC after nRCT according to many guidelines (1, 2, 18) or some countries incorporate NOM into their guidelines (19). Many clinicians are compelled to perform TME even in the presence of cCR after nRCT, despite the known potential perioperative complications, morbidities and mortality as well as reduced quality of life (11, 12, 20, 21). Furthermore, cardiopulmonary and thromboembolic postoperative complications are independently associated with worse overall survival (22). In cases where individualized NOM with the W&W strategy is offered, no consensus on follow-up or surveillance exists in national guidelines to detect local regrowth or distant recurrence, unlike after TME. Ever since the pioneering work of Nakagawa et al. in 2002 and Habr-Gama et al. in 2004 (23, 24), the use of NOM for the treatment of rectal cancer has gained popularity worldwide. In recent reviews, no difference in overall survival or disease-free survival was found between patients treated with TME and patients managed with the W&W strategy (13, 25, 26). Under vigorous surveillance with early detection of local regrowth, a W&W strategy appears feasible and safe and allows a high rate of successful salvage surgery without increasing the risk of systemic disease or without compromising survival outcomes (25).

Local regrowth occurs mostly within 2 years after nRCT (27). Therefore, we decided to perform follow-up evaluations every 3 months for the first 3 years and thereafter every 6 months until the fifth year after initial diagnosis. The evaluations included digital rectal examination, rectoscopy, CEA measurements, chest radiology, abdominal ultrasound and pelvic MRI. If a lesion, e.g., in the liver, could be suspected or if elevated CEA levels could be measured, a CT scan of the abdomen would have been performed to rule out distant metastasis. Using this stringent follow-up schedule it was possible to monitor the patient appropriately without fear of missing out a local regrowth or distant recurrence. In addition, this approach increased patient satisfaction and reduced psychological distress, which is an aspect of quality of life. We agree fully with Huisman et al. that by using a structured follow-up in the case of cCR after nRCT, an organ-preserving NOM with the W&W strategy can be a safe procedure (28). In their study, they planned the first evaluation 8 weeks after completion of the nRCT and the second 12–16 weeks later. The evaluations in the W&W program included endoscopy, rectal MRI, abdominal and thoracic CT, and CEA screening every 3–6 months. Interestingly, they had a 3-year cumulative local regrowth incidence of 42%, and one patient was even censored out of the W&W program due to incurable distant recurrence after 5 months. This highlights the need for careful patient selection and reflects the persistent challenge of identifying complete responders as well as incomplete responders through a genuine surveillance strategy (29).

The management of LARC is continually progressing, and total neoadjuvant therapy (TNT) with NOM may become the standard of care for approximately one-third of patients in the future since responses to nRCT appear to be heterogeneous because of differences in immunological and genetic profiles (26, 30).

Additionally, Chatila et al. reported compressively the clinical relevance of genomic and transcriptomic determinants such as insulin-like growth factor 2 (IGF2) and L1 cell adhesion molecule (L1CAM) (31). Overexpression IGF2 and L1CAM was associated with decreased response to neoadjuvant therapy and therefore correlates with poor outcomes in LARC. Furthermore, it has been shown that patients with high microsatellite instability tumors respond differently to neoadjuvant therapy compared to those with microsatellite stable tumors (32). Thus, patients with microsatellite instability tumors can benefit from immunotherapy and less from nRCT or TNT. The results of recent trials, e.g., the RAPIDO, PRODIGE 23, CAO/ARO/AIO-12 and OPRA trials (33–36), showed that NOM or WW strategies should be part of the treatment discussion for LARC. However, substantial evidence of long-term outcomes, including quality of life, is needed for patients with cCR managed by NOM via the W&W strategy after nRCT or TNT from multinational, prospective and randomized trials to formulate future guidelines. Furthermore, these trials should account for the challenges that clinicians face in real-world clinical assessment by identifying responders after nRCT or TNT treatment regimens.

In summary, based on our experience in a series of cCR cases, we recommend the following surveillance intervals for follow-up program; digital rectal examination, rectoscopy, CEA level measurements and pelvic MRI every 3–4 months in the first 2 years, and then once every 6 months until the fifth year after diagnosis. A chest and abdominal CT should be performed annually to rule out distant metastasis.

Conclusion

We highlighted the use the W&W strategy in cases of cCR after an nRCT for rectal cancer with a structural follow-up program of more than 5 years. Through a genuine surveillance approach the W&W strategy does not seem to increase the risk of systemic disease or compromise survival outcomes in selected locally advanced rectal cancer patients. Nevertheless, for successful NOM with the W&W strategy, detailed patient information about the consistency of the follow-up program and patient compliance is mandatory. Thus embracing the need for personalized medicine in treatment discussion of locally advanced rectal cancer.

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 Medical Ethics Committee of Carl von Ossietzky University. 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.

Author contributions

DO: Data curation, Methodology, Writing – original draft, Writing – review & editing. VU: Formal Analysis, Methodology, Visualization, Writing – review & editing. DW: Writing – review & editing. NT: Supervision, Writing – review & editing.

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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.

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Case Report: The molecular fingerprint and the clinical implication of an exceptional response to neoadjuvant therapy in a metastatic cardia adenocarcinoma

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Background: Globally, gastric cancer holds the fifth position in terms of prevalence among malignant tumors and is the fourth leading cause of cancer-related mortality. Particular attention should be paid to cardia adenocarcinoma (CA) due to its increasing incidence and poor prognosis. Diagnosis of CA frequently occurs in advanced stages because of its late symptoms. In such cases, neoadjuvant chemotherapy is the primary treatment option. The response to chemotherapy depends on multiple variables including the tumor's molecular profile, the patient's performance status, and the feasibility of using targeted therapy. Patients exhibiting an exceptional response, defined as a complete response to medical therapy lasting more than 1 year, or a partial response or stable disease lasting more than 2 years, are rarely described. This case report presents one of the longest-lasting exceptional responses to chemotherapy in metastatic cardia adenocarcinoma and discusses its clinical implications.
Case presentation: A 49-year-old male patient presented with cardia adenocarcinoma (human epidermal growth factor receptor 2 negative, mismatch repair proficient) and liver metastases. Molecular profiling identified a pathogenic mutation in the TP53 gene (R123W; Arg123Trp) as the sole alteration found. Five months after initiating the neoadjuvant chemotherapy with fluorouracil–leucovorin–oxaliplatin–docetaxel, the patient achieved a complete clinical response. The molecular profile was compared with others previously documented in an international data portal, revealing a similar pattern. At 4 years and 3 months from diagnosis, the exceptional response was still confirmed. The patient underwent a cumulative number of 33 cycles of chemotherapy, leading to chemotherapy-induced liver damage.
Conclusions: Exceptional responses to neoadjuvant chemotherapy in cardia adenocarcinomas are rarely reported. The documentation of exceptional responses to cancer therapies should be included in large data repositories to explore the molecular fingerprint of these tumors. In such cases, the clinical implications of long-term chemotherapy should always be taken into account.

KEYWORDS

cardia adenocarcinoma, preoperative treatment, complete tumor regression, exceptional response, TP53

Introduction

Gastric cancer (GC) is globally ranked as the fifth most common malignant tumor and the fourth leading cause of cancer mortality (1).

Nowadays, particular attention should be paid to cardia adenocarcinoma (CA) due to its increasing incidence reported worldwide over the last five decades (2).

The five-year survival rate for CA currently stands at 10%–20%, significantly reduced for patients who do not undergo surgical resection, plummeting to 3%–5% (3). Indeed, the majority of CA cases present as advanced diseases, making neoadjuvant chemo/chemoradiotherapy the primary treatment option (4).

In case of locally advanced or metastatic disease, the recommended regimens for first-line systemic therapy include a fluoropyrimidine (fluorouracil or capecitabine) combined with either oxaliplatin or cisplatin (category 2B) (5).

More precisely, according to the latest European Society for Medical Oncology (ESMO) guidelines, fluorouracil–leucovorin–oxaliplatin–docetaxel (FLOT) is the regimen of protocol that leads to a higher rate of regression in locally advanced CA and it represents the preferred scheme of chemotherapy in patients capable of tolerating it (6).

Subsequently, GC may exhibit varying degrees of response, often documented as regression grades in the surgical specimen (7). In this context, a better clinical profile, human epidermal growth factor receptor 2 (HER2) expression, and intestinal histotype are characteristics often correlated with tumor regression (8). However, beyond pathologic regression, the definition of response can encompass a clinical outcome over time. Based on criterion, an exceptional response (ER) is defined as a complete response to medical therapy lasting more than 1 year, or a partial response or stable disease lasting more than 2 years (9).

Here we present one of the longest-lasting exceptional responses to chemotherapy in a cardia adenocarcinoma with liver metastases, along with its molecular fingerprint and clinical outcome. The molecular findings were also compared with those of other exceptional responders documented in the literature.

Case presentation

The patient is a 49-year-old Caucasian male with CA and synchronous multiple liver metastasis. His oncological history began in June 2019, when he experienced asthenia, dyspepsia, and dysphagia with solids, along with a reported weight loss of 5 kg over the preceding three months. An esophagogastroduodenoscopy (EGDS) revealed an ulcerated neoplasm in the lower third of the esophagus, with circumferential thickening extending distally to the gastric lesser curve. A biopsy was performed and the histological examination was consistent with a poorly differentiated adenocarcinoma, HER2 negative, and presence of MLH1, MSH2, MSH6, PMS2 protein expression (microsatellite stable) on the immunohistochemistry (IHC) analyses.

Subsequent contrast-enhanced total body computed tomography (CT) and positron emission tomography (PET) scans documented a cT3 tumor with locoregional lymphadenopathy cN3, and multiple hepatic lesions (cM1).

The case was discussed during the Institutional multidisciplinary meeting, and it was decided to proceed with neoadjuvant therapy, which consisted of nine cycles of FLOT followed by three cycles of 5-florouracil and folinic acid (de Gramont scheme).

Remarkably, just 2 months after starting chemotherapy, a CT scan indicated an optimal response, as the thickening of the cardia was no longer evident, lymphadenopathy and liver metastases had significantly reduced in size, and a new EGDS showed a substantial reduction in the size of the tumor, now measuring 2 cm.

Five months into chemotherapy, a follow-up PET scan revealed complete metabolic resolution of all previously metastatic areas, and another EGDS demonstrated a macroscopically clear esophagogastric junction (Figures 1, 2). Liver metastases were further re-evaluated using magnetic resonance imaging (MRI), which revealed a necrotic-colliquative aspect of the repetitive hepatic lesions, with the largest one in segment VIII.

Genetic mutational status was also assessed, and DNA extracted from selected neoplastic tissue samples underwent sequencing. The sequencing was performed by a targeted next-generation sequencing (NGS) panel (Agilent Technologies, Inc., Santa Clara, CA, USA) on the Illumina MySeq platform. DNA was quantitatively and qualitatively evaluated using the QIAxcel DNA High Resolution Kit on QIAxcel Advanced (Qiagen): quality and quantity were judged suitable for the requested analysis. A pathogenic mutation in the TP53 gene (R123W; Arg123Trp) was the only alteration found.

This finding was compared with the data from the National Cancer Institute's (NCI's) Genomic Data Commons (GDC), which collects gene mutations from around 13,714 cases (10). The comparison revealed that TP53 was the most frequent simple somatic mutation involved in gastric cancer exceptional responders (Figure 3).

In February 2020, the patient underwent laparoscopic staging, which showed an absence of peritoneal carcinomatosis and no tumoral evidence at the esophagogastric junction. Intraoperative liver ultrasonography detected diffuse nodularity affecting both lobes. The cytological examination of peritoneal washing was negative for neoplastic cells. Consequently, the patient continued with five cycles of chemotherapy using folinic acid, fluorouracil, and oxaliplatin (FOLFOX), which had to be suspended four months later owing to its toxicity (Figure 4). At this stage, a CT scan revealed a further modest reduction in size of all liver lesions and the patient resumed the De Gramont scheme.

Following a new liver MRI, which indicated possible persistence of disease, a laparoscopic liver resection of segment VIII was performed. However, the histological examination of the resected specimen revealed the absence of neoplastic cells, indicating complete regression.

A subsequent EGDS, conducted in February 2023, confirmed an esophagogastric junction free from lesions and revealed severe gastric varices (F3), requiring two subsequent endoscopic ligation

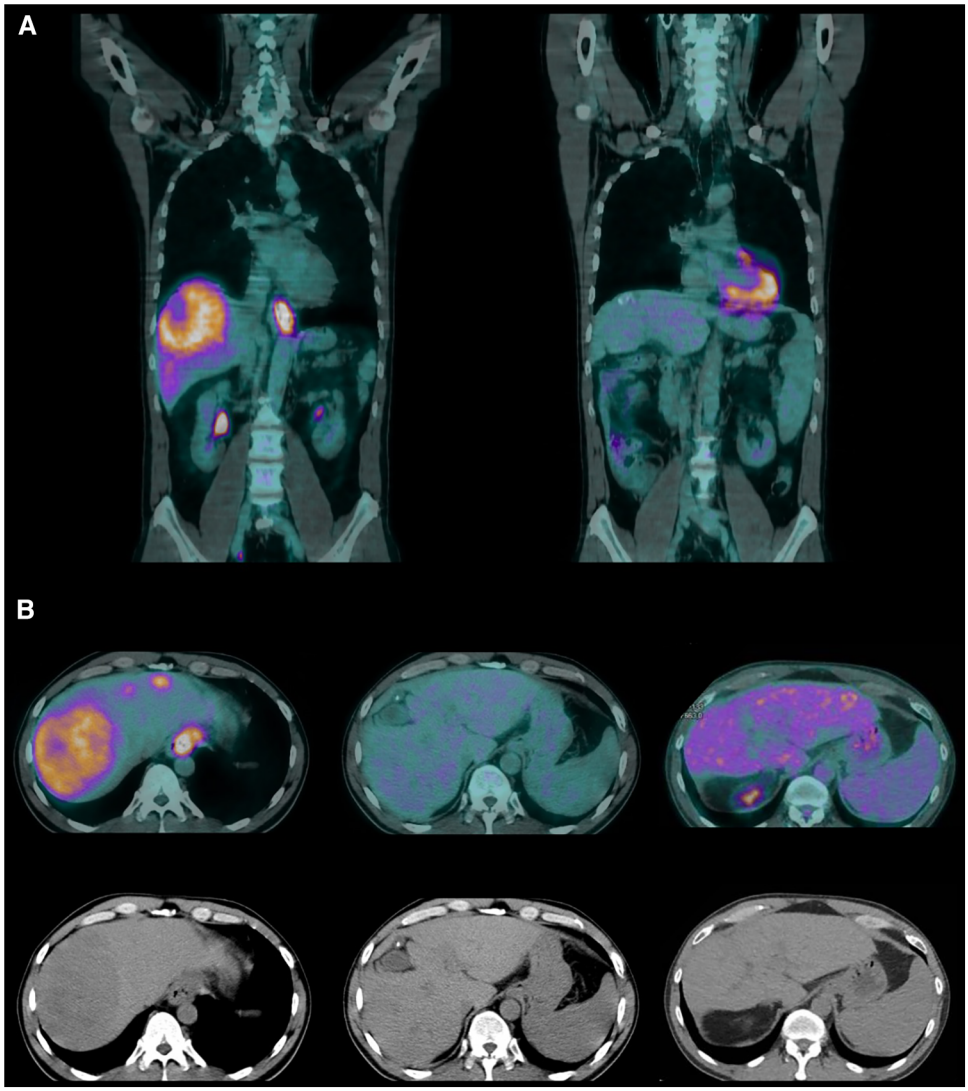

FIGURE 1
(A) Coronal PET scans (June 2019 and March 2021). (B) Axial PET and CT scans (June 2019, March 2021, and August 2022).

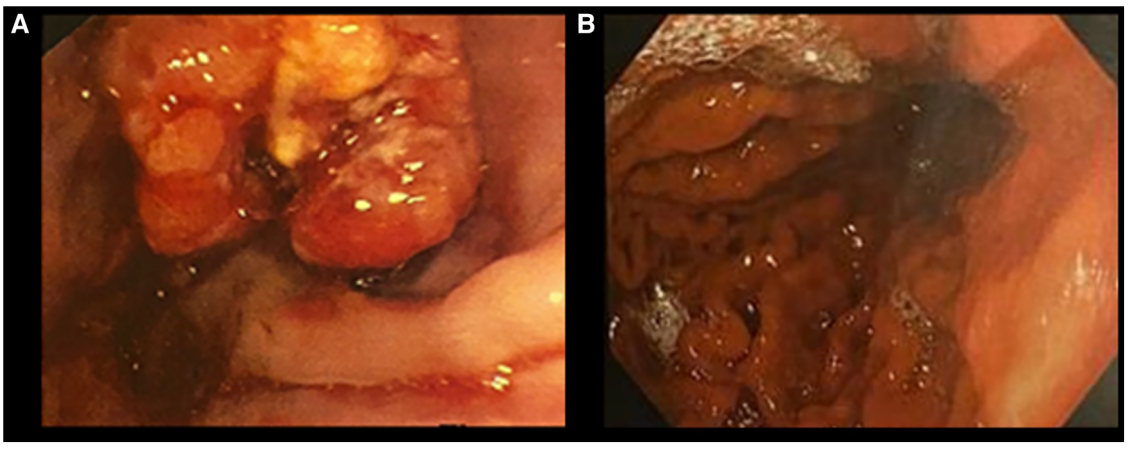

FIGURE 2
Endoscopic findings: (A) June 2019 and (B) May 2022.

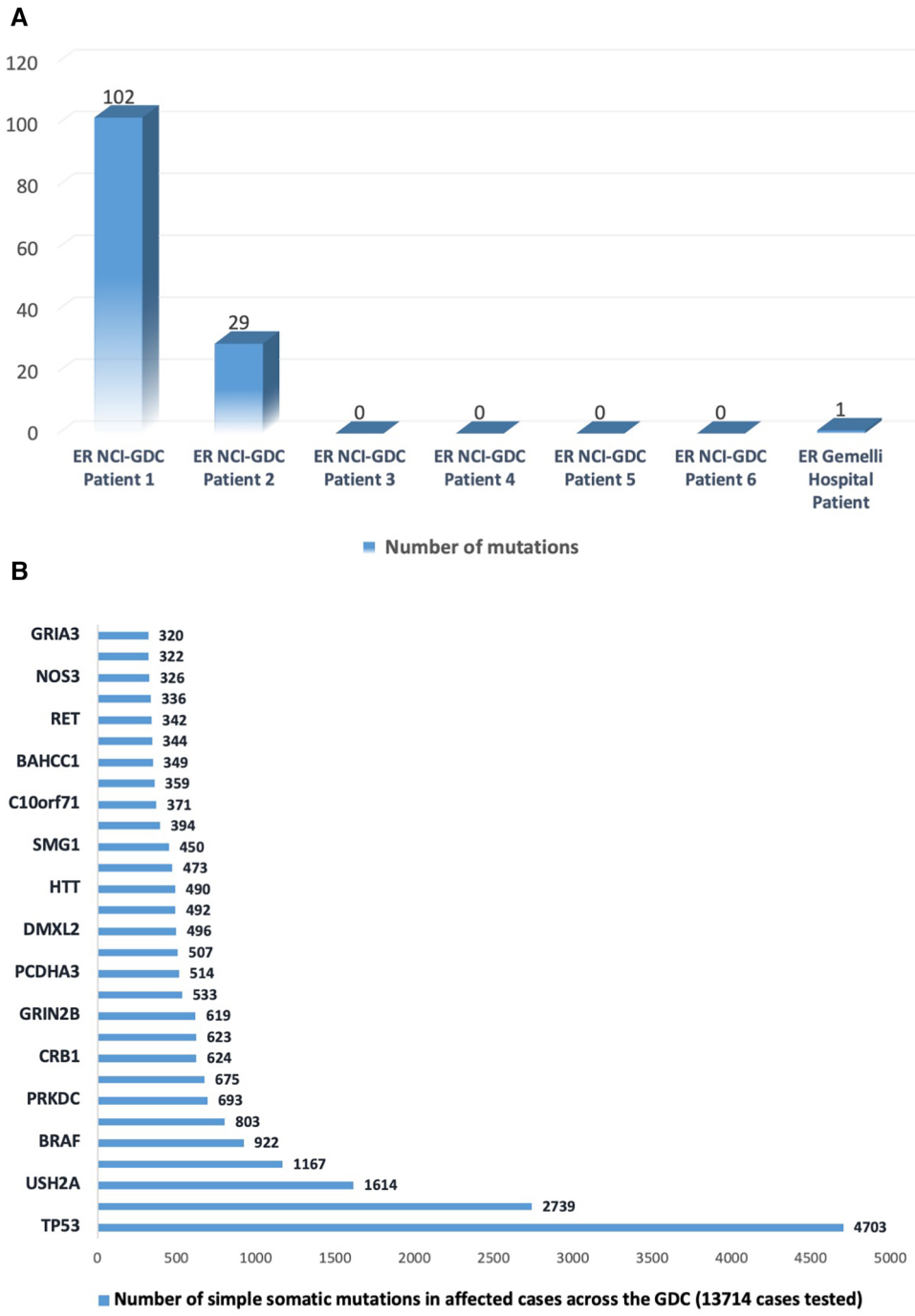

FIGURE 3
(A) Number of somatic mutations in the National Cancer Institute's Genomic Data Commons data portal (https://portal.gdc.cancer.gov/projects/EXCEPTIONAL_RESPONDERS-ER) in six patients and in the case reported at Gemelli Hospital. (B) Number of somatic mutations in the top 30-mutated genes as reported in the data portal (https://portal.gdc.cancer.gov).

treatments (in March and July 2023). An abdominal ultrasound in July 2023 showed splenomegaly (spleen diameter: 17.6 cm) and signs of portal hypertension.

Furthermore, recent blood tests revealed a low white blood cell count and platelet count (2.82 and 69×10^9 /L, respectively), creatinine 1.37 mg/dl (normal range < 1.17 mg/dl), and the following hepatic enzymes and cholestasis indexes: transaminases AST 36 UI/L (normal range < 34 UI/L), transaminases ALT 30 UI/L (normal range < 49 UI/L), total bilirubin 3.6 mg/dl (normal range < 1.2 mg/dl), direct bilirubin 0.8 mg/dl (normal range < 0.3 mg/dl), gamma-glutamyl transferase 105 UI/L (normal range < 73 UI/L), and alkaline phosphatase 96 UI/L (normal range < 116).

Curiously, the blood values of tumor markers have remained within the normal range over time (Figure 4).

FIGURE 4
(A) Disease timeline and clinical course. Red circles mark the beginnings of medical history and the achievement of the exceptional clinical response. (B) time course of oncological markers: CA 19-9 (normal range < 35 U/ml) and CEA (normal range < 3 ng/ml). CEA, Carcino-Embryonic Antigen.

At 4 years and 3 months from diagnosis, and after a cumulative total of 33 cycles of chemotherapy, all CT and PET scans confirmed the exceptional response, with no metabolic activity observed in all body regions (Figures 1, 4).

To measure the patient's physical, psychological, and social functions, he completed the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life questionnaire (EORTC QLQ-C30), showing optimal results, as reported in Table 1 (11).

Discussion

In Western countries, CA is frequently diagnosed in advanced stages due to its non-specific symptoms and the lack of systematic screening policies.

Surgical resection with extended lymph node dissection represents the sole curative therapeutic option for resectable cases (5). However, at the time of diagnosis, only 40% of patients are eligible for surgery (11).

TABLE 1 EORTC QLQ-C30 questionnaire (version 3.0): patient's reported outcomes and reference values in target population.

	All cancer patients: males[a]	All cancer patients: <50 years[a]	Esophageal cancer: <50 years[a]	Patient
Global health status/QoL			N/A	83.3
Mean (SD)	62.9 (23.8)	61.4 (23.4)		
Median (IQR)	66.7 (50–83.3)	66.7 (50–83.3)		
Physical functioning			N/A	93.33
Mean (SD)	78.5 (23)	80.2 (20.8)		
Median (IQR)	86.7 (66.7–100)	86.7 (66.7–100)		
Role functioning			N/A	100.0
Mean (SD)	73.4 (32.4)	68.6 (31.7)		
Median (IQR)	83.3 (50–100)	66.7 (50–100)		
Emotional functioning				83.3
Mean (SD)	73.9 (23.6)	69.2 (24.4)	62.0 (26.6)	
Median (IQR)	75 (58.3–91.7)	75 (58.3–91.7)	66.7 (50–83.3)	
Cognitive functioning				83.3
Mean (SD)	83.7 (21.1)	82.9 (21.6)	85.6 (21.8)	
Median (IQR)	83.3 (66.7–100)	83.3 (66.7–100)	100 (83.3–100)	
Social functioning				100.0
Mean (SD)	76.3 (28.4)	72.1 (29.5)	73.9 (29.9)	
Median (IQR)	83.3 (66.7–100)	83.3 (50–100)	83.3 (50–100)	
Fatigue				33.3
Mean (SD)	32.4 (27.4)	33.9 (26.1)	34.1 (22.5)	
Median (IQR)	33.3 (11.1–44.4)	33.3 (11.1–55.6)	33.3 (22.2–44.4)	
Nausea and vomiting				0.0
Mean (SD)	7.7 (17.2)	9.4 (19.1)	15.0 (21.7)	
Median (IQR)	0 (0–0)	0 (0–16.7)	0 (0–33.3)	
Pain				16.6
Mean (SD)	25.4 (29.6)	27.2 (28.8)	33.9 (25.8)	
Median (IQR)	16.7 (0–33.3)	16.7 (0–50)	33.3 (16.7–50)	
Dyspnea				0.0
Mean (SD)	21.1 (28.4)	17.1 (25.8)	13.9 (21.4)	
Median (IQR)	0 (0–33.3)	0 (0–33.3)	0 (0–33.3)	
Insomnia				0.0
Mean (SD)	26.7 (31.3)	30.2 (32.2)	36.7 (36.4)	
Median (IQR)	33.3 (0–33.3)	33.3 (0–66.7)	33.3 (0–66.7)	
Appetite loss				0.0
Mean (SD)	19.2 (30.2)	19.7 (29.1)	30.9 (35.8)	
Median (IQR)	0 (0–33.3)	0 (0–33.3)	33.3 (0–66.7)	
Constipation				0.0
Mean (SD)	16.2 (27.7)	15.3 (26.5)	22.0 (28.4)	
Median (IQR)	0 (0–33.3)	0 (0–33.3)	0 (0–33.3)	
Diarrhea				33.3
Mean (SD)	8.7 (20)	9.0 (19.9)	6.4 (17.2)	
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	
Financial difficulties				0.0
Mean (SD)	15.6 (27.9)	23.6 (32)	21.2 (30.2)	
Median (IQR)	0 (0–33.3)	0 (0–33.3)	0 (0–33.3)	

QoL, Quality of Life; IQR, interquartile range.
[a]As reported in https://www.eortc.org/app/uploads/sites/2/2018/02/reference_values_manual2008.pdf.

Despite advances in perioperative treatments and targeted therapy, the prognosis for CA remains poor.

The current 5-year survival rate for CA is only 10%–20%, with a median overall survival (OS) of just 1 year in cases of metastatic disease (12).

The response to chemotherapy varies depending on multiple factors and, in rare instances, becomes exceptional for reasons that are still not entirely clear (13).

Although HER2 overexpression is relatively uncommon in CA (ranging from 12% to 22%), it represents one of the primary therapeutic targets owing to the availability of anti-HER2 monoclonal antibody-based agents (14).

The FLOT or FOLFOX scheme is currently the recommended first-line therapy to improve the OS in cases of locally advanced HER2-negative CA (6, 15). In addition, high microsatellite instability (MSI-H) and Mismatch Repair deficient (dMMR) tumors appear to be favorable prognostic factors (16), both in terms of nodal status and downstaging (17, 18).

This patient represents an extremely rare case of an exceptional response to treatment for metastatic HER2-negative CA, in the

absence of MSI-H and dMMR, treated with FLOT and de Gramont schemes.

Thanks to its excellent response to medical therapy, there has been no need so far for preoperative radiotherapy or surgical treatment on the primary tumor.

Notably, the only mutation detected through NGS was curiously TP53 (R123W; Arg123Trp), which is consistent with the profile of gastric cancer exceptional responders described in NCI's GDC.

However, it is important to note that this remarkable response to treatment resulted in severe post-chemotherapy liver disease, as evidenced by the discovery of liver nodularity during diagnostic laparoscopy, the development of F3 varices that necessitated endoscopic ligation, and suboptimal blood test results.

It is also crucial to note a significant "misleading" aspect in the liver MRI, after chemotherapy, suggesting a possible persistence of the disease. The discrepancy between MRI detection and the histopathological examination raises important questions about the reliability and accuracy of the diagnostic methods used, underlining in these cases the need for further investigation and consideration of alternative diagnostic approaches.

According to the NCI's GDC (10), an excellent response to chemotherapy for patients with stomach and gastroesophageal junction carcinoma may be achieved regardless of the number and type of gene mutations. Therefore, it is necessary to collect a substantial amount of data to identify patients eligible for an excellent response to systemic therapy.

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements. 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

LL: Data curation, Methodology, Writing – review & editing. AC: Data curation, Investigation, Writing – original draft. AD: Data curation, Investigation, Writing – review & editing. FG: Data curation, Supervision, Writing – review & editing. FB: Data curation, Investigation, Writing – review & editing. DD: Supervision, Validation, Writing – review & editing.

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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

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Impact of cavity shave margins in patients with ductal carcinoma *in situ* undergoing conserving breast surgery

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Aim: The main challenge during breast-conserving surgery (BCS) is to obtain clear margins, especially in patients with ductal carcinoma *in situ* (DCIS) due to the absence of well-defined nodules. Many surgical approaches have been used in an attempt to reduce the positive margin rate. The aim of this retrospective study is to compare the cavity shave margin technique with standard surgery and the intraoperative evaluation of surgical margins.

Methods: This is a single-center retrospective study analyzing margin status, need for re-excision, and surgical time in a cohort of 227 patients who underwent surgery from September 2016 to September 2022.

Results: In patients subjected to cavity shaving, we reported a significant reduction in positive margins of 17.1% versus 28.7% (p-value = 0.042). Also, a difference in terms of surgical re-excision was reported as p-value = 0.039 (12.4% versus 23.8%, respectively, for the cavity shave and control group). In the multivariate analysis, intraoperative evaluation of the margins was a risk factor for margins re-excision (Wald = 4.315, p = 0.038, OR: 2.331 [95% CI: 1.049–5.180]). Surgical time was lower in patients subjected to cavity shaves (p = 0.024), and the relative mean time was 68.4 min $\pm$ 37.1 min in the cavity shave group versus 93.9 min $\pm$ 40.6 min in the control group.

Conclusion: The cavity shave margin technique in conserving breast surgery results in a reduction in positive margin rate, surgical re-excision, and operative time.

KEYWORDS

ductal carcinoma *in situ*, cavity shave, positive margins, reduce re-excision, breast cancer

1 Introduction

Ductal carcinoma *in situ* (DCIS) is a malignant epithelial cell proliferation confined to the myoepithelial cell's basement membrane (1). During the past 20 years, the incidence of such disease has increased by approximately 25% of all new breast cancer diagnoses (1). The surgical treatment for the invasive carcinoma consists of either breast-conserving surgery (BCS) or mastectomy with an equivalent overall and recurrence-free survival (2–4). The main challenge for the surgeons during conserving breast surgery is to obtain clear or negative margins while saving normal tissue in order to achieve good aesthetic results (5). It has been proven that negative margins reduce future local recurrence. According to the 2016 guidelines for breast-conserving surgery in DCIS, published by the Society of Surgical Oncology and the Society of Radiation Oncology, oncological safety is reached when the distance between the lesion and the resection margin is ≥ 2 mm (6). However, clinical judgment takes precedence when margin safety is not obtained during the first surgery.

In several clinical trials, resection of the cavity shave margin was found to reduce positive margin rates by at least 50% in breast-conserving surgery for invasive cancer (7–9). To our knowledge, one randomized controlled trial evaluating the impact of cavity shave margins was reported in the literature, demonstrating an advantage in terms of negative margin for this technique (10).

DCIS are known to have a different growth pattern when compared to invasive cancer. Lesions are rarely nodular, but they have the tendency to grow in a more discontinuous or skip-like fashion, especially in low-grade DCIS (11). This feature could indicate a need for wider margins.

Intraoperative evaluation of resection margins is now standardized in breast-conserving surgery in order to achieve negative margins. However, due to the absence of clear nodules, intraoperative evaluation of resection margins presented several limitations for DCIS and a higher rate of resulting "false positives" (10).

The aim of this retrospective study was to evaluate the potential benefits of cavity shaves for the management of resection margins in DCIS treated with breast-conserving surgery.

2 Materials and methods

A single-center retrospective study including all patients with a diagnosis of DCIS who underwent BCS from September 2016 to September 2022 was evaluated by the Breast Unit of the Policlinico Tor Vergata, Rome. The study was approved by the local ethics committee (approval number 12/24). All data were retrieved from clinical notes and surgical and pathological reports.

Preoperative diagnosis was achieved by fine needle aspiration, microbiopsy, vacuum-assisted biopsy, or vacuum-assisted excision and replated from preoperative histological examination results.

Breast surgery was divided into breast-conserving surgery or mastectomy. Breast-conserving surgeries included all the procedures with partial gland removal. When possible, lumpectomy was the main procedure performed with oncoplastic principles. Oncoplastic level II surgeries were excluded from the study given the large resection volume and the technically longer surgical time.

Mastectomy is considered when a complete asportation of the gland is performed, including a skin or nipple-sparing mastectomy. Patients subjected to mastectomy were also excluded.

All axillary procedures for lymph node staging were evaluated in the study. Axillary surgery was performed in all patients with a high risk of lymph node involvement, such as high-grade CDIS, and clinical or radiological suspicion of axillary disease.

Removal of sentinel lymph with or without complementary nodes was classified as sentinel lymph node biopsy (SNLB); otherwise, it was considered an axillary lymph node dissection (ALND). Data regarding surgical incision and skin resection were collected from clinical notes. In our practice, we follow the breast cancer national guidelines (11). Therefore, any patient with a clinical or radiological suspicion of invasive cancer underwent axillary surgery in the first place. In one other ongoing study, we found that nodular lesions have a higher risk of upstaging. For this reason, we raise a discussion on the choice to perform SLNB in the first surgery or to delay it to a second surgery in case of invasion or microinvasion at the final histopathological exam, always in accordance with the patient's preference.

The cohort was divided into two groups based on whether the intraoperative evaluation of margins was performed or not according to the surgical report, control, and cavity shave groups, respectively.

The number and site of margin widening after intraoperative evaluation were reported. The cavity shave group (CS group) includes all patients in whom the surgeon performed an additional circumferential resection of the tissue within the excision cavity, widening all margins with no need for an intraoperative evaluation. Cases of intraoperative specimen radiography were reported from surgical reports and analyzed.

Histopathological characteristics of the tumor were retrieved from the final pathological examination report, including nuclear grade and breast cancer prognostic and predictive factors such as estrogen receptor (ER) and progesterone receptor (PR), as indicated by the recommendations of the 2018 ASCO/CAP. Tumor dimension refers to the maximum diameter expressed in millimeters. Surgical margins were defined as the distance between tumoral cells and resection margins expressed in millimeters; all margins of > 2 mm were considered negative. A second surgery for positive margins performed within 120 days was considered a re-operation.

Surgical time, defined as the time in the operating room, was collected from operative records and reported in minutes.

2.1 Statistical analysis

Data were recorded into an EXCEL database (Microsoft, Redmond, WA, USA). Categorical variables were reported as the mean and standard deviation. The Mann–Whitney *U* test was used to compare two different groups. Continuous variables presented as numbers and percentages were analyzed using the Student's *t*-test.

The Chi-squared test (or Fisher's exact test, depending on group size) is used to analyze categorical dichotomous variables. For no-dichotomous variables, the Monte Carlo test was adopted. All variables with a p-value of < 0.05 were considered statistically significant. Multivariate logistic regression analysis was used to assess the effect of the type of margin resection, independent of potential confounders. Statistical analysis was performed using SPSS statistical package version 23.0 (SPSS Inc., Chicago, IL, USA).

3 Results

From September 2016 to September 2022, 268 patients with a diagnosis of DCIS were evaluated at the Breast Unit of the Policlinico Tor Vergata, Rome. A total of 41 (15.3%) patients underwent a mastectomy and were excluded from the analysis. The 227 (84.7%) patients who underwent CBC were considered in this retrospective study. The mean age was 61.3 years ± 13.6 years, and the BMI was 24.4 ± 5.0. The mean follow-up was 4.1 years ± 1.9 years. In 53 (23.8%) patients, resection margin was < 2 mm, and 42 (18.5%) patients underwent re-operation for positive margins. At three years of follow-up, 16 (7.1%) patients presented homolateral recurrence (Figure 1). Out of these 16 patients, nine (56.2%) were diagnosed with DCIS, while seven (43.8%) were diagnosed with an invasive disease.

A total of 105 (46.2%) patients underwent cavity shaving (CS group), while 122 (53.8%) patients received intraoperative evaluation of margins and were considered the control group (C group). Age was comparable between the two groups 60.7 years ± 11.1 years versus 63.2 years ± 13.8 years (p-value = 0.789). In the CS group, BMI was 26.3 kg/m^2 ± 5.5 kg/m^2 versus 24.9 kg/m^2 ± 4.7 kg/m^2 (p-value = 0.079). The mean follow-up was 4.3 years ± 2.1 years in the CS group versus 4.0 years ± 1.8 years, p-value = 0.168.

The number of multifocal lesions was comparable in the CS group 6 (6.5%) versus 17 (13.9%) in the C group with a relative p-value of 0.079. All data regarding preoperative features are resumed in Table 1.

The tumor dimension was comparable between groups: 10.5 mm ± 7.8 mm in the CS group vs 9.7 mm ± 6.4 mm in the C group (p-value = 0.439).

The type of surgical incision adopted by the surgeon for the BCS did not show any statistically significant difference between the two groups and a relative p-value of 0.114 (Table 1). The site of cancer according to the breast quadrant did not show any statistically significant difference $p = 0.203$. Distributions of lesions according to breast quadrant are displayed in Table 1. Skin removal during BCS did not show any statistical significance, and the relative p-value was 0.088, with an incidence rate of 17.9% ($n = 16$) in the CS group versus 28.6% ($n = 35$) in the C group. A total of 29 (27.6%) cases presented microcalcifications at preoperative mammography in the CS group versus 38 (31.3%) in the C group, and the relative p-value was 0.661. Patients who required wire-guided lesion localization before surgery were 65 (69.1%) in the CS group versus 95 (77.8%) in the C group, and the p-value was 0.156. In the CS group, 57 (54.3%) cases needed intraoperative specimen radiography versus 64 (52.5%) in the C group and a relative p-value of 0.269.

Intraoperative evaluation, with a frozen section, of sentinel lymph nodes was performed in eight (7.6%) patients in the CS group and in 38 (31.1%) in the control group, showing a significant statistical difference (p-value = 0.001). Axillary lymph node dissection was performed in two (1.9%) cases in the CS group versus five (4.1%) (p-value = 0.455). Four patients presented with an invasive disease with lymph node involvement; one of them underwent lymph node dissection, which had a negative final histopathological exam result. Two patients presented clinically suspicious lymph nodes, both positive at the final histopathological exam result; both of these latter patients were submitted to mastectomy to widen their margins; most probably, the invasive component was missed during the preoperative biopsy examination.

The CS group saw omission of sentinel biopsy in 63 cases (60.0%), compared to 68 cases (55.7%) in the control group. The

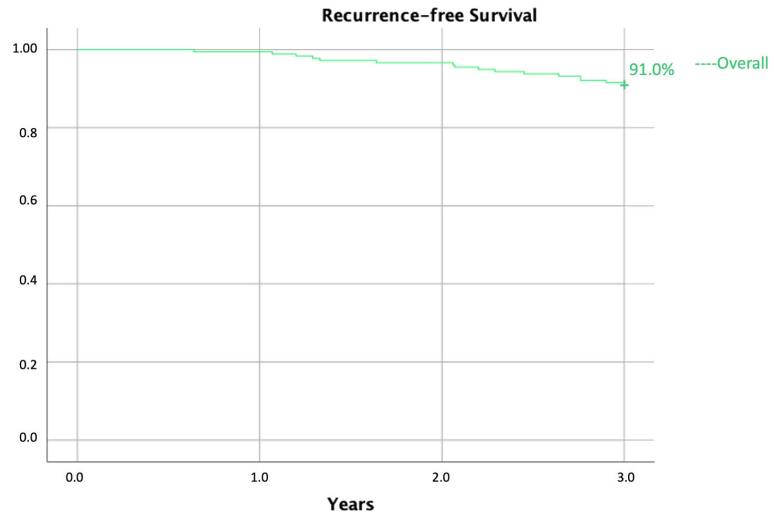

FIGURE 1
Overall 3-year recurrence-free survival.

TABLE 1 Tumor preoperative characteristics and intraoperative findings between groups.

	CS group (n = 105)	C group (n = 122)	p-value
Multifocality	6 (6.5%)	14 (11.4%)	0.079
Multicentricity	0	1 (0.8%)	0.380
Wire guide localization	65 (69.1%)	95 (77.8%)	0.156
Type of incision			0.114
Radial	34 (30.3%)	29 (23.7%)	
Periareolar	30 (28.6%)	32 (26.2%)	
Paraareolar	8 (7.6%)	16 (13.1%)	
Lesions quadrant			
Upper outer quadrant UOQ	38 (36.2%)	60 (49.2%)	0.203
UOQ-LOQ	8 (7.6%)	11 (9.1%)	
Upper inner quadrant UIQ	9 (8.6%)	8 (7.1%)	
LOQ-LIQ	4 (3.8%)	15 (12.3%)	
Lower outer quadrant LOQ	9 (8.6%)	6 (4.9%)	
Central portion	2 (1.9%)	0 (0)	
UOQ-UIQ	12 (11.4%)	7 (5.7%)	
Lower inner quadrant LIQ	2 (1.91%)	2 (1.7%)	
Specimen radiographs	57(54.3%)	64 (52.5%)	0.269
Removal of skin	16 (17.9%)	35 (28.6%)	0.088
Intraoperative evaluation SNLB	8 (7.6%)	38 (31.1%)	**0.001**
Upsgtaging	11(10.1%)	17 (13.9%)	0.544
Axillary surgery			
SNLB	40 (38.1%)	49 (40.2%)	0.171
ALND	2 (1.9%)	5 (4.1%)	
Omission	63 (60.0%)	68(55.7%)	

SNLB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

difference was not statistically significant (p-value = 0.590). Similarly, no statistically significant difference was found between the two groups when comparing axillary procedures using the Monte Carlo test (p-value = 0.171) (Table 1).

In the CS group, 17.1% (n = 18) of resection margins were < 2 mm, therefore considered positive, compared to the 28.7% (n = 35) in the C group (p-value = 0.042).

The mean resection distance was 6.9 mm ± 0.5 mm in the CS group and 4.7 mm ± 0.4 mm in the C group, with a relative p-value of 0.001 (Table 2).

Looking at the need for re-excision due to positive margins, 12.4% (n = 13) of the patients in the CS group needed a second surgery, compared to 23.8% (n = 29) in the C group, with a statistically significant p-value of 0.039.

TABLE 2 Evaluation of margins between groups.

	CS group (n = 105)	*C group (n = 122)*	*p-value*
Resection margin distance			
Deep margin (mm)	9.3 ± 2.4	8.4 ± 3.5	**0.045**
Superficial margin (mm)	8.7 ± 3.1	7.6 ± 4.1	**0.041**
Lateral margin (mm)	9.3 ± 2.2	8.1 ± 3.7	**0.006**
Medial margin (mm)	8.8 ± 2.9	9.1 ± 2.8	0.469
Upper margin (mm)	9.8 ± 1.1	8.5 ± 3.4	**0.001**
Lower margin (mm)	9.4 ± 2.1	9.5 ± 2.1	0.744
Closer margin			
Negative	87 (82.8%)	87 (71.3%)	**0.001**
Deep margin	2 (1.9%)	2(1.6%)	
Superficial margin	6 (5.7%)	12 (9.8%)	
Lateral margin	2 (1.9%)	12 (9.8%)	
Medial margin	6 (5.7%)	0(0)	
Upper margin	0 (0)	8 (6.5%)	
Lower margin	2 (1.9%)	1 (0.8%)	
Multiple positive margins	4 (3.8%)	18 (15.7%)	**0.006**

The recurrence rate at 3-year follow-up was 5.1% in the CS group versus 12.2% in the C group; disease-free survival is shown in the Kaplan–Meier curve; and the relative log range was 0.098 (Figure 2).

The operative time for the different techniques was 71.2 min ± 37.6 min in the CS group, while in the C group it was 101.6 min ± 42.9 min, and the relative p-value was 0.002. Excluding patients subjected to intraoperative evaluation of the sentinel lymph node, the operative time was 68.4 min ± 37.1 min in the CS group versus 93.9 ± 40.6, p-value = 0.024.

In the univariate logistic regression analysis of the multifocal lesions, cancer grade and technique adopted for cavity or intraoperative evaluation of resection margins presented a p-value inferior to 0.010, and they were considered predictive factors of resection margins re-excision (Table 3). A multivariate logistic regression was performed to evaluate the effect of multifocal lesions, cancer grade, and intraoperative evaluation of lesions on the re-excision risk. According to the multivariate analysis, only intraoperative evaluation of the lesion was a risk factor for resection margin re-excision (Wald = 4.315, p = 0.038, OR: 2.331 [95% CI: 1.049–5.180]).

4 Discussion

The evaluation of patients submitted to BCS with a diagnosis of pure DCIS carried out in this retrospective study revealed that the cavity shave margin technique lowered the rate of positive margins. In our monocentric experience, 17.1% of patients in the CS group

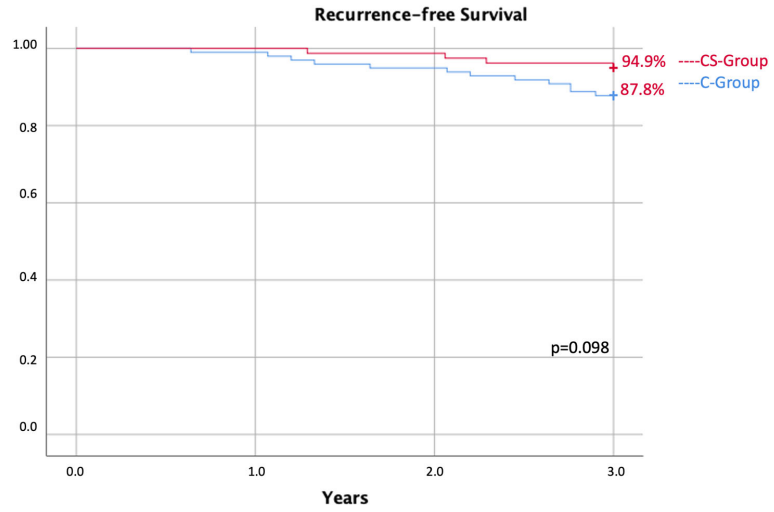

FIGURE 2
Recurrence-free survival of 3 years between the CS group and the C group.

had a resection margin of < 2 mm and were therefore considered positive, compared with 28.7% in the C group. Moreover, we found that removing an extra layer of tissue, as in the cavity shave technique, lowered the rate of surgical re-excision by 12.4% versus 23.8% in the C group. Not taking the cavity shave margin resulted in an almost twofold increase in the need for surgical re-excision of the margins (OR: 2.331 [95% CI: 1.049–5.180]; *p*-value = 0.038), regardless of the type of lesions and DCIS grade. This outcome is similar to previous multicenter randomized controlled trials (10). In the same study, authors found a correlation between positive margins and lesion size (10). In our analysis, size is correlated with positive margins; however, this is outside the scope of the study. Moreover, in our study, the size is not a predictive factor of positive margins, and the technique adopted for the management of surgical margins is not correlated with lesion size. This difference could be explained by the improvement in diagnostic techniques such as magnetic resonance and contrast-enhanced mammography that nowadays allow a better preoperative evaluation of the lesion extension and therefore the real need for mastectomies.

TABLE 3 Multivariate logistic regression for re-excision of margins.

Univariate			
Variables	OR	95% CI	*p*-value
Multifocality	0.503	0.245–1.032	0.061
Tumor grade	0.355	0.211–1.403	0.048
Intraoperative evaluation of margins	2.183	1.068–4463	0.032
Multivariate			
Multifocality	0.648	0.201–2.089	0.467
Tumor grade	0.681	0.222–1.521	0.067
Intraoperative evaluation of margins	2.331	1.049–5.180	0.038

OR, odds ratio; CI, confidence interval.

Current literature shows how a preoperative evaluation of the real tumor extension with contrast-enhanced mammography can be detrimental to the surgical choice and therefore to obtaining both optimal oncological and esthetical results. A second-level exam such as CEM or MRI allows us to understand the extent of the needed resection prior to surgery. This most likely will ensure healthy tissue sparing for a better reconstruction of the left tissue without compromising the oncological outcome (12, 13).

DCIS is known to have a different pattern of growth, usually with a skip-like distribution; nodular lesions are less common, especially in low nuclear grade, as reported in a previous study performed by Faverly et al. (14). Merrill et al. reported that the majority of DCIS presents a multifocal distribution with a gap width of < 5 mm (15). Obtaining clear margins in patients with DCIS might therefore be problematic. We believe that routine cavity shaving could help the physician obtain a negative margin. Our previous retrospective analysis, comparing cavity shaving and intraoperative evaluation of resection margin by the pathologist in invasive cancer, highlighted a significant reduction of positive margins; however, there was no statistically significant difference in margins after re-excision (16). This dissimilarity between *in situ* lesions and invasive breast cancer could be justified by the different growth patterns between the lesions (16). Furthermore, the absence of tactile feedback from the nodule in DCIS lesions can make it more difficult to obtain a disease-free surgical margin, and especially in these patients, the cavity shaving technique could reduce the risk of positive margins and the need for surgical re-excision.

Many other techniques have also been used to reduce the positive margin rate in CBS. Racz et al., as in the control group of our study, analyzed 688 patients with a diagnosis of DCIS subjected to BCS and intraoperative evaluation of frozen sections of margins

(17). They reported that about 63% of DCIS patients presented close or positive margins (17). Although our study also revealed an increased incidence of positive margins in patients subjected to the intraoperative frozen section of margin compared to cavity shave, the rate was lower than the above-cited study. Intraoperative analysis of resection margins has shown good results in terms of positive margin rate reduction; however, it is not available in most institutions, so we believe that the cavity shave margin technique could be a valid tool to reduce the positive margin risk.

In our retrospective study, we did not report a significant difference in terms of locoregional recurrence at 3-year follow-up. In the CS group, recurrence at 3 years of follow-up was 6.1% and 12.2% in the control group. Assuming that many DCIS lesions could be indolent, recurrence could not be necessarily associated with resection margins (18, 19). As reported in our previous analysis, a positive margin in indolent DCIS may also never lead to recurrence due to the nonprogression of the tumor (20). This hypothesis could explain the absence of a difference in terms of recurrence, regardless of the high incidence of positive margins in the C group. We strongly believe, as many researchers in the scientific community do, that gene biosignature can predict recurrence risk (21–24). In patients subjected to cavity shaving, we reported a significant reduction in operative time of about 25 min compared with the control group. A different result was reported by Mohamedahmed et al. (25). In their analysis, the authors reported a longer surgical time when cavity shaving is performed (79 min ± 4 min vs. 67 min ± 3 min; mean difference: 12.14; $p = 0.002$) (25). In the analysis by Mohamedahmed et al., the control group was not subjected to intraoperative evaluation of resection margins. Differently, Monib et al. reported that cavity shaves, ensuring microscopic clearance, do not increase operating time (26). We reported a longer operative time in the C group; this is most likely linked to the technical time needed for the intraoperative evaluation of surgical margins.

The main limitations of our study include its retrospective nature, limited small sample size, and the short follow-up period. In addition, the choice of surgical technique is often led by the surgeon's preference based on the type of the lesion and their own personal experience.

5 Conclusion

One of the main challenges in BCS for patients with a DCIS diagnosis is obtaining clear margins while preserving healthy tissues. This retrospective study highlights how the cavity shave margin technique results in a reduction in the positive margin rate and surgical re-excision. Moreover, this technique also reduces operative time. Based on these findings, the cavity shave technique should be considered a valid surgical approach for patients diagnosed with DCIS.

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 Comitato etico lazio area 2, Policlinico Tor Vergata, Viale Oxford 81, 00133, Roma. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because of retrospective nature of the study.

Author contributions

GV: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. MP: Conceptualization, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. MM: Data curation, Formal Analysis, Writing – review & editing. VM: Data curation, Writing – review & editing. VU: Data curation, Writing – review & editing. AN: Formal Analysis, Writing – review & editing. OB: Supervision, Writing – review & editing.

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Preoperative prediction of nodal status using clinical data and artificial intelligence derived mammogram features enabling abstention of sentinel lymph node biopsy in breast cancer

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Introduction: Patients with clinically node-negative breast cancer have a negative sentinel lymph node status (pN0) in approximately 75% of cases and the necessity of routine surgical nodal staging by sentinel lymph node biopsy (SLNB) has been questioned. Previous prediction models for pN0 have included postoperative variables, thus defeating their purpose to spare patients non-beneficial axillary surgery. We aimed to develop a preoperative prediction model for pN0 and to evaluate the contribution of mammographic breast density and mammogram features derived by artificial intelligence for de-escalation of SLNB.

Materials and methods: This retrospective cohort study included 755 women with primary breast cancer. Mammograms were analyzed by commercially available artificial intelligence and automated systems. The additional predictive value of features was evaluated using logistic regression models including preoperative clinical variables and radiological tumor size. The final model was internally validated using bootstrap and externally validated in a separate cohort. A nomogram for prediction of pN0 was developed. The correlation between pathological tumor size and the preoperative radiological tumor size was calculated.

Results: Radiological tumor size was the strongest predictor of pN0 and included in a preoperative prediction model displaying an area under the curve of 0.68 (95% confidence interval: 0.63–0.72) in internal validation and 0.64 (95% confidence interval: 0.59–0.69) in external validation. Although the addition of mammographic features did not improve discrimination, the prediction model provided a 21% SLNB reduction rate when a false negative rate of 10% was accepted, reflecting the accepted false negative rate of SLNB.

Conclusion: This study shows that the preoperatively available radiological tumor size might replace pathological tumor size as a key predictor in a preoperative prediction model for pN0. While the overall performance was not improved by mammographic features, one in five patients could be omitted from axillary surgery by applying the preoperative prediction model for nodal status. The nomogram visualizing the model could support preoperative patient-centered decision-making on the management of the axilla.

KEYWORDS

breast cancer, de-escalation, sentinel lymph node biopsy, artificial intelligence, mammography, prediction model, personalized medicine

1 Introduction

Sentinel lymph node biopsy (SLNB) is the recommended surgical axillary staging method in patients with clinically node-negative breast cancer, although approximately 75–80% have non-malignant axillary lymph nodes in the definitive pathology report (1–4). Consequently, patients with negative sentinel lymph node status (pN0) do not benefit from SLNB. The American College of Surgeons Oncology Group Z0011(ACOSOG Z0011) study questioned the necessity of axillary lymph node dissection and showed that abstaining from ALND in patients with T1-T2 clinically node negative primary breast cancer with 1-2 sentinel lymph nodes containing metastases was non-inferior to ALND regarding overall survival. This raised the question of the necessity of SLNB. The randomized Sentinel Node vs Observation After Axillary Ultra-Sound (SOUND) trial recently showed that abstaining SLNB in patients with T1 tumors having breast-conserving surgery was non-inferior to SLNB regarding distance-free survival at five years (5). However, implementation of the findings from the SOUND trial is not applicable to all breast cancer patients. The ASCO guidelines already recommended abstaining from SLNB in 2021 for patients ≥ 70 years with a luminal subtype undergoing breast-conserving surgery and the recommended adjuvant endocrine therapy (2). There is an increasing awareness of the importance of the long-term effects of surgery on patient's function and well-being. The Intergroup Sentinel Mamma study (INSEMA) evaluating invasive disease-free survival and morbidity after breast-conserving surgery with or without SLNB reported that morbidity was lower in the group without SLNB than in the group with SLNB at one, three, and 18 months postoperative (3). This warrants strategies for implementation of de-escalation of axillary surgery and methods for preoperative identification of patients for whom SLNB can be safely omitted.

Several clinicopathological models for prediction of axillary lymph node (ALN) and sentinel lymph node (SLN) status have been developed during the past decade (6–9). In 2019, Dihge et al. (10) developed an artificial neural network (ANN) model to predict pN0. The selected variables in the model are well known predictors and most were previously included in Bevilacqua et al.'s prediction model (7, 10). However, previous prediction models were developed using postoperatively available variables, defeating the purpose of a patient-centric preoperative decision tool for safe omission of SLNB. A commonly used key predictor for pN0, pathological tumor size, is a postoperative measure that could be replaced by radiological tumor size. Studies have indicated that primarily mammographic tumor size is similar to the postoperatively available pathologic tumor size, while other imaging modalities often over- or underestimate the tumor size (6, 7, 11). To our knowledge, a comparison of pathological tumor size and radiological tumor size has not previously been described in the setting of ALN status prediction.

Prediction models for ALN status using mammograms have been presented using presence of microcalcifications, breast density, and radiomic signatures, exclusively or in combination with clinicopathological variables, most of which were postoperatively obtained (12–15). In addition, several studies have investigated using other breast imaging modalities for nodal prediction, including ultrasound and contrast-enhanced mammography (16–21). To our knowledge, no prediction model for pN0 currently incorporates commercially available AI cancer detection features from mammograms and exclusively preoperatively available clinicopathological variables.

Thus, we aimed to evaluate non-operative nodal staging and the possibility to omit axillary surgery by developing a prediction model for pN0 using only preoperatively available data. The additional predictive value of mammographic variables extracted by a commercially

Abbreviations: AI, Artificial intelligence; AIC, Akaike information criterion; ALN, Axillary lymph node; ANN, Artificial neural network; AUC, Area under the receiver operating characteristic curve; CI, Confidence interval; ER, Estrogen receptor; FNR, false negative rate; INSEMA, Intergroup Sentinel Mamma study; LIBRA, Laboratory for Individualized Breast Radiodensity Assessment; MLR, Multivariable logistic regression; pN0, Negative sentinel lymph node status; pN+, Positive sentinel lymph node status; PACS, Picture Archiving and Communication System; PR, Progesterone receptor; ROC, Receiver operating characteristic; SLN, Sentinel lymph node; SLNB, Sentinel lymph node biopsy; SOUND, Sentinel Node vs Observation After Axillary Ultra-Sound.

available AI cancer detection system and an automated breast density assessment system in patients with clinically node-negative primary breast cancer is explored. A nomogram is developed as a preoperative decision-tool to enable a patient-centered approach to SLNB. Additionally, we aimed to evaluate radiological tumor size as a preoperative alternative to the postoperative pathological tumor size as a predictor in a preoperative prediction model for pN0.

2 Materials and methods

2.1 Study population

A total of 770 women diagnosed with primary breast cancer between January 2009 and December 2012 were prospectively included in a registry at the Department of Pathology at the Skåne University Hospital (Lund, Sweden). Patients with clinically node negative primary breast cancer undergoing primary breast surgery and SLNB were included as previously described by Dihge et al. (6, 10). Clinically node negative was defined as no palpable mass in the physical examination. All patients underwent SLNB as axillary staging, and if needed, axillary lymph node dissection. Another cohort including 586 patients from Skåne University Hospital (Malmö, Sweden in 2020) and Helsingborg Regional Hospital (Helsingborg, Sweden in 2019–2020) was used for external validation (22).

2.2 Clinicopathological data

Patient and tumor information was collected from patients' electronic files and a pathology database, as described by Dihge et al. (6, 10) and Skarping et al. (22). The histological type was divided into two groups after variable selection: the first group included no special type and lobular, and the second group included other and mixed types (7). Estrogen receptor (ER) status, progesterone receptor (PR) status, HER2 status, and Ki67 percentage were analyzed and categorized according to guidelines (23, 24). Mode of tumor detection was divided into symptomatic presentation and by the national mammography screening program. Tumor localization was defined by location in the four quadrants and central, and after statistical variable selection, categorized as upper inner quadrant vs. other locations (7).

SLN status was categorized as negative or positive (pN0 or pN+). pN0 was defined as breast cancer without lymph node metastasis or with isolated tumor cells. pN+ was defined as ≥1 SLN with micrometastasis or macrometastasis, defined as >200 cells and/or cluster size of 0.2 – 2 mm, and cluster size >2 mm, respectively (25).

2.3 Mammographic images and image analysis systems

All available mammographic images from screening and diagnostic imaging were included in the analyses. A modified Breast Imaging Reporting and Data System malignancy score (1–5) was used for mammographic and ultrasound images, as they are part of the clinical routine work-up. For this study mammographic malignancy score (1–5), ultrasound malignancy score (1–5), the largest specified radiologic tumor size in mm, and laterality were collected from the Picture Archiving and Communication System (PACS). In cases of missing mammographic tumor size, size from ultrasound was used since both modalities are preoperative and included in the initial clinical work-up. Mammography has been shown to have a high accuracy when compared to the surgical specimen, while ultrasound tends to underestimate the tumor size (26).

Transpara (version 1.7.0, Screenpoint Medical, Nijmegen, the Netherlands), a breast cancer detection tool uses deep learning algorithms to detect suspicious soft tissue lesions and microcalcifications (calc) that may indicate breast cancer. Each suspicious region is assigned a score between 1 and 100. When used for screening mammography, Transpara sorts cases into ten different risk categories (1-10) based on the regional suspicion scores. It is calibrated to sort roughly equal numbers of cancers into each category, with a goal of 90%+ of cancers in category 10 (27). Several retrospective studies (28–31) have shown Transpara to be effective in increasing cancer detection and reducing workload in screening, and the prospective Mammography Screening with Artificial Intelligence (MASAI) trial has demonstrated it to be effective in a clinical screening setting (32). Additionally, Transpara has been reported to predict stage II breast cancer years before diagnosis, indicating detection of properties beyond the cancer diagnosis (33). For this study, the highest calc cluster score and soft tissue lesion score were extracted from Transpara. The scores were included in the set of candidate predictors as continuous variables (0–100) and dichotomized as presence of finding (0 vs 1–100). All available mammograms were included and were manually cross-checked for laterality and correct tumor localization in Transpara before data extraction.

LIBRA (version 1.0.5) is an automated breast density estimation algorithm, which analyzes images based on gray-level values and segments them into dense and non-dense areas, developed at the University of Pennsylvania (17). Gastounioti et al. (34) and Keller et al. (35), among others, have validated LIBRA as a breast density measurement system. In this study, dense area [cm2] and density [%] were extracted from LIBRA. Craniocaudal and mediolateral oblique projections were available for all patients and therefore included in the analyses. The mean values from LIBRA of the projections on the ipsilateral side were used as the contralateral side was not available for all patients. Moreover, several studies revealed an association between breast density and breast cancer as well as with ALN status (33–38).

2.4 Statistical analysis

Descriptive analyses were performed to explore the associations between clinical, pathological, and radiological variables, and SLN status using the Mann–Whitney U test and Chi-square test for continuous and categorical variables, respectively. Pathological and mammographic tumor size were compared using Pearson

correlation and Bland-Altman analysis. Univariable logistic regression was used for radiological variables to predict pN0. The top ten variables included in the model published by Dihge et al. (10) were used as a framework and included in a multivariable logistic regression (MLR) analysis. In the published article, an ANN model was developed with cross-validation and compared with an MLR model. The performance of the simpler MLR model was found to be marginally inferior. Therefore, we proceeded with the MLR model (area under the receiver operating characteristics curve (AUC) 0.73) in the present study, hence referred to as the postoperative framework model (10). In this study, vascular invasion and multifocality were excluded due to clinical unavailability or poor preoperative quality. The postoperative variables, Ki67 and pathological tumor size, were exchanged for the preoperatively available variables, histological grade and radiological tumor size. Stepwise backward elimination MLR with a p-value threshold for removal of 0.157 was performed to obtain a clinical preoperative model. Radiological variables were evaluated as additional candidates to improve the clinical preoperative model, using stepwise backward elimination. The model stability was assessed by performing the model selection procedure in 1000 bootstrap samples as well as by five-fold cross-validation repeated ten times. Prediction models were compared using AUC and the Akaike information criterion (AIC). The SLNB reduction rate was calculated with a cut-off based on a 10% false negative rate (FNR), reflecting the clinically accepted FNR of SLNB (39, 40). In addition, SLNB reduction rate was calculated with a 20% FNR for comparison. Point estimates for the clinical preoperative prediction model were illustrated by a nomogram. The proposed prediction model was externally validated, temporally and geographically, in a separate cohort. The calibration in the validation cohort was evaluated using the Hosmer-Lemeshow approach. Briefly, the predicted probabilities of pN0 were plotted against the mean predicted probability of pN0 according to the model. Perfect calibration will hence respond to 10 plot symbols on a line with a 45-degree slope.

P-values were not corrected for multiple comparisons due to the explorative nature of the study. All p-values are two-sided and interpreted as level of evidence against the null hypothesis without reference to a cut-off for significance. Stata (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX; StataCorp LLC) was used for all statistical analyses.

3 Results

Mammograms were identified in 755 of the 770 patients included in the study. All patients and images were included in the LIBRA subgroup. Transpara failed to analyze mammograms from three patients and 30 patients were excluded due to technical issues in PACS. Inconclusive cases, according to radiologists, and cases without a clear indication of tumor location in PACS were excluded due to the inability to cross-check the AI findings. The inclusion and exclusion of patients with annotated mammograms are presented in Figure 1. The AI assessment of tumor localization on mammograms was correct in 96.1% of the cases.

The patient, tumor, and radiological characteristics of the primary cohort are presented in Table 1 and the external validation cohort in Supplementary Table 1. Patient and tumor characteristics were similar in the two cohorts, apart from the prevalence of pN0. In the primary cohort, 35% were pN+, while only 26% were pN+ in the external cohort. The patient and tumor characteristics that showed the strongest evidence for association with pN0 were pathological tumor size ($p < 0.001$), mode of tumor detection ($p < 0.001$), multifocality ($p < 0.001$), vascular invasion ($p < 0.001$), Ki67 ($p < 0.001$), histological grade ($p=0.007$), age ($p=0.027$), and histological type ($p=0.046$). The radiological variables strongest associated with pN0 were radiological tumor size ($p < 0.001$), and the highest soft tissue lesion score ($p < 0.001$).

A comparison of tumor size by pathological and mammographic assessment is presented in Supplementary Table 2. The agreement between tumor size variables was also evaluated in a Bland-Altman plot of differences vs. average (Figure 2). The mean pathological and radiological tumor sizes were 16.7 and 17.1 mm, respectively, and the Pearson correlation coefficient was 0.62.

The univariable logistic regression analyses of pN0 are presented in Supplementary Table 3 and AUCs for radiological variables in Supplementary Table 4. Radiological tumor size (odds ratio (OR) 0.97 per mm, 95% confidence interval (CI) 0.95–0.98, $p < 0.001$) had the strongest evidence of association with pN0 in univariable analyses.

The MLR resulted in a clinical preoperative model including radiological tumor size, ER status, age, mode of detection, histological type, and tumor localization (upper inner quadrant vs. other), with an AUC of 0.68 (95% CI: 0.63–0.72) (Table 2). A nomogram visualizing the point estimates for the clinical preoperative model was developed (Figure 3). The remaining radiological variables added to this model using the same method, resulted in a combined preoperative model including radiological tumor size, ER status, age, mode of detection, histological type, tumor localization, highest soft tissue lesion score (continuous), and soft tissue lesion (binary) with an AUC of 0.68 (95% CI: 0.63–0.72) (Table 2). The corresponding AUC for the postoperative framework model was 0.76 (0.71–0.80). Each model's AIC is presented in Supplementary Table 5. The candidate variable selection procedure was evaluated in 1000 bootstrap samples as well as by cross-validation. Radiological tumor size was selected in 96.5% of the bootstrap analyses (Supplementary Table 6) and in 100% of the cross-validation analyses. The clinical preoperative prediction model was externally validated with an AUC of 0.64 (95% CI: 0.59–0.69). A Hosmer-Lemeshow calibration plot is presented in Supplementary Figure 1. Applying the clinical preoperative prediction model to assign pN0 resulted in a possible SLNB reduction rate of 21% or 34% (Table 3), corresponding to a cut-off that accepts a 10% or 20% FNR, respectively.

4 Discussion

In this study, a truly preoperative prediction model for pN0 in primary breast cancer was developed combining radiological and

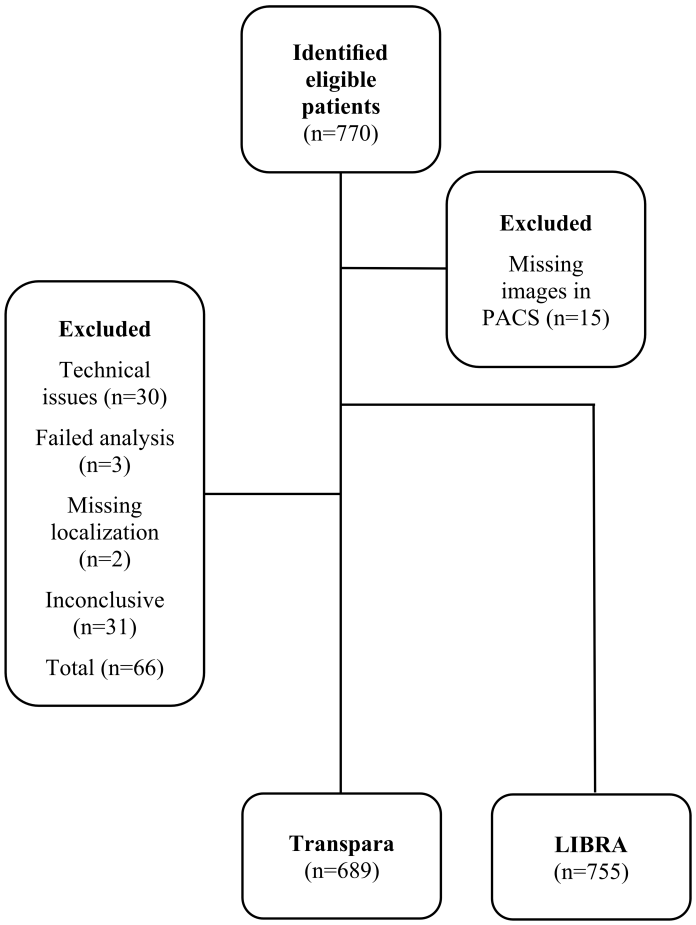

FIGURE 1
Flow chart of patient inclusion. At inclusion there were missing images (n=15) in PACS, additional images (n=30) were excluded due to technical issues. Abbreviations: Laboratory for Individualized Breast Radiodensity Assessment (LIBRA); Picture Archiving and Communication System (PACS).

TABLE 1 Patient, tumor, and radiological variables stratified by sentinel lymph node status.

	All (n=770)	pN0 (n=501)	pN+ (n=269)	*P*
Age, years (continuous)*[c]	64.7 (24.2–91.9)	65.9 (32.6–91.5)	64.2 (24.2–91.9)	0.027[a]
Pathological tumor size, mm (continuous)*[d]	15 (0.5–90)	13 (0.5–55)	18 (0.9–90)	<0.001[a]
Missing	1	1	0	
Mode of tumor detection[c]**				<0.001
Symptomatic	321	184 (37)	137 (51)	
Screening	449	317 (63)	132 (49)	
Multifocality[d]**				<0.001[b]
Yes	186	96 (19)	90 (33)	
No	584	405 (81)	179 (67)	
Tumor localization[c]**				0.108[b]
Central	22	14 (3)	8 (3)	
Upper inner	105	76 (15)	29 (11)	
Lower inner	46	32 (6)	14 (5)	

(Continued)

TABLE 1 Continued

	All (n=770)	pN0 (n=501)	pN+ (n=269)	*P*
Upper outer	253	160 (32)	93 (35)	
Lower outer	78	41 (8)	37 (14)	
Overlapping	266	178 (36)	88 (33)	
Histological type**[c]				0.046[b]
NST and lobular	713	457 (91)	256 (95)	
Other or mixed	57	44 (9)	13 (5)	
Histological grade**[c]				0.007[b]
I	186	137 (28)	49 (18)	
II	350	224 (45)	126 (47)	
III	226	133 (27)	93 (35)	
Missing	8	7	1	
Vascular invasion**[d]				<0.001[b]
Yes	91	27 (6)	64 (32)	
No	526	390 (94)	136 (68)	
Missing	153	84	69	
ER status**[c]				0.056[b]
Negative	69	53 (11)	16 (6)	
Positive	699	446 (89)	253 (94)	
Missing	2	0	2	
PR status**[c]				0.077[b]
Negative	122	89 (18)	33 (12)	
Positive	646	410 (82)	236 (88)	
Missing	2	0	2	
HER2 status**[c]				0.606[b]
Negative	624	411 (89)	213 (87)	
Positive	84	51 (11)	33 (13)	
Missing	62	39	23	
Ki67 (continuous)*[c]	15 (0–94)	14 (0–94)	17 (1–81)	<0.001[a]
Missing	43	15	28	
Radiological tumor size, mm (continuous)*[c]	15 (4–78)	13 (4–78)	17 (5–57)	<0.001[a]
Missing	179	119	60	
Highest calc cluster score (continuous)*[c]	0 (0–98)	0 (0–98)	0 (0–97)	0.445[a]
Missing	81	44	37	
Calc cluster (binary)**[c]				0.976[b]
Present	243	161 (35)	82 (35)	
Absent	446	296 (65)	150 (65)	
Missing	81	44	37	
Highest soft tissue lesion score (continuous)*[c]	91 (0–97)	90 (0–97)	92.5 (0–97)	<0.001[a]

(Continued)

TABLE 1 Continued

	All (n=770)	pN0 (n=501)	pN+ (n=269)	*P*
Missing	81	44	37	
Soft tissue lesion (binary)**[c]				0.345[b]
Present	572	375 (82)	197 (85)	
Absent	117	82 (18)	35 (15)	
Missing	81	44	37	
Breast density, %*[c]	16.8 (1.7–99.8)	16.1 (1.7–99.8)	18.7 (2.0–99.7)	0.215[a]
Missing	22	10	12	
Breast dense area, cm^2*[c]	22.9 (1.64–208.0)	22.2 (1.6–208.0)	23.4 (3.8–197.9)	0.529[a]
Missing	22	10	12	
Mammography malignancy score**[c]				0.386[b]
1	26	16 (4)	10 (4)	
2	8	7 (2)	1 (0)	
3	59	41 (9)	18 (8)	
4	205	143 (32)	62 (28)	
5	369	236 (53)	133 (59)	
Missing	103	58	45	
Ultrasound malignancy score**[c]				0.100[b]
1	35	28 (6)	7 (3)	
2	8	6 (1)	2 (1)	
3	32	22 (5)	10 (5)	
4	132	96 (22)	36 (16)	
5	453	286 (65)	167 (75)	
Missing	110	63	47	

Negative sentinel lymph node status (pN0), positive sentinel lymph node status (pN+), no special type (NST), estrogen receptor (ER), progesterone receptor (PR).
*Median (range).
**Number (%).
[a]Mann–Whitney U test.
[b]Chi-square test.
[c]Preoperatively available.
[d]Postoperatively available.

preoperatively available routine clinicopathological variables. The inclusion criteria were not restricted by age, tumor size, or type of surgery. This supports that the model can be used on a case-by-case basis evaluation of pN0 outside the ASCO guidelines on abstaining SLNB in older patients with ER+/HER2- tumors (2). Radiological tumor size was the strongest preoperative predictor of pN0 reflected by its low p-value and high selection rate (≈100%) in bootstrap analyses and cross-validation. This indicates that mammographic tumor size could replace pathological tumor size in preoperative models. Moreover, it was strongly associated with pathological tumor size. The soft tissue lesion score was associated with pN0 in univariable analyses, supporting the hypothesis that mammographic features could aid in preoperatively identifying these patients. However, although associated with the outcome, addition of radiological variables to the clinical preoperative model did not improve discrimination. The clinical and combined preoperative model had AUCs of 0.68 (95% CI: 0.63–0.72), indicating that the addition of radiological variables did not improve the overall performance of the model. External validation of the clinical preoperative prediction model resulted in an AUC of 0.64 (95% CI: 0.59–0.69). The Hosmer-Lemeshow calibration plot demonstrated that the prediction model underestimates the probability of node negativity, although the estimates follow the 45-degree line. A likely explanation is the difference in pN+ prevalence between the cohorts. Nevertheless, the clinical preoperative prediction model could putatively support the omission of SLNB in 21% of patients, if a 10% FNR is accepted, reflecting the accepted FNR of the SLNB procedure and support

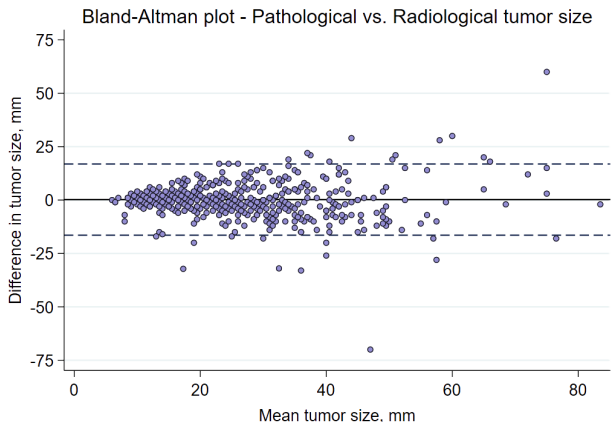

FIGURE 2
A Bland-Altman plot illustrating the difference in mean values between the preoperative radiological tumor size and the pathological tumor size from the surgical specimen.

the implementation of the ASCO guidelines and the results of the SOUND trial (2, 5). The reduction rate is directly dependent on the accepted FNR. The FNR reflecting SLNB could be considered conservative, and accepting a higher FNR might be acceptable in clinical practice. Applying a 20% FNR resulted in a 34% SLNB reduction rate. An alternative to a fixed cut-point, enabling a more patient-centered care, would be to allow different cut-points to be discussed and decided with the patient, on a case-by-case basis.

Pathological tumor size is a strong predictor of SLN status and often included in published prediction models, although it is assessed on the postoperative surgical specimen (10, 12, 13). In accordance with previous research, pathologic and radiologic measurements of tumor size were strongly correlated. The correlation coefficient was 0.62, in the present study, which can be compared to the correlation between pathologic tumor size and radiologic tumor size measured by mammography or ultrasound, depending on histological subtypes, in a study by Gruber et al. (11). This indicates that radiologic tumor size could be used as an alternative measure for pathological tumor size. Mammography has also been shown to estimate the tumor size more accurately than ultrasound, which underestimates the size with a varying degree depending on the histological tumor type (11). In this study radiologic tumor size was strongly associated with pN0 indicating that mammographic tumor size could replace pathological tumor size as a predictor of pN0. However, there may be subgroups, such as patients with dense breasts, in which radiological tumor size needs further evaluation.

TABLE 2 The clinical and combined preoperative prediction models for pN0. Backward variable selection with threshold p≥0.157 for removal.

	Clinical preoperative prediction model		Combined preoperative prediction model	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Radiological tumor size, mm (continuous)*	0.965 (0.947–0.983)	<0.001	0.977 (0.964–0.990)	<0.001
Age, years (continuous)	1.024 (1.008–1.040)	0.003	1.018 (1.006–1.029)	0.002
Mode of tumor detection		0.001		0.001
Symptomatic	1 (reference)		1 (reference)	
Screening	1.847 (1.267–2.693)		1.565 (1.198–2.045)	
Histological type		0.025		0.035
Other or mixed	1 (reference)		1 (reference)	
NST or lobular	0.419 (0.196–0.899)		0.565 (0.332–0.961)	
ER status*		0.001		0.001
Negative	1 (reference)		1 (reference)	
Positive	0.269 (0.123–0.587)		0.403 (0.234–0.694)	
Tumor localization		0.100		0.063
Other	1 (reference)		1 (reference)	
Upper inner quadrant	1.553 (0.919–2.624)		1.417 (0.981–2.048)	
Highest soft tissue lesion score (continuous)			0.984 (0.968–1.001)	0.076
Soft tissue lesion (binary)				0.087
Absence			1 (reference)	
Presence			4.051 (0.814–20.15)	
Constant	3.724		1.862	

Negative sentinel lymph node status (pN0), odds ratio (OR), confidence interval (CI), no special type (NST), estrogen receptor (ER).

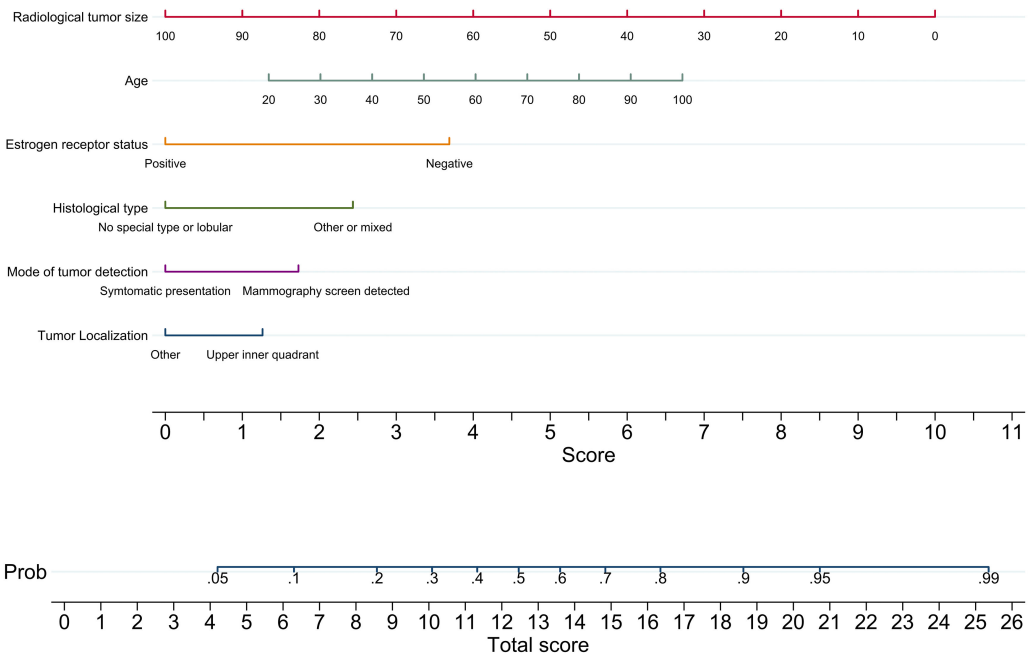

FIGURE 3
A nomogram illustrating the point estimates of the included variables' coefficients for the clinical preoperative prediction model for prediction of negative sentinel lymph node status.

The clinical preoperative and combined preoperative models (AUC 0.68) had lower AUCs than the postoperative framework model (AUC 0.76). This was expected as strong predictors, determined on the surgical specimen, were excluded from the model to make it clinically useful in a preoperative setting. The AIC of the postoperative framework prediction model was lower than those of the clinical preoperative and combined preoperative models, which was expected considering the superior discriminative capacity. Additionally, the AUC of the clinical preoperative prediction model was slightly lower in the external validation cohort, which was expected. The difference may be due to differences in prevalence of pN0 in the cohorts, where the external validation cohort had a higher prevalence. Additional analyses adjusting for the prevalence (data not shown) showed an AUC similar to the AUC of the internal validation. A prediction model for heavy nodal burden by Meteroja et al. (41) included prevalence of the outcome as a variable in the model to adjust for differences between populations. This is, however, not applicable in the present study due to the single center approach.

TABLE 3 SLNB reduction rate using the clinical preoperative prediction model to assign sentinel lymph node status.

FNR 10%				
	TP	TN	FP	FN
No.	189	105	276	20
SLNB reduction rate	(TN + FN)/(TP + TN + FP + FN) = 21%			
FNR 20%				
	TP	TN	FP	FN
No.	168	157	224	41
SLNB reduction rate	(TN + FN)/(TP + TN + FP + FN) = 34%			

Sentinel lymph node biopsy (SLNB), false negative rate (FNR), true positive (TP), true negative (TN), false positive (FP) and false negative (FN).

When elaborating on the radiological variables used in this study, it is important to note that Transpara was not intended to be used as a tool for SLN status prediction, although this study indicates its potential predictive value. Additional development of Transpara features in this direction may improve its predictive ability for pN0. However, the potential clinical use and definitions of medicolegal regulations regarding this type of diagnostic tools are debated and yet to be determined before clinical implementation (27, 42). Other forms of AI such as feature extraction from other imaging modalities, such as ultrasound, magnetic resonance imaging, and computed tomography, as well as machine learning methods have been evaluated for prediction of ALN status in several studies receiving high AUCs (16, 18–20). However, to our knowledge, none are yet available for implementation in clinical practice. Implementation of image analysis software in clinical practice could have other applications apart from screening and should therefore be evaluated for other possibilities (43). The

implementation of a prediction model in clinical practice would entail additional costs, whereas omission of SLNB would likely reduce costs associated with surgery as previously described for the ANN model proposed by Dihge et al. (10, 44). Striving for de-escalation in cancer care, omission of SLNB could also improve the quality of life and reduce postoperative morbidity, as reported in the INSEMA trial (3). The ASCO guidelines on management of the axilla in early-stage breast cancer stated that patients should be evaluated on a case-by-case basis to ensure oncological safety (2). Therefore, a truly preoperative prediction model for pN0 based on routine information on the individual patients would be of high clinical relevance and act as a foundation for patient-centered decision making. The presented nomogram could be an easy-to-use decision tool to support the preoperative multidisciplinary decision-making to omit SLNB for one in five patients with predicted pN0 status, consequently reducing the succeeding complications. Considering the preoperative nature of the proposed model, it could be considered an improvement compared to the previously published prediction model, regardless of the inferior discriminative capacity. However, the proposed model was developed and validated in retrospective cohorts, thus requiring additional research to ultimately benefit patients. In order to enable implementation of the clinical preoperative prediction model, the model should be validated in prospective studies.

A limitation of previous clinical prediction models is that key variables can only be obtained postoperatively (6, 7, 10). In other studies, this problem was circumvented by including radiological variables from different imaging modalities exclusively or in addition to clinicopathological variables. Liu et al. proposed an exclusively radiological ANN model using contrast-enhanced computed tomography (16). However, this approach is only feasible for clinical implementation for patients with breast cancer who undergo contrast-enhanced computed tomography during the initial routine work-up, an argument which also applies to models that include magnetic resonance imaging (18, 19). Given the wide implementation of mammography as a cornerstone in the clinical work-up for suspicious breast cancer including screening programs, mammographic images are available for all patients and can be used for preoperative diagnostics. Cen et al. proposed a model that included postoperative clinicopathological variables and microcalcification density on mammographic images, resulting in a model with an AUC of 0.70 (12). In the study, microcalcification density >20 cm^2 was associated with a positive ALN status. This was not observed in the present study, which might be a result of differing measuring techniques. Yang et al. (14) created a prediction model for ALN status (n=147) using a radiomic signature on mammography with an AUC of 0.88 in the validation cohort, but no independent validation has hitherto been performed. Studies have shown a positive association between breast density and malignant axillary lymph nodes when measured by radiologists and automated methods (36, 38), but when evaluated in a prediction model for pN0 including multifocality, pathological tumor size, histological type, Ki67 and histological grade, Hack et al. (13) found no additional predictive value, which is in line with the present study. In this study, images from the ipsilateral side were included in the LIBRA analysis. This was decided as mammographic images on the contralateral side were not available for all patients. The variation in tumor size (0.5 – 90 mm) can be assumed to have affected the results of the breast density variable in descriptive and univariable logistic regression as well as the performance of the variable in the MLR to some extent. However, the results are in accordance with previous results (13). LIBRA, which is a fully automated assessment tool that analyzes processed images, has been validated for breast density measurements on mammographic images by Gastounioti et al. (34) and Keller et al. (17), among others. The discrepancy between previous reports on the association between breast density and ALN status (13, 36, 38) could be due to differences between methods as revealed by Keller et al. (35).

A strength of this study is the relatively large cohort of 770 patients and that the inclusion criteria were not restricted by age, tumor size or type of surgery. All eligible cases during a four-year period were consecutively included, and the cohort should therefore be representative of the breast cancer population at Skåne University Hospital in Lund during the time period. Another strength is the assessment of Transpara's accuracy through cross-checking for the correct tumor location. Regardless of the cross-checking, all cases were included to resemble a clinical setting. The pN0 nomogram presents a graphical easy-to-interpret visualization of the included predictors and the relative importance of each independent variable is visible at a glance. There are several limitations to this study, such as the low prevalence of pN0 compared to recent cohorts. This could be due to the fact that breast cancers are discovered at an earlier stage now than in past decades. Another limitation is the exclusion of 30 cases due to technical issues in the Transpara sub-cohort, a cause of which could not be identified despite repeated contact with the technical support at the hospital and PACS provider. The authors believe that the reason may be a technical issue with the PACS provider during the archiving process. However, the missing images represent less than 4% of the cohort and the authors have found no reason to believe that the missingness is systematic. The impact of the technical issues on the model development should therefore be minimal. Additionally, Transpara failed to analyze the images of three patients (<0.4%), with unspecified errors. Furthermore, radiological tumor size was missing in 23% of cases, likely due to the fact that the radiological tumor size measurement was not always provided at the time of inclusion of patients in the present study. Thus, the performance of the radiological variables could be biased owing to the missing data. The inclusion of sonographic tumor size in cases where mammographic size was not available has likely decreased the correlation between pathological and radiological tumor size as ultrasound underestimates the size. The correlation can be expected to be higher in a cohort using only mammographic tumor size, increasing the performance of the model. Considering the high correlation presented in this study and the performance of the radiological tumor size in all analyses, the inclusion of sonographic data should not have affected the results. Another limitation is the inclusion of only ipsilateral images in the LIRBA

analysis, however, the effect on the overall conclusions can be presumed to be limited. Additionally, the prediction model on which this study is based is an ANN model that has the potential to capture non-linear associations and interactions, whereas the MLR model used in this study captures only linear effects on the log odds scale. This is a limitation and a strength, as the risk of overfitting is lower with less complex models such as MLR than with complex models. Moreover, to minimize the number of variables compared with the number of pN0 patients in the cohort, no interaction variables were included.

4.1 Conclusion

Radiological tumor size was strongly predictive of SLN status, thus supporting the hypothesis that radiological tumor size could replace pathological tumor size as a predictor of pN0. Additionally, although they did not improve the clinical preoperative prediction model, mammographic features might have nodal predictive capabilities. The presented clinical preoperative prediction model is visualized by a nomogram that could support the preoperative multidisciplinary decision-making to omit SLNB on a case-by-case basis for one in five patients with clinically node negative primary breast cancer with predicted pN0 status.

Data availability statement

The datasets presented in this article are not readily available because of sensitive information according to current data legislation but are available from the corresponding author upon reasonable request. Requests to access the datasets should be directed to cornelia.rejmer@med.lu.se.

Ethics statement

The study involving humans were approved by The Regional Ethical Review Board of Lund, Sweden, and KVB Samråd, Region Skåne. The study were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

CR: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing, Validation. LD: Data curation, Writing – review & editing, Investigation. P-OB: Writing – review & editing, Conceptualization, Formal analysis, Methodology, Validation. DF: Writing – review & editing, Investigation, Resources. MD: Conceptualization, Resources, Writing – review & editing. LR: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

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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.2024.1394448/full#supplementary-material

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An unusual occurrence of multiple primary malignant neoplasms: a case report and narrative review

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Introduction: Multiple primary malignant neoplasms (MPMNs) are cancers presenting distinct pathological types that originate from different tissues or organs. They are categorized as either synchronous or metachronous. Nowadays, the incidence of MPMN is increasing.

Patients and methods: We present a case of a 71-year-old male patient with a medical history of hepatitis B and a family history of breast and endometrial cancers. The patient reported a nasal tip skin lesion with recurrent bleeding, and the history disclosed lower urinary tract symptoms. Further investigations revealed the coexistence of four primary cancers: basosquamous carcinoma of the nasal lesion, prostatic adenocarcinoma, hepatocellular carcinoma, and clear cell renal cell carcinoma.

Results: A multidisciplinary team cooperated to decide the proper diagnostic and therapeutic modules.

Conclusion: To the best of our knowledge, the synchronization of these four primary cancers has never been reported in the literature. Even so, multiple primary malignant neoplasms, in general, are no longer a rare entity and need proper explanations, a precise representation of definition and incidence, further work-up approaches, and treatment guidelines as well.

KEYWORDS

multiple primary malignant neoplasms, multidisciplinary team, basosquamous carcinoma, prostatic adenocarcinoma, hepatocellular carcinoma, clear renal cell carcinoma

1 Introduction

Multiple primary malignant neoplasms (MPMNs) are defined as two or more primary malignant tumors, each presenting a distinct pathological type that originates from a different tissue or organ (1, 2). MPMNs are categorized as either synchronous or metachronous by the Surveillance Epidemiology and End Results (SEER) Program, the International Association of Cancer Registries (IACR), and the International Agency for Research on Cancer (IARC) based on the period between each cancer diagnosis (3).

MPMNs were first described by Billroth in 1889 (4) and extensively studied by Warren and Gates in 1932 (1). Since then, MPMNs have been widely explored, and many cases have been reported. Despite it being considered rare, MPMN incidence is increasing due to the evolution of diagnostic methods and screening programs in addition to improved treatment modalities, resulting in enhanced survival rates for cancer patients (5, 6). Recent literature mentioned incidence of 2%–17%.

There are multiple theories discussing potential risk factors: family history, genetic defects, environmental factors, and previous primary cancers in the same patient, among others (7–9). Regarding the tumors' origin, the theory is that they occur in a random manner (7). A comprehensive diagnostic approach is essential for primary tumor evaluation and early detection of possible consecutive neoplasms. Regarding treatment decisions, multidisciplinary team (MDT) is preferred for better evaluation of therapeutic choices and prioritization decisions.

In this article, we present a 71-year-old male patient with four primary malignancies: basosquamous carcinoma of the nasal tip, prostatic adenocarcinoma, hepatocellular carcinoma, and clear cell renal cell carcinoma. In addition, we provide a narrative review of the current state of knowledge in MPMNs. To the best of our knowledge, the synchronization of these four primary cancers has never been reported in the literature.

2 Case presentation

A 71-year-old married male patient presented to our hospital complaining of a nasal tip skin lesion for 18 months. His past clinical history is remarkable for hypertension, recurrent urinary retention, a 5-year history of hepatitis B that has been treated with lamivudine, and a surgical history of appendectomy, with no known drug or food allergies. His family history is significant for breast and endometrial cancer in the patient's sister. The patient is not a smoker or an alcoholic and works as a driver.

The patient noticed a nasal tip skin lesion with recurrent bleeding. On examination, the lesion was on the tip of the nose, measured 3 cm, and was black in color with ulceration. Due to the suspicious nature of the lesion, a punch biopsy was performed, which revealed basosquamous carcinoma (Figure 1). Subsequently, a complete resection of the lesion was performed with negative margins, followed by nasal reconstruction.

Six months later, the patient presented with lower urinary tract symptoms, including recurrent painless gross hematuria, urinary retention, frequency, weak stream, and nocturia. A physical examination was normal. Lab tests showed elevated alkaline phosphatase, gamma-glutamyl transferase, and alpha-fetoprotein (AFP) of 1,283.0 ng/ml and total prostate-specific antigen (PSA) of 70.6 ng/ml. Leukopenia and progressive thrombocytopenia were reported as well.

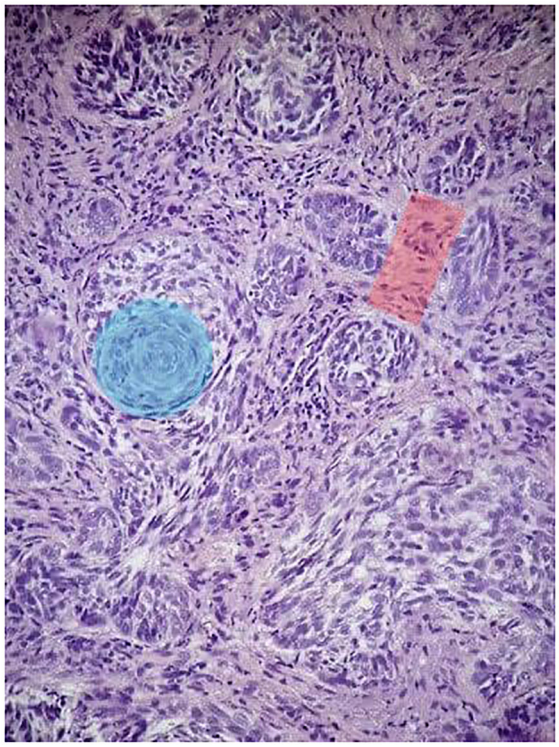

FIGURE 1
Histopathologic features of the patient's nasal tip skin lesion punch biopsy. H&E (x10): the tumor is composed of a nest of basaloid cells with peripheral palisading (red shadow) and features of BCC admixed with areas of squamoid cells (blue shadow).

Chest, abdomen, and pelvis computed tomography (CT) scans revealed a markedly enlarged prostate gland indenting the urinary bladder; a right renal upper lobe solid mass arising from the cortex; and four enhanced hepatic lesions, mainly in the right lobe (Figure 2).

The urologists executed a transrectal prostate biopsy. Histopathology revealed adenocarcinoma, with a Gleason score of 6 (3 + 3) in the right parietal lobe and 7 (4 + 3) in the left parietal lobe (Figure 3).

The renal mass was suspected to be renal cell carcinoma, leading the urologists to perform a right radical nephrectomy. Histologic examination of the tissue revealed a unifocal, 4.5 cm × 4 cm × 4 cm, WHO grade 3 clear cell renal carcinoma confined to the kidney (Figure 4).

An ultrasound-guided core needle biopsy of the largest hepatic lesion was also executed, and histopathology revealed well-differentiated hepatocellular carcinoma (Figure 5).

After discussing the patient's findings, a multidisciplinary team decided to treat the prostate cancer with bicalutamide for 2 weeks, succeeded by goserelin, abiraterone acetate, and prednisolone. Hepatic lesions were infiltrative; hence, the decision was to treat

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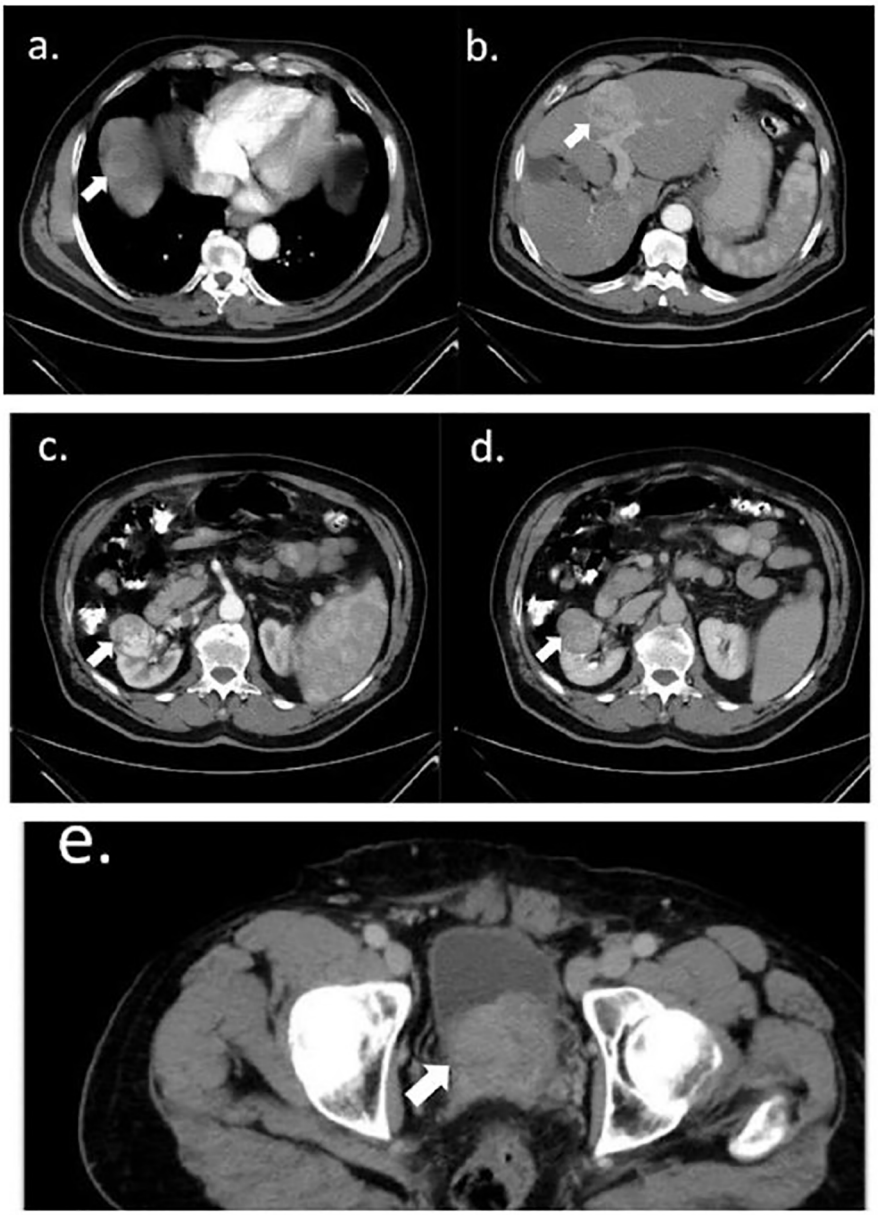

FIGURE 2
Abdomen and pelvis axial CT scan. **(A, B)** Hepatic isodense round lesions in the right lobe: a 5-cm lesion in segment four **(A)** and a 3.5-cm lesion in the dome of the liver **(B)**, with heterogeneous enhancement in the portal phase. In addition to two smaller enhanced lesions in segment eight **(B)**, the liver was normal in size and shape. **(C, D)** Right renal heterogeneously enhanced 4-cm lesion, arising from the right renal cortex, distorting adjacent mid-calyx and renal pelvis; **(C)** with and **(D)** without contrast. **(E)** An enlarged prostate of 6.3 cm projected to the base of the urinary bladder. All intended lesions are marked with arrows.

the patient with atezolizumab and bevacizumab, starting 6 weeks after his radical nephrectomy. Regrettably, the patient failed to adhere to the prescribed management regimen for his hepatic malignancy. Table 1 presents a comprehensive summary of the therapeutic modalities employed for our patient, encompassing indications, initiation time, dosages, and durations.

One year later, a positron emission tomography (PET) scan exhibited a stable state of hepatic lesions; hypermetabolic malignant intraprostatic multifocal areas, invading the right seminal vesicles; hypermetabolic malignant left external iliac lymph nodes; hypermetabolic L1 spinous process lytic lesions; and nonmetabolically active multiple pelvic bone sclerotic lesions. The findings indicated possible prostate metastatic deposits; hence, a prostate-specific membrane antigen (PSMA) PET scan was planned to confirm the diagnosis. Genetic testing, BRCA gene testing, and Oncomine Pan-Cancer Cell-Free Assay reported no mutations.

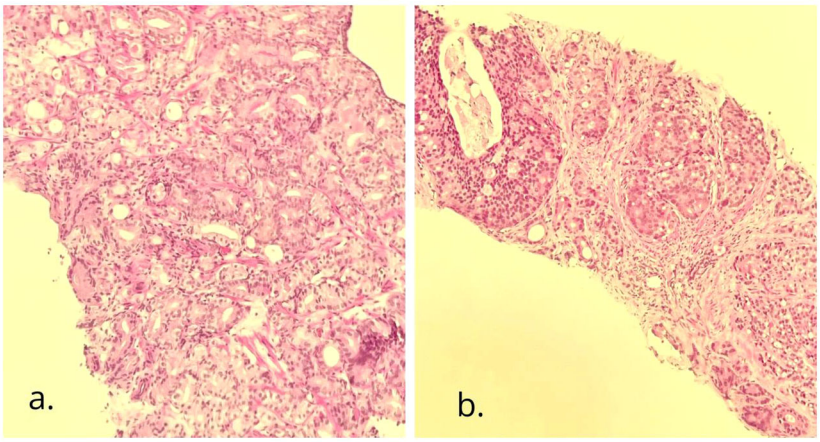

FIGURE 3
Needle biopsy of the prostate gland. H&E (x10): adenocarcinoma with cribriform pattern. **(A)** The right side of the gland with a Gleason score of 6 (3 + 3), grade group 1; **(B)** the left side of the gland with a Gleason score of 7 (4 + 3), grade group 3.

3 Narrative review and discussion

3.1 Definition of MPMNs

Multiple primary malignancies are defined as the presence of more than one cancer in a single individual with exclusion to metastasis, recurrence, or local spread. According to the SEER project and the IACR/IARC, there are two distinct definitions (7). SEER categorizes tumors as synchronous if they develop within 2 months of the previous cancer diagnosis and as metachronous if they occur after that period (10). Additionally, SEER considers a single tumor in different parts of the same organ as multiple sites (5). In contrast, IARC rules are more exclusive; it uses a 6-month window to differentiate between synchronous and metachronous tumors (10). Furthermore, the IARC follows the one-site definition, where only one tumor is registered for a specific organ (2).

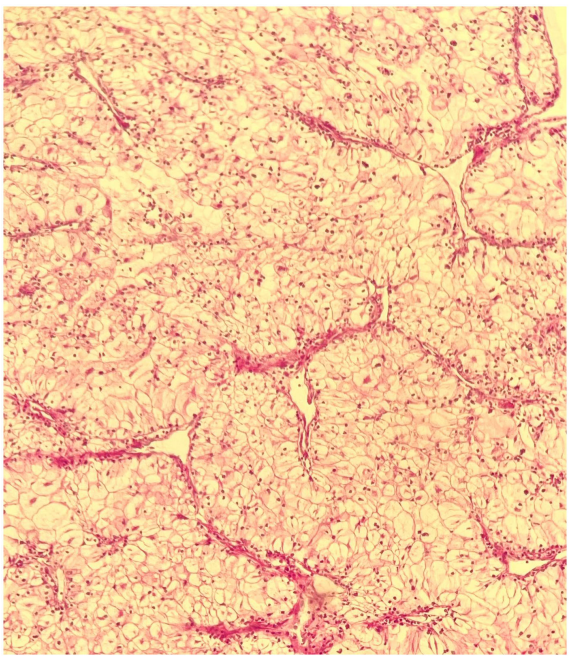

FIGURE 4
Biopsy of the right kidney tumor. H&E (x10): clear cell renal cell carcinoma, with WHO/ISUP histologic grade 3, and tumor pathologic stage of PT1b Nx Mx.

3.2 Incidence of multiple primaries

The literature shows that the overall incidence of MPMNs ranges widely from 2% to 17% (11), depending on the definition used, the analysis type, the data collection duration, the follow-up time, and the patient's ethnicity (10). Warren first described the concept of multiple primary malignancies as early as 1932. Most studies express two cancers rather than triple or quadruple. Watanabe et al. noted second primaries in 5.2% of the cases and only 1.1% with triple or more cancers (12). Németh et al. reported the incidence of triple and quadruple primaries as 0.5% and 0.3% of cancer patients, respectively (13). In Antal and Vallent's study, around 49 patients with MPMNs consisted of two cancers, and only four cases had three primary cancers. Furthermore, the majority of MPMNs were metachronous rather than synchronous (3). Therefore, our case is unique in that the patient presented with four synchronized primary malignancies, each with a different histopathology: nasal skin basosquamous carcinoma, which is considered a rare malignancy; prostate adenocarcinoma; hepatocellular carcinoma; and clear cell renal cell carcinoma. After thoroughly reviewing the literature, we concluded that this is the first case of this combination of malignancies. In addition, there was no proven association between them.

The incidence rates of MPMNs are on the rise. This is primarily attributed to the advancements in diagnostic methods' sensitivities and the implementation of screening programs, especially for prostate and breast cancer (5, 6). Furthermore, the improved understanding of shared genetic and behavioral risk factors, among other factors, has contributed to this rise (3). This increase in incidence can also be attributed to the continuous evolution of

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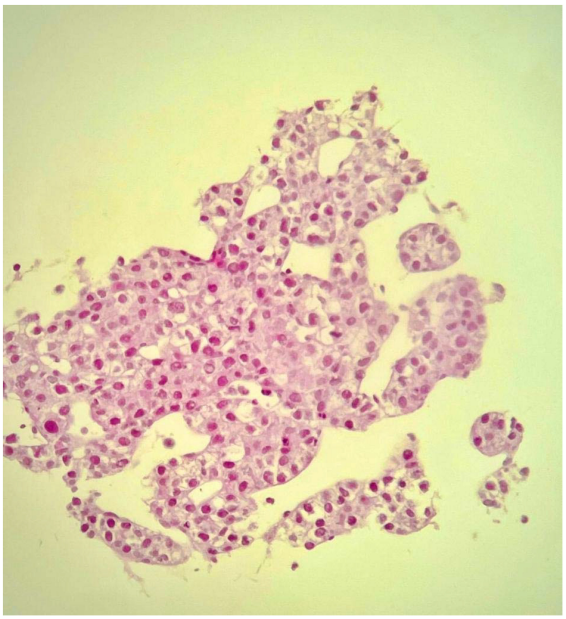

FIGURE 5
Core biopsy of the hepatic mass. H&E (x10): well-differentiated hepatocellular carcinoma.

treatment modalities, resulting in enhanced survival rates for cancer patients (6). An example of the progression in screening programs is the recent implementation of mammography, which is likely to result in an increase in the incidence of breast cancer (6). Screening programs have also pointed up new cases, particularly asymptomatic ones with low stages (10).

3.3 Etiology and risk factors

Risk factors of MPMNs involve host, lifestyle, environmental, and genetic factors: host factors include men (14), advanced age (5), black patients (14), and immune function; lifestyle include smoking, excessive alcohol use (14), obesity (15), physical inactivity, dietary patterns (16); environmental factors include previous cancer therapy, carcinogens, hormones, and infections; genetics factors represent family history, Caucasian ethnicity, and genetic mutations (10).

Patients over 50 years old account for more than 75% of MPMN cases due to prolonged carcinogenesis, immune attenuation, and increased cytokine production (17). Smokers are at increased risk for multiple primaries (10), especially stomach, liver, pancreas, kidney, uterine cervix, and myeloid leukemia (16), while excess alcohol use is related to cancers of the oral cavity, esophagus, colorectal, liver, and breast (16). Obesity is linked to an increased risk of endometrial and colon cancers (10). On the other hand, physical inactivity increases the risk of colon, breast, and endometrial cancers (16).

Prior cancer therapies, including chemotherapy and radiotherapy, contribute to multiple tissue injuries (18) and increase the risk of leukemia and lymphoma within the first 5 years and solid tumors after 5 years (19). Moreover, breast cancer hormonal therapy, like tamoxifen, increases the risk of endometrial cancer (20).

Immunodeficiency syndromes, either acquired or inherited, have a role in MPMNs (21). Human papillomavirus (HPV) infections represent the main cause of uterine cervical cancer as well as affect the anogenital tract, including the vulva, vagina, perineum, anus, and penis. In addition, oropharyngeal malignancies have been linked to HPV-16 (22). Patients with the human immunodeficiency virus (HIV) are more likely to develop cervical and anal cancer, non-Hodgkin lymphoma, and Kaposi sarcoma. In Palestine, the prevalence of HPV and HIV is considered low, so routine screening for these infections is not typically conducted.

Multiple primary tumors sometimes present as familial cancer syndromes that account for 1% to 2% of all cancers. They include multiple endocrine neoplasia types 1 and 2, von Hippel–Lindau disease, hereditary breast and ovarian cancer syndrome, and others (5). The role of genetics in the development of cancer has revealed more than 100 mutant predisposing genes (23). Patients with familial cancer syndromes face a 3% risk of developing a second primary cancer each year after their initial cancer diagnosis (24).

Regarding childhood cancers, more than a quarter of survivors suffer from new cancers (25). Furthermore, the incidence of cancer

TABLE 1 Summary of the therapeutic modalities employed for our patient.

Treatment	Indication	Initiation time	Dosage	Duration
Surgical resection with negative margins	Nasal tip basosquamous cell carcinoma	1/2022	NA	NA
Radical nephrectomy	Clear renal cell carcinoma	7/2022	NA	NA
Bicalutamide followed by goserelin, abiraterone, and prednisolone	Prostatic adenocarcinoma	8/2022	**Bicalutamide:** 50 mg once daily for two weeks PO, followed by: **Goserelin:** 3.5 mg once monthly **Abiraterone:** 1000 mg daily, and **Prednisolone:** 5 mg twice daily	To be determined after re-evaluation.
Atezolizumab and bevacizumab	Hepatocellular carcinoma	The patient neglected his hepatic malignancy treatment	NA	NA

NA, Non Available.

patients who are between 60 and 69 years old developing a second cancer is 13% (11). Studies have shown that renal cell carcinoma and lymphoma are recently occurring more frequently as second primaries compared to their occurrence as first primaries (26).

Another important risk factor is ethnicity. For example, Japan has a high incidence of stomach cancer but a low incidence of prostate cancer (27). Additionally, patients of Caucasian origin have higher frequencies of multiple primaries in contrast to other ethnicities (10).

In the present case, the patient's age and gender may be potential risk factors. His family history is significant for breast and endometrial cancer in his sister, but there is no evidence suggestive of a hereditary cancer syndrome; he also has no history of chemotherapy or radiation exposure; and he does not smoke or drink alcohol. Regarding genetic testing results, BRCA gene testing and Oncomine Pan-Cancer Cell-Free Assay results were negative. Oncomine Focus Assay, however, targets a panel of 52 genes. A comprehensive genetic sequencing could inspect other mutations that are not targeted by the oncomine assay.

3.4 Diagnosis

Knowing that malignancy survivors are at increased risk for subsequent tumors (8, 10), a comprehensive clinical assessment, including sophisticated imaging studies such as PET-CT scan and whole-body MRIs, should be executed for proper tumor staging and detection of other possible primaries. Furthermore, patients should be followed up regularly using guideline-based plans and recommended screening programs (2, 14, 23).

Alexia et al. have listed several clinical features indicating the possibility of a second primary tumor: atypical metastatic pattern of a primary tumor; disproportionate tumor burden and tumor marker load; markedly late onset for metastasis; and a single new metastatic lesion, among other features (14).

Pathological confirmation and independent staging and evaluation for each tumor should be pursued if MPMN patients are considered for active treatment. The primary tissue should always be available for comparison, especially in cases of undifferentiated tumor histology. In addition, clinicians should collect more than one specimen from a patient with multiple metastatic sites (2, 14).

When clinicians suspect a hereditary cancer phenomenon (e.g., several family members with MPMNs or certain cancers affecting young family members for several generations) (5), genetic testing can be informative. Currently, gene panels can assess most tumor-predisposing mutated genes (23), which can guide patient management (i.e., novel targeted agents and checkpoint inhibitors) (14), in addition to a follow-up plan and the need for further testing for patients' relatives (14, 23). Cezary et al. discussed the indications, advantages, and limitations of genetic testing for MPMN patients (23).

3.5 Treatment

Therapeutic options for patients with multiple primaries are rarely discussed, besides the exclusion of these cases from most clinical trials involving novel treatments. Furthermore, available drug–drug interaction data for cytotoxic, biologic, and immunotherapy cancer treatments are neither reliable nor efficient.

To ensure an appropriate treatment plan, a MDT should discuss an individualized therapeutic strategy for each patient depending on the pathological type, the stage of each tumor, and the patient's physical condition, besides plan adaptation as needed. The patient should be aware of treatment challenges, predicted prognosis, and possible signs and symptoms for recurrent or second primary tumors (5, 14). It is recommended to treat MPMN patients with an aggressive strategy due to potential long-term survival, except for elderly and asymptomatic patients with more than three primaries (14).

For localized tumors, surgery, radiation, or chemoradiation may be suitable for two primaries. However, for more advanced tumors, or in the case of more than two primaries, the challenge is to find a therapeutic strategy, mostly systemic therapies, that covers all cancer types without increasing toxicity, possible pharmacological interactions, or worsening the prognosis. Alexia et al. have discussed points to take into consideration while treating synchronous versus metachronous multiple primaries (14).

As a general rule, the tumor with the greatest contribution to the patient's survival or quality of life should be prioritized in the treatment. Surgical resection, accompanied by adjuvant therapy for fitting tumors, should be a priority. In cases where single chemotherapy is not appropriate for all MPMNs, the chemotherapy controlling later-stage malignancy is prioritized (2).

Regarding the treatment plan implemented for our patient, his nasal tip basosquamous cell carcinoma was managed by surgical resection with negative margins, obviating the necessity for adjunctive therapy. Six months later, the patient underwent a right radical nephrectomy for an incidentally discovered renal mass in the right renal cortex, with histopathology of clear cell renal cell carcinoma. Given the tumor's staging, adjuvant therapy was deemed unnecessary. For the synchronous prostate adenocarcinoma of stage IV with bone metastasis, following nephrectomy, he was initiated on a therapeutic regimen consisting of bicalutamide hormone therapy for 2 weeks, followed by goserelin and abiraterone hormone therapies with prednisolone. In consideration of his synchronous hepatocellular carcinoma, the discovered masses were infiltrative and unresectable; therefore, MDT decided to treat the patient with atezolizumab immunotherapy and bevacizumab antiangiogenic drug, scheduled 6 weeks postnephrectomy, but the patient lost follow-up for his hepatic malignancy treatment plan. At the 1-year follow-up assessment, there was no evidence of recurrence of the nasal skin lesion or renal carcinoma. PET imaging also reported stable hepatic masses and evidence of metastatic lesions involving the L1 spinous process and pelvic bones. Remarkably, the PSA levels demonstrated a substantial reduction from 70.6 to 8 ng/ml.3.6.

3.6 Prognosis

Survival of patients with multiple primary neoplasms varies and is influenced by cancer origin, tumor stage, onset, and site of consecutive primaries (10) (i.e., hepatocellular cancer being a synchronous primary tumor carries the worst prognosis (25)).

Other factors influencing the outcome include genetics, the patient's lifestyle, and comorbidities (10).

Amer has stated that patients with multiple primaries have a much higher survival rate compared with single tumor patients, with the life expectancy for patients with three or more primaries being similar to that of age- and sex-matched normal population (10). Moreover, the longer the time between the first and second primaries, the better the outcome. Correspondingly, metachronous primaries have a better prognosis in comparison with synchronous primaries (10). On the other hand, Min Yi et al. have concluded from their study on breast cancer patients with MPMNs that MPMNs have a worse prognosis compared with a single primary tumor (15).

In addition to proper investigations and follow-up of the primary tumor and potential treatment adverse effects, cancer survivors should be guided with cancer prevention and early detection recommendations, including smoking cessation, a healthy diet, and physical activity (5).

4 Conclusion

Multiple primary malignant neoplasms are no longer a rare entity, yet the topic lacks proper explanations and guidelines. There is wide variability regarding incidence and different methods in describing definitions. Furthermore, the data in the literature has discussed possible varying theories considering etiologies and significant risk factors. Eventually, diagnostic approaches consistent with single primaries in MPMN patients may lead to a delay in the detection of further malignancies and miss possible underlying genetic predisposition.

Therefore, a standardized reporting protocol is needed to detect the precise representing definition and incidence. In addition, patients with MPMNs require cancer screening programs since they are a high-risk population. Moreover, guidelines for treatment techniques that include therapeutic prioritizations, possible drug interactions, long-term adverse effects, and predicted outcomes are necessary. Lastly, reports in the literature addressing individualized cases and their workup approaches with reported outcomes could be carefully applied to similar situations with the intention of providing practitioners with valid guidelines.

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

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

RSa: Writing – original draft, Writing – review & editing. ZG: Writing – original draft, Writing – review & editing. WB: Project administration, Supervision, Writing – review & editing. RS-A: Project administration, Supervision, Writing – review & editing. HH: Project administration, Supervision, Writing – review & editing. RSw: Supervision, Writing – review & editing. IB: Supervision, Writing – review & editing.

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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

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Case Report: A report on the countermeasures after PICC line breakage in 3 postoperative breast cancer patients

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Peripherally inserted central catheter (PICC) is a widely used technique in oncology chemotherapy, characterized by safety, reliability, and long dwell time. However, a catheter can break due to various causes. When an acute rupture occurs, it always lead to sever complications which may threaten patients' safety and potentially result in medical disputes. In this study, we collected and analyzed 3 cases of PICC line breakage causing drug leakage in our hospital from 2018 to 2023. All these 3 cases were postoperative breast cancer patients accepting chemotherapy, with 2 cases involving external partial breakage and 1 case involving internal partial breakage. Due to timely and appropriate management, no acute rupture occurred. We propose some ideas such as selecting high-quality catheter materials and avoiding over extension or repeated bending are crucial in preventing PICC line breakage. In addition, we also recommend establishing a standardized and scientific management pattern of PICC to ensure the safety and effectiveness of its clinical application, including comprehensive assessment, "four-element" intervention, and continuous evaluation.

KEYWORDS

breast cancer, peripherally inserted central catheter, breakage, countermeasures, case report

Introduction

Chemotherapy is the main and commonly used treatment for breast cancer, and intravenous infusion is its main method of administration (1). Traditional intravenous infusion requires repeatedly inserting the infusion needle into the vein. However, chemotherapy drugs are highly irritating with severe toxic side effects, and the chemotherapy cycles for malignant tumors such as breast cancer are long. Traditional intravenous infusion not only increases the patients' suffering but also adds to the workload of nursing staff (2). Peripherally inserted central catheter (PICC) not only reduces the pain caused by repeatedly inserting but also effectively avoids vascular damage caused by long-term infusion of irritating drugs. Its application in clinical settings, especially during chemotherapy for malignant tumor patients, is becoming increasingly widespread (3).

PICC refers to a catheterization technique that enters the central venous system through peripheral veins (such as the cephalic vein, median cubital vein, and basilic vein), with the catheter tip reaching the cavoatrial junction (4). After successful placement, maintenance is required once a week, involving procedures like dressing changes, flushing, etc., with a duration of approximately one year. PICC is characterized

by minimal trauma, ease of operation, long retention time, and avoidance of drug extravasation. It is widely used in fields such as parenteral nutrition, chemotherapy, and antibiotic therapy, providing a safe and reliable intravenous infusion channel for patients (5). However, with prolonged catheterization, various complications may occur, especially catheter rupture. The ruptured end of the catheter may drift with the blood flow to the heart or pulmonary artery, causing serious complications such as pulmonary embolism and arrhythmias, potentially endangering life (6). Literature reports a rupture rate of PICC catheters ranging from 0.67% to 3.5% (4). Since the introduction of PICC technology in our hospital in 2018, 252 cases have been successfully catheterized, with 3 cases of catheter breakage occurring (a rate of 1.19%). Among them, there was 1 case of external partial breakage and 2 cases of internal partial breakage, none of which led to severe acute complete rupture. Due to timely detection and appropriate management, no harm was caused to the patients. The following describes the process and nursing experiences in response to these incidents.

Case presentation

A review of 3 cases of PICC line breakage in the breast surgery ward of Jinan Maternal and Child Health Hospital from 2018 to 2023 was conducted. Patients' age, PICC batch number, catheter insertion site, puncture times, dwelling length, exposed length, damage location, PICC tip positioning, maintenance times, cause of breakage, treatment measures, and prognosis were summarized and analyzed. All 3 patients had successful and uneventful first-time insertions, with no adverse reactions during the indwelling period. Case 1 and case 2 had catheters placed in the left upper limb (PICC batch numbers REGN0292), maintained for 19 and 7 times respectively. After 125 and 50 days of indwelling respectively, intracorporeal partial breakages occurred (dwelling lengths were 40 cm and 44.5 cm, PICC tip positions at T6 and T7, damage locations at 39.8 cm and 44.2 cm). Case 3 had a catheter placed in the right upper limb (PICC batch number REFT2318), maintained for 19 times. After 132 days of indwelling, extracorporeal partial breakage occurred (catheter dwelling length 39 cm, PICC position at T7, damage location at 39.5 cm) (Table 1).

Case 1

The patient was admitted on October 16th, 2023 for the 6th cycle of chemotherapy following breast cancer surgery. Observation revealed no change in the dwelling length of the catheter or arm circumference, no redness or swelling in the surrounding skin, no leakage or tenderness at the insertion site, no abnormalities in the dressing, and the catheter was functioning well.

On October 17th, the PICC line was flushed before chemotherapy, and the process was normal. About 20 min after the chemotherapy drug was administered, approximately 0.2 ml of milky white fluid was found to be leaking from the PICC insertion site. There was no pain or redness in the surrounding skin. Suspecting damage to the catheter at some point, the nurse clamped the fluid infusion immediately, used sterile gauze to absorb leaked liquid and cleaned the surrounding skin with saline solution. Afterwards, it was discovered the fluid is leaking from the inside of puncture site after multiple flushes (the insertion point scale at 40 cm). To further investigate the cause, the catheter was pulled out by 1 cm. During the subsequent flushing, water beads were found at 39.8 cm, indicating damage to the catheter at that point leading to fluid leakage. After informing the patient of the risk of line breakage and treatment plan, the nurse withdrew the catheter to 34 cm and trimmed with 5 cm exposed.

A chest x-ray showed the tip of the PICC line reaching the upper edge of the 4th thoracic vertebra, deviating from its normal position. To ensure the patient's safety, the nurse removed the catheter after the completion of this chemotherapy cycle.

Case 2

The patient was admitted on October 23th, 2023 for the 3rd cycle of chemotherapy after breast cancer surgery. Observation revealed no change in the dwelling length of the catheter or arm circumference, no redness or swelling in the surrounding skin, no leakage or tenderness at the puncture site, no abnormalities in the dressing, and the catheter was functioning well.

We flushed the PICC line before chemotherapy on October 24th, and the process was normal. However, approximately 0.5 ml of clear fluid was found to be leaking from the PICC insertion site about 15 min after infusion with no pain or redness in the surrounding skin. Suspecting damage to the catheter at some point, immediate measures were taken to avoid the acute rupture, including clamping the fluid infusion, absorbing the leakage with sterile gauze and rinsing the surrounding skin with saline solution. After multiple flushes, we discovered the fluid was leaking from the needle eye (the insertion point scale at 44.5 cm).

TABLE 1 Information of 3 patients with PICC line breakage.

Patient number	Age (year)	Insertion site	Dwelling length (cm)	Exposed length (cm)	Tip position	Rupture position (cm)	Puncture times / Smoothly?	Batch number	Maintenance times
1	40	Left upper limb	40	7	T6	39.8	1/ Yes	REGN0292	19
2	42	Left upper limb	44.5	7	T7	44.2	1/ Yes	REGN0292	7
3	50	right upper limb	39	7	T7	39.5	1/ Yes	REFT2318	19

To further investigate the cause, we withdrew the catheter by 1 cm. Upon further flushing, it was observed that there was a water droplet formation at 44.2 cm, indicating a possible damage at that point causing the leakage. After informing the patient of the risk of line breakage and treatment plan, we withdrew the catheter to 39 cm and trimmed it with 5 cm exposed.

The chest x-ray result revealed the presence of the PICC line shadow, with its tip positioned at the upper edge of the 4th thoracic vertebra, deviating from the normal position. To ensure the patient's safety, we removed the catheter after the completion of this chemotherapy cycle.

Case 3

The patient was admitted on October 23th, 2023 for the 6rd cycle of chemotherapy after breast cancer surgery. Observation revealed no change in the dwelling length of the catheter or arm circumference, no redness or swelling in the surrounding skin, no leakage or tenderness at the puncture site, no abnormalities in the dressing, and the catheter was functioning well.

On October 24th, we flushed the catheter before chemotherapy, and the process was normal. About 20 min after the intravenous infusion of glutathione, approximately 0.5 ml of clear fluid was found to be seeping from the PICC insertion site without any pain or redness on the surrounding skin. Suspecting a break in the catheter, the fluid infusion was immediately clamped and sterile gauze was used to absorb the leaked fluid. After multiple flushes, we observed that there was water droplet-like leakage forming on the exterior part of the line (0.5 cm away from the insertion point), confirming a break at this point leading to fluid leakage. We informed the patient of the treatment plan and withdrew the line to 34 cm and trimmed it with 5 cm exposed.

A chest x-ray revealed the positioning of the PICC line, with its tip located above the right upper edge of the 4th thoracic vertebra, slightly deviating from the normal position. To ensure the patient's safety, the nurse removed the catheter after the completion of this chemotherapy cycle.

Discussion

In the 1990s, PICC technology was introduced in China. Due to its advantages such as small trauma, easy operation, long retention time, and avoiding drug extravasation, it is now widely used in clinical practice (7). For breast cancer patients, clinical treatment usually focuses on surgical treatment supplemented by chemotherapy to effectively control the systemic spread of malignant tumors and prevent postoperative recurrence and metastasis (8). Due to the often lengthy chemotherapy cycles and the strong acid or alkali characteristics of chemotherapy drugs, blood vessels are susceptible to drug damage, leading to problems such as peripheral venous inflammation and drug extravasation. Therefore, the higher safety factor of PICC is often used in clinical practice (9).

Considering that breast cancer patients may experience complications such as lymphedema in the affected limb postoperatively, the catheter is generally placed in the healthy limb to avoid such issues. However, this can potentially cause frequent bending or even breakage to the catheter due to patients' excessive reliance on the healthy limb for daily activities (10). In addition, rough handling during catheter maintenance, long-term exposure to medications and disinfectants, as well as the material of the catheter itself, are also factors that cannot be ignored in causing catheter damage (11).

Since the introduction of PICC technology in our hospital in 2018, 252 catheterizations have been successfully performed with 3 cases of catheter breakage occurring (an incidence rate of 1.19%). Among these cases, 2 involved internal partial breakage and 1 involved external partial breakage, with none being severe cases of acute complete rupture. Experience include: (1) Standardized training. Regular training and assessment can improve the puncture skills of PICC specialist nurses, ensuring that the first operation is smooth with a success rate of 100%. (2) Strict monitoring. Especially during chemotherapy infusion, nurses observe patients' condition closely and inquire about their complaints with regular checks every 15–30 min. (3) Promptly dispose. Nurses are able to identify signs of catheter breakage in a timely manner, such as leakage at the puncture site, catheter dislodgement, etc., and promptly deal with them according to the emergency procedures for PICC line rupture. For example, immediate ECG monitoring should be performed to detect early abnormal rhythm, and chest x-ray examination should also be conducted as soon as possible to better prevent complications related to internal rupture through chest x-ray images. However, in order to investigate the causes of the catheter breakage, a review and analysis were conducted by interviewing medical staffs, patients and their family members, as well as the manufacturer, respectively.

1. Catheter factors: The catheters used in the 3 cases are Bard three-way valve catheters made of silicone material. Silicone has poor toughness and is prone to damage and cracking. Relevant studies (12, 13) have shown that different chemotherapy solutions have no significant effect on the degradation of polyurethane and silicone materials. However, as the implantation time increases, the differences in mechanical properties between different materials become more pronounced. The mechanical properties of polyurethane materials do not show a significant decrease, while silicone materials exhibit an increase in mechanical test unevenness with the increase of implantation time. Currently, in many Western hospitals, silicone catheters have been completely abandoned and replaced with PICC catheters made of higher-grade materials such as polyurethane. Clinical use has shown that the new generation of polyurethane PICC catheters have better biocompatibility, higher tensile strength, become softer upon entering the body, and have stronger resistance to chemical drugs. Therefore, the only reasonable "strategy" to effectively reduce PICC catheter breakage is to avoid using silicone catheters. However, considering that in most developing countries including China, different

populations are constrained by economic conditions, and the influence of medical insurance policies, it is currently not possible to fully popularize the use of higher-grade material PICC catheters, especially in grassroots areas. Based on this, it is suggested that the government, under the current level of medical care and socio-economic development, should promptly achieve the update of PICC catheter materials and include more higher-grade PICC catheters within the scope of medical insurance policy support to reduce the burden on patients and increase clinical popularization and usage.

2. Patient factors: On one hand, patients receiving long-term chemotherapy may have vascular spasms caused by the strong irritative effects of the drugs, leading to damage to the PICC line (14). On the other hand, subjective non-compliance of patients can be influenced by objective conditions (15). The 3 patients in this report were all housewives with poor financial conditions and unable to afford the expenses of hiring a maid. High workload in daily household chores leaded to frequent and significant excessive movements of the limbs with indwelling catheters. Relevant literature (16) reports that excessive frequent bending of the limb on the punctured side causes repeated folding at the junction of the catheter and connector, resulting in wear of the silicone catheter's inner membrane, leading to catheter damage or breakage. This explains why these 3 catheter breakages all occurred near the insertion site.

Based on the above analysis, standardized and normalized scientific management model should be established for the management of PICC placement in postoperative breast cancer patients, including assessment, intervention, and evaluation as three continuous and complete processes. Firstly, comprehensive assessment. Healthcare professionals should comprehensively assess various indicators of PICC placement patients, fully anticipate the limitations in various factors of environmental, social psychological, physiological, and health-related behavior domains (17). Before carrying out interventions for specific patients, focus should be placed on potential issues the patients may have, timely supplementing other disease-related issues, emphasizing personalized education and guidance work, and strengthening self-management compliance and enthusiasm. Secondly, the "Four-element" intervention. Considering the insufficient professional nursing resources for post-discharge care of breast cancer postoperative patients with PICC, exploration should be made into establishing a multidisciplinary collaborative team led by a nursing referral specialist, utilizing "Internet + nursing" services (18), constructing systemic, universal, and operational discharge plan projects, transitioning from nursing within the hospital to long-term continued care for patients post-discharge (19). A PICC management record should be established during the patient's hospitalization, and it should be referred to the community (or other medical institutions) through a nursing referral specialist before discharge; after discharge, with the help of the "PICC maintenance network", continuous assessment and educational guidance of patient and family self-management abilities should be provided by the nursing referral specialist, as well as coordination with community or other medical institution medical staffs, ensuring continuous information, management, and care-patient relationship for post-discharge care (20). By implementing the "four-element linkage" continuity care management model of "hospital-community-family-patient", the management of PICC for postoperative breast cancer patients can be effectively improved. Finally, continuous evaluation. To ensure the safety and effectiveness of PICC, an continuous evaluation plan should be implemented for patients and their family caregivers, including aspects such as skin assessment, catheter position evaluation, catheter function assessment, medication administration evaluation, catheter infection assessment, patient self-assessment, etc (21). Based on the evaluation results, continuous improvement should be made to comprehensively address the complex needs of patients after discharge, reduce the incidence of catheter breakage or rupture, and further enhance the clinical application effectiveness of PICC technique.

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

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

YJ: Conceptualization, Investigation, Project administration, Writing – original draft. JQ: Data curation, Formal Analysis, Writing – original draft. SJ: Formal Analysis, Investigation, Writing – original draft. XW: Supervision, Validation, Writing – original draft, Writing – review & editing.

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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.

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Development and validation of a digital biopsy model to predict microvascular invasion in hepatocellular carcinoma

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Background: Microvascular invasion is a major histopathological risk factor of postoperative recurrence in patients with hepatocellular carcinoma. This study aimed to develop and validate a digital biopsy model using imaging features to predict microvascular invasion before hepatectomy.

Methods: A total of 217 consecutive patients who underwent hepatectomy for resectable hepatocellular carcinoma were enrolled at two tertiary-care reference centers. An imaging-based digital biopsy model was developed and internally validated using logistic regression analysis with adjustments for age, sex, etiology of disease, size and number of lesions.

Results: Three imaging features, i.e., non-smoothness of lesion margin (OR = 16.40), ill-defined pseudocapsula (OR = 4.93), and persistence of intratumoral internal artery (OR = 10.50), were independently associated with microvascular invasion and incorporated into a prediction model. A scoring system with 0 - 3 points was established for the prediction model. Internal validation confirmed an excellent calibration of the model. A cutoff of 2 points indicates a high risk of microvascular invasion (area under the curve 0.87). The overall survival and recurrence-free survival stratified by the risk model was significantly shorter in patients with high risk features of microvascular invasion compared to those

patients with low risk of microvascular invasion (overall survival: median 35 vs. 75 months, P = 0.027; recurrence-free survival: median 17 vs. 38 months, P < 0.001)).

Conclusion: A preoperative assessment of microvascular invasion by digital biopsy is reliable, easily applicable, and might facilitate personalized treatment strategies.

KEYWORDS

biomarker, radiology, resection, perioperative oncology, hepatectomy

Introduction

Hepatocellular carcinoma (HCC) is a major global health challenge with a rising incidence worldwide (1). HCC development is closely related to chronic liver disease with viral hepatitis, alcoholic and non-alcoholic steatohepatitis as leading etiologies (1). Due to the reliance on tumor burden and the functional hepatic reserve for determining patient treatment and outcomes, managing HCC proves exceptionally challenging (2). The complexity of this heterogenous disease and its treatment is reflected in markedly variable outcomes following potentially curative therapy such as surgical resection, liver transplantation, or local ablation (3). Patients undergoing these treatments typically exhibit a 5-year survival rate of approximately 62-70% (4, 5). Moreover, HCC recurrence in patients after potentially curative treatment remains a major burden with rates up to 70% within 5 years after treatment (6). Microvascular invasion (MVI), characterized by the microscopic presence of tumor cells in hepatic vessels (arteries, hepatic vein, and portal vein) lined with endothelial cells, stands as the most crucial determinant of disease recurrence and long-term survival (7). Unfortunately, MVI can only be histopathologically diagnosed based on the resected surgical specimen and therefore its use to guide personalized treatment strategies remains limited. Recently, the prediction of MVI before surgery has gained increasing attention, with several promising noninvasive methods utilizing imaging features or tumor markers embedded into risk models (8–12). However, current evidence is primarily characterized by complex risk models involving multimodal biomarkers, or restriction of imaging modalities to either magnetic resonance imaging (MRI) or computed tomography (CT) (13, 14). Furthermore, the vast majority of risk models were developed in selective subsets of HCC patients (i.e., predominantly viral hepatitis) with significant imbalances of the number of predictor variables and high MVI rates in the cohorts hampering its transferability to the clinical routine (12, 15, 16).

In this study, we aimed to develop a noninvasive digital biopsy risk model to predict MVI using preoperative imaging features and assess its prognostic outcome in patients undergoing hepatectomy for HCC.

Methods

Study population

This retrospective cohort study was approved by the institutional review board (2023–831) and conducted in line with the Declaration of Helsinki and the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines (17). All consecutive patients who underwent hepatectomy for HCC between April 2008 and June 2023 at the Department of Surgery, University Hospital Mannheim and Department of Gastrointestinal, Thoracic and Vascular Surgery, University Hospital Carl Gustav Carus at the Technische Universität Dresden were identified from prospectively recorded databases and screened for eligibility. Informed consent was obtained from each patient to store data on prospective databases. The following inclusion criteria were used: a) adult patients (age 18 years or older) who underwent hepatectomy in curative-intent for resectable HCC; b) histopathologically documented status of MVI; c) preoperative imaging including computed tomography (CT) and/or magnetic resonance imaging (MRI) within 3 months of surgery. We excluded patients who had an inadequate quality of imaging for the evaluation of imaging features associated with MVI, and patients with mixed-type HCC-cholangiocarcinoma.

Definitions and data acquisition

Patient records were reviewed for clinical variables such as age, gender, underlying liver disease, presence of liver cirrhosis, Child-Pugh classification, preoperative treatment, preoperative laboratory values such as alanine-aminotransferase, aspartate-aminotransferase, albumin, bilirubin, platelet count, and

international normalized ratio. Pathological data included the number of resected lesions (classified as single, oligonodular (2-3 lesions) or multinodular (> 3 lesions)) (18), the diameter of lesions, resection margin, and the presence of microvascular invasion. Operative details, including the type and extent of hepatectomy, were also extracted. The Brisbane classification was used to categorize liver resections (19). Major hepatectomy was defined as resections of four or more Couinaud segments. HCC lesions were considered for resection irrespective of lesion size if patients had resectable lesions (single or multifocal) with an adequate future liver remnant, liver function, and performance status as well as the absence of distant metastasis or portal vein thrombosis. Postoperative surveillance included routine abdominal multiphasic computed tomography or magnetic resonance imaging and chest radiography every three months. Dates of last follow-up, recurrence, and death were recorded to calculate overall- and recurrence-free survival from the time of hepatectomy. Recurrence-free survival was defined as the time from hepatectomy to the first documented disease recurrence (radiologic or histologic evidence of local, regional, or distant metastasis) or death by any cause.

Imaging analysis

Preoperative CT and MRI images were independently evaluated by two radiologists at each center who were blinded to clinical, surgical, pathologic, and follow-up results. At each center, discordance between two radiologists was solved by a third senior radiologist until consensus was generated. The presence of the following radiologic markers was assessed for its potential association with MVI as previously described in the literature (8, 10, 16, 20, 21): 1. extrahepatic growth pattern, i.e., exophytic lesions; 2. intratumoral hemorrhage; 3. intratumoral necrosis; 4. intratumoral vascularity, i.e. hyper-arterial enhancement in the arterial phase within the tumor; 5. internal artery, i.e. persistence of intratumoral arterial enhancements in the portal phase; 6. ill-defined incomplete pseudocapsula, i.e., irregular peritumoral hyperenhancement on portal phase of a radiological tumor capsule; 7. nonsmooth margin, i.e., nodular lesions with extranodular growth, confluent multinodular lesions or focal infiltrative margins; 8. peritumoral halo, i.e., peritumoral hypodense or hypointense halo in the portal phase; 9. rim enhancement, i.e., irregular circumferential peritumoral enhancement in the arterial phase; 10. wedge-shaped lesion, i.e. peritumoral hypodense or hypointense lesion located outside of the tumor margin in the delayed or hepatobiliary phase.

Reference standard

Microvascular invasion was defined as nests of tumor cells lining vascular cavities of endothelial cells or portal and hepatic systems on hematoxylin and eosin staining (22). To determine the histopathological MVI status, all specimens were analyzed by two independent pathologists blinded to the clinical outcomes at each center.

Statistics

Data between the study groups were evaluated using the Fisher's exact test for categorical data and t- or Mann-Whitney-U tests for continuous data. In the training cohort, a logistic regression analysis with adjustments for age, sex, underlying liver disease, size, and number of lesions was conducted to identify significant predictors of preoperative imaging features to predict MVI. Significant variables ($P < 0.05$) on univariate analysis were applied to a multivariate analysis while controlling for age, sex, underlying liver disease, size, and number of lesions to develop the digital biopsy prediction model. A scoring system was derived from the β regression coefficient values divided by 2 to the nearest integer and an optimal threshold for patients at high risk of MVI was determined by the Youden's index. Two risk categories were defined (low versus high risk) and internally validated by 1,000 bootstrap samples (23). The model performance, predictive strength, and model accuracy were evaluated by the area under the curve (AUC), the Nagelkerke's R^2 (a value of 1 indicates perfect fit), and the Brier scores (a value of 0 indicates total accuracy) (23). The calibration performance of the model was visualized by a calibration plot. The Kaplan-Meier method was used to calculate survival outcomes (log-rank test). To estimate the sample size for adequate modeling (24), the presence of MVI in the training cohort was anticipated to be 15% (25) and the number of candidate predictors to be included in the multivariate model was restricted to three variables. Assuming an estimated input C-statistic of 0.95, a shrinkage factor of 0.9, and an optimism of 0.05 in the apparent R^2, a minimum sample size of 196 patients were calculated. A two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed using R version 4.1.2.

Results

A total of 217 patients underwent hepatectomy for hepatocellular carcinoma at both institutions during the study period (Figure 1). Of these, 37 patients (17%) had a histopathological positive MVI. The baseline characteristics of patients with and without MVI are detailed in Table 1. In the MVI-positive group, more patients showed lesions exceeding 5 cm (68% vs. 43%, P = 0.030) and required major hepatectomies (46% vs. 17%, P = 0.030) as compared to patients in the MVI-negative group. Other characteristics were well-balanced between the groups.

Analysis of imaging risk factors for MVI

To develop a digital biopsy prediction model, we initially performed a logistic regression analysis (with adjustments for age, sex, etiology of disease, size, and number of lesions) on 10 potential

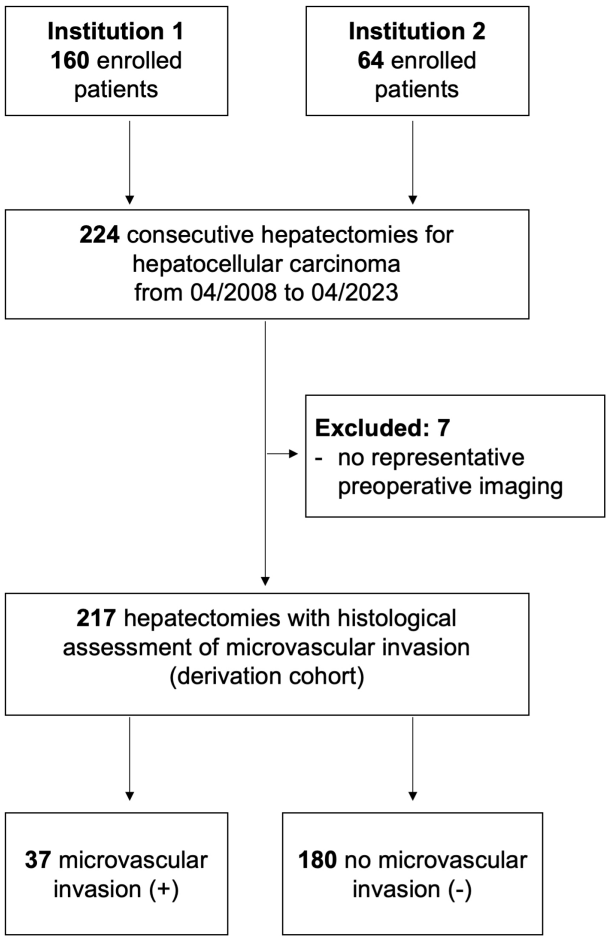

FIGURE 1
Patient flow chart.

predictive variables, which were previously shown to be associated with MVI (Table 2) (8, 10, 16, 20, 21). We identified three distinct imaging features, on univariate analyses to be associated with MVI i.e., 1) internal artery (OR 29.90, P < 0.001), 2) irregular pseudocapsula (OR 4.42, P < 0.001), and 3) non-smooth peritumoral margin (OR 12.40, P < 0.001). Multivariate analysis confirmed all three features as strong independent predictors of MVI. A non-smooth peritumoral margin predisposed a 16-fold increase, while an internal artery or an irregular pseudocapsula was associated with a 10-fold and 5-fold increase of the likelihood for the histopathological diagnosis of MVI, respectively. Figure 2 illustrates these distinct imaging features to predict MVI.

Digital biopsy model

In the next step, we assigned scores proportional to the β regression coefficient with a single point for each risk factor. The digital biopsy model resulted in a discrimination ability of an AUC of 0.91 (95%CI 0.85 – 0.96) to predict MVI (Figure 3A). Of 37 patients with histopathologically confirmed MVI, 36 (98%) had at least one point on the model. The overall MVI positivity rate was 2%, 4%, 47%, and 88% in patients with 0, 1, 2, and 3 points, respectively. Internal validation of the digital biopsy model using 1,000 bootstrap samples confirmed a high discrimination ability with a corrected AUC of 0.90. Supplementary Figure S1A displays the calibration plot with an excellent calibration between predicted and observed MVI frequencies. Further model metrics revealed high prediction value (Brier-Score of 0.08) and relationship between the predictors and MVI (Nagelkerke R^2 of 0.56).

TABLE 1 Baseline characteristics of microvascular invasion positive and negative patients.

	MVI positive N = 37	MVI negative N = 180	P
Age (years) †	69 (64 – 76)	70 (63 – 78)	0.829
Sex ratio (Male: Female)	26:11	150:30	0.104
Etiology of liver disease			0.744
Alcoholic liver disease	12 (32)	60 (33)	
Metabolic liver disease	20 (54)	103 (58)	
Viral hepatitis	5 (14)	17 (9)	
Liver cirrhosis	25 (68)	98 (54)	0.151
Child-Pugh classification			0.491
Child A	23 (62)	89 (49)	
Child B	2 (5)	9 (5)	
Preoperative laboratory values			
ALT, U/l	56 (65)	45 (39)	0.333
AST, U/l	74 (125)	43 (28)	0.079
Albumin, g/l	37 (6)	35 (5)	0.511
Bilirubin, mg/dl	0.8 (0.5)	0.7 (0.4)	0.319
Platelet count, x 10^9/l	211 (99)	220 (105)	0.703
INR	1.1 (0.1)	1.1 (0.1)	0.114
No. of lesions			0.394
single	29 (79)	155 (86)	
oligonodular	6 (16)	15 (8)	
multinodular	2 (5)	10 (6)	
Lesion size, mm			0.030
30	5 (14)	40 (22)	
30 - 50	7 (19)	63 (35)	
50	25 (68)	77 (43)	
Type of hepatectomy			0.123
Non-anatomic resection	2 (5)	30 (17)	
Anatomic resection	35 (95)	150 (83)	
Extent of resection			0.007
Minor hepatectomy	17 (46)	127 (71)	
Major hepatectomy	20 (54)	53 (29)	

MVI microvascular invasion, ALT alanine aminotransferase, AST aspartate aminotransferase, INR international normalized ratio, mm millimeter.
† Values are median (interquartile range).

TABLE 2 Univariate und multivariate analysis of radiological factors associated with microvascular invasion.

	Univariate		Multivariate		
	OR (95%CI)	P	OR (95%CI)	β	P
Growth pattern					
Intrahepatic (Ref.)	1				
Extrahepatic	0.40 (0.10 – 1.59)	0.194	–		
Intratumoral necrosis					
Absent (Ref.)	1				
Present	2.39 (0.88 – 7.00)	0.083	–		
Intratumoral hemorrhage					
Absent (Ref.)	1				
Present	1.31 (0.59 – 2.91)	0.501	–		
Intratumoral vascularity					
Mild (Ref.)	1				
Hypervascularity	2.91 (0.99 – 8.54)	0.051	–		
Internal artery					
Absent (Ref.)	1				
Present	29.90 (10.20 – 87.90)	<0.001	10.50 (3.37 – 32.50)	2.35	<0.001
Pseudocapsula					
Well-defined (Ref.)	1				
Irregular	4.42 (1.91 – 10.20)	<0.001	4.93 (1.59 – 15.30)	1.60	<0.001
Margin smoothness					
Smooth (Ref.)	1				
Non-smooth	12.40 (4.75 – 32.10)	<0.001	16.40 (4.39 – 61.50)	2.80	<0.001
Peritumoral halo					
Absent (Ref.)	1				
Present	1.81 (0.84 – 3.90)	0.133	–		
Rim enhancement					
Absent (Ref.)	1				
Present	1.46 (0.69 – 3.08)	0.320	–		
Wedge-shape lesion					
Absent (Ref.)	1				
Present	1.70 (0.79 – 3.67)	0.175	–		

No. number, Ref. reference.
Adjustments were made for age, sex, etiology of liver disease, size and number of lesions.

Stratification between high and low risk MVI

To enhance the clinical utility of the digital biopsy model, we applied a threshold analysis to discriminate between high risk and low risk MVI patients. A threshold of 2 points was determined to predict a high risk for MVI with a sensitivity of 87% and specificity of 88%. Of 53 patients with 2 points on the digital biopsy risk model, 32 (60%) had confirmed MVI on histopathological analysis, compared to 5 (10%) out of 164 patients with < 2 points (Table 3). The discrimination analysis of this digital biopsy risk model yielded an AUC of 0.87 (95%CI 0.85 – 0.96) (Figure 3B). Bootstrap validation of the risk model resulted in a corrected AUC of 0.87, a Brier-Score of 0.08, and a Nagelkerke R^2 of 0.52. The calibration plot of the risk model is shown in Supplementary Figure S1B.

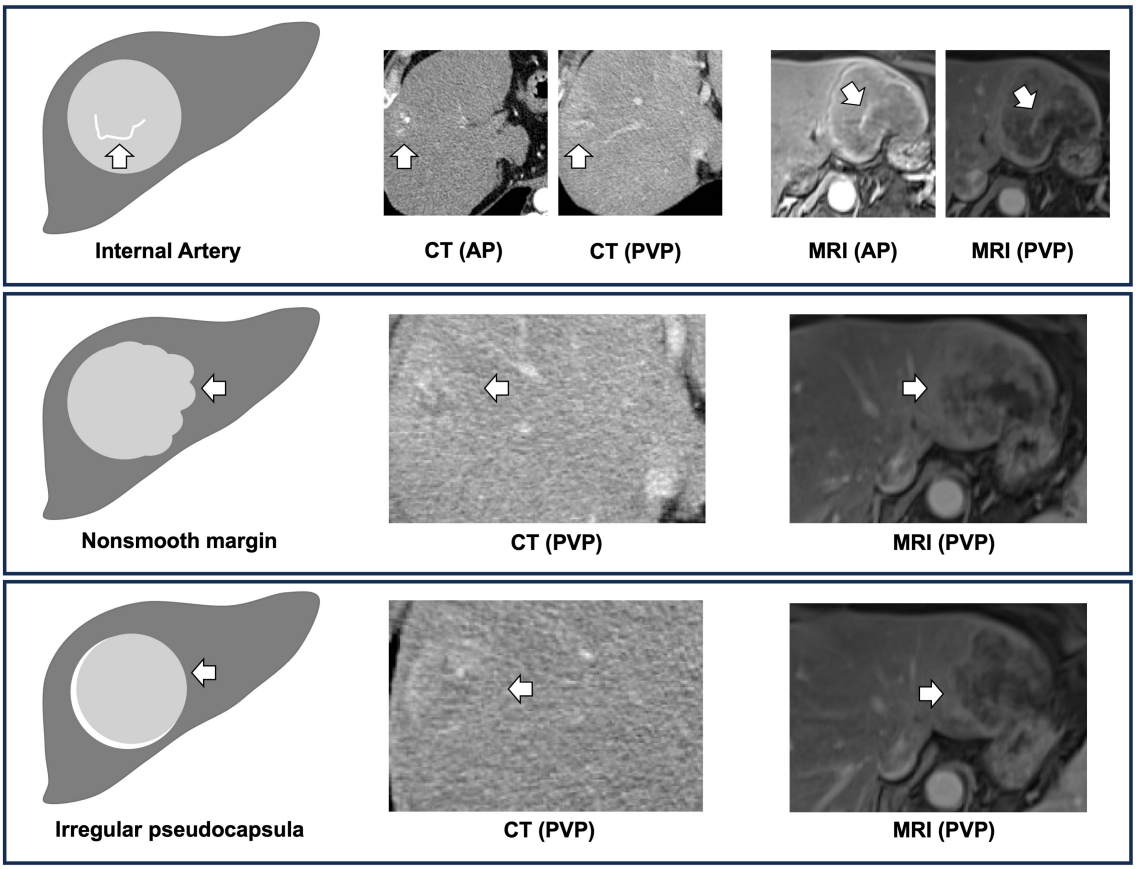

FIGURE 2
Digital biopsy features of microvascular invasion. The digital biopsy features (i.e. internal artery, nonsmooth margin, irregular pseudocapsula) are illustrated with white arrows (CT, computed tomography; MRI, magnetic resonance imaging; AP, arterial phase; PVP, portal venous phase).

Survival outcome

The median follow-up was 20 months (interquartile range: 4 - 40). Patients with histopathological confirmed MVI had a shorter recurrence-free survival (16 months, 95%CI: 7 - 23, vs. 34 months 95%CI: 26 - 52; P < 0.001), while there were no significant differences in overall survival compared to patients without MVI (35 months, 95%CI: 8 - NA, vs. 72 months 95%CI: 60 - NA, P <

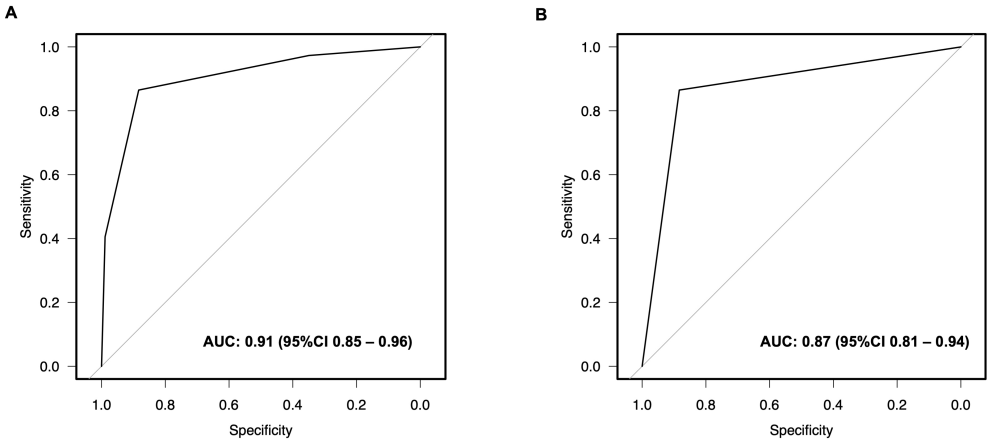

FIGURE 3
Receiver Operating Characteristics (ROC) curves of the digital biopsy microvascular invasion predictive system. The digital biopsy model with 0- to 3 points (yielded an area under the curve (AUC) of 0.91 (95% CI 0.93 - 0.99) **(A)**. An AUC of 0.87 (95% CI 0.81 - 0.94) was calculated for the digital biopsy risk model with high vs. low risk of microvascular invasion **(B)**.

TABLE 3 Risk classification system of digital biopsy proved microvascular invasion.

Risk classification	Total Points	Patients N = 217	MVI + N = 37	MVI rate % (95% CI)
Low	0	64 (29)	1 (3)	2 (1 – 8)
	1	100 (46)	4 (11)	4 (1 – 10)
High	2	36 (17)	17 (46)	47 (30 – 65)
	3	17 (8)	15 (41)	88 (64 – 99)

MVI + microvascular invasion positivity.

0.102) (Figures 4A, B). Notably, patients with high risk of MVI according to our digital biopsy risk model had both a significantly shorter overall survival and recurrence-free survival as opposed to patients with low risk of MVI (overall survival: 35 months, 95%CI: 20 - NA, vs. 75 months 95%CI: 60 - NA, P < 0.027; recurrence-free survival: 17 months, 95%CI: 7 - 21, vs. 38 months 95%CI: 30 - 55; P < 0.001) (Figures 4C, D).

Discussion

In the present dual-center study, we developed a straightforward scoring system to predict MVI in patients with HCC using distinct preoperative radiologic features. Our digital biopsy model included the presence of a non-smooth peritumoral margin, intratumoral arterial enhancement, and irregular peritumoral hyperenhancement. The presence of at least two out of three radiologic features was associated with high sensitivity (87%) and specificity (88%) for predicting MVI before hepatectomy. Moreover, the survival outcomes stratified by our digital biopsy risk model achieved a significant difference of overall and recurrence-free survival in patients with predicted high risk versus low risk of MVI.

MVI is defined as the microscopic presence of cancer cells in hepatic vessels, indicating aggressive tumor biology (7). On preoperative imaging, a non-smooth peritumoral margin implies an upfront sign of tumor aggressiveness characterized by tumor protrusion into peritumoral areas (26). A meta-analysis on the predictive value of a nonsmooth peritumoral margin revealed that a non-smooth peritumoral margin is associated with a diagnostic

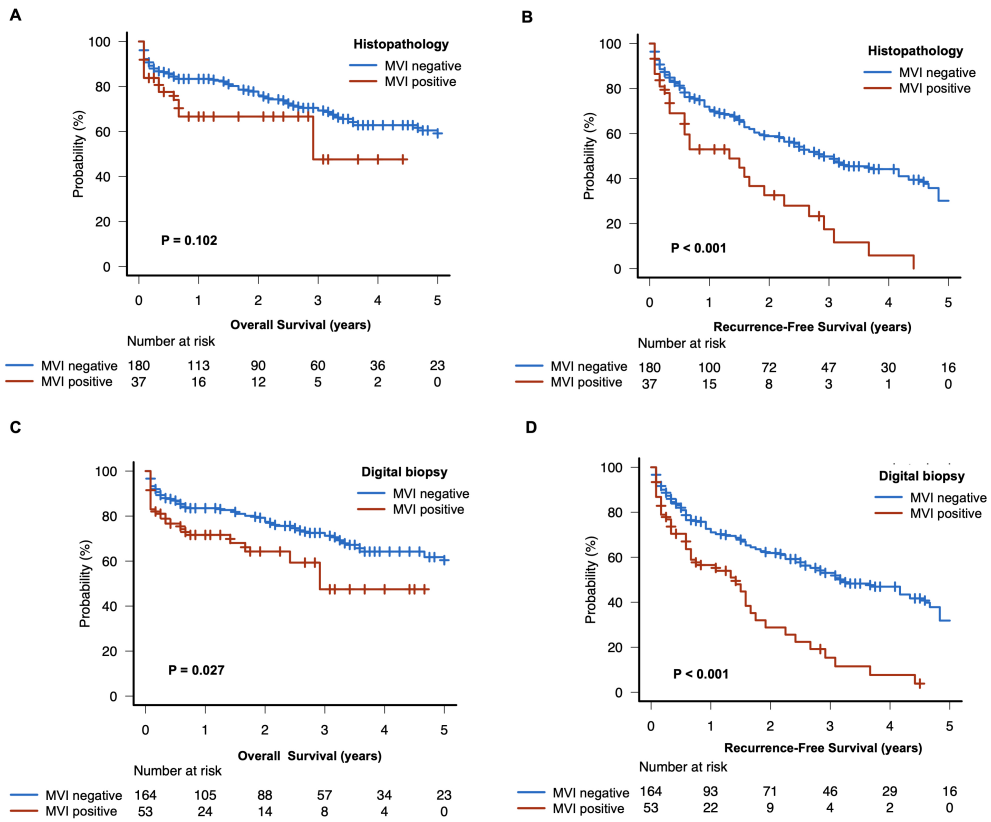

FIGURE 4
Survival plot stratified by pathologic and digital biopsy of microvascular invasion. The overall and recurrence-free survival plots of histopathological MVI **(A, B)** and digital biopsy proven MVI **(C, D)** are displayed.

odds ratio of >20 for MVI (27). Three other meta-analyses on the impact of different preoperative imaging features to predict MVI determined that a nonsmooth peritumoral margin is an important independent predictor of MVI (28–30). In the present study, we confirmed that this marker was the strongest predictor of MVI.

The presence of internal arteries in the portal phase is another substantial radiologic marker of MVI. Previous studies reported that internal arteries in HCC are correlated with angiogenesis and cellular proliferation which in turn results in tumor progression (31, 32). In 2007, a radiogenomic biomarker to predict MVI was developed in 28 patients with HCC and further validated in a cohort of 157 patients (29% with MVI) (20, 33). This radiogenomic biomarker was based on the correlation of two combined radiologic features (i.e., presence of internal arteries and peritumoral hypodense halo) with angiogenesis gene expression patterns and resulted in a sensitivity and specificity of 76% and 94% to predict MVI (20, 33). Some studies confirmed the predictive value of these two combined radiogenomic features (8, 34), while other studies including larger patient cohorts reported conflicting results (35, 36) and discovered an even higher predictive and prognostic value for internal arteries compared to peritumoral hypodense halo (12). Thus, in our study, we evaluated no combined imaging features and depicted a high predictive value of internal arteries for MVI, while peritumoral hypodense halo failed statistical significance to predict MVI.

Another characteristic imaging feature of advanced HCC is the presence of a radiologic tumor capsule (referred to pseudocapsula or peritumoral hyperenchancement), found in 70% of HCC cases (37). While the absence of a pseudocapsula might indicate an early HCC, an irregular or incomplete pseudocapsula is associated with MVI (diagnostic odds ratio of 1.85) according to a meta-analysis (38). In the present study, an irregular pseudocapsula was one of the three independent imaging features associated with MVI.

So far, a plethora of risk models exists in the literature, incorporating imaging features to predict MVI (11, 39, 40). However, the majority of available risk models were developed in patients with viral HCC having a high incidence of MVI. These models included multiple candidate variables in multivariate analyses based on the "rule of thumb", without considering sample size considerations (8, 9, 12, 16). Renzulli et al. identified three "worrisome" features (i.e., nonsmooth tumor margin, the radiogenomic features (combination of internal arteries and hypodense peritumoral halo), and irregular pseudocapsula) to be associated with MVI in a total of 140 patients (64% with MVI and 6 candidate variables) with a c-index of 0.85 and 0.90 (8). However, these features were not tested in a multivariate analysis (8). Similarly, Min et al. described a diagnostic model in a total of 100 patients (39% with MVI) including four radiologic features (i.e., non-smooth margin, irregular pseudocapsula, peritumoral hyperenhancement, peritumoral hypointensity) with a c-index of 0.80, again without multivariate testing (9). Lee et al. developed a 6-point risk model including two radiologic features (i.e., peritumoral arterial enhancement, peritumoral hypointensity) and two serological biomarkers in a total of 276 patients (28% with MVI and 15 candidate variables) with a c-index of 0.87 (16). Recently, Jiang et al. presented a complex 10-point risk model that outperformed the models of Renzulli et al., Min et al., and Lee et al. in a comparative analysis. However, the risk model by Jiang et al. was developed in 319 patients (47% with MVI), evaluating 22 candidate variables in a multivariate analysis. Hence, the current risk models in literature are at high risk of statistical overfitting owing to the high number of candidate variables and the selection of MVI patients (MVI incidence ranging between 27% - 64%) (24). The major strength of our digital biopsy risk model is that we performed a formal sample size calculation and adjusted our analysis by controlling for several confounders (i.e., etiology of disease, lesion pattern, age, sex) which were not addressed in previous studies (8, 9, 16, 20, 33). Our digital biopsy risk model achieved a high discrimination value (c-index of 0.87) and yielded excellent calibration metrics. Notably, we included only three imaging features on CT or MRI, making it highly applicable in the daily routine compared to other models comprising more features with or without additional serum analyses as well as restrictions on the imaging modality (i.e., MRI or CT) (8–12). Additionally, the prognostic utility of our risk model was further proven by stratified survival analyses. Remarkably, patients with a high risk of MVI on the digital biopsy risk model reflected an even worse prognosis in terms of overall survival compared to patients with histopathologically proven MVI. This finding is in line with other reports in literature, indicating a higher prognostic performance of pretreatment radiologic features as compared to histopathological MVI (41, 42). Therefore, our risk model provides a "digital biopsy" and may represent an additional noninvasive armamentarium to facilitate personalized HCC treatment strategies and improve patient outcome. To this end, patients with high risk of MVI might benefit from neoadjuvant local (i.e., chemoembolization, radioembolization) or systemic treatment prior surgical resection. Given that patients with high risk of MVI recur more frequently, the digital biopsy model could also be helpful to stratify candidates for liver transplantation and, thus, impacting organ allocation policies.

There are some limitations to our study. This is a retrospective prognostic study with a potential selection bias. To increase the generalizability of our results, we performed a rigorous methodology with adjusted analyses, and imaging features were evaluated by local radiologists at each center. Still, our study lacks an external validation cohort, and the findings of our study need to be tested in a separate HCC population.

In conclusion, we developed and internally validated a robust and reliable prediction model of MVI.

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 Ethikkomission II, Heidelberg University, Medical Faculty Mannheim. 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

EB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. HN: Data curation, Formal analysis, Investigation, Writing – review & editing. SA: Data curation, Formal analysis, Investigation, Writing – review & editing. JR: Data curation, Formal analysis, Investigation, Writing – review & editing. MF: Data curation, Formal analysis, Investigation, Writing – review & editing. SH: Formal analysis, Investigation, Methodology, Writing – review & editing. MR: Data curation, Investigation, Writing – review & editing. PT: Data curation, Investigation, Writing – review & editing. ER: Data curation, Formal analysis, Investigation, Writing – review & editing. ChR: Writing – review & editing. JW: Project administration, Writing – review & editing. SS: Supervision, Writing – review & editing. CaR: Data curation, Supervision, Writing – review & editing. VP: Data curation, Formal analysis, Supervision, Writing – review & editing. NR: Conceptualization, Formal analysis, Investigation, Project administration, Supervision, Writing – review & editing.

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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.

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Supplementary material

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Non-surgical nursing care for tumor patients: an overview of sedation, analgesia, and recent innovations

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With the increasing prevalence of tumors, effective symptom management has emerged as a cornerstone of patient care. While surgical interventions remain pivotal, non-surgical nursing methods have gained prominence in providing relief from pain, discomfort, and other tumor-related symptoms. This review delves into the various non-surgical approaches employed, emphasizing tumor sedation and analgesia. We discuss the array of non-pharmacological and pharmacological strategies, shedding light on their indications, contraindications, and potential side effects. Furthermore, the importance of addressing individual differences in pain perception and the ethical considerations in symptom management are highlighted. We conclude by providing insights into the recent innovations in the field, emphasizing the need for personalized and comprehensive care to enhance patients' quality of life. Tumor sedation, Tumor analgesia, Non-surgical nursing care, Pain management, Non-pharmacological interventions, Palliative care, Recent innovations, Symptom management.

KEYWORDS

tumor sedation, tumor analgesia, non-surgical nursing care, pain management, nonpharmacological interventions, palliative care, recent innovations, symptom management

Highlights

- Non-Surgical Nursing Methods: Pivotal shift from surgical to non-surgical approaches in tumor symptom management, expanding care options for patients.
- Comprehensive Strategies: Balanced examination of non-pharmacological and pharmacological methods, offering a holistic view on pain and symptom management.
- Individual Pain Perception: Emphasis on the variability in pain perception, advocating for personalized treatment plans.

- Ethical Considerations: Integration of ethical perspectives in symptom management, addressing complex healthcare dilemmas.
- Innovations in the Field: Insights into recent advancements and future possibilities in tumor symptom management, guiding research and clinical practice.

1 Introduction

With the increasing prevalence of tumors, effective symptom management has emerged as a cornerstone of patient care. While surgical interventions remain pivotal, non-surgical nursing methods have gained prominence in providing relief from pain, discomfort, and other tumor-related symptoms. This review delves into the various non-surgical approaches employed, emphasizing tumor sedation and analgesia. We discuss the array of non-pharmacological and pharmacological strategies, shedding light on their indications, contraindications, and potential side effects. Furthermore, the importance of addressing individual differences in pain perception and the ethical considerations in symptom management are highlighted. We conclude by providing insights into the recent innovations in the field, emphasizing the need for personalized and comprehensive care to enhance patients' quality of life (1).

In recent years, the medical community has witnessed a renewed emphasis on the significance of pain and discomfort management in patients with tumors (2). As the global incidence of tumors continues to rise, so does the urgency to address the multifaceted challenges these patients face (3). Pain, often a relentless companion of tumor growth, has profound implications not only on a patient's physical well-being but also on their psychological health, impacting facets of daily life, from sleep quality to interpersonal relationships (4). Recent research underscores that unmanaged or poorly managed pain can lead to heightened levels of anxiety, depression, and even decreased survival rates in some cases (5). In this evolving landscape, non-surgical nursing care has emerged as a critical player (6). These approaches, ranging from pharmacological interventions to holistic care models, have showcased potential in not only alleviating pain but also in enhancing the overall quality of life for patients (7). Recent studies indicate that patients receiving comprehensive non-surgical care often report improved outcomes, reduced hospital stays, and a more positive prognosis (8). As the dynamics of tumor care shift towards a more patient-centric model, the pivotal role of non-surgical nursing care in bridging the gap between medical intervention and enhanced patient well-being cannot be overstated.

2 Tumor sedation

A study on high-quality care for postoperative inflammation and prognosis in advanced non-small cell lung cancer (NSCLC) patients suggests that high-quality care significantly reduces hospitalization duration, improves postoperative inflammation management, symptom control, and quality of life when compared to patients receiving standard care. In comparison to regular care, high-quality care reduces anxiety, depression levels, and psychological distress in postoperative advanced NSCLC patients. The results indicate that high-quality care prolongs the survival time and reduces the recurrence rate of postoperative advanced NSCLC patients (9). Tumor sedation has garnered considerable attention in contemporary oncological care, reflecting its significance in improving patient comfort and quality of life (10). Defined as the deliberate use of medications to relieve extreme symptoms, especially refractory pain and distress in advanced cancer patients (11), tumor sedation aims to achieve a state where the patient's consciousness is reduced while ensuring their comfort and dignity (12). The core objective of this approach is to mitigate suffering, especially when other treatments fail to provide relief. In recent times, advancements in pharmacology have introduced new agents and refined protocols that offer more controlled and individualized sedation, minimizing potential side effects (13). Moreover, the development of precision monitoring tools aids healthcare professionals in ensuring that sedation is maintained at optimal levels (14), allowing the patients to interact with their loved ones and respond to their environment, even if minimally. These recent strides in tumor sedation techniques underline the medical community's commitment to enhancing the end-of-life experience for patients, emphasizing comfort, autonomy, and humanity. Table 1 provides a comparison of medications used for tumor sedation, including Midazolam, Propofol, and Dexmedetomidine, along with their respective mechanisms of action, common uses, and potential side effects.

The landscape of tumor sedation has evolved considerably in the past few years, enriched by a confluence of innovative methods and advanced medications tailored to meet the unique needs of tumor patients (15). Traditionally, benzodiazepines, such as midazolam, have been a mainstay for sedation due to their rapid onset and short duration of action (16). However, the introduction of newer agents, including propofol and dexmedetomidine, has expanded the therapeutic arsenal (17). Propofol, in particular, offers rapid sedation with a smooth recovery profile, while dexmedetomidine, an alpha-2 adrenergic receptor agonist, provides sedation without causing respiratory depression (18). Beyond pharmacological advances, non-pharmacological

TABLE 1 Comparison of medications used for tumor sedation.

Medication Name	Mechanism of Action	Common Uses	Potential Side Effects
Midazolam	Benzodiazepine	Short-term sedation	Drowsiness, respiratory depression
Propofol	GABA receptor agonist	Induction and maintenance of anesthesia	Hypotension, bradycardia
Dexmedetomidine	Alpha-2 adrenergic receptor agonist	Sedation in ICU settings	Bradycardia, dry mouth

techniques, like progressive muscle relaxation and guided imagery, have gained traction as adjunctive therapies, enhancing the sedative experience while minimizing drug-related side effects (19). Furthermore, the integration of continuous monitoring systems allows for real-time adjustments of sedative doses, ensuring optimal sedation levels and patient safety (20). These advancements underscore a holistic and patient-centered approach, where the choice of method and medication is intricately aligned with the patient's clinical status, preferences, and the intended depth of sedation.

In the ever-evolving realm of oncology, clear guidelines for when and when not to employ tumor sedation are pivotal to ensuring patient safety and optimal outcomes (21). Recent consensus and evidence-based guidelines have delineated the indications for tumor sedation more explicitly (22). Primarily, it is reserved for patients with refractory symptoms—those distressing symptoms unresponsive to standard medical interventions, such as uncontrolled pain, agitated delirium, or severe dyspnea (11). The goal is to alleviate suffering when other treatments fall short. In certain end-of-life scenarios, sedation may also be employed to ensure a peaceful transition for terminal patients (23). On the flip side, contraindications have been more rigorously defined (24). Tumor sedation is generally avoided in patients with reversible causes of distress, those who might benefit from other interventions, or where the intent might be misunderstood or misconstrued by the patient's family (25).

A systematic review and meta-analysis studying the impact of enhanced care in liver cancer patients indicate that enhanced care significantly improves patient anxiety, depression, and quality of life. Most liver cancer patients receiving enhanced care are highly satisfied with their quality of life. Furthermore, the analysis also demonstrates significant improvements in patients' physical functioning and overall activity scores due to enhanced care (26).

A study on the effectiveness of patient-reported personalized symptom management in liver cancer intervention therapy found that patients who received personalized management experienced significantly milder symptoms such as pain, nausea, anxiety, and fatigue compared to those receiving standard care. Moreover, patients in the intervention group showed a significant improvement in Karnofsky performance scores and satisfaction with care (27) Table 2 outlines various alternative therapies and their potential benefits, including Acupuncture, Aromatherapy, and Music Therapy. Additionally, certain medications used for sedation may be contraindicated in patients with specific allergies or organ dysfunctions. With advancements in diagnostic tools and a better understanding of patient physiology, the decision-making process around tumor sedation has become more refined, ensuring that it is applied judiciously and benefits those truly in need. Table 3 offers strategies to manage common side effects of pain medications, such as constipation, respiratory depression, and gastrointestinal distress. These strategies are particularly useful when dealing with opioids, high doses of opioids, and NSAIDs, respectively.

Lastly, a cluster randomized clinical trial explored the effectiveness of primary palliative care interventions provided by oncology nurses, which did not improve patients' quality of life, symptom burden, or mood symptoms within 3 months. However, the study highlighted that higher-dose interventions may be beneficial for most advanced cancer patients who lack access to palliative care specialists (28).

TABLE 2 Alternative therapies and their potential benefits.

Therapy Type	Description	Potential Benefits
Acupuncture	Traditional Chinese therapy using needles	Pain relief, reduced nausea
Aromatherapy	Use of essential oils for therapeutic purposes	Stress reduction, improved sleep
Music Therapy	Use of music interventions to address physical, emotional, cognitive, and social needs	Mood enhancement, reduced anxiety

3 Tumor analgesia (pain management)

In the contemporary landscape of oncology, the emphasis on pain management in tumor patients has never been more pronounced (29). Pain, often chronic and debilitating, is an all-too-common companion for many tumor patients, profoundly impacting their physical and psychological well-being (30). Recent studies underscore that inadequately managed pain not only diminishes the quality of life but also can exacerbate tumor progression, potentially influencing metastasis and immune suppression (31). The physiological stress induced by persistent pain can lead to elevated cortisol levels, which, in turn, can have detrimental effects on the body's ability to fight off tumor cells (32). Moreover, effective pain management is intricately linked to improved patient outcomes, including better treatment adherence, reduced hospitalization durations, and enhanced overall survival rates (33). The realm of tumor analgesia has also witnessed a paradigm shift towards a holistic model, where pain is viewed not merely as a physiological symptom but as a complex interplay of emotional, social, and psychological factors (34). This comprehensive approach underscores the critical need for personalized pain management strategies, ensuring that patients can lead a life with dignity, comfort, and hope.

The pharmacological landscape of tumor analgesia has witnessed remarkable advancements in recent years, offering

TABLE 3 Strategies to manage common side effects of pain medications.

Side Effect	Cause	Management Strategy	Additional Notes
Constipation	Opioids	Laxatives, increased fiber intake, hydration	Monitor for abdominal pain or bloating
Respiratory Depression	High doses of opioids	Patient monitoring, naloxone	Educate patients about the risks
Gastrointestinal Distress	NSAIDs	Co-prescription with proton pump inhibitors	Encourage patients to take with food

patients a broader and more tailored spectrum of pain relief options (35). Opioids, such as morphine, oxycodone, and fentanyl, remain at the forefront of managing moderate to severe cancer pain (36). Their effectiveness is, however, often counterbalanced by concerns of tolerance, addiction, and side effects like constipation and respiratory depression (37). To address these challenges, extended-release formulations and targeted delivery systems have been developed, optimizing pain control while minimizing adverse effects (38). Parallelly, non-opioids like acetaminophen and NSAIDs provide relief for milder pain and can synergistically enhance opioid efficacy (39). Adjuvant analgesics, including anticonvulsants and antidepressants, have emerged as pivotal players, especially for neuropathic pain, a type of pain frequently associated with tumors and cancer treatments (40). The recent emphasis on personalized medicine has also fostered innovations in drug delivery (33). While oral administration remains common, the rise of transdermal patches, intravenous infusions, and even implantable drug delivery systems cater to specific patient needs (41), ensuring consistent pain relief while reducing systemic side effects (42). Collectively, these advancements underscore a commitment to a multifaceted and patient-centric approach to tumor analgesia, aiming for optimal pain relief with the least possible inconvenience or discomfort to the patient.

The management of pain in tumor patients, while imperative, is often accompanied by a range of medication-induced side effects that can pose substantial challenges to both patients and healthcare providers (43). Recognizing this, recent advances have been directed towards not just enhancing analgesic efficacy but also mitigating these adverse effects (44). For opioids, constipation remains a predominant concern; the introduction of peripherally-acting mu-opioid receptor antagonists, such as naloxegol, has been transformative in managing opioid-induced constipation without affecting central pain relief (45). Respiratory depression, another critical opioid-related side effect, is now better managed with the advent of naloxone nasal sprays and injectables, offering rapid reversal in emergent situations (46). To combat the gastrointestinal side effects of NSAIDs, co-prescription with proton pump inhibitors or the use of selective COX-2 inhibitors has gained traction (47). Furthermore, the practice of rotating opioids, a technique where one opioid is substituted for another, has shown promise in reducing tolerance and side effects (48). Patient education, regular monitoring, and the use of digital health platforms for real-time symptom tracking and reporting have also become integral to a proactive management approach (49). These strategies, born out of a blend of technological innovation and refined pharmacological understanding, represent a concerted effort to ensure that pain management is both effective and tolerable for tumor patients.

4 Other non-surgical nursing care methods

In the realm of tumor care, the surge of interest in alternative therapies has redefined the boundaries of non-surgical nursing interventions (50). While conventional treatments remain foundational, a growing body of evidence suggests that alternative therapies can play a significant role in enhancing patient well-being and potentially alleviating tumor-related symptoms. Acupuncture, a traditional Chinese medical practice, has made notable inroads in the oncological setting (51). Recent studies indicate its efficacy in managing chemotherapy-induced nausea, postoperative pain, and even cancer-related fatigue (52). Aromatherapy, the therapeutic use of essential oils, has been spotlighted for its potential in reducing anxiety, improving sleep, and enhancing overall mood in tumor patients (53). Lavender, chamomile, and frankincense are among the oils frequently utilized (54). Meanwhile, music therapy, a confluence of art and science, has emerged as a potent tool (55). Tailored musical interventions, whether passive listening or active participation, have been linked to reduced pain perception, decreased levels of stress hormones, and improved emotional well-being (56). While these therapies might not replace conventional treatments, their integration into the holistic care model underscores a broader understanding of patient needs, emphasizing not just physical health but also psychological and emotional harmony.

As the complexities of tumor care continue to unfold, addressing multifaceted tumor-related symptoms has become paramount. Beyond pain, symptoms like fatigue, nausea, and cognitive disturbances can severely impede a patient's quality of life (57). In recent years, targeted interventions have been developed to combat these challenges (58). Fatigue, often cited as one of the most debilitating symptoms by tumor patients, is now being addressed through a combination of pharmacological agents, like modafinil, and non-pharmacological strategies (59), such as graded exercise therapy and cognitive behavioral therapy. Nausea, particularly post-chemotherapy, has seen significant advancements in management (60). The introduction of newer antiemetic drugs, like the NK1 receptor antagonists and olanzapine, has improved control rates, especially in patients undergoing highly emetogenic treatments (61). Additionally, techniques like progressive muscle relaxation and guided imagery have shown promise in alleviating nausea (62). For cognitive disturbances or "chemo brain," interventions ranging from cognitive rehabilitation programs to mindfulness meditation have been explored (57). The integration of digital health tools, offering real-time symptom tracking and personalized interventions, is also revolutionizing the approach to symptom management (63). These innovations underscore the evolving nature of tumor care, where a nuanced understanding of symptoms and a multi-pronged approach to their management ensure that patients lead a life not just free of pain, but also enriched in well-being (64).

Palliative care, once perceived as a last-resort intervention for terminal patients, has undergone a paradigm shift in recent years (65). Today, it's recognized as an integral component of comprehensive tumor care, introduced early in the disease trajectory and woven seamlessly alongside curative treatments (66). The primary objective of modern palliative care is to enhance the quality of life, addressing physical symptoms, emotional distress, spiritual concerns, and social challenges (67). Recent studies have illuminated its profound impact: patients receiving early palliative care interventions report better symptom

control, improved mood, and even, in some cases, extended survival (68). This holistic approach emphasizes person-centered care, focusing on the patient's goals, values, and preferences (69). Technological advancements, such as telemedicine platforms, have further broadened the reach of palliative care, ensuring that even those in remote areas or with limited mobility can access these crucial services (70). Interdisciplinary collaboration, encompassing doctors, nurses, therapists, and counselors, ensures that every facet of a patient's well-being is addressed (71). As the medical community continues to understand the complexities of tumor care, the role of palliative care as a beacon of comfort, dignity, and hope in the patient's journey becomes ever more central.

5 Challenges in non-surgical nursing care

Navigating the intricacies of non-surgical nursing care for tumor patients has brought to light the profound individual variability in pain perception and tolerance (72). Recent research underscores that pain, far from being a uniform experience, is deeply personal, shaped by a mosaic of genetic, physiological, psychological, and cultural factors (73). Genetic polymorphisms can influence the metabolism of analgesic drugs, leading some patients to require higher or lower doses for effective relief (74). Additionally, psychological states, such as anxiety or depression, can modulate pain perception, often amplifying the experience of pain (75). Cultural beliefs and past experiences can also play pivotal roles in shaping how pain is expressed and tolerated (76). Addressing these individual nuances has posed significant challenges in standardizing care (77). However, the emergence of precision medicine and pharmacogenomics offers promise (33). Tailored pain management strategies, based on an individual's genetic makeup and holistic assessment, are being explored (78). Furthermore, interdisciplinary approaches, combining medical, psychological, and socio-cultural insights, are being employed to ensure a more comprehensive understanding and management of pain (79). While the path is fraught with challenges, the commitment to individualized, patient-centric care remains unwavering in the face of these complexities (80).

The multifaceted pharmacological landscape of tumor care, while pivotal in managing symptoms, has brought to the fore the intricate challenge of potential drug interactions and side effects (81). As patients often receive a plethora of medications, ranging from chemotherapeutic agents to adjuvant analgesics, the risk of unforeseen interactions escalates (82). These interactions can potentiate drug toxicity, diminish therapeutic efficacy, or introduce new, unanticipated side effects (83). To address this, recent advancements have prioritized comprehensive drug interaction databases and real-time monitoring systems (84). Advanced algorithms, informed by vast pharmacological data, now provide clinicians with immediate alerts if a proposed medication regimen risks harmful interactions (85). Alongside this, there's a growing emphasis on pharmacovigilance, where systematic post-market monitoring of drugs ensures timely detection and mitigation of side effects (86). Patient education has also emerged as a cornerstone; empowering patients with knowledge about potential side effects and fostering open communication channels allows for early detection and intervention (7). Additionally, the rise of personalized medicine, where treatment regimens are tailored based on genetic and metabolic profiles, offers hope in minimizing adverse reactions (87). Through a blend of technology, vigilant monitoring, and patient engagement, the medical community is steering towards safer and more effective pharmacological management in tumor care (88).

Amidst the complex dynamics of pain and symptom management in tumor care, ethical considerations have risen to the forefront (89), demanding a delicate balance between alleviating suffering and ensuring patient autonomy and dignity (90). The recent discourse has intensified around issues like over-prescription of opioids, where the intent to relieve pain may inadvertently lead to dependence or misuse (91). Consequently, there's a pressing call for clear guidelines, informed consent, and regular monitoring to ensure opioids are used judiciously (92). Similarly, the decision to initiate, withhold, or withdraw treatments, especially in end-of-life scenarios, is fraught with ethical dilemmas (93). Shared decision-making models, emphasizing transparent communication between patients, families, and healthcare providers, are gaining prominence (94). These models prioritize the patient's values, beliefs, and preferences, ensuring that interventions align with their overall well-being and life goals (95). Furthermore, the potential disparities in access to pain and symptom management resources, especially in underserved populations, have raised ethical concerns about equitable care (96). Efforts are underway to bridge these gaps through policy reforms and community outreach (97). As the medical community navigates these ethical waters, the commitment remains clear: to offer compassionate, respectful, and individualized care, always placing the patient's holistic well-being at the heart of every decision.

6 Recent advances and innovations

The last few years have ushered in a renaissance of innovation in non-surgical tumor care, driven by groundbreaking research and technological advancements (98).

In support of the viewpoint advocating early specialized palliative care, the results of this study provide compelling evidence. While the CONNECT program did not significantly improve patients' quality of life and symptom burden within 3 months, this finding underscores the challenges faced by current oncology patients. Many patients lack access to early specialized palliative care, which may impact their quality of life and symptom management. However, it's worth noting that the CONNECT program showed a greater effect in patients who completed the full course, suggesting that high-dose primary palliative care may be particularly beneficial for certain patients. Therefore, we recommend that despite the current results not fully endorsing the effectiveness of early specialized palliative care, future research should focus more on high-dose primary palliative care

interventions to meet specific patient needs and enhance their quality of life (99).

At the nexus of this evolution lies the burgeoning field of digital health, with wearable sensors and telemedicine platforms offering real-time symptom monitoring and personalized interventions (100). These tools, harnessing the power of artificial intelligence and big data analytics, enable clinicians to preemptively address symptoms, enhancing patient comfort and reducing hospitalizations (101). Another significant leap has been in the realm of pharmacogenomics, where individualized drug regimens, tailored to a patient's genetic makeup, promise optimized therapeutic effects with minimized side effects (102).

The research on depression and anxiety among people living with and beyond cancer emphasizes the psychological well-being of cancer patients, particularly highlighting significant variations in anxiety and depression levels across different stages of cancer treatment (103). These differences profoundly impact the quality of life for patients. Throughout the process of cancer treatment, considering psychological health factors becomes crucial, especially in pain management and enhancing patient comfort. The paper on "Stress and Cancer" delves into the roles of psychological therapy and medication in managing cancer-related psychological stress, depression, and anxiety (104–106). These studies also mention emerging psychological treatment methods, such as tailored psychological interventions for advanced cancer patients. This research supports your perspective of emphasizing personalized treatment and comprehensive care in managing cancer symptoms. Therefore, it is imperative to focus not only on patients' physical health but also on their psychological well-being.

Moreover, Wang et al.'s meta-analysis provides evidence of the relationship between depression, anxiety, and cancer incidence and mortality rates among various cancer types (107). The study results indicate a significant correlation between depression and anxiety with cancer incidence, cancer-specific mortality rates, and overall mortality rates among cancer patients. These findings once again underscore the pivotal role of psychological states in cancer treatment and prognosis, especially in pain management and improving the quality of life for patients. Other discussion explores how psychological stress affects tumor development through biobehavioral pathways (108). This review article emphasizes the close connection between psychological well-being and the management of tumor-related symptoms and patient care. While clinical evidence regarding the relationship between psychological stress and cancer may be inconsistent, animal studies suggest that prolonged psychological stress can significantly promote tumor progression. This discovery underscores the need to prioritize psychological health management alongside physical treatment in cancer care to provide holistic care and enhance the overall quality of life for patients.

Additionally, the exploration of neuromodulation techniques, such as transcranial magnetic stimulation, offers novel avenues for managing refractory pain and other tumor-related symptoms (109). Non-invasive brain stimulation methods are being researched for their potential in modulating pain pathways, offering relief without drugs (110). On the holistic front, integrative therapies combining Western medicine with traditional practices, such as yoga and mindfulness meditation, are gaining empirical validation (111), showcasing their efficacy in enhancing overall well-being. As the tapestry of non-surgical tumor care continues to expand and diversify, it's clear that the future holds a multidimensional approach, seamlessly blending technology, pharmacology, and holistic care to revolutionize the patient experience (112). The horizon of non-surgical tumor care is brimming with possibilities, shaped by an interplay of technological innovation, scientific discovery, and evolving patient needs (113). One of the most anticipated advancements is the fusion of precision medicine with artificial intelligence, enabling predictive modeling of individual patient responses to various treatments, thereby optimizing therapeutic outcomes (114). This synergy promises to tailor interventions not just based on genetic profiles, but also by analyzing real-time physiological, behavioral, and environmental data (115). Another promising avenue is the exploration of bioelectronic medicine, harnessing the potential of electrical signals within the body to modulate pain and other symptoms without the use of drugs (116). As our understanding of the human microbiome deepens, there's growing optimism about leveraging its potential to modulate pain and inflammation, offering novel therapeutic interventions (117). On the holistic front, there's a palpable momentum towards integrating traditional healing practices from various cultures into mainstream care, backed by rigorous scientific validation. Additionally, the role of virtual and augmented reality in pain management and patient education is an emerging area of interest. As these innovations coalesce, the future of non-surgical tumor care envisions a holistic, integrated, and patient-centric model that transcends boundaries, ensuring the best possible quality of life for patients.

7 Conclusion

In reflection, the evolving landscape of tumor care underscores the undeniable significance of non-surgical nursing interventions in managing the multifaceted challenges faced by patients. Beyond the immediate relief from pain and discomfort, these interventions play a pivotal role in enhancing the overall quality of life, influencing physical well-being, psychological health, and social interactions. Recent advancements, whether technological, pharmacological, or holistic, have all converged towards one central theme: the importance of personalization. Recognizing that each patient's journey with a tumor is unique, the emphasis has shifted towards tailored interventions that account for individual genetic, physiological, and emotional nuances. Furthermore, the move towards a more integrated and comprehensive care model, which seamlessly blends traditional and innovative practices, is a testament to the medical community's commitment to ensuring that every patient receives the best possible care. As we navigate the complexities of tumor care, the value of a patient-centric, compassionate, and

holistic approach remains at the heart of all endeavors, guiding the future trajectory of non-surgical interventions.

Author contributions

WW: Data curation, Methodology, Supervision, Conceptualization, Validation, Writing – original draft, Writing – review & editing. PW: Data curation, Supervision, Conceptualization, Formal analysis, Funding acquisition, Writing – original draft, Writing – review & editing. PQ: Data curation, Supervision, Conceptualization, Validation, Writing – original draft, Writing – review & editing. ZL: Data curation, Methodology, Supervision, Conceptualization, Formal analysis, Visualization, Writing – review & editing. QH: Writing – original draft, Writing – review & editing.

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A health belief model-based community health education on mammography screening among reproductive-aged women in Ethiopia: a randomized controlled trial

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Background: Early intervention in mammography use prevents breast cancer-related deaths. Therefore, this study aimed to apply health education interventions to mammography use in reproductive-aged women.

Methods: This was a sequential exploratory design using qualitative and quantitative methods. The qualitative part used to gain insights into the design and development of interventions. For the randomized trial, a sample of 405 participants was recruited in each arm. The mean difference of interventions on the study variables was determined using a general linear model for repeated measures (ANOVA). For dichotomous variables, nonparametric tests (Cochran *Q*) were used. Path analysis was used to observe how the constructs of the Health Belief Model interacted. We registered PACTR database (https://pactr.samrc.ac.za/): "PACTR201802002902886."

Results: The study found that there was a strong interplay between perceptions of mammography screening and the intervention, showing that the likelihood of mammography use and comprehensive knowledge increased from baseline to endpoint ($p < 0.005$). Likewise, health motivation and all constructs of the health belief model had a statistically significant mean difference between the intervention and control groups ($p < 0.005$). However, the mean value of perceived barriers in the intervention group was statistically significantly reduced after three and six months (mean difference = −2.054 between Measure 1 and measure 2 and −1.942 between Measure 2 and Measure 3). The hypothesized causal paths effect of the model was explained by 64.3% that shows there is strong relationship of the variables significantly ($p < 0.005$).

Conclusion: The study found that model-based mammography screening interventions had a significant impact at various time periods. We recommend future researchers consider the intensity and range of information to advance the field and figure out the problem while investigating the dose and peak of the intervention.

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KEYWORDS

randomized trial, health education, mammography screening, health belief model, intervention

Introduction

In developed countries, the decline in breast cancer mortality observed over the past three decades is partly due to intensive interventions and improved patient management, which may affect the benefit-to-harm ratio of mammography screening (1–3). According to global estimates, breast cancer affects approximately 2.1 million women annually and is the leading cause of cancer-related death among women in developing and developed countries (4, 5). Recent studies in the Western world showed an absolute reduction in breast cancer risk associated with cancer education about early detection and screening. The difference, even in the effectiveness of treatment and screening, is increasing (5). Although the prevalence of breast cancer is higher in the developed world, the rate in developing countries remains unacceptably high (5–9).

Breast cancer is the deadliest cancer in Ethiopia. Of course, early detection and self-referral for mammography screening have led to a noticeable change, recognizing that the timing of detection influences the effectiveness of breast cancer treatment (9–11). Many factors influencing the use of mammography could change as public health initiatives are introduced and poorly understood (11). For this reason, several observational studies have identified factors that lead to the occurrence of breast cancer (10–14). Therefore, intuitive scientists worldwide have suggested that the implementation of recommended breast cancer intervention methods, such as mammography, has a significant impact on early detection (15, 16). Breast cancer education has a significant impact on increasing awareness of early detection and improving chances of survival (15–17).

In Ethiopia, despite various breast cancer prevention mechanisms suggested by health professionals, early recognition of the symptoms and self-referral for treatment are still in question, and their chances of survival are nil due to a late report (8–10). Several observational studies have been conducted on mammography use among women, but none of these were interventional studies among women of reproductive age in Ethiopia. Regarding the art of mammography screening in Ethiopia, most of the screening services are given in the central part of the country, and a decade of collaborative work and lessons learned from developed countries to improve breast cancer outcomes. Though evidence shows poor awareness of breast cancer symptoms, prevention mechanisms, risk factors, and treatment options has usually been associated with patient delay in seeking help, the service availability to the have's and have-not's at the community level is limited, making treatment less effective and having a having a minimal survival rate (9–11). Thus, binding the community to seek the health services (mammography) where they are found and what the cost is (15, 16). Various health belief model-based studies predicted the perception of the individuals in one or another behavior (11, 12, 16, 17).

HBM is a socio-psychological model that attempts to explain and predict health behaviors in terms of certain belief patterns by focusing on the attitudes and beliefs of individuals. It was developed by social psychologists to explain the lack of public participation in health screening and prevention programs. Since then, it has been adapted to a variety of long-and short-term health behaviors, including breast screening behaviors. The HBM addresses the individual's perceptions of the threat posed by a health problem (susceptibility, severity), the benefits of avoiding the threat, and factors influencing the decision to act (barriers, cues to action, and self-efficacy); it also states specific health beliefs related to the health problem and recommended health actions that influence the likelihood of taking recommended health actions (mammography use) (18–21). Therefore, this study aimed to apply health education interventions to mammography use in women of childbearing age within the theoretical framework of the Health Belief Model (HBM). Moreover, the study hypothesized that a health belief model-based community health education on mammography screening among reproductive-aged women will bring amicable change in Ethiopia.

Materials and methods

Study design, populations and setting

This was a sequential exploratory design using qualitative and quantitative methods. An exploratory qualitative was used to get insight from women and health workers to design and development of intervention using focus group discussions (FGD) and in-depth interviews, respectively and published elsewhere (21). A sample of 405 participants in each arm was recruited for a randomized trial in the quantitative part and evaluated at baseline and three and six months after the educational intervention. Then, a randomized controlled trial proceeded by cross-sectional study lasting for six months was used to assess effectiveness of the health education intervention on mammography use among reproductive-aged women. The study included women in the childbearing age group (15–49) who were physically and mentally capable of giving informed written consent and able to follow the provided intervention without any assistance, as well as willing to provide their consent and data to the researcher admit. The exclusion criteria were participants who could not stay until the intervention was completed/participants who were mobile during the intervention period and participants who did not attend more than two sessions of the training were excluded from the study.

This study was conducted on women of childbearing age in the Hadiya zone of central Ethiopia region. There were 332 kebeles and kifleketemas in the zone, as well as 13 rural districts and seven city administrations. Hossana, the region's capital, is located 230 kilometers from Addis Ababa, the capital of Ethiopia. It is estimated that 1,850,104 people live in the zone. The estimate of women of childbearing age (15–49) is 193,967. The total number of health facilities in the zone corresponds to the Kebele number and others. Health extension workers and community health agents play a crucial

role in the prevention of communicable and non-communicable diseases. The study was conducted between April 2018 and May 2019.

Recruitment

At the time of data collection, we included six districts from the zone. We then selected 30 kebeles from the selected districts and distributed them equally between intervention and control groups (i.e., 30 kebeles were divided into 15 intervention groups and 15 controls). Systematic sampling was used to select each participant from each kebele by summing all *K* values in the initial 23 households. To prevent contamination of information, random assignment was used to ensure that control and intervention sites were far apart. We assigned 405 participants to each arm and distributed them proportionally across each kebeles. Hence, the total number of study kebeles was 30 based on the WHO sampling recommendation (WHO 2008) (20).

Women who were potentially eligible for the study were selected for enrollment, and each woman was invited to participate in the study through a verbal invitation from the principal investigator and health extension workers of each selected kebele. If she agreed to participate, an appointment was arranged. After written informed consent, women were accepted as study participants, baseline data were collected, and participants were assigned to either the intervention or control group. After informed consent and baseline data collection, participants in the randomized controlled trial were randomly assigned to one of two arms: intervention or control. The different kebeles were coded alphabetically (A, B, C, D, etc.) and the participants assigned to each kebele were given numerical codes (e.g., participants in kebele 1 were numbered 1,001, 1,002, 1,003, etc.). Following three months and six months, follow-up data was gathered from both groups. We confirm that the original protocol was prepared for all breast screening behaviors (breast self-examination, breast clinical exam, and mammography use as a sequential exploratory study including qualitative and quantitative, and the two baselines were published elsewhere (21, 22). The length of the data collection period exceeded the initial protocol's stated duration. Interventionist, data collectors, statistician were not the same persons. Interventionists also acknowledged all those contacted in the intervention arm.

Sampling and sample size determination

In this randomized trial, a double population proportion formula was used to calculate the sample size. This included 77.6% of participants who had knowledge of breast cancer screening methods (P1 = 77.6%) (23); P2 is the prevalence of screening rates in the intervention districts (87.6%). (Assumption: increase of 10%); *K* is the coefficient of variation of the true proportions of the outcome variable across counties within each group; the margin of error is 5%, with a significance level of 5% (two-tailed), i.e., a 95% confidence interval of certainty. Since there is no study estimating *k*, the value is assumed to be 0.25. Then the sample size was 368. Finally, the sample size was further increased by 10% to account for contingencies such as non-responses or recording errors, i.e., $368 \times 10/100 + 368 = 404.8 \approx 405$. Therefore, the final sample size was 810 due to the design effect.

Measurement and variables

The intended outcome of this study was the likelihood of mammography screening (perceived benefits minus perceived barriers). The exposure variables were socio-demographic factors, knowledge about breast cancer and mammography screening, and previous breast screening behaviors. Age, marital status, religion, place of residence, educational and professional status as well as the current living situation of the respondents are socio-demographic factors and measured by seven items. There are eleven knowledge questions with the answer format "yes" or "no." If respondents did not know the correct answer, they were asked to mark the "I do not know" answer option instead of guessing. Respondents who answered 50% or more of all knowledge questions about breast cancer and mammography screening were considered knowledgeable.

Respondents who answered less than 50% of all knowledge questions about breast cancer and mammography screening methods were classified as not knowledgeable. Perceived susceptibility is the self-perception of a respondent's vulnerability to breast cancer as measured by a total of five belief items on a 5-point Likert scale. The perceived severity of breast cancer is the respondent's belief about the impacts of breast cancer severity, as measured by a total of eleven belief items on a 5-point Likert scale. Perceived benefits of screening are respondents' beliefs about the effectiveness of the method as a breast cancer prevention strategy, measured by a total of five belief items on a 5-point Likert scale. The perceived barriers to breast screening are respondents' beliefs about how simple it is to perform the particular preventative actions, measured by a total of ten belief items on a 5-point Likert scale. Self-efficacy is defined as a respondent's confidence in using breast screening procedures on her own in any circumstance or setting to avoid breast cancer, as measured by a total of five belief items on a 5-point Likert scale. Cues to action are conditions in the respondents' environment that may encourage people to adopt breast screening procedures using a yes/no response style and measured by a total of five items. Past behavior (practice) refers to reproductive-aged women's exposure to mammography screening at least once throughout the recommended period to avoid breast cancer, as measured using nominal measurements and measured by a total of six items. Before generating a summed score for each concept, negative-worded items were reversed. Community-based health education intervention description: Health education intervention was prepared based on health belief model constructs which are interlinked with mammography screening behavior. On top of this, the intervention emerged out of qualitative parts that were taken as very important components to know salient beliefs in the study area and later used as a very important base for intervention designing. Participants in the intervention arm received community based educational intervention in every 15 days for 3 months and registered their names and phone numbers (even family phone numbers) for tracking and reminding purposes. Educational intervention was provided on mammography use by training and teaching using different methods and materials like poster.

All of the participants were promised of the confidentiality throughout the process. For this, the enumerated lists of the participants were secured from the registry book of health workers after getting the consent. Immediately, after baseline data collection, the participants were categorized as intervention and control groups. All the required information of the both groups were taken and then registered in a temporarily prepared attendance sheet and followed accordingly. The participants were given an appointment to a health center or health posts near to them where the usual community forum was being conducted or the usual community meeting places for their

community forum. The interventionists together with health extension workers facilitate the condition and deliver health education.

The control group received the usual services from health extension workers. These participants only received a welcome message at the beginning to validate their entry into the study and a message at the end of the follow-up to thank them for their participation. However, at the end of the 6 months, the same education was provided for the controlled groups.

Data management and analysis

Data were collected using designed and adapted structured interviewer-administered questionnaires. To ensure consistency, the questionnaires were translated into the local language and then back-translated into English by another person. There was a 2 day training session for data collectors and supervisors. Supervisors and principal investigators conducted direct supervision daily. Data were analyzed using SPSS V. 24.0. Before analysis, the data were checked for normality and homogeneity and then analyzed and interpreted by a research team and a biostatistician. Intervention results were analyzed according to the reporting standards of the Consolidated Reporting Standards for Trials (CONSORT standards) (Figure 1). To compare the intervention and control arms, the rate of mammography screening at baseline, three months, and the end of 6 months was compared using chi-square and ANOVA. A general linear regression model for repeated measures was used to determine the effectiveness of the intervention and predict independent predictors of mammography screening. And nonparametric tests (Cochran *Q*) were used for dichotomous variables to measure the effect size of mammography screening intervention. Path analysis was used to determine the

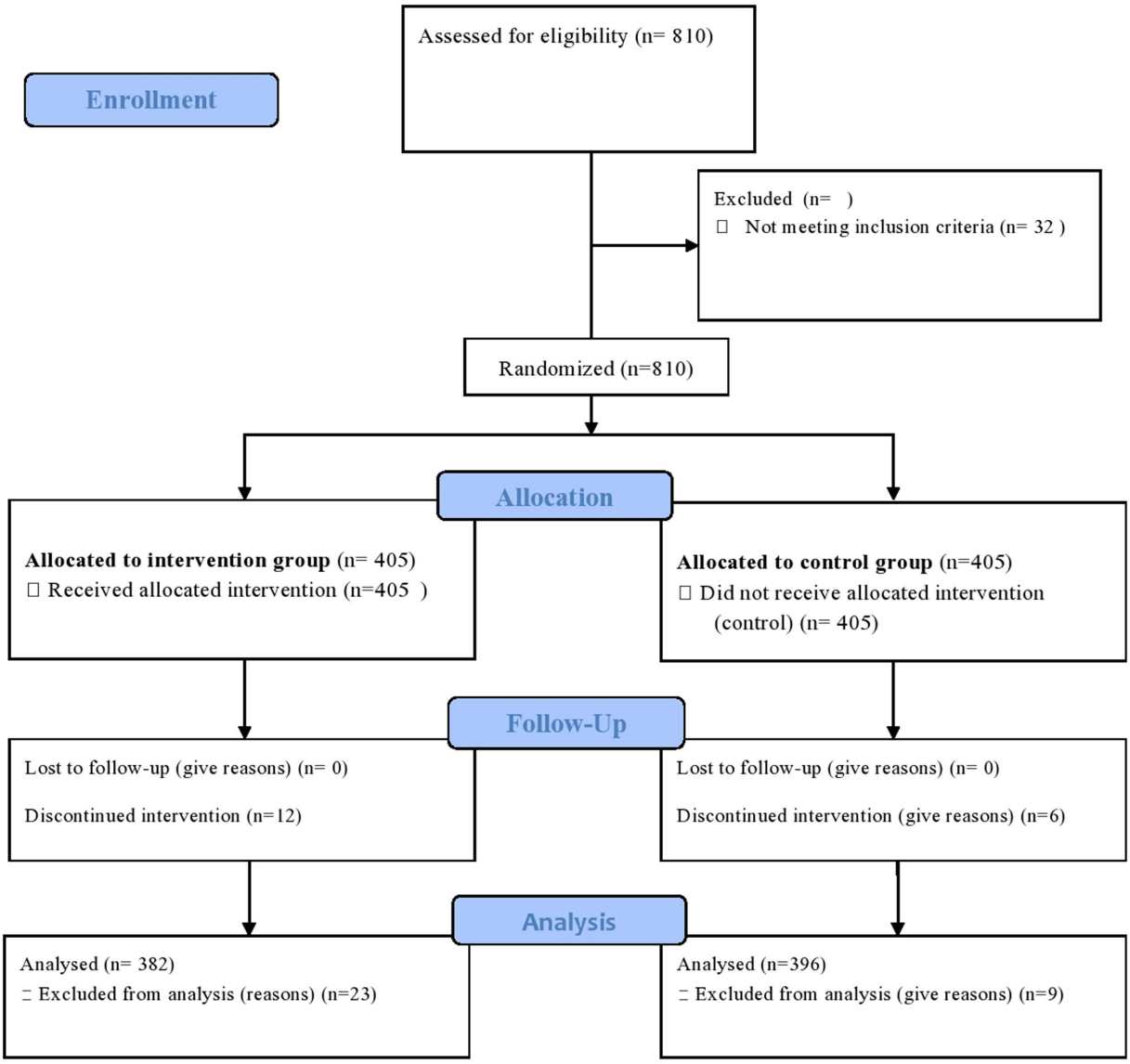

FIGURE 1
CONSORT flow diagram of the progress through the phases of a parallel randomized trial of two groups (that is, enrolment, intervention allocation, follow-up, and data analysis). Available at: http://www.consort-statement.org/consort-statement/flow-diagram.

direct and indirect effects of variables and to estimate the values of the coefficients in the underlying linear model at the end of 6 months.

Ethics statement

The Research Ethical Review and Approval Board (RERB) of Tehran Medical University approved this for ethics (IR.TUMS.SPH.REC.1396.4088). Subsequently, the Research and Ethical Review Approval Committee (RERC: 6-19/5524) of the Southern Ethiopia Regional Health Bureau approved the study. This study also strictly adhered to the ethical guidelines of the Helsinki Declaration of Medical Research (24). Letters from TUMS-IC and the Southern Ethiopia Regional Health Office was given to the Hadiya Zone Health Department for legal permission. After the objectives and benefits of the study were explained in detail, each participant provided written informed consent. Study participants had the right to withdraw from the study at any time. Participants were also informed that their responses would remain confidential and their names would not be disclosed. To maintain ethical issues, the same training was offered to the controlled groups at the end of data collection. During the course of our investigation, we strictly adhered to all international and institutional ethical conventions for research on randomized control trials. This study was registered in the Pan African Clinical Trial Registry database (https://pactr.samrc.ac.za/) with the unique identification number PACTR201802002902886.

Results

Socio-demographic characteristics of the participants

At baseline, a total of 405 participants were assigned to each group as the intervention and control groups. However, a total of 778 women of childbearing age responded to the interview questionnaire throughout the study period, yielding a response rate of 96.05%. The mean age of participants in the intervention and control arms was 31.9 (SD 7.4) and 32.2 (SD 7.8) years, respectively. Thirty-two participants were excluded because they did not attend two sessions of mammography training. There were no statistically significant differences between the two groups for any socio-demographic characteristics at baseline ($p > 0.05$). However, after the intervention, there were significant differences in ethnic group, educational status, occupational status and living conditions ($p < 0.05$) (Table 1).

Breast cancer knowledge and mammography screening

At the baseline of the study, 95.6% of participants in the intervention and control groups had heard of breast cancer. However, at the baseline, 36.9% of the participants had already heard of the all breast screening methods including mammography screening. However, after the intervention, all participants in the intervention group had heard about mammography screening. However, there were no significant changes in prevalence in the control group. Similarly, participants' mean comprehensive knowledge at baseline was 1.18 ± 0.54 and 1.17 ± 0.57 in both the intervention and control groups, with no significant difference. However, participants' mean comprehensive knowledge increased by 3.8 ± 0.48 and 3.7 ± 0.53 after three months and six months of the intervention, respectively. However, in the control group, the mean (1.17 ± 0.57) increased after three months and at the end of the intervention, but there was no significant difference at both time points of data collection (1.76 ± 0.51 and 1.77 ± 0.52) (Figure 2).

Perception towards breast cancer and mammography screening

The likelihood of mammography use of the participants was computed from the perception scores of the benefits minus barriers of the threat. Table 2 shows participants' perceptions of breast cancer and the use of mammography. As a result, the likelihood of using mammography at baseline was 30.06% in the intervention group and 29.01% in the control group. However, the likelihood of using mammography at three months and at the end of the intervention at six months was 56.48 and 56.77%, respectively. At baseline, perceived susceptibility to breast cancer had mean values of (mean ± standard deviation) (16.9 ± 4.3) in the intervention group and (16.5 ± 4.6) in the control group based on threat appraisals. However, there was a significant mean difference after three and six months of intervention ($p < 0.05$). Likewise, the perceived severity of breast cancer at baseline had corresponding average values of (mean ± standard deviation) (38.1 ± 8.6) in the intervention group and the control group (37.2 ± 9.1). However, the significant difference was observed at three and six months ($p < 0.05$). The likelihood ratings, perceived benefits, and barriers of breast cancer screening methods had an average value of (mean ± standard deviation) in the intervention group (18.9 ± 3.6 and 37.4 ± 5.5) and in the control group (18.9 ± 3.5 and 35.8 ± 5.7) at the baseline, respectively. However, there was a statistically significant mean difference after three months of intervention and at the end of six months in the intervention group (21.4 ± 1.5 and 21.4 ± 1.6) in the respective order compared to the control group ($p < 0.05$) (Table 2).

Regression analysis to identify independent predictors of mammography screening

To examine the effect of interventions on the study variables, a general linear model of repeated measures was used. Table 3 shows a general linear regression model analysis of repeated measures comparing the mean difference (two-way ANOVA for repeated measures). As a result, there was a statistically significant mean difference between the intervention and control groups in the model constructs for health belief and health motivation ($p < 0.005$). Likewise, the intervention group's mean perceived barrier score was statistically significantly lower after

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TABLE 1 Socio-demographic characteristics of the participants at baseline.

Variables	Category	Intervention and control categories		*p*-value
		Baseline		
		Intervention group (n = 405)	Control group (n = 405)	
		Number (%)	Number (%)	
Age	15–34	246 (60.7)	233 (57.5)	0.329
	35–49	159 (39.3)	172 (42.5)	
Current residence	Rural	205 (50.6)	320 (79.0)	0.427
	Urban	200 (49.4)	85 (21.0)	
Religion	Protestant	289 (71.4)	308 (76.0)	0.687
	Orthodox	70 (17.3)	71 (17.5)	
	Muslim	31 (7.7)	14 (3.5)	
	Catholic	15 (3.7)	12 (3.0)	
Marital status	Single	32 (7.9)	45 (11.1)	0.162
	Married	350 (86.4)	344 (84.9)	
	Divorced	23 (5.7)	16 (4.0)	
Educational status	Cannot read and write	265 (65.4)	188 (46.4)	0.0004*
	Can read and write	95 (23.5)	102 (25.2)	
	Primary school	11 (2.7)	30 (7.4)	
	High school	14 (3.5)	45 (11.1)	
	College and above	20 (4.9)	40 (9.9)	
Occupational status	House wife	282 (69.6)	285 (70.4)	0.045
	Employee	36 (8.9)	28 (6.9)	
	Merchant	28 (6.9)	39 (9.6)	
	Private business	33 (8.1)	32 (7.9)	
	Students	26 (6.4)	21 (5.2)	
Categorized income	<=1,500	366 (90.4)	377 (93.1)	0.339
	>1,500	39 (9.6)	28 (6.9)	

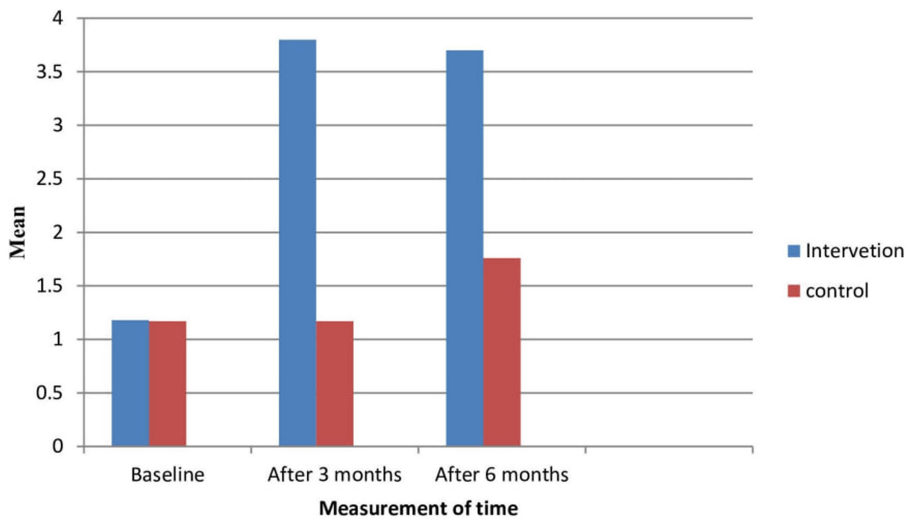

FIGURE 2
Knowledge of the participants about breast cancer and mammography screening in intervention and control groups.

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TABLE 2 Mean scores of perception of the participants about breast cancer and mammography screening based on health belief model constructs.

Variables	Score ranges	Intervention and control categories across the study period								
		Baseline		Mid-line (After 3 months)			End-line (After 6 months)			
		Intervention	Control	Intervention	Control	*p*-value	Intervention	Control	*p*-value
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Perceived benefits	5–25	18.9 ± 3.6	18.9 ± 3.5	21.4 ± 1.5	19.2 ± 4.6	0.000	21.3 ± 1.7	19.1 ± 4.5	0.00003
Perceived barrier	10–50	37.4 ± 5.5	35.8 ± 5.7	42.6 ± 3.2	35.2 ± 10.1	0.000	42.5 ± 4.1	35.7 ± 9.8	0.00001
Perceived Susceptibility	5–25	16.9 ± 4.3	16.5 ± 4.6	19.9 ± 2.1	16.4 ± 4.6	0.000	19.9 ± 1.9	17.0 ± 4.5	0.00001
Perceived severity	11–55	38.1 ± 8.6	37.2 ± 9.1	48.0 ± 3.8	41.5 ± 7.4	0.000	48.2 ± 2.2	41.8 ± 6.9	0.00011
Self-efficacy	5–25	18.1 ± 6.5	17.9 ± 7.5	21.4 ± 3.8	18.0 ± 7.9	0.000	21.4 ± 3.4	18.1 ± 9.3	0.00010
Cues to action	0–5	3.4 ± 2.2	3.7 ± 1.9	4.8 ± 1.5	3.9 ± 1.9	0.000	4.4 ± 1.8	3.8 ± 2.1	0.00014
Likelihood of mammography use	Weighted mean	30.06	29.01	56.48	31.31	0.000	56.77	31.21	0.00001

three and six months (mean difference = −2.054 between Time 1 and Time 2 and −1.942 between Time 2 and Time 3). However, the mean difference in action cues below one indicated that the intervention explained the least variance in the current context (Table 3).

Impact of health education on perceptions of each constructs (variance explained)

The variance of the impact of health education on perceptions of each construct was assessed and described in percentages. Table 4 shows the impact of each community health education intervention on each construct (variance explained by interventions). As a result, the community-based health education intervention accounted for 77.8% of the variance in knowledge, with a statistically significant effect on the intervention group ($p < 0.05$). In addition, the program had a statistically significant effect on health motivation, accounting for 41.4% of the variance ($p = 0.000$). Concerning threat appraisal, the intervention explained 20.8% of the variance in perceived susceptibility to and 23.5% of the variance in severity of breast cancer, with a statistically significant influence on the intervention group $p < 0.05$) (Table 4).

Impact of health education interventions on actual behavior (effect size measurement)

Actual breast screening behavior was assessed as past behavior. This part included all the options of screening as a past history screening (breast self-examination, breast clinical exam and mammography use). Table 5 shows the effect size for dichotomous variables on screening behavior as determined by nonparametric testing (Cochran *Q*). Accordingly, the impacts of intervention in hearing about breast cancer were demonstrated, and breast screening method at various time periods or under varied conditions had a statistically significant influence on the study population ($p < 0.05$). The intervention had a statistically significant effect on breast screening perception ($p < 0.05$) and yielded greater percentages in perception than actual screening in case mammography screening. In terms of information source, participants' exposure to media and health worker information rose considerably after intervention and was maintained in the maintenance stage (six months) ($p < 0.05$) (Table 5).

The effect of intervention across the study districts (Woredas)

Figures 3–8 presents the effects of interventions on outcomes across the study districts. This was analyzed by a general linear model for repeated measures (ANOVA) and regressive analysis obtained were depicted in the form of charts. Accordingly, generally, susceptibility, severity, benefits, self-efficacy, and cues to action scores were slightly the same across the intervention and control groups at baseline. Unlikely, the cues to action were significantly higher at baseline in Hossana town. However, after three and six months of intervention, the estimated regressive marginal means of measures indicated the

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TABLE 3 Mean difference of the perception scores to see the effect of the intervention using general regression model for repeated measure.

Variables	Measures (1, 2, 3)		Intervention vs Control (mean difference)	Standard error	95% Confidence interval for mean difference		*p*-value
					Lower bound	Upper bound	
Perceived susceptibility	Measure 1	Measure 2	1.359	0.198	0.879	1.840	0.00001
		Measure 3	1.328	0.220	0.856	1.834	0.00001
Perceived severity	Measure 1	Measure 2	6.152	0.262	5.282	9.221	0.00013
		Measure 3	6.316	0.265	5.431	9.182	0.00011
Perceived benefits	Measure 1	Measure 2	1.286	0.156	0.912	2.659	0.00001
		Measure 3	1.252	0.158	0.873	2.630	0.00001
Perceived barriers	Measure 1	Measure 2	−2.054	0.260	−2.570	−1.322	0.00010
		Measure 3	−1.942	0.268	−2.483	−1.196	0.00012
Perceived self-efficacy	Measure 1	Measure 2	2.721	0.176	2.299	4.890	0.00010
		Measure 3	2.723	0.173	2.342	4.754	0.00000
Cues to action score	Measure 1	Measure 2	0.453	0.087	0.236	0.667	0.00010
		Measure 3	0.437	0.084	0.325	0.685	0.00001
Health motivation	Measure 1	Measure 2	1.179	0.305	0.446	1.898	0.00001
		Measure 3	2.558	0.249	2.114	3.199	0.00012

Based on estimated marginal means; b. Adjustment for multiple comparisons: Bonferroni.

TABLE 4 General regression model analysis for repeated measures of mammography screening after adjustment for multiple comparisons (ANOVA) to see the effect of intervention.

Variables	Source	Df	*F*	Partial Eta squared	Sig.
Knowledge score	Intercept	1	34517.429	0.940	0.0000
	Intervention	1	3180.680	0.778	0.0001
Health motivation	Intercept	1	175552.614	0.957	0.0000
	Intervention	1	564.700	0.414	0.0000
Susceptibility	Intercept	1	45987.585	0.945	0.0000
	Intervention	1	206.951	0.208	0.0001
Severity	Intercept	1	73219.609	0.952	0.0000
	Intervention	1	241.420	0.235	0.0001
Benefit	Intercept	1	104699.566	0.954	0.0000
	Intervention	1	184.539	0.196	0.00011
Barrier	Intercept	1	141232.019	0.956	0.00011
	Intervention	1	682.320	0.459	0.00012
Self-efficacy	Intercept	1	69914.539	0.950	0.00003
	Intervention	1	250.449	0.242	0.00014
Cues to action	Intercept	1	10228.389	0.895	0.00011
	Intervention	1	8.041	0.010	0.00300

*Bonferroni tests of between-subjects effects of pairwise comparisons.

intervention districts increased in all outcome variables. As far as the graphical presentation of the estimated mean is concerned, there were no visible differences across the groups at the maintenance stage (at six months). In each graph, the variation was fully described in three lines, starting from baseline to six months (Figures 3–8).

The interactions of constructs of HBM on likelihood of mammography screening

In order to estimate the values of the coefficients in the underlying linear model and ascertain the direct and indirect effects of variables (HBM), path analysis was carried out. Measuring the direct and indirect effects of a set of independent variables on a dependent variable, path analysis is just a standardized partial regression coefficient that divides the correlation coefficients. The term "model identification" describes the number of items we must estimate (e.g., the path coefficients and correlations) in relation to the amount of information that can be derived from the data, be it about the observed variances of the variables or the covariance between them. The quantity of information in this regression model is just the number of paths that need to be estimated; it is easily identified. The result would be concluded that a causal model deleting the direct influence of threat and the indirect influence of susceptibility and severity channeled through benefits and barriers fits the data more strongly than did the model including these paths. The hypothesized causal paths effect of the model was explained by 64.3% that shows there is strong relationship of the variables significantly ($p < 0.005$). The path analysis model yielded direct and indirect effects, which are displayed in Figure 9 to illustrate the interaction. Final path model fitted for six hypothesized HBM constructs =0.019 Susceptibility + 0.077 Severity + 0.692 Benefits + 0.538 Barriers + 0.057 Self-Efficacy + 0.036 Cues to Action + 0.442 (Figure 9).

Discussion

This randomized controlled trial was carried out using the core elements of the health belief model, followed by a qualitative study that provided insights into the design and development of health education

TABLE 5 Effect size measured for general breast screening using non-parametric tests (Cochran *Q*).

Variables	Categories	Measurement of time (breast screening behavior)							
		Baseline		At 3 months		At 6 months		Effect size	
		Intervention *n* (%)	Control *n* (%)	Intervention *n* (%)	Control *n* (%)	Intervention *n* (%)	Control *n* (%)	At 3 months *n* (%)	At 6 months *n* (%)
Ever heard BC?	Yes	383 (94.6)	391 (97.0)	393 (100.0)	394 (98.7)	382 (100.0)	391 (98.7)	22.5 ($p = 0.000$)	22.5 ($p = 0.0001$)
Heard screening methods?	Yes	161 (39.8)	138 (34.1)	393 (100.0)	142 (35.3)	382 (100.0)	140 (35.4)	140.1 ($p = 0.000$)	132.2 ($p = 0.000$)
Source of information	Health worker	157 (97.5)	119 (86.2)	393 (100.0)	124 (87.7)	382 (100.0)	122 (87.1)	95.0 ($p = 0.025$)	95.0 ($p = 0.025$)
	Media	99 (61.5)	84 (60.9)	177 (45.0)	72 (50.7)	173 (45.3)	71 (50.7)	62.2 ($p = 0.000$)	61.7 ($p = 0.0001$)
	Relative	99 (61.5)	84 (60.9)	139 (35.4)	91 (64.1)	135 (35.3)	89 (63.6)	75.1 ($p = 0.000$)	74.1 ($p = 0.0001$)
	Friends	81 (50.3)	59 (42.8)	167 (42.5)	68 (47.9)	164 (42.9)	67 (47.9)	0.7 ($p = 0.413$)	0.7 ($p = 0.413$)
BC screened	Yes	47 (29.2)	23 (17.2)	107 (27.2)	32 (22.5)	99 (25.9)	22 (15.7)	70.0 ($p = 0.000$)	70.0 ($p = 0.0001$)
Method of screening used?	Mammography	3 (6.4)	3 (13.0)	3 (2.8)	2 (6.3)	6 (10.6)	5 (21.0)	3.0 ($p = 0.083$)	1.0 ($p = 0.317$)
	BCE	12 (25.5)	5 (21.7)	9 (8.4)	5 (15.6)	9 (9.1)	5 (21.7)	3.0 ($p = 0.083$)	3.0 ($p = 0.0831$)
	BSE	32 (68.1)	15 (65.2)	95 (88.8)	25 (78.1)	90 (90.9)	18 (78.3)	73.0 ($p = 0.000$)	61.0 ($p = 0.0001$)
Frequency of breast screening	Sometimes	27 (57.4)	13 (56.5)	65 (60.7)	19 (59.4)	57 (57.6)	12 (52.2)	44.0 ($p = 0.000$)	29.0 ($p = 0.0001$)
	Usually	1 (2.1)	2 (8.7)	5 (4.7)	2 (6.3)	5 (5.1)	2 (8.7)	4.0 ($p = 0.046$)	4.0 ($p = 0.046$)
	Consistently	4 (8.5)	3 (13.0)	16 (15.0)	7 (21.9)	16 (16.2)	6 (26.1)	16.0 ($p = 0.000$)	15.0 ($p = 0.0001$)
	Others (once, ill)	15 (31.9)	5 (21.7)	21 (19.6)	4 (12.5)	21 (21.2)	3 (13.0)	5.0 ($p = 0.025$)	4.0 ($p = 0.046$)

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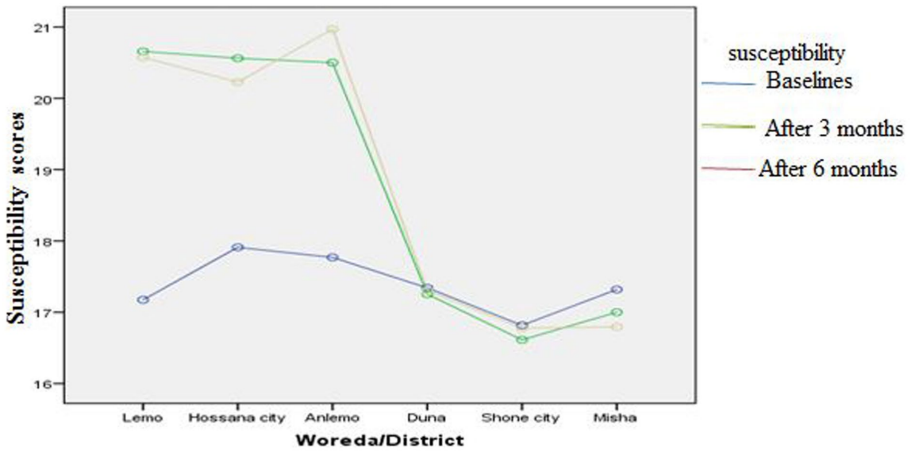

FIGURE 3
The effect of intervention on susceptibility of the participants across the study districts.

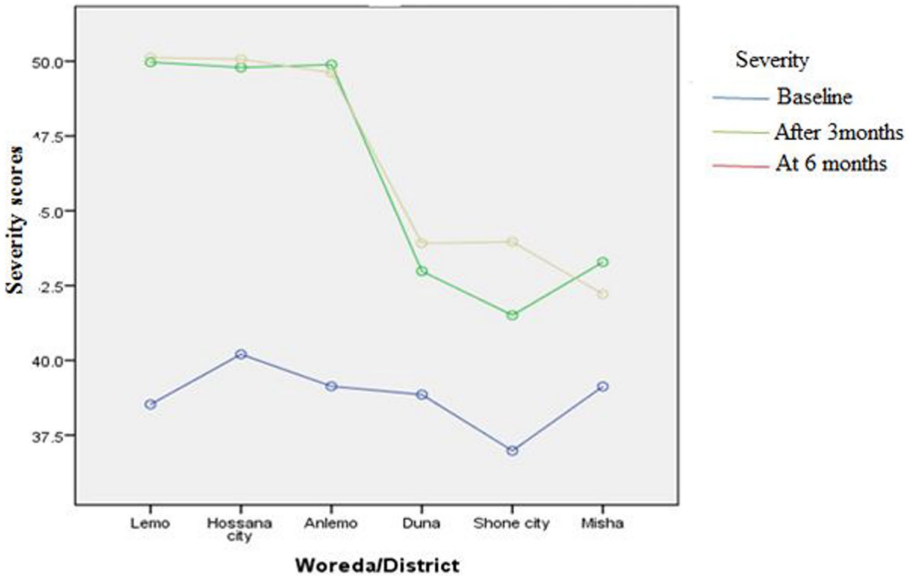

FIGURE 4
The effect of intervention on severity of the participants across the study districts.

interventions for mammography screening. Qualitative and cross-sectional studies at baseline found that there was a strong interplay between perception and breast screening (published elsewhere) (21).

Model-based interventions to improve mammography are generally effective across each construct, at least in terms of improving perceptions of screening and general knowledge. This is similar to studies conducted in several parts of the world that found that education based on tasted behavioral models increases the likelihood of adopting a certain behavior when appropriately targeted (25–27). This finding is also supported by the fact that some studies using single behavioral approaches targeting patients were ineffective, confirming those multi-approach interventions were successful (26, 28). The possible explanation could be that no study focuses on the intensity of optimal intervention where the doze and peak of the intervention are reached rather than simply giving education intervention on the specific behavior of the interest. This also suggested that there was a strong interaction between perception and mammography screening in the qualitative and baseline survey of this study, which was published elsewhere (21).

This study found that repeated health education interventions increased the knowledge of the intervention group of participants significantly and expressed a knowledge variance of 77.8% at different points in time. This figure is greater than the results obtained in various interventional and systematic reviews synthesis studies (15, 16, 25–28). This might be the current study, which used various methods to demonstrate mammography screening methods and intense mammography education every fifteen days. The present study found that after three and six months of the intervention, the intervention group had a statistically significant increase in threat appraisals (susceptibility and severity), efficacy appraisals (benefit outweighed barrier), and self-efficacy and knowledge of the study participants. This is similar to the several systematic reviews and

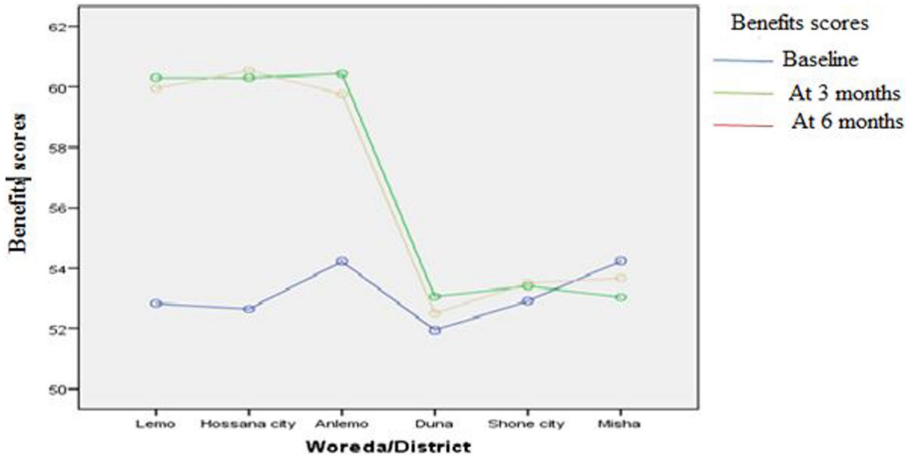

FIGURE 5
The effect of intervention on benefits of the participants across the study districts.

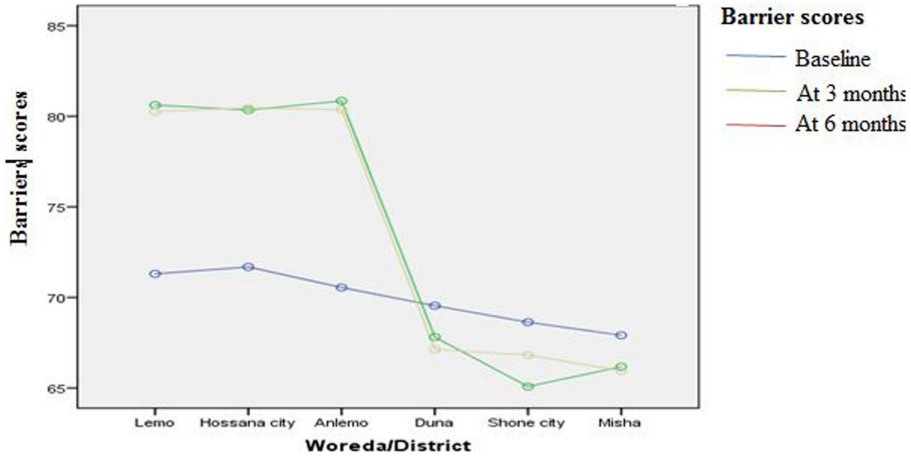

FIGURE 6
The effect of intervention on barriers of the participants across the study districts.

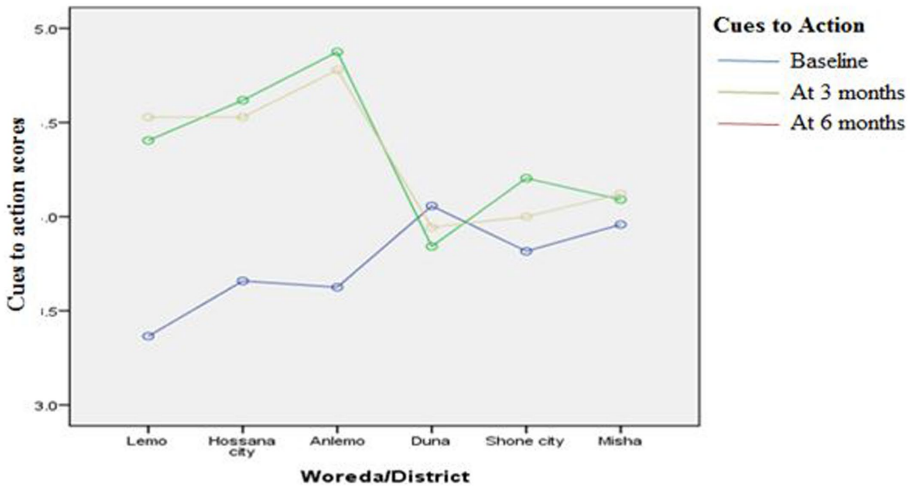

FIGURE 7
The effect of intervention on cues to action of the participants across the study districts.

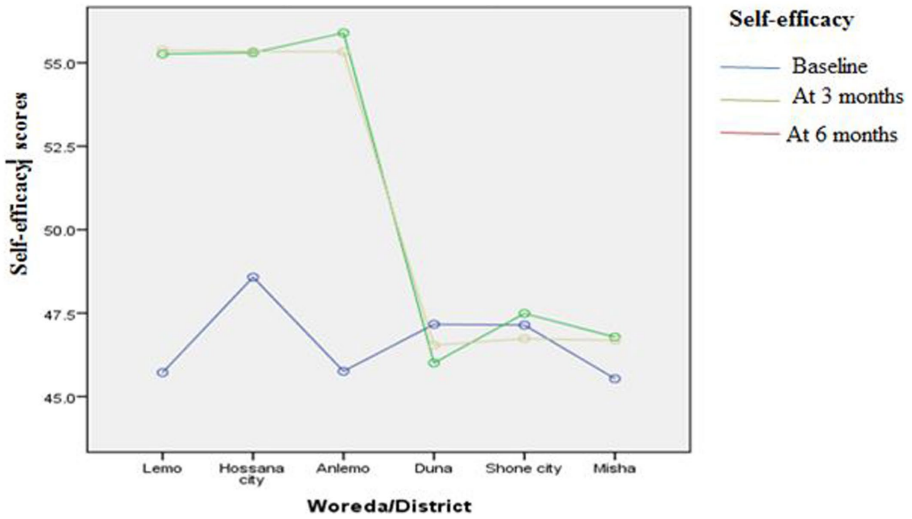

FIGURE 8
The effect of intervention on self-efficacy of the participants across the study districts.

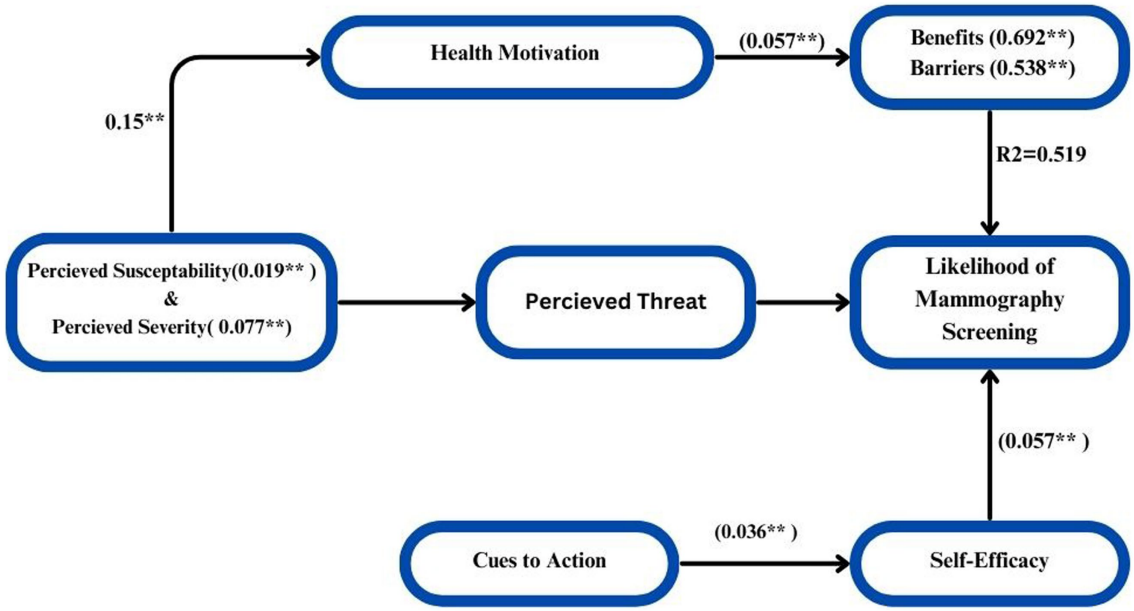

FIGURE 9
Final structure model with all HBM hypothesized causal paths. $^{**}p < 0.001$.

meta-analyses conducted in the mammography use education that documented model-based education on breast screening as having a successful ending (26, 28, 29). However, naturally, the uptake of breast screening behavior varies from place to place. Our preceding baseline qualitative findings showed a strong interplay between perception and mammography screening and were published elsewhere (21).

The systematic review on health promotion interventions as a way of knowing the situation of the world and local evidence for this randomized trial showed that mammography screening is determined by the actual accessibility of the services and affordability of the individual women (28). The current study found that though the actual screening is low, the intention to have mammography screening has shown statistically higher scores of barriers and lower scores of benefits.

The current study found that health motivations and valuing one's health status significantly explained higher variances in the intervention group than the control group. Naturally, after certain reminders, people value or are motivated to be healthy in their lives (30, 31). Previous publications as well as successful motivational interventions confirm the persuasiveness of personal and individualized risks (32, 33). This is supported by the concept of HBM, which states that the perceived benefits of individuals increased where there were no or limited barriers to hinder preventive health behavior (18, 19).

The current study also found that the practice of actual breast screening by mammography showed no change after intervention. Previously published studies also supported this idea (34–36). This is supported by the concept of HBM, which states that the perceived

benefits of individuals increased where there were no or limited barriers to hinder preventive health behavior (19). The possible reason for this could be that mammography is largely situated in the center of Ethiopia, and the costs associated with it are extremely high.

This study's strength is that it ensures and promotes more control over the intervention, allowing for a clear distinction between the intervention and control groups. Another advantage of this randomized controlled trial is that it produces an unbiased estimate of the effect for both the intervention and control groups. To my knowledge, this is one of the first randomized controlled trials in Ethiopia to apply community-based interventions, which may aid in recognizing the value of intervention rather than simply describing them.

As limitations, because this randomized controlled trial intervention is based on health belief model constructs, thus the model is a psychological model, it does not take into account other factors that may influence health behaviors, such as environmental or economic factors, social norms, and peer influences, indicating the need to fulfill enabling factors. The other limitation of the model is that it may have a gap between actual behavior and psychological responses, i.e., participants who were in a positive zone may not be in a protective zone, which may lead to over-reporting of safe behavior. The possible limitation is that the sufficiency of information may vary depending on the person delivering health education, though the intervention document is the same. The other possible limitation is a trial using health education interventions at the district level, in case information contamination may exist due to the nature of behavioral intervention research.

In conclusion, the study emphasizes the advantages of HBM interventional initiatives, such as educational and motivational programs, in improving public perception of mammography screening. Repetitive education has been shown to improve comprehension of the mammography problem and increase willingness to attend screening. Though a slight difference is normal, there was no significant difference between the districts; instead, all intervention districts had significantly higher perceptions. This study also found that community-based intervention, followed by an exploratory qualitative approach using gap analysis, had a significant impact on mammography screening rates. The results of this study showed that actual mammography use was very low. This shows there is a need to bring the services as close as the people can get and afford to avail screening services in the community. As for future prospects, it is clear that interventions aiming to improve general breast health lead to an increase in the likelihood of mammography screening among reproductive-age women in Ethiopia. Organizations involved in breast cancer prevention and control should focus on health education programs to enhance mammography use benefits and increase women's self-efficacy in screening. Future researchers should examine the intensity and range of information to determine the optimal intervention dose and peak.

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 authors.

Ethics statement

The studies involving humans were approved by the Ethics committee of Tehran University of Medical Sciences. 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

FA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. GG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. RS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. ES: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MY: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. ZK: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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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

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