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Treatment strategies for head and neck cancer confronting cancer through multidisciplinary collaboration

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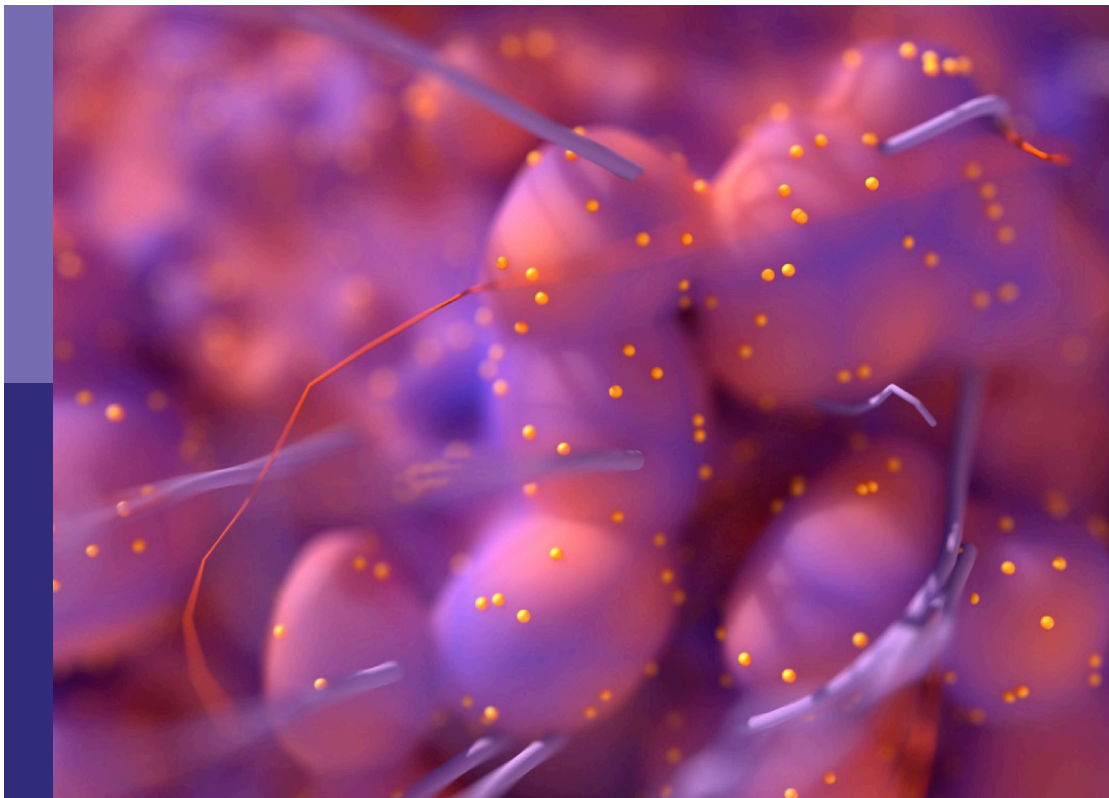
Published in
Frontiers in Oncology



ISSN 1664-8714
ISBN 978-2-8325-6096-9
DOI 10.3389/978-2-8325-6096-9

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Treatment strategies for head and neck cancer confronting cancer through multidisciplinary collaboration

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Citation

Yamazaki, T., Yokota, T., Hsieh, J. C.-H., Saito, S., eds. (2025). *Treatment strategies for head and neck cancer confronting cancer through multidisciplinary collaboration*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-6096-9

Table of contents

frontiers | Frontiers in Oncology

TYPE Review
PUBLISHED 30 August 2023
DOI 10.3389/fonc.2023.1257853

OPEN ACCESS

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RECEIVED 13 July 2023
ACCEPTED 14 August 2023
PUBLISHED 30 August 2023

CITATION
Yokota T, Mukaigawa T, Yasunaga Y, Ogawa H, Onoe T, Yurikusa T and Yamashita A (2023) Multidisciplinary tumor board for head and neck cancer from the perspective of medical oncologists—optimizing its effectiveness.
Front. Oncol. 13:1257853.
doi: 10.3389/fonc.2023.1257853

Multidisciplinary tumor board for head and neck cancer from the perspective of medical oncologists—optimizing its effectiveness

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Head and neck cancer (HNC) treatment is becoming increasingly multidisciplinary, and patient characteristics vary. Therefore, a multidisciplinary tumor board (MTB) is essential in clinical practice. This review provides insights into the benefits and tips for improving head and neck MTB from the perspective of medical oncologists. The MTB is a platform to discuss the optimal application of the standard of care to each case, reach a consensus, and establish a recommendation to support patients' decision-making. A productive and educational MTB also provides an opportunity to share information on ongoing clinical trials with physicians. Case presentations should be systematic to discuss all new and challenging cases before, during, and after the treatment. Human resource development, particularly of head and neck medical oncologists, is crucial. The type of multidisciplinary network between medical staff and the extent of patient intervention differs among MTB teams. Subsequently, a virtual MTB can establish a medical network between institutions that will contribute to the equalization and centralization of head and neck oncologic care.

KEYWORDS

head and neck oncology, medical oncologists, multidisciplinary intervention, multidisciplinary tumor board, evidence-based medicine, personalized medicine

Abbreviations: SCCHN, squamous cell carcinoma of the head and neck; LA, locally advanced; RT, radiotherapy; CRT, chemoradiotherapy; CDDP, cisplatin; ICT, induction chemotherapy; TPF, Docetaxel plus CDDP and 5-fluorouracil; CGP, comprehensive cancer genomic profiling; TKIs, tyrosine kinase inhibitor.

1 Introduction

Treatment targets and strategies for head and neck cancer (HNC) are becoming more diversified and complicated. Indeed, clinicians need to consider the general condition, tumor staging, comorbidities, current and previous therapies, and patient preferences to ensure optimal cancer care for each patient. Therefore, a multidisciplinary approach is crucial in HNC care.

The National Cancer Institute (NCI) defines a multidisciplinary tumor board (MTB) as a treatment planning approach in which a group of health-care professionals, who are experts in different specialties, review and discuss the medical condition and treatment options of patients (1). MTB are now conducted worldwide for the management of patients with various cancers. A review by Fleissig et al. reported the effectiveness of MTB in terms of better team dynamics, communication, and educational opportunities for health care professionals, improved patient satisfaction, and improved clinical outcomes for patients considered by MTB versus individual care (2). Furthermore, a study revealed that a review by MTB at an NCI-designated cancer center has a diagnostic impact for many patients with breast cancer (3).

Clinical practice in HNC may differ by country owing to the reimbursement system, socioeconomic situation, and culture. For instance, HNC practice in Japan has long been led by otorhinolaryngologists, head and neck surgeons, and oral and maxillofacial surgeons. Japanese physicians hesitated to extrapolate evidence from Western countries to their practice, particularly in HNC pharmacotherapy. Since the 2000s, pharmacotherapy has been recognized as an independent subspecialty of cancer treatment in Japan, owing to its complexity and evolution. With the increasing need for knowledgeable and experienced HNC medical oncologists, multidisciplinary approach through MTB has been considered best practice in the care of HNC.

Here, we reviewed the benefits of MTB in the clinical practice of HNC from the perspective of medical oncologists. We then discussed suggestions for implementing a productive MTB. Finally, we addressed MTB concerns that require improvement and future directions.

2 The importance of MTB in the clinical practice of HNC

A recent meta-analysis demonstrated that the MTB improved cancer evaluation processes and survival across multiple subtypes (4). Notably, one study demonstrated that treating squamous cell carcinoma of the head and neck (SCCHN) *via* a multidisciplinary team improved survival (5). Furthermore, the Spanish Society for Head and Neck Cancer elaborated expert consensus on the multidisciplinary approach for SCCHN, and concluded that MTB is essential for achieving the best results, not only in terms of outcome, but also in terms of organ-function preservation and quality of life (6, 7).

HNC treatment is more multidisciplinary than other malignancies, because managing patients with locally advanced, recurrent, or metastatic HNC is complex. For successful HNC treatment, close cooperation among medical staff is necessary for supportive care of mucositis, skin toxicity, and nutritional support in CRT management. Various specialties provide supportive care for individual patients; thus, MTB offers an opportunity to share patient information among medical staff. Furthermore, expertise is required for its management. For instance, the development of minimally invasive surgical techniques, including transoral laser microsurgery and transoral robotic surgery (TORS), has resulted in surgery being the primary treatment for oropharyngeal cancer (8). Currently, intensity-modulated radiotherapy is more frequently used than three-dimensional conformal radiation for definitive and postoperative CRT. Proton beam and boron neutron capture therapies have also been introduced into clinical practice for HNC (9). Near-infrared photoimmunotherapy targets the EGFR and is a novel cancer phototherapy molecule (10). Furthermore, molecular targeting agents such as anti-EGFR antibodies, immune checkpoint inhibitors, tyrosine kinase inhibitors (TKIs), and classical cytotoxic agents are available for HNC treatment. In practice, it is challenging for recent clinicians to make therapeutic decisions and manage patients within an organ-specific team. Thus, MTB discussion is crucial in assessing the indications for each treatment modality and making a consensus decision.

HNC prevalence in geriatric patients is increasing (11–13), and most cases are associated with heavy smoking and drinking habits. Therefore, patients with HNC are often diagnosed with cardiovascular or cerebrovascular diseases, chronic obstructive pulmonary disease, diabetes, and renal impairment, which reduces their performance status. In MTB discussions, patient comorbidities and disease characteristics should guide the preferred treatment option.

Taken together, MTB is the best setting for such medical staff interactions.

3 Composition of HNC-MTB member

HNC-MTB membership varies depending on the institution. Specialists in treatment modalities, such as head and neck surgeons, otorhinolaryngologists, radiation oncologists, plastic surgeons, and medical oncologists, primarily comprise MTBs. Advice from diagnostic radiologists and pathologists helped us with the initial staging, histopathological diagnosis, and histological examination of the surgical specimens. In cases of skull base surgery, eye tumors, and malignant melanoma of the head and neck, neurosurgeons, ophthalmologists, and dermatologists may be included in the MTB. In addition to medical doctors, MTB membership is frequently expanded to include dentists, dental hygienists, physical therapists, dieticians, nurses, pharmacists, and social workers who provide supportive care. Furthermore, medical students' participation

should be encouraged because participating in the MTB is an oncology practice useful for their education. Head and neck surgeons of organ-specific divisions are often selected as the chairperson in the MTB. However, rotation may be considered.

4 MTB benefits from the perspective of medical oncologists

4.1 Establishing collaboration among medical staff in multidisciplinary cancer treatment

MTB helps to identify high-risk patients after surgery and to discuss on indications for postoperative CRT, induction or neoadjuvant chemotherapy, and optimal supportive care approaches to reduce treatment-related morbidity (14). Advanced tongue cancer treatment is an example of a multidisciplinary approach with the collaboration of medical oncologists, radiation oncologists, radiologists, head and neck surgeons, and reconstructive surgeons in HNC. This synergy enables the prompt development of an effective treatment plan for each patient in a series of glossectomies, tongue reconstruction, percutaneous endoscopic gastrostomy, and postoperative CRT (15). Furthermore, dieticians, physical therapists, dentists, and dental hygienists provide nutritional support (16, 17), rehabilitation of chewing ability and oral intake, oral care, and follow-up of radiotherapy-related toxicities, such as osteoradionecrosis, to maintain patients' quality of life (QOL).

Medical oncologists are general physicians in cancer care who communicate closely with patients and their families. Medical oncologists are pivotal, particularly in HNC pharmacotherapy; however, they should also consider local and systemic therapies in multimodal combination and sequencing (18). Consequently, they need to be able to negotiate with other specialists as coordinators appropriately. For instance, surgical resection or palliative radiation may be required to manage locoregional diseases, even during palliative chemotherapy for recurrent or metastatic (RM)-SCCHN. In head and neck emergencies, such as tumor bleeding, infection, and airway obstruction, early referral to a head and neck surgeon is recommended. Thus, head and neck medical oncologists should always consider diverse treatment strategies.

Esophageal cancer and head and neck cancers are frequently observed simultaneously (19–21); however, their treatment strategies are often complex and challenging. The MTB, in which gastrointestinal oncologists participate, is ideal for discussing how to approach each cancer—simultaneously or sequentially. The treatment strategies include synchronous resection of both cancers, synchronous CRT for both cancers, staged resection and CRT (22, 23), or induction chemotherapy for each cancer (24). These options were selected per case based on tumor staging, invasiveness, complications, curability, and QOL, such as swallowing function. Treating multiple synchronous cancers allows medical oncologists to demonstrate their tumor-agnostic treatment skills.

4.2 Improvement of pharmacotherapy quality——checking the complex and diverse pharmacotherapy system

Pharmacotherapy is an important treatment modality for patients with HNC. CDDP is essential in HNC treatment, and CDDP-based concurrent CRT confers a survival benefit and laryngeal preservation in locally advanced (LA) SCCHN over radiotherapy alone (25). Treatment with cetuximab and immune checkpoint inhibitors improves the prognosis of patients with RM-SCCHN. Multitarget and selective TKIs are used for treating unresectable thyroid cancer (26–28). Thus, medical oncologists play roles in determining pharmacotherapy indications and fully and safely utilizing these agents.

Since HNC patients are often geriatrics and typically have several comorbidities, standard therapy is applied for a limited number of patients in real-world clinical practices. For instance, CDDP administration is associated with toxicities and serious adverse events in elderly patients or those with cardiac, renal, or neurogenic dysfunction. Therefore, surgeons and radiation oncologists often select radiotherapy alone for patients with LA-SCCHN. With effective communication among medical oncologists, surgeons, and radiation oncologists, MTB members may propose alternative treatment options to reduce or prevent the toxicity of high-dose CDDP-based CRT, including CDDP dose modification, modified administration scheduling, or use of alternative drugs based on individual organ function (29).

Notably, personalized treatment strategies should be proposed based on the risk-benefit ratio of each treatment option for patients ineligible for standard care. The following challenges may be discussed by the MTB for patients for whom the optimal standard care is unsuitable (Table 1):

1) Definitive or postoperative CRT for patients for whom CDDP is unsuitable.
2) Induction chemotherapy for patients with LA-SCCHN with high-risk disease or those for whom organ preservation is the goal but are ineligible for the docetaxel plus CDDP and 5-fluorouracil regimen.

4.3 Establishing a consensus to support patients' decision-making

Some patients with HNC need support in decision-making regarding treatment modalities and nutritional support. For

TABLE 1 Issues to be discussed in head and neck MTB.

Tumor types	Treatment setting	Topics
SCCHN, resectable	Curative setting	Choice of upfront surgery or non-surgical treatment
LASCCHN	Definitive RT or CRT	Radiation dose, fraction, field Alternatives to definitive CRT regimen in CDDP-ineligible patients
LASCCHN, high-risk stage II laryngeal cancer	Definitive RT or CRT	Choice of RT alone or CRT
LASCCHN	ICT	Indication and purpose of ICT Alternatives to the ICT-TPF regimen
LASCCHN	Post-definitive RT/CRT	Diagnosis of post-definitive RT/CRT and its management Indication for salvage surgery
LASCCHN, oral cancer	Neoadjuvant chemotherapy	Indication and purpose of neoadjuvant chemotherapy
LASCCHN, pharyngeal/laryngeal/oral cancer, and others	Surgery and reconstruction	Surgical technique—such as setting the resection margin and reconstruction
LASCCHN, nasal and paranasal sinus cancer	Skull base surgery	Surgical technique, operation workflow
Postoperative high-risk SCCHN	Postoperative CRT	Choice of RT alone or CRT Alternatives to postoperative CRT regimen in CDDP-ineligible patients
Recurrent or metastatic disease	Palliative pharmacotherapy	Indication for pharmacotherapy Treatment regimen Indication for CGP test in rare cancer
	Palliative RT	Indication for re-irradiation Indication for stereotactic radiosurgery
Unresectable thyroid cancers	Palliative pharmacotherapy	Indication and timing of initiation of TKIs Indication for CGP test
All	Definitive and palliative setting	Symptomatic management Nutritional management Management for acute and late treatment-related toxicities Functional assessment Psychological and socioeconomic issues

SCCHN, squamous cell carcinoma of the head and neck; LA, locally advanced; RT, radiotherapy; CRT, chemoradiotherapy; CDDP, cisplatin; ICT, induction chemotherapy; TPF, Docetaxel plus CDDP and 5-fluorouracil; CGP, comprehensive cancer genomic profiling; TKI, tyrosine kinase inhibitor.

instance, CRT is preferred for young patients with LA-SCCHN who wish to preserve their organs; however, total laryngectomy is often performed in elderly patients at high risk of aspiration pneumonia induced by definitive CRT. The patient can decide whether to undergo laryngectomy or CRT; however, medical support is essential for decision-making directly related to survival outcomes and QOL, such as eating, swallowing, and voice functions. Rather than always leaving the choice of treatment to the patient and family, establishing a consensus on the recommended treatment by the MTB and guiding the patient in decision-making are fundamental.

4.4 Sharing information on ongoing clinical trials

High-volume centers are often invited to company- and physician-initiated clinical trials in head and neck oncology. These institutions are responsible for participating in clinical trials. Head and neck surgeons and otorhinolaryngologists often make primary contact with new patients with HNC. The MTB shares information with these divisions on ongoing clinical trials and announces the recruitment of candidates regularly.

5 Tips for implementing a productive MTB

5.1 To optimally present all new cases

All new patients should be presented and examined by multidisciplinary specialists on the MTB, regardless of planning their initial treatment strategies, such as upfront surgery, radiotherapy, or endoscopic resection, for early-stage cancer because alternative treatment options may be proposed. The approval in the MTB should be documented.

Cases should be sequentially presented based on the categorization from the perspective of each medical department. Thus, all cases can be systematically included in the agenda. The categorization may include the following examples (Table 1):

1) For cases mainly treated with surgery with or without reconstruction, surgical techniques, such as setting the resection margin and reconstruction, are discussed among surgeons. Neurosurgeons and ophthalmologists also participate in discussions on skull base surgery for nasal and paranasal sinus cancers.
2) The dose, fraction, field, and palliative or definitive settings are determined for cases primarily treated with radiation. Indications for stereotactic radiosurgery of metastatic lung lesions and re-irradiation are also discussed.
3) New cases that require multimodal treatment.
4) Challenging cases during or after treatment (Section 4.2)

Head and neck medical oncologists should have the following discussions (Table 1).

1) Upfront surgery or non-surgical treatment in resectable laryngeal and pharyngeal cancers
2) Indications for induction chemotherapy before CRT and its purpose, such as survival improvement with a distant control and laryngeal preservation
3) Indication for neoadjuvant chemotherapy before surgery for oral cancer (30)
4) Definitive radiotherapy alone or CRT for high-risk stage II laryngeal cancer (31)
5) Adjuvant CRT or radiotherapy alone for postoperative high-risk SCCHN
6) Pharmacotherapy indication for recurrent and metastatic disease
7) Risks and benefits of re-irradiation for recurrent diseases
8) TKI initiation time for thyroid cancer
9) Indication for a comprehensive genomic profiling test for rare cancer

5.2 To discuss challenging cases during or after treatment

In addition to all new HNC cases, prompt information sharing on challenging cases within the MTB is necessary during or after treatment with surgery, radiation, or chemotherapy (Table 1). The patients tolerate the standard of care; however, the subsequent treatment course for each individual varies. Therefore, irregular adverse events may occur during the treatment.

For instance, the MTB can reach a consensus on posttreatment diagnosis and management after definitive CRT, enabling us to perform additional diagnostic modalities, such as free needle biopsy, positron emission tomography, or observation. Medical oncologists find it challenging to resolve anatomical and radiological diagnostic issues; therefore, asking head and neck surgeons and diagnostic radiologists for their opinions on MTB helps. Furthermore, determining the indications for salvage surgery for residual disease after CRT is possible. MTB can also confirm whether patients with RM-SCCHN have indications for palliative RT aimed at locoregional control (Table 1).

5.3 Discussion on an individual case basis using evidence

Standards of care and clinical practice guidelines are established based on evidence from clinical trial data. Therefore, determining a treatment plan for patients without these factors is impossible. First, all physicians involved in treating HNC should understand the updated guidelines.

However, MTB is responsible for discussing the preferred treatment strategy on an individual case basis, using evidence and guidelines. The National Comprehensive Cancer Network guidelines provide recommendations for the appropriate care of approximately 95% of patients (32). However, administering only standard treatment to each case is not feasible. Physicians should recognize that the patient characteristics in clinical trials do not completely reflect those in clinical practice. Most patients with HNC cannot be completely treated according to guidelines alone owing to various factors such as organ dysfunction, comorbidities, multiple cancers, and socioeconomic issues such as alcohol dependence, living without relatives, and being on welfare. Unfortunately, these patients are often declared untreatable and treated out of pocket because of the unavailability of standard care or a lack of evidence. Ironically, this may be the disadvantage of guideline supremacy. Evidence derived from clinical trials and standard treatments is essential; however, sufficient evidence to manage all patients with HNC with varying pathophysiology is not available. Therefore, individual patient conditions should be considered in MTB when applying these recommendations. Furthermore, patients' requests to their healthcare providers should be provided according to their diverse values.

Thus, the MTB is a forum for discussing the appropriate assessment and response to each patient's condition based on their physical and social needs rather than solely relying on evidence (33).

5.4 To create a relaxed atmosphere in MTB

MTB educates medical students, residents, and fellowship-trained young doctors; thus, they should regularly present cases and actively exchange opinions from the standpoint of their respective specialties. However, because medical staff with different positions and occupations gather at the MTB, young doctors hesitate to express their opinions. Therefore, creating a relaxed atmosphere where participants can freely speak on various issues may create a high-quality democratic MTB.

6 Issues to be solved in HNC multidisciplinary team

Human resource development is critical. Recently, medical oncologists with backgrounds in head and neck surgery and otorhinolaryngology have been trained. However, the number of head and neck medical oncologists remains small, and a large regional disparity exists. HNC is a highly specialized field; however, many aspects are to be learned from other fields, such as gastrointestinal and respiratory oncology. Therefore, organ-agnostic training programs for head and neck medical oncologists should be promoted in university hospitals and cancer centers.

Attending physicians are central to patient management as leading physicians (Figure 1). The attending physician for patients undergoing non-surgical treatment in the MTB team may vary depending on the institution and region. Medical oncologists are involved in non-surgical treatment as attending physicians in the EU, the USA, and high-volume centers in Japan. Head and neck surgeons, otorhinolaryngologists, and radiation oncologists are in general hospitals in Asia-Pacific countries/regions because of the limited number of head and neck medical oncologists.

Non-attending physicians in MTBs tend to focus only on the treatment modalities of their specialties, such as radiation therapy, pharmacotherapy, reconstruction, and rehabilitation. Thus, they are undertaking only one part of the multimodal treatments. However, the attending physician oversees various patients' management for general medical care and supportive and socioeconomical care (Figure 1). For instance, in treating CRT, the attending physician is involved in obtaining informed consent, managing systemic care, administering all medications, observing acute and late radiotherapy-related adverse events, emergency hospitalization, medical insurance documentation, and communication with a home doctor. However, all these responsibilities are burdensome for one physician. Approximately 56% of oncologists report an episode of emotional stress in caring for cancer patients, known as burnout, at some stage of their careers (34).

Therefore, all physicians in the MTB should view patients holistically and be proactively involved in systemic management in treating their patients. One of the solutions in the limited human resources may be to rotate attending physician among the medical departments. By doing so, it would be possible to avoid concentrating the burden of patient management on a particular department. If physicians follow each other in a multidisciplinary team and promote specialization, division, and efficiency of labor, a specific department or staff members will not be exhausted, and the resultant mental relaxation of the staff will positively affect patients and their families.

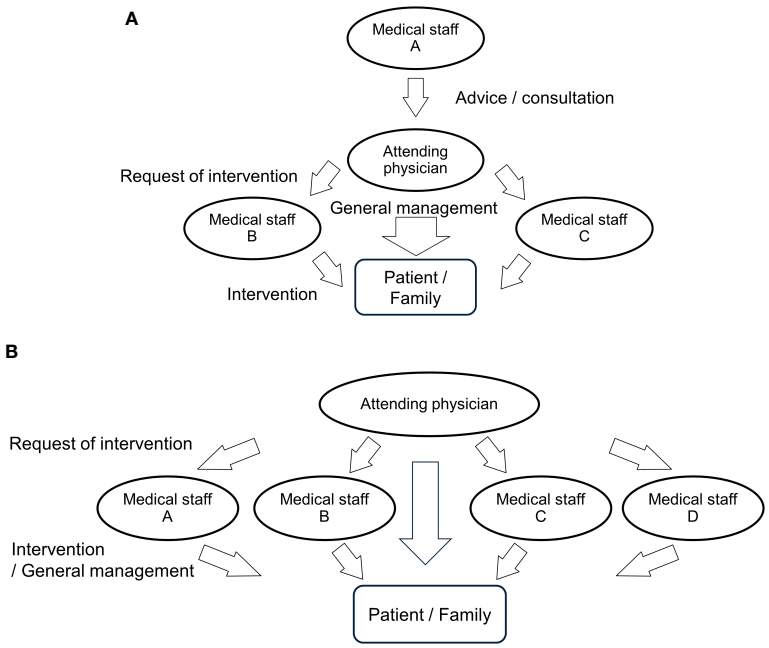

FIGURE 1
Type of multidisciplinary network among medical staff. The type of multidisciplinary network among medical staff and the extent of patient intervention differ among MTB teams. **(A)** Attending physicians are in charge of general management and communicate closely with patients. Staff A provides the attending physician with advice but lacks direct contact with patients. Medical staff B and C work on their treatment modalities at the request of the attending physician; however, they are not as involved in general management as attending physicians. **(B)** All staff members are involved in patient management, including treatment modalities and general management.

7 Conclusions and future direction of the head and neck MTB

The treatment strategy for HNC is becoming more complex and multidisciplinary, and patient characteristics vary; therefore, MTB is indispensable in clinically treating HNC. The MTB discusses the optimal application of standard care on an individual case basis, through which a consensus MTB recommendation is established to support patients' decision-making. Additionally, MTB is educational, and case presentations should be systematic.

Having faced difficulties with limited clinical resources and healthcare office availability during the COVID-19 pandemic, head and neck care coordination has changed substantially. MTB has transitioned into a remote and virtual format (35–37). Virtual communication platforms will enable the implementation of MTB within large academic medical centers and multiple satellite hospitals in the future. Virtual MTB also contributes to establishing a medical network in regions of low resource availability, enhancing decentralization of head and neck oncologic care.

Author contributions

ToY: Conceptualization, Writing – original draft, Writing – review & editing. TM: Conceptualization, Writing – review & editing. YY: Conceptualization, Writing – review & editing. HO: Conceptualization, Writing – review & editing. TO: Conceptualization, Writing – review & editing. TaY: Conceptualization, Writing – review & editing. AY: Conceptualization, Writing – review & editing.

Funding

This study was supported by the Japan Agency for Medical Research and Development (23ck0106767h0002).

Acknowledgments

We would like to thank Editage (www.editage.com) for the English language editing.

Conflict of interest

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

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

Publisher's note

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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 15 September 2023
DOI 10.3389/fonc.2023.1145323

OPEN ACCESS

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RECEIVED 16 January 2023
ACCEPTED 30 August 2023
PUBLISHED 15 September 2023

CITATION
Horinouchi A, Enokida T, Suzuki S, Kamata H, Kaneko A, Matsuyama C, Fujisawa T, Ueda Y, Ito K, Okano S, Kawasaki T and Tahara M (2023) A pharmacist-led opioid de-escalation program after completion of chemoradiotherapy in locally advanced head and neck cancer. *Front. Oncol.* 13:1145323. doi: 10.3389/fonc.2023.1145323

A pharmacist-led opioid de-escalation program after completion of chemoradiotherapy in locally advanced head and neck cancer

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Background: Persistent opioid use frequently leads to substantial negative impacts on quality of life, and as the outlook for numerous cancer types continues to improve, these complications become increasingly crucial. It is essential to acknowledge that extended or excessive opioid use may result in adverse effects in patients who completed radiation therapy (RT).

Methods: In this time-series analysis, we compared the outcomes of patients who participated in the pharmacist-led opioid de-escalation (PLODE) program after completing concurrent radiotherapy (CRT) between June 2018 and February 2019 against patients who completed CRT between June 2017 and March 2018 and did not participate in the program.

Results: Among 61 patients, 16 (26%) used opioids after completing CRT and participated in the PLODE program. Before starting the program, 93 patients completed CRT between June 2017 and March 2018 and 32 (34%) used opioids at CRT completion. These patients were deemed the control group. In the PLODE group, outpatient pharmacist intervention was performed, with 29 total interventions related to opioid use, of which 16 (55%) recommended tapering or discontinuing opioids according to the definition of this program. Patients who participated in the PLODE program discontinued opioids significantly earlier than those in the control group (median time to opioid discontinuation 11 days vs. 24.5 days, $p < 0.001$). None of the patients in the PLODE group resumed opioid use following discontinuation or escalated opioid dosing due to worsening pain.

Conclusion: This study showed the utility of pharmacist-initiated interventions for opioid use in patients with head and neck cancer who had completed CRT.

KEYWORDS

head and neck cancer, opioid, tapering, chemoradiation therapy, oral mucositis

1 Introduction

Surgery and radiation therapy are definitive treatments for local squamous cell carcinoma of the head and neck (SCCHN), and concurrent platinum-based chemoradiotherapy has been used as the standard of care in both definitive and adjuvant settings (1–5). One of the most common and debilitating toxicities of the treatment is radiation-induced mucositis due to several factors, including DNA damage caused by reactive oxygen generated by radiation and chemotherapy, and a bacterial infection caused by reduced local immune function (6–8) Reportedly, the incidence of oral mucositis in the population ranges from 50 to 90%, depending on the radiotherapy field, dose, fractionation, and chemotherapy administration (9). Notably, it has been reported that radiation-induced mucositis can be the main reason for unplanned breaks in radiotherapy. Thus, management of oral mucositis in head and neck cancer (HNC) patients treated with concurrent radiotherapy (CRT) is a critical issue as it comprises one of the most common complications leading to unexpected treatment interruption as well as hospitalization, associated with a remarkably worse prognosis (10–15).

Efforts were made to reduce mucositis through supportive therapies such as the oral care program reported by Yokota et al., as well as the implementation of cryotherapy, mucosal protective agents, and lidocaine preparations advocated by the NCCN (11, 14). Regarding the use of analgesics, Acetaminophen is primarily used for mild pain, while opioids are used for moderate to severe pain to achieve a high CRT completion rate while managing pain (12, 13). At our hospital, the initial response for all patients undergoing radiation therapy involves providing oral care utilizing Azunol mouthwash and lidocaine-containing mouthwash. If the mucositis-related pain worsens, acetaminophen or opioids are administered based on the pain level, following the protocol outlined in a previously reported opioid-based pain control program (12). However, the pain caused by CRT usually gradually disappears after the completion of treatment. A phase 2 study, which investigated an oral care program for radiation-induced oral mucositis (functional/symptomatic), reported that grade 3 oral mucositis was observed in 24.8% and 6.3% at two weeks and four weeks after CRT, respectively (14). In these circumstances, irresponsible opioid administration without consideration of the dynamic course can cause opioid-related adverse events that are detrimental to the patient. Currently, it is not feasible to engage in discussions regarding opioid taper or discontinuation with physicians, even if pharmacists are responsible for managing opioids in the outpatient setting after CRT. This is primarily due to the lack of evidence or relevant previous studies that can offer guidance on the appropriate timing for tapering opioids. Consequently, the medication is maintained at the same dosage.

Herein, we report the potential value of a pharmacist-led opioid de-escalation program in patients with locally advanced SCCHN who had completed chemoradiotherapy and used opioids to manage the treatment-related pain with a focus on opioid tapering in order to avoid opioid overdosing in the population.

2 Materials and methods

2.1 Study design and subjects

This time-series analysis compared the outcomes of patients who participated in the pharmacist-led opioid de-escalation (PLODE) program, in which outpatient pharmacists assisted decision-making regarding opioid tapering in collaboration with the medical oncologist after completing CRT or bioradiotherapy (BRT), against those who did not participate in the program in the same clinical settings, in order to evaluate the usefulness of the program. All subjects in this study were treated at the National Cancer Center Hospital East (NCCHE) and used opioids for pain due to treatment-related mucositis. Patients who participated in the de-escalation program between June 2018 and February 2019 were classified into the PLODE group, and those who did not participate in the program between June 2017 and March 2018 were used as historical controls. We retrospectively reviewed their medical records regarding the duration of opioid use and the clinical course after radiation.

The exclusion criteria to extract the population included patients who (1) participated in a clinical trial, (2) used opioids other than mucositis due to RT, (3) stopped using opioids before the completion of RT, (4) were treated with proton beam therapy, and (5) received a single dose of cisplatin during CRT.

In this study, the sample size encompassed all eligible patients during the specified case collection period, and there was no patient overlap observed between the PLODE and control groups.

2.2 PLODE program

The services provided by clinical pharmacists collaborating with oncologists were divided into three categories based on time: (1) before the oncologist outpatient examination, (2) during the oncologist outpatient examination, (3) and after the oncologist outpatient examination.

In the PLODE program, the outpatient pharmacist checked (1) the number of short-acting opioid rescues, (2) complaints of pain before and after opioid tapering, and (3) the purpose of opioid use, such as pain when swallowing meals or at other times on the day of clinic visit before the doctor visit, according to the flow chart (Figure 1). If the pharmacist judged that the pain had improved enough to taper the opioid, they suggested opioid tapering during the doctor's visit. The doctor thoroughly reviewed the pain-related information provided by the pharmacist and the patient's actual symptoms before reaching a final decision. In cases where opioid tapering was implemented, the pharmacist instructed the patient to use an opioid rescue option when the pain recurred as a result of the tapering process. Since the Palliative Medicine Society, based on ESMO guidelines, recommends that the use of opioid rescue doses more than four times may require an increase in the regular dose of opioids (16), we considered three or fewer uses of rescue doses as a sign of tapering opioid use in this program. Briefly, (1) if a rescue

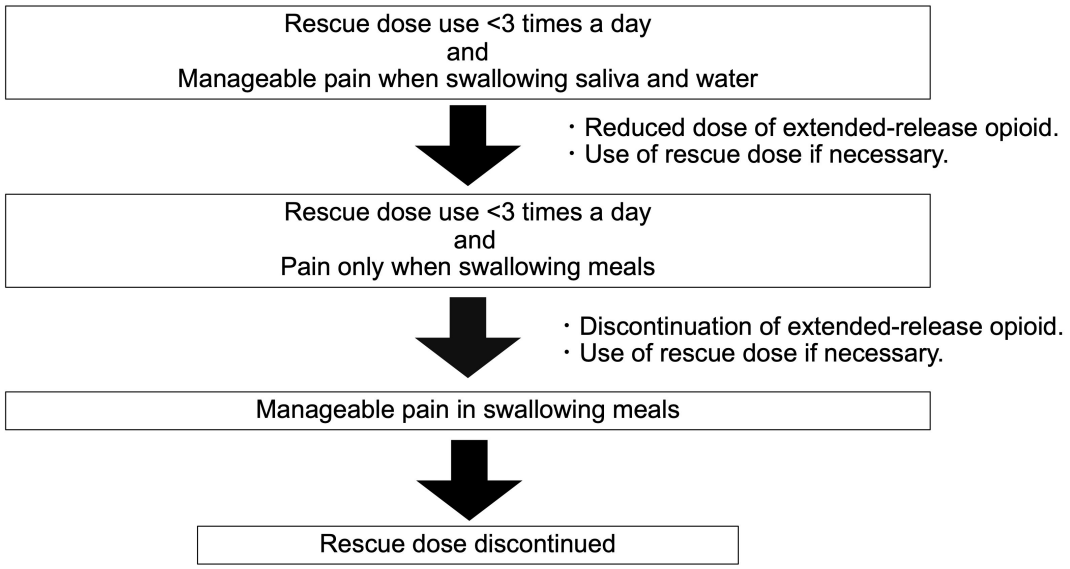

FIGURE 1
Protocol of the pharmacist-led opioid de-escalation (PLODE) program.

dose was used less than three times a day, and the pain was manageable even while swallowing saliva and water, a reduction in the extended-release opioid dose was suggested against using the rescue dose; (2) when patients were administered the minimum dose of extended-release opioids and the rescue dose was used less than three times a day, and the pain was observed only when swallowing meals, discontinuation of extended-release opioids under a free use of rescue dose was suggested; and (3) in cases where patients used only opioid rescue doses with the pain being acceptable while swallowing, discontinuation of rescue dose opioid and complete switching to non-opioid pain management if necessary was suggested. At any stage, if the opioid rescue dose was used more than four times after reducing or discontinuing an extended-release opioid, it was considered a pain relapse and the extended-release opioid could be reintroduced.

2.3 Data analysis

In the PLODE group, the duration of opioid use was defined from the end of radiation to the last day of opioid use, which was confirmed based on records maintained by the patient. In the control group, the last day of opioid use was the day after the last prescription day if the patient had only used a short-acting opioid. In case an extended-release opioid was used, the last prescription day of the opioid was defined as the last opioid use date for the particular subject.

Along the course of treatment, the maximum daily dose of opioid use, dose of acetaminophen used at the initiation of opioid use, the incidence of grade 3 mucositis (symptom/function), the radiation dose at the onset of mucositis, the maximum grade and the initiation of opioid use, the duration from the start of radiation to opioid use, duration of opioid use after completion of radiation, and total duration of administration were investigated. In addition, opioid-related adverse events such as nausea/vomiting, constipation, and sleepiness at the start of the PLODE program were also investigated. Oral mucositis and opioid-related adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0.

2.4 Interventions for opioid use by a pharmacist

Pharmacist-initiated interventions referred to actions such as interviews with the patient who used opioids by pharmacists before the oncologist's outpatient examination to confirm the occurrence of opioid-induced side effects, pain levels, medication compliance, and suggest a prescription. Pharmacists' suggestions to physicians regarding opioid prescriptions were defined as prescribing interventions.

2.5 Statistics

Fisher's exact probability test was used for categorical variables, whereas the Mann-Whitney U-test was used to compare the period from the start or completion of radiation to the occurrence of each event between the two groups. All statistical analyses were

performed using SPSS software (version 17.00, SPSS, Inc., Chicago, IL, USA) for the statistical analysis. Statistical significance was set at $p < 0.05$. In this study, a *post-hoc* power analysis was used to calculate the *post-hoc* power and to evaluate the sample size.

2.6 Ethics approval

This study was approved by the National Cancer Institutional Review Board (approval #2018-362). Since this was a retrospective study, the requirement for informed consent was waived.

3 Results

3.1 Patients characteristics

Sixty-one patients underwent CRT between June 2018 and February 2019. Among these, 16 (26%) used opioids at the time of CRT completion and participated in the PLODE program. Since 93 patients completed CRT between June 2017 and March 2018 and 32 (34%) used opioids at CRT completion, these patients were deemed the control group. At our hospital, a gastrostomy is performed for all patients before starting CRT, as radiation therapy can worsen oral mucositis and hinder oral medication administration. Therefore, in all cases, morphine granules were used for extended-release opioid doses, and oral morphine solution was utilized for rescue doses. These options are chosen because they can be easily administered through the gastrostomy. Most of the chemotherapy combined with radiation was cisplatin. Patient characteristics are shown in Table 1. There was a remarkable difference between the two groups only in the percentage distribution of clinical stages but not in stage 4 proportions. Other backgrounds were similar between the two groups. During the study period, all patients in the PLODE and control groups demonstrated no residual or recurrent tumors following CRT.

3.2 Side effects of opioids observed at the initiation of the PLODE program

Figure 2 shows the opioid-induced side effects at the initiation of the PLODE program, which were subsequently coped by pharmacists in the PLODE group. The overall incidence of adverse effects was 93%, and the incidence of nausea, constipation, and sleepiness was 20%, 69%, and 43%, respectively.

TABLE 1 Patient characteristics.

Characteristic	No. of patients (%)		*p*-value†
	PLODE (n=16)	Control (n=32)	
Gender			0.72
Male	13 (81)	23 (72)	
Female	3 (19)	9 (28)	
Age median years [range]	64 [31–73]	60 [32–75]	0.35
Primary site			0.58
Nasopharynx	1 (6)	4 (12)	
Oropharynx	6 (38)	16 (50)	
Hypopharynx	3 (19)	6 (19)	
Oral cavity	4 (25)	5 (16)	
Larynx	1 (6)	1 (3)	
Unknown primary	1 (6)	0 (0)	
Stage (UICC 8th edit)			0.0006
I	3 (19)	9 (28)	
II	3 (19)	0 (0)	
III	2 (13)	10 (31)	
IV	8 (50)	13 (40)	
Clinical setting			0.28
Definitive	12 (75)	28 (88)	
Postoperative	4 (25)	4 (12)	

(Continued)

TABLE 1 Continued

Characteristic	No. of patients (%)		*p*-value†
	PLODE (n=16)	Control (n=32)	
Treatment strategy			0.66
IC→CRT	6 (38)	10 (31)	
CRT/BRT	10 (62)	22 (69)	
Combination chemotherapy			0.15
CDDP	14 (88)	32 (100)	
Cmab	1 (6)	0 (0)	
CBDCA	1 (6)	0 (0)	
CBDCA+5-FU	0 (0)	0 (0)	
Median radiation doses, Gy [range]	66 [66–70]	66 [64–70]	0.72
Median radiation dose at the onset of mucositis, Gy [range]	24 [14–36.04]	23 [13–48.56]	0.62
Median radiation dose at the maximum grade of mucositis, Gy [range]	54 [34–70]	58 [13–70]	0.93
Incidence of grade 3 oral mucositis at the completion of RT	11 (68)	23 (72)	0.82
Median radiation dose at the onset of mucositis, Gy [range]	24 [14–36.04]	23 [13–48.56]	0.31
Median radiation dose at the maximum grade, Gy [range]	54 [34–70]	58 [13–70]	0.46
Median radiation dose at the start of opioid use, Gy [range]	45 [22–69.96]	36 [16–63.6]	0.17
Average maximum dose of opioid use at the completion of RT ± SD, mg/day*	27 ± 15	30 ± 18	0.39
Average dose of acetaminophen used at the completion of RT ± SD, mg/day	1,818 ± 811	2,115 ± 752	0.21
Median duration from the start of radiation to opioid use, days [range]	32 [14–50]	24 [9–46]	0.12

CBDCA, carboplatin; CDDP, cisplatin; Cmab, cetuximab; CRT, chemoradiation therapy; IC, induction chemotherapy; 5-FU, 5-fluorouracil; SD, standard deviation. *Oral morphine equivalent dose. †p-values were determined using the χ^2 test and Mann–Whitney U test.

Unfortunately, in the control group, only the side effects documented in the medical record could be verified in the retrospective survey. Nonetheless, the overall incidence of adverse effects was 65%, and the incidences of nausea, constipation, and sleepiness were 62%, 57%, and 29%, respectively.

3.3 Pharmacist interventions for opioid use

In the PLODE group, the total number of pharmacist-led interventions for opioid use during and after CRT was 57 (16 patients). Among them, the total number of prescriptions proposed by pharmacists was 24, of which the physician accepted 22 prescriptions (91%) in 15 patients with a median acceptance of one time/patient. The most common pharmacist's suggestion was to discontinue opioids (14/24 times, 58.3%). However, there were only two suggestions for opioid dose increase (Figure 3).

3.4 Change in the number of patients using opioids after completion of radiotherapy

The rate of opioid use two weeks after the completion of radiation was significantly different between the two groups (PLODE vs. control, 31% vs. 81%, $p < 0.01$, Figure 4), and only one (6.3%) of the 16 patients in the PLODE group used opioids after four weeks. After five weeks, although there was no significant difference between the two groups, approximately 40% (13/32) of the patients in the control group still used opioids. Altogether, the median duration of opioid use after the completion of radiation was significantly shorter in the PLODE group than in the control (11.5 days [range: 15–50] vs. 24 days [range: 9–46] (Table 2). The median duration of opioid use after the completion of radiation due to differences in clinical setting between postoperative and definitive was 7 days [range: 2–20] and 11 days [range: 6–49], respectively, in the PLODE. In the control, the median duration was 28 days [range: 15–36] and 23.5 days [range: 2–153], respectively.

We conducted a *post-hoc* power analysis to calculate the *post-hoc* power of our results, which was 77.9%.

3.5 Opioid rescue usage after opioid de-escalation by the PLODE program

Among the 16 patients who received an opioid de-escalation in the PLODE program, two patients (12.5%) used rescue doses after the opioid-de-escalation; one patient used a rescue dose twice until the subsequent visit after reducing the dose of an extended-release opioid,

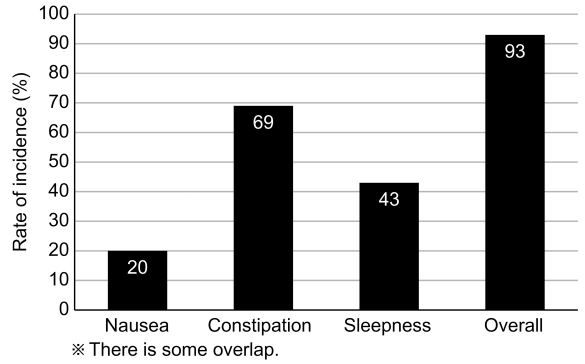

FIGURE 2
Opioid-induced side effects (All Grade) observed at the initiation of PLODE program.

and another similarly used it twice after discontinuing an extended-release opioid. None of the patients used a rescue dose before the next outpatient visit.

4 Discussion

In patients with locally advanced SCCHN who completed CRT or BRT, a pharmacist-led opioid de-escalation program in collaboration with a physician could reasonably shorten the duration of opioid use for treatment-related pain without apparent exacerbation of pain compared with the historical control group.

Long-term prescription of opioids has potential adverse effects on bodily functions, such as nausea, drowsiness, hypogonadism, gastrointestinal motility disorder, constipation, hyperalgesia, and sleep disorders (17, 18). Therefore, unnecessary opioid use should always be avoided. Further, opioid-induced somnolence, considered one of the signs of a relative overdose of opioids, was observed in 43% of patients even after the completion of CRT in the PLODE program, suggesting the presence of opioid overuse in a fraction of the population. Regarding gastrointestinal side effects, such as nausea, vomiting, and constipation, the preceding two usually disappear within 1–2 weeks; however, opioid-induced constipation (OIC) has minimal or no tolerance and generally increases with the duration of opioid analgesic use. Although the current study could not trace the change in the degree of constipation after tapering or discontinuing opioids, we believe that avoiding unnecessary and relatively excessive use of opioids as revealed by the PLODE program should benefit the patient population, which was experienced by approximately 70% of cases in the group by the time of initiation of the intervention in the current study. Furthermore, our study had a limitation with regards to sample size evaluation. The posterior power of our study was 77.9%, slightly below the desired threshold of 80%. However, it was determined that a certain level of power could still be secured.

Regarding the effect of postoperative or definitive clinical setting on the duration of opioid use, the small sample size in the postoperative group precludes any conclusion, but we do not believe that differences in clinical settings consistently affect the duration of opioid use.

Another issue that should be addressed is pain relapse after de-escalation using the PLODE program. A few patients required opioid rescue doses after opioid de-escalation, while most subjects could successfully taper opioids without re-introduction or re-escalation of the extended-release opioid dose, suggesting the feasibility of the program.

Collaboration between pharmacists and oncologists is essential to ensure safer treatment of patients with cancer. Since the

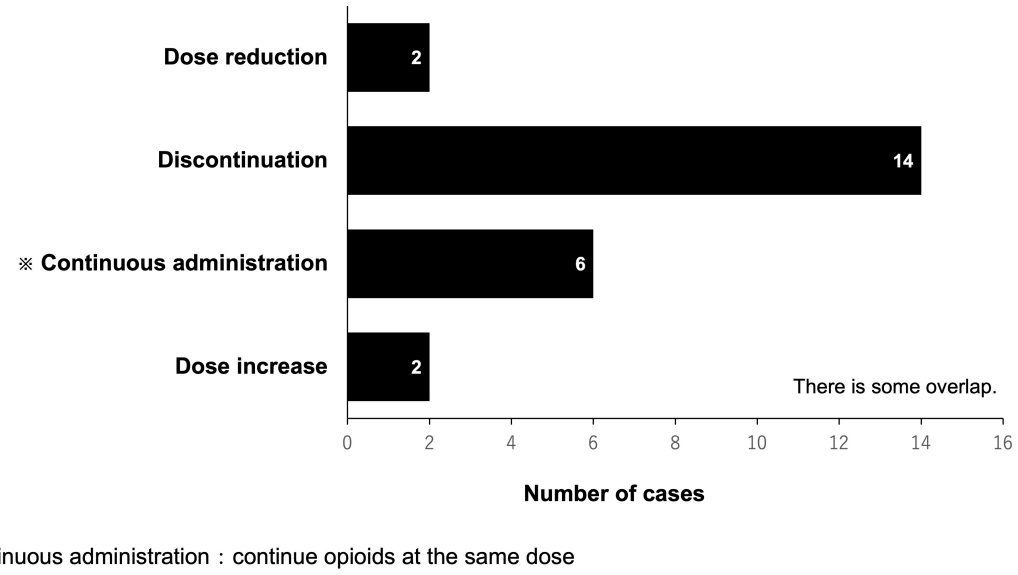

FIGURE 3
Pharmacist-led interventions for opioid use after CRT.

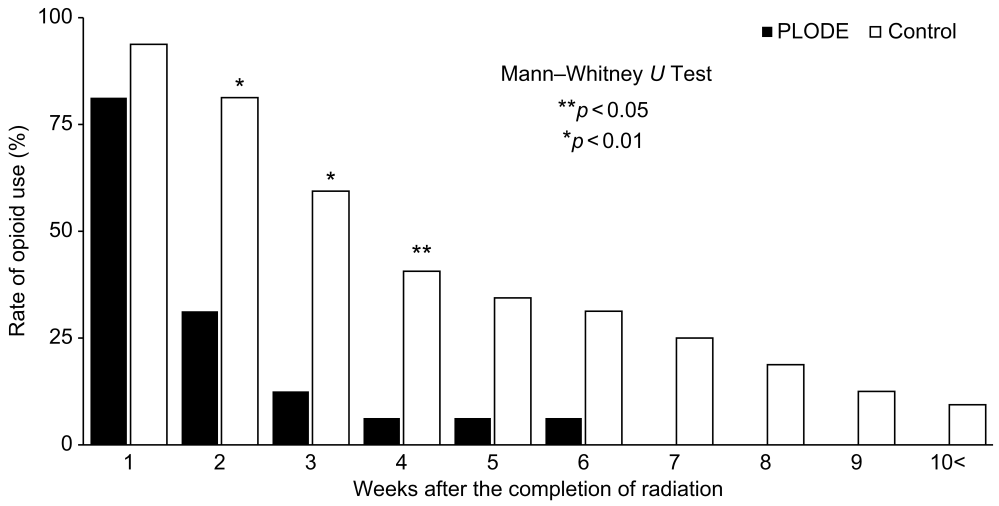

FIGURE 4
Change in the number of patients using opioid after completion of radiotherapy.

TABLE 2 Duration of opioid use after completion of RT.

	PLODE (n=16)	Control (n=32)	*p*-value
Median duration of opioid use after completion of radiation, days [range]	11.5 [2–49]	24.5 [2–153]	< 0.001
Median total duration of opioid use, days [range]	28 [1–85]	48 [5–177]	< 0.01

The duration of opioid use after completion of RT and the total duration of opioid administration were compared using the Mann-Whitney U test.

Department of Pharmacy at the National Cancer Center Hospital East (NCCHE) established the first Japanese outpatient clinic where pharmacists worked directly with oncologists in 2007, we have reported the benefits of pharmacists managing side effects in collaboration with oncologists (19–21). Notably, outpatient pharmacists who checked and reviewed both patients' symptoms and doctors' prescriptions can directly contribute to the field, as indicated in the current study, which, for the first time, showed the significance of pharmacist-led opioid de-escalation in the setting of radiotherapy in patients with locally advanced SCCHN. Considering the potential correlation between opioid use for managing psychological and spiritual distress and the risk of drug abuse and dependence (22), as well as the strong association between alcohol abuse, commonly observed among HNC patients, and an elevated risk of prolonged opioid abuse (23), we assert that the program supporting the tapering process is highly pertinent and advantageous for the population.

In conclusion, a pharmacist-led opioid de-escalation program is feasible and practical for tapering the drug in patients with SCCHN who require opioids to control radiotherapy-related pain and complete radiotherapy. The program may prevent unnecessary opioid use to avoid jeopardizing toxicities without pain relapse.

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

This study was approved by the National Cancer Institutional Review Board (approval #2018-362). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

AH, YU, TF, SS, and MT conceived and designed the study, interpreted the data, and drafted the manuscript. KI, TE, and SO participated in the study concept and design and interpreted the data. MT extracted, managed, and analyzed the data. All authors contributed to the article and approved the submitted version.

Acknowledgments

This manuscript was prepared without any funding sources. The authors thank all patients and co-investigators for supporting the study.

Conflict of interest

MT reports receiving grants and personal fees from Eisai during the study's execution; grants and personal fees from Ono Pharmaceutical, BMS, Bayer, MSD, Eli Lilly, GSK, Pfizer, AstraZeneca, Rakuten Medical, and Merck Biopharma; grants from Novartis; and personal fees from Boehringer Ingelheim, Janssen, Nanobiotix, Astellas Pharma, and Genmab outside the scope of the submitted work. SO reports receiving lecture fees from Merck Serono, BSM, Ono Pharmaceutical, and Kyowa Kirin during the study's execution. TE reports personal fees from Ono Pharmaceutical, Bayer, MSD, and Merck Biopharma outside the submitted work.

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

Publisher's note

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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 18 October 2023
DOI 10.3389/fonc.2023.1269118

OPEN ACCESS

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RECEIVED 29 July 2023
ACCEPTED 03 October 2023
PUBLISHED 18 October 2023

CITATION
Zhou J, Jiang Z, Li Y, Shao X and Liao H (2023) Cause of death during nasopharyngeal carcinoma survivorship: a population-based analysis. *Front. Oncol.* 13:1269118. doi: 10.3389/fonc.2023.1269118

Cause of death during nasopharyngeal carcinoma survivorship: a population-based analysis

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Background: Recently, the survival rate of nasopharyngeal carcinoma (NPC) patients has improved greatly due to developments in NPC treatments. But cause-specific mortality in NPC patients remains unclear. This study aims to investigate the common causes of death in NPC patients.

Methods: Eligible patients with NPC were included from the Surveillance, Epidemiology, and End Results (SEER) database. Standardized mortality ratios (SMRs) were calculated to compare death rates in NPC patients with those in the general population.

Results: A total of 3475 patients with NPC were included, of whom 1696 patients died during the follow-up period. 52.83% of deaths were caused by NPC, followed by other cancers (28.13%) and non-cancer causes (18.46%). The proportion of patients who died of NPC decreased over survival time. Moreover, non-cancer causes of death increase from 12.94% to 51.22% over time after 10 years of diagnosis. Heart diseases was the most common non-cancer cause of death in NPC patients.

Conclusions: Although NPC remains the leading cause of death after NPC diagnosis, other non-NPC causes of death represent an increased number of death in NPC patients. These findings support the involvement of multidisciplinary care for follow-up strategy in NPC patients.

KEYWORDS

nasopharyngeal carcinoma, cause of death, SEER, survival, standardized mortality ratios (SMRs)

1 Introduction

Nasopharyngeal carcinoma (NPC) is an epithelial carcinoma characterized by distinct geographical and ethnic distribution. Multiple risk factors contribute to the occurrence of NPC, including Epstein-Barr virus (EBV) infection, genetic predisposition and environmental factors (1, 2). Recently, there have been rapid evolution of the treatments in NPC patients. With the progress of radiotherapy techniques, optimization of chemotherapy strategies and breakthroughs of immune checkpoint inhibitors, the mortality of NPC patients has been substantially reduced (3–5). In long-term NPC survivors, understanding different causes of death is significant to develop individual follow-up strategies.

Previous studies have well described the causes of death from prostate cancer, breast cancer, small cell lung cancer and other cancers (6–10). But few existing studies have focused on the causes of death from NPC, especially for non-cancer reasons (11). Therefore, risk of death can be underestimated, and early intervention can not be carried out timely. In the current study, we endeavored to concentrate on each cause of death during NPC patients survivorship. We provided the analysis based on demographic-related and tumor-related characteristics and compared the risk of death from each cause with that of the general population.

2 Materials and methods

2.1 Data source

This was a retrospective cohort study. Data was collected from the Surveillance, Epidemiology, and End Results (SEER) 17 registries, November 2021 submission (2000–2019) for SMRs, which includes approximately 26.5% of the U.S. population.

2.2 Patients

We identified all patients diagnosed with NPC as their first malignancy between 2004 and 2015 from SEER database. Patients diagnosed through autopsy or death certificates only were excluded. We also excluded patients with an unknown vital status, survival time, cause of death or staging information. Figure 1 shows the flowchart of participant selection.

2.3 Study variables

Demographic and clinical information was extracted from SEER database, including sex, age, race, marital status, year of diagnosis, the 6th AJCC stage, histology type and treatment (surgery, radiotherapy or chemotherapy). Causes of death were mainly classified into cancer-related death and non-cancer death.

2.4 Outcome assessments

The number of all deaths after NPC diagnosis was calculated in different variables during all follow-up time and at each follow-up period. The cause of death record in SEER database was based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision.

2.5 Statistical analysis

We computed standardized mortality ratios (SMRs), defined as the ratios of observed number of deaths in included NPC patients to expected number of deaths in the general population. Expected number of deaths was adjusted by age, sex, race and calendar year. We calculated the SMRs with 95% confidence intervals by

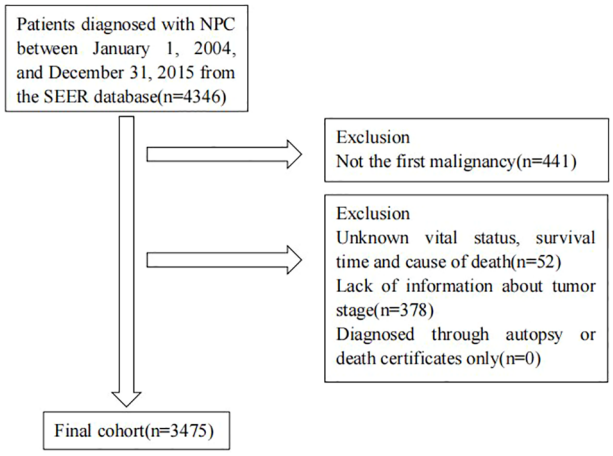

FIGURE 1
Flowchart of participant selection.

SEER*Stat (version 8.4.0.1). All statistical tests were two-sided and a p value < 0.05 was considered to be statistically significant.

3 Results

3.1 Baseline characteristics

A total of 3475 patients diagnosed with NPC were included in our study. The number of male patients (72.26%) was 2.6 times higher than that of female patients (27.74%). Most patients (78.73%) were < 65 years old. The proportion of stage I-II patients (29.99%) and stage III patients (29.72%) was similar, while stage IV patients (40.29%) outnumbered. The majority of patients had keratinizing squamous cell histology type (43.71%) and non-keratinizing cell histology type (54.99%). Both radiotherapy and chemotherapy were common treatments for NPC patients.

During the follow-up, 1696 (48.81%) patients died. Of total deaths, 26.89% occurred within the first year of diagnosis, 50.18% occurred from 1 to 5 years, 18.10% occurred from 5 to 10 years, and 4.83% individuals survived longer than 10 years. In addition, 52.83% of death were caused by NPC, followed by other cancers (28.13%) and non-cancer causes (18.46%). Besides, NPC patients were at a higher risk dying from most other cancers. As for non-cancer causes, heart disease was the most common one (4.6%).

Table 1 shows the baseline characteristics of patients with NPC included in our study. Table 2 shows observed deaths and SMRs for causes of death after diagnosis of NPC. Figure 2 shows causes of death after NPC diagnosis within each follow-up period.

3.2 Cause of death within 1 year following NPC diagnosis

Within 1 year after the diagnosis of NPC, a total of 456 death occurred. 51.54% died of NPC, 35.30% died of other cancers, and 12.94% died of non-cancer causes. Miscellaneous malignant cancer (13.82%) was the most common causes of other cancer deaths, followed by oral cavity and other pharynx cancers (6.36%). For non-cancer causes, the leading causes were heart diseases (3.51%), other cause of death (2.41%), and infections (1.97%), respectively. Besides, the risks of NPC patients dying from pregnancy/childbirth/puerperium (SMR 365.55#; 95%CI 9.25-2036.71), infections (SMR 44.26#; 95%CI 20.24-84.02), suicide and self-inflicted injury (SMR 9.33#; 95%CI 2.54-23.90), and pneumonia and influenza (SMR 7.65#; 95%CI 2.08-19.58) were 5 times higher than what expected in general population.

3.3 Cause of death within 1-5 years following NPC diagnosis

Within 1-5 years following NPC diagnosis, a total of 851 death occurred. NPC was the leading cause of death (61.69%), while other cancers (25.62%) and non-cancer causes (12.22%) accounting for the remaining proportion. Miscellaneous malignant cancer (10.11%) and heart diseases (2.70%) continued to be the most common causes of other cancer deaths and non-cancer cause of death. The SMR elevated to the highest level for pregnancy/childbirth/puerperium (SMR 101.95#; 95%CI 2.58-568.02), diseases of arteries (SMR 65.50#; 95%CI 17.85-167.71), and infections (SMR 15.11#; 95%CI 6.52-29.77) for non-cancer causes.

3.4 Cause of death within 5-10 years following NPC diagnosis

Within 5-10 years following NPC diagnosis, a total of 307 death occurred. 38.76% died of NPC, 24.76% died of other cancers, and 35.18% died of non-cancer causes. The respiratory system cancers (8.14%) turned to be the most common cause of other cancer death. Heart diseases (9.12%) remained to be the leading non-cancer cause of death. The mortality rate of infections was the highest in non-cancer causes of death (SMR 27.08#; 95%CI 10.89-55.80).

3.5 Cause of death after 10 years following NPC diagnosis

After 10 years of survival after NPC diagnosis, 82 patients died. 20.73% died of NPC, 26.83% died of other cancers, and 51.22% died of non-cancer causes. The proportion of respiratory system cancers (9.76%) was the highest one for patients died of other cancer causes. The frequency of NPC patients dying of heart diseases reached 13.41% among patients who survived more than 10 years. Patients with NPC also had a higher risk of infections related death (SMR 11.11#; 95%CI 1.35-40.14).

3.6 Subgroup analysis

Male and female NPC patients had a similar risk of cancer related death and non-cancer causes of death, but female patients (SMR 10434.51#; 95%CI 9150.85-11847.82) had a higher risk of death from NPC than male patients (SMR 3616.59#; 95%CI 3345.50-3903.80) (Tables S1, 2). Patients aged < 65 years old had a higher risk of death than that of patients ≥ 65 years, no matter it was a cancer or non-cancer factor (Tables S3, 4). The risk of all cause death in patients of other races (SMR 10.09#; 95%CI 9.28-10.96) was higher than white(SMR 6.95#; 95%CI 6.51-7.42) and black (SMR 7.45#; 95%CI 6.51-8.48) patients (Tables S5, 7). Compared with patients who are married or in other marital statues, patients who have never been married had a higher risk of death, regardless of cancer or non-cancer causes (Tables S8-10). Patients diagnosed in recent years showed an increase in non-cancer causes of death (Tables S11-13). Patients with stage IV NPC had a higher risk of death from caner or non-cancer causes than patients with I-III NPC (Tables S14-16). The prognosis of patients with nasopharyngeal basaloid squamous cell carcinoma (BSCC) was the worst, while the prognosis of patients with nasopharyngeal non-keratinizing carcinoma (NKC) was the best (Tables S17-19). Patients who underwent surgery (SMR 14.77#; 95%CI 12.27-

10.3389/fonc.2023.1269118

TABLE 1 Baseline characteristics of patients with nasopharyngeal carcinoma.

Group	All Patients Diagnosed With NPC,No. (%)	Time of Death After Diagnosis,No. (%)				
		All Years	<1 year	1 to <5 years	5 to <10 years	≥10 years
All patients	3475 (100%)	1696 (100%)	456 (100%)	851 (100%)	307 (100%)	82 (100%)
Sex						
Male	2511 (72.26%)	1284 (75.71%)	334 (73.25%)	655 (76.97%)	231 (75.24%)	64 (78.05%)
Female	964 (27.74%)	412 (24.29%)	122 (26.75%)	196 (23.03%)	76 (24.76%)	18 (21.95%)
Age,years						
<65	2736 (78.73%)	1180 (69.58%)	265 (58.11%)	632 (74.27%)	221 (71.99%)	62 (75.61%)
≥65	739 (21.27%)	516 (30.42%)	191 (41.89%)	219 (25.73%)	86 (28.01%)	20 (24.39%)
Race						
White	1651 (47.51%)	906 (53.42%)	275 (60.31%)	414 (48.65%)	168 (54.72%)	49 (59.76%)
Black	411 (11.83%)	226 (13.33%)	66 (14.47%)	120 (14.10%)	33 (10.75%)	7 (8.54%)
Other	1413 (40.67%)	564 (33.25%)	115 (25.22%)	317 (37.25%)	106 (34.53%)	26 (31.71%)
Marital status						
Married	2035 (58.56%)	932 (54.95%)	227 (49.78%)	463 (54.41%)	190 (61.89%)	52 (63.41%)
Never married	785 (22.59%)	364 (21.46%)	103 (22.59%)	191 (22.44%)	57 (18.57%)	13 (15.85%)
Other	655 (18.85%)	400 (23.58%)	126 (27.63%)	197 (23.15%)	60 (19.54%)	17 (20.73%)
Year of diagnosis						
2004-2007	1027 (29.55%)	603 (35.55%)	139 (30.48%)	256 (30.08%)	134 (43.65%)	74 (90.24%)
2008-2011	1185 (34.10%)	601 (35.44%)	157 (34.43%)	299 (35.14%)	137 (44.63%)	8 (9.76%)
2012-2015	1263 (36.35%)	492 (29.01%)	160 (35.09%)	296 (34.78%)	36 (11.73%)	0 (0)
Stage						
I/II	1042 (29.99%)	374 (22.05%)	63 (13.82%)	168 (19.74%)	109 (35.50%)	34 (41.46%)
III	1033 (29.73%)	455 (26.83%)	106 (23.25%)	240 (28.20%)	91 (29.64%)	18 (21.95%)
IV	1400 (40.29%)	867 (51.12%)	287 (62.94%)	443 (52.06%)	107 (34.85%)	30 (36.59%)
Histology						
KSCC	1519 (43.71%)	920 (54.25%)	298 (65.35%)	432 (50.76%)	151 (49.19%)	39 (47.56%)
NKC	1911 (54.99%)	751 (44.28%)	153 (33.55%)	409 (48.06%)	147 (47.88%)	42 (51.22%)
BSCC	45 (1.29%)	25 (1.47%)	5 (1.10%)	10 (1.18%)	9 (2.93%)	1 (1.22%)

(Continued)

TABLE 1 Continued

Group	All Patients Diagnosed With NPC,No. (%)	Time of Death After Diagnosis,No. (%)				
		All Years	<1 year	1 to <5 years	5 to <10 years	≥10 years
Surgery						
Yes	387 (11.14%)	160 (9.43%)	33 (7.24%)	86 (10.11%)	29 (9.45%)	12 (14.63%)
No/unknow	3088 (88.86%)	1536 (90.57%)	423 (92.76%)	765 (89.89%)	278 (90.55%)	70 (85.37%)
Radiation						
Yes	3079 (88.60%)	1403 (82.72%)	312 (68.42%)	731 (85.90%)	284 (92.51%)	76 (92.68%)
No/unknow	396 (11.40%)	293 (17.28%)	144 (31.58%)	120 (14.10%)	23 (7.49%)	6 (7.32%)
Chemotherapy						
Yes	2944 (84.72%)	1393 (82.13%)	318 (69.74%)	739 (86.84%)	265 (86.32%)	71 (86.59%)
No/unknow	531 (15.28%)	303 (17.87%)	138 (30.26%)	112 (13.16%)	42 (13.68%)	11 (13.41%)

NPC, nasopharyngeal carcinoma; KSCC, keratinizing squamous cell carcinoma; NKC, non-keratinizing carcinoma; BSCC, basaloid squamous cell carcinoma.

TABLE 2 Observed deaths and SMRs for causes of death after diagnosis of nasopharyngeal carcinoma.

	Timing of Death After Diagnosis									
	All years		<1 year		1 to <5 years		5 to <10 years		≥10 years	
	No. (%)	SMR (95% CI)	No. (%)	SMR (95% CI)	No. (%)	SMR (95% CI)	No. (%)	SMR (95% CI)	No. (%)	SMR (95% CI)
Cause of Death	1696 (100%)	7.83# (7.46-8.21)	456 (100%)	17.25# (15.7-18.91)	851 (100%)	8.81# (8.22-9.42)	307 (100%)	4.41# (3.93-4.93)	82 (100%)	3.44# (2.73-4.27)
All Malignant Cancers	1373 (80.96%)	23.30# (22.09-24.57)	396 (86.84%)	54.27# (49.05-59.89)	743 (87.31%)	28.05# (26.07-30.15)	195 (63.52%)	10.41# (9-11.98)	39 (47.56%)	6.09# (4.33-8.32)
Nasopharynx	896 (52.83%)	4,376.10# (4094.22-4672.28)	235 (51.54%)	9,246.20# (8101.73-10507.04)	525 (61.69%)	5,585.67# (5118.03-6084.56)	119 (38.76%)	1,859.63# (1540.55-2225.33)	17 (20.73%)	796.22# (463.83-1274.83)
Oropharynx	26 (1.53%)	202.78# (132.47-297.13)	14 (3.07%)	1,001.17# (547.35-1679.79)	10 (1.18%)	181.91# (87.23-334.54)	2 (0.65%)	46.28# (5.6-167.18)	0 (0)	0 (0-229.93)
Oral Cavity and Other Pharynx	80 (4.72%)	22.67# (17.97-28.21)	29 (6.36%)	38.05# (25.48-54.65)	38 (4.47%)	21.94# (15.53-30.11)	8 (2.61%)	8.34# (3.60-16.44)	5 (6.10%)	65.30# (21.20-152.38)
Digestive System	41 (2.42%)	2.29# (1.64-3.11)	8 (1.75%)	3.73# (1.61-7.35)	17 (2.00%)	2.13# (1.24-3.41)	12 (3.91%)	2.09# (1.08-3.64)	4 (4.88%)	1.99 (0.54-5.1)
Respiratory System	103 (6.07%)	6.22# (5.07-7.54)	28 (6.14%)	12.93# (8.59-18.69)	42 (4.94%)	5.54# (3.99-7.49)	25 (8.14%)	4.86# (3.15-7.17)	8 (9.76%)	4.76# (2.06-9.38)
Bones and Joints/Soft Tissue	5 (0.29%)	18.07# (5.87-42.17)	1 (0.22%)	28.94 (0.73-161.24)	1 (0.12%)	6.24 (0.16-34.79)	3 (0.98%)	36.58# (7.54-106.89)	0 (0)	0 (0-0)
Skin excluding Basal and Squamous	23 (1.36%)	21.69# (13.75-32.54)	11 (2.41%)	82.60# (41.23-147.79)	9 (1.06%)	18.82# (8.6-35.72)	3 (0.98%)	8.83# (1.82-25.81)	0 (0)	0 (0-33.73)

(Continued)

TABLE 2 Continued

	Timing of Death After Diagnosis									
	All years		<1 year		1 to <5 years		5 to <10 years		≥10 years	
Breast/Genital/Urinary/ Endocrine System	6 (0.35%)	13.60# (4.99-29.61)	0 (0)	0 (0-54.47)	3 (0.35%)	12.96# (2.67-37.86)	3 (0.98%)	21.16# (4.36-61.85)	0 (0)	0 (0-0)
Brain and Other Nervous System	8 (0.47%)	5.37# (2.32-10.58)	4 (0.88%)	22.73# (6.19-58.19)	4 (0.47%)	6.02# (1.64-15.42)	0 (0)	0 (0-7.64)	0 (0)	0 (0-22.16)
lymph/Blood	14 (0.83%)	9.74# (5.32-16.34)	3 (0.66%)	9.83# (2.03-28.73)	8 (0.94%)	8.36# (3.61-16.48)	2 (0.65%)	15.61# (1.89-56.38)	1 (1.22%)	20.96 (0.53-116.79)
Miscellaneous Malignant Cancer	171 (10.08%)	40.43# (34.6-46.97)	63 (13.82%)	119.70# (91.98-153.15)	86 (10.11%)	45.28# (36.22-55.92)	18 (5.86%)	13.43# (7.96-21.23)	4 (4.88%)	8.63# (2.35-22.1)
In situ, benign or unknown behavior neoplasm	10 (0.59%)	8.06# (3.87-14.82)	1 (0.22%)	6.65 (0.17-37.08)	4 (0.47%)	7.27# (1.98-18.6)	4 (1.30%)	9.97# (2.72-25.52)	1 (1.22%)	7.22 (0.18-40.23)
Noncancer	313 (18.46%)	9.25# (8.25-10.33)	59 (12.94%)	13.10# (9.97-16.89)	104 (12.22%)	6.16# (5.03-7.47)	108 (35.18%)	10.23# (8.39-12.35)	42 (51.22%)	22.04# (15.88-29.79)
Infections	26 (1.53%)	22.20# (14.50-32.52)	9 (1.97%)	44.26# (20.24-84.02)	8 (0.94%)	15.11# (6.52-29.77)	7 (2.28%)	27.08# (10.89-55.80)	2 (2.44%)	11.11# (1.35-40.14)
Diabetes Mellitus	6 (0.35%)	0.72 (0.26-1.56)	3 (0.66%)	3.05 (0.63-8.92)	1 (0.12%)	0.27 (0.01-1.52)	0 (0)	0 (0-1.36)	2 (2.44%)	2.03 (0.25-7.32)
Alzheimers (ICD-9 and 10 only)	6 (0.35%)	1.4 (0.51-3.04)	0 (0)	0 (0-33.16)	2 (0.24%)	1.07 (0.13-3.88)	3 (0.98%)	2.05 (0.42-6)	1 (1.22%)	2 (0.05-11.14)
Diseases of Heart	78 (4.60%)	1.52# (1.20-1.89)	16 (3.51%)	2.49# (1.42-4.04)	23 (2.70%)	1.00 (0.63-1.50)	28 (9.12%)	1.70# (1.13-2.46)	11 (13.41%)	1.98 (0.99-3.54)
Hypertension without Heart Disease	5 (0.29%)	1.99 (0.65-4.64)	0 (0)	0 (0-72.07)	1 (0.12%)	0.92 (0.02-5.13)	2 (0.65%)	2.39 (0.29-8.63)	2 (2.44%)	6.53 (0.79-23.60)
Cerebrovascular Diseases	21 (1.24%)	1.97# (1.22-3.01)	0 (0)	0 (0-14.81)	6 (0.71%)	1.26 (0.46-2.75)	11 (3.58%)	3.22# (1.61-5.77)	4 (4.88%)	3.37 (0.92-8.63)
Diseases of Arteries	4 (0.24%)	28.01# (7.63-71.71)	0 (0)	0 (0-45.12)	4 (0.47%)	65.50# (17.85-167.71)	0 (0)	0 (0-0)	0 (0)	0 (0-0)
Pneumonia and Influenza	17 (1.00%)	4.05# (2.36-6.49)	4 (0.88%)	7.65# (2.08-19.58)	8 (0.94%)	4.33# (1.87-8.53)	4 (1.30%)	2.91 (0.79-7.46)	1 (1.22%)	2.22 (0.06-12.37)
Chronic Obstructive Pulmonary Disease and Allied Cond	29 (1.71%)	2.61# (1.75-3.75)	3 (0.66%)	2.25 (0.46-6.58)	9 (1.06%)	1.84 (0.84-3.49)	13 (4.23%)	3.58# (1.91-6.13)	4 (4.88%)	3.19 (0.87-8.16)
Chronic Liver Disease and Cirrhosis	6 (0.35%)	1.33 (0.49-2.90)	0 (0)	0 (0-63.65)	4 (0.47%)	1.97 (0.54-5.04)	1 (0.33%)	0.69 (0.02-3.85)	1 (1.22%)	2.08 (0.05-11.57)
Nephritis/Nephrotic Syndrome/Nephrosis	1 (0.06%)	0.24 (0.01-1.34)	1 (0.22%)	1.99 (0.05-11.06)	0 (0)	0 (0-2.00)	0 (0)	0 (0-2.77)	0 (0)	0 (0-7.71)
Pregnancy/Childbirth/ Puerperium	2 (0.12%)	100.92# (12.22-364.57)	1 (0.22%)	365.55# (9.25-2036.71)	1 (0.12%)	101.95# (2.58-568.02)	0 (0)	0 (0-640.84)	0 (0)	0 (0-2432.82)
Symptoms,signs and ill-defined conditions	5 (0.29%)	2.51 (0.82-5.87)	1 (0.22%)	3.85 (0.10-21.45)	2 (0.24%)	2.18 (0.26-7.88)	2 (0.65%)	3.23 (0.39-11.67)	0 (0)	0 (0-19.21)
Accidents and Adverse Effects	22 (1.30%)	2.15# (1.35-3.25)	5 (1.10%)	4.08# (1.32-9.52)	7 (0.82%)	1.52 (0.61-3.13)	8 (2.61%)	2.44# (1.05-4.80)	2 (2.44%)	1.78 (0.22-6.43)
Suicide and Self-Inflicted Injury	6 (0.35%)	1.76 (0.65-3.84)	4 (0.88%)	9.33# (2.54-23.90)	1 (0.12%)	0.63 (0.02-3.53)	1 (0.33%)	0.94 (0.02-5.26)	0 (0)	0 (0-10.95)

(Continued)

TABLE 2 Continued

	Timing of Death After Diagnosis									
	All years		<1 year		1 to <5 years		5 to <10 years		≥10 years	
Homicide and Legal Intervention	3 (0.18%)	2.67 (0.55-7.80)	1 (0.22%)	6.80 (0.17-37.87)	2 (0.24%)	3.79 (0.46-13.70)	0 (0)	0 (0-11.09)	0 (0)	0 (0-31.33)
Other Cause of Death	76 (4.48%)	2.58# (2.03-3.23)	11 (2.41%)	3.26# (1.63-5.83)	25 (2.94%)	1.94# (1.25-2.86)	28 (9.12%)	2.87# (1.91-4.15)	12 (14.63%)	3.50# (1.81-6.12)

CI, confidence interval; SMR, standardized mortality ratio.
#p < 0.05.

17.62) had a lower risk of cancer related death than those without surgery (SMR 24.71#; 95%CI 23.36-26.12) (Tables S20-21). All causes of death were lower in patients who received radiotherapy (SMR 7.06#; 95%CI 6.69-7.43) than those who did not (SMR 16.56#; 95%CI 14.72-18.57) (Tables S22-23). There was no significant difference in risk of death among patients given chemotherapy or not (Tables S24, 25).

4 Discussion

The survival time of NPC patients is extended because of improved anti-tumor treatments. Several studies have explored the malignant causes of NPC-related mortality, but information on non-cancer causes of death remains limited in NPC survivors (12, 13). Using population-based data from the united states, our study detailed the causes of death in NPC patients. These results provide vital guidance for the health maintenance of NPC patients.

Our findings shown that the proportion of NPC-related death decreased gradually with the extension of survival time, while death due to non-cancer causes increased. Among NPC patients who survived more than 10 years, the incidence of non-cancer related death reached 51.22%.

The most common non-cancer related cause of death from NPC patients was heart disease during the whole follow-up periods after NPC diagnosis. Previous studies have indicated that cancer patients confronted a higher risk of cardiovascular death throughout their lives (14–16). This may be attributable to the adverse effects from anti-tumor treatments (17). Concurrent chemoradiation therapy is the mainstay treatment for NPC patients, leading to a progressive and dynamic cardiovascular autonomic dysfunction (18). Besides, immune checkpoint inhibitors (ICIs) have greatly improved the survival rate of NPC patients in recent years. Meanwhile, cardiac toxicities caused by ICIs should not be ignored (19, 20). Therefore, early interventions with cardiologists in these patients is suggested to provide individualized comprehensive care.

The frequency of other non-cancer related causes of death changed over time, with cerebrovascular diseases, infectious diseases, COPD and allied conditions becoming more frequent as time passed after NPC diagnosis. Radiotherapy for NPC patients may cause cerebrovascular diseases including transient ischemic attack and ischemic stroke, which can lead to severe disability (21). Besides, intracranial aneurysms are a rare complication of radiotherapy, but irradiated NPC patients had higher morbidity and mortality rates after aneurysm rupture and a higher angiographic recurrence rate after treatment (22). In addition, NPC patients had a higher risk of death from infectious diseases. This may be due to the use of chemotherapy, which is associated with the dysfunction of immune system. In our analysis, COPD was another common non-cancer cause of death. Smoking is a risk factor affecting the occurrence of NPC and related to higher NPC mortality (23–25). Tight association between NPC and COPD may be partly owing to shared risk factor of tobacco use.

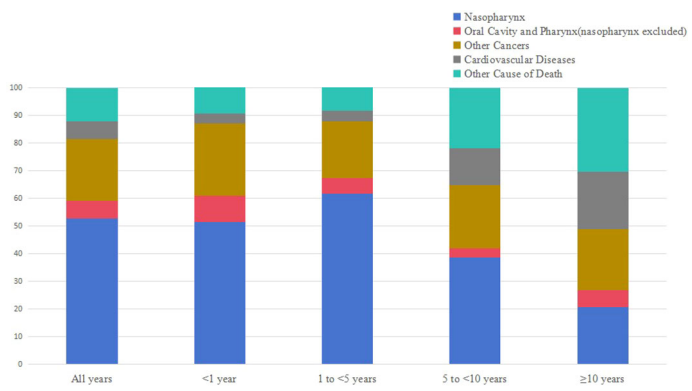

FIGURE 2
Causes of death after nasopharyngeal carcinoma diagnosis within each follow-up period.

Furthermore, in the present study, we found that NPC patients are more likely to develop second primary cancers such as respiratory, digestive and miscellaneous malignant cancers. Previous studies also have shown an increased risk for second primary cancers in NPC patients (26). Immune suppression, shared genetic factors and shared environmental risk factors might account for the associations (27). Besides, second cancer risk after definitive intensity-modulated radiotherapy (IMRT) was substantial in NPC patients (28). So it is advocated that NPC survivors should follow proper screening measures for other cancers.

The anatomical location and high sensitivity of NPC to radiotherapy make it the main treatment modality. Radical radiotherapy is the preferred treatment for early-stage NPC patients and the cornerstone of multidisciplinary treatment for locally advanced NPC patients. Lower risk of all causes of death was also found in NPC patients who received radiotherapy in our study. With the developments of irradiation techniques, the way of radiotherapy in NPC is constantly changing. Compared to conventional radiotherapy, IMRT has improved local control rate and been widespread adopted in clinical practice (29, 30). Besides, previous studies have suggested that IMRT was associated with decreased risk of radiation-induced injury (31, 32). To manage the errors in the positioning of patients or compensate for movements of organs, various methods of image guided radiotherapy (IGRT) are being developed. Meanwhile, intensity-modulated proton therapy (IMPT) has shown excellent locoregional control rate and significantly reduce complications in comparison with IMRT, and prospective studies are warranted (33).

Chemotherapy is associated with multiple adverse events depending on anti-tumor drugs. Cisplatin is commonly used to treat locally advanced and metastasis NPC patients. Cisplatin-based concurrent chemoradiotherapy has been identified as standard treatment for locally advanced NPC patients. But cisplatin-based chemotherapy is known to increase the adverse effects of radiotherapy (34). The main adverse events of cisplatin is nephrotoxicity, which limits the use of cisplatin. Apart from hydration regimens, several possible therapeutic targets preventing nephrotoxicity have been identified (35). Other multiple adverse effects such as gastrointestinal reactions, hematotoxicity, neurotoxicity may also influence the quality of life in second-line or higher treatment settings of NPC patients.

Reirradiation in recurrent NPC patients presents unique challenges with significant treatment-related toxicities, such as subcutaneous necrosis, large-vessel integrity, dysphagia and middle ear dysfunction. Hyperfractionated IMRT could improve overall survival and decrease the risk of severe late complications (36). In addition, with recent progress of endoscopic techniques, endoscopic resection of locally recurrent NPC have been reported in recent years. Local endoscopic resection achieved higher survival rates with fewer adverse events (37, 38). In our study, NPC patients who underwent surgery had a lower risk of cancer related death than those without surgery. We hypothesize that surgery could be recommended for recurrent NPC patients with operable tumors.

Several limitations should be acknowledged in our study. First, the study was retrospective and we tried our best to reduce bias. We designed strict screening criteria to reduce selection bias and used SMRs to control differences in age, sex and race to reduce confounding bias. Second, information about treatments and complications is incomplete in SEER database, which may influence survival durations and death patterns. Finally, NPC is particular prevalent in East and Southeast Asia, but most participants in our study were white. Whether our findings can be expended into other races needs to be further investigated. Despite these limitations, our study provides the most comprehensive assessments of causes of death in NPC patients.

5 Conclusions

In summary, deaths from non-NPC causes account for approximately 1/2 during follow-up after NPC diagnosis. Moreover, as survival time prolonged, the incidence of death from non-NPC causes increased. Heart diseases, infections diseases, COPD and allied conditions were the most common non-cancer causes of death in NPC patients. Therefore, we should not only pay attention to anti-tumor therapy, but also take notice of the occurrence of other risks to achieve better long-term outcomes in NPC patients.

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

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.

Author contributions

JZ: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. ZJ: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. YL: Data curation, Methodology, Writing – original draft, Writing – review & editing. XS: Data curation, Methodology, Writing – original draft, Writing – review & editing. HL: Data curation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Funding

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

Acknowledgments

The authors are thankful for all the individuals at the National Cancer Institute(USA) for their contribution to the SEER database.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1269118/full#supplementary-material

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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 22 November 2023
DOI 10.3389/fonc.2023.1298439

OPEN ACCESS

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RECEIVED 21 September 2023
ACCEPTED 10 November 2023
PUBLISHED 22 November 2023

CITATION
Bergamini C, Cavalieri S, Resteghini C, Alfieri S, Nuzzolese I, Colombo E, Ottini A, Calareso G, Vingiani A, Iacovelli NA, Franceschini M, Guzzo M, Deganello A and Licitra L (2023) Multidisciplinary management of pregnancy-associated and early post-partum head and neck cancer patients.
Front. Oncol. 13:1298439.
doi: 10.3389/fonc.2023.1298439

Multidisciplinary management of pregnancy-associated and early post-partum head and neck cancer patients

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Background: Pregnancy-associated cancer (PAC) occurs during pregnancy or within 12 months after the delivery. Head and neck cancer (HNC) during pregnancy is infrequent, therefore diagnosis and personalized therapy are intricate.

Methods: We investigated outcomes of 15 PAC patients (5 salivary, 4 nasopharyngeal, 3 thyroid, 2 oral cavity, one HPV-related carcinoma) diagnosed in the period 2005-2019. A literature review on PAC is provided.

Results: Median gestational age at PAC diagnosis was 28 weeks (range: 16–40 weeks) in ten cases, at 5 months after delivery (range: 1 week–6 months) in the remaining five. Treatments included surgery (3 during pregnancy, 5 after childbirth), chemoradiation (8), and 3 patients with upfront metastatic disease received chemotherapy. Median survival was 6.6 years (eight women remain with no evidence of disease six years after diagnosis).

Conclusion: All patients received state-of-the-art therapy, with encouraging long-term results, highlighting treatment safety in women with HNC during pregnancy.

KEYWORDS

head and neck cancer, prognosis, multidisciplinary management, pregnancy associated cancer, diagnosis

1 Introduction

Cancer is one of the most common causes of death in women during their reproductive years (1), though, cancer during pregnancy is an atypical clinical issue (2). Pregnancy-associated cancer (PAC) is usually defined as a malignancy diagnosed during pregnancy and up to 1 year after the end of pregnancy. Current knowledge about PAC is limited because PAC is rare (3), with an estimated incidence of 1 in 1000 pregnancies (4). Maternal age distribution influences PAC incidence rates because the risk of cancer increases with age (5). With the increase in average maternal age over the last 30 years (6) a rising incidence of PAC might be expected.

Due to its rarity, the diagnosis of PAC might be delayed, leading to a potentially more advanced stage of disease at presentation, with subsequent worse outcomes. The most prevalent PACs are breast cancers (1 out of 3000 pregnancies) (7), followed by brain, cervical, gastrointestinal, genitourinary, lymphoma, leukemia, melanoma, and ovarian, cancers (1, 8, 9). Pregnancy-associated head and neck cancers (PA-HNC) among PACs are exceedingly rare, accounting for only 0.4% of all HNC diagnoses in women aged 16–49 years (10).

The management of PA-HNC represents a substantial challenge. Pregnant patients should be treated with the equivalent intensity adopted for non-pregnant individuals. However, treatment selection and the choice of its administration should be adapted to ensure the mother's and her baby's safety. In the literature, there is no consensus about the definition of PA-HNC, defined as HNC diagnosed either during pregnancy, lactation, or up to 1 year post-delivery (11, 12).

The most frequently reported PA-HNCs are laryngeal carcinoma, thyroid carcinoma, melanoma and lymphoma (13). Nasopharyngeal carcinoma in pregnant women has been reported in endemic areas, such as Asia, Northern Africa, and among Inuit populations (14–16).

Younger age at HNC diagnosis (17–20), together with the tendency to delay pregnancy until late reproductive age, have increased the risk of PA-HNC (21–26). Although the tumorigenic role of hormones was hypothesized, currently, there is no evidence that pregnancy in itself may increase the risk of HNC (26, 27).

These comparatively infrequent malignancies deter in conducting extensive studies examining their diagnosis, management and outcomes. The present work describes a single institution case series of 15 patients with PA-HNC. The available data on PA-HNC and the consequence of pregnancy on cancer prognosis are summarized. Moreover, we reviewed the medical, surgical, and radiation oncological routes chosen in the care of pregnant patients with HNC. The novelty of this work is the multidisciplinary view of the patients' management as well as the literature review and the provided recommendations.

2 Materials and methods

2.1 Patient selection

In this retrospective study, we analyzed data from medical charts of consecutive patients with HNC during pregnancy diagnosed and treated at the Fondazione IRCCS Istituto Nazionale dei Tumori of Milan, Italy, from 2011 to 2020. All cases were discussed in multidisciplinary HNC tumor board meetings, including gynecologists. Socio-demographic (age and comorbidities) and clinical details (gravidity, diagnosis, cancer detection method, symptoms, tumor histology, treatment features, pregnancy and neonatal outcomes, and mother's vital status) were recorded. Cancers were staged according to the eighth edition of the AJCC/UICC staging systems.

The present study was approved by the Ethical Committee of Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy in November 2020 (local study identifier INT 268/20).

2.2 Statistical methods

Patient characteristics were analyzed with descriptive statistics as appropriate. Survival curves were estimated using the Kaplan-Meier method, and median follow-up using the reverse Kaplan-Meier method. Statistical analyses were performed using Prism GraphPad (version 5.02) software.

3 Results

3.1 Patient characteristics

Fifteen cases were included in this study, with the median age at diagnosis being 37 years (range: 27–43 years). The most frequent tumor sites were salivary glands (five patients; 33%), nasopharyngeal carcinoma (four; 27%), thyroid cancer (three; 20%), oral cavity squamous cell carcinoma (two; 13%), and HPV-related oropharyngeal squamous cell carcinoma (one; 7%). Patient characteristics are described in Table 1.

In 10 patients (67%), HNC diagnosis occurred at a median gestational age of 28 weeks (range: 16–40 weeks). The remaining five patients (33%) were diagnosed after a median of 5 months from delivery (range: 1 week–6 months).

In one asymptomatic patient, cancer diagnosis was incidental, whereas the remaining 14 individuals (93%) had HNC-specific symptoms at diagnosis. One-third of patients were diagnosed at an early stage (stage I, 14%; stage II, 20%), and the remaining 66% had loco-regionally advanced disease (stage III, 26%; stage IV, 40%). Radiological assessments were performed after childbirth in 80% of patients. Seven women had nodal involvement and four had distant metastases at diagnosis (Table 2).

3.2 HNC management

Three women (cases 1, 4 and 5 in Table 2) received cancer treatment during pregnancy. Surgery of the primary tumor was performed in three patients (two with salivary gland cancer and one with oral cavity cancer). After childbirth, five patients received surgery (three thyroid cancers - of which two with metastatic disease, one patient with salivary gland cancer, and one with oral

TABLE 1 Patient characteristics of the case series (15 pregnant patients with HNC).

Variables	Number	%
Age (years)		
<25	0	0
25-29	2	13
30-34	3	20
35-39	6	40
>40	4	27
Gravidity		
1	12	80
2-3	3	20
>3	0	0
Education		
Elementary school	0	0
Middle school	0	0
High school	15	100
Marital status		
Single	0	0
Married	14	94
Other	1	6
Familial risk of cancer		
Yes	0	0
Unknown	15	100

cavity cancer), eight patients received concomitant chemoradiation with curative (33%) or postoperative intent, and three of four patients with metastatic disease at diagnosis were treated with chemotherapy (Table 2).

3.3 Maternal and pregnancy outcomes

Delivery occurred at term in 73% of individuals. In the remaining patients, the pregnancy outcome was elective childbirth in 3 patients, and a voluntary abortion related to PAC diagnosis was induced in one case. Cesarean section was chosen instead of vaginal delivery in two metastatic thyroid cancer patients due to their disease (pelvic bone metastases in one case; bulky mediastinal tumor involvement with dyspnea and bone metastasis-related lumbar pain in the second woman).

All 14 live births were reported with satisfactory neonatal conditions (APGAR not available). One premature childbirth was induced at 30 weeks due to growth retardation during pregnancy. Good neonatal conditions were reported for all 14 live births, with neither congenital anomalies nor major maternal morbidities.

In the PA-HNC cohort, the median overall survival was 5.8 years (range: 14+ months–12+ years). Eight patients still remain in complete remission six years after diagnosis.

Seven maternal deaths occurred during the study: three patients were affected by salivary gland cancer, two patients by thyroid cancer, one by oral cavity cancer, and one patient with salivary gland cancer died due to SARS-CoV-2 infection. Out of the 8 survivors, at last follow-up 7 were alive and cancer-free, while only one was alive with evidence of disease (Table 2). Median follow-up was 114.41 months (95% CI 57.96-NR), median overall survival was 129.31 months (95% CI 55.62-NR).

The median time between diagnosis and death was 5.5 years (range: 19 months–10 years). In one case, childbirth occurred at 30 weeks of pregnancy. A fetus up to 28 weeks is deemed as 'severe preterm' when the chances of neonatal death or permanent disability are high. In this scenario, delivery after 37 weeks is recommended without compromising the mother's safety.

4 Clinical features of the case series and literature review

In the following paragraphs, while presenting the management of the selected PA-HNC patients, we reviewed the relevant literature on the topic, referring to the current procedure that would have been offered to non-pregnant individuals. Pregnancy termination should not be justified by the cancer diagnosis itself. Treatment was similar to that for non-pregnant patients, except that radiation is not recommended at any stage of pregnancy, and the choice of delivering chemotherapy should be cautiously evaluated case by case. For ideal clinical decision-making, a multidisciplinary approach is mandatory.

4.1 Clinical presentation

The vast majority of our patient population (14 cases) was diagnosed with HNC in a symptomatic phase. Most HNCs were diagnosed as self-palpated cervical masses or painful ulcerated mucosal lesions.

Older maternal age is associated with mutation accumulation, and this might lead to an increased risk of malignancies. Recent studies reported that epithelia from these tumors contain a high expression of essential hormone-regulated genes linked to cell proliferation, metabolism, tumor aggressiveness and recurrence. Breast cancer is one of the most extensively studied malignancies during pregnancy. Notably, breast cancer cells have a significantly higher expression of genes guiding the cell cycle process, most of which are hormone-dependent (28).

One thyroid cancer patient had venous thromboembolism (VTE) and required blood transfusions. However, these complications are expected in pregnancy-associated thyroid cancers (29). The babies delivered by the three thyroid cancer patients under study had no harmful neonatal outcomes, no inborn malformations, intrauterine growth limitation, fetal death or premature labor.

4.2 Imaging and staging procedures

The radiological staging was performed after childbirth in 80% of our patients. Most studies and reviews considered PAC to have a suboptimal prognosis due to a late diagnosis and the restrictions in

TABLE 2 Tumor characteristics, clinical profile, characteristics of diagnosis and therapeutic management.

Case	ECOG PS	Tumor site	Histology	Age *(year)*	Pregnancy week	Pregnancy complications	Mode of cancer detection	Stage	M1**	Therapy	OS (years)	Maternal outcome	Fetal outcome
1	1	Salivary glands	Adenocarcinoma	43	22	yes	Symptom	II (T2 N0 M0)	absent	S*; RT	1.22	NED	Vital
2	3	Thyroid	Differentiated carcinoma	38	32	no	Symptom	IV (T3 N1b M1)	present (bone, lung, mediastinal nodes, soft tissue)	S; RT; CT (1L CBDCA + ADM; 2L lenv)	4.63	DOD	Vital (cesarean section)
3	0	Salivary glands	Salivary duct carcinoma	27	28	no	Symptom	IV (T3 N2b M1)	present (lung)	RT; CT (CDDP + trastuzumab)	3.00	DOD	Vital
4	0	Oral cavity	Squamous cell carcinoma	27	26	no	Symptom	I (T1 N0 M0)	absent	S*	1.58	DOD	Vital
5	0	Salivary glands	Mucoepidermoid Carcinoma	32	28	no	Symptom	II (T2 N0 M0)	absent	S*; RT	5.72	DOD	Vital
6	0	Nasopharynx	Undifferentiated carcinoma	37	>40	yes	Symptom	IV (T4 N2 M0)	absent	RT	9.52	NED	Vital
7	0	Nasopharynx	Undifferentiated carcinoma	30	>40	yes	Symptom	III (NA)	absent	RT	12.42	NED	Vital
8	0	Salivary glands	Adenoid cystic carcinoma	36	28	no	Symptom	IV (T4a N0 M0)	absent	S	10.76	DOD	Vital
9	0	Nasopharynx	Undifferentiated carcinoma	37	16	no	Symptom	III (T2 N1 M0)	absent	RT	5.74	NED	VIP
10	1	Salivary glands	Myoepithelial carcinoma	41	>40	no	Symptom	IV (NA)	present (lung)	RT; CT (ADM)	10.78	DOD	Vital
11	0	Thyroid	Medullary carcinoma	37	18	no	Symptom	II (T2 N0 M0)	absent	S; RT	7.55	DOD	Vital
12	0	Nasopharynx	Undifferentiated carcinoma	34	28	no	Symptom	III (T1 N2 M0)	absent	RT	6.43	NED	Vital

(Continued)

10.3389/fonc.2023.1298439

TABLE 2 Continued

Case	ECOG PS	Tumor site	Histology	Age (year)	Pregnancy week	Pregnancy complications	Mode of cancer detection	Stage	M1**	Therapy	OS (years)	Maternal outcome	Fetal outcome
13	1	Thyroid	Differentiated carcinoma	37	40	yes	Fortuitous	IV (T2 N0 M1)	present (bone)	S; RT	10.67	ED	Vital (cesarean section)
14	0	Oral cavity	Squamous cell carcinoma	40	>40	no	Symptom	I (T1 N0 M0)	absent	S; RT	4.82	NED	Vital
15	0	Oropharynx	Squamous cell carcinoma	40	>40	no	Symptom	III (T2 N1 M0)	absent	RT	3.27	NED	Vital

1L, first-line; 2L, second-line; ADM, doxorubicin; CBDCA, carboplatin; CDDP, cisplatin; DOD, died of disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status; lenv, lenvatinib; NA, not available; NED, no evidence of disease; S, surgery; RT, radiotherapy; CT, chemotherapy; VIP, voluntary interruption of pregnancy; *Treatment during pregnancy; ** M1 staging was assessed after birth in all cases.

oncologic therapy. Any treatment delay may impair the maternal prognosis. Therefore, radiological staging should be offered when malignancy is suspected or known.

In all our patients, ultrasonography (US) was the first line imaging technique evaluating the cervical mass during pregnancy because of the ability of US to differentiate between solid and cystic lesions with sufficient sensitivity (30). Besides, the US lacks ionizing radiation, negating the possible cause of congenital disorders.

Theoretically, computed tomography (CT) could be performed during any trimester of pregnancy with proper abdominopelvic shielding. When the fetus is outside the field of view, the radiation exposure is estimated to be low for CT. The mean fetal dose produced from a chest CT is 0.06 mGy with a maximum possible limit of 0.96 mGy — less than half an amount than an abdominal radiograph (31). However, in daily operations, CT should be avoided because the internal scatter of the radiation to the fetus cannot be evaded (32).

The best radiologic assessment for HNC is Magnetic Resonance Imaging (MRI); however, contrast-enhanced MRI scans are not recommended during pregnancy (33). Gadolinium-based contrast, with gadolinium as a potential teratogen, can cross the blood-placental barrier (34). During breastfeeding, contrast-enhanced MRI scans are considered safe (35). The images may be difficult to be interpreted due to the increased background enhancement related to hypervascularization and inflammatory changes. Although negligible doses of gadolinium-based agents are known to be excreted into breast milk, the chances of complications, such as direct toxicity or allergic reactions, are minimal and have not been reported. Weighing the nominal risks, the American College of Radiology endorses the safety of breastfeeding after MRI. However, avoidance of breastfeeding for the 12-24 hour period after gadolinium administration is recommended (36). Although accurate MRI scans should be obtained after contrast administration, functional imaging techniques, such as Diffusion Weighted Imaging (DWI), may help obtain a satisfactory tumor delineation independently of contrast administration.

Systemic staging studies are indicated for advanced cancers. Nevertheless, pregnant and non-pregnant patients are differently managed due to radiation risks and the deleterious effects of the contrast agents on the developing fetus or embryo. In pregnant patients, positron emission tomography/CT (PET/CT) exposes the fetus to a comparatively high radiation dose caused by the 18F-FDG uptake and CT dose combination. Therefore, PET/CT is recommended to be deferred until after the pregnancy completion (37).

In addition, placental histology is monitored in women with malignant melanoma or metastatic disease to evaluate the fetal risk of metastasis (38, 39). Even though we lack this information in our patient cohort, the application of non-invasive prenatal testing, equipped to detect preclinical cancer, might lead to an earlier cancer diagnosis at a preclinical stage (40).

4.3 Surgery

In our case series, five patients were treated with surgery after childbirth. Two patients were affected by initial HNC (respectively

by papillary thyroid carcinoma and oral squamous cell carcinoma). Conversely, three patients had advanced disease (two patients with metastatic thyroid carcinoma, respectively with papillary and medullary carcinoma, and one with locally advanced adenoid cystic carcinoma). While these three patients showed an advanced HNC, the maternal treatment was not delayed because all patients received state-of-the-art surgical treatment as per their clinical condition. Surgery was safely performed without any delay.

For all patients with gestational thyroid cancer needing surgery, a team of proficient endocrinologists and oncologists is fundamental to personalize their treatment.

Even though neck lymph node dissection is fundamental in the proper management of locally advanced HNC amenable to surgery, our patients were only operated on primary tumors. This has been planned due to HNC histology (adenocarcinoma and mucoepidermoid carcinoma for salivary gland carcinomas) or the limited stage at diagnosis (for oral squamous cell carcinoma).

Surgical recommendations for PA-HNC patients are comparable to those for patients who are not pregnant. Indications depend on the clinical stage, genetic status, tumor biology, prenatal age, and the mother's surgical requests. Gestational age at diagnosis is vital for surgical planning because of the associated risks of spontaneous abortion and preterm labor (21). For this reason, the HNC multidisciplinary team should also involve maternal-fetal medicine specialists.

Surgery can be safely executed anytime during pregnancy providing maternal and embryo/fetal safety is addressed. Pregnancy-induced changes in maternal physiology and anatomy majorly impact surgical planning because they may determine potential issues for the mother and fetus/embryo receiving anesthesia. The baby may be exposed to potential danger due to intraoperative hypoxemia or asphyxia triggered by several physiological alterations within the maternal and fetal bodies. Additionally, exposure to teratogenic drugs and the risk of premature delivery because of the surgical process or administered drugs are equally harmful (41). Adverse post-surgery fetal outcomes, suggested by a population study, may be triggered by the underlying maternal disease instead of the direct influence of anesthesia (42). In most cases, the fetus passively receives the anesthesia from the mother, does not bear blood losses and experiences passive changes but direct alterations instigated by surgeries. Despite the minimal teratogenicity of anesthetic agents, surgery is not usually advised until after the first trimester to lessen possible risks to the fetus.

The current guidelines propose to avoid optional surgeries until the second or third trimester (43), with the second trimester being the safest period. The stress of surgery can lead to premature labor and premature delivery during the third trimester. With access to a neonatal intensive care unit, neonatologic and obstetric help should be in place (43, 44).

4.4 Radiation therapy

In this case series, eight PA-HNC patients were treated with radiation therapy after childbirth, five patients with radical intent, and three cases in the postoperative setting.

The safe administration of radiation to pregnant women is challenging. The highest sensitivity of fetal cells to radiation occurs during early organogenesis (up to the eighth gestational week), with doses over 0.05 Gy. The most common radiation-induced abnormality in this setting includes developmental disability. In PA-HNC patients diagnosed during the first trimester, treatment with radiation (with fetal exposure >0.1–0.2 Gy) is linked to a greater risk of congenital abnormalities. Therefore, these cases must be recommended for pregnancy termination (45).

Radiation therapy is generally not offered to PA-HNC patients because of the following significant risks: teratogenicity, probable installation of childhood malignancies and hematological disorders. The fetal developmental stage and the dose, intensity, and distribution of radiation are directly connected to irradiation toxicity during pregnancy. During the first trimester, radiation-induced growth and mental deficiency may take place (46).

The radiotherapy-related risks can be lowered by avoiding the direct exposure of the fetus to radiation by utilizing pelvic shielding or modifying the beams' physical characteristics limiting the dose delivered to the fetus. However, these therapeutic adjustments may lead to suboptimal management of PAC (47–49).

Nonetheless, several successful radiation treatments during pregnancy, with the birth of healthy children, have been described (50–57).

Luis et al. reported that out of the 109 cases following up on the offspring, 13 reported adverse outcomes, including spontaneous abortions, perinatal deaths and neurological deficits (58). It is emphasized that if radiotherapy is required before the post-partum period, treatment should be managed by a qualified team of physicists and radiation oncologists, ensuring careful planning, appropriate shielding devices, and distribution of fractional doses for a prolonged period reducing the scattered dose to the fetus. In this setting, there is evidence that an accurate pre-treatment simulation in a PA-HNC patient is fundamental to predicting the fetal dose (59).

However, due to the complexity of treatment (the physicists calculate the fetal radiation dose and adjust the treatment plan), the current European guidelines prefer to delay radiation therapy to the post-partum period, regardless of the treated site, except a site located adequately far from the uterus demands an urgent intervention (60).

4.5 Systemic therapy

While considering systemic treatments for PA-HNC patients, pregnancy-related changes in maternal physiology and fetal developmental stage should be taken into account. These include altered metabolism and clearance that may influence drug bioavailability and toxicity profiles. None of the PA-HNC patients in our case series was treated with chemotherapy during pregnancy.

One of the most relevant factors in choosing and scheduling systemic therapy is the potential consequence of chemotherapy on fetal development. Following implantation (circa two weeks after conception), organogenesis occurs over the subsequent 8-10 weeks. This period has the highest probability of significant malformations

and fetal loss (61). Although studies reporting chemotherapy in the first trimester are few, some evidenced fetal abnormalities, including neural tube defects, cardiac defects, cleft lip/palate, and fetal loss (61–63). Therefore, chemotherapy administered during the first trimester, especially during organogenesis (weeks 4 to 12), could potentially result in teratogenesis (3, 64).

Although chemotherapy is contraindicated during the first trimester, cytotoxic chemotherapy is more widely accepted during the second and third trimesters of pregnancy. Low rates (3%–5%) of fetal malformations were reported by most of the studies inspecting chemotherapy safety beyond the first trimester (65–70).

Chemotherapy-associated congenital deformities have been reported at 16%, 8%, and 6% of cases in the first, second and third trimesters, respectively. These fetal consequences in the second and third trimesters include restraint intrauterine growth, prematurity, and lower birth weight. Chemotherapy-induced maternal toxicity may also lead to fetal hair loss and myelosuppression (64).

Chemotherapy regimens used to treat PAC patients include 5-fluourouracil, doxorubicin, cyclophosphamide (65) and carboplatin plus paclitaxel (71–73). Data in the field are limited, and although taxane and/or platinum therapy bring about encouraging fetal outcomes, these are based on a relatively small number of patients with limited follow-up.

Taxanes and platinum agents should be employed carefully to treat pregnant patients with salivary gland carcinoma, only if standard anthracycline-based therapy is not feasible as the preferred option. Another relevant aspect is chemotherapy pharmacokinetics. Indeed, a higher cytochrome P-3A4 activity is detected in the third trimester. Therefore, a greater taxane clearance is likely, with possible limitations on drug activity (74).

Carboplatin may be preferred over cisplatin due to its better pregnancy-related safety profile. Single-agent platinum regimens have already been reported in this context. Mir et al. evaluated 43 patients with PAC, of whom 28 had ovarian cancer. Cisplatin was found to be linked with various adverse consequences: restricted intrauterine growth (in 8.3% of patients), premature birth (8.3%), respiratory distress (8%), and neonatal anemia (5.6%). Compared with cisplatin, carboplatin does not lead to fetal defects, toxicities, or adverse outcomes in the newborn (73).

For PAC patients treated with chemotherapy during pregnancy, delivery timing must be synchronized with therapies to avoid cytopenias at delivery. Platelets might be transfused, if needed, >30,000/mL for a vaginal delivery or 50,000/mL for a cesarean section. A vaginal delivery is recommended, and a cesarean section should be deemed only for a pelvic tumor (e.g., cervical, anal, or rectal cancer) or routine obstetric symptoms (75).

Thus, single-agent chemotherapy opens up a promising future in managing pregnancy-associated cancers, with a subsided exposure of chemotherapeutic agents to the fetus.

Studies evaluating children exposed to long-term *in utero* chemotherapy imply that chemotherapy is not necessarily linked to inadequate postnatal growth or compromised cognitive or cardiac functions. Nevertheless, more data on long-term outcomes are needed to assess the safety and cancer risk (38).

In the field of ancillary therapy, based on animal and human studies, the effects of corticosteroids are contradictory but tend to designate increased risks in the first trimester. Chemotherapy is feasible after the 14th gestational week, but a few broadly used drugs, like platinum derivatives, taxanes, and etoposide, present substantial infusion reaction events (76). Steroid-based premedications are usually administered to prevent such reactions (77). Corticosteroids are particularly beneficial in these cases. Moreover, the H2 histamine antagonists ranitidine, famotidine and cimetidine are not associated with an increased risk of congenital disabilities (78, 79).

In the field of targeted therapy, no robust data are available. A drug's placental passage is subjected to its class and size: large molecules, like monoclonal antibodies (e.g., trastuzumab, rituximab), need an active passage through the placenta, which is fully developed at the beginning of the 14th gestational week. On the other hand, tyrosine kinase inhibitors and other small molecules can cross the placenta throughout the pregnancy. Cases of detectable concentrations of antitumor TKI (alectinib in a pregnant woman affected by an ALK-rearranged non-small cell lung cancer) were described, with a fetal plasma concentration at birth 14 times lower than the one observed in the mother (80).

Targeted therapies may increase the risk of fatal morbidity and pregnancy-related difficulties due to the activity of antitumor drugs on biological pathways involved in both tumor pathogenesis and physiologic fetal development.

As angiogenesis is crucial for the placenta's and fetus's normal development, the teratogenic angiogenesis inhibitors could incite pregnancy loss, skeletal retardations and fetal growth restriction. Therefore, during pregnancy, anti-vascular endothelial growth factors and other antiangiogenic drugs are avoided (38). One metastatic differentiated thyroid patient included in our case series was treated with lenvatinib after childbirth. Targeted therapies for cancer treatment are not recommended during pregnancy and should be administered after delivery, apart from the possibility of giving rituximab and imatinib in the second and third trimesters (81).

In the framework of immunotherapy, programmed death-1 (PD-1)/PD-L1 and cytotoxic T-cell lymphocyte-4 (CTLA-4) interactions play key roles in maintaining normal fetal tolerance. Nivolumab and pembrolizumab are monoclonal antibodies directed against PD-1. Recently introduced as a cancer therapy agent, anti-PD-1 is considered safe during pregnancy. PD-1 acts in the negative immune regulation crucial for maternal tolerance of pregnancy with an apparent effect on human pregnancy (82). Evidently, immune checkpoint inhibitors like anti-PD1/PD-L1 drugs are associated with increased spontaneous abortion rates in animals (83). In humans, a case of advanced melanoma patient treated with nivolumab was reported during the first seven weeks of pregnancy. Conceivably the first case of a fetal immune-related adverse effect from maternal anti-PD-1 exposure, the prematurely born fetus was identified with intrauterine growth restriction and congenital hypothyroidism (84). Nonetheless, a few case reports identified no miscarriages in melanoma patients treated during their first trimester (85, 86).

To precisely schedule systemic therapy during pregnancy, several factors must be respected: clinicopathologic characteristics (i.e., stage at diagnosis, grade, lymph node and receptor status), the gestational age at HNC diagnosis and the prospect of a full-term delivery to ensure maternal and fetal outcomes. Based on available data, we would endorse initiating systemic chemotherapy after completing the first trimester without an urgent contraindication. Finally, although milk production may be negatively affected by cancer treatments (87), breastfeedings should be avoided while continuing systemic treatments after birth (88).

5 Discussion

Pregnancies complicated by cancer are comparatively rare. However, since women in Western societies tend to delay childbearing until their 30s and 40s, this possibility may be more frequent in the future. In this setting, it is expected that older women may have a higher probability of HNC risk factor exposure (e.g., HPV infection, smoking, alcohol).

Cancer diagnosis during pregnancy is a tricky issue. On the one hand, the mother should be optimally treated, and on the other, the consequences of cancer treatment on the fetus should be minimal (89).

The small number of patients may be a limitation. Other drawbacks of this work are its retrospective nature, the lack of data on patients' education, and the fact that the study patients were affected by different cancer sites, histologic types, and stages of disease, making it difficult to assess survival outcomes. Nevertheless, the presented data are worthwhile because our case series is a representative sample of PA-HNC treated at a tertiary cancer center.

No major delays between cancer diagnosis and treatment start and no adverse events because of pregnancy were observed in the study cohort.

Given the prevalence of symptoms and the disease stage at clinical presentation in the presented series (all the patients were aware of their pregnant status before the diagnosis), the diagnosis was late for the majority of cases. Literature data reported a higher age-adjusted incidence rate of late stage HNC in men when compared to women in the US (90). In cancer registries we lack data about PA-HNCs, so no direct comparisons can be made between our data and the available literature. However, since almost all cases described here were diagnosed at a late stage, we cannot exclude that pregnancy could have had a promoting action in cancer development and progression. It is well known these phenomena are promoted by complex biological mechanisms. At the same time, pregnancy-related exposures impact fetal growth cell division and organ functioning. The balance between the need to tackle tumor cell proliferation while not impairing normal fetal development is a key point for the principles of PAC management. Indeed, cancer and its treatments are expected to interfere with the complex phenomena of pregnancy.

Cancer diagnosis, staging and treatment are based on the knowledge developed treating non-pregnant HNC patients. To administer the safest and optimal treatment plan to the mother and developing fetus, several challenges in systemic treatments, surgery, radiotherapy and obstetrics must be thoughtfully evaluated in patients with PA-HNC. Indeed, a careful and comprehensive multidisciplinary discussion should be conducted in each case. Given the cited literature, the following factors should be taken into account: maternal age; pregnancy stage; cancer type, site, size and stage; potential embryo-fetal risks associated with anticancer treatment; wishes of the woman and her family; close monitoring of both mother's and baby's health during the whole treatment period and in the subsequent follow-up; psychological support.

Cancer treatment delay until achieving fetal maturity may be considered in selected cases, provided that tumor evolution is closely monitored.

The delivery term depends on the date of cancer diagnosis (beyond 35 weeks of gestation in most cases). Pregnancy in itself does not have a deleterious effect on cancer prognosis, but it is often associated with a diagnostic delay.

According to the available evidence, non-obstetrical surgeries may be conducted during pregnancy without any increased risk of adverse outcomes. However, some cancer treatments should be postponed to the second and third trimesters due to the higher risk of fetal harm during the first three months of pregnancy.

6 Conclusions

Head and neck cancers during pregnancy present significant ethical and professional challenges for patients and physicians. Several aspects from diagnostic, medical, surgical and radiation oncology standpoints must be addressed to ensure the safety of the mother and the infant. An informed discussion between the patient and her medical team is essential to ascertain a precisely individualized treatment plan maximizing benefits and minimizing risks to the mother and the fetus. Long term effects on children, adolescents and adults, related to maternal cancer treatment during pregnancy should be investigated and longitudinally surveilled.

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: stefano.cavalieri@istitutotumori.mi.it.

Ethics statement

The studies involving humans were approved by Ethical Committee of the Fondazione IRCCS Istituto Nazionale dei Tumori, via Venezian 1, 20133 Milan, Italy. 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

CB: Writing – original draft, Writing – review & editing. SC: Writing – original draft, Writing – review & editing. CR: Writing – review & editing. SA: Writing – review & editing. IN: Writing – review & editing. EC: Writing – review & editing. AO: Writing – review & editing. GC: Writing – review & editing. AV: Writing – review & editing. NI: Writing – review & editing. MF: Writing – review & editing. MG: Writing – review & editing. AD: Writing – review & editing. LL: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research and the preparation of this manuscript were supported thanks to the generous donation of a private -funds raised in memory of Paolo Sardella. This research was partially funded by Italian Ministry of Health "Ricerca Corrente" funds.

Acknowledgments

We are grateful to all the patients and their families whose precious support allowed the conduct of this study. We also thank Somsuvro Basu (medical writing consultant), who has provided editorial assistance in the preparation of this article.

Conflict of interest

LL declares the following conflicts of interest: research funds donated directly to the institute for clinical trials from AstraZeneca, BMS, Boehringer Ingelheim, Celgene International, Eisai, Exelixis, Debiopharm International SA, Hoffmann-La Roche ltd, IRX Therapeutics, Medpace, Merck-Serono, MSD, Novartis, Pfizer, Roche, Buran; occasional fees for participation as a speaker at conferences/congresses or as a scientific consultant for advisory boards from Astrazeneca, Bayer, MSD, Merck-Serono, AccMed, Neutron Therapeutics, Inc. CR declares honoraria from SunPharma.

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

SC and LL declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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frontiers | Frontiers in Oncology

TYPE Review
PUBLISHED 18 December 2023
DOI 10.3389/fonc.2023.1273430

OPEN ACCESS

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RECEIVED 06 August 2023
ACCEPTED 27 November 2023
PUBLISHED 18 December 2023

CITATION
Vester S, Muhr A, Meier J, Süß C, Kummer P and Künzel J (2023) Prehabilitation of dysphagia in the therapy of head and neck cancer- a systematic review of the literature and evidence evaluation. *Front. Oncol.* 13:1273430. doi: 10.3389/fonc.2023.1273430

Prehabilitation of dysphagia in the therapy of head and neck cancer- a systematic review of the literature and evidence evaluation

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Background: Prehabilitation is becoming increasingly important in oncology because of the significant survival benefits that the reduction of malnutrition provide. Specifically, tumor- and therapy-related dysphagia leads to malnutrition in more than half of head and neck tumor patients. Studies describe the positive effects of an early onset of swallow-specific prehabilitation on the protection of the swallowing function. This paper intents to evaluate the existing evidence on the efficacy of preventive forms of swallowing therapy.

Methods: A systematic literature search was performed in February 2022 in the Cochrane Library, MEDLINE via PubMed, and ClinicalTrials.gov databases for randomized controlled trials investigating preventive swallowing therapy in head and neck tumor patients. This Procedure complies with the PRISMA statement. The RCTs were evaluated by using the PEDro Scale and the Cochrane Risk of Bias tool RoB2.

Results: Five randomized-controlled trials with 423 participants were identified. Four Studies showed moderate to high quality in the PEDro analysis, one showed less. The risk of bias was high in all studies because there was no possibility for blinding and there were high dropout rates. Heterogeneity in interventions, measurement instruments, measurement time points, and outcomes limits a general statement about which swallowing exercises are suitable for the prevention of dysphagia in head and neck tumor patients. Evidence is provided for short-term effects (≤24 months) on functional aspects of swallowing and quality of life. Overall, a decreasing adherence over time was observed in the intervention groups.

Discussion: Initial studies describe swallowing-specific prehabilitation programs in head and neck tumor patients as effective, at least in the short term, whereas long-term effects need to be further investigated. At the current time the evidence base for clear recommendations does not appear to be sufficiently high and studies share a high risk of bias. Further well-designed research,

especially considering the conditions in the national health care system, is needed.

Other: There was no funding and no registration.

KEYWORDS

prehabilitation, dysphagia, aspiration, speech therapy, head and neck squamous cell carcinoma, flexible endoscopic evaluation of swallowing

1 Introduction

Latest studies show positive effects of intense pretherapeutic preparations on the outcome of frail and malnourished oncological patients (1, 2). More than a third of hospitalized patients show signs of malnutrition; far more than assumed until now (3). The aim of prehabilitation is to recognize frailty, anemia as well as malnutrition and to improve until the actual therapy starts (4).

The German guidelines for oral-cavity- and larynx-carcinoma do not clearly recommend the structured, therapeutic preparation to secure patients' nutrition (5, 6), although higher age and multimorbidity of HNC-patients lead to an increased risk of morbidity (7). Therein, the oncology's focus lies on enhanced therapeutical measures, e.g. intensity-modulated radiation, minimally invasive or reconstructive surgery, deescalating strategies of therapy and the traditional rehabilitation. In Germany the occurring of dysphagia is the starting point of a professional swallowing therapy, mostly in a rehabilitation after the surgery or the chemoradiation (8).

HNC patients particularly have a higher risk for malnutrition as the localization of cancer in the upper pharyngolaryngeal system causes dysphagia. A second risk factor is the unhealthy lifestyle. Other complications of dysphagia are aspiration pneumonia with increasing mortality, social isolation and loss of quality of life (9–11). The prevalence of dysphagia depends on the carcinoma's localization and size and is up to 80% in HNC patients (12, 13).

Foreign studies present better outcomes for HNC patients if the therapy of dysphagia is started before or during the radiation treatment (10, 13). The idea is that preventive swallowing exercises can reduce the complications of dysphagia that is preexisting or is a consequence of cancer treatment (14).

The aim of this study was to explore if there is evidence of preventive swallowing exercises to maintain swallowing function before and during the primary tumor therapy of HNC patients. Special interest was to see which outcomes and which exercises were useful.

2 Methods

An explorative systematic review of the literature was performed. The second author (A.M.) did the literature research in February 2022. This procedure complies with the PRISMA statement (checklist is available in Supplementary 1) (15).

According to the criteria of subject focus, document type, possible search and filter functions, and free access to the subject database, the appropriate selection of the databases Cochrane Library, MEDLINE via PubMed, and ClinicalTrials.gov was made. The search language for these databases is English.

The search terms in Table 1 were chosen by the PICO method, according to the PICO question: How does preventive swallowing therapy (=I) work to conserve the swallowing function (=O) in head neck cancer patients (=P) compared to head neck cancer patients without preventive swallowing therapy (=C), supplemented with timing before tumor therapy (=T) and study type(=S) randomized controlled trials (RCT). The synonymous keywords are linked with the Boolean operator OR, the search components with AND (16).

Multiple trial searches of the MEDLINE database via PubMed were performed to verify and appropriately adjust the search strategy before the search. The database indicated errors such as incorrect bracketing or use of the stop words "and, during, before, and the". Accordingly, the search syntax was edited. In addition to correcting typos and bracketing, major revisions included adding the search component (swallowing OR deglutition OR dysphagia) in conjunction with the AND operator to exclude studies in which dysphagia did not represent study content. The Peer Review of Electronic Search Strategies (PRESS) checklist (17) was used for final review of the search string. Depending on the database the search matrix was adapted (as seen in Supplementary Material 2).

Using the inclusion and exclusion criteria shown in Table 2, library records were selected, and duplicates were sorted out. Publications that did not answer the research question were excluded from the further search. These included studies that examined medication, administration or different doses of radiation therapy as an intervention instead of exercise therapy measures, as well as studies that did not assess swallowing function as an outcome. The inclusion criterion that participants were HNC patients had to be met, so studies in patients with esophageal cancer were excluded. Furthermore, results were excluded if they were not randomized controlled trials. Also excluded were studies registered on ClinicalTrials.gov whose outcome data could not be viewed.

For reasons of transparency and to secure the search, the hits were exported to the literature management program Citavi 6 (Swiss Academic Software GmbH; Wädenswil, Swiss). The assignment into categories allows a selection.

TABLE 1 Search terms.

Patient P=Head and Neck Cancer	Intervention I=swallowing therapy	Outcome O=swallowing function	Timing T=before cancer therapy	Study type S=RCT
• neck and head cancer • Cancer of head and neck • cancer of the head and neck • cancer of neck and head • cancer of the neck and head • cancer of neck • cancer of the neck • head and neck neoplasm • head and neck neopl* • neck cancer • neck neoplasms • neck neoplasm • squamous Cell Carcinoma of Head and Neck	• speech and language • disease management • treatment	• deglutition • dysphagia	• preventive • prophylactic • during • before • preoperative • prehabilitate*	• randomized controlled trials (RCT)

After identifying eligible studies, the most important data and results were extracted and summarized. Particular emphasis was placed on the type of intervention in the comparison groups, as well as the outcome parameters and timing of outcome measurement. Statistically significant results were highlighted. (see Tables 3, 4).

The RCTs were evaluated using the PEDro-Scale (26, 27). The PEDro scale (27) allows studies to be assessed in terms of their external validity (criterion 1), internal validity (criteria 2 to 9), and the presence of sufficient statistical information to make results interpretable (criterion 10 to 11). It provides a valid measurement tool for assessing the methodological quality of RCTs (23). Accordingly 6 points and more indicate a moderate to high study quality (23, 24).

The risk of bias was evaluated using the Revised Cochrane risk-of-Bias tool for randomized trials (RoB 2) (25). We decided to assess the effect of adhering to intervention in Domain 2 (25)., while using the main outcome parameter of each study.

3 Results

1114 studies were identified in the first literature research. 42 studies underwent the full text analysis, from which 5 RCT's (18–22) finally were evaluated (Figure 1).

Only randomized controlled trials that met the PICO criteria were included in the further analysis. In view of the specific research question regarding the efficacy of preventive exercise therapy measures, studies investigating enteral versus oral nutrition during radiotherapy or adherence or feasibility as an outcome were excluded from the 41 hits. Similarly, sub-studies and studies without available results were excluded. These included study protocols, reports of preliminary data, or the follow-up study by Kraaijenga et al. (28), which no longer differentiated between the intervention and control groups of the underlying study by Kotz et al. (20). When updates to studies were available, the current results were chosen for further evaluation. Van der Molen et al. (29, 30) investigated the effectiveness of a prevention program using the TheraBite® Jaw Motion Rehabilitation System™ compared to standard care. Because the study was conducted in the Netherlands, where prehabilitation therapy is already part of usual care (30), it did not meet the PICO criterion of no preventive exercises as a comparison, so this study was excluded. The studies by Virani et al. and Wall et al. (31) also lacked comparison groups without preventive interventions. Three other studies did not meet the inclusion criterion of starting prehospital interventions because they were postoperative or after radiotherapy (32–34). Only preliminary data and study protocol are available for the Redyor randomized controlled trial (35), which collected data in 2018-2019 to review preventive swallowing exercises (35–37). Because full text has not yet been published on the study results, the study was excluded.

TABLE 2 Inclusion and exclusion criteria of the systematic literature research.

Inclusion Criteria	Exclusion Criteria
• Randomized controlled trial (RCT) • Intervention: physical exercise to improve or preserve the swallowing function before or during the primary therapy (operation or radiotherapy/chemoradiation) • Primary diagnosis of HNC • Control group without swallowing exercises • Full-text available in English	• Swallowing function not evaluated • RCTs without results or no access to read the results • Intervention: no swallowing exercises

It should be mentioned that criteria five and six of the PEDro-scale cannot be matched as blinding is not possible, neither for participants nor therapists, due to the nature of the evaluated treatment. However, the studies of Hajdú et al. (18), Messing et al. (21), Kotz et al. (20) and Carnaby-Mann et al. (19) achieve 6 or 7 points, i.e. showing a moderate to high quality (see Table 5). Only the study of Mortensen et al. (22) achieves 4 points and therefore reveals less quality and validity.

Details of the included RCTs are presented in Table 3. Tumor stages and localizations are distributed heterogeneously, same is true for the intervention and outcome parameters. The common denominator of the evaluated RCTs is the treatment of primary radiation or chemoradiation. Collectives that underwent primary surgery were not yet investigated. Outcome measurement tools

TABLE 3 Overview of interventions and outcome measures of the RCTs (18–22).

Study Country Number n	Age (MW) Tumor-localization Tumor stage Therapy	Intervention	Outcome after 6 weeks	Outcome short term after 2-3 month	Outcome mid term after 4-6 month	Outcome long term after 7-12 month
Hajdú et al. (18) **DK n = 235**	38-88 (63) Pharynx, Larynx, Oral cavity, CUP UICC I-IVb Curatively intended Radiotherapy	I: 2x/week physiotherapy, 3x/week swallowing therapy with occupational therapist, 3x/day self-administered swallowing exercises during radiation C1: Usual treatment, occuptional therapist. (1x/week) (active group) C2: No treatment (non-active group)	• **[I]mouth opening** • wight • FOIS • MDADI • depression • **[I]anxiety(SCL-92)** • **[I]pain** • **[I]EORTC-QLQ-C30** • **[I]EORTC-HN-35**	• mouth opening • wight • PAS • **[c]Yale Scale** • FOIS • MDADI • depression • anxiety (SCL-92) • pain • **[I]EORTC-QLQ-C30** • **[I]EORTC-HN-35**	• mouth opening • wight • FOIS • MDADI • depression anxiety (SCL-92) • pain • EORTC-QLQ-C30 • EORTC-HN-C35	• mouth opening • wight • PAS • Yale-Scale • FOIS • MDADI • depression • anxiety (SCL-92) • pain • EORTC-QLQ-C30 • EORTC-HN-C35
Messing et al. (21) **USA n = 60**	39-79 (56) Oral cavity, Pharynx, Larynx UICC III -IV Chemoradiotherapy	I: 2x/day Swallowing exercises; oromotor strength/strength exercises and swallow maneuvers, during CRT and 3 month post CRT, 1x/week swallow therapy c: No swallow therapy, TheraBite (Usual care)	not evaluated	• mouth opening • wight • oromotor assessment • CTCAE mucositis and oral ulceration • Gastric feeding tube • **[I]OPSE** • **[I]pharyngeal phase impairments** • PAS • FOIS • pain • **[I]EORTC-QLQ-C30** • **[I]EORTC-HN-35**	• mouth opening • wight • **[I]oral disorders** • CTCAE mucositis and oral ulcerations • gastric feeding tube • OPSE • pharyngeal phase impairments • PAS • FOIS • pain • EORTC-QLQ-C30 • EORTC-HN-35	• mouth opening • wight • oromotor assessment • CTCAE mucositis and oral ulceration • gastric feeding tube • OPSE • pharyngeal phase impairments • PAS • FOIS • pain • EORTC-QLQ-C30 • EORTC-HN-35
Mortensen et al. (22) **DK n=44**	39-77 (58) Pharynx, Larynx, Oral cavity, CUP UICC I-IV Primary Radiotherapy	I: Swallowing exercises at home from RT till 11 month post RT (3x/day, 7 exercises á 10 repetitions), 9 occuptional therapy, exercise diary C: usual care	Not evaluated	• mouth opening • wight • gastric feeding tube • penetration • aspiration • DAHANCA • SPSS • **[c]EORTC-QLQ-C30** • EORTC-HN-35	• mouth opening • wight • gastric feeding tube • penetration • aspiration • DAHANCA • SPSS • **[c]EORTC-QLQ-C30** • EORTC-HN-35	• mouth opening • wight • gastric feeding tube • penetration • aspiration • DAHANCA • SPSS • **[c]EORTC-QLQ-C30** • **[c]EORTC-HN-35**
Kotz et al. (20) **USA n=26**	59 all Head and Neck cancers UICC IV Chemoradiotherapy	I: before and during CRT, 1 per week swallowing therapy, 5 swallowing exercises (effortful swallowing, super-supraglottic swallowing, 2 tongue base retraction exercises, Mendelssohn-Maneuver) K: swallowing therapy if necessary	• FOIS • PSS-H&N	• **[I]FOIS** • **[I]PSS-H&N**	• **[I]FOIS** • **[I]PSS-H&N**	• FOIS • PSS-H&N
Carnaby-Mann et al. (19)	54+-11.3 Oropharynx T-Stage 1-4	I: active swallowing exercises (2x/day swallowing therapy, exercises (Falsetto, tongue press exercises, effortful swallowing, TheraBite)	• **[I]muscle size/ composition in MRI and T_2 -relaxation time**	• not evaluated	• muscle size/ composition in MRI and T_2-relaxation time	• not evaluated

(Continued)

TABLE 3 Continued

Study Country Number n	Age (MW) Tumor-localization Tumor stage Therapy	Intervention	Outcome after 6 weeks	Outcome short term after 2-3 month	Outcome mid term after 4-6 month	Outcome long term after 7-12 month
USA n=58	Chemoradiotherapy; Radiotherapy	and diet C1: usual care C2: 2x/Tag swallowing therapy„ Valchuff"-Maneuver and diet	• **^{I}mouth opening** • **^{I}salivation** • **^{I}taste and smell** • wight • Videofluroscopy/ aspiration • **^{I}swallowing function (MASA)** • **^{I}oral feeding** • FOIS • dysphagia related complications		• mouth opening • salivation • taste and smell • wight • Videofluroscopy/ aspiration • swallowing function (MASA) • oral feeding • FOIS • dysphagia related complications	

Bold and preceding I: significance in favor of the intervention group.
Bold and preceding C: significance in favor of the control group.
grey: no significant differences.
C (Control group).
CRT (Chemoradiotherapy).
CTCAE (Common Terminology Criteria of Adverse Events).
CUP (Cancer unknown primary).
DAHANCA dysphagia score (Danish Group Head and Neck Cancer).
EORTC-HN35 (European Organization for Research and Treatment of Quality of Life Questionnaire Head and Neck (H&N) -35).
EORTC_QOL_C30 (European Organization for Research and Treatment of Cancer Quality of Life questionnaire C30).
FOIS (Functional Oral Intake Scale).
HADS (Hospital Anxiety and Depression Scale).
H&N (Head and Neck).
I (Intervention group).
MASA (Mann Assessment of Swallowing Abilities).
MDADI (MD Anderson Dysphagia Inventory).
OPSE: Oral Pharyngeal Swallow Efficiency.
PAS (Penetration-Aspiration Scale of Rosenbek).
PSS-HN (Performance Status Scale for Head and Neck Cancer).
RT (Radiotherapy).
SCL-90 (Symptomchecklist-90).
SPSS (Swallowing Performance Status Scale).
Yale Scale (Yale pharyngeal residual severity rating scale).

include physiological parameters, such as muscle thickness/muscle size and its composition in magnetic resonance imaging (19), oral motor function (21), mouth opening (18, 19, 21, 22), swallowing function parameters collected by FEES (Flexible Endoscopic Evaluation of Swallowing) (18, 19) or VFSS (Video fluoroscopic Swallowing Study) (19, 21), for example, using the PAS (Penetration-Aspiration Scale of Rosenbek) (18, 19, 21) and Yale pharyngeal residual severity rating scale (18), feeding-related parameters, such as tube dependence, weight (22), and dietary form (19), collected with FOIS (Functional Oral Intake Scale) (18, 20, 21), SPSS (Swallowing Performance Status Scale) (22) and MASA (Mann Assessment of Swallowing Abilities) (19).

Questionnaires were used to assess general (EORTC_QOL_C30/ HN35) (13, 18, 21, 22) and swallowing-related quality of life (MDADI) (18), depression and anxiety (HADS, SCL-95) (13, 18). The occurrence of complications such as pneumonia or dehydration was also assessed (19).

The interventions used in the RCTs (18–22) demonstrate a strong heterogeneity (Table 4). Tongue motor and strengthening exercises, the Masako maneuver, and forceful swallowing were most frequently used as preventive exercises. The selected exercise frequencies and repetition rates are not justified in the studies (18, 19, 21, 22). Only Kotz et al. (20) critically comment that there is no evidence for the appropriate dose of swallowing exercises and that the performance of three sets of ten repetitions of each exercise was arbitrarily set. They note that performing the exercises three times daily could be associated with "breakfast, lunch and dinner or morning, noon and night" to support compliance (20).

Significant group differences in favor of the intervention group were found at different measurement time points. Hajdú et al. (mouth opening, anxiety, pain and QoL) (18) and Carnaby-Mann et al. (muscle composition an T2 relaxion time, swallowing function, oral feeding, mouth opening, salivation, sense of taste and smell) (19) after 6 weeks. After 2 to 3 months in QoL (18, 21), oral feeding (18, 20, 21) and after 6 months in oral motor function (21) and oral feeding (20). Only Messing at al. show a significant better mouth opening 24 months after therapy (21), there were no differences between groups in the long term follow up in the other studies (18–20, 22). Mortensen et al. show significant better outcome in parts of QoL in the control group (22).

All studies indicate that adherence to exercise treatment in the intervention groups decreases over time; drop-out rates range from 25% (18) to 49% (22) within the study period. Among the reasons for discontinuing exercise, severe therapy-associated pain in the

TABLE 4 Applied exercises in the intervention groups (18–22).

Study exercices in Intervention group	Hajdú (18)	Messing (21)	Mortensen (22)	Kotz (20)	Carnaby-Mann (19)
tongue strength and stretch exercises	+	+	+		+
lip motor exercises		+			
chewing	+	+	+		
gurgling	+		+		
yawning	+				
mouth opening	+	+			
Valsalva-Maneuver	+				
Shaker	+		+		
Mendelsohn-Maneuver	+	+		+	
Masako-Maneuver	+	+	+	+	
effortful swallowing	+	+		+	+
neck stretching		+			
TheraBite-System		+			+
Falsetto			+		+
Larynx *range of motion (hold your breath)*			+		
super supraglottic swallowing				+	
tongue base retraction	+	+		+	

mouth, throat discomfort, and general fatigue were mentioned (20). Mortensen et al. refer to the publication by Shinn et al. (38) and describe "lack of understanding of the importance of swallowing exercises, the effort involved, pain, and forgetfulness" as causes of poor adherence (22).

The overall risk of bias is high in all studies (see Table 6). They all have a low risk of bias in the randomization process (Domain 1) and the reported result (Domain 5). Three studies (18, 21, 22) present some concerns and two (19, 20) high risk of bias in Domain 2, where we decided to assess the effect of adhering to intervention. Because of high dropout rates (18, 19, 21, 22) there is a high risk of bias in Domain 3 (missing outcome data). When the outcome is patient reported (20, 21), then there are some concerns in Domain 4 (risk of bias in measurement of the outcome).

4 Discussion

Despite all efforts for a rapid diagnosis and initiation of therapy in cases of suspected HNC, there are unused time windows in the diagnostic phase, namely the waiting period until the upper airway and esophagus can be examined under general anesthesia (panendoscopy) and the subsequent phase of therapy planning. Thus, on average, there is a period of two to four weeks that would lend itself to targeted prehabilitation without delaying therapy.

The need for identification of critical and prognostic swallowing disorders may be substantial if more than a half of the patients at a typical head and neck tumor center suffer from dysphagia (12). In subgroups, specifically concerning oropharyngeal carcinomas, such disorders also occur in up to 80% of cases. This effect is particularly relevant because the proportion of younger patients in this group increases due to the association with human papillomavirus (13, 39). Thus, it has already been shown that marked postoperative dysphagia without the ability to take oral food is an early indicator of poorer survival regardless of tumor stage (40). In addition, aspiration pneumonia may have prognostic significance, with a three- to fourfold increased incidence in HNC patients compared with a control group, as shown by data from the American SEER registry (11).

The detection of nutrition-related factors and their management in prehabilitation programs is already considered essential because of their prognostic importance (3). The European Society for Clinical Nutrition and Metabolism mentioned important aspects in guidelines for nutritional management in cancer patients. Before the therapy started all patients should be screened for their risk of malnutrition or for their body mass index, respectively. If necessary, this is followed by a detailed nutritional assessment and multimodal individualized intervention to increase dietary intake and physical activity (41).

In order to compare our results, we searched for other reviews on these topics and found four (13, 14, 42, 43) more review articles that examined not only randomized studies but also non-randomized studies. The heterogeneity in intervention and outcome parameters is also reflected in these papers as well as the high risk of bias (13, 14, 42, 43).

Little attention has been paid to prehabilitation aspects in HNC patients, although they may show organ-specific risk factors of

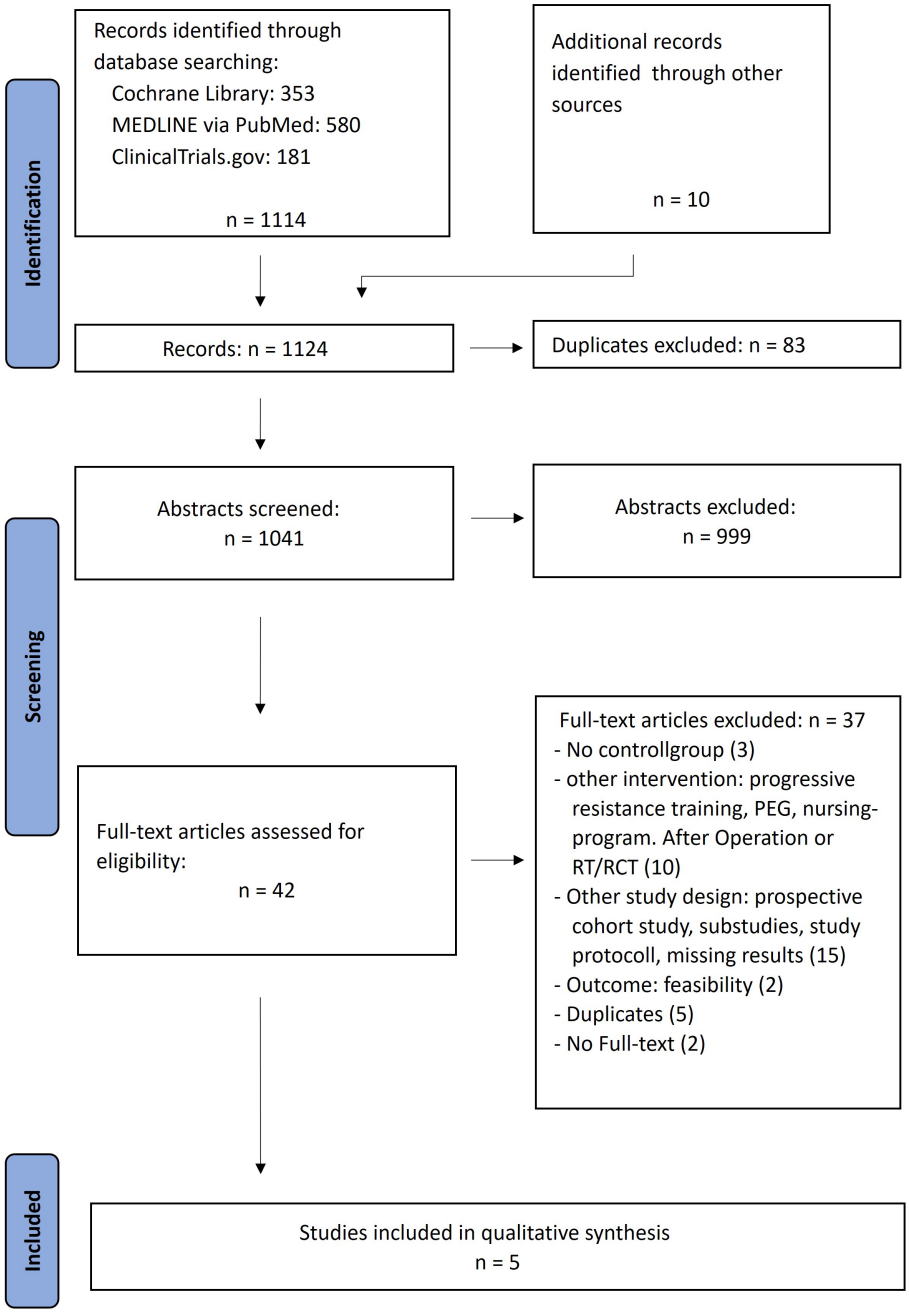

FIGURE 1
Modified PRISMA flow chart for the representation of the systematic research (own representation, modified according to PRISMA (15)).

TABLE 5 Quality of the selected studies according to the PEDro scale.

PEDro-criteria / Studies	1	2	3	4	5	6	7	8	9	10	11	Total score
Hajdú et al. (18)	+	+	+	+	-	-	-	-	+	+	+	**6**
Messing et al. (21)	+	+	+	+	-	-	-	-	+	+	+	**6**
Mortensen et al. (22)	+	+	-	+	-	-	-	-	-	+	+	**4**
Kotz et al. (20)	+	+	-	+	-	-	-	+	+	+	+	**6**
Carnaby-Mann et al. (19)	+	+	+	+	-	-	+	-	+	+	+	**7**

TABLE 6 Risk of bias assessment using Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (25).

Study	Domain1	Domain2	Domain3	Domain4	Domain5	Overall
Mortensen et al. (22)	Low	Some concerns	High	Some concerns	Low	High
Messing et al. (21)	Low	Some concerns	High	Low	Low	High
Hajdú et al. (18)	Low	Some concerns	High	Low	low	High
Carnaby-Mann et al. (19)	Low	High	High	Low	Low	High
Kotz et al. (20)	Low	High	Low	Some concerns	Low	High

Domain 1: Risk of bias arising from the randomization process.
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention).
Domain 3: Missing outcome data.
Domain 4: Risk of bias in measurement of the outcome.
Domain 5: Risk of bias in selection of the reported result.
Overall risk of bias.

tumor- or therapy-related oropharyngeal dysphagia. Therefore, swallow-specific intervention could be an essential component within a multimodal prehabilitation approach. The present systematic evidence review shows initial success in this area, but also several limitations. There is consensus that dysphagia should be treated as early as possible, even if an "early" start of intervention is interpreted variably in the studies reviewed (13, 42).

In comparison to the control group there were short term effects in the prehabilitation-groups, such as better QoL 2 or 3 months after therapy (18, 21) and better mouth opening after therapy (18, 19), but no long-term effects were found. Interestingly there are also conflicting results in QoL reported in some studies (21, 22).

Several factors could have a moderating influence on the effectiveness of the intervention, one being whether the therapy is delivered in person or in the form of written exercise instructions (20). Studies evaluating the relationships of delivery mode, patient-related factors, and therapy adherence in HNC patients show that professionally guided therapies achieve the best adherence in the first three weeks, while an app-assisted version still leads to better adherence than letting the patient practice alone. Nicotine use at intervention onset and concurrent chemotherapy in the setting of primary radiotherapy were found to be significant negative predictors of adherence (31). Moreover, clinically relevant anxiety or depression symptoms are regularly associated with dysphagia, in almost 50% of cases (44), unsurprisingly given the central social importance of eating and drinking together. This important influence as well as outcome parameter should be considered in the design of future studies.

All efforts at preventive measures must take the deficit in health literacy into account, especially among HNC patients (45). It remains essential to inform patients before tumor treatment of possible consequences, such as dysphagia, and of ways to show them self-efficacious methods to maintain their health and prevent further symptoms (46).

4.1 Limitations of evidence

After all, several studies of moderate to high quality are available, even if we see a high risk of bias in the individual studies, caused by the lack of opportunity for blinding due to the intervention and the lack of adherence of the study participants. Not only the rather small study populations and high dropout rates limit the validity of the studies, but also the existing large heterogeneity regarding the interventions and outcome parameters impede a metaanalysis (14, 43). Evidence is further limited by the large differences in inclusion and exclusion criteria and measurement time points, which make a reliable assessment difficult. Thus, a clear statement is neither possible regarding the efficacy of preventive measures nor concerning the optimal intervention timing, intervention duration and frequency, as well as exercise selection (13). A similar issue exists in neurological swallowing rehabilitation, where evidence for the correct or most effective number and frequency of swallowing exercises is also lacking (47).

The majority of publications only account for patients that were treated with radiation and chemoradiation treatment, surgically treated patients were not considered. In Germany, surgery often precedes adjuvant radio- or chemo-radiotherapy in an early or selected high tumor stage, whereas primary radio- or chemo-radiotherapy is frequently implemented in advanced tumor stages primarily (45, 48). Study results from collectives, that were exclusively irradiated, must not be transferred to representative German collectives of patients, because QoL and swallowing function are heavily influenced by the chosen treatment (12).

The research project titled "The Effects of Phoniatric Prehabilitation in Head and Neck Cancer Patients on Aspiration and Preservation of Swallowing (PREHAPS)" (DRKS00029676), sponsored by G-BA (Gemeinsamer Bundesausschuss) is partly based on this systematic review. PREHAPS provides a prospective randomized trial that investigates the prehabilitation of swallowing disorders of patients at a German Head-Neck-cancer-center for the first time.

In order to utilize the potential advantages of prehabilitation according to the needs of HNC patients, additional human resources (especially speech therapy, phoniatrics) have to be provided, which are currently not refinanced in the German health care system. However, studies indicate that care costs even can be reduced (49, 50) and that early rehabilitation of swallowing disorders can mitigate the financial consequences of the disease (51). In selected populations, the combination of prehabilitation

and early rehabilitation has been shown to be less costly than the traditional symptom-only approach (52).

4.2 Limitations of the review process

The review process was first carried out by only one person (second author A.M., professional speech language therapist) in the sense of an exploratory literature search, which is a limitation of the methodology presented here. All included articles were read by all authors and discussed in the working group.

5 Conclusion

Prehabilitation is becoming increasingly important in oncology, and the prognostic significance of dysphagia has been recognized, particularly in the treatment of head and neck tumors. However, the efficacy of prehabilitative interventions has been only rudimentarily investigated. Active exercises of swallowing function may lead to demonstrably better outcomes immediately after radio(-chemo)-therapy, although evidence of long-term benefit is lacking to date. Preventive exercises provide the possibility of reducing the consequences of dysphagia, maintaining swallowing function, and improving quality of life. All currently available studies exclusively investigated patients with primary radiotherapy. High-quality research that also focuses on patient collectives including surgical treatment strategies are therefore urgently needed. It is of great importance to investigate questions of a suitable prehabilitation approach in particular, regarding the selection of patients, the start of therapy, the form of therapy, and the selection and frequency of exercise.

Author contributions

SV: Visualization, Writing – original draft. AM: Data curation, Formal analysis, Visualization, Writing – original draft. JM: Resources, Writing – review & editing. CS: Resources, Writing – review & editing. PK: Methodology, Supervision, Validation, Writing – review & editing. JK: Project administration, Supervision, Writing – review & editing.

Funding

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

Acknowledgments

Parts of this work are part of the bachelor thesis of Mrs. AM at the Ostbayerische Technische Hochschule (OTH) in Regensburg, Germany, Faculty of Applied Social and Health Sciences, course of studies Logopedics B.Sc.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1273430/full#supplementary-material

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frontiers | Frontiers in Oncology

TYPE Review
PUBLISHED 04 January 2024
DOI 10.3389/fonc.2023.1288695

OPEN ACCESS

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RECEIVED 04 September 2023
ACCEPTED 05 December 2023
PUBLISHED 04 January 2024

CITATION
Pannunzio S, Di Bello A, Occhipinti D, Scala A, Messina G, Valente G, Quirino M, Di Salvatore M, Tortora G and Cassano A (2024) Multimodality treatment in recurrent/metastatic squamous cell carcinoma of head and neck: current therapy, challenges, and future perspectives.
Front. Oncol. 13:1288695.
doi: 10.3389/fonc.2023.1288695

Multimodality treatment in recurrent/metastatic squamous cell carcinoma of head and neck: current therapy, challenges, and future perspectives

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Squamous cell carcinoma of the head and neck is a complex group of diseases that presents a challenge to the clinician. The prognosis in the recurrent/metastatic disease is particularly dismal, with a median survival of approximately 12 months. Recently, the personalized and multimodal approach has increased prognosis by integrating locoregional strategies (salvage surgery and stereotactic radiotherapy) and systemic treatments (chemotherapy, immunotherapy, and target therapy). Malnutrition is a significant clinical problem that interferes with dose intensity, and thus, feeding supplementation is critical not only to increase the quality of life but also to improve overall survival. With this review, we want to emphasize the importance of the multidisciplinary approach, quality of life, and nutritional supportive care and to integrate the latest updates of predictive biomarkers for immunotherapy and future therapeutic strategies.

KEYWORDS

head and neck, squamous cell carcinoma, recurrent, metastatic, multimodality treatment, surgery, radiation therapy, chemotherapy

1 Introduction

Worldwide, head and neck squamous cell carcinoma (HNSCC) accounts for 900,000 cases and 400,000 deaths annually and is the sixth most common cancer worldwide (1). The incidence varies across the different areas of the globe and has a high prevalence in Eastern Asia. Approximately 75%–85% of HNSCC is due to tobacco use and alcohol consumption, although human papillomavirus (HPV) infection as a cause of oropharyngeal cancer (OPC) is increasing (2). In the United States, approximately 71% of OPC cases are attributed to HPV (3).

Patients with HPV+ oropharyngeal cancers have a better prognosis than patients diagnosed with HPV-negative disease. The genomic features of HNSCC are very complex and include some driver mutations that might be suitable for targeted therapy, among them HRAS and PI3KCA. As we will discuss in the following paragraphs, many are under investigation (4).

Approximately 10% of patients have distant metastases at diagnosis, while 20%–30% will develop them during the course of the disease. At the same time, patients with locally advanced disease at diagnosis (approximately 2/3 of patients) will develop locoregional recurrence at 2 years in 50% of cases, and 20%–30% of them will also develop distant metastases (2).

In general, the prognosis of these recurrent/metastatic (R/M) patients is poor, with a median overall survival between 6 and 15 months (2).

During the last 30 years, the best therapy for metastatic HNSCC was based on platinum-based poly-chemotherapy with a median overall survival (OS) of 7 months, until 2008 when the EXTREME trial demonstrated a benefit in OS with the addition of cetuximab with platinum salts and 5-fluorouracil (5-FU). Recently, the results of CheckMate 141 and the subsequent KEYNOTE-048 established the role of immunotherapy in the treatment of these patients.

With this review, we want to analyze the current clinician's weapons against HNSCC in the recurrent/metastatic setting, focusing particularly on immunotherapy and future perspectives.

2 Systemic management

The choice of treatment should be based on the evaluation of clinical and molecular parameters: the first includes patients naive to systemic treatments, patients previously treated with adjuvant therapies, the burden of disease (locoregional *vs.* metastatic), local disease recurrence, symptomatic disease, risk of acute complications, Performance Status (PS), platinum-resistant *vs.* platinum-sensitive disease, weight loss, active smoking habit, and significant comorbidities. The second includes HPV-related oropharyngeal disease and PD-L1 expression (5). Moreover, patients with these diseases should be referred to high-volume centers where cases should be discussed in multidisciplinary teams (6).

2.1 Naive patients to systemic treatments

According to the cancer-immunity cycle proposed by Chen, Coukos, and Mellman, anticancer activity is modulated by the immune cells, at first with cancer immune recognition, then with an adaptive immune response, and finally with cancer cell elimination. Every step of this process represents a potential target for treatment and strategies to reduce the immune escape phenomenon. Nowadays, multiple predictors and prognostic factors are identified, but only PD-L1 is predictive of the response of immunotherapy (7).

Following this evidence, the standard scenario of medical treatment of metastatic/recurrent naive patients has been enriched by the results of the KEYNOTE-048 phase III trial. In this study, patients were randomized in one of the three following arms: pembrolizumab alone *vs.* pembrolizumab + platinum + 5-FU *vs.* cetuximab + platinum + 5-FU (EXTREME regimen). Patients were stratified according to PD-L1 expression, P16 status, and performance status of Eastern Cooperative Oncology Group (PS ECOG) 0-1. The primary endpoints were OS and progression-free survival (PFS) with the intention to treat (ITT) population (8).

The results of the final analysis suggested that the use of pembrolizumab in PD-L1-positive R/M HNSCC, either as monotherapy or in combination with chemotherapy, was preferred to treatment with EXTREME schedule, considered the standard of care from 2008 to 2019. In particular, the pembrolizumab plus chemotherapy regimen significantly increased OS compared with the EXTREME schedule (13.0 months *vs.* 10.7 months, HR = 0.71; 95% CI, 0.59 to 0.85; p = 0.00008) in the overall population. Objective response rate (ORR), PFS, and incidence of adverse events were similar in the two arms (ORR 36.3% and 36.3%, PFS 4.9 and 5.3 months, grade 3 adverse events (AEs) 71.7% versus 69.3%).

Consistent with expectation, the OS in the population treated with pembrolizumab as monotherapy *vs.* EXTREME regimen was superior in neoplasms with high PD-L1 expression: patients with combined positive score (CPS) ≥ 20 had a median OS of 14.9 months *vs.* 10.8 months (HR = 0.61; CI, 0.46 to 0.81), while patients with CPS ≥ 1 had a median OS of 12.3 months *vs.* 10.4 months (HR = 0.71; CI, 0.61 to 0.89). Pembrolizumab as monotherapy in the overall population did not show an advantage in survival but was not inferior: 11.5 months *vs.* 10.7 months (HR = 0.81; CI, 0.68 to 0.97). Pembrolizumab alone did not improve PFS or ORR compared with cetuximab–chemotherapy (ORR was 23.3% versus 36.1% and 19.1% versus 34.9% in the CPS ≥ 20 and CPS ≥ 1 groups, respectively). The duration of response (DOR), investigated as an exploratory endpoint, in the pembrolizumab alone group with CPS ≥ 1 was approximately 2 years (9).

The 5-year OS rate for pembrolizumab *vs.* EXTREME was 19.9% *vs.* 7.4% in CPS ≥ 20, 15.4% *vs.* 5.5% in CPS ≥ 1, and 14.4% *vs.* 6.5% in the total population. The 5-year OS rate for pembrolizumab + chemotherapy *vs.* EXTREME was 23.9% *vs.* 6.4% in CPS ≥ 20, 18.2% *vs.* 4.3% in CPS ≥ 1, and 16.0% *vs.* 5.2% in the total population (8).

In *post-hoc* subgroup analysis in the PD-L1 CPS < 1 for pembrolizumab alone versus cetuximab–chemotherapy, the median overall survival was 7.9 versus 11.3 months (HR = 1.51), while for pembrolizumab–chemotherapy versus cetuximab–chemotherapy, the median overall survival was 11.3 versus 10.7 months (HR = 1.21). Although not prespecified in the design of the

study, the PD-L1 CPS 1-19 subgroup obtained a median OS of 10.8 for pembrolizumab monotherapy versus 10.1 months of the cetuximab–chemotherapy subgroup (HR = 0.86). In the pembrolizumab–chemotherapy arm, the median OS was 12.7, and in the cetuximab–chemotherapy arm, it was 9.9 months (HR = 0.71) (10).

Following these results, pembrolizumab monotherapy can be considered starting from high PD-L1 expressions with CPS ≥ 1 but should be preferred in patients with CPS ≥ 20 and in cases where the disease is not progressing quickly. In contrast, the combination (pembrolizumab plus chemotherapy) could be the best option in patients symptomatic or with rapidly progressing disease, when rapid tumor shrinkage is required, regardless of PD-L1 expression.

To date, pembrolizumab is approved by the Food and Drug Administration (FDA) in combination with chemotherapy, independently of PD-L1 expression, and as monotherapy for patients with PD-L1-expressing tumors (CPS ≥ 1); on the contrary, the European Medicines Agency (EMA) has approved pembrolizumab with or without chemotherapy in patients with CPS ≥ 1, thus designating patients with CPS < 1 for chemotherapy-only regimens.

In consideration of the potential activity of immunotherapy in patients with metastatic/recurrent disease, the efficacy of the ipilimumab–nivolumab combination was investigated in CheckMate 651; in this phase III study, nivolumab plus ipilimumab did not result in a statistically significant improvement in OS versus EXTREME in platinum-eligible R/M HNSCC. The primary endpoints were OS in the all randomly assigned and PD-L1 CPS ≥ 20 populations. The median OS was 13.9 months with nivolumab plus ipilimumab versus 13.5 months with EXTREME in the all randomly assigned population (HR = 0.95; CI, 0.80 to 1.13; p = 0.4951); it was 17.6 months versus 14.6 months in the CPS ≥ 20 population (HR = 0.78; CI, 0.59 to 1.03; p = 0.0469) and did not reach statistical significance in either two primary endpoints. Safety with nivolumab plus ipilimumab was favorably compared with EXTREME: grade 3/4 treatment-related adverse events occurred in 28.2% versus 70.7%, respectively (11).

Although the study did not reach the endpoints, it is notable that the population with CPS ≥ 20 obtained a median OS that was close to statistical significance (HR = 0.78, p = 0.0469) and could be considered clinically meaningful; the objective response rate was 34%, nearly overlapping the control arm (36%), and the median duration of response of 32.6 months (*vs.* 7.0) is the longest recorded in this stage disease. In addition, in the CPS ≥ 20 population, the median time to symptom deterioration was 16.7 *vs.* 7.6 months (11). Finally, we should mention that the median OS in the EXTREME arm in the intention-to-treat population was higher (13.5 months) than the historically reported time of 10.1 months.

The phase II trial CheckMate 714 is underway, which randomized patients to receive nivolumab alone or in combination with ipilimumab in recurrent or metastatic HNSCC (NCT02823574).

In patients with contraindications to immunotherapy or with CPS < 1, the EMA-approved standard first-line treatment remains the EXTREME schedule with cisplatin–5-fluorouracil–cetuximab. In the randomized phase III EXTREME trial, the experimental arm significantly prolonged survival (median 10.1 versus 7.4 months, HR for death = 0.80; 95% CI, 0.64 to 0.9), PFS (median 5.6 versus 3.3 months), and ORR (36% versus 20%) compared with the chemotherapy-only arm (platinum plus fluorouracil) (12).

The use of a taxane as an alternative to 5-fluorouracil may be considered in patients who are not candidates for fluoropyrimidine. Evidence in favor of this combination comes from the phase II non-inferiority B-490 trial that randomized 148 patients to receive cetuximab plus cisplatin with or without paclitaxel (13) and the GORTEC phase II study that randomized 539 patients to receive the (cis)EXTREME scheme for 6 cycles *vs.* the TPEx (platinum–docetaxel–cetuximab) scheme for 4 cycles (14). The study results should be considered negative, as they did not meet the primary endpoint of superiority in OS of the experimental arm (14.5 months *vs.* 13.4 months, HR = 0.89; 95% CI, 0.74 to 1.08; p = 0.23) and did not show statistically significant differences in PFS and ORR. A point in favor of the experimental arm was the better toxicity profile, probably due to the lower number of cycles, lower dose of cisplatin (100 mg/mq *vs.* 75 mg/mq), and systematic granulocyte colony-stimulating factor (G-CSF) primary prophylaxis. Due to these results, the TPEx schedule could be considered in patients who are not candidates for 5-fluorouracil treatment.

The KEYNOTE-B10 is an ongoing single-arm phase IV trial that enrolled 92 patients, previously untreated, to receive pembrolizumab–carboplatin–paclitaxel, regardless of PD-L1. Although data are still immature, and longer follow-up is needed. The ORR was 43% (95% CI, 32 to 54), and the median OS showed a positive trend with 12.1 months (NCT04489888).

The combinations of platinum and taxanes were demonstrated to be active either in phase II or in phase III studies, but they were not superior to the platinum–fluorouracil combinations, with overlapping response rates and survival (15) (16).

2.2 Non-platinum-based regimens

Other combinations may be useful in patients who are not candidates for platinum-based chemotherapy.

The SWOG trial was a single-arm phase II study that evaluated 57 patients with metastatic or recurrent head and neck cancer, with the combination of gemcitabine (3,000 mg/mq) plus paclitaxel (150 mg/mq) administered biweekly, and was associated with a 28% ORR (17).

Median PFS and OS were 4 and 8 months, respectively. However, there are no data about the superiority of this combination in comparison to single-agent taxane therapy. In an open-label phase II trial, the combination of weekly paclitaxel and cetuximab showed 54% ORR, with median PFS and OS of 4 and 8 months, respectively (18).

As we discussed in the Quality of Life section, many patients with HNSCC are frail, and many of them are ineligible for cisplatin for several reasons: renal failure, cardiologic comorbidities, age > 70 years, and PS ECOG > 2. In this category of patients, there is no strong evidence for an alternative regimen to cisplatin. A retrospective study demonstrated the efficacy and safety of weekly carboplatin AUC 2 in combination with weekly paclitaxel in patients ineligible for cisplatin (19).

These results led to investigating the combination of durvalumab with weekly paclitaxel and carboplatin AUC 2 in frail patients ineligible for cisplatin in a single-arm phase II study (FRAIL-IMMUNE). This study met its primary endpoint by achieving a median OS of 18 months; 20.4% of patients experienced a grade G3 adverse event, which has a better toxicity profile than KEYNOTE-048 (in the pembrolizumab–chemotherapy arm, grade 3–4 adverse events were 47%). These results need to be confirmed in a comparative phase III trial (20).

2.3 Platinum refractory

Platinum refractory refers to all patients who relapse in less than 6 months after the end of platinum treatment. In these patients, the prognosis is poor.

Both nivolumab and pembrolizumab are recommended by the National Comprehensive Cancer Network (NCCN) guidelines, based on the results of two phase III trials: CheckMate 141 and KEYNOTE-040. Both studies enrolled patients regardless of PD-L1 expression, showing, however, a better effect of both agents in the PD-L1-positive population (21).

The CheckMate 141 trial demonstrated the superiority of nivolumab in comparison with standard single-agent treatments (docetaxel, methotrexate, or cetuximab) in terms of OS, which was the primary endpoint: 7.5 months *vs.* 5.1 (HR = 0.70; 97.73% CI, 0.51 to 0.96; p = 0.01). The treatment-related events of grade 3 or 4 occurred in 13.1% of the patients in the nivolumab group versus 35.1% of those in the standard treatment (22).

In the KEYNOTE-040 phase III study, which compared pembrolizumab *vs.* standard of care, the median OS was higher but not statistically significant (8.4 versus 6.9 months; HR = 0.80, 0·65–0·98; nominal p = 0.0161). In the subgroup analysis of patients with PD-L1 expression of more than 50% (tumor proportion score (TPS)), the median OS was 11.6 versus 7.9 months (HR = 0.54) (23). Pembrolizumab was approved by the EMA only for patients with PD-L1 ≥ 50%.

Several trials attempted to evaluate the efficacy of dual checkpoint-inhibitor (IO-IO) combination therapy. The results seem to suggest that the combination is not characterized by a synergistic activity. In 2019, the randomized phase II study CONDOR enrolled 267 patients with progression during or after first-line treatment with platinum-based for R/M disease and with absent or low PD-L1 expression (<25% TC). Patients were randomized in a 2:1:1 ratio to receive combination therapy with durvalumab/tremelimumab (IgG2 antibody to CTLA-4) versus durvalumab monotherapy versus tremelimumab monotherapy. This study did not prove the hypothesis that tremelimumab combined with durvalumab could exert a synergistic therapeutic effect, in terms of RR, in this population with low or no expression of PD-L1 (24).

The phase III EAGLE trial enrolled patients with relapsed/metastatic disease progressing during or after first-line platinum-based treatment; they were randomized to receive 1:1:1 durvalumab, durvalumab plus tremelimumab, or standard therapy (SoC) (cetuximab, taxanes, methotrexate, or a fluoropyrimidine). No benefit in terms of overall survival was observed either in the durvalumab arm versus SoC (HR = 0.88; 95% CI, 0.72 to 1.08; p = 0.20) or in the durvalumab versus tremelimumab arm versus SoC (HR = 1.04; 95% CI, 0.85 to 1.26; p = 0.76); OS at 12 months was 37% for durvalumab, 30.4% for combination arm, and 30.5% for SoC (25).

With these results, current international guidelines do not recommend IO-IO combination therapy.

In patients who received immunotherapy in the first line, no standard of care exists; single-agent chemotherapy could be proposed, such as docetaxel, methotrexate, paclitaxel, or capecitabine. Until now, there are no data about the best option after immunotherapy from randomized trials, while there are few published retrospective data regarding combinations of chemotherapy after upfront immune checkpoint inhibitor (ICI) demonstrating intriguing response rates both with platinum- and 5-FU-based doublet (26) or cetuximab-based (27) therapies (Figure 1). Several prospective studies beyond the progression of ICI are underway (Table 1).

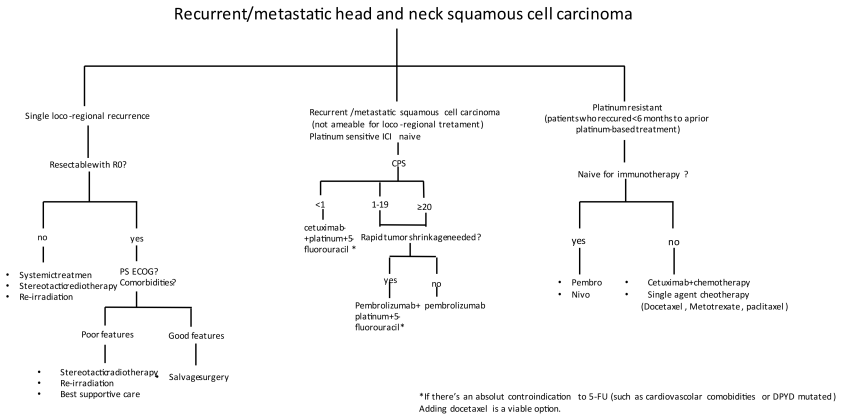

FIGURE 1
Decision-making algorithm in the recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC).

TABLE 1 Ongoing selected studies beyond progression on ICI.

Clinical trial.gov NCT identifier	Study type	Regimen	Study population
NCT05721443	Open-label, single-arm, phase II study	Cetuximab plus dalpiciclib (CDK4/6 inhibitor)	HPV-negative, PD-1-resistant R/M HNSCC
NCT05063552	Phase II/III study	Standard therapy (CT + cetuximab) *vs.* CT + atezolizumab *vs.* atezolizumab + bevacizumab	R/M HNSCC progressed on 1st-line pembrolizumab
NCT05054439	Multicenter, open-label, phase II study	SI-B001 (anti-EGFR/HER3 Ab) plus paclitaxel	R/M HNSCC progressed on prior 1st or 2nd line with anti-PD-1 + platinum-based CT (non-nasopharyngeal carcinoma)
NCT05283226	Multicenter, open-label, single-arm, phase II study	Oral NRC-2694-A (anti-EGFR small-TKI) plus paclitaxel	PD-1-resistant R/M HNSCC
NCT05751512	Multicenter, open-label, phase III	MRG003 (anti-EGFR ADC) *vs.* cetuximab/methotrexate	R/M HNSCC progressed on prior 1st or 2nd line with anti-PD-1 + platinum-based CT

HNSCC, head and neck squamous cell carcinoma; CT, chemotherapy; ICI, immune checkpoint inhibitor; Ab, antibody; ADC, antibody–drug conjugate; TKI, tyrosine kinase inhibitor.

3 Salvage surgery

Locoregional recurrence, with no other evidence of metastasis, can be treated in a curative intent with salvage surgery. Time to first recurrence was the single most important factor affecting survival.

A recent meta-analysis conducted by Bulbul et al. analyzed 15 studies (a large part retrospective studies) comparing salvage surgery versus non-surgical treatments in patients with locoregional recurrence of HNSCC including tumors of the oral cavity, pharynx, and larynx. This meta-analysis demonstrated a consistent 5-year OS advantage of surgery compared to non-surgical treatments, with an HR of 0.25 (28). In a previous meta-analysis of 32 studies, with a total of 1,080 patients, Goodwin et al. showed a 5-year OS benefit of 39% (29).

The site of the primary tumor and its radical resection are important prognostic factors. The reason can be attributed to the relationship of anatomical structures that are critical to ensure the operability of the tumor.

Recurrences of hypopharynx tumors are characterized by poor prognosis in relation to the anatomical structures involved in the field of the primary tumor; on the contrary, recurrences of laryngeal tumors are associated with a better prognosis, with 70% of OS at 5 years after salvage resection that may include radical laryngectomy or conservative surgical treatment (30).

The greatest challenge of the multidisciplinary team concerns the correct selection of patients suitable for salvage surgical resection. In Lupato's meta-analysis, 25 studies were included, with a total of 1,280 patients undergoing salvage surgery. The pre-surgical prognostic factors associated with a statistically significant worsening were disease-free interval <12 months (HR = 1.91), age > 60 years (HR = 1.82), and stage III–IV at diagnosis (HR = 1.5). Positive surgical margins (HR = 2.34), extra-capsular lymph node extension (HR = 4.31), and complications after surgery (HR = 1.91) were correlated with a post-surgical worse prognosis (31). Post-surgical complications are a huge problem in these patients: in a systematic review of 3,293 patients who underwent laryngectomy after the failure of radio-chemotherapy complication rates were 67.5%, including the most common fistulas with an incidence of 28.9% (32).

In a patient who has a single metastasis or with a single locoregional recurrence, is it better to have salvage surgery or "curative" radiation therapy? There are no randomized clinical trials, and the only available evidence is from retrospective studies; the data seem to show that salvage surgery prolongs locoregional failure (LRF) and OS (33). The goal to be achieved in salvage surgery is to obtain R0. Patients with gross residual disease after surgery had LRF at 2 years similar to that of permanently treated patients (47.4% *vs.* 46.3) (34).

In patients who cannot be treated with salvage surgery, radiation therapy for "curative" purposes remains an option in selected cases with good PS and a recurrence-free interval (35). Adjuvant radiotherapy is an option after salvage surgical treatment, especially in high-risk patients (36). A phase III study attempted to answer the question of whether chemotherapy (hydroxyurea and 5-FU) should be added with radiotherapy. The study showed an increase in disease-free survival (DFS) but not in OS, at the cost of a consistent increase in toxicity. Therefore, to date, there is no indication for the addition of chemotherapy to radiotherapy in these patients (37).

Recently, immunotherapy has emerged as a potential treatment for this disease scenario. The ADJORL study evaluated the use of nivolumab immunotherapy after salvage surgery treatment. It is a non-randomized phase II study that enrolled 57 patients who relapsed after previous radiotherapy treatment and were subsequently treated with curative intent with salvage surgery. After a 2-year follow-up, DFS was 46.6%, and OS was 67.3% (38).

In conclusion, in a patient with locoregional recurrence without further metastasis or with a single metastatic site, with good PS ECOG, when R0 is technically feasible, salvage surgery should be taken as the first treatment option. In case the patient cannot receive surgical treatment due to poor general condition, or comorbidities, or when R0 surgery is not possible, reirradiation is a viable option.

4 Radiotherapy in recurrent/metastatic head and neck cancer

Technological and clinical advances achieved in the field of radiation therapy (RT) have improved the balance between tumor control and its effects on normal tissue (39).

Curative-intent radiation therapy is delivered with doses from 6,000 to 7,000 cGy divided into 180- to 200-cGy fractions and is frequently combined with chemotherapy. The most frequent toxicities with these regimens are mucositis, dysphagia, xerostomia, dysgeusia, and radiation dermatitis. In contrast, palliative regimens try to lower the radiation dose to below the threshold for severe side effects in order to maximize the balance between risk and benefits (40).

4.1 Palliative radiation regimens

To date, there are no standard recommendations from guidelines on which regimen to adopt, and the choice is often at the discretion of the radiotherapist. One possible treatment regimen is the "QUAD shot", which consists of the administration of 4 Gy over 2 days in two fractions per day. Patients could receive up to 2 additional cycles if they have not demonstrated tumor progression at the time of follow-up. In a phase II study, an ORR of 53% was observed, and 44% of patients had an improvement in quality of life (41). In a retrospective study by Nguyen, a palliative regimen consisting of three fractions of 8 Gy each, given on day 0, day 7, and day 21 for a total of 24 Gy, showed a 40% complete response for symptoms and 50% ORR (42). The AIIMS trial evaluated the use of the short-course regimen of 20 Gy in five fractions, one per week; this schedule relieves difficult physical symptoms for a period of approximately 7 months. Of 505 patients, 37% achieved a partial response (43). "QUAD shot" regimen, 24 Gy in three fractions, or 20 Gy in five fractions allows symptom palliation in patients with symptomatic disease and poor prognosis (less than 4 months), with a reduction of treatment toxicity rate. Patients with an intermediate prognosis (less than a year) who do not have other treatment options may benefit from a conventional palliative regimen (40).

4.2 Oligometastatic disease

Selected patients with oligometastatic and oligo-recurrent head and neck cancer may benefit from a therapeutic approach.

In patients with up to five metastatic sites from any primary tumor site, the phase II SABR-COMET trial exhibited improvements in OS (50 *vs.* 28 months, p = 0.006; HR = 0.47) when metastatic sites were treated with stereotactic body radiotherapy (SBRT) (44). Other evidence in selected patients with oligometastatic HNSCC who underwent surgery or SBRT to metastases reported 5-year survival rates of 20%. Given this evidence, in patients with oligometastatic disease and good performance status, a course of 70 Gy in 35 fractions should be considered (45). The OMIT study is a randomized phase II trial evaluating radiotherapy alone versus radiotherapy + chemotherapy in oligometastatic patients. Fifty-nine patients with oligometastatic disease, defined as one to three metastases, were enrolled, and the 1-year OS was almost overlapping (63.4% with SABR-alone *vs.* 61.7% with chemo-SABR); the 1-year PFS rate was decreased. One of the most important data in the study was toxicity, with a clear advantage rate of all grade toxicities in patients receiving SARB-alone (29.4%) versus (94.3%) with chemo-SABR, without quality of life (QoL) deterioration (46).

A single-institution retrospective study reviewed the outcomes of 1,000 consecutive stage III to IVB HNSCC previously treated with radical intent who developed oligometastases. Patients with single metastasis experienced significantly improved OS (25.7 months) *vs.* those with two to four (11.3 months) or five or more metastases (7.5 months) (p = 0.002). Most of these patients underwent local therapy of metastases with either surgery or radiotherapy with definitive intent. In multivariate analysis, the parameters related to survival after distant metastasis treatment included the time to develop metastases, Karnofsky performance status greater than 70, non-oral cavity primary tumor, and a single metastatic lesion (47).

4.3 Reirradiation

There are a few data regarding palliative-intent reirradiation; the RTOG 9610 (48) and RTOG 9911 (49) trials assessed curative-intent salvage reirradiation after radio-chemotherapy. The role of reirradiation in the current era of intensity-modulated radiation therapy (IMRT) is not exactly defined. The selection of patients to undergo reirradiation is challenging and needs to be led by a multidisciplinary team. Patients with more than 2 years since their first course of radiation (34) and ECOG performance score of 0 (50) had better outcomes in this sample.

Proton therapy is increasingly used as an accepted form of reirradiation to reduce the complications associated with a second course of radiation. In a single-institution retrospective cohort, Lee et al. found that proton therapy reirradiation (PT-ReRT) may be associated with good survival in patients with recurrent HNSCC, with an aggressive regimen associated with better outcomes. However, surviving patients remain at risk of early and late complications (51). Proton beam treatment (PBT) is supported by data that primarily come from non-randomized institutional reports and a small number of systematic studies, which have demonstrated that PBT is safe in a controlled setting. However, without high-quality prospective comparative data, it is premature to conclude that proton therapy has been established as superior to other modern radiation techniques such as IMRT (52). Prospective comparative clinical trials are ongoing (NCT03164460).

4.4 Immunotherapy and radiotherapy

Several preclinical and clinical studies have elucidated possible mechanisms by which radiotherapy enhances the effect of ICI. Nonetheless, RT works as an *in situ* vaccination promoting tumor antigen cross-presentation and inducing the production of chemokines and cytokines to enhance the local and abscopal antitumor immune response (53).

RT immunosuppressive effects result in the inactivation of approximately 90% of lymphocytes exposed to 3 Gy *in vitro* colony (54). Preoperative RT in oral squamous cell carcinoma has been shown to significantly induce the proliferative activity of

CD8+ tumor-infiltrating lymphocytes (TILs), and TILs' relative radioresistance has been attributed to transforming growth factor (TGF), which is already induced by low-dose RT (55). Nevertheless, RT can increase the concentration of immunosuppressive cells in the HNSCC tumor microenvironment (TME), and the magnitude of this effect seems to depend on RT details: hypofractionated RT increases T-cell tumor infiltration, downregulates intratumoral immunosuppressive vascular endothelial growth factor (VEGF), and leads to a lower increase in myeloid-derived suppressor cells (MDSCs) as compared to conventionally fractionated RT (56). RT can also influence TME increasing cancer stem cells (CSCs) much more in HPV− HNSCC than in HPV+ HNSCC (57).

At the same time, RT causes a dose-dependent increase in major histocompatibility complex (MHC) I expression *in vitro* as well as *in vivo* (58). Furthermore, RT enhances the diversity of PD-1+CD8+ T cells, which are positive predictors of response to anti-PD-1 therapy (59). RT produces free cytosolic DNA, especially in cells with loss of p53 function, which is lost in a majority of HPV− HNSCC (60, 61).

The phase II trial by McBride et al. randomized 62 patients with metastatic HNSCC to nivolumab *vs.* nivolumab + SBRT (3 × 9 Gy). Patients had at least two metastatic lesions: one that could be safely irradiated and one measurable by Response Evaluation Criteria in Solid Tumors (RECIST). The primary endpoint was ORR in non-irradiated lesions. There were no significant differences between nivolumab alone and combination arm in terms of ORR, median PFS, OS at 1 year, or toxicities. In the 56 patients with positive expressions of PD-L1 (TC ≥ 1%), the ORR was higher (50%) compared to that of PD-L1-negative patients (23.5%). HPV-positive patients had a higher ORR (41.9%) compared to HPV-negative patients (20.7%). Although the test for interaction, when evaluated in a multivariate analysis of ORR that included both treatment groups and viral status, was not significant ($p = 0.16$), the proportion of responding patients with virus-negative disease was higher with nivolumab plus SBRT than with nivolumab alone. According to these data, tumors that are less inflammatory and virus-negative may benefit more from radiotherapy-increased antigen presentation (62).

One of the possible reasons for the failure of this study could be the correct timing of radiotherapy (before, during, or after immunotherapy treatment)?, which still remains a topic of debate; different studies are evaluating sequential radiation treatment (63). Moreover, not all metastatic sites have the same proportion of immunogenicity. Evidence from non-small cell lung cancer (NSCLC) studies has shown that irradiation on liver metastases has stronger immunogenicity than irradiation on lung metastases (64).

Another possible explanation could be in the type of immunotherapy. Evidence demonstrated that anti-CTLA-4 may facilitate a stronger radiation-mediated vaccination effect and deplete myeloid-derived suppressor cells (65).

In conclusion, radiotherapy in combination with immunotherapy is a great topic of scientific research that poses many unsolved challenges, which may be highlighted by more preclinical studies.

4.5 The abscopal effect

The therapeutic effect of RT is mediated not only by direct energy deposition to the exposed target but also by the so-called abscopal effect wherein distal lesions respond to the local treatment (66).

Concurrent RT and anti-CTLA-4 antibody therapy successfully induced the abscopal effect in animal trials (67). RT regimens delivered in higher total doses and hypofractionation show no evidence of the abscopal effect despite benefits in tumor control and symptom relief (68), while fractionated RT (3 × 8 Gy or 5 × 6–10 Gy) in combination with anti-CTLA-4 induces a higher abscopal response (69).

Preclinical studies have shown that partial tumor irradiation is not inferior to full-volume irradiation in the same dose. In the non-irradiated section, an increase in CD8+ T-cell concentration was observed. Hemibody irradiation also elicited an abscopal effect, which was comparable to the one observed after whole tumor irradiation (70). Clinical experience appears to support these findings. Seventy-nine patients with metastatic cancers, of which four had HNSCC, received SBRT in various fractionations for two to four metastases followed by pembrolizumab within 7 days after SBRT; at 6 months, there was no difference in local control between fully and partially irradiated lesions (71). Only partially irradiating peritumoral tissue could provide benefits with concurrent immunotherapy, reducing severe damage.

5 Quality of life

Patients with head and neck cancers have usually a poor quality of life, compared with patients affected by other neoplasms (72) (73). This is mainly due to the impaired ability to feed related either to anatomical organs involved by neoplasm or to the toxicity of treatments like surgery and high doses of radiotherapy. These patients, in addition to important anatomical limitations, develop depression and psychosocial impairment that frequently are the basis of their disease (74).

Diagnosis is often performed because of pain; for this reason, pain assessment is a key focus of the patient's evaluation, and standardized measurements should be used to assess pain intensity (75). The clinician can choose treatment according to the needs and type of pain (neuropathic pain, joint pain, general malaise, post-radiation pain, or post-surgical pain) (76).

There are other issues to watch out for, including painful swallowing and mechanical/functional inability to swallow.

Breakthrough pain in patients with head and neck cancers is characterized by a large number of episodes/day and the predictability, particularly with ingestion of food; thus, it is necessary to set up proper pain therapy based on drugs that meet the needs of patients and allows proper feeding (77), avoiding oral drugs and preferring transdermal drugs and nasal fentanyl preparations (78).

Another key issue is the patient's ability to feed and breathe independently. Patients with head and neck disease are at major risk

of developing severe malnutrition and early cachexia, affecting the ability to carry out treatments with a negative impact on prognosis (79). Careful initial screening of higher-risk patients could enable the scheduling of elective percutaneous endoscopic gastrostomy (PEG) or tracheostomy, preventing the onset of dysfunction and reducing complications of emergency surgeries (80).

The safety profile for pembrolizumab monotherapy in KEYNOTE-048 was better than cetuximab–chemotherapy (grade 3–4, 55% *vs.* 83%) and was comparable in the groups receiving chemo-immunotherapy or EXTREME regimen (grade 3–4, 85% *vs.* 83%).

Patients treated with first-line pembrolizumab, pembrolizumab–chemotherapy, or cetuximab–chemotherapy were evaluated according to the European Organisation for Research and Treatment of Cancer (EORTC) 30 quality-of-life (81), EORTC 35-question quality-of-life head and neck cancer-specific modules (82), and EuroQoL five-dimension three-level instruments (EQ-5D-3L) (83) questionnaires.

Patients still enrolled at week 15 who had received first-line pembrolizumab monotherapy or pembrolizumab–chemotherapy had stable health-related QoL (HRQoL). Pembrolizumab or pembrolizumab–chemotherapy versus cetuximab–chemotherapy led to no clinically meaningful difference in EORTC QLQ-C30 global health status (GHS)/QoL, functioning, and symptom scores (84).

Using the same questionnaires, in the KEYNOTE-040 patient's cohort, it was shown that in patients treated with pembrolizumab, the median time to deterioration in GHS and QoL scores was 4.8 months versus 2.8 months in patients treated with SoC (HR = 0.79, 95% CI, 0.59 to 1.05), resulting in a trend toward prolonged time to deterioration (TTD) with pembrolizumab versus SoC (85).

In the CheckMate 141 study, nivolumab also demonstrated a delay in clinically meaningful deterioration according to EORTC QLQ-C30, the absence of clinically meaningful worsening at week 15 according to EORTC QLQ-H&N35, and a clinically meaningful improvement from baseline to week 15 on the EQ-5D visual analog scale, in contrast to a clinically meaningful deterioration in the SoC group (86).

The use of ICI (pembrolizumab or nivolumab) as monotherapy in patients either in the first line or in further lines is an effective option that allows to avoid significant toxicities related to chemotherapy and discontinuation of treatment. Although characterized by toxicity, immunotherapy ensures high standards of quality of life.

5.1 Nutritional status

Most patients with head and neck cancer have weight loss, as their nutrition is often compromised due to many factors, such as disease, surgery, radiotherapy, and systemic cytotoxic treatment (87). Nutritional status is a key part of the oncology examination. In addition to measuring basic parameters such as body weight, weight change over the past few months, and PS ECOG, during each visit, it is necessary to focus on the signs and symptoms that may be the cause of the patient's malnutrition such as dysphagia, mucositis, fatigue, and xerostomia.

There are many tools to assess the state of malnutrition, and none prevails over the others.

Among them, one of the most widely used is the Malnutrition Universal Screening Tool (MUST). This tool is quick and easy to use, and it has been shown to have clinical benefits in identifying patients with a risk of malnutrition early and receiving nutritional intervention (Malnutrition Advisory Group (MAG)) (88).

Nutritional problems begin with disease onset, with several studies suggesting that 25%–65% of head and neck cancer (HNC) patients present with malnutrition, while during treatment, it reaches 80% of cases (89) (90). Malnutrition is defined as more than 10% weight loss from normal body mass over 6 months or 5% weight loss over 3 months. Patients with a malnutrition status have a higher risk of infection, a poor quality of life, and a decrease in overall survival (91).

Nutritional status, before, during, and after the treatment, is highly recommended by international guidelines. When possible, oral food intake is preferred over enteral and parental nutrition. Resting energy expenditure (REE) measures the amount of total energy consumed at rest necessary to maintain vital physiological functions, and in patients with head and neck cancer, REE is approximately 22 $kcal \cdot kg^{-1} \cdot day^{-1}$ (92).

To preserve adequate nutritional support, current European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend an intake of 35 $kcal \cdot kg^{-1} \cdot day^{-1}$ and ≥1.5 g $protein \cdot kg^{-1} \cdot day^{-1}$ (93).

When the ability to eat is partially impaired, a semi-liquid diet combined with an oral nutritional supplement (ONS) is necessary. There are different formulations of ONS, but there are features that must be followed. They must have a high protein content and preferably also contain leucine and omega-3 fatty acids, helpful in preventing cachexia (94). ONS needs high energy density (2 kcal/mL) to increase patient compliance. Also, in this type of case, it is important for the patient to have small meals many times a day.

In cases where the patient is unable to eat, treatment is enteral or parenteral feeding. Enteral nutrition is preferred over parenteral because it avoids atrophy of the gastrointestinal tract, causes fewer infectious complications, and also reduces hospital length of stay. There are several methods for enteral feeding, but the most common is PEG.

The nasogastric tube (NGT) is used for a short period, usually less than 4 weeks, and is cheap and manageable. NGTs are used in patients with conserved airway reflexes who need enteral feeding for less than 30 days, and PEG is currently the "gold standard" for medium- to long-term enteral feeding for more than 30 days (95).

In patients with severe gastrointestinal tract dysfunction, the only option for nutritional support is the intravenous route. In oncology, parenteral nutrition (PN) is usually used in very advanced stage and end-of-life patients. It has to be introduced slowly, starting with 15–20 calories per kg of body weight per day with a maximum of 1,000 calories per day. PN carries the risk of potentially severe complications, including catheter-related infection, occlusion and thrombosis, electrolyte imbalance, and

hepatopathy. Therefore, the indication for parenteral nutrition must be taken on a case-by-case basis under the judgment of the multidisciplinary team (96).

6 Biomarker

Immunotherapy is a key weapon in the treatment of metastatic/recurrent head and neck cancers, but only 20%–30% of patients have long-term benefits. The discovery of biomarkers that can predict immunotherapy response represents a major challenge in cancer research.

6.1 PD-L1

There are different scoring algorithms for PD-L1 staining: the TPS is a PD-L1 measurement in which only membranous staining of tumor cells is regarded as a significant staining. In contrast, the combined positive score (CPS) and inflammatory cell scoring (ICS) include and are restricted to PD-L1 expression in certain inflammatory cells, respectively.

Several trials have used TPS, among them CheckMate 141; in the prespecified exploratory analysis of a subgroup of patients with a PD-L1 expression level of 1% or more (57%), nivolumab provided OS benefit with a 45% reduction in the risk of death (HR = 0.55; 95% CI, 0.39 to 0.78). In PD-L1 non-expressors, nivolumab demonstrated a lower efficacy, with a 27% reduction in the risk of death compared with SoC (HR = 0.73; 95% CI, 0.49 to 1.09) (22). In exploratory qualitative immune profile analysis, the percent of PD-L1+ immune cells in the tumor microenvironment was associated with a higher median OS and greater likelihood of response to nivolumab *vs.* SoC (Cancer Research 2017) (97).

The KEYNOTE-040 used both CPS and TPS to assess PD-L1 expression, showing different HR in OS. In the intention-to-treat population, HR was 0.80 (0.65–0.98; p = 0.0161); among patients with PD-L1 CPS ≥ 1%, HR was 0.75 (0.59–0.95, p =0.0078); among patients with PD-L1 TPS ≥ 50%, HR was 0.54 (0.35–0.82, p = 0.0017) (23).

In phase III KEYNOTE-048, efficacy data correlate with PD-L1 expression and support the use of CPS as the optimal biomarker. Pembrolizumab monotherapy significantly improved OS in the PD-L1 CPS ≥ 20 (HR = 0.61) and CPS ≥ 1 (HR = 0.74) populations and led to non-inferior OS in the total population (HR = 0.81). Pembrolizumab–chemotherapy significantly improved OS in the PD-L1 CPS ≥ 20 (HR = 0.62), CPS ≥ 1 (HR = 0.64), and total populations (HR = 0.71) compared with cetuximab–chemotherapy (9). In *post-hoc* subgroup efficacy analyses of the PD-L1 CPS < 1, neither pembrolizumab monotherapy nor pembrolizumab–chemotherapy demonstrated improvement in OS over cetuximab–chemotherapy (HR = 1.51 and 1.21, respectively) (10).

In addition, attempts have been made to increase the reliability of PD-L1 expression detection through artificial intelligence technologies. Puladi et al. conducted a study using a novel approach with three sequentially applied neural networks for a fully automated assessment of PD-L1. Three PD-L1 scores were assessed: TPS, CPS, and ICS. This approach was validated using whole slide imaging (technology in which pieces of histologic tissues are scanned to produce digitized images) of HNSCC cases and compared with manual scoring of PD-L1 performed by human researchers. The inter-rater correlation (ICC) between humans and machine was very similar to the human–human correlation. The ICC was slightly higher in human–machine compared to human–human for the CPS and ICS but slightly lower for the TPS because human–human concordance was excellent for the TPS (98).

Nowadays, artificial intelligence applied to the measurement of PD-L1 in HNSCC tumors does not seem to be useful; further studies, are needed to account for operator-dependent heterogeneity in CPS assessment.

Another important topic is the temporal and spatial heterogeneity of CPS. In the 2021 European Society for Medical Oncology (ESMO) abstract, S.J. De Keukeleire presented data about biopsies in the primary tumor and metastatic site (lymph nodes or distant metastasis), and the discordance of CPS was approximately 34%. Recently, P. Bossi et al. analyzed the differences in CPS value in the primary tumor versus the metastatic site. Biopsies were taken in 56 patients either on the primary tumor or on the metastatic site (local or distant recurrence), and there was a concordance of CPS of 66%. These results are very similar, confirming a discordance about CPS PD-L1 expression of 33% between the primary tumor and the metastatic site (99).

Expression of PD-L2, the other ligand of PD-1, could be another potential biomarker of response to anti-PD-1 therapy. KEYNOTE-012 demonstrated that PD-L2 protein expression is correlated with a higher response to anti-PD-1 therapy (in terms of response rate), independently from PD-L1 expression (100).

6.2 HPV

Several preclinical studies showed how HPV-positive tumors correlate with a better prognosis and a better response to ICI, mainly due to an immunologically "warm" microenvironment.

In the CheckMate 141 study, regardless of the p16 status, the survival in the therapy arm with nivolumab was significantly longer (22). The single-arm phase II HAWK study evaluated durvalumab as monotherapy in platinum-refractory patients. In this study, an increase in ORR, PFS, and OS was demonstrated in HPV+ patients (101). In contrast, in KEYNOTE-040, HPV− cancers appeared to experience greater benefit from pembrolizumab (OS: HR = 0.77; CI, 0.61 to 0.97) rather than HPV+ cancers (23).

A pooled analysis of four studies (CheckMate 141, KEYNOTE-012, KEYNOTE-055, and HAWK) with a total of 425 patients showed that OS and ORR were better in HPV-positive patients than HPV-negative patients using PD-1/PD-L1 inhibitors (OS: HR = 0.71, p = 0.02; ORR: OR = 1.79, p = 0.01). Moreover, HPV-positive HNSCC patients exhibited greater T-cell infiltration than HPV-negative patients (p = 0.003) (102).

Due to the conflicting evidence regarding HPV's role as a predictive biomarker for immunotherapy, HPV infection is not used in clinical practice as a predictive biomarker.

TABLE 2 Summary characteristics of cited studies in target therapy.

Targeted agents		
Class	Drug or molecule	Key findings
EGFR	Cetuximab/ nivolumab	Phase II study, median OS for Cohort A (prior therapy for R/M HNSCC), 11.4 months; median OS for Cohort B (not prior therapy), 20.2 months (104)
	Cetuximab/ durvalumab	Phase II study, ORR 39% (105)
	Erlotinib/ bevacizumab Cetuximab sarotalocan	Phase I/II study, ORR 15%; median PFS and OS of 4.1 and 7.1 months, respectively (106) Phase I/II ORR 28%, median PFS 5.7 months and OS 9.3 months (107)
HRAS	Tipifarnib	Phase II study, ORR 55%; median PFS 5.4 months; OS 15.4 months (108)
mTOR	Temsirolimus/ cetuximab *vs.* temsirolimus	Phase II study, no difference for median PFS (TC arm, 3.5 months; T arm, 3.5 months) (109)
VEGFR	Axitinib	Phase II study, ORR 42% (75% for pts with mutations in the PI3K pathway and 17% for wild-type pts) (110)
	Lenvatinib/ pembrolizumab	Phase I/Ib study (22 pts.); ORR 46%; median PFS 4.7 months (111)
PI3K	Buparlisib *vs.* placebo/ paclitaxel	Phase II study (158 pts.); ORR 31%; median OS and PFS 10.4 and 4.5 months, respectively, in buparlisib arm (112)
HGF	Ficlatuzumab/ cetuximab *vs.* ficlatuzumab	Phase II study; median PFS (combination arm 3.7 months); ORR 19% (113)
TGF-β and EGFR	BCA 101/ pembrolizumab	Phase I/Ib study, ORR (in ITT population 48% (15/31), in HPV-negative patients 65% (13/20))
Nectin-4	Enfortumab vedotin	Phase II study, ORR 23.9%; median PFS 3.9 months; OS of 5.9 months (114)
Tissue factor	Tisotumab vedotin	Phase II study, ORR 40% (115)
Other immune checkpoint inhibitor combinations		
IDO	Epacadostat/ pembrolizumab	Phase II study, ORR 34%, DCR 61% (116)
NK2GA	Monalizumab/ cetuximab	Phase II study; ORR 36% in immunotherapy naive, 17% in immunotherapy pretreated (117)
HPV16 vaccine	PDS0101/ pembrolizumab	Single-arm phase II study, median PFS 10.4 months, 12-month OS rate 87.1% (118)
T-cell exhaustion (LAG-3)	Eftilagimod alpha/ pembrolizumab	Phase II study (36 pts.); ORR 36% (119)

HNSCC, head and neck squamous cell carcinoma; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; DCR, disease control rate; HGF, hepatocyte growth factor; ITT, intention to treat; EGFR, epidermal growth factor receptor; R/M, recurrent/metastatic; HPV, human papillomavirus.

6.3 Tumor mutational burden

Tumor mutational burden (TMB), referred to as the sum of somatic mutations in cancer DNA with the following antigens recognized and targeted by the immune cells, is used as a biomarker for immunotherapy in different cancer types, especially in NSCLC.

A clear trend toward decreasing hazard ratio of death with increasing TMB cut-off was observed across cancer types demonstrating increasing benefit from ICI with higher TMB. Stratified analysis by selecting the higher mutation load quintile (top 20%) performed in different tumors stated that the TMB cut-point of HNSCC was 10 mut/Mb (103).

In a retrospective analysis of the EAGLE trial, the TMB was evaluated in plasma samples before treatment. This analysis showed that patients who have TMB values >16 mut/megabase benefit more in terms of OS from immunotherapy (with durvalumab or durvalumab and tremelimumab compared with chemotherapy). In contrast to patients who had low TMB (<16 mut/megabase), a clear benefit of immunotherapy versus chemotherapy was not evident. In the comparison of durvalumab *vs.* chemotherapy, OS HR was 0.39 in patients with blood TMB (bTMB) ≥ 16 and 0.91 in patients with bTMB < 16. The bTMB was independent of other clinical and prognostic factors such as HPV status, PD-L1 expression, age, gender, tumor location, and ECOG performance score (25).

This evidence indicates that high TMB predicts improved benefit from checkpoint inhibition in HNSCC, but so far, there is not yet consensus about a definitive threshold. At the moment, TMB testing in HNSCC is not recommended by the FDA and EMA.

7 The emerging role of target and combination therapy

With the increase of knowledge of molecular characterization of HNSCC, several studies have demonstrated the efficacy of target therapy individually or in combination with current standard treatments (Table 2).

7.1 EGFR

Among the main targets, epidermal growth factor receptor (EGFR) is overexpressed in 80%–100% of head and neck squamous cell carcinomas. Significantly amplified EGFR occurred primarily in HPV-negative patients (120).

In a phase II trial, Chung et al. investigated the impact on OS of the nivolumab + cetuximab combination in patients with R/M HNSCC following the evidence about the release of interferon (IFN)-gamma and chemokines from natural killer (NK) cells after binding cetuximab to EGFR with the subsequent increase of PD-L1. The median OS in the 45 patients of Cohort A (who had prior therapy) was 11.4 months, with a 1-year OS of 50% (90% CI, 0.43 to 0.57), while the median OS in the 43 patients of Cohort B (who had no prior therapy) was 20.2 months, with a 1-year OS of 66% (90%

CI, 0.59 to 0.71). This doublet could be a powerful strategy in this setting of disease in both I and II lines (104).

A combination of durvalumab and cetuximab was recently evaluated in a single-arm, phase II, non-randomized trial in patients with R/M HNSCC in the second line. ORR, the primary endpoint, was 39%, and the benefit was independent of PD-L1 expression (105).

In addition to monoclonal antibodies, several researchers focused on small molecules, such as tyrosine kinase inhibitors (TKIs) of EGFR, which are ineffective in HNSCC, although early results from other trials with combination therapies were promising. Erlotinib, for example, demonstrated modest improvements in PFS when used in combination with an anti-VEGF antibody (bevacizumab) in R/M HNSCC (106).

7.2 RAS

Braig et al. observed that RAS-activating mutations (HRAS/KRAS) are not very common in patients with cetuximab-naive HNSCC, while after treatment with cetuximab, one-third of patients developed acquired mutations in KRAS, NRAS, and HRAS. Furthermore, these were detected only in half of patients progressing to treatment, suggesting that the selective pressure exerted by cetuximab on tumor cells could determine the onset of the aforementioned resistance mutations responsible for disease progression (121).

Mutations in the HRAS (mHRAS) proto-oncogene occur in 4%–8% of patients with R/M HNSCC. L. Ho et al., in a single-arm, open-label, phase II trial, demonstrated the encouraging efficacy of tipifarnib, a farnesyltransferase inhibitor that disrupts HRAS function, in patients with R/M HNSCC with mHRAS variant allele frequency (VAF) of ≥20% (high VAF). In particular, ORR for patients with high VAF was 55%, and the median OS was 15.4 months (95% CI, 7.0 to 29.7) (108).

Data from 50 patients with high VAF were presented at the ESMO 2023 congress. The ORR in these patients was 30%, with one patient in complete response (CR). The most frequent grade 3 side effects (38%) were related to bone marrow toxicities, neutropenia (24%), anemia (20%), and leukopenia (14%) (122).

7.3 PI3K/AKT/mTOR and small TKI anti-VEGFR

Genomic alterations in one of the major components of the PI3K/AKT/mTOR pathway (e.g., PI3KCA, AKT1/2/3, and PTEN) were instead found in approximately 66% of HNSCC tumors and are also responsible for the development of resistance to the anti-EGFR therapy. PTEN loss might be part of a signature characteristic for resistance, as this may lead to compensatory activation of the PI3K/AKT pathway (123). To overcome these resistance mechanisms, the combination of PX-866, an oral PI3K inhibitor, with cetuximab was analyzed in 83 patients with advanced, platinum-refractory HNSCC who had received at least one, but no more than two, prior systemic treatments. Despite encouraging preclinical results, combined treatment was not superior to cetuximab monotherapy in terms of PFS (80 days *vs.* 80 days), OS (211 days *vs.* 256 days), and RR (10% *vs.* 7%) (124). The randomized phase II MAESTRO trial investigated the efficacy of temsirolimus, an mTOR inhibitor, with or without cetuximab. The study did not meet its primary endpoint (PFS), showing limited clinical activity of the combination in HNSCC R/M patients (109). Although co-targeting PI3K/mTOR and EGFR could be supported by inhibition of this pathway, preventing resistance to EGFR inhibitors, this combination has a severe toxicity profile and needs further investigation.

It is also known that tumors with PI3K alterations often induce angiogenesis through VEGF-regulated cytokine mechanisms. Swiecicki et al. demonstrated that treatment with axitinib, a potent inhibitor of VEGFR2, VEGFR3, and PDGFR, was associated with a relative response rate of 75% in patients with mutations of the PI3K pathway and 17% in wild-type patients (6 of 8 patients *vs.* 2 of 12 patients) (110). This is also the first study demonstrating that the targeted oral drug axitinib improves survival in patients with R/M HNSCC heavily pretreated: the overall survival rate at 6 months was 71%, while the median PFS and median OS were 3.5 months and 9.8 months, respectively.

Preclinical and clinical evidence suggests the possibility of enhancing the immunotherapeutic effectiveness of immune checkpoint inhibitors by modulating VEGF-mediated immune suppression through angiogenesis inhibition. In a phase I/Ib trial, the combination of pembrolizumab and lenvatinib was also investigated. The ORR was 46% (10/22 patients), and the median PFS was 4.7 months among the 22 patients with HNSCC (111).

Buparlisib is a pan-PI3K inhibitor and was evaluated alone and in combination with paclitaxel in a phase II randomized study (BERIL-1) in patients with platinum-pretreated recurrent metastatic HNSCC. It showed an ORR of 31% in the buparlisib group with a median PFS and OS of 4.5 and 10.4 months, respectively, compared with 3.5 and 6.5 months in the placebo group, regardless of PI3KCa mutations (112).

7.4 IDO-1

The IDO1 enzyme may be upregulated by tumors as a means of evading immune surveillance. A strong and extremely specific IDO1 enzyme inhibitor is epacadostat. Epacadostat plus pembrolizumab demonstrated an ORR of 34% and a disease control rate of 61% in ECHO-202/KEYNOTE-037; despite this result, the phase II study was prematurely stopped because of underwhelming findings in other tumor types (116).

7.5 NKG2A

An antibody called monalizumab is designed to block NKG2A receptors on CD8+ T cells and natural killer cells that infiltrate tumors and boost the immune system against cancer cells. In a phase II trial, the combination of monalizumab and cetuximab resulted in an ORR of 36% in patients who had never had

immunotherapy and 17% in those who had. The 12-month OS estimate was 44% (117). The phase 3 INTERLINK-1 trial evaluated monalizumab plus cetuximab *vs.* cetuximab alone in patients with recurrent or metastatic HNSCC who have previously been treated with platinum-based chemotherapy and PD-L1 inhibitors but failed to meet the endpoints (125).

7.6 LAG-3

Eftilagimod alpha is a soluble agonist of the protein encoded by the LAG-3 gene that binds to a subset of the major histocompatibility complex class II molecules, facilitating the activation of antigen-presenting cells (APCs) and the recruitment and activation of CD4 and CD8 T cells. With an ORR of 36%, a phase II study evaluated the activity of eftilagimod alpha with pembrolizumab in the second line (36 patients) and presented encouraging results (119).

7.7 Hepatocyte growth factor

Hepatocyte growth factor/cMet pathway activation is a resistance mechanism of EGFR inhibition. Multicenter, randomized, non-comparative phase II study evaluated ficlatuzumab, an anti-hepatocyte growth factor, with or without cetuximab in R/M HNSCC in patients refractory to platinum and pembrolizumab. The study reached its primary endpoint with a median PFS of 3.7 months and an ORR of 19% (6/32). Interestingly, the patients who had an objective response had HPV-negative status (113).

7.8 TGF-β and EGFR

Transforming growth factor-beta (TGF-β) is a potent inhibitor of cell proliferation in the early stages of cancer, while in advanced stages, it has an opposite effect, increasing progression and tumor aggressiveness (126).

This controversial effect is known as the "TGF-β paradox". This mechanism remains unknown, but one possible explanation could be in the cross-talk between TGF-β and EGFR signaling. These two pathways have a synergistic effect and amplify the process of epithelial–mesenchymal transition, thus supporting the process of metastasis (127).

A phase I/Ib study is evaluating first-line treatment in patients with metastatic HNSCC with CPS > 1, the BCA 101, a bifunctional antibody designed to inhibit the EGFR and TGF-β in combination with pembrolizumab. The ORR in all populations was 48% (15/31), but the most promising finding is in the HPV-negative population with an ORR of 65% (13/20). The most common adverse event was acneiform rash present in 75% of the population. These data need further evaluation in randomized clinical trials, especially in the HPV-negative population (128).

7.9 Antibody–drug conjugate

Nectin-4 is a protein involved in cell adhesion and is highly expressed in HNSCC, particularly expressed in non-smoking and p16-negative patients. Interestingly, nectin-4 expression was associated with a better prognosis (129). Enfortumab vedotin (EV) is an antibody–drug conjugate (ADC) directed against nectin-4 and is currently approved in the treatment of metastatic urothelial carcinoma. EV was evaluated in a phase II basket study assessed in various types of pretreated metastatic solid tumors. Among them, the HNSCC cohort was 44 patients, and most had received more than two lines of therapy in the metastatic setting. The ORR was 23.9%, and the disease control rate (DCR) was 56.5%. The most common side effects were skin reaction (43%), peripheral neuropathy (32.6%), and hyperglycemia (4.3%). These results are encouraging and need further investigation (114).

HER3 is responsible for aberrant activation of PI3K/mTOR signaling and is one of the mechanisms of resistance to therapy against EGFR; moreover, its overexpression is associated with a worse prognosis across solid tumors (130). In a phase I study, Zhang et al., in various heavily pretreated metastatic solid tumors, evaluated BL-B01D1, a conjugated bispecific antibody directed against EGFR/HER3 and linked to a topoisomerase I inhibitor. The cohort of patients with HNSCC was 13 patients, with an ORR of 7.7%. The most frequent side effects were bone marrow toxicity (including leukopenia in 60%), alopecia in 30%, and vomiting in 28% (131).

Tisotumab vedotin (TV) is a conjugated antibody directed against tissue factor, currently approved for the treatment of metastatic cervical cancer. In the interim analysis of InnovaTV 207 study, a multicenter phase IIb study evaluating TV for advanced tumors, including patients with R/M HNSCC. The HNSCC cohort consisted of 15 heavily pretreated patients with at least containing platinum and checkpoint inhibitors. The ORR was 40% (95% CI, 16.3 to 67.7), with one complete response and five partial responses. Side effects were manageable, and the most frequent were asthenia and peripheral neuropathy. To date, the trial is still enrolling (115).

Cetuximab sarotalocan is an ADC directed against EGFR and bound to a light-activatable dye. Preclinical research shows that activation of the dye with non-thermal red light (690 nm) results in rapid antitumor action driven by biophysical processes that alter cell membrane integrity (132). The phase IIa study evaluated the antitumor activity of sarotalocan cetuximab in 30 heavily pretreated R/M HNSCC patients. Twenty-four hours after infusion administration of the drug, non-thermal red light was used to illuminate tumor areas. The ORR was 28%, and the median PFS and OS were 5.7 months and 9.3 months, respectively. The most common side effect of grade ≥ 3 was skin reaction (18%) and paronychia cracking (12%) (107). From these results, cetuximab sarotalocan has been approved by the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan for the treatment of locally advanced or recurrent unresectable HNSCC. In Western countries, it is not yet approved, and further investigations are needed.

7.10 HPV16 vaccine

PDS0101 is a vaccine composed of neoantigens of liposomal E6/E7 HPV16, leading to a polyclonal expansion of HPV16-specific CD8 and CD4 T cells, and exhibits antitumor activity in combination with checkpoint inhibitors through upregulation of type I interferons and promotion of antigen processing and presentation. In the phase 2 VERSATILE-002 study, PDS0101 and pembrolizumab were used to treat patients with recurrent or metastatic HPV16-related HNSCC. The results were discussed at the 2023 American Society of Clinical Oncology (ASCO) annual meeting. Among the 48 patients naive to checkpoint inhibitor therapy (ICI naive), nine had a partial response (including complete response), and 15 had stable disease. The median PFS was 10.4 months, and the estimated overall survival at 12 months was 87.1%. These promising results are under investigation in a confirmatory phase III trial (NCT04260126) (118).

8 Future perspectives

The TME plays a key role in promoting all "hallmarks of cancer" (133). Cancer-associated fibroblasts (CAFs) are a component of the TME, are responsible for the production of the extracellular matrix (ECM), and contribute to an extremely complex network of connections between various cells in the microenvironment and cancer cells. Interestingly, CAFs can modulate the immune system through several mechanisms (134).

The release of cytokines by CAFs is responsible for the "corruption" of macrophages into tumor-associated macrophages (TAMs) that help generate an immunosuppressive state. CAFs also strongly interfere with NK cells, particularly through the production of cytokines that inhibit NK cell cytotoxicity. Through the release of TGF, CAFs induce T-cell apoptosis (135).

According to Sasaki (2018) (136), CAFs may also play a role in the formation of a fibrous capsule surrounding tumors, and this may block the process of migration and infiltration of T lymphocytes toward the tumor.

One of the most important pathways regulating the differentiation of fibroblasts into CAFs is the NOX pathway, a group of enzymes that play an important role in the cellular stress response through the production of reactive oxygen species (ROS) (137).

The antitumoral activity of setanaxib, a potent inhibitor of NOX4 and NOX1 isoforms, is under investigation in a multicenter, randomized, phase II trial for R/M HNSCC patients with a CPS score >1 and a positive level of CAF (defined as a level of CAF in ≥5% in the tumor) in combination with pembrolizumab (NCT05323656).

9 Conclusions

The treatment of head and neck cancer is a tough challenge for clinicians. The holistic approach to a frail patient like the one affected by R/M HNSCC is based on the support of new different professional figures such as nutritionists, dentists, molecular pathologists, pain therapy specialists, and psychologists who can cooperate with traditional surgeons, radiotherapists, and medical oncologists. Teamwork is the prelude to proper treatment planning according to biological and clinical evaluation. Only by following this strategy will it be possible to identify the correct frame within which to attribute the best setting for each patient. In this context, the integration of systemic and locoregional treatments is critical in order to answer the needs of a single patient with either symptomatic or curative intent. Radiotherapy and salvage surgery are the only curative treatment choices in patients with locoregional recurrence and should be considered in high-volume and highly specialized centers. Palliative radiotherapy has a significant role in improving the patient's symptoms, and several ongoing studies allow a de-escalation of the radiation with a reduction of toxicities.

After decades of standard chemotherapy characterized by limited activity and a high toxicity profile, the appearance of cetuximab first and the immunotherapy later significantly improved the outcome of these patients. Despite these encouraging results, there are still important questions regarding the identification of predictive and prognostic factors (what does the future hold after PD-L1)? and the correct combination or sequences of available tools. Until now, no prospective data about the activity of systemic treatments after immunotherapy have been published. Although data about molecular profiling are available, there is poor evidence regarding the activity of new target therapies. At the moment, the cornerstone of treatment in R/M HNSCC patients derives from the KEYNOTE-048 phase III trial, which demonstrated the significant role of immunotherapy either in combination or alone in patients sensitive to ICI. This study offered the possibility of an active treatment to patients not suitable to be treated with chemotherapy. Chemotherapy in combination with cetuximab or with immunotherapy is still the best option for patients who need tumor shrinkage because of early metastatic or symptomatic disease. Quality of life is one of the main topics in this category of frail patients, and we hope that the new scientific knowledge will allow us to improve not only OS but also this important clinical aspect.

Author contributions

SP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing, Software. AD: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing, Software. DO: Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. AS: Data curation, Formal analysis, Investigation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing. GM: Data curation, Formal analysis, Investigation,

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Funding

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

Conflict of interest

GT, served as an advisory board member for BMS and Novartis and was or is principal investigator of clinical trial sponsored by BMS, MSD.

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

Publisher's note

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frontiers | Frontiers in Oncology

TYPE Case Report
PUBLISHED 08 January 2024
DOI 10.3389/fonc.2023.1251492

OPEN ACCESS

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RECEIVED 01 July 2023
ACCEPTED 11 December 2023
PUBLISHED 08 January 2024

CITATION
Chen S-P, Li P, Pan Y-F and Jiang X (2024) Case report: Rare presentation of double primary malignancies of the lung and thyroid: a difficult diagnosis. *Front. Oncol.* 13:1251492. doi: 10.3389/fonc.2023.1251492

Case report: Rare presentation of double primary malignancies of the lung and thyroid: a difficult diagnosis

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This report describes a rare case of double primary cancer in a female patient aged 49 years who died 2 years after diagnosis. The patient was diagnosed with BRAFV600E-mutant metastatic papillary thyroid carcinoma (PTC) and *ALK* fusion-positive metastatic lung adenocarcinoma. She presented with multifocal thyroid lesions and underwent radical thyroidectomy and bilateral cervical lymphadenectomy. Thyroid ultrasound revealed the presence of five hypoechoic nodules with irregular margins and microcalcifications; an irregular inhomogeneous hypoechoic level IV cervical lymph node was also found on the right side. Histological analysis confirmed the presence of metastatic PTC, and the tumor tested positive for the BRAFV600E mutation. Ultrasound of the neck, which was performed 4 months postdischarge, revealed enlargement of the left-sided cervical lymph nodes; a biopsy from these nodes confirmed a diagnosis of metastatic PTC. Positron emission tomography-computed tomography scans revealed the presence of multiple pulmonary hypermetabolic foci scattered across bilateral lung fields. Multiple hypermetabolic foci were also observed in the lymph nodes on both sides of the neck, axillae, and mediastinum; in addition, there was evidence of bone destruction with hypermetabolic foci. Supplementary reports from the histological and immunohistochemical analyses of cervical lymph node tissue obtained during primary surgery confirmed the presence of metastatic PTC and poorly differentiated lung adenocarcinoma. In particular, one enlarged cervical lymph node located on the right side of the neck demonstrated tumor components of both PTC and lung adenocarcinoma. Pathological analysis of axillary lymph node puncture biopsy confirmed the presence of metastatic lung adenocarcinoma, and gene analysis revealed the presence of *ALK* fusion. The patient received targeted therapy based on a multidisciplinary discussion. However, she had a poor prognosis and died 2 years after the diagnosis. The initial thyroid ultrasound findings were reviewed retrospectively; the findings suggested that the possibility of double primary cancers should be considered in cases where the enlarged cervical lymph nodes are highly suspicious of PTC and present as inhomogeneous hypoechoic masses with irregular morphology.

KEYWORDS

double cancer, multiple primary cancers, MPCs, papillary thyroid carcinoma, PTC, lung adenocarcinoma, BRAFV600E, ALK

1 Introduction

Multiple primary cancers (MPCs) refer to two or more primary malignant tumors occurring simultaneously or successively in one or more organs or tissues of the same patient. Warren proposed the following criteria for the diagnosis of MPCs (1): (1) every tumor must be malignant; (2) every tumor has to be confirmed histopathologically; (3) each tumor must occur at different sites and not be continuous with each other; and (4) the possibility of metastatic or recurrent tumors should be eliminated. MPCs are rarely found (2, 3); the five most frequent sites include the breast, liver, head and neck, colorectum, and prostate (2). Unlike the five most frequent sites (2, 3), which account for 3.1% of all MPC diagnoses (2), the thyroid is a rare site for their occurrence.

The increased incidence of MPCs, especially those involving rare thyroid carcinomas, is a major health challenge worldwide. Elucidation of the characteristics of MPCs involving the thyroid may therefore aid in the development of improved management plans (2), improve patient quality of life, and prolong overall survival in these patients. In this report, we describe a rare case of double primary cancers (papillary thyroid carcinoma (PTC) and lung adenocarcinoma) that had a poor prognosis.

2 Case description

A female patient aged 49 years was admitted for evaluation of thyroid nodules that were detected more than 4 years previously (on 28 August 2018). Thyroid ultrasound (US) revealed the presence of five hypoechoic nodules (two in the inferior pole of the left lobe, two in the middle pole of the right lobe, and one in the isthmus of the thyroid gland) with irregular margins, variable diameters (3–13 mm), and microcalcification (Figures 1A-D).

A highly suspicious irregular inhomogeneous hypoechoic cervical lymph node (size = 1.5 cm × 0.9 cm) was also observed at level IV on the right side (Figure 2).

The chest radiograph did not reveal any abnormalities, and the laboratory parameters were within the physiological range. Total thyroidectomy and bilateral cervical lymphadenectomy (levels II, III, IV, V, and VI on the right side and level VI on the left side) were performed. Postoperative histological examination revealed one lesion of PTC and four lesions of papillary thyroid microcarcinoma (PTMC), along with the nodal metastases (stage IVa, T1N1bM0). On gene mutation testing, the PTC tested positive for the BRAFV600E mutation.

Two weeks after surgery, the patient was hospitalized owing to a neck swelling that was refractory to antibiotic therapy. Neck US

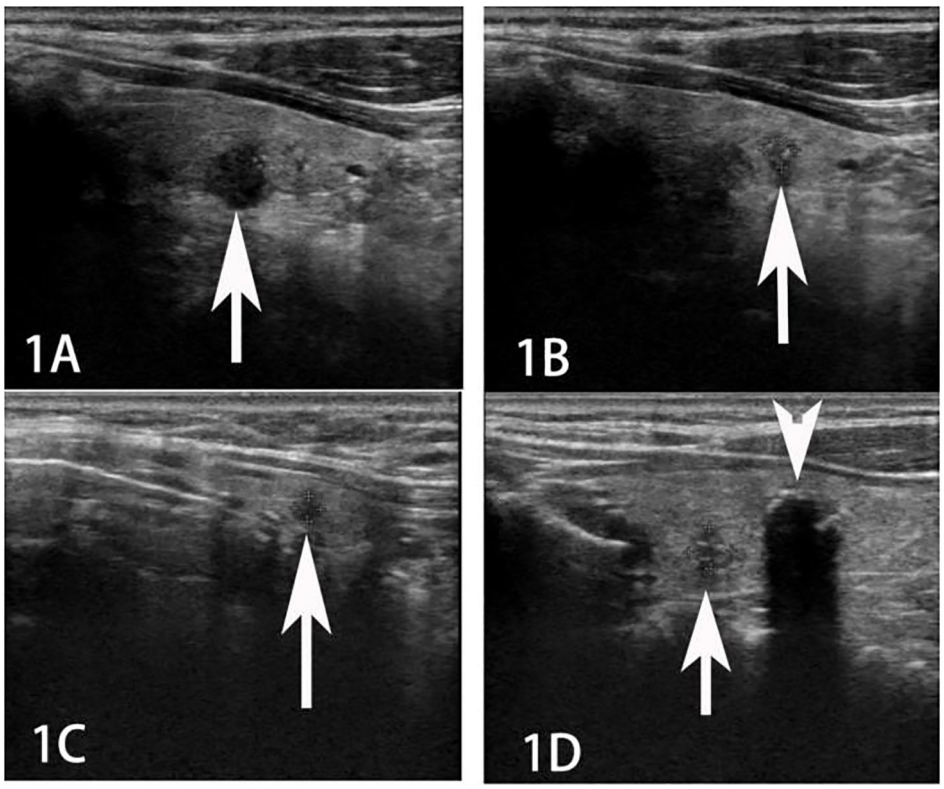

FIGURE 1
Ultrasound imaging of multiple thyroid cancers (**A, B** tumor in the left lobe; **C** tumor in the isthmus, and **D** tumor in the right lobe; indicated by arrows).

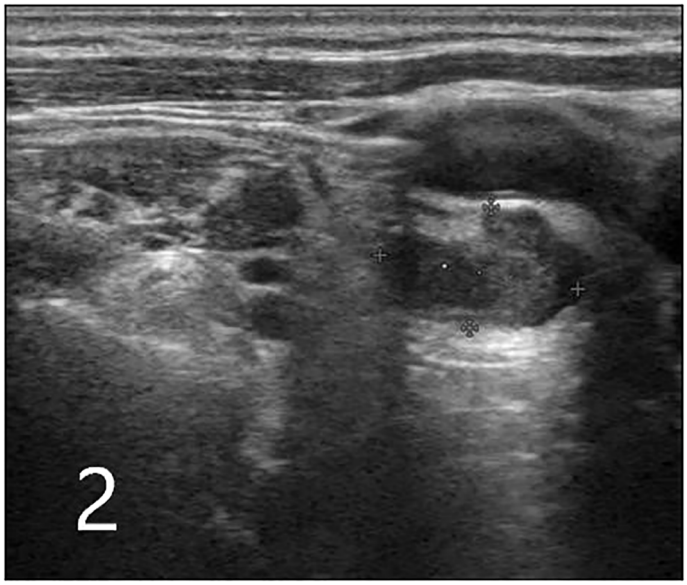

FIGURE 2
Ultrasound image of an enlarged inhomogeneous hypoechoic cervical lymph node with irregular morphology in level IV on the right side (indicated by arrows; plus sign indicates the measurement of lymph node size, which was 1.5 cm × 0.9 cm).

revealed bilateral cervical lymphadenopathy that was suspicious of metastatic thyroid cancer. The 18-fluorodeoxyglucose positron emission tomography-computed tomography scan (FDG PET/CT), which was performed for further evaluation, revealed multiple bilateral pulmonary hypermetabolic foci (Figure 3, maximum standard uptake value: 4.7) with indistinct borders and multiple bilateral hypermetabolic lymph nodes (maximum size: 24 mm, maximum standard uptake value up to 20) in the neck, bilateral axillae, and mediastinum (stations 2R, 3A, 4R/L, and 5–8); bone destruction with hypermetabolic foci was also observed in the sacrum, right scapula, vertebral arch of L2, and vertebral body of L4. In order to determine whether these lesions represented metastatic thyroid cancer, the sections from the cervical lymph nodes (10 from level VI on the right side, 23 from levels II, III, IV, and V on the right side, and two from level VI on the left side) were evaluated using immunohistochemistry (IHC).

The IHC results from the nodal tissue were as follows: AB (+), CD56 (weakly +), CDX-2 (−), CgA (−), CK (+), CK20 (−), CK5/6 (weakly+), CK7 (+), ER-α (−), GATA3 (−), GCDFP-15 (weakly+), HMB45 (−), Melan-A (−), napsin A (poorly differentiated areas +, glandular duct areas −), P63 (+), PR (−), Sox-10 (−), Syn (−), thyroglobulin (TG) (poorly differentiated areas −, glandular duct areas +), TIF-1 (+), Villin (−), and WT-1 (−). A biopsy of the axillary lymph nodes was considered based on the results. Supplementary reports from the histological and immunohistochemical analyses of cervical lymph nodes (following the first surgery) and the pathological findings from axillary lymph node puncture confirmed the presence of metastatic

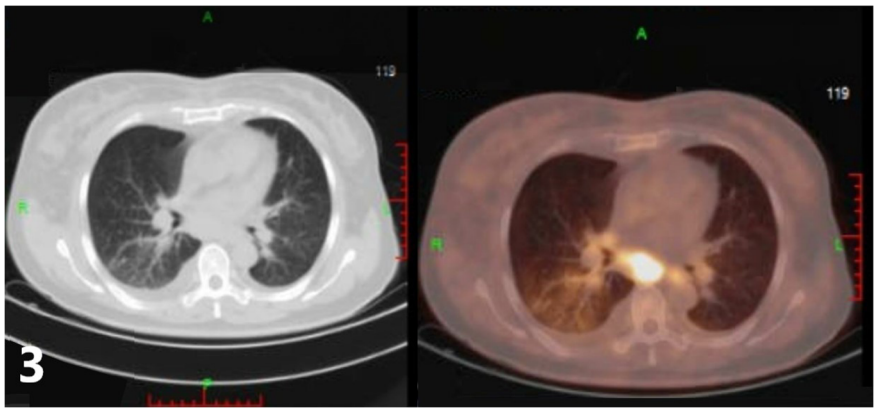

FIGURE 3
The18-fluorodeoxyglucose positron emission tomography-computed tomography scan (FDG PET/CT) of the lung revealed multiple bilateral pulmonary hypermetabolic foci.

PTC and lung adenocarcinoma. The IHC findings from the tissue obtained on biopsy of the right axillary lymph nodes were as follows: CK20 (−), CK5/6 (+), CK7 (+), napsin A (+), P63 (+), TIF-1 (+), 34BE12 (+), Ki67 (60%+), TG (−), CDX-2 (−), AB (+), and P40 (weakly +). In particular, components of both malignancies were detected simultaneously in one right-sided cervical lymph node (Figure 4).

Gene analysis of axillary lymph node tissue revealed the lesion to be ALK1-positive, EGFR-negative, ROS1-negative, and BRAFV600E-negative.

Following a multidisciplinary discussion, the patient was started on targeted treatment with crizotinib at 5 months postsurgery. Intravenous pamidronate was also administered for the treatment of the bone metastases. Although targeted therapy offered partial tumor response at approximately 6 months, crizotinib resistance developed a year later; she was therefore subsequently treated using alectinib. At 2 years postsurgery, the patient died owing to the development of multiple lesions of primary lung adenocarcinoma. The timetable of the treatment strategy is shown in Table 1.

3 Discussion

Carcinomas of unknown primary origin are defined by the presence of histologically confirmed metastatic carcinomas in the absence of an identifiable primary tumor site, despite extensive multidisciplinary investigations (4). FDG PET/CT scans offer high specificity and sensitivity in the diagnosis of cancer. However, it is difficult to obtain a definite diagnosis of the primary and metastatic tumors in the presence of multiple abnormalities. IHC is a reliable and inexpensive tool for the identification of the site of origin in carcinomas with an unknown primary. In the case described, the diagnosis of PTC had been confirmed; however, biopsies had not been obtained from the multiple bilateral pulmonary lesions. Notably, the presence of multiple abnormalities on the FDG PET/CT scan hinders the identification of the primary site. Although an IHC examination of the cervical lymph nodes was not initially performed in this case, supplemental IHC findings from the cervical and right axillary lymph nodes aided in the determination of the primary site.

In this context, keratins are a family of intermediate filament proteins that are expressed in epithelial cells. Different molecular expression patterns allow for the accurate and elaborate classification of epithelial cells and their neoplasms into different subtypes (5). Among the cytokeratins, CK7 and CK20 have been used most widely to predict the primary site; notably, the CK7 +/CK20− expression profile was established in the present case. Complementary organ-specific antibodies, including TTF-1, TG, and napsin A allowed identification of the origin(s) of the two coexisting tumors in the thyroid and lung. TTF-1 and napsin A are used to distinguish primary tumors of the thyroid or lung from those with other tissues of origin. TTF1 is a nuclear transcription factor that promotes embryogenic pulmonary and thyroid differentiation; it is expressed by most, but not all, lung or thyroid neoplasms (6). Although a minority of anaplastic and poorly differentiated thyroid carcinomas may express napsin A, it is also expressed by some lung adenocarcinomas (7).

Primary thyroid carcinomas usually demonstrate TG production; however, primary lung cancers or tumors originating from other sites test negative for this biomarker (8).

In the present case, the tissue specimens from the cervical and axillary lymph nodes were evaluated using IHC staining for CK7, CK20, TTF-1, napsin A, and TG; the specimens from the axillary lymph nodes revealed negative immunoreactivity to CK20 and TG and positive reactivity to CK7, TTF-1, and napsin A. The cervical lymph node specimens included poorly differentiated regions (with positive immunoreactivity to CK7, TTF-1, and napsin A but negative reactivity to CK20 and TG) and glandular regions (with

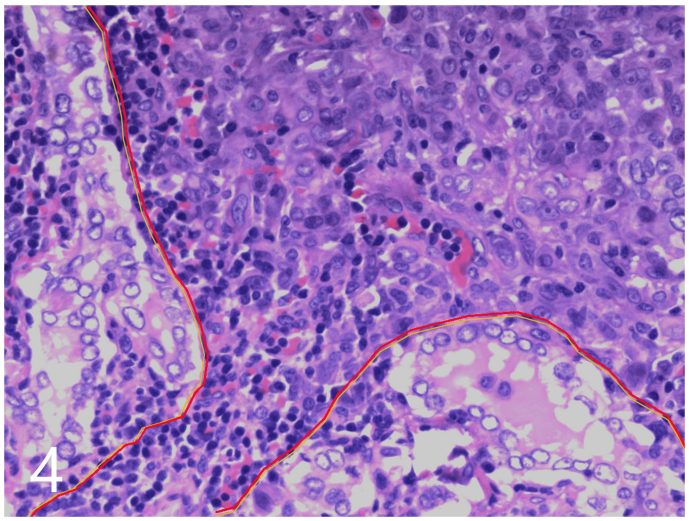

FIGURE 4
Pathological map of two metastatic tumor components. Thyroid cancer (delineated in yellow on the left and lower side) and lung cancer (delineated in red on the right and upper side) in an enlarged cervical lymph node (hematoxylin and eosin, × 200).

TABLE 1 The timetable of the treatment strategy of the patient.

Date	Chief complaint	Treatment/ auxiliary inspection	Diagnosis
30 March 2018	Thyroid nodules detected by US	Total thyroidectomy and bilateral cervical lymphadenectomy/ gene testing	Thyroid microcarcinoma with the nodal metastases
21 September 2018	Neck swelling	Antibiotic anti-infection treatment	Exclusion of infection for poor anti-inflammatory effect
22 January–1 February 2019	Neck swelling	Neck US, CT, PET CT, biopsy of the axillary lymph nodes, IHC and gene testing	Double primary malignancies of the lung and thyroid with lymph node metastasis
3 February 2019	Neck swelling	Etotinib (25 mg bid, po)	Double primary cancers
24 March 2019	None	Etotinib (25 mg qd, po), decreased dose by herself	Double primary cancers
24 May 2019	Lumbago	Etotinib (25 mg qod, po), discontinue medication for lumbago	Double primary cancers
30 May 2019	Lumbago	CT, MRI	Double primary cancers with bone metastasis
5 June 2020	Lumbago	Aletinib (4 pieces bid, po) combined with pamidronate (90 mg, iv drip)	Double primary cancers with bone metastasis
29 September 2020	Lumbago	Aletinib (4 pieces bid, po) combined with pemetrexed (80 mg, iv drip)/CT	Double primary cancers with bone metastasis and liver metastasis

positive immunoreactivity to CK1, TTF-1, and TG but negative reactivity to CK20 and napsin A); one of the cervical lymph nodes obtained from the right side of the neck demonstrated coexistence of both components. These results suggested the presence of double primary carcinomas originating from the thyroid and lung.

Although MPCs are reported to be rare, the morbidity related to these cancers has been gradually increasing. The reported incidence of MPCs varies between 0.73% and 11.7% (9, 10). Depending on the time between diagnosis of the first and second primary tumors, MPCs may be classified as either synchronous (where the second tumor is diagnosed within 6 months of primary cancer) or metachronous (where the second tumor is diagnosed more than 6 months after primary cancer diagnosis) (11). The IHC findings from the cervical and axillary lymph node tissue suggested the presence of synchronous double primary carcinomas originating from the thyroid and lung; the BRAFV600E mutation promoted the development of PTC, while ALK fusion promoted the lung adenocarcinoma. Interestingly, the lymph nodes comprised metastasized cells from both PTC and lung adenocarcinoma. To the best of our knowledge, this is the first study to report the presence of two cancerous components (PTC and lung adenocarcinoma) in a single lymph node; this is an extremely rare finding.

Notably, PTC is the most common malignancy of the thyroid gland; PTMCs are defined as PTCs with diameters of ≤ 10 mm. These tumors (including PTMCs) exhibit an indolent clinical course and are associated with an excellent prognosis. However, a small subset of PTCs may exhibit aggressive phenotypes (including an increased incidence of extrathyroidal extension, lymph node metastases, recurrence, and even death). Unlike other patients with PTC, for whom overtreatment should be avoided, patients with aggressive PTCs should be treated actively. Most current studies focus on the genetic profile (especially the BRAFV600E mutation status) of PTCs to predict tumor behavior; these mutations are prevalent in 40%–70% of PTCs (12) and 57.4% of PTMCs (13). In PTCs (including PTMCs), BRAFV600E mutations are reported to be associated with an increase in aggressive behavior (12).

In this context, thyroid US is the imaging modality of choice for the evaluation of thyroid lesions and the detection of lymph node metastases (12, 14). In the US, PTCs usually manifest as irregularly shaped hypoechoic masses, lesions with microcalcifications, or masses with an aspect ratio of > 1 (15). In cases with cervical lymph node metastases, multiple lesions are more commonly found than single lesions. In the present case, the lesions exhibited more than one of the malignant features mentioned above. Cervical metastases from PTC usually manifest as round, cystic, or microcalcified cervical nodules in the US (16, 17). One cervical lymph node in the present case appeared as an irregular inhomogeneous hypoechoic mass on initial US examination. These features are in contrast to those of the classical presentation of PTC-related metastases.

ALK, which encodes a receptor-type tyrosine kinase, is considered to be the driver gene for tumorigenesis. *ALK* fusion occurs in cases of breakage and fusion with other genes, with the fusion between *EML4* and *ALK* being the most important. The *EML4-ALK* fusion gene, which is found in 3%–5% of non-small cell lung cancer cases (18) and occasionally in PTC (19), encodes the EML4-ALK fusion protein that can directly form an ALK dimer. The dimer subsequently activates the ALK and downstream signaling pathways, including the RAS/ERK/STAT3/mTOR or BRAF pathways, and contributes to carcinogenesis in non-small cell lung cancer (20, 21). The carcinogenic fusion of EML4-ALK mostly occurs in female patients with non-small cell lung cancer who have no prior history of smoking (22). In the present case, the patient was a woman and had no history of smoking; she was asymptomatic and was diagnosed and treated after the detection of thyroid nodules during physical examination. Investigations revealed the presence of cervical and axillary lymphadenopathy and bone destruction. Various targeted therapeutic drugs have been developed in recent years for treating cases with EML4-ALK fusions. Crizotinib, which was the first targeted therapy drug to be used, is more effective than traditional standard chemotherapy (23, 24). It offers an objective response rate of 53% with a mean progression-free survival of 8.5 months; however, resistance to crizotinib usually develops within 1 year of treatment. Second-generation EML4-ALK-targeted drugs (such as ceritinib, brigatinib,

and alectinib), the third-generation targeted drug lorlatinib, and the fourth-generation targeted drug repotrectinib (TPX-0005) have been developed to overcome crizotinib resistance (20). Drug resistance was also observed in the study case, necessitating an alteration of the therapeutic regimen. The patient died 20 months after initiation of targeted drug therapy; the poor prognosis in this case was consistent with findings from previous studies (2, 3, 25), which reported poor outcomes in young female patients with MPCs.

A review of the initial cervical US images revealed only one unique finding: an enlarged cervical lymph node, which appeared as an irregular hypoechoic nodule. This differed from the usual features (round shape, microcalcification, or cystic change) of PTC-related metastases. In this context, it is essential to suspect the presence of metastases from other malignant tumors in cases of PTC where the US reveals enlarged inhomogeneous hypoechoic and irregular cervical lymph nodes; alternatively, this finding may indicate the coexistence of metastases from PTC and malignant tumors of different origins (suggesting the occurrence of double primary cancers). Postoperative pathological evaluation should preferably be further supported by IHC and gene testing to confirm the origin of the metastasis. This may enable early accurate diagnosis and comprehensive treatment.

4 Conclusions

Although biopsies could not be obtained from the lung lesions (in view of the retrospective evaluation of the present case), IHC examination of the cervical and right axillary lymph nodes identified the primary sites to be the thyroid and lung. Despite these limitations, this report describes a rare case with double primary cancers (BRAFV600E-mutant metastatic PTC and ALK fusion-positive metastatic lung adenocarcinoma) that had a poor prognosis.

To the best of our knowledge, this is the second report on the diagnosis of concomitant pulmonary and thyroid primary adenocarcinomas using FDG PET/CT and IHC. The cervical lymph node metastases comprised both PTC and lung adenocarcinoma components. In particular, the tumor components of PTC and lung adenocarcinoma were detected in one cervical lymph node from level VI; this is the first report to describe these findings. The mentioned cervical lymph node presented as an irregular inhomogeneous hypoechoic mass during the initial thyroid US examination. These features differed from the typical features of metastases from PTCs. Radiologists and clinicians therefore need to be aware of these US features in enlarged cervical lymph nodes, as they may indicate the presence of metastases from double primary cancers. Additional histological examination, immunostaining, and gene testing may be needed to establish an accurate diagnosis and facilitate treatment earlier in the course of the disease.

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 The Ethics Committee in Clinical Research of the First Affiliated Hospital of Wenzhou Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. 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

Data collection and analysis: PL and Y-FP. Writing—original draft and literature research: S-PC and XJ. Writing—review and editing: XJ. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

Publisher's note

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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 16 January 2024
DOI 10.3389/fonc.2023.1273798

OPEN ACCESS

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RECEIVED 07 August 2023
ACCEPTED 31 December 2023
PUBLISHED 16 January 2024

CITATION
Wu W-J, An P-G, Zhong Y-W, Hu X, Wang L and Zhang J (2024) Tislelizumab plus nimotuzumab is effective against recurrent or metastatic oral squamous cell carcinoma among patients with a performance status score ≥ 2: a retrospective study.
Front. Oncol. 13:1273798.
doi: 10.3389/fonc.2023.1273798

Tislelizumab plus nimotuzumab is effective against recurrent or metastatic oral squamous cell carcinoma among patients with a performance status score ≥ 2: a retrospective study

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Objectives: The efficacy of treatments targeting recurrent or metastatic head and neck squamous cell carcinoma are unsatisfactory in practice for patients with a ECOG PS score ≥ 2. Thus, this study retrospectively evaluated the safety and efficacy of a programmed cell death 1 inhibitor (tislelizumab) combined with an epidermal growth factor receptor inhibitor (nimotuzumab) in treating patients with a PS score ≥ 2 who suffer from recurrent or metastatic oral squamous cell carcinoma (OSCC).

Materials and methods: Fifteen patients were treated with tislelizumab (200 mg IV Q3W) and nimotuzumab (200 mg IV Q3W). Programmed cell death-ligand 1 (PD-L1) expression in tumor biopsies was assessed with immunohistochemistry. Whole-exome sequencing was used to evaluate treatment efficacy based on PD-L1 expression and gene mutation.

Results: At a median follow-up of 9.6 months, median overall survival was 10.1 months, and median progression-free survival was 4.0 months. Overall response rate was 40%, with 6/15 patients achieving partial response. Eight patients exhibited nine adverse events, eight out of nine being grade 2 and the remaining being grade 3. Whole-exome sequencing showed that *DYNC1I2, THSD7A*, and *FAT1* mutations were associated with patient prognosis.

Conclusion: Combination therapy involving tislelizumab plus nimotuzumab is a promising, low-toxicity treatment for recurrent or metastatic OSCC in patients with a PS score ≥ 2.

KEYWORDS

tislelizumab, nimotuzumab, immunotherapy, oral squamous cell carcinoma, performance status score

Introduction

Programmed cell death 1 (PD-1) inhibitors are first- and second-line treatments for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) (1, 2). Several clinical trials have reported the overall efficacy of various PD-1 inhibitors. For example, objective response to first-line treatment of pembrolizumab + chemotherapy was 36%, whereas pembrolizumab alone yielded 17% objective response (2). Platinum chemotherapy with nivolumab resulted in a 13.3% response rate among patients (1). The epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab similarly yielded a 13% response rate (3). Furthermore, cetuximab not only inhibited the target of EGFR, but also upregulated the expression level of PD-L1 in NK cells, enhancing the efficacy of immunotherapy. In addition, PD-L1 blockade could also enhance the antibody-dependent cellular cytotoxicity of cetuximab against HNSCC cells {Okuyama, 2023 #188492}. Two recent phase 2 clinical trials found that combination therapy with PD-1 inhibitors and EGFR inhibitors leads to higher response rates than monotherapy (4, 5). In a phase 2 trial, patients were treated with pembrolizumab plus cetuximab, resulting in 45% objective response rate (ORR), median overall survival (OS) of 18.4 months, and median progression-free survival (PFS) of 6.5 months (4). Another phase 2 trial showed that nivolumab plus cetuximab yielded 22% ORR in patients who had received prior therapy and 37% ORR in patients who had not. And the median OS was 11.4 months and 20.2 months, respectively (5).

Despite these promising results, HNSCC patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score ≥ 2 do not respond well in practice. Exacerbating the problem, patients with poor PS are excluded from large clinical trials.

Tislelizumab is an anti-PD-1 monoclonal immunoglobulin G4 antibody approved for the treatment of nine cancer types in multiple clinical trials (6). Nimotuzumab is a humanized anti-EGFR immunoglobulin G1 monoclonal antibody with mild toxicity (7). This study aimed to evaluate the safety and efficacy of tislelizumab plus nimotuzumab in patients with a ECOG PS score ≥ 2 who have recurrent or metastatic oral squamous cell carcinoma (OSCC).

Materials and methods

Study design

This retrospective study was performed in accordance with the Declaration of Helsinki. Procedures were approved by the Ethics Committee of Peking University School and Hospital of Stomatology and in compliance with international ethical standards (IRB number: PKUSSIRB-202059162). Written informed consent was obtained from all patients.

Patients were enrolled in this retrospective study from April 2021 to October 2022 according to the following inclusion criteria: (a) patients with recurrent or metastatic OSCC and (b) patients with a ECOG PS score ≥ 2. The exclusion criteria were as follows: (a) history of other tumors and (b) ineligibility for PD-1 inhibitors. Fifteen patients with recurrent or metastatic OSCC were enrolled and treated consecutively with tislelizumab plus nimotuzumab from September 2020 to February 2021. All participants received fixed-dose nimotuzumab (200 mg) and tislelizumab (200 mg) intravenously on the first day of each 3-week cycle until intolerable adverse events or progression disease (PD) or death occurred. For patient baseline data, see Table 1. Supplementary Table 1 showed the treatment history of these 15 patients.

Samples for programmed cell death-ligand 1 (PD-L1) immunohistochemistry and whole-exome sequencing were obtained from biopsies of the primary tumor before treatment.

Outcome definition and response assessment

Responses were assessed was based on Response Evaluation Criteria In Solid Tumors (RECIST1.1). Images were obtained every 8 weeks and evaluated by two experienced radiologists and an

TABLE 1 Baseline characteristics.

		N=15 (%)
Age	Median	78 (38,85)
Gender	Male	4 (26.7%)
	Female	11 (73.3%)
ECOG	2	9 (60%)
	3	6 (40%)
Recurrence pattern	Local or regional recurrence only	14 (93.3%)
	Distant metastasis only	1 (6.7%)
PD-L1 CPS	<1	1 (6.7%)
	20>CPS≥1	10 (66.7%)
	≥20	4 (26.8%)
PD-L1 TPS	<1%	4 (26.8%)
	≥1%	11 (73.3%)
Treatment cycle	Median	7 (2-22)
Outcome	DCR PR	6 (40%)
	SD	6 (40%)
	PD	3 (20%)
State	Alive	3 (20%)
	Death	12 (80%)
Cause of death	Tumor progression	8 (53.3%)
	Pulmonary infection	2 (13.3%)
	Pulmonary infection + Hypokalemia	1 (6.7%)
	Intracranial infection	1 (6.7%)

ECOG, Eastern Cooperative Oncology Group; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ORR: Objective Response Rate; DCR: Disease control rate; NA, not applicable;.

experienced surgeon. The ORR is the sum of the proportions of complete response (CR) and partial responses (PR). The PFS was defined as the period from the enrollment to the latest follow-up, PD, or death from any cause. The OS was defined as the period from the enrollment to the latest follow-up, or death from any cause during the follow-up. Adverse events (AE) were assessed according to Common Terminology Criteria for Adverse Events version 5 (CTCAE V5.0). The primary endpoint was OS. Secondary endpoints included ORR, PFS, and AE.

PD-L1 immunohistochemistry assay

The 22C3 pharmDx assay (Agilent Technologies, Santa Clara, CA, USA) was used for PD-L1 staining. Immunohistochemistry was performed following manufacturer protocol. All specimens from patient tumors were fixed with formalin, then embedded in paraffin and sliced into 4 μm sections. Antigens were retrieved using a target retrieval solution (pH 6.1) at 97°C for 20 min and washed with a wash buffer. Slides were then incubated with specific primary antibodies (mouse anti-human PD-L1 monoclonal antibody, clone 22C3) and washed three times with a wash buffer. Next, they were incubated with secondary antibodies (rabbit anti-mouse immunoglobulin G polymer) at room temperature and washed three times with a wash buffer. Slides were stained with 3,3'-diaminobenzidine tetrahydrochloride to detect PD-L1 presence and counterstained with hematoxylin to visualize nuclei. The comprehensive positive score (CPS) was defined as the number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells × 100. The tumor cell proportion score (TPS) was defined as the number of PD-L1-positive tumor cells divided by total number of tumor cells × 100%.

Whole-exome sequencing

DNA extraction

Informed consent was obtained from patients for genetic analysis. Genomic DNA was extracted from tumor samples and paired peripheral blood samples using the Library Extraction Kit (MyGenostics, Beijing).

DNA library preparation

At least 3 μg of DNA was used to construct indexed Illumina libraries, following manufacturer protocol (MyGenostics). Fragments 350–450 bp in size, including adapter sequences, were selected for DNA libraries. Validation was performed with a Nanodrop 2000 spectrophotometer (Thermo Fisher, USA) and the Agilent 2100 Bioanalyzer (Agilent, USA).

Targeted gene capture and sequencing

Total coding sequences of genes were selected via gene capture using the GenCap custom enrichment kit (MyGenostics). Paired-end reads (150 bp) were sequenced on a NextSeq 500 sequencer (Illumina, San Diego, CA, USA) for library construction.

Data analysis

After sequencing, low-quality reads (quality score ≥ 20) were filtered out. Clean reads were aligned to the human reference genome (hg19) with the Burrows-Wheeler Aligner. Single nucleotide polymorphisms and insertions or deletions were identified using the Genome Analysis Toolkit, while Delly determined structural variations. Copy number variants were detected with the CNVkit, based on the depth distribution of reads compared with the reference genome.

Statistical analysis

The Kaplan–Meier method was used for analyses of PFS and OS. Differences between groups were compared with the use of the stratified (unweighted) log-rank test. An 95% CI was estimated for PFS and OS. The *P* values are two-tailed and $P < 0.05$ was considered statistically significant. All analyses were performed in GraphPad Prism (version 9) and IBM SPSS (version 24). Heatmaps were created with the R package "Pheatmap" in R Studio.

Results

Efficacy evaluation

Median follow-up was 9.6 months (range: 2–15.2 months) at the data cutoff of November 30, 2022. Average patient age was 78 years, and most were women (Table 1). Median OS was 10.1 months (95% CI = 4.6–15.6 months), and median PFS was 4.0 months (95% CI = 2.0–6.0 months) (Figure 1). Among all participants, 12 patients (80%) responded to treatment (Supplementary Figure 1), six of them (40%) partially (PR). The best result was tumor shrinkage by 82.1% (Figure 2). Six patients (40%) had stable disease (SD), but three (20%) had progressive disease (PD). One patient had an SD status for 2 months and then received chemotherapy. The ORR was 40% and median OS was 15.2 months (95% CI = 7.4–23.0 months), 11.65 months (95% CI = 4.1–16.1 months), and 7.1 months (95% CI = not available [NA]) in the PR, SD, and PD groups, respectively, with significant differences between groups (p = 0.028). Median PFS also significantly different between groups (p = 0.030), being 7.8 months (95% CI = 0–15.602 months), 2.5 months (95% CI = 0.4–3.6 months), and 2.0 months (95% CI = NA), respectively (Figure 3A).

Adverse events

The 15 patients generally responded well to treatment, with nine adverse events (AEs) in 8 patients (53.3%) (Table 2). Grade 2 acneiform rash had the highest incidence (26.7%), followed by

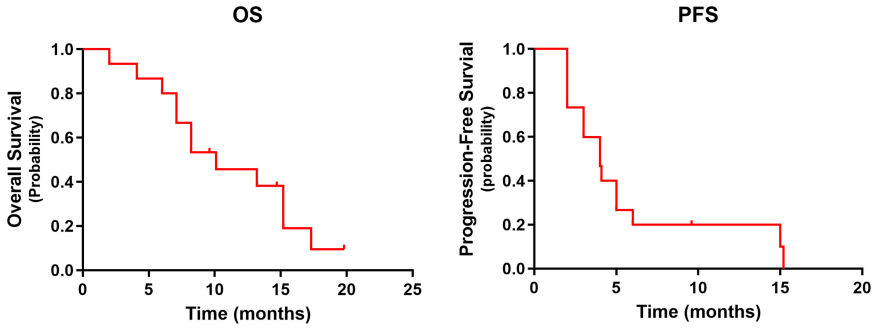

FIGURE 1
The OS and PFS in 15 patients. OS, overall survival; PFS, progression-free survival.

hypothyroidism (13.3%), interstitial pneumonia (13.3%), and myocarditis (6.7%). Notably, one patient developed pneumonia after three cycles of combined treatment and was then treated with nimotuzumab alone for 16 cycles; her status was maintained at PR. One patient discontinued treatment after two cycles due to pneumonia and underwent chemotherapy. Tumor progression was observed in this patient. One patient discontinued combined treatment after 2 months due to myocarditis and was treated with cardiac support.

Efficacy analyses based on PD-L1 immunohistochemistry

To further explore combined treatment efficacy, we evaluated OS and PFS based on CPS and TPS. Eleven individuals (73.2%) had PD-L1 CPS < 20, including one patient with PD-L1 CPS < 1. Four patients (26.8%) had PD-L1 CPS ≥ 20. Median OS was 13.2 months (95% CI = 5.991–20.409 months) and 6.55 months (95% CI = 3.060–8.940 months) in patients with PD-L1 CPS < 20 and PD-L1 CPS ≥ 20, respectively. Median PFS was 4 months (95% CI = 2.436–5.564 months) and 4.55 months (95% CI = 1.160–7.040 months) in the PD-L1 CPS < 20 and PD-L1 CPS ≥ 20 groups, respectively. There was no significant difference in OS (p = 0.126) and PFS (p = 0.066) (Figure 3B). Next, we examined patients based on TPS. Four patients had TPS < 1% and 11 had TPS ≥ 1%. Median OS was 8.9 months (95% CI = 2.908–13.492 months) and 13.2 months (95% CI = 7.37–419.026 months) in the PD-L1 TPS < 1% and PD-L1 TPS ≥ 1% groups, respectively. Median PFS in the two groups was 3.0 months (95% CI = 2.482–5.718 months) and 4.1 months (95% CI = 2.611–5.389 months). Neither OS (p = 0.373) nor PFS (p = 0.761) differed between groups (Figure 3C).

Additionally, we identified differences in treatment outcomes between the CPS/TPS groups (Figure 3D). The amount of patients with SD was significantly higher when CPS < 20 than when CPS ≥ 20. The amount of patients with PR was higher when TPS ≥ 1% than when TPS < 1%.

Efficacy analyses based on mutations

We performed whole-exome sequencing on tumor tissue and venous blood from 13 patients to clarify the influence of key genes on treatment efficacy (Figure 4). We found 26 mutations shared by

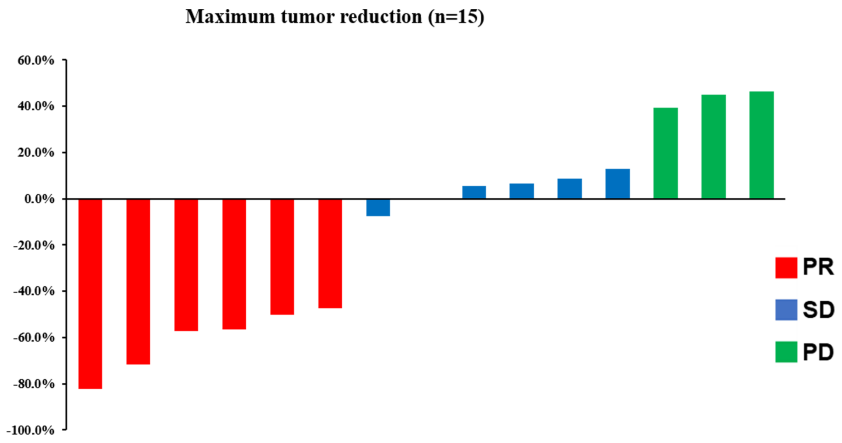

FIGURE 2
The therapy outcome of 15 patients.

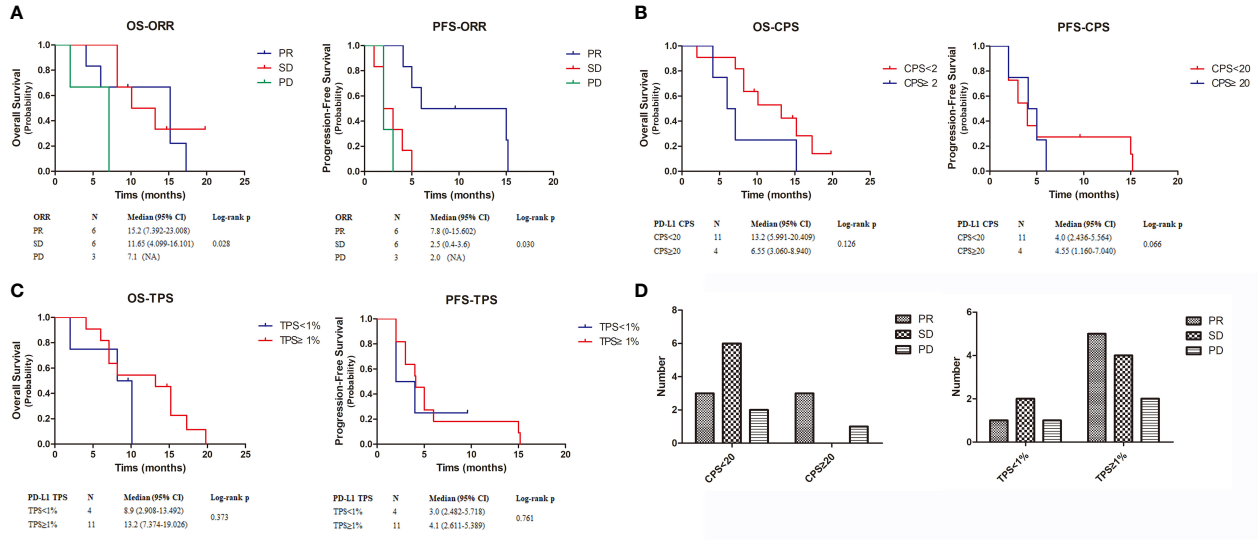

FIGURE 3
Kaplan-Meier estimates the OS and PFS of 15 patients. **(A–C)**. The OS and PFS of ORR, CPS and TPS. **(D)**. The relationship between CPS and TPS and patient treatment outcome. OS, overall survival; PFS, progression-free survival.

more than three patients: 11 had *TP53* mutations; 5 had *NOTCH1* mutations; 4 had *PCLO, TTN, ABCA13, CEP350*, and *MUC16* mutations; and 3 had mutations in all of the following genes: *CFAP47, FAT1, FRMPD4, SCN3A, SYNE2, VPS13B, ZFYVE26, HUWE1, LYST, SYNE1, ZNFX1, DYNC112, NRXN1, CASP8, CDKN2A, LRP1B, THSD7A*, and *SACS* mutations. Next, we analyzed the prognosis of patients with mutations. Median OS and PFS in patients with mutated *TP53* were 9.15 months (95% CI = 3.551–12.849 months) and 4.0 months (95% CI = 2.482–5.518 months), respectively. Median OS and PFS of patients with wild-type *TP53* were 8.2 months (95% CI = 6.44–9.96 months) and 5 months (95% CI = 1.799–8.201 months), respectively. Neither OS nor PFS differed significantly between patients with mutated and wild-type *P53* (Figures 4B, C) (p = 0.506 and p = 0.608, respectively). In contrast, only 3genes, *DYNC1I2, THSD7A*, and *FAT1*, were associated with patient prognosis (Figure 4D). *DYNC112* was associated with median OS (p = 0.017), which was 4.1 months (95% CI = 0.739–7.461 months) and 11.65 months (95% CI = 2.352–17.848 months) in mutation and wild-type groups, respectively. *THSD7A* was associated with median PFS (p = 0.007), which was 2.0 months (95% CI = NA) and 4.55 months (95% CI = 2.482–5.518 months) in the mutation and wild-type groups, respectively. Finally, *FAT1* was associated with OS (p = 0.014) and PFS (p = 0.046). Median OS in patients with mutated and wild-type *FAT1* was 15.2 months (95% CI = NA) and 7.65 months (95% CI = 5.93–68.804 months), respectively. Median PFS was 15 months (95% CI = 0.32–32.604 months) and 3.5 months (95% CI = 0.934–5.066 months).

TABLE 2 Adverse Events.

	Grade 2	Grade 3
Rash acneiform	4 (26.7%)	
Hypothyroidism	2 (13.3%)	
Interstitial pneumonia	2 (13.3%)	
Myocarditis		1 (6.7%)

Discussion

Combining chemotherapy with targeted therapy or immunotherapy can achieve an objective remission rate of >35% in recurrent or metastatic HNSCC (2, 8). However, treatment remains challenging for patients with a PS score ≥ 2 who cannot tolerate routine chemotherapy. In an observational study of nivolumab treatment in patients with recurrent or metastatic HNSCC, median OS was 9.2 months in individuals with a PS score of 0–1 and 4.0 months in those with a PS score > 2 (9). Similarly, the HANNA study showed that median OS was 25.6 months in patients with a PS score of 0 and 5.7 months in patients with a PS score > 2 (10). A phase 2 trial testing cetuximab plus weekly paclitaxel as first-line therapy for recurrent or metastatic HNSCC showed that median OS was 18.6 months in patients with a PS score of 0 and 7.3 months in patients with a PS score of 2 (11). These studies demonstrated that the PS score is an important prognostic factor, especially under anti-PD-1 monotherapy. In our study, PS score ≥ 2 patients had longer median OS and PFS than in other studies, indicating that tislelizumab plus nimotuzumab was relatively effective and safe. This drug combination may be a transitional treatment for PS score ≥ 2 patients who do not tolerate conventional chemotherapy. If combination treatment is effective, chemotherapy may be added to improve remission rates. However, causes of death in these patients are more likely to be systemic diseases than local ones, so the addition of a powerful treatment such as chemotherapy must be considered with caution.

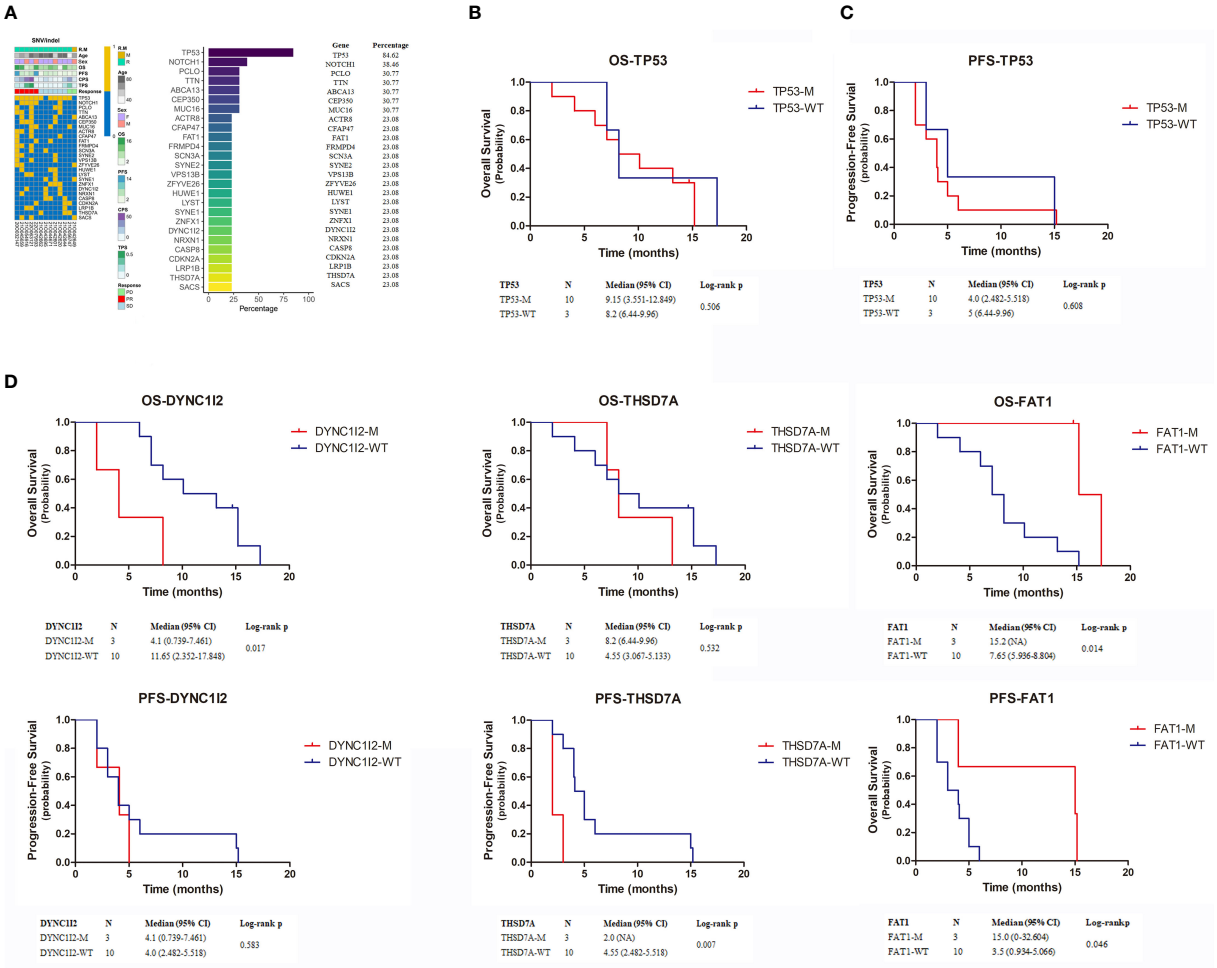

FIGURE 4
(A) The top 26 genes with the highest mutation rate in exon sequencing. **(B–D)** Kaplan-Meier estimates the OS and PFS of patients with TP53, DYNC1I2, THSD7A and FAT1 mutation. OS, overall survival; PFS, progression-free survival.

Among chemotherapy-free options, a PD-1 inhibitor combined with an EGFR inhibitor has been very effective against recurrent or metastatic HNSCC. In a phase 2 trial for these cancers, patients were treated with pembrolizumab plus cetuximab, resulting in 45% ORR, median OS of 18.4 months, and median PFS of 6.5 months (4). Another phase 2 trial showed that nivolumab plus cetuximab yielded 22% ORR in patients who had received prior therapy and 37% ORR in patients who had not. Respectively, median OS was 11.4 months and 20.2 months (5). The 40% ORR in our study was consistent with these previous studies, although median OS and PFS were shorter. In the Keynote-048 trial, anti-PD-1 monotherapy was more effective in patients with metastases than in those with only recurrence, whereas EGFR inhibitors provided more clinical benefit for the latter (2). Combination therapy could be an alternative for patients with only recurrence.

Our study showed that tislelizumab plus nimotuzumab was relatively well-tolerated. Eight out of 15 patients experienced grade 2–3 AEs (mostly grade 2), with acneiform rash and hypothyroidism being the most common. However, in other clinical studies using cetuximab, AEs were often grade 3 or even grade 4. The most common AEs were rash, hypomagnesemia, and oral mucositis (2, 12, 13).

Nimotuzumab and cetuximab are both EGFR inhibitors. Although a higher dose of nimotuzumab is required to achieve effective outcomes, the drug has low toxicity. Nimotuzumab has low affinity for EGFR and only exhibits satisfactory activity in cells with higher EGFR expression, thus reducing its effect on healthy epithelial tissue cells (14). Nimotuzumab has performed well in clinical trials, improving patient survival and causing few adverse reactions (15, 16). Nimotuzumab combined with PD-1 inhibitors could be a treatment option that causes fewer AEs than PD-1 inhibitor monotherapy.

The Keynote-048 revealed that PD-L1 is a good biomarker for predicting ORR and OS in anti-PD-1 monotherapy for recurrent or metastatic HNSCC (2). In CheckMate-141 trials, among patients using nivolumab alone, patients with PD-L1 expression had a higher ORR than PD-L1 non-expressors (17 (CI, 10.7–26.8; N=96) vs 11.8 (CI, 5.6–21.3; n=76)). While, there seemed to be no significant difference between PD-L1 expressors and non-expressors in OS (17). In contrast, our study found that patients

in the CPS < 20 group had a higher median OS than patients in the CPS ≥ 20 group (13.2 months vs. 6.55 months). Patients with CPS ≥ 20 also had slightly higher median PFS than patients with CPS < 20 (4.55 months vs. 4.00 months). Comparable results were reported from a phase 2 trial for recurrent or metastatic HNSCC (5). For patients treated with nivolumab plus cetuximab, median OS in the CPS < 20 group was 19.9 months, significantly higher than in the CPS ≥20 group (10.7 months) or the CPS < 1 group (8.9 months). Median PFS of Patients in the CPS ≥ 20 group also had higher median PFS than patients in the CPS < 20 group (5.6 months vs. 3.8 months) (5). Patients with higher CPS generally respond better to PD-L1 inhibitors, achieving longer OS and PFS (1, 2). However, this pattern was not borne out with combined treatment. Patients who test negative for PD-L1 may benefit more from a combination of PD-1 and EGFR inhibitors (5, 12), likely because EGFR pathway inhibition alters the immune structure of the tumor microenvironment (18, 19).

TP53 has one of the highest mutation rates in HNSCC (20). *TP53* mutation has been associated with a decrease in immune cell infiltration and PD-L1 expression. Therefore, *TP53* mutation status may be a negative predictor of response to treatment with immune checkpoint inhibitors (21). In our study, *TP53* mutation status was not significantly associated with OS or PFS, suggesting that patients with these mutations may not benefit from immunotherapy. In contrast, *FAT1* mutation status was significantly associated with OS and PFS. Patients with *FAT1* mutations had higher median OS (p = 0.014) and PFS (p = 0.046). *FAT1* encodes tropocadherin, a protein that regulates intercellular adhesion and extracellular matrix structure. *FAT1* mutations are the most common in squamous cell carcinoma, especially OSCC (30–40%) (2013). In HNSCC, *FAT1* mutations induce EMT status, thereby promoting tumor occurrence, progression, invasiveness, and metastasis (22). In OSCC, therapy targeting *FAT1* successfully inhibited tumor progression and increased sensitivity to chemotherapy (23). In HNSCC cell lines, knocking out the *FAT1* gene could reduce the expression of pEGFR, pHER2, and pERK proteins, meaning to inactivate the EGFR signaling axis. In clinical research, there was a significant correlation between the expression of FAT1 and EGFR in SCC of the lung, cervix, and head and neck, with *FAT1* more commonly seen in HPV (-) HNSCC. In summary, mutations in *FAT1* may lead to resistance to EGFR targeted therapy (24–26). Considering these findings, future studies should aim to further clarify the effects of *FAT1* on immunotherapy and targeted therapy.

Although we provided evidence supporting the efficacy of tislelizumab plus nimotuzumab in treating recurrent and metastatic OSCC, our study had several limitations. First, the sample size of 15 patients is inadequate compared with other clinical studies. Second, only one patient exhibited metastasis, meaning we could not fully evaluate the effect of our proposed combination therapy on such patients.

Nevertheless, similar to studies that have evaluated the use of combination therapies with PD-1 and EGFR inhibitors in recurrent or metastatic HNSCC, the use of tislelizumab plus nimotuzumab demonstrated satisfactory response rates and OS in patients with a ECOG PS score ≥ 2 who have recurrent or metastatic OSCC. The drug combination also exhibited low toxicity and was relatively safe.

Conclusions

Our results suggest that tislelizumab in combination with nimotuzumab is a promising, low-toxicity therapy for recurrent or metastatic OSCC among patients with a ECOG PS score ≥ 2.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: https://dataview.ncbi.nlm.nih.gov/object/PRJNA907775?reviewer=vcmj5u5t8ijbnp3o784nh8h9r4.

Ethics statement

The studies involving humans were approved by Ethics Committee of Peking University School and Hospital of Stomatology (IRB number: PKUSSIRB-202059162). 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

W-JW: Formal analysis, Software, Writing – original draft, Data curation, Validation. P-GA: Methodology, Formal analysis, Software, Writing – original draft. Y-WZ: Data curation, Writing – original draft, Investigation. XH: Investigation, Writing – original draft. LW: Formal analysis, Writing – original draft. JZ: Conceptualization, Funding acquisition, Methodology, Project administration, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by Beijing Xisike Clinical Oncology Research Foundation (Y-MSDPU2022-0547) and Clinical Medicine Plus X - Young Scholars Project, Peking University, the Fundamental Research Funds for the Central Universities (PKU2022LCXQ19).

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1273798/full#supplementary-material

SUPPLEMENTARY FIGURE 1
|A 72-year-old male presented with bilateral cervical lymph node metastasis after surgery and radiotherapy for the cancer of the floor of the mouth. **(A)**. Bilateral cervical metastatic lymph nodes (the white arrow). **(B)**. The image PR was achieved after 3 cycles of tislelizumab plus nimotuzumab. **(C)**. H&E (10x). **(D)**. PD-L1 staining (the CPS was 2 and TPS was 2%, 10x) was performed using the 22C3 pharmDx assay (Agilent Technologies, Santa Clara, CA, USA).

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frontiers | Frontiers in Oncology

TYPE Systematic Review
PUBLISHED 16 January 2024
DOI 10.3389/fonc.2023.1303132

OPEN ACCESS

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RECEIVED 27 September 2023
ACCEPTED 31 December 2023
PUBLISHED 16 January 2024

CITATION
Zhang J and Dai S (2024) Prognostic and clinicopathological role of pretreatment systemic immune-inflammation index in patients with oral squamous cell carcinoma: a meta-analysis.
Front. Oncol. 13:1303132.
doi: 10.3389/fonc.2023.1303132

Prognostic and clinicopathological role of pretreatment systemic immune-inflammation index in patients with oral squamous cell carcinoma: a meta-analysis

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Background: There are many studies regarding the use of systemic immune-inflammation index (SII) to help predict oral squamous cell carcinoma (OSCC) prognosis, but findings have been inconsistent. The present meta-analysis was conducted to determine whether SII could contribute to predicting OSCC prognosis.

Methods: PubMed, Embase, Cochrane Library and Web of Science databases were thoroughly searched from their inceptions through August 20, 2023. The role of SII in predicting OSCC prognosis was determined through combined hazard ratios (HRs) with relevant 95% confidence intervals (CIs). Correlations of SII with clinicopathological characteristics of OSCC patients were analyzed based on combined odds ratios (ORs) with 95% CIs.

Results: This meta-analysis utilized 11 articles in total, involving 3,464 patients. According to the results, an elevated SII was markedly associated with dismal overall survival (OS) (HR=1.85, 95%CI=1.48-2.29, p<0.001) and poor disease-free survival (DFS) (HR=1.77, 95%CI=1.20-2.61, p=0.004) of OSCC. Moreover, a higher SII was markedly correlated with stage T3-T4 (OR=2.47, 95%CI=1.40-4.37, p=0.002), TNM stage III-IV (OR=2.29, 95%CI=1.53-3.44, p<0.001), and low differentiation (OR=1.74, 95%CI=1.25-2.43, p=0.001).

Conclusion: According to the present meta-analysis, an increased SII is significantly associated with dismal OS and DFS, advanced tumor stage and poor differentiation in OSCC. SII could be a potential and important biomarker for clinical management and predicting the prognosis of patients with OSCC.

Systematic review registration: https://inplasy.com/inplasy-2023-9-0033/), identifier INPLASY202390033.

KEYWORDS

SII, oral squamous cell carcinoma, meta-analysis, evidence-based medicine, prognostic markers

Introduction

Head and neck cancer (HNC) is the sixth most common cancer across the world, affecting nearly 650,000 patients and contributing to 350,000 deaths every year (1, 2). Oral squamous cell carcinoma (OSCC), has the highest morbidity in HNC and constitutes 48% of all HNC cases (3). Moreover, OSCC includes cancers that occur in the lips, gums, tongue, mouth, and palate (4). Although there have been improvements in multidisciplinary collaboration and comprehensive therapy, such as surgery, radiotherapy, and chemotherapy, OSCC has had a low 5-year survival rate (under 50%) over the past two decades (5). Nowadays, the tumor-node-metastasis (TNM) classification system is widely used to guide the selection of treatment strategies and predict survival outcomes; however, patients of an identical TNM stage can have diverse disease courses (6). Therefore, identifying reliable and cost-effective prognostic markers for OSCC patients is urgently needed to intervene treatment measures and improve overall prognosis.

Accumulating evidence has shown that cancer-related immune and inflammatory responses have pivotal effects on tumor occurrence, growth, invasion, and progression (7). Many blood-based indexes that reflect inflammatory statuses have been identified as prognostic biomarkers in different cancer types. These indexes include neutrophil-to-lymphocyte ratio (NLR) (8), platelet-to-lymphocyte ratio (PLR) (9), C-reactive protein/albumin ratio (CAR) (10), lymphocyte-monocyte ratio (LMR) (11) and lymphocyte-to-C-reactive protein ratio (LCR) (12). Systemic immune-inflammation index (SII), a hematological parameter, is calculated by the following formula: SII = (platelet number × neutrophil number)/lymphocyte number. Moreover, SII has been widely demonstrated to significantly predict diverse cancer prognostic outcomes, such as thyroid cancer (13), cholangiocarcinoma (14), hepatocellular carcinoma (HCC) (15), glioma (16), and pancreatic cancer (17). The ability of SII to predict OSCC prognosis has been explored previously, but no consistent findings have been reported (18–28). For example, a higher SII was reported as a distinct prognostic indicator of OSCC in certain articles (19, 26, 28). In contrast, some researchers indicated the absence of any obvious association of SII with survival outcomes in OSCC (23–25). Consequently, to identify the precise impact of SII on predicting OSCC prognosis, this work carried out comprehensive literature retrieval for meta-analysis. Furthermore, the relationship between SII and clinicopathological features of OSCC patients was also investigated.

Abbreviations: SII, systemic immune-inflammation index; OSCC, oral squamous cell carcinoma; HR,hazard ratio; CI,confidence interval; OR,odds ratio; OS, overall survival; DFS, disease-free survival; HNC, head and neck cancer; TNM, Tumor-Node-Metastasis; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CAR, C-reactive protein/albumin ratio; LMR, lymphocyte-monocyte ratio; LCR, lymphocyte-to-C-reactive protein ratio; HCC, hepatocellular carcinoma; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NOS, Newcastle–Ottawa Scale; CCRT, concurrent chemoradiotherapy; RT, radiotherapy; ROC, receiver operating characteristic; MMP-9, matrix metalloproteinase-9; IL-8, interleukin-8; TNF-α, tumor necrosis factor α; CTCs, circulating tumor cells; TILs, tumor-infiltrating lymphocytes; PFS, progression-free survival; bRFS, biochemical recurrence-free survival.

Materials and methods

Study guideline and protocol registration

The present study was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (29), and registered in INPLASY (registration ID: INPLASY202390033, https://inplasy.com/inplasy-2023-9-0033/).

Literature retrieval

Literature was retrieved from the PubMed, Embase, Cochrane Library and Web of Science databases, starting with the earliest possible date through August 20, 2023. The following terms were used to search and select literature for the meta-analysis: (systemic immune-inflammatory index or SII or systemic immune-inflammation index or systemic-immune-inflammation index) and (oral squamous cell carcinoma or OSCC or oral cancer or tongue cancer or mouth cancer or oral carcinoma or oral cavity cancer or lip cancer or gingiva cancer). More details about these search strategies are provided in Supplementary File 1. Only English publications were considered. Besides, references in each publication were manually retrieved to identify the possible relevant articles.

Study eligibility criteria

Included studies had the following features (1): pathological diagnosis of primary OSCC (2); explored a relationship between pre-treatment SII and OSCC prognosis (3); hazard ratios (HRs) with 95% confidence intervals (CIs) can be determined according to the available data (4); the threshold SII is identified; and (5) articles written in the English language. Exclusion criteria were as follows (1): meeting abstracts, reviews, letters, comments, and case reports (2); does not have sufficient or available data (3); contains overlapped patients; and (4) animal studies.

Data collection and quality evaluation

Qualified publications were evaluated by two independent reviewers (JZ, SD), who also extracted data. Any discrepancy was settled through negotiation until a consensus was reached. Data collected included, first author, publication year, study country/region, sample size, age, gender, study center, study design, study period, tumor subsite, TNM stage, treatment, threshold, threshold determination approach, survival outcomes, survival analysis type, follow-up, HRs and 95% CIs. Our primary and secondary outcomes were overall survival (OS) and disease-free survival (DFS), separately. We employed the Newcastle–Ottawa Scale (NOS) for assessing study quality (30). The NOS contains three perspectives, selection (0–4 points), comparability (0–2 points), and outcome assessment (0–3 points), with a total score of 0-9 points. NOS scores ≥ 6 indicate high-quality.

Statistical analysis

Significance of SII in predicting OSCC prognosis was estimated based on combined HRs with 95% CIs. Additionally, I^2 statistics and Cochrane's Q test were utilized to evaluate inter-study heterogeneity. The random-effects model was utilized in the case of obvious heterogeneity (I^2>50%, P<0.10), otherwise, a fixed-effects model was applied. The source of heterogeneity was detected by different factors-stratified subgroup analyses. Correlations of SII with clinicopathological characteristics of OSCC were evaluated through combined odds ratios (ORs) as well as 95% CIs. Sensitivity analysis was used to compare pooled effects, by eliminating one individual study in the sequence and observing any potential changes to the result, repeating the process for each study. We performed Egger's and Begg's tests for assessing publication bias, and conducted statistical analyses using Stata version 12.0 (Stata Corporation, College Station, TX, USA). P-values < 0.05 were defined as statistically significant differences.

Results

Study screening

There were 117 articles obtained initially, among which 69 were retained following the removal of duplicates (Figure 1). Through title- and abstract-selection, 51 articles were then excluded due to irrelevance. Full-text review of the remaining 18 articles was conducted, among which, seven were eliminated for the following reasons, not focused on OSCC (n=3), no survival data provided (n=2), no cut-off value (n=1), and no report on SII (n=1). Ultimately, 11 articles were utilized for the remainder of the analysis, involving a total of 3,464 patients (18–28) (Figure 1, Table 1).

Enrolled study features

Table 1 provides baseline study features (18–28). All included studies were retrospective in nature, published in the English language and had publication years ranging from 2018 to 2022. Four studies were carried out in China (18, 20, 22, 23), two in Taiwan (21, 25), and one each in Turkey (19), Korea (24), Japan (26), Spain (27), and Malaysia (28). Sample sizes ranged from 58-993 (median, 269). Ten articles described single center studies (19–28) and one was a multicenter study (18). Seven studies recruited patients with OSCC (18, 22, 24–28), two recruited oral cavity cancer cases (19, 21), and two involved tongue cancer cases (20, 23). Ten articles described studies involving patients with TNM stage I-IV (18–21, 23–28), whereas one study only included stage III-IV patients (22). Seven studies treated patients with surgery (18, 20, 22–25, 27), three studies used surgery and concurrent chemoradiotherapy (CCRT) (21, 26, 28), and one study only applied radiotherapy (RT) (19). The threshold SII ranged from 204-1,137 (median, 569) in all 11 studies. Seven articles described the threshold through receiver operating characteristic curve (19, 21, 22, 24, 25, 27, 28), three studies applied the X-tile software (18, 20, 23), whereas another one was determined using previous literature (26).

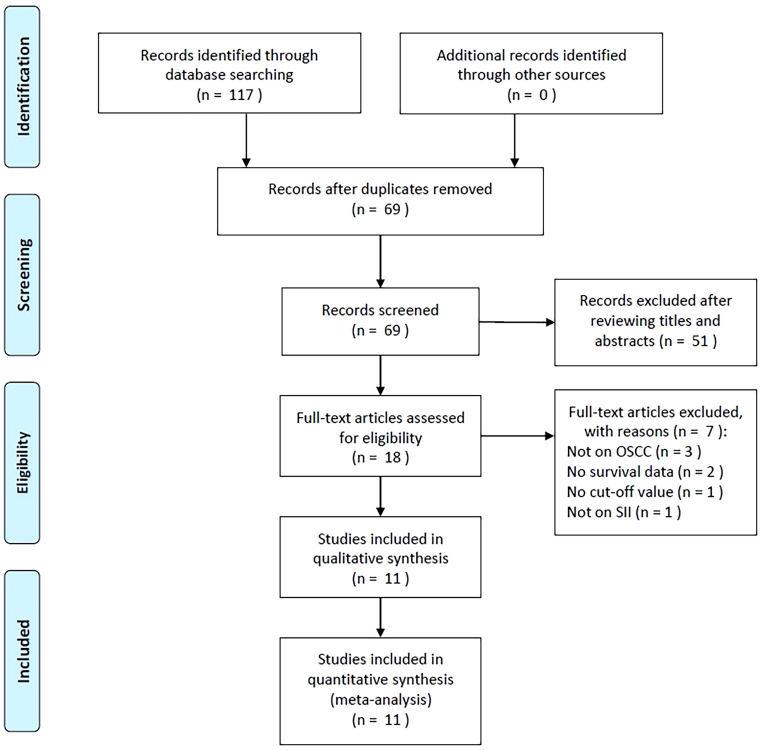

FIGURE 1
The PRISMA flowchart of study selection.

TABLE 1 The baseline characteristics of included studies in this meta-analysis.

Study	Year	Country/ region	Sample size	Age (years) Median (range)	Gender (M/F)	Study center	Study period	Tumor subsite	TNM stage	Treatment	Cut-off value	Cut-off determination	Survival endpoint	Survival analysis	Follow-up (month) Median (range)	NOS score
Diao, P.	2018	China	309	≤60 y: 112 >60 y: 197	171/138	Multicenter	2006-2016	Unspecified OSCC	I-IV	Surgery	484.5	X-tile	OS, DFS	Multivariate	48 (4–134)	9
Erdis, E.	2020	Turkey	58	67 (23–90)	40/18	Single center	2009-2018	Oral cavity	I-IV	RT	954	ROC curve	OS, DFS	Univariate	1-140	8
Lu, Z.	2020	China	120	55 (20–86)	79/41	Single center	2012-2017	Oral tongue	I-IV	Surgery	569	X-tile	OS, DFS	Multivariate	37.5(3-92)	8
Hung, S. P.	2021	Taiwan	993	51	922/71	Single center	2005-2012	Oral cavity	I-IV	Surgery+ RT/CCRT	810.6	ROC curve	OS	Multivariate	105.6	7
Nie, Z.	2021	China	269	62(21-85)	204/65	Single center	2007-2020	Unspecified OSCC	III-IV	Surgery	535.5	ROC curve	OS, DFS	Multivariate	55(2-95)	8
Wei, L. F.	2021	China	172	69(25-88)	96/76	Single center	2008-2019	Oral tongue	I-IV	Surgery	204	X-tile	OS	Univariate	65	7
Cho, U.	2022	Korea	269	55(18-90)	173/96	Single center	2003-2019	Unspecified OSCC	I-IV	Surgery	548.9	ROC curve	DFS	Multivariate	1-150	7
Huang, C. H.	2022	Taiwan	592	54	518/74	Single center	2011-2020	Unspecified OSCC	I-IV	Surgery	459	ROC curve	OS, DFS	Multivariate	100(6-173)	7
Kubota, K.	2022	Japan	183	66(26-93)	103/80	Single center	2005-2017	Unspecified OSCC	I-IV	Surgery+ RT/CCRT	569	Literature	OS, DFS	Univariate	1-150	8
Ruiz-Ranz, M.	2022	Spain	348	62(28-92)	221/127	Single center	1996-2007	Unspecified OSCC	I-IV	Surgery	1137	ROC curve	OS, DFS	Univariate	54(3-280)	7
Zakaria, S. S.	2022	Malaysia	151	59.7	56/95	Single center	2000-2020	Unspecified OSCC	I-IV	Surgery+ RT/CCRT	914	ROC curve	DFS	Multivariate	30(1-217)	8

M, male; F, female; OSCC, oral squamous cell carcinoma; OS, overall survival; DFS, disease-free survival; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; ROC, receiver operating characteristic; NOS, Newcastle-Ottawa Scale.

10.3389/fonc.2023.1303132

Nine articles reported a prognostic effect of SII for OS (18–23, 25–27) and nine mentioned a relationship between SII and DFS (18–20, 22, 24–28) in OSCC. Seven articles mentioned HRs with 95% CIs based on multivariate regression (18, 20–22, 25, 26, 28) and four studies used univariate analyses (19, 23, 24, 27). For all enrolled articles, NOS scores were from 7-9 (median, 8), demonstrating high quality (Table 1).

SII and OS of OSCC

Nine articles, involving 3,044 patients (18–23, 25–27), mentioned a significance of SII to predict OS in OSCC. Due to significant heterogeneity (I^2 = 50.2%, p=0.041), we selected the random-effects model. According to Figure 2 and Table 2, HR=1.85, 95%CI=1.48-2.29, and p<0.001, which indicates that a higher SII was markedly related to the dismal OS of OSCC patients. According to subgroup analyses, sample size, study center, TNM stage, threshold, threshold determination method, and survival analysis type did not affect the significant role of SII to predict OS (p<0.05; Table 2). Moreover, higher SII still significantly predicted poor OS in the following subgroups: in Asian regions (p<0.001), tongue tumor site (p=0.004) or OSCC (p<0.001), and patients who received surgery (p<0.001) or RT (p=0.001) (Table 2).

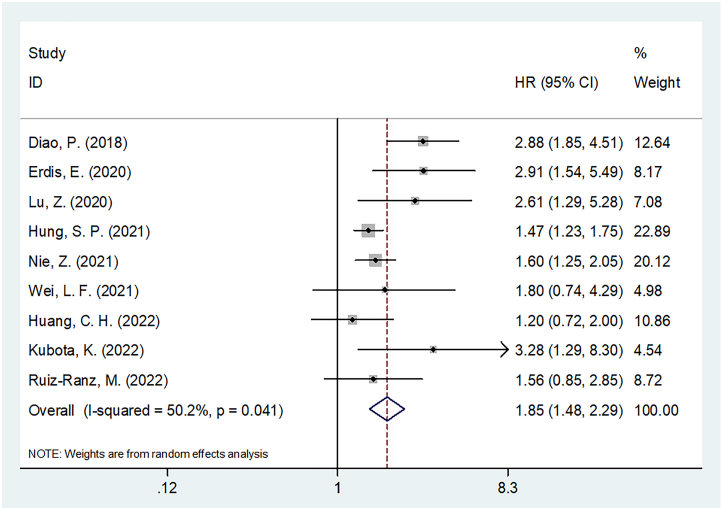

FIGURE 2
Forest plots on prognostic value of SII for overall survival in patients with OSCC.

TABLE 2 The subgroup analysis of the prognostic role of SII for OS in patients with OSCC.

Subgroups	No. of studies	No. of patients	Effects model	HR (95%CI)	p	Heterogeneity I^2(%) Ph	
Total	9	3,044	Random	1.85(1.48-2.29)	<0.001	50.2	0.041
Geographical region							
Asian	8	2,696	Random	1.89(1.49-2.41)	<0.001	56.3	0.025
Non-Asian	1	348	–	1.56(0.85-2.85)	0.153	–	–
Sample size							
<300	5	802	Fixed	1.85(1.51-2.28)	<0.001	29.4	0.225
≥300	4	2,242	Random	1.67(1.18-2.37)	0.004	65.7	0.033
Study center							
Single center	8	2,735	Fixed	1.59(1.40-1.81)	<0.001	28.1	0.204
Multicenter	1	309	–	2.88(1.85-4.51)	<0.001	–	–
Tumor subsite							
Oral cavity	2	1,051	Random	1.92(1.00-3.71)	0.051	75.7	0.042
Oral tongue	2	292	Fixed	2.26(1.31-3.91)	0.004	0	0.516

(Continued)

TABLE 2 Continued

Subgroups	No. of studies	No. of patients	Effects model	HR (95%CI)	p	Heterogeneity I^2(%) Ph	
Unspecified OSCC	5	1,701	Random	1.84(1.32-2.56)	<0.001	57.0	0.054
TNM stage							
I-IV	8	2,775	Random	1.96(1.48-2.60)	<0.001	56.1	0.026
III-IV	1	269	–	1.60(1.25-2.05)	<0.001	–	–
Treatment							
Surgery	6	1,810	Fixed	1.76(1.47-2.10)	<0.001	43.3	0.117
RT	1	58	–	2.91(1.54-5.49)	0.001	–	–
Surgery+ RT/CCRT	2	1,176	Random	1.92(0.91-4.03)	0.086	63.9	0.096
Cut-off value							
<569	4	1,374	Random	1.77(1.23-2.55)	0.002	59.4	0.060
≥569	5	1,670	Random	2.00(1.40-2.85)	<0.001	52.6	0.077
Cut-off selection							
ROC curve	5	2,260	Fixed	1.53(1.34-1.75)	<0.001	22.0	0.275
X-tile	3	601	Fixed	2.62(1.85-3.70)	<0.001	0	0.644
Literature	1	183	–	3.28(1.29-8.32)	0.012	–	–
Survival analysis							
Univariate	4	761	Fixed	2.19(1.52-3.14)	<0.001	0	0.408
Multivariate	5	2,283	Random	1.73(1.34-2.24)	<0.001	62.6	0.030

SII, systemic immune-inflammation index; OS, overall survival; OSCC, oral squamous cell carcinoma; ROC, receiver operating characteristic; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

SII and DFS in OSCC

Altogether, nine articles, involving 2,299 patients (18–20, 22, 24–28), mentioned the prognostic effect of SII for DFS in OSCC. Based on our pooled results, higher SII was significantly related to inferior DFS in OSCC (HR=1.77, 95%CI=1.20-2.61, p=0.004) (Figure 3; Table 3). According to subgroup analyses, high SII significantly predicted DFS, and remained unaffected by the study center or TNM stage (p<0.05; Table 3). Additionally, elevated SII was markedly related to dismal DFS for the following subgroups: in Asian regions (p=0.002), sample size < 300 (p=0.001), multicenter studies (p<0.001), oral cavity tumor site (p=0.001) or OSCC (p=0.026), patients who received RT (p=0.001) or surgery + CCRT (p<0.001), SII threshold ≥ 569 (p=0.004), threshold determined by X-tile (p=0.022) or literature (p=0.002), and multivariate analysis (p=0.034) (Table 3).

Association of SII with clinicopathological characteristics of OSCC

Three studies, encompassing 1,382 patients (20, 21, 24), presented data explaining a relationship of SII with OSCC clinicopathological features. According to the combined results, shown in Table 4, Figures 4 and 5, higher SII was remarkably related to stages T3-T4 (OR=2.47, 95%CI=1.40-4.37, p=0.002), TNM stages III-IV (OR=2.29, 95%CI=1.53-3.44, p<0.001), and low differentiation (OR=1.74, 95%CI=1.25-2.43, p=0.001). However, SII did not show any significant correlation with age (OR=0.93, 95%CI=0.68-1.25, p=0.617), gender (OR=0.47, 95%CI=0.08-2.73, p=0.402), tumor site (OR=0.79, 95%CI=0.62-1.01, p=0.056), lymph node metastasis (OR=1.03, 95%CI=0.63-1.69, p=0.906), invasion depth (OR=1.46, 95% CI=0.43-4.93, p=0.545), vascular invasion (OR=0.82, 95% CI=0.47-1.46, p=0.506), or perineural invasion (OR=1.14, 95%CI=0.89-1.45, p=0.297) (Table 4, Figures 4, 5).

Sensitivity analysis

Every article was removed individually during each sensitivity analysis. Results were recalculated each time, based on the remaining studies' OS and DFS. According to Figure 6, in the overall analysis of OS and DFS, there was no significant difference after eliminating each work, suggesting the reliability of our combined results.

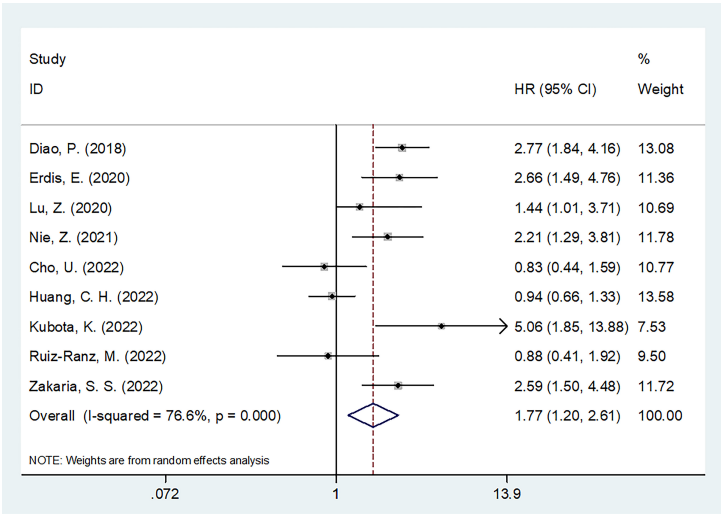

FIGURE 3
Forest plots on prognostic value of SII for disease-free survival in patients with OSCC.

TABLE 3 The subgroup analysis of the prognostic role of SII for DFS in patients with OSCC.

Subgroups	No. of studies	No. of patients	Effects model	HR (95%CI)	p	Heterogeneity I^2(%) Ph	
Total	9	2,299	Random	1.77(1.20-2.61)	0.004	76.6	<0.001
Geographical region							
Asian	8	1,951	Random	1.90(1.26-2.86)	0.002	77.7	<0.001
Non-Asian	1	348	–	0.88(0.41-1.92)	0.753	–	–
Sample size							
<300	6	1,050	Random	2.03(1.33-3.11)	0.001	62.6	0.020
≥300	3	1,249	Random	1.35(0.61-3.01)	0.459	88.3	<0.001
Study center							
Single center	8	1,990	Random	1.65(1.09-2.50)	0.017	74.1	<0.001
Multicenter	1	309	–	2.77(1.84-4.16)	<0.001	–	–
Tumor subsite							
Oral cavity	1	58	–	2.66(1.49-4.76)	0.001	–	–
Oral tongue	1	120	–	1.44(0.75-2.76)	0.273	–	–
Unspecified OSCC	7	2,121	Random	1.72(1.07-2.77)	0.026	80.9	<0.001
TNM stage							
I-IV	8	2,030	Random	1.72(1.11-2.66)	0.015	78.8	<0.001
III-IV	1	269	–	2.21(1.29-3.80)	0.004	–	–
Treatment							
Surgery	6	1,907	Random	1.38(0.88-2.18)	0.161	77.6	<0.001
RT	1	58	–	2.66(1.49-4.76)	0.001	–	–
Surgery+ RT/CCRT	2	334	Fixed	3.02(1.87-4.88)	<0.001	23.4	0.253
Cut-off value							

(Continued)

TABLE 3 Continued

Subgroups	No. of studies	No. of patients	Effects model	HR (95%CI)	p	Heterogeneity I^2(%) Ph	
<569	4	1,439	Random	1.49(0.81-2.76)	0.201	85.6	<0.001
≥569	5	860	Random	2.07(1.27-3.39)	0.004	60.9	0.037
Cut-off selection							
ROC curve	6	1,687	Random	1.49(0.94-2.37)	0.087	76.4	0.001
X-tile	2	429	Random	2.10(1.12-3.95)	0.022	62.4	0.095
Literature	1	183	–	5.06(1.85-13.86)	0.002	–	–
Survival analysis							
Univariate	3	589	Random	2.21(0.89-5.51)	0.089	76.1	0.015
Multivariate	6	1,710	Random	1.63(1.04-2.56)	0.034	79.4	<0.001

SII, systemic immune-inflammation index; DFS, disease-free survival; OSCC, oral squamous cell carcinoma; ROC, receiver operating characteristic; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

Publication bias

Begg's funnel plots and the Egger's test were conducted to assess possible publication bias. The funnel plots observed in Figure 7 show symmetry, suggesting no significant publication bias for OS (p=0.175 and p=0.082 upon Begg's and Egger's tests, separately) or DFS (p=1 and p=0.542 upon Begg's and Egger's tests, separately).

Discussion

Previously, the effect of SII to predict OSCC prognosis has been explored, but no consistent findings have been reported (18–28). This work combined results from 11 articles involving 3,464 patients. According to our results, an elevated SII was remarkably related to dismal OS and inferior DFS of OSCC. Moreover, SII had a stable role when predicting prognosis, as examined by sensitivity, subgroup, and publication basis analyses. Higher SII was also evidently related to T3-T4, TNM III-IV, and poor tumor differentiation. Taken together, a higher SII significantly predicted the short- and long-term survival of OSCC, which was also dramatically related to tumor metastasis and poor differentiation. To our knowledge, this is the first meta-analysis investigating whether SII could be used to predict OSCC prognosis.

To understand the biological mechanism behind SII's prognostic value, it is necessary to understand the function of neutrophils, platelets, and lymphocytes. First, neutrophils release inflammatory mediators such as neutrophil elastase, interleukin-8 (IL-8) and matrix metalloproteinase-9 (MMP-9)

TABLE 4 The association between SII and clinicopathological features in patients with OSCC.

Variables	No. of studies	No. of patients	Effects model	OR (95%CI)	p	Heterogeneity I^2(%) Ph	
Age (year) (≥55 vs <55)	3	1,382	Fixed	0.93(0.68-1.25)	0.617	25.9	0.259
Gender (male vs female)	3	1,382	Random	0.47(0.08-2.73)	0.402	95.7	<0.001
T stage (T3-T4 vs T1-T2)	3	1,382	Random	2.47(1.40-4.37)	0.002	64.5	0.060
LN metastasis (yes vs no)	3	1,382	Random	1.03(0.63-1.69)	0.906	66.5	0.050
TNM stage (III-IV vs I-II)	3	1,382	Fixed	2.29(1.53-3.44)	<0.001	0	0.664
Depth of invasion (>1cm vs ≤1cm)	3	1,382	Random	1.46(0.43-4.93)	0.545	91.8	<0.001
Tumor differentiation (poor vs well/moderate)	2	1,113	Fixed	1.74(1.25-2.43)	0.001	40.5	0.195
Vascular invasion (yes vs no)	2	1,262	Fixed	0.82(0.47-1.46)	0.506	0	0.589
Perineural invasion (yes vs no)	2	1,262	Fixed	1.14(0.89-1.45)	0.297	46.2	0.173
Tumor site (tongue vs others)	2	1,262	Fixed	0.79(0.62-1.01)	0.056	0	0.795

SII, systemic immune-inflammation index; OS, overall survival; OSCC, oral squamous cell carcinoma; LN, lymph node; TNM, tumor (T), node (N), and metastasis (M).

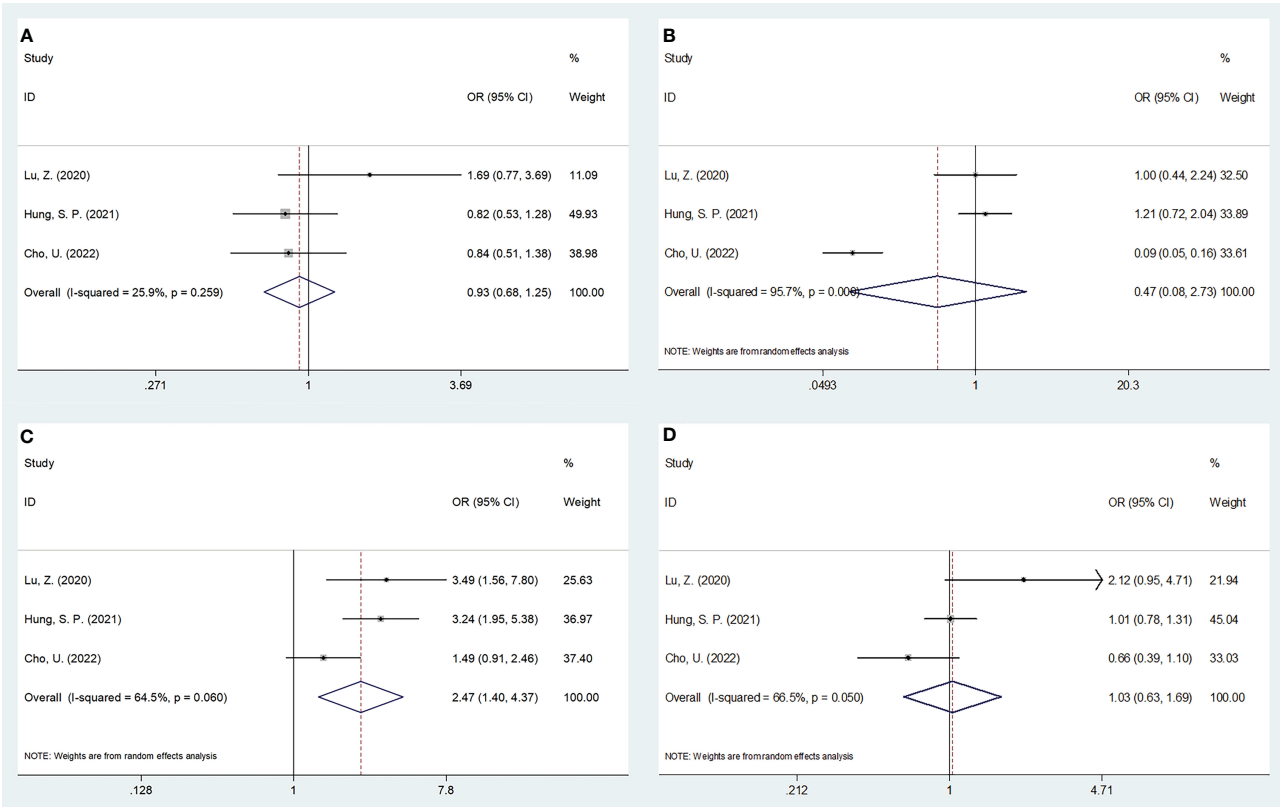

FIGURE 4
Forest plots on the association between SII and clinicopathological features in OSCC. **(A)** age (year) (≥55 vs <55); **(B)** gender (male vs female); **(C)** T stage (T3-T4 vs T1-T2); and **(D)** lymph node metastasis (yes vs no).

which enhance tumor cell growth, migration and invasion (31). Increased neutrophil counts can also produce reactive oxygen species, nitric oxide, and arginase, resulting in disordered T cell activation (32). Consequently, the body loses its ability to target tumor cells, indirectly contributing to tumor progression (33). Second, platelets can protect cancer cells from natural killer cells and tumor necrosis factor-α (TNF-α) by using glycoprotein (GP) receptors and tumor cell integrin α vβ-dependent pathway (34). Platelets also induce epithelial-mesenchymal transition and support transendothelial migration in circulating tumor cells, ultimately protecting tumor cells from immune destruction and promoting distant metastasis (35, 36). Third, lymphocytes are responsible for the adaptive immune response and participate in cancer immunosurveillance and immunoediting. Tumor-infiltrating lymphocytes promote tumor cell apoptosis and remove dead cells by way of humoral and cellular immunity, and these processes are necessary for the host's immune defense and surveillance (37). Therefore, SII has a biological rationale for its role in predicting OSCC prognosis. Notably, a recent single study by Yoshimura et al. investigated the prognostic effect of multiple inflammation-nutrition parameters including NLR, PLR, LMR, CRP-albumin ratio (CAR), Glasgow prognostic score (GPS), modified GPS (mGPS), prognostic nutritional index (PNI), controlling nutrition status (CONUT), and modified CONUT (mCONUT) in patients with OSCC receiving surgery (38). They found that a low PNI was associated with shorter OS and DFS in patients with OSCC through multivariate analysis (38). Although that study did not include SII for analysis in OSCC, their results were important to investigate mechanisms (38). In peripheral blood analyses, inflammation-related markers were mainly composed of upregulated factors (neutrophils, platelets, monocytes, and CRP) and downregulated factors (lymphocytes, albumin, total cholesterol, and hemoglobin). Different combinations of these factors became prognostic indicators and the prognostic parameters were more stable than using a single element.

Many recent studies have also reported that SII could be used to predict the prognosis of different cancer types by conducting meta-analyses (39–43). A meta-analysis on 2,101 patients conducted by Zeng et al. found that elevated pretreatment SII was markedly associated with poor OS and progression-free survival (PFS) in esophageal squamous cell carcinoma (39). According to Wang et al., SII could independently predict OS and PFS of nasopharyngeal carcinoma patients through a meta-analysis that included nine studies (40). In the meta-analysis, which included 833 patients conducted by Salazar-Valdivia et al., indicated that high SII values are related to poor OS and PFS of testicular cancer (41). Moreover, a recent meta-analysis, including 1,426

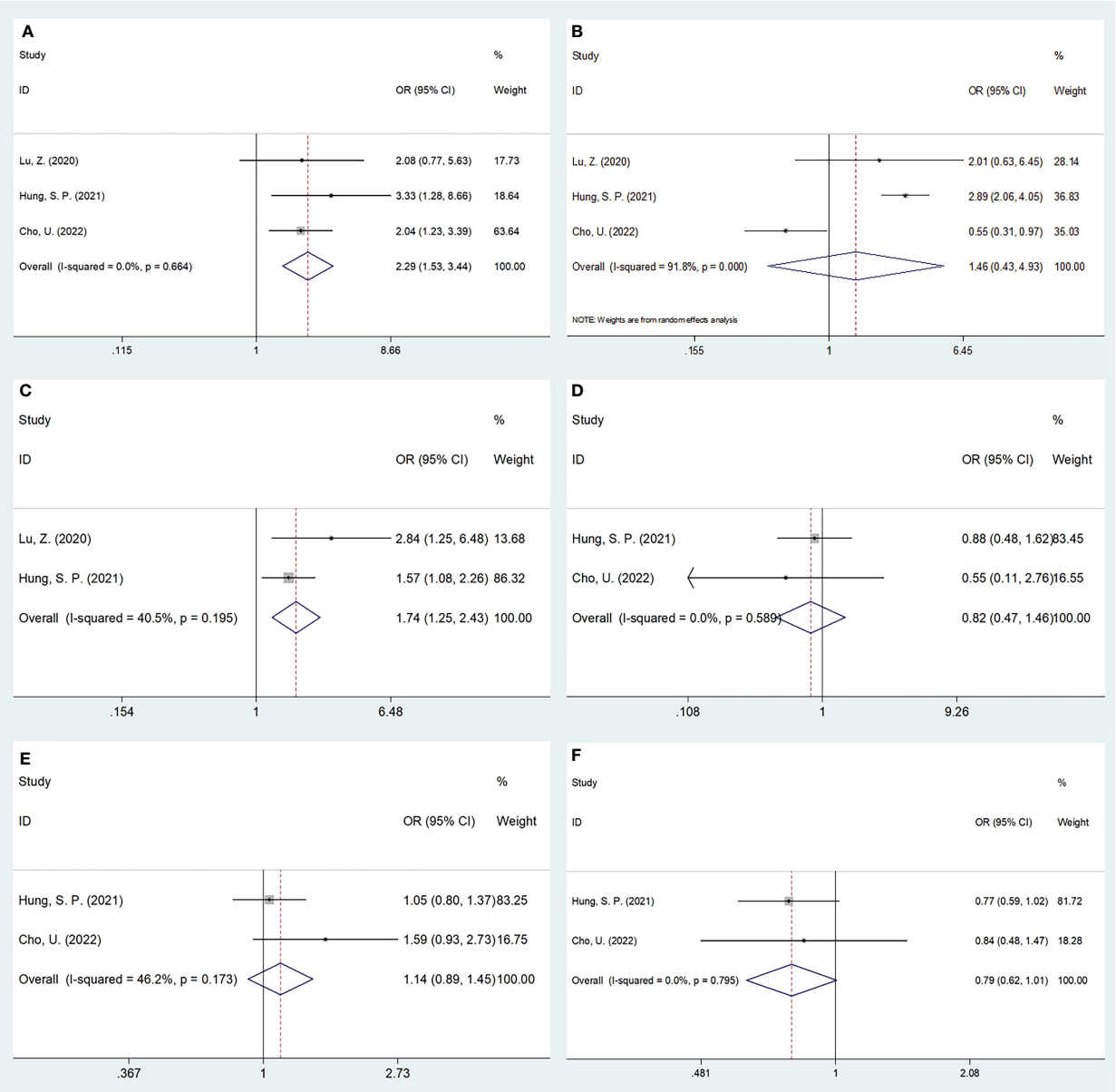

FIGURE 5
Forest plots on the association between SII and clinicopathological features in OSCC. **(A)** TNM stage (III-IV vs I-II); **(B)** depth of invasion (>1cm vs ≤1cm); **(C)** tumor differentiation (poor vs well/moderate); **(D)** vascular invasion (yes vs no); **(E)** perineural invasion (yes vs no); and **(F)** tumor site (tongue vs others).

patients, indicated that higher SII was significantly related to dismal OS and PFS in glioma patients (42). According to Zhang et al., a higher SII is linked dramatically to dismal OS and worse PFS/biochemical recurrence-free survival (bRFS) of prostate cancer in their meta-analysis enrolling 8,133 patients (43). The results of this SII focused meta-analysis mostly conforms to those obtained in additional cancer types.

There were some limitations to be noted. First, every enrolled article had a retrospective design, which could introduce selection bias. Second, many enrolled articles were conducted in Asia (10 out of 11). Although the study region was not restricted, all included studies were published in English. Therefore, the findings of this work may be more applicable in Asian OSCC populations. Third, threshold SII was not uniform across the included studies, so there could be differences to each conclusion. Due to these limitations, more multi-regional prospective trials are still necessary to further validate the utility of SII when predicting the prognosis of OSCC patients.

Conclusions

In conclusion, this meta-analysis demonstrates that higher SIIs are significantly related to dismal OS and DFS in OSCC.

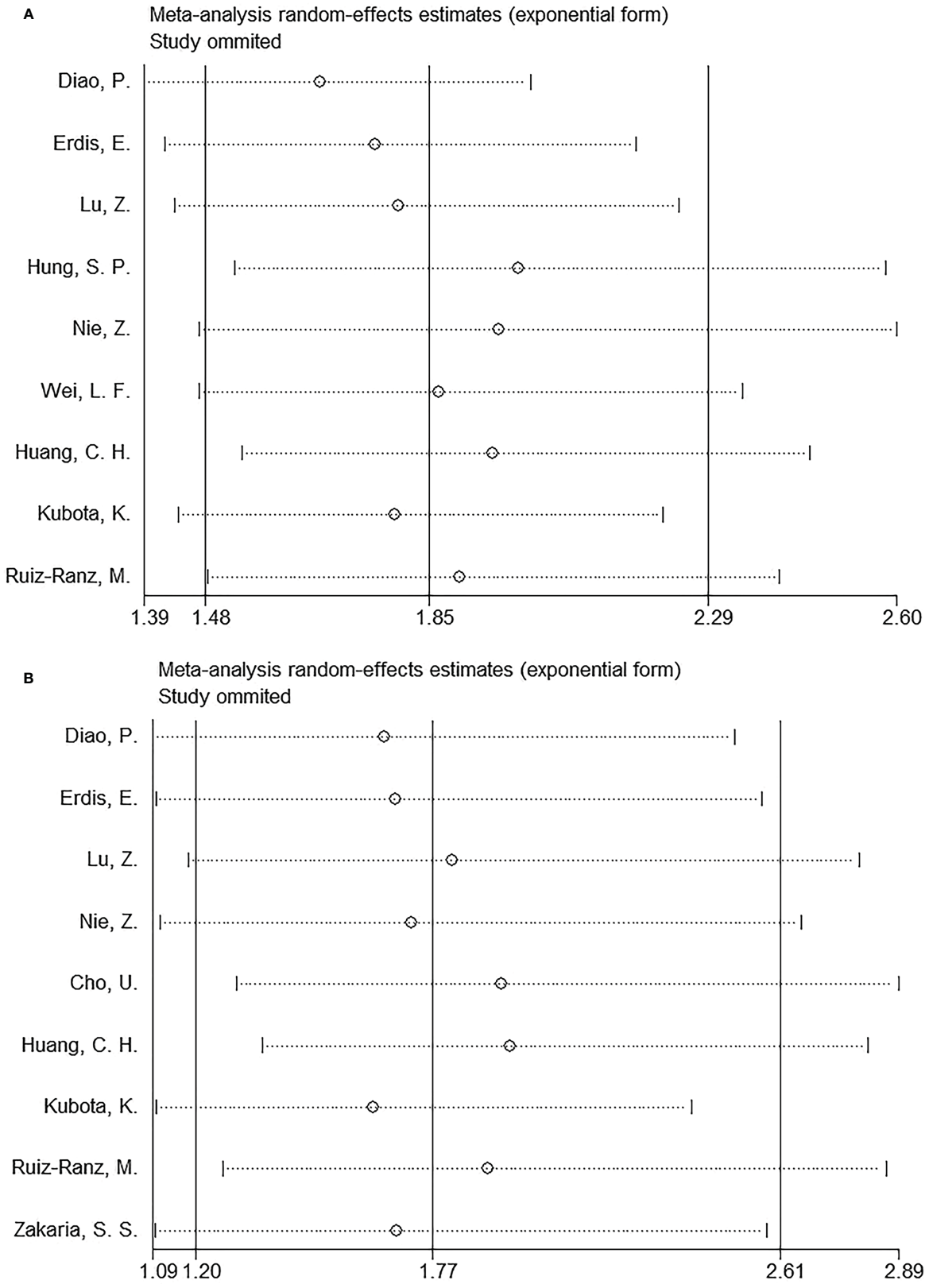

FIGURE 6
Sensitivity analysis. **(A)** OS; and **(B)** DFS.

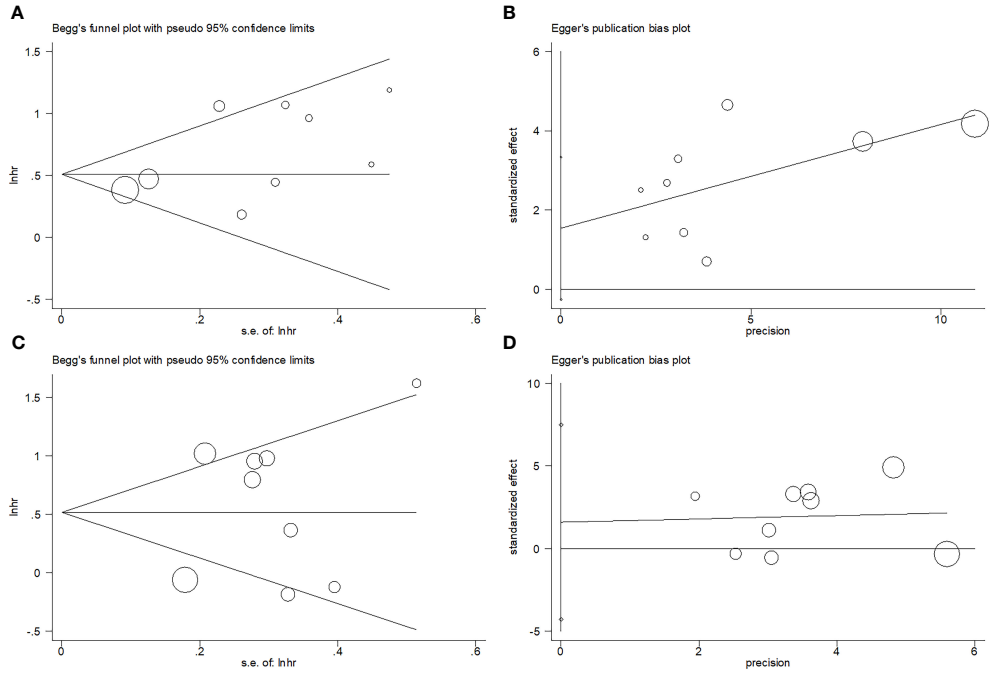

FIGURE 7
Publication bias test. **(A)** Begg's test for OS, p=0.175; **(B)** Egger's test for OS, p=0.082; **(C)** Begg's test for DFS, p=1; and **(D)** Egger's test for DFS, p=0.542.

Additionally, high SIIs are markedly related to advanced tumor stages and poor differentiation in OSCC. SII could be a potential and important biomarker for clinical management and prognosis prediction of OSCC patients.

Data availability statement

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

Author contributions

JZ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. SD: Conceptualization, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – review & editing.

Funding

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

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1303132/full#supplementary-material

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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 23 January 2024
DOI 10.3389/fonc.2023.1221616

OPEN ACCESS

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RECEIVED 12 May 2023
ACCEPTED 31 December 2023
PUBLISHED 23 January 2024

CITATION
Chung C-S, Wu C-Y, Lin Y-H, Lo W-C, Cheng P-C, Hsu W-L and Liao L-J (2024) Screening and surveillance of esophageal cancer by magnifying endoscopy with narrow band imaging improves the survival of hypopharyngeal cancer patients.
Front. Oncol. 13:1221616.
doi: 10.3389/fonc.2023.1221616

Screening and surveillance of esophageal cancer by magnifying endoscopy with narrow band imaging improves the survival of hypopharyngeal cancer patients

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Introduction: Patients with head and neck cancer may develop a second primary neoplasm (SPN) of the esophagus due to field cancerization. This study investigated the impacts of esophageal cancer screening using magnifying endoscopy with narrow-band imaging (ME-NBI) on the outcomes of hypopharyngeal cancer patients.

Methods: Patients with hypopharyngeal cancer diagnosed from 2008 to 2021 in a tertiary hospital were reviewed retrospectively. Screening and surveillance using ME-NBI examination of the esophagus were divided into three patterns: (1) ME-NBI never performed or more than 6 months after diagnosis of index primary hypopharyngeal cancer, (2) ME-NBI within 6 months only, and (3) ME-NBI within 6 months and regular surveillance.

Results: A total of 261 were reviewed and 21 (8%) patients were in stage I, 20 (8%) in stage II, 27 (10%) in stage III, 116 (44%) in stage IVA, 65 (25%) in stage IVB, and 12 (5%) in stage IVC. Sixty-seven (26%) patients had SPN (50 esophagus, 10 oral cavity, 3 oropharynx, 2 nasopharynx, 1 larynx and 1 lung). Among esophageal SPN, 35 (70%) and 15 (30%) patients developed synchronous and metachronous neoplasia, respectively. In multivariate Cox regression analysis, advanced stages III and IV (compared with stages I and II, HR: 1.86, 1.18-2.95, p=0.008), ME-NBI examination of the esophagus received within 6 months and regular surveillance (HR: 0.53, 0.36-0.78, p=0.001) were independent factors affecting the overall survival of patients with hypopharyngeal cancer.

Discussion: Our findings demonstrated that screening and surveillance of esophageal SPN by ME-NBI improves the survival of patients with hypopharyngeal cancer.

KEYWORDS

narrow band imaging (NBI), screening, esophageal cancer, head and neck (H&N) cancer, second primary tumors (SPTs)

Introduction

Currently, head and neck cancer (HNC) and esophageal cancer are among the top ten causes of cancer death (1, 2). Most of the deaths from HNC are due to disease recurrence and progression. HNC is a malignancy that develops in the oral cavity and pharynx, including the nasopharynx, oropharynx, hypopharynx, and pharynx or larynx. Its occurrence is closely related to carcinogen consumption, such as cigarette smoking, alcohol drinking, betel quid chewing and human papillomavirus exposure (2). Chewing betel quid is part of the culture in some Asian countries, and the incidence rates of HNC are higher in these regions (3). Compared with other HNCs, hypopharyngeal cancer is relatively rare, accounting for approximately 3% of all HNCs (4–6). Unfortunately, hypopharyngeal cancer has the worst prognosis, with a reported 5-year survival rate of approximately 30-35% (4).

Anatomically, the hypopharynx is defined by its subregions, including the posterior hypopharyngeal wall, the lateral pyriform sinus, and the postcricoid area, which is an entrance to the esophagus. Hypopharyngeal cancer often presents at an advanced symptomatic stage and requires aggressive treatment. This disease can greatly affect the patient's quality of life (5). Despite medical advances in treatment, the overall oncological prognosis of hypopharyngeal cancer remains relatively poor (6). One of the most important factors for this dismal malignancy is the occurrence of a second primary neoplasm (SPN) of the head and neck region, lung and esophagus (7, 8). The prevalence of SPN was approximately 12%, with the most common site being the head and neck region, followed by the lungs and esophagus in a meta-analysis of 51,454 HNC patients, and 13% of them were reported to have high-grade dysplasia or invasive carcinoma of the esophagus (9). A nationwide cohort study of 9,996 SPNs recorded among 93,891 HNC patients demonstrated the worst prognosis with SPNs of the esophagus and lung, with a cure rate of only 11% (10). Additionally, SPNs of the esophagus may occur synchronously and metachronously. The 5- and 10-year cumulative incidence rates of metachronous esophageal cancer have been reported as 1.4% and 2.7%, respectively, among HNC patients with a negative index endoscopic finding initially (11). Therefore, it is presumed that the strategy of screening, surveillance and treatment of esophageal SPN is associated with the prognosis of patients with hypopharyngeal cancer.

The aim of this study was to review the treatment outcomes as well as to understand the impacts of different strategies of endoscopic screening for esophageal SPN on the survival of patients with hypopharyngeal cancer.

Materials and methods

Study design

This was a retrospective study that reviewed the medical records of patients with hypopharyngeal cancer from 2008 to 2021. The study protocol was approved by the ethical review committee of Far Eastern Memorial Hospital (IRB No.: 111165-E), and the informed consent form was waived by the review committee. All patients with hypopharyngeal carcinoma who were diagnosed and treated were included for review. Demographic data on age, sex, primary site and TNM stage according to the American Joint Committee on Cancer, AJCC 8th edition of index HNC, treatment method and the pattern of endoscopic examination of the esophagus were reviewed. Whether magnifying endoscopy with narrow-band imaging (ME-NBI) examination of the esophagus was performed or not was recorded, and if patients underwent ME-NBI, they were divided into three groups: (1) ME-NBI within half a year only, (2) ME-NBI performed more than half a year, and (3) ME-NBI within half a year and further regular surveillance. Finally, the overall survival (OS) time of the patients was calculated and defined as the time from diagnosis of hypopharyngeal cancer to the last follow-up time or death time.

Endoscopic examination of esophageal SPNs

Endoscopic evaluation of the esophagus was performed by gastroscopes with magnifying or near-focus function under the NBI system. Any brownish color change in the esophageal mucosa under NBI was further scrutinized for morphological changes in

intraepithelial capillary loops (IPCLs) by magnification. Abnormal mucosa was defined as type B1, B2 and B3 according to the Japanese Esophageal Society classification IPCL by means of ME-NBI examination (12). Biopsies were taken for endoscopically suspicious esophageal neoplasms for histopathological evaluation.

Statistical analysis

All statistical analyses were performed using STATA, version 14.0. Categorical variables are expressed as numbers (percentages), continuous variables are expressed as the mean values (± standard deviation; SD), and follow-up time is expressed as medians (interquartile range; IQR). We used Kaplan–Meier curves to understand the survival situation between different risk factor groups and finally used the log-rank test to compare whether the survival curves of different groups were statistically significant. We further used Cox regression analysis to estimate the impact of various risk factors on survival and calculated hazard ratios (hazard ratios, HRs) and 95% confidence intervals (95% confidence intervals, CIs). A p value <0.05 indicated statistical significance.

Results

A total of 3,387 patients with HNC were extracted from the database. Among them, 324 patients were diagnosed with hypopharyngeal cancer, and 63 patients were excluded due to a lack of data on the treatment course. Finally, 261 patients with hypopharyngeal cancer were included for analysis (Figure 1). Demographic data of the enrolled subjects are shown in Table 1. There were 252 (97%) males and 9 (3%) females with a mean age (± SD) of 63.2 (± 10.4) years. Habits of cigarette smoking, alcohol drinking, and betel nut chewing were as follows: 190 (73%) patients with smoking habits, 21 (8%) without smoking habits and 50 (19%) of unknown; 158 (61%) patients with alcohol drinking habits, 53 (20%) without drinking habits and 50 (19%) of unknown; 123 (47%) patients with betel nut chewing habits, 88 (34%) without chewing habits and 50 (19%) of unknown. For the subsites of index HNC, the pyriform sinus was the most common site with 185 (71%) patients, followed by the posterior pharyngeal wall with 41 (16%) patients and the postcricoid area with 12 (5%) patients. Another 16 (6%) patients had tumors covered on the pyriform sinus and posterior pharyngeal wall, 4 (1%) patients with tumors covered on the pyriform sinus and postcricoid area and 3 (1%) patients with tumors covered on the pyriform sinus and posterior pharyngeal wall and postcricoid area. The distribution of cancer stages was as follows: 21 (8%) patients diagnosed at stage I, 20 (8%) at stage II, 27 (10%) at stage III, 116 (44%) at stage IVA, 65 (25%) at stage IV B and 12 (5%) at stage IVC.

A total of 67 (26%) patients were diagnosed with SPN (Table 1), of which 45 (67%) were diagnosed with SPN within half a year and 22 (33%) more than half a year after the diagnosis of the index primary hypopharyngeal cancer. Fifty (75%) patients had SPNs in the esophagus. Among them, 33 (66%) were squamous cell carcinoma (SCC), and 17 (34%) were high-grade intraepithelial neoplasia (HGIN). Other SPN sites were in the oral cavity (10 (15%) patients), oropharynx [3 (4%)], and nasopharynx (2), one with laryngeal cancer and one with lung cancer.

Regarding the location of esophageal SPNs (Table 2), the majority (66%) were located in the middle part of the esophagus, whereas 14 (28%) patients had SPNs located in the upper esophagus and 3 (6%) had SPNs located in the lower part. The stages of esophageal cancer were 14 (43%) at stage I (including HGIN), 4 (12%) at stage II, 10 (30%) at stage III and 5 (15%) at stage IV. Among these esophageal cancers, 35 in 50 patients (70%) were synchronous, and the stage distribution was as follows: 13 (36%) patients at stage I, 3 (9%) at stage II, 7 (20%) at stage III, 3 (9%) at stage IV and 9 (26%) with HGIN. Fifteen (30%) patients had metachronous esophageal SPNs, and one (7%) patient was at stage I, one (7%) patient was at stage II, 3 (20%) were at stage III, 2 (13%) were at stage IV and 8 (53%) had HGIN.

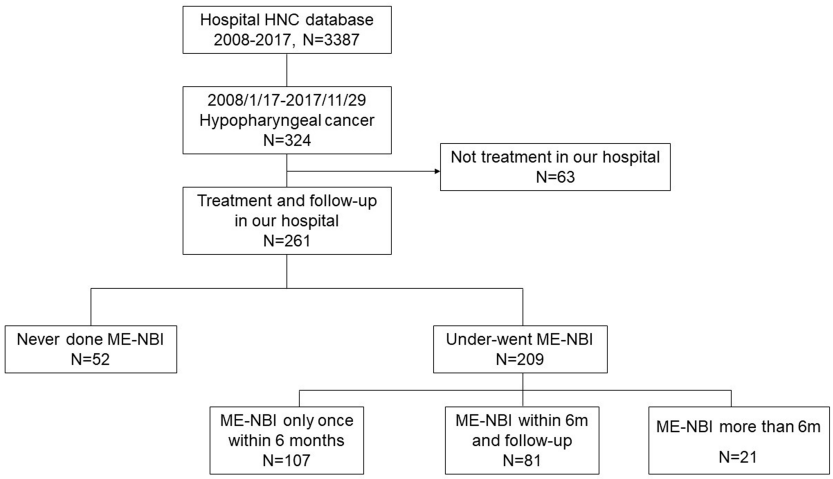

FIGURE 1
Study flow diagram.

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TABLE 1 Demographic data of enrolled subjects with hypopharyngeal cancer (n=261).

Variables		Number (%)/mean ± SD/ median (IQR)
Gender	Male	252 (97%)
	Female	9 (3%)
Age		63.2 ± 10.4 (40-97)
Cigarette smoking	Yes	190 (73%)
	None	21 (8%)
	Unknown	50 (19%)
Alcohol drinking	Yes	158 (61%)
	None	53 (20%)
	Unknown	50 (19%)
Betel nuts chewing	Yes	123 (47%)
	None	88 (34%)
	Unknown	50 (19%)
Primary site	Pyriform sinus	185 (71%)
	Posterior pharyngeal wall	41 (16%)
	Post-cricoid area	12 (5%)
	Pyriform sinus、posterior pharyngeal wall	16 (6%)
	Pyriform sinus、post-cricoid area	4 (1%)
	Pyriform sinus、posterior pharyngeal wall、post-cricoid area	3 (1%)
C-Stage (AJCC 8th)	I	21 (8%)
	II	20 (8%)
	III	27 (10%)
	IVA	116 (44%)
	IVB	65 (25%)
	IVC	12 (5%)
SPN development	Yes	67 (26%)
	Synchronous	45 (67%)
	Metachronous	22 (33%)
SPN site	Esophagus	50 (75%) (SCC 33 (66%), HGIN 17 (34%))
	Oral cavity	10 (15%)
	Oropharynx	3 (4%)
	NPC	2 (3%)
	Larynx	1 (1%)
	Lung	1 (1%)
Treatment of primary HNC	CCRT alone	209 (80%)
	Surgery + CCRT	23 (8%)
	CT alone	14 (5%)
	RT alone	10 (4%)
	Surgery + CT	4 (2%)
	Surgery alone	1 (1%)

AJCC, The American Joint Committee on Cancer; CCRT, concurrent chemoradiotherapy; CT, chemotherapy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HGIN, high-grade intraepithelial neoplasia; HNC, head and neck cancer; IQR, interquartile range; ME-NBI, magnifying endoscopy with narrow-band imaging; NPC, nasopharyngeal cancer; RT, radiotherapy; SD, standard deviation; SPN, second primary neoplasm.

The treatment strategy for primary HNC included radiotherapy combined with chemotherapy (CCRT) in 209 (80%) patients, followed by surgery with CCRT in 23 (8%) patients, chemotherapy alone in 14 (5%) patients, radiotherapy alone in 10 (4%) patients, surgery and chemotherapy in 4 (2%) patients, and surgery alone in one patient. Surgical procedures included total laryngectomy or partial laryngectomy combined with total or partial pharyngectomy. Regarding the treatment of esophageal SPN, 23 (46%) patients underwent CCRT, 13 (26%) underwent endoscopic submucosal dissection (ESD), 4 (8%) refused treatment, 3 (6%) underwent esophagectomy, 3 (6%) underwent chemotherapy alone, 1 (2%) underwent endoscopic mucosal resection (EMR), 1 (2%) did not undergo treatment due to mortality, 1 (2%) underwent endoscopic radiofrequency ablation (RFA) and 1 (2%) underwent endoscopic argon plasma coagulation (APC).

A total of 209 (80%) patients underwent ME-NBI examination, of which 107 (41%) received ME-NBI screening within half a year after diagnosis, 21 (8%) received ME-NBI screening more than half a year after diagnosis, and 81 (31%) patients received ME-NBI screening within half a year after diagnosis and further regular surveillance. The median (IQR) follow-up period was 1.6 (2.9) years.

The results of univariate and multivariate Cox regression analyses of overall survival (OS) are shown in Table 3. Cancer stage was associated with OS by univariate analyses (III+IV stage compared with I+II stage, hazard ratio (HR): 1.78, 95% confidence interval (CI) 1.13-2.80, p=0.014). The Kaplan–Meier diagram and log-rank test are shown in Figure 2. The univariate Cox regression analysis showed that patients with advanced cancer had poorer survival (p=0.014, Table 3, Figure 2), while patients who received ME-NBI (p=0.003) showed better OS (Table 3, Figure 3A). By multivariate analysis, after adjusting for confounders such as sex and age, we found that patients with advanced cancer stage III & IV (compared stage I&II, HR: 1.86, 95% CI 1.18-2.95, p=0.008) had

10.3389/fonc.2023.1221616

TABLE 2 Staging, treatment and surveillance of esophageal SPN.

Variables		Number (%) / mean ± SD/ median (IQR)
Esophageal SPN location	Upper	14 (28%)
	Middle	33 (66%)
	Lower	3 (6%)
Esophageal SCC-T	1	14 (42%)
	2	6 (18%)
	3	10 (30%)
	4	3 (10%)
Esophageal SCC-N	0	20 (61%)
	1	7 (21%)
	2	6 (18%)
Esophageal SCC-M	0	32 (97%)
	1	1 (3%)
Esophageal SPN C-stage	I	14 (43%)
	II	4 (12%)
	III	10 (30%)
	IV	5 (15%)
Esophageal SPN Synchronous-T	**Synchronous**	**35 (70%)**
	1	13 (50%)
	2	5 (19%)
	3	5 (19%)
	4	3 (12%)
Synchronous-N	0	19 (73%)
	1	3 (12%)
	2	4 (15%)
Synchronous-M	0	25 (96%)
	1	1 (4%)
C-Stage (AJCC 8th)	I	13 (36%)
	II	3 (9%)
	III	7 (20%)
	IV	3 (9%)
	HGIN	9 (26%)
Metachronous-T	**Metachronous**	**15 (30%)**
	1	1 (14%)
	2	1 (14%)
	3	5 (72%)
	4	0 (0%)
Metachronous-N	0	1 (14%)
	1	4 (57%)
	2	2 (29%)
Metachronous-M	0	7 (100%)
	1	0 (0%)
C-Stage (AJCC 8th)	I	1 (7%)
	II	1 (7%)
	III	3 (20%)
	IV	2 (13%)
	HGIN	8 (53%)
Treatment of esophageal SPN	CCRT	23 (46%)
	ESD	13 (26%)
	Follow-up without treatment	4 (8%)
	Surgery	3 (6%)
	CT alone	3 (6%)
	EMR	1 (2%)
	Mortality without treatment	1 (2%)
	RFA	1 (2%)
	APC	1 (2%)
ME-NBI examination timing	Never done	52 (20%)
	≤ 6 months of diagnosis of HNC	107 (41%)
	> 6 months of diagnosis of HNC	21 (8%)
	≤ 6 months of diagnosis of HNC and surveillance every 6~12 months	81 (31%)
Follow-up, years		1.6 (±2.9) (0.7-3.6)

APC, argon plasma coagulation; AJCC, The American Joint Committee on Cancer; CCRT, concurrent chemoradiotherapy; CT, chemotherapy; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; RFA, radiofrequency ablation; HGIN, high-grade intraepithelial neoplasia; IQR, interquartile range; ME-NBI, magnifying endoscopy with narrow-band imaging; RT, radiotherapy; SCC, squamous cell carcinoma; SD, standard deviation; SPN, second primary neoplasm.

poor survival, and patients who received ME-NBI within half a year and further surveillance follow-up (HR: 0.53, 95% CI 0.36-0.78, p=0.001) had a better prognosis (Figure 3B).

Discussion

Our findings are the first to demonstrate improved overall survival in patients with hypopharyngeal cancer undergoing ME-NBI and emphasize the importance of ME screening and further surveillance.

10.3389/fonc.2023.1221616

TABLE 3 Univariate and multivariate Cox regression analyses of overall survival of enrolled hypopharyngeal cancer patients.

	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Sex				
Female	Ref.		Ref.	
Male	1.05 (0.47-2.38)	0.898	1.33 (0.58-3.04)	0.504
Age				
<65 years old	Ref.		Ref.	
>=65 years old	1.26 (0.94-1.70)	0.118	1.18 (0.88-1.59)	0.275
Stage				
I+II	Ref.		Ref.	
III+IV	1.78 (1.13-2.80)	0.014	1.86 (1.18-2.95)	0.008
Primary site				
Pyriform sinus	Ref.			
Posterior pharyngeal wall	0.81 (0.52-1.25)	0.332		
Post-cricoid area	0.75 (0.35-1.60)	0.454		
Overlapping	1.18 (0.70-1.99)	0.528		
ME-NBI				
No	Ref.			
Yes	0.57 (0.40-0.80)	0.001		
ME-NBI strategy				
Never done or > 6 months	Ref.		Ref.	
Once only ≤ 6 months	1.11 (0.78-1.56)	0.570	1.10 (0.77-1.55)	0.603
≤ 6 months and surveillance	0.55(0.38-0.81)	0.003	0.53 (0.36-0.78)	0.001

HR, hazard ratio; ME-NBI, magnifying endoscopy with narrow-band imaging; Ref., reference.

Treatment of hypopharyngeal cancer remains challenging and requires a multidisciplinary team to establish the optimal treatment options. The primary goal is to improve survival from an oncological perspective and provide functional organ preservation wherever feasible (13). Because there is a substantial proportion of patients with HNC with cigarette smoking, chewing betel nuts and drinking alcohol habits, which are common carcinogens for esophageal SCC, the risk of developing malignancies in the entire aerodigestive tract, including the lungs and esophagus, is high (8–10, 14, 15). Several studies have found that a very high proportion of patients with HNC are complicated by SPNs. After comprehensive review and analysis, we found that approximately 12% of HNC patients will develop second primary cancer (9). If the second primary cancer is located in the esophagus, the mortality rate will be higher than those with other SPNs, with a 5-year survival rate of only 6% (9, 10, 14, 15). The synchronous and metachronous rates of the development of esophageal SPNs in HNC patients are approximately 13-23.3% and 10-12%, respectively (7, 11, 16–19). In our study, 70% of esophageal SPNs developed synchronously, while 30% of them were metachronous SPNs (Table 2). Fortunately, most of the SPNs of the esophagus detected by screening in patients with HNC are at asymptomatic precancerous dysplastic or early cancer stages (7, 18, 19). According to the results of this study, the esophageal SPNs of HGIN and stage I SCC were 26% and 36% synchronous and 53% and 7% metachronous lesions, respectively (Table 2). Therefore, we

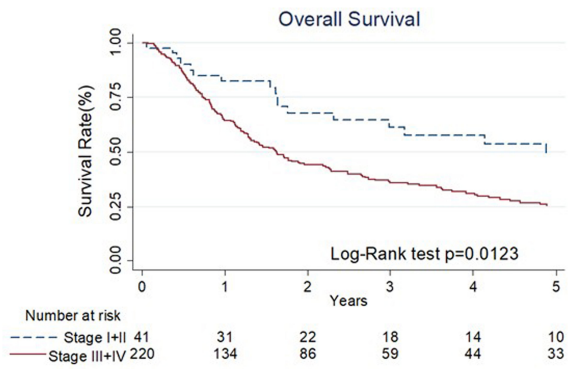

FIGURE 2
The Kaplan-Meier diagram and log-rank test of overall survival among different stages of primary index cancer.

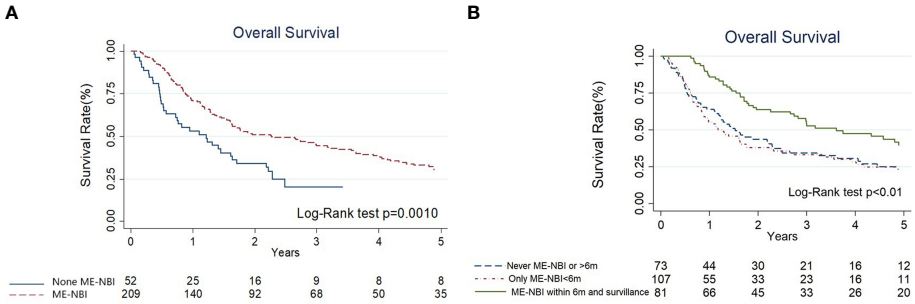

FIGURE 3
(A) The Kaplan-Meier diagram and log-rank test of overall survival among hypopharyngeal cancer patients with and without magnifying endoscopy under narrow-band imaging screening of esophagus. **(B)** The Kaplan-Meier diagram and log-rank test of overall survival according to different endoscopy surveillance strategies.

believe that early diagnosis of esophageal SPN not only provides opportunities for early treatment but also may improve the overall survival rate of patients with HNC (20). Regarding the primary site of index HNC, we found that the risk of hypopharyngeal cancer patients who develop second primary esophageal cancer is four times that of patients with oral cancers (7). Thus, it is presumed that the screening, surveillance and treatment of esophageal SPNs should be an important prognostic strategy for the management of patients with hypopharyngeal cancer.

The survival rate of hypopharyngeal cancer is worse than that of other HNCs. It may be related to concurrent esophageal cancer, nutritional status during treatment, swallowing dysfunction and whether advanced hypopharyngeal cancer patients received aggressive surgical treatment. In patients with HNCs, prognosis may be more affected by the esophageal SPN due to its poorer prognosis as compared to SPN of other sites (14, 15). When estimating the impact of various risk factors on survival among these patients, it is crucial to take into consideration the influence of esophageal cancer. Therefore, screening and surveillance of esophageal SPN, especially at asymptomatic early stages, become of paramount importance to improve overall outcome. In our study, the incidence of HGIN and stage I esophageal SPN were 26% and 36% synchronously, and 53% and 7% metachronously (Table 2) which were much higher than those in nationwide data (only 11% at stage I) (21). However, it is not well understood whether routine endoscopic screening of esophageal SPNs and regular follow-up can improve the prognosis of patients with hypopharyngeal cancer. In our previous study of a total of 1,577 HNC patients, those who underwent endoscopic screening of esophageal SPNs with negative findings initially had a better prognosis than those without screening (22). Additionally, with advancements in image-enhanced endoscopy (IEE) technology, particularly NBI systems and chromoendoscopy using iodine-containing solution spraying, the diagnosis of precancerous or early cancerous neoplasia of the esophagus could be achieved (23–25).

To date, there is no clear consensus or guideline for the treatment of hypopharyngeal cancer with secondary esophageal neoplasia. Early esophageal neoplasia can be managed by minimally invasive endoscopic resection techniques, which provide equivalent long-term survival compared to surgery but better quality of life (26–28). In our study, we aggressively treated primary index hypopharyngeal cancer as well as synchronous or metachronous esophageal SPNs concomitantly. For esophageal SPNs at precancerous or early status, we used endoscopic ablative or resection methods, including EMR, ESD, RFA or APC, according to the conditions of the patients and the characteristics of the lesions (Table 2). By proactively managing both primary and second primary neoplasms (Figure 4), patients with hypopharyngeal cancer can be maintained in complete remission or stable disease status. In this study, we further categorized the strategy of ME-NBI examination of the esophagus. The results have demonstrated that a better overall survival could be provided to hypopharyngeal cancer patients when ME-NBI screening of synchronous esophageal SPN within 6 months after initial diagnosis of index primary HNC and regular endoscopic surveillance for metachronous lesions can be implemented (Table 3, Figure 3B).

In our experience, both ME-NBI screening and regular endoscopic surveillance for metachronous lesions are important for the survival of hypopharyngeal cancer patients. In Figure 4, we demonstrate one 52-year-old man with left hypopharyngeal cancer, stage cT4N0M0, with initial synchronous low-grade dysplastic esophageal neoplasm after ME-NBI screening. He underwent concurrent chemotherapy followed by total laryngectomy. Surveillance endoscopic examination using ME-NBI 6 months after completion of the treatment of primary index hypopharyngeal cancer revealed disease progression of dysplastic esophageal mucosa, and biopsy reported HGIN. He underwent endoscopic radiofrequency ablation with complete remission. Unfortunately, after 4 years of follow-up, an exophytic mass in the upper-middle part of the esophagus developed, and biopsy revealed squamous cell carcinoma with staging cT2N0M0. He received definitive CCRT for esophageal cancer. Six months after the treatment, endoscopy surveillance showed complete resolution of esophageal cancer with scarring.

There were some limitations of this study. First, it was a retrospective study in a single tertiary hospital, and the results may not be generalized. Second, the timing and surveillance interval of ME-NBI examination of the esophagus was not standardized,

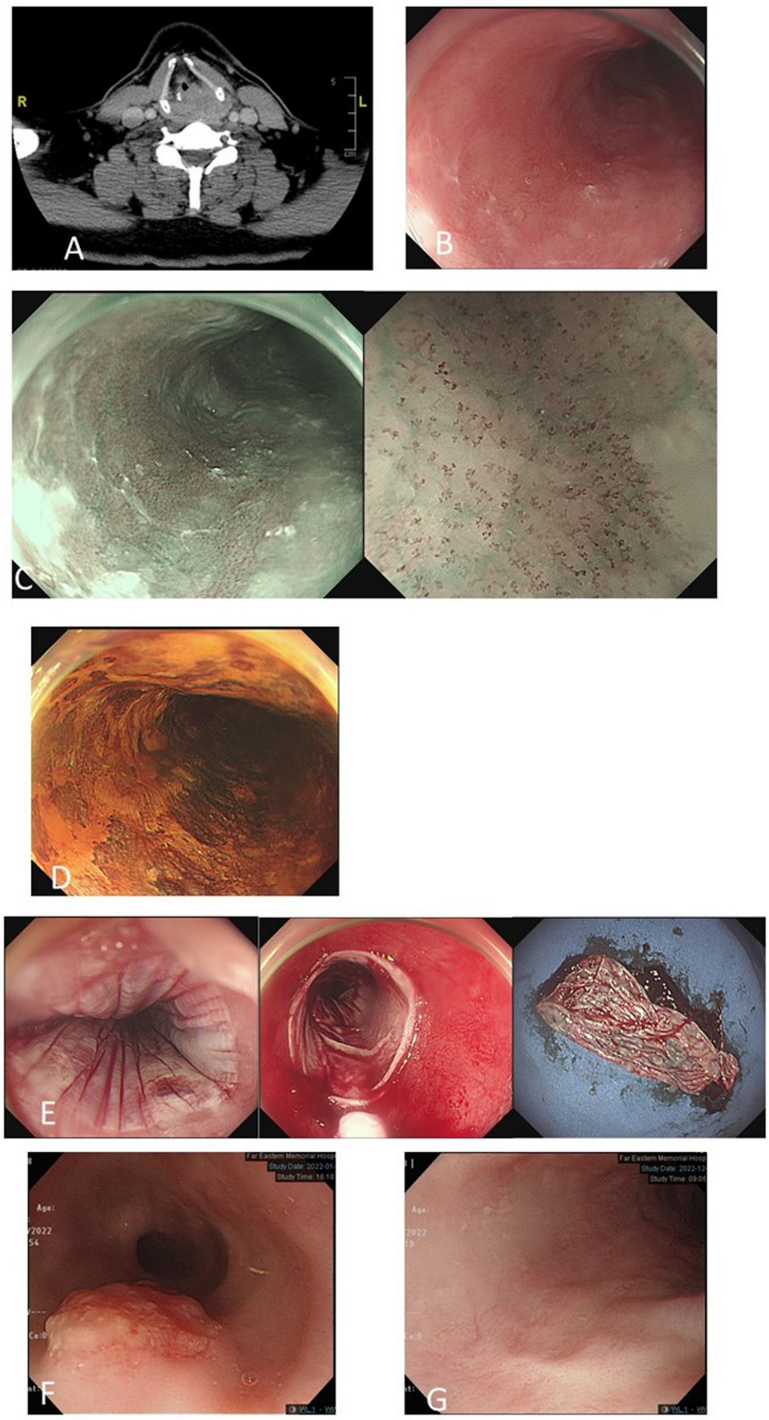

FIGURE 4
A 52-year-old man with left hypopharyngeal cancer, stage cT4N0M0 **(A)**. Magnifying endoscopy with narrow-band imaging (ME-NBI) endoscopic screening of the esophagus revealed a mild hyperemic surface **(B)** under white-light imaging, brownish discoloration with irregular intraepithelial papillary capillary loops under ME-NBI **(C)** and multifocal Lugol-voiding areas **(D)** in the middle part of the esophagus. Biopsy revealed squamous hyperplasia and low-grade dysplasia. He underwent concurrent chemotherapy followed by total laryngectomy. Follow-up ME-NBI 6 months after completion of the treatment for primary index hypopharyngeal cancer revealed disease progression of dysplastic esophageal mucosa with biopsy reporting high-grade intraepithelial neoplasia. He underwent endoscopic radiofrequency ablation **(E)**. After 4 years of follow-up, an exophytic mass in the upper-middle part of the esophagus **(F)** and biopsy revealed squamous cell carcinoma (cT2N0M0). He received definitive CCRT for esophageal cancer. Six months after the treatment, endoscopy surveillance showed complete resolution of esophageal cancer with scarring **(G)**.

and the optimal surveillance intervals could not be revealed. Finally, we did not investigate the cause of death in the survival analysis, and whether patients who died of disease progression of primary index hypopharyngeal cancers or SPN of the esophagus was not well understood.

Conclusions

In conclusion, we suggest screening esophageal SPNs in all newly diagnosed hypopharyngeal cancer patients as well as regular endoscopic surveillance thereafter. By proactive ME-NBI examination of the esophagus and treatment of primary and secondary neoplasms accordingly, the survival of patients with hypopharyngeal cancer can be improved. We believe that patient adherence to treatment and surveillance program which improves early detection and management of either metachronous primary or secondary tumors and possible lifestyle modification is one of the direct impacts on cancer outcome.

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 ethical review committee of Far Eastern Memorial Hospital (IRB No.: 111165-E). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

Study conception and design: C-SC, C-YW, Y-HL, W-CL, P-CC, W-LH, and L-JL. Acquisition of data: C-SC, C-YW, YHL, and L-JL. Analysis and interpretation of data: C-SC, C-YW, W-CL, P-CC, W-LH, and L-JL. Drafting of manuscript: C-SC, C-YW, and L-JL. Critical revision: C-SC, C-YW, and L-JL. All authors contributed to the article and approved the submitted version.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by grants from the Far Eastern Memorial Hospital (FEMH -2023-C-032). We also thank our colleagues in the Head and Neck Cancer Surveillance & Research Group, Far Eastern Memorial Hospital.

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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frontiers | Frontiers in Oncology

TYPE Clinical Trial
PUBLISHED 07 February 2024
DOI 10.3389/fonc.2024.1283266

OPEN ACCESS

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RECEIVED 25 August 2023
ACCEPTED 22 January 2024
PUBLISHED 07 February 2024

CITATION
Brandt A, Schultheiss C, Klinghammer K, Schafhausen P, Busch C-J, Blaurock M, Hinke A, Tometten M, Dietz A, Müller-Richter U, Hahn D, Alt J, Stein A and Binder M (2024) Tolerability and efficacy of the cancer vaccine UV1 in patients with recurrent or metastatic PD-L1 positive head and neck squamous cell carcinoma planned for first-line treatment with pembrolizumab – the randomized phase 2 FOCUS trial. *Front. Oncol.* 14:1283266. doi: 10.3389/fonc.2024.1283266

Tolerability and efficacy of the cancer vaccine UV1 in patients with recurrent or metastatic PD-L1 positive head and neck squamous cell carcinoma planned for first-line treatment with pembrolizumab – the randomized phase 2 FOCUS trial

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Background: Globally, head and neck squamous cell carcinoma (HNSCC) is the seventh most common malignancy. Despite aggressive multimodal treatment approaches, recurrent and/or metastatic (R/M) disease develops in >50% of patients. In this setting, pembrolizumab was approved for patients with PD-L1 expression. However, response rates with checkpoint inhibitor monotherapy remain limited and strategies to strengthen tumor-directed immune responses are needed.

Objective: The FOCUS trial is designed to estimate the effectiveness of UV1 vaccination in combination with pembrolizumab versus pembrolizumab as a single agent in patients with R/M HNSCC.

Methods and analysis: The FOCUS trial is a two-armed, randomized, multicenter phase II study which was designed to evaluate the efficacy and feasibility of the hTERT-targeted cancer vaccine UV1 as add-on to pembrolizumab in the 1st line

treatment of patients with R/M PD-L1 positive (combined positive score ≥1) HNSCC. Secondary objectives are the exploration of patient subgroups most likely deriving benefit from this novel combination and the establishment of liquid biopsy tumor monitoring in HNSCC.

Ethics and dissemination: This clinical study was designed and will be conducted in compliance with Good Clinical Practice and in accordance with the Declaration of Helsinki. It is intended to publish the results of this study in peer-reviewed scientific journals and to present its content at academic conferences.

Conclusions: A significant number of patients with R/M HNSCC are frail and may not tolerate chemotherapy, these patients may only be suitable for pembrolizumab monotherapy. However, long term disease stabilizations remain the exception and there is a need for the development of efficacious combination regimens for this patient population. The FOCUS study aims to optimize treatment of R/M HNSCC patients with this promising new treatment approach.

Clinical Trial Registration: https://clinicaltrials.gov/study/NCT05075122, identifier NCT05075122.

KEYWORDS

head and neck squamous cell carcinoma (HNSCC), UV1, pembrolizumab, cancer vaccine, cancer immunotherapy

1 Introduction

Worldwide, head and neck squamous cell carcinoma (HNSCC) is the seventh most common malignancy with more than 660,000 new cases and 350,000 deaths per year (1). Risk factors include tobacco use, alcohol consumption, and human papilloma virus (HPV) infection (2).

At early stages, therapy is given with curative intent. However, despite aggressive treatment with multimodal approaches, recurrent and/or metastatic (R/M) disease develops in more than half of patients with HNSCC and prognosis of these patients is poor (3). Many patients suffering from R/M disease present with unresectable disease and only qualify for palliative treatment (4). Until 2019, the EXTREME regimen (cetuximab combined with platinum and fluorouracil) was the standard of care first line treatment for patients with R/M HNSCC with good performance status (ECOG 0-1) (5). More recently, pembrolizumab was approved for R/M HNSCC as monotherapy or in combination with platinum-fluorouracil for PD-L1 positive disease. Approval was based on the KEYNOTE-048 trial, a randomized, phase 3 study, which showed a significant survival benefit when compared with the EXTREME protocol (6). In this trial, pembrolizumab plus chemotherapy improved overall survival compared to cetuximab plus chemotherapy (median 13.0 *vs.* 10.7 months, HR 0.77 [95% CI 0.63-0.93], p=0.0034). In the subgroups of patients with PD-L1 CPS ≥1 and CPS of ≥20, pembrolizumab given as a single agent improved overall survival compared to cetuximab plus chemotherapy (12.3 *vs.* 10.3 months, HR 0.78 [95% CI 0.64-0.96], p=0.0086, and 14.9 *vs.* 10.7 months, HR 0.61 [95% CI 0.45-0.83], p=0.0007) demonstrating increased efficacy of pembrolizumab with increasing PD-L1 expression (7).

Although some patients have durable responses to immune-checkpoint inhibitors, many patients with R/M HNSCC either show no response or benefit only in the short-term from this treatment (3). One reason might be an insufficient T cell effector response (8). To improve the T cell response against tumor antigens, therapeutic cancer vaccines in combination with immune-checkpoint inhibitors are investigated in HNSCC and other tumor entities (8, 9). UV1 is a peptide vaccine targeting human telomerase reverse transcriptase (hTERT), found to be activated in 85-90% of all cancers (8) representing an essential step in carcinogenesis (10). The UV1 vaccine induced persistent immune responses which lasted up to 7.5 years in phase I clinical trials which included patients with non-small cell lung cancer, malignant melanoma, and prostate cancer (8). When combined with the checkpoint-inhibitor ipilimumab, the vaccine-induced T cell response in the melanoma trial occurred more often and more rapidly indicating improved efficacy with the combined approach (8). In patients with advanced melanoma, UV1

was also combined with pembrolizumab (11). In this phase I clinical trial, treatment was well tolerated and response rate was 60% with a 1-year survival rate of 85% (11).

In patients with HNSCC, the combination of immune-checkpoint inhibition with UV1 has not been studied. In 75-100% of HNSCC high levels of hTERT expression have been detected (12). The most common mechanism of hTERT activation are mutations in the promoter region of hTERT (13). In HNSCC frequencies of hTERT promoter mutations vary among different studies (14). Frequencies up to 64,7% have been reported depending on tumor site, risk factors such as human papillomavirus status and ethnicity (14). Thus, hTERT represents an attractive target for therapeutic vaccination in HNSCC.

The FOCUS trial was designed to estimate the effectiveness of UV1 vaccination in combination with pembrolizumab versus pembrolizumab as a single agent in patients with R/M HNSCC.

2 Methods and analysis

2.1 Study objective

The primary objective of this study is to assess the efficacy of UV1 vaccination in combination with pembrolizumab in patients with R/M HNSCC and PD-L1 CPS ≥1 based on progression free survival according to iRECIST (progression-free survival rate at 6 months after randomization, PFS@6) (15).

Secondary clinical endpoints of this study are overall survival, objective response rate and duration of response according to iRECIST. Other secondary objectives are the UV1 vaccine induced immune responses and the clearance rate of ctDNA from blood during treatment. Additionally, this study will explore the safety and tolerability of UV1 vaccination in combination with pembrolizumab according to NCI CTCAE v5.0. Other objectives are the exploration of what patient subgroups benefit most from this combined approach and the establishment of liquid biopsy tumor monitoring in HNSCC.

2.2 Study design

The FOCUS trial is an open-label, randomized, phase II study which investigates the tolerability and efficacy of the UV1 vaccine in patients with R/M PD-L1 positive (CPS ≥1) HNSCC planned for first-line treatment with pembrolizumab. The study is multicentric and includes several study sites in Germany. 75 patients will be randomized with an estimated recruitment phase of 24 months. Planned duration of follow-up per patient is until death or 12 months after last patient in (Figure 1).

2.3 Treatment

Eligible patients (Table 1) will be randomized to either pembrolizumab, Arm A, about 25 patients, or pembrolizumab in combination with UV1 vaccination plus sargramostim (GM-CSF) as an adjuvant, Arm B, about 50 patients (Figure 2).

All patients will receive pembrolizumab until disease progression and up to two years in both arms.

The UV1 vaccine (Ultimovacs, Oslo, Norway) and sargramostim are considered investigational medical products (IMPs) in this study.

Data on efficacy in in terms of vaccine-specific immune response and safety from completed phase I/II clinical trials support a total of 8 vaccinations with a UV1 dose of 300µg administered intradermally with 75µg of the adjuvant sargramostim (8). The administration regimen for UV1 vaccination during day 1-10 is optimized for effective priming and expansion of naïve hTERT-specific T cells in the local lymph nodes draining the vaccine injection site. The following vaccinations are optimized for re-activation of T cell effector activity in the tumor microenvironment in synergy with pembrolizumab.

Arm A:

Patients in arm A receive pembrolizumab at 200mg flat dose iv every 3 weeks. Administration starts at week 1 (one week earlier than arm B). The duration of treatment will be 12 weeks.

Arm B:

Patients in arm B receive pembrolizumab at 200mg iv every 3 weeks in combination with UV1 vaccination (300µg UV1 plus 75µg GM-CSF as adjuvant). Three UV1 vaccinations are applied during the week before initiation of pembrolizumab, followed by 5 vaccinations applied every 3 weeks on d1 of each cycle (5 cycles in total). Administration of pembrolizumab starts at week 2. In total, the duration of treatment will be 13 weeks.

2.4 Assessments

Baseline assessment is performed according to Table 2. Radiological imaging by computed tomography (CT) of the neck, chest, abdomen and pelvis according to RECIST v1.1 should not be older than 4 weeks before randomization.

Assessments during treatment will be done on visit 1 (week 1 [W1] day 1 [D1]), visit 2 [W1 D3], visit 3 [W1 D5], visit 4 [W2], visit 5 [W5], visit 6 [W8], visit 7 [W11], visit 8 [W14] and end of treatment (EOT) according to Table 3. Screening and visit 1 can be performed on the same day. Assessments at progressive disease (PD) during treatment (if applicable) will be performed according to Table 4.

2.5 Follow-up

All patients will be evaluated every 3 months after EOT until death or maximal 12 months after last patient in (Table 5). At progressive disease during follow-up (if not progressed during treatment), assessments will be done according to Table 6. All patients will be monitored 30 days after EOT for safety reasons (Table 7).

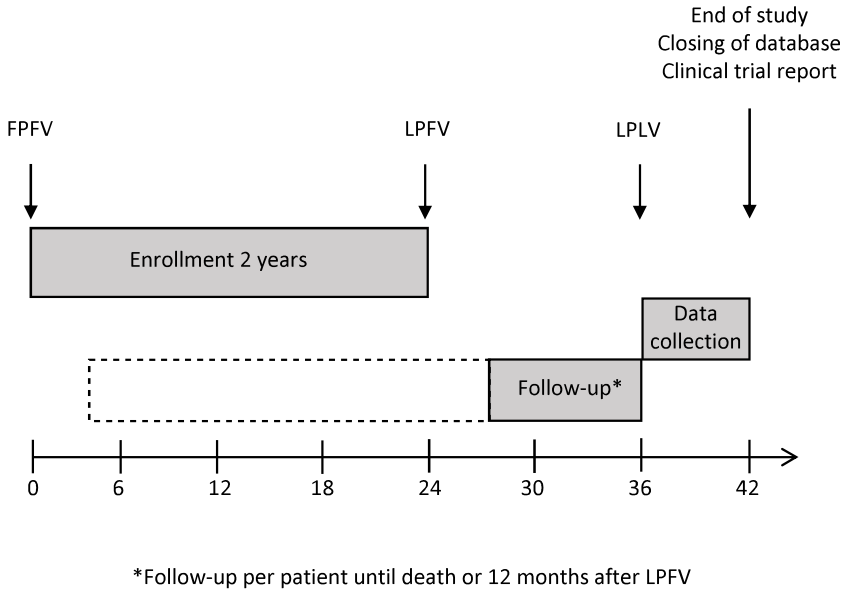

FIGURE 1
Study recruitment and follow-up. FPFV, first patient, first visit; LPFV, last patient, first visit; LPLV, last patient, last visit.

2.6 Sample collection for biomarker program

Blood samples for immune analysis (Table 8) will be collected at visit 1, 5, 6, 8 (EOT) as well as at safety follow-up (FU), FU1, FU2 and at PD (Figure 2).

In centers with expertise in collecting and locally freezing peripheral blood mononuclear cells (PBMCs), additional blood will be collected at visit 1, 6 and at PD from patients receiving UV1 vaccination (from patients of both arms only at site 01 Halle only) for immune response assays (Table 8).

Tumor tissue acquired before treatment initiation at first diagnosis or at relapse (biopsy of primary tumor, surgical material, or biopsy material of metastatic lesions) and potential biopsy or surgical material acquired during the study will be analyzed (Table 8, Figure 2).

TABLE 1

Inclusion criteria
• Males and Females who are at least 18 years of age • Histologically confirmed diagnosis of a non-resectable recurrent or metastatic head and neck squamous cell carcinoma (not necessarily reconfirmed at time of enrolment) • At least one measurable tumor lesion as per RECIST v1.1, (scan not older than 4 weeks before randomization) • Eligible for pembrolizumab monotherapy (PD-L1 CPS ≥1 and adequate laboratory parameters for pembrolizumab monotherapy as assessed by the investigator) • ECOG-performance score 0-2 • Written informed consent obtained according to international guidelines and local laws • Ability to understand and give informed consent • Safe contraception measures for males and females. Procedures with a pearl index of less than 1% apply as safe pregnancy prevention measures

Fecal samples will be collected prior to treatment to evaluate the gut microbiome (Table 8).

2.7 Analysis of primary study endpoint

The primary study endpoint progression PFS@6 will be analyzed as the proportion of all intention-to-treat patients being known to be alive without progression at 6 months after randomization, providing the 95%, 90% and 80% confidence intervals for this estimate.

2.8 Statistics and data handling

The FOCUS trial is designed as a randomized phase II study to estimate the therapeutic effectiveness of pembrolizumab in combination with UV1 vaccination in relation to the standard treatment (single drug pembrolizumab). The assumptions on outcome after standard therapy is derived from available data and controlled for by a randomized reference (or calibration) arm. Due to this design, analysis of both treatment arms but no formal statistical comparison will be performed. All secondary endpoint analyses are considered explorative. Further clinical development of this combination depends on the primary endpoint (and its confidence interval), the findings in the control arm, and the supporting safety and feasibility findings.

2.9 Sample size estimation

The progression-free survival rate after 6 months (PFSR@6) with single agent pembrolizumab as first-line treatment in R/M

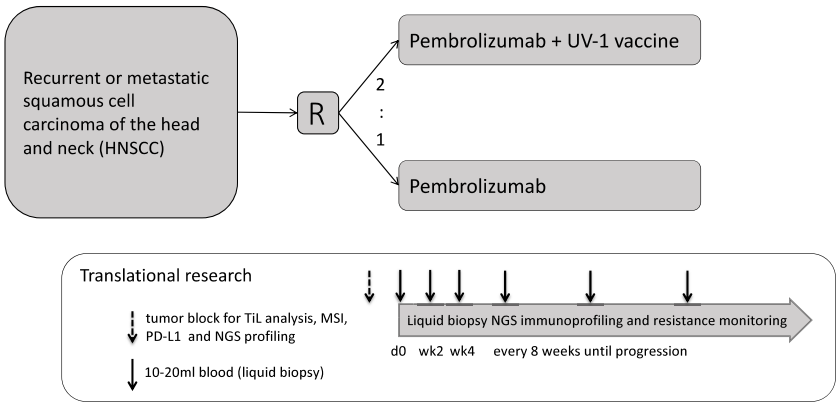

FIGURE 2
Study schedule.

HNSCC is about 25%. Pembrolizumab in combination with UV1 vaccination should result in a PFSR@6 of 40% to be regarded as promising for further development in a phase III setting. Based on these assumptions and by applying a one-sided test with an alpha error level of 0.1 and a beta error of 0.2 (corresponding to a power of 80%), 46 evaluable patients are needed in the experimental arm. According to the 2:1 randomization, about 23 patients will be included in the control arm. To allow for a 10% drop out rate, a total of 75 patients should be included.

3 Discussion

Patients with R/M HNSCC have a poor prognosis (3, 4). Many of these patients are frail and cannot tolerate chemotherapy.

Eligible patients with R/M HNSCC may be treated with immunotherapy. Nivolumab was shown to significantly prolong survival when compared with standard systemic therapy in patients progressing within six months after platinum-chemotherapy (16). Due to these promising results, patients in the KEYNOTE-048 trial (6) received either the EXTREME regimen, or pembrolizumab as a single agent, or platinum/5-fluorouracil with pembrolizumab as first-line therapy (17). After a follow-up of 4 years, a survival benefit and a longer duration of response was observed with single-agent pembrolizumab and pembrolizumab in combination with chemotherapy compared with cetuximab in combination with chemotherapy (18). Two phase III studies evaluated the combination of anti-PD1/PDL1 and anti-CTLA antibodies in R/M HNSCC patients (19, 20). In both studies the combination proved to be tolerable but showed no statistically significant improvement in overall survival versus the EXTREME protocol (CheckMate 651) or single agent standard of care (EAGLE) (19, 20). The combination of checkpoint inhibition plus cetuximab was investigated in two phase II studies in patients with R/M HNSCC (21, 22). Pembrolizumab plus cetuximab had an overall response rate of 45% (21). Nivolumab plus cetuximab was also effective in pretreated patients with a 1-year overall survival of 50% (22). These studies provide a rationale for a larger randomized study. In a phase IB/II trial of the angiogenesis inhibitor lenvatinib plus pembrolizumab which included 22 HNSCC patients, these patients had an objective response rate of 36% at week 24 (23).

TABLE 2

Baseline assessment
• Informed consent • Review of inclusion and exclusion criteria • Relevant medical history • Laboratory tests: Hematology panel, chemistry panel, including also TSH, fT3/fT4, PT/PTT, INR/Quick • Hepatitis B/C screening test, HIV screening test (not older than 4 weeks before randomization) • Physical examination • Vital signs and ECOG • Radiological imaging by computertomography of the neck, chest, abdomen and pelvis (according to RECIST v1.1, not older than 4 weeks before randomization) • Urine pregnancy test • Concomitant medication • C-lab: Stored tumor tissue collection (paraffin block or 10 slides), remaining tumor tissue from the first diagnosis or at relapse • C-lab: Fecal sample

TABLE 3

Assessments during treatment
• Vital signs and ECOG (only for visit 1, 4, 5, 6, 7, 8 and EOT) • Laboratory tests: Hematology panel, chemistry panel (only for visits 1, 4, 5, 6, 7 and 8) • TSH, fT3/fT4 at visits 4, 5, 6, 7, 8 and EOT • Urine pregnancy test at visits 5, 6 and 7 • C-lab blood sampling (20ml) for tumor-DNA (only at visits 1, 5, 6, 8 and EOT) • On site preparation and storage: blood sampling (50ml) for PBMC, arm B only (for both arms at site 01 Halle) at visits 1 and 6 • Pembolizumab infusion (arm A) every 3 weeks according to the label at Visits 4, 5, 6, 7 and EOT (Visit 8) • Additional UV1 vaccination (arm B) 3 times the week before initiation of pembrolizumab followed by 5 additional applications on d1 cycle 1-5. • Adverse events • Concomitant medication • Radiological response (according to iRECIST) will be assessed at visit 8 (routine diagnostics)

TABLE 4

Assessments at progressive disease (PD) during treatment
• Vital signs and ECOG • Laboratory tests: Hematology panel, chemistry panel • TSH, fT3/fT4 • C-lab blood sampling (20ml) for tumor-DNA • On site preparation and storage: blood sampling (50ml) for PBMC, arm B only (for both arms at site 01 Halle) • Adverse events • Concomitant medication • Radiological response (according to iRECIST) (routine diagnostics) until PD • If not done at screening: C-lab: Stored tumor tissue collection (paraffin block or 10 slides)

TABLE 6

Visit at PD during follow up (if not progressed during treatment)
• Results of Radiological imaging (according to iRECIST) regarding disease status (from routine diagnostics) • Subsequent anti-cancer therapies • C-lab blood sampling (20ml) for tumor-DNA • Survival and disease status • Assessment of adverse events, concomitant therapies and subsequent anti-cancer therapies • Blood sampling (50ml) for PBMC (on site preparation and storage) arm B only (for both arms at site 01 Halle) • If not done at screening: C-lab: Stored tumor tissue collection (paraffin block or 10 slides)

However, frail patients may not tolerate this regimen and the development of efficacious combination regimens for this patient population is urgently needed.

The FOCUS trial investigates the tolerability and efficacy of the cancer vaccine UV1 combined with first-line pembrolizumab monotherapy in patients with R/M HNSCC and CPS ≥1.

The therapeutic cancer UV1 consists of three synthetic peptides which cover a sequence within the active catalytic site of hTERT (24). hTERT promoter mutations which are a common mechanism of hTERT activation are found in the two major hotspots C228T and C250T (14). In HNSCC hTERT promoter mutations were found to be associated with poorer overall survival in some studies (25, 26).

UV1 vaccination was investigated in phase I trials in patients with metastatic prostate cancer combined with androgen blockade (27) and as monotherapy in patients with stage III/IV non-small cell lung cancer (NSCLC) (24).

Patients with metastatic prostate cancer (n=22) were treated with 3 dose levels of UV1 combined with GM-CSF (27). In this study, treatment with UV1 was well tolerated and specific immune responses were noted in 18 of 21 patients (27).

UV1 treatment was also safe and immunogenic in patients with advanced NSCLC (24). 18 patients with advanced stage NSCLC without brain metastasis were enrolled (24). Patients who did not show an immune response had a median overall survival of 21.3 months whereas the overall survival was 38.4 months in patients who did show an immune response (24).

Long-term monitoring revealed a persistent telomerase peptide-specific immune response which lasted up to 7.5 years following the initial vaccination (8).

Vaccine-based therapies may be more effective in combination with other immunotherapies as the immunosuppressive environment of the tumor may interfere with vaccine-activated T cells (9). By way of example, checkpoint-inhibitors block the immunosuppression induced by the PD-1/PD-L1 axis which may be accompanied by a more efficient vaccine mediated anti-tumor T cell response (9).

Potential synergistic effect of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade and hTERT vaccination was investigated in metastatic melanoma in a phase I/IIa clinical trial (28). 12 melanoma patients were treated with UV1 in combination with ipilimumab (28). Most patients had T cell responses to UV1 peptides, 3 patients partially responded, one patient had a complete response, and overall survival was 50% at 5 years (28). Adverse events included diarrhea, rash, pruritus, fatigue, and nausea (28). The combination of UV1 and ipilimumab was safe and toxicity was mainly low-grade (28), however, patients in the FOCUS study will be carefully evaluated for potential toxicities. All patients will be monitored 30 days after EOT for safety reasons.

Four phase II studies currently evaluate the combination of different checkpoint inhibitors plus UV1 vaccination in metastatic malignant melanoma (NCT04382664), mesothelioma (NCT04300244), ovarian cancer (NCT04742075), and non-small cell lung cancer (NCT05344209).

To identify potential patients that benefit most from the combination of UV1 and pembrolizumab and to uncover potential mechanisms of resistance, the FOCUS trial is accompanied by a biomarker program which includes assessment of tumor biopsies prior to treatment, immunomonitoring by next-

TABLE 5

Follow-up
• Results of Radiological imaging (according to iRECIST) regarding disease status (from routine diagnostics) until PD • Pembrolizumab infusion is continued according to SmPC at the discretion of the physician • C-lab blood sampling (20ml) for tumor-DNA (only at FU1 and FU2) • Assessment of adverse events, concomitant therapies (only until FU1), subsequent anti-cancer therapies and survival status

TABLE 7

Safety follow-up
• Vital signs and ECOG status • Physical examination • Laboratory tests: Hematology panel, chemistry panel, including also TSH, fT3/fT4 • C-lab blood sampling (20ml) for tumor-DNA • Pembrolizumab infusion is continued according to SmPC at the discretion of the physician • Assessment of adverse events, concomitant therapies and subsequent anti-cancer therapies

TABLE 8

Translational work-up
• Immunohistochemistry (IHC) for PD-L1 to deduce tumor proportion score (TPS), immune cell (IC) score and combined positivity score (CPS), and IHC for telomerase tissue expression • Next-generation T cell receptor repertoire sequencing of circulating and tumor-infiltrating lymphocytes (TiL) • Next-generation gene panel sequencing for mutational profiling of tumor or circulating tumor DNA (ctDNA, liquid biopsy) • In individual patients liquid biopsy courses will be confirmed with digital droplet PCR (ddPCR) as an alternative methodology • Immune response assays against hTERT peptides measured by 3H-Thymidine proliferation and IFNgamma ELISPOT assays

generation sequencing (NGS), and liquid biopsy monitoring of tumor subclones during treatment.

The peripheral blood T cell space shows age-specific architectures with cancer patients overall displaying reduced repertoire richness and diversity (29). Previous studies showed that immune checkpoint blockade led to diversification of the peripheral blood T cell space in patients with melanoma and other solid tumors, which was associated with response to treatment in some studies (30–32). In the FOCUS study, the characteristics of tumor-infiltrating lymphocytes and blood-circulating T cells will be studied by NGS and immunological analyses will be correlated with vaccine-specific immune responses assessed by standardized T cell proliferation assays.

Furthermore, tumor tissue and liquid biopsy testing will be done at baseline using a gene panel which covers frequent driver and resistance mutations in HNSCC. The circulating tumor DNA clearance over time will be correlated with overall response, progression-free survival, and overall survival. To search for tumor subclones potentially resistant to pembrolizumab or UV1, the liquid biopsy panel includes genes involved in resistance to checkpoint inhibitors as well as the coding region of hTERT as the UV1 target.

In conclusion, the FOCUS trial investigates the potential synergistic effect of UV1 vaccination and checkpoint blockade with pembrolizumab in patients with R/M HNSCC. To optimize tumor response in this often frail and pretreated patient population, an extensive biomarker program accompanies the FOCUS trial.

Data availability statement

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

Author contributions

AB: Writing – original draft, Writing – review & editing. CS: Conceptualization, Writing – review & editing. KK: Conceptualization, Writing – review & editing. PS: Conceptualization, Writing – review & editing. C-JB: Conceptualization, Writing – review & editing. MBl: Conceptualization, Writing – review & editing. AH: Conceptualization, Writing – review & editing. MT: Conceptualization, Writing – review & editing. AD: Conceptualization, Writing – review & editing. UM-R: Conceptualization, Writing – review & editing. DH: Conceptualization, Writing – review & editing. JA: Conceptualization, Writing – review & editing. AS: Conceptualization, Writing – review & editing. MBi: Conceptualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was funded by the University Hospital Basel.

Acknowledgments

We thank the patients and their families participating in this trial. We thank all the sites and study teams. We thank Ultimovacs for their support.

Conflict of interest

Author AH was employed by the company Clinical Cancer Research Consulting CCRC. AS received research funding from MSD and serves as an advisory board member for MSD. UM-R serves as a consultant or advisor and/or received honoraria from AstraZeneca, BioNTech, BMS, KuraOncology, Merck, MSD, Novartis, and Sanofi. JA serves as an advisor for AstraZeneca, MSD, Novartis, Roche, BMS, Janssen, and Merck and received honoraria from AstraZeneca, BMS, Roche, and Boehringer Ingelheim. KK serves as a consultant or advisor and/or received honoraria from MSD, Merck, BMS, Roche, Novartis, Sanofi, Bayer, BioNTech, Boehringer Ingelheim, and onkowissen.

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

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

Publisher's note

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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 14 February 2024
DOI 10.3389/fonc.2024.1287178

OPEN ACCESS

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RECEIVED 01 September 2023
ACCEPTED 30 January 2024
PUBLISHED 14 February 2024

CITATION
Jungbauer F, Affolter A, Brochhausen C, Lammert A, Ludwig S, Merx K, Rotter N and Huber L (2024) Risk factors for immune-related adverse effects during CPI therapy in patients with head and neck malignancies – a single center study. *Front. Oncol.* 14:1287178. doi: 10.3389/fonc.2024.1287178

Risk factors for immune-related adverse effects during CPI therapy in patients with head and neck malignancies – a single center study

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Introduction: Checkpoint inhibitors, such as PD1 inhibitors, represent an important pillar in the therapy of advanced malignancies of the head and neck region. The most relevant complications are immune-related adverse effects (irAEs), which represent an immense burden for patients. Currently, no sufficient stratification measures are available to identify patients at increased risk of irAEs. The aim of this retrospective study was to examine whether demographic, histopathological, clinical, or laboratory values at the start of CPI therapy represent a risk factor for the later occurrence of autoimmune complications.

Material and methods: Data from 35 patients between 2018 and 2021 who received therapy with nivolumab or pembrolizumab for head and neck malignancy were analyzed and assessed for any associations with the subsequent occurrence of irAEs.

Results: IrAE developed in 37% of patients, with pneumonitis being the most common form (14%). Pneumonitis was found in patients with an average significantly lower T-stage of primary tumors. An increase in basophilic leukocytes was found in patients with dermatitis later in the course. When thyroiditis developed later, the patients had a higher CPS score and lower monocyte levels.

Discussion: Even though individual laboratory values at the beginning of therapy might show a statistical association with the later occurrence of irAEs, neither demographic, histopathological, nor laboratory chemistry values seem to be able to generate a sound and reliable risk profile for this type of complication. Therefore, patients need to be educated and sensitized to irAEs, and regular screening for irAEs should be carried out.

KEYWORDS

HNSCC (head and neck squamous cell carcinoma), HNC (head and neck cancer), checkpoint inhibition, irAE, irAE diagnostic approach, PD-L1

Introduction

In the treatment of recurrent or metastasized, non-operable malignancies of the head and neck region (R/M-HNC), checkpoint inhibitors (CPI) represent an important therapeutic option. Human somatic cells are subject to immunosurveillance (1). Thus, not only potential external pathogens, such as bacteria or viruses, but also (pre) cancerous pathogens, are targeted by immune cells. Advanced tumors can also be infiltrated and attacked by immune cells, which has relevance in patient outcomes (2). The counter mechanism of tumor cells is called immunoevasion and comprises structures that individually and collectively ensure that tumor cells are either not recognized by the immune system or that antitumor immune responses are suppressed, which further promotes tumor progression. In doing so, tumor cells make use of regulatory mechanisms whose actual purpose is peripheral tolerance (i.e., they are intended to prevent autoimmunity through immunosuppressive activity) (3, 4).

An important pathway for immunoevasion is the programmed death 1 (PD-1) axis. PD-1 is a transmembrane glycoprotein consisting of 288 amino acids, which are expressed on the surfaces of T and B cells. It belongs to the immunoglobulin superfamily and inhibits the activity of T cells (5). PD-1 knockout mice develop autoimmune diseases, demonstrating the importance of PD-1 in regulating the immune system (6). Stimulation of PD-1 by its ligands PD-L1 and PD-L2 (7) triggers signaling cascades that prevent immune cells from targeting tumor cells (8). Based on this finding, new therapeutic approaches address the mechanism of immunoevasion (9).

The antibodies pembrolizumab and nivolumab bind to PD-1, thus blocking the PD-L1/PD-1 interaction, preventing the suppression of the immune cells. This enables the patient's immune cells to detect the tumor cells and to act against them. Pretherapeutically, tumor tissue samples are used to determine the PD-L1 status, i.e., the expression of PD-L1 in the tumor tissue and the infiltrating immune cells. This serves to assess the probability of a successful treatment response. Nivolumab was first approved in Europe in 2015 for the treatment of malignant melanoma (10), and it was then approved for R/M-HNC in the U.S. in 2016 based on the results of the Checkmate 141 trial (11). Nivolumab is currently approved for R/M-HNC in adults with progression during or after platinum-based therapy. Pembrolizumab is approved as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy for first-line treatment of R/M-HNC in adults with PD-L1-expressing tumors (combined positivity score "CPS" ≥ 1). Pembrolizumab is also approved as monotherapy for the treatment of R/M-HNC with PD-L1-expressing tumors (tumor proportion score "TPS" ≥ 50%) and cancer progression during or after prior platinum-based therapy in adults.

Typical side effects and complications of CPI are immune-related adverse events (irAEs). This occurs because the immune system, which is restored by CPI therapy, attacks not only the tumor cells but also the body's own organs, as the natural self-tolerance mechanism is suppressed.

The most common irAEs include dermatological low-grade reactions, such as rash, pruritus, or vitiligo (12). Pulmonary inflammation, predominantly pneumonitis, is a potentially life-threatening irAE (13). Gastrointestinal inflammation, such as colitis and enterocolitis, also occurs and is primarily noted by diarrhea (14). Autoimmune hepatitis may also occur (15). irAEs affecting the endocrine system manifest most commonly as thyroiditis, pituitary inflammation, and much less commonly as diabetes mellitus (16). Cardiovascular irAEs also occur infrequently. They can manifest as myocarditis, pericarditis, or vasculitis, among others, and require careful monitoring because of their potentially fatal course (17, 18). Other irAEs involve the musculoskeletal system (19) and the nervous system (20). Some irAEs may be revealed by routine laboratory blood chemistry checks (especially those of the endocrine system); others require an inquiry by the patient about relevant symptoms (e.g., diarrhea). Depending on the severity of the irAEs, CPI therapy is continued, paused, or terminated, and immunosuppressive therapy, typically with cortisone, is initiated if necessary.

These irAEs represent a relevant burden for patients and pose a threat to effective antitumor therapy. However, the possibility of using biomarkers to assess the risk of the occurrence of these irAEs is very limited. Reviews of risk factors for irAEs on CPI therapy exist, but these do not include HNC patients due to a lack of data (21).

Therefore, the aim of this retrospective study was to examine whether demographic, histopathological, clinical, or laboratory values at the start of CPI therapy represent a risk factor for the later occurrence of autoimmune complications.

Materials and methods

All patients who had received CPI therapy with pembrolizumab or nivolumab in the Department of Otolaryngology, Head- and Neck-Surgery of Mannheim University Hospital between January 1, 2018, and December 31, 2021, were included. Clinical, histopathological, and laboratory chemistry data were extracted from digital patient records (Table 1). Statistical analysis was performed using GNU PSPP 1.6.2 software. Descriptive analyses, t-tests, and bivariate correlations were performed. A p-value ≤ 0.05 was considered statistically significant. The results are given in absolute numbers ± standard deviations. The study was approved by the local ethics committee of Heidelberg University (# 2022-838).

Results

Within the study period, 35 patients were treated with CPI therapy. A total of 29 patients were male (82.9%), and 6 were female (17.1%). The mean age at initiation of CPI therapy was 65 years (± 11.1 years, range 40–91 years). A total of 22 patients received therapy with pembrolizumab (53.7%), and 13 received therapy with nivolumab (31.7%).

The primary tumor was located in the oropharynx in 22 patients (62.9%), in the hypopharynx in 4 patients (11.4%), in the larynx in 3 patients (8.6%), and in the oral cavity in 2 patients (5.7%). In one patient each (2.9% each), the primary tumor was

TABLE 1 Excerpt from the clinical/histopathological data of the study collective: CPI (Checkpoint inhibitor therapy), irAE (immune related adverse event).

Patient No	sex [male; female]	age at start of CPI [years]	primary tumor	p16 [0=negativ, 1=positiv]	CPI drug [pembrolizumab; nivolumab]	irAE	T(umor) stage at time of first diagnosis	N(odal) stage at time of first diagnosis	M (etastasis) stage at time of first diagnosis	indication for CPI [1: local recurrence; 2: local residuum; 3: remote metastasis; 4: ADRISK study]	result first re-staging	previous chemotherapy	previous radiation treatment
1	m	82	oropharynx	1	pembrolizumab	dermatitis	1	0	0	3	favorable	no	yes
2	f	60	paranasal sinus	not examined	nivolumab	0	3	1	0	3	unfavorable	yes	yes
3	m	64	oropharynx	1	pembrolizumab	0	2	1	0	4	favorable	yes	yes
4	m	48	oropharynx	0	nivolumab	thyreoditis	3	3	0	1	favorable	yes	yes
5	m	62	oral cavity	1	pembrolizumab	arthritis	4	0	0	2	favorable	yes	yes
6	m	81	larynx	not examined	pembrolizumab	0	2	2	0	3	unfavorable	yes	yes
7	m	44	oropharynx	0	nivolumab	0	4	2	0	3	unfavorable	yes	yes
8	m	73	oropharynx	1	pembrolizumab	0	1	2	1	3	favorable	yes	yes
9	f	80	oral cavity	0	nivolumab	pneumonitis / colitis	2	0	0	1	favorable	no	yes
10	m	65	oropharynx	0	nivolumab	pneumonitis / colitis	2	1	0	3	favorable	yes	yes
11	m	59	oropharynx	1	pembrolizumab	colitis	2	2	0	1	favorable	yes	yes
12	m	66	hypopharynx	not examined	pembrolizumab	0	3	2	0	3	favorable	yes	yes
13	m	74	oropharynx	1	pembrolizumab	0	2	1	0	4	favorable	yes	yes
14	m	80	oropharynx	0	pembrolizumab	0	3	0	0	3	died before restaging	no	yes
15	m	68	oropharynx	not examined	pembrolizumab	pneumonitis	2	0	0	1	favorable	no	yes
16	m	64	oropharynx	1	nivolumab	dermatitis / thyreoditis	4	2	1	3	unfavorable	yes	yes
17	m	40	oropharynx	1	nivolumab	0	4	1	0	3	died before restaging	yes	yes
18	m	55	oropharynx	not examined	pembrolizumab	0	4	2	1	2	died before restaging	yes	yes

(Continued)

10.3389/fonc.2024.1287178

TABLE 1 Continued

Patient No	sex [male; female]	age at start of CPI [years]	primary tumor	p16 [0=negativ, 1=positiv]	CPI drug [pembrolizumab; nivolumab]	irAE	T(umor) stage at time of first diagnosis	N(odal) stage at time of first diagnosis	M (etastasis) stage at time of first diagnosis	indication for CPI [1: local recurrence; 2: local residuum; 3: remote metastasis; 4: ADRISK study]	result first re-staging	previous chemotherapy	previous radiation treatment
19	f	74	larynx	not examined	pembrolizumab	0	1	0	0	1	died before restaging	no	yes
20	m	63	hypopharynx	0	nivolumab	0	4	0	0	3	unfavorable	no	yes
21	f	67	oropharynx	0	pembrolizumab	0	4	2	0	3	favorable	yes	yes
22	m	91	external auditory canal	not examined	pembrolizumab	arthritis	2	0	0	1	favorable	no	yes
23	m	55	oropharynx	0	pembrolizumab	vasculitis / hepatitis	1	3	1	3	unfavorable	yes	yes
24	m	76	hypopharynx	0	pembrolizumab	0	4	3	1	3	favorable	no	no
25	m	61	larynx	not examined	pembrolizumab	0	3	3	0	4	favorable	yes	yes
26	m	73	oropharynx	1	pembrolizumab	0	4	2	0	3	died before restaging	yes	yes
27	m	60	oropharynx	0	pembrolizumab	arthritis	4	0	1	3	favorable	yes	yes
28	m	61	hypopharynx	0	pembrolizumab	0	1	2	0	3	favorable	yes	yes
29	f	72	oropharynx	0	nivolumab	0	4	0	0	1	favorable	yes	yes
30	m	55	oropharynx	1	pembrolizumab	0	2	1	0	4	favorable	yes	yes
31	m	71	oropharynx	0	nivolumab	0	4	0	0	3	favorable	yes	yes
32	m	65	carcinoma of unknown primary	0	nivolumab	pneumonitis	0	3	1	3	favorable	yes	yes
33	f	66	oropharynx	0	pembrolizumab	0	4	2	0	3	favorable	yes	yes
34	m	50	oropharynx	1	nivolumab	pneumonitis	2	2	0	3	favorable	yes	yes
35	m	67	parotid gland	1	nivolumab	0	3	2	0	3	favorable	yes	yes

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found in the paranasal sinuses, external auditory canal, parotid gland, and carcinoma of unknown primary (CUP).

Human papillomavirus (HPV) status was determined by immunohistochemical staining of the surrogate parameter p16 as part of the histopathological routine assessment. A total of 15 tumors were determined to be p16-negative (42.9%); 12 tumors were determined to be p16-positive (34.3%); and in 8 tumors, p16-status was not examined (22.9%).

The indications for therapy with CPI were remote metastasis after platinum therapy in 19 patients (54.3%), unresectable recurrences in 8 patients (22.9%), and local residual tumors after primary therapy in 3 patients (8.6%). 5 patients received pembrolizumab in the ADRISK trial (ClinicalTrials.gov identifier: NCT03480672) in combination with cisplatin (14.3%).

Almost all patients received radiotherapy beforehand (n = 34), and the majority also received platinum-containing chemotherapy before starting CPI therapy (n = 27). There were no significant differences in the occurrence of irAE depending on any previous radio(chemo)therapy.

Abuse of both alcohol and nicotine was present in 13 patients (37.1%); 12 patients used nicotine only (34.3%), and 3 patients used alcohol regularly (8.6%). Seven patients denied regular noxious substance use (20%). No statistically significant associations were shown between continued substance abuse and the occurrence of irAEs. Similarly, there were no statistically significant differences in the outcome of the first re-staging. Group comparisons between patients who did not consume noxious substances and those who consumed only nicotine showed a significantly higher relative proportion of lymphocytes in the differential blood count before the initiation of CPI therapy in patients without nicotine ($p = 0.041$). The group consuming only alcohol showed a significantly higher mean tumor status than the group without noxious substances ($p = 0.004$). This difference in tumor status was also seen in the comparison of the group without noxious substances with the patients who consumed both nicotine and alcohol ($p = 0.028$). Patients who used both noxious substances were significantly younger on average (72.43 ± 13.53 vs. 60.46 ± 9.8 years, $p = 0.035$). These patients also had a significantly lower proportion of p16-positive tumors ($p = 0.018$). Prior to initiation of CPI therapy, they showed higher leukocyte counts ($p = 0.019$), a significantly higher percentage of neutrophil granulocytes ($p = 0.024$), and a lower percentage of lymphocytes ($p = 0.03$) and basophil granulocytes ($0 = 0.04$) in the differential blood count. In the group comparison of patients who consumed at least one noxious substance and those who did not consume noxious substances, the first group showed a significantly higher T-stage ($p = 0.003$), a lower proportion of p16-positive tumors ($p = 0.003$), and higher relative proportions of neutrophil granulocytes ($p = 0.05$), and lower proportions of lymphocytes ($p = 0.007$) in the differential blood count at the beginning of therapy than the second group. The dynamics of the biological values are shown in Figure 1.

During the course of therapy, 13 patients experienced at least one irAE (37.1%) (Figure 2). Pneumonitis occurred in 5 patients (14.3%). Arthritis and enterocolitis occurred in 3 patients (8.6%) each. Dermatitis occurred in 2 patients (5.7%), and thyroiditis also occurred in 2 patients (5.7%). Small vessel vasculitis and autoimmune hepatitis occurred in 1 patient (2.9%).

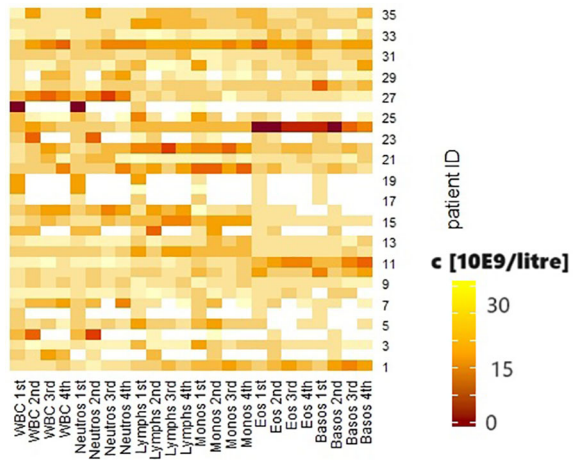

FIGURE 1
Heatmap of the biological values. White blood cells (WBC), neutrophil granulocytes (neutros), lymphocytes (lymphs), monocytes (monos), eosinophil granulocytes (eos), basophil granulocytes (basos) before the first, second, third and fourth courses of immunotherapy. Concentration shown in 10E9/liter.

Complications occurred at a mean of 15.3 weeks (± 16.6 weeks), with the earliest complication occurring after 2 weeks and the latest at 60 weeks after the first administration.

Under ongoing CPI treatment, dermatitis occurred on average after 12.5 weeks (± 3.5 weeks), thyroiditis after 6 weeks (± 5.6 weeks), arthritis after 3.3 weeks (± 0.5 weeks), pneumonitis after 26.2 weeks (± 21.3 weeks), and enterocolitis after 14.7 weeks (± 11.6 weeks). One patient developed vasculitis with concomitant hepatitis after 4 weeks.

The occurrence of dermatitis showed a significant association with the occurrence of thyroiditis in the same patient ($p = 0.004$). Patients with dermatitis during the study period had a significantly

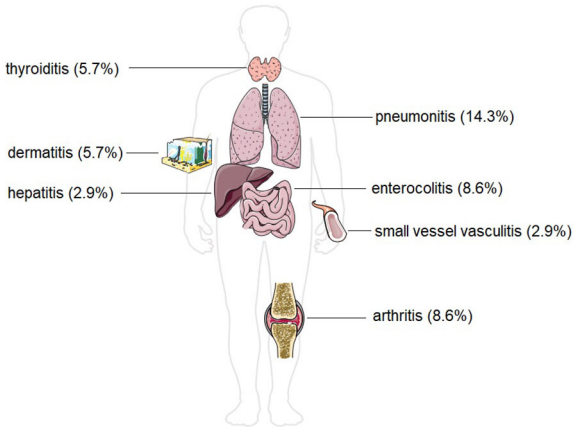

FIGURE 2
Incidence of different forms of immune-related adverse effects in our study group of patients with head and neck malignancies. The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

higher increase in relative basophil granulocytes between the second and third administrations (p = 0.005) and the third and fourth administrations (p = 0.001) of CPI compared to patients without dermatitis.

Patients who developed thyroiditis as an irAE showed significantly lower relative monocyte levels in the differential blood count at baseline (p = 0.029), which was also the case in the bloodwork done before the second administration of CPI (p = 0.007). In addition, they showed higher total leukocyte counts (p = 0.018) with higher relative (p = 0.045) and absolute (p = 0.007) neutrophil granulocytes. In addition, higher absolute values of basophilic granulocytes were seen at this time point (p = 0.044).

On average, patients with arthritis as an irAE showed significantly higher CPS scores (p = 0.006), lower nodal status (p = 0.022), higher differentiation of primary tumors (lower grading) (p = 0.021), and higher leukocyte levels (p = 0.048), with higher neutrophil granulocyte levels (p = 0.031) before the third administration of CPI than patients without arthritis.

The occurrence of pneumonitis was significantly associated with the delayed occurrence of enterocolitis (p = 0.006). Moreover, it occurred in patients with a significantly lower tumor size (p = 0.023).

The occurrence of enterocolitis was otherwise not significantly associated with any of the factors studied.

Because irAEs in the form of vasculitis and concomitant hepatitis occurred in only one patient in our collective, no meaningful statistical analysis of these two manifestations was possible.

Before the occurrence of any complications, two patients received oral cortisone therapy (5.7%) due to comorbidities (both patients received dexamethasone 4 mg, three times a day).

The occurrence of irAEs in general, as well as the individual subtypes, was not significantly associated with patient age or sex. There were no significant correlations between primary tumor localization and the occurrence of irAEs. There were no associations of the occurrence of irAEs in total in relation to any perineural sheath invasion (Pn), vein infiltration, lymphatic vessel infiltration (V, L), or p16 status. There was a significant association between smaller primary tumors and the occurrence of pneumonitis (p = 0.02, Somer's D = -0.19), a low lymph node involvement (a smaller N stage), and the occurrence of arthritis (p = 0.05, Somer's D = -0.16). A significant positive correlation was seen between lymph node status (N stage) and the possible presence of remote metastases (M status) (p = 0.027, r = 0.375). The negative correlation between N-stage and patient age was significant (p = 0.027, r = -0.374), as was the positive correlation between perineural sheath infiltration in the primary tumor and venous infiltration (p = 0.038, r = 0.427) and lymphatic vessel infiltration (p = 0.027, r = 0.450).

The presence of remote metastases correlated with a higher immune cell score (IC, percentage of area of PD-L1-positive immune cells from area of vital tumor cells) (p = 0.014, r = 0.484), while poorer tumor differentiation (corresponding to higher grading/G-value) correlated with a lower CPS value (p = 0.037, r = -0.419).

The ratio of neutrophil granulocytes to lymphocytes (NLR) showed no relevant correlations with the occurrence of irAEs or re-staging outcomes.

After the first re-staging, 13 patients showed a response in terms of partial remission (PR) (37.1%); 6 patients showed stable disease (SD) (17.1%); 6 patients showed progressive disease (PD) (17.1%); and 1 patient showed a mixed response (2.9%). The 4 patients who were treated in the ADRISK study showed a complete remission (CR) (11.4%). Five patients (14.3%) died before the first re-staging.

Discussion

Compared to conventional chemotherapies, which for HNC are mainly represented by platinum-based drugs, the tolerability of CPI is rather good. Under cisplatin, typical complications occur, some of them lethal, such as renal failure (22), neuropathies (23), and myelosuppression with neutropenic susceptibility to infection and sepsis (24). In addition, patients typically suffer from marked nausea (25). The only targeted therapy in HNC is cetuximab, an antibody against the epidermal growth factor receptor, which is frequently administered and also generally well-tolerated (26).

IrAEs are the main complications of therapy with CPI. In our study, we recorded 37.1% of patients with these complications. It should be noted that, in some cases, the assignment of the symptoms that occurred (e.g., diarrhea or pneumonitis) or the laboratory chemical changes (e.g., increase in transaminases as an indication of hepatitis) cannot be reliably assigned to CPI therapy, as they can be due to multiple causes. In our study group, however, no other or more plausible causes were found in the subsequent clinical clarification. Moreover, the remission of symptoms or blood count changes after pausing CPI therapy and, if necessary, cortisone administration argued for their evaluation as irAEs. The most common irAE in our study was pneumonitis.

Time of occurrence and progression

Both the frequency and the nature of irAEs vary depending on the tumor entity and CPI medication (27). It seems logical that organically manifested irAEs occur mainly in those anatomical areas where tumor cells are found, i.e., where activation of the disinhibited immune system occurs. Thus, pneumonitides are found mainly under CPI therapy in patients with non-small cell lung cancer (NSCLC) (28). However, the fact that the lung is also the primary metastatic site for HNC may explain why pulmonary irAEs are also relatively common in our patient population. Although not all of these patients had clinically/radiologically diagnosed pulmonary metastases, it seems possible that already scattered tumor cells in the lung provided a target for CPI and thus a preferential organ for irAE manifestation. This is consistent with other retrospective studies, in which pulmonary irAE was the most common in NSCLC and the second most common in HNC (29). Nevertheless, because pneumonitis also occurs as a relatively common irAE in other entities, an organotopically independent etiology also seems likely.

The time to onset of irAEs was highly variable in our study. While some patients developed irAEs after two weeks, i.e., after only one drug administration, in other patients they occurred only after a prolonged period of up to 60 weeks, i.e., after multiple drug administrations. The onset of arthritis after about three weeks seems to be the most stable in time; otherwise, the time of onset was widely scattered within the individual irAEs. The underlying pathomechanisms—why, in some patients, irAEs occur only after a very long delay—are still subject to research, as are the partly described chronic persistent irAEs, which did not occur in our cohort (30). Several different theories on the underlying pathomechanisms have been discussed thus far, on the basis of which the high heterogeneity of intensities and temporal occurrence of irAE could be explained. Most of them concern the individual nature of single components of the immune system, which are more or less predisposed to irAE. In this regard, a mismatch between T effector cells and regulatory T cells (Tregs) has been described. Tregs play an important role in peripheral tolerance, as demonstrated by mouse models, in which a deficiency of Tregs leads to a pronounced autoimmune response (31). Since PD-1 is expressed on Tregs, it can be assumed that CPIs used in the therapy of R/M-HNC also target Tregs in the tumor environment and lead to a shift in the balance between autoimmunity and tolerance (32). Thus, the occurrence of irAEs also depends on the initial presence and extent of the immunosuppressive effect of Tregs in an individual patient.

Histopathological studies have shown that infiltrates of specific T cells with similar T-cell receptor profiles were found in the tumors of patients, as well as in the organs affected by irAEs (33). Here, shared antigens in tumor tissue and endogenous healthy tissue seem to trigger the activation of specific autoimmune T-cell clones with consecutive inflammatory responses. Depending on the antigen distribution for these specific T cells in tumor tissue and patient organs, patients seem to be more or less susceptible to the development of irAEs. Furthermore, specific proinflammatory cytokine profiles seem to favor the development of irAEs (34). From this, Deng et al. deduced a more frequent occurrence of irAE in patients with a high body mass index, since overweight patients have a different cytokine profile, which apparently predisposes them to irAE more strongly (35). The role of preexisting autoantibodies prior to the initiation of CPI therapy is still controversial, and their significance also appears to be organ dependent. For instance, while researchers found a significant association of preexisting antithyroperoxidase antibodies and/or antithyrotropin receptor antibodies with the development of autoimmune thyroiditis (36, 37), patients with rheumatoid/arthritic irAEs showed few conventional rheumatoid autoantibodies, such as rheumatoid factor and anticyclic citrullinated peptide antibodies (38). In a study investigating the significance of autoantibodies during ipilimumab therapy, autoantibodies were associated with the occurrence of irAE but not necessarily with the respective organ-specific autoantibodies (39). Thus, there appears to be some underlying patient-specific profile that influences the likelihood of occurrence and the mode of irAE, but the significance of this observation cannot yet be conclusively quantified. Although much of the literature is devoted to the importance of T cells in the development of irAE, B cells also appear to have an influence, at least indirectly, on the development of irAE. Interestingly, in a study on the time course of irAE, a correlation was demonstrated between the decrease of B cells overall and the increase of a subset of $CD21^{lo}$ B cells, as well as of plasmablasts (40).

In summary, the time course seems to be subject to multifactorial immunological, tumor-specific, and drug-specific influences and is currently unpredictable for individual patients.

Demographic factors

The occurrence of irAEs in general, as well as the individual subtypes, was not significantly associated with patient age or sex. The literature of CPI therapies outside of HNC includes studies that attribute a risk factor for the occurrence of irAEs to young age (41) and sex (depending on the CPI, male or female) (42), as well as those that found no association with the occurrence of irAEs for either age (43) or sex (44). Overall, the likeliest summary is that the occurrence of irAEs in general, and the tolerability of CPI therapy in general, are not associated with age. However, specific subtypes, such as endocrine and gastrointestinal irAEs, seem to occur preferentially in younger patients, while skin and joint manifestations occur more often in older patients (43, 45). In this context, our data did not demonstrate an association with the occurrence of irAEs in general or their subtypes in HNC, despite a wide range of ages from 40 to 91 years in our cohort.

Localization of the primary tumor

In head and neck oncology, depending on the localization of the primary tumor (oral cavity/pharynx/larynx, etc.), therapeutic approaches often vary; for example, depending on the localization, the resectability of a tumor is more or less feasible. It would have been conceivable that anatomic regions with increased lymphoepithelial tissue, such as the oropharynx, would have a stronger antitumor immune response, with a correspondingly higher risk of irAE. However, significant correlations between individual localizations and the occurrence of irAEs could not be demonstrated.

Histopathological factors

Our results regarding the significant association of the occurrence of pneumonitis with a smaller tumor size and arthritis as an irAE with a lower N stage are controversial compared to previous studies on lung carcinoma and multiple melanoma patients (46). In those studies, T and N stages were not compared, but tumor burden in general was compared via the number of metastatic sites; a significant association was found between tumor burden and the occurrence of irAEs. It should be emphasized that the statistical association in our data was significant but rather weak (Somer's D 0.16 and 0.19); appropriate caution should be exercised in evaluating this

association. As a finding, however, it remains that insights from other entities regarding the association between tumor burden and the occurrence of irAEs cannot be readily applied to HNC patients.

No sufficient data to suggest histological tumor grade as a possible risk factor for the occurrence of irAEs are available.

Dermatitis

Our HNC patients who developed dermatitis as an irAE during CPI therapy showed an increase in basophilic granulocytes over the course of the treatment period. Scientific evidence shows the role of basophil granulocytes in the development of allergic skin reactions (47) and inflammatory skin diseases (48). In addition, there are already studies describing an association between high basophil granulocytes and the occurrence of skin irAEs (49), albeit before the start of CPI therapy. In our data, a trend toward such correlations can also be recognized, derived, and statistically proven, but it is difficult to deduce a possible causal relationship. At present, no pathophysiological explanation for this has been found. Therefore, it is advisable to sensitize patients to the occurrence of skin changes and to make regular inquiries in this regard, as they are not necessarily associated with CPI therapy.

Thyroiditis

Thyroiditis, as the most relevant representative of endocrinological irAEs, is mainly manifested by a new onset of hypothyroidism. Cases of initial hyperthyroidism with a subsequent transition to hypothyroidism have also been described in the literature (50), but this did not occur in our collective. Instead, all patients had transient asymptomatic hypothyroidism that regressed spontaneously during the course of treatment without further specific therapy.

When associated factors for the occurrence of thyroiditis as irAEs were examined, the main differences were seen in the differential blood counts of patients who developed thyroiditis and those who did not. Interpretation of the prognostic/predictive significance of leukocytes and their subsets is limited because of high variability, dynamics, and multiple influencing factors. Therefore, in previous studies, mainly histopathological examinations were performed, and tissue macrophages in the affected endocrine glands were shown to be partly responsible for the autoimmune response (51). However, the extent to which increased tissue macrophage content might be related to decreased peripheral blood monocyte content remains speculative. In contrast, when biomarkers for irAE were identified during CPI therapy in melanoma patients, the occurrence of pancreatitis was associated with elevated monocyte levels at therapy initiation (52). Thus, while different levels of monocytes appear to be related to the occurrence of endocrine irAEs, no clear direction or value can yet be demonstrated. Our data regarding elevated leukocyte levels with an increased proportion of neutrophil granulocytes are in line with previous observations in other entities, but there is limited valence, with a high variability of values (21).

Arthritis

In other autoimmune rheumatoid diseases, such as adult-onset Still's disease, elevated levels of leukocytes and neutrophil granulocytes are also typically found (53). Overall, this laboratory chemistry constellation is suggestive of a systemic inflammatory response and is not specific to irAE. The fact that these blood count changes occurred only before the third administration of CPI therapy compared to patients who did not develop arthritis does not support suitable usability as a biomarker for early detection. The high CPS levels found would be a possible explanation in the sense that, with strong PD-L1 expression, there is a greater target for CPI therapy and thus an increased risk for irAE. It must be emphasized that PD-L1 levels in the tumor do not necessarily represent those of the rest of the body's cells. However, this association was found only in patients with arthritis as an irAE, not in the other irAE subgroups, so the predictive power of CPS seems questionable.

Pneumonitis

Pulmonary irAE, especially pneumonitis, is a potentially life-threatening complication for patients and occurs mainly in those undergoing PD-1 inhibitor therapy (54). As discussed later, the predictive or prognostic significance of irAE remains the subject of current studies. However, the occurrence of pneumonitis during CPI therapy has already shown an association with worsened overall survival in NSCLC patients in studies (13). This illustrates that, for the evaluation of irAE, not only should the activated immune system be seen as a possible response to therapy, but the threat of the complication itself should also not be underestimated. The occurrence of pneumonitis under CPI therapy is difficult to predict. In a study of NSCLC patients receiving CPI therapy, the presence of high levels of baseline peripheral blood absolute eosinophil count was described as being associated with the development of pneumonitis irAE (55). Whether this also represents an independent risk factor could not be inferred by these authors. In contrast, no such laboratory associations were identified in our study. Other studies have found an association between the occurrence of pneumonitis and other metachronous irAE forms (29). It is possible that both NSCLC and HNC patients are susceptible to pulmonary diseases, such as irAE manifestations, because nicotine use is the most relevant risk factor for both entities. However, no statistical association between nicotine use and the occurrence of pneumonitis was found in our data, which is consistent with other studies that included HNC patients (29).

Enterocolitis

Regarding enterocolitis as an irAE, our evaluations did not demonstrate any significant associations with the factors studied. In meta-analyses, the occurrence of enterocolitis as an irAE with CPI therapies is shown to be mainly dependent on the type of therapy (more frequent with CTLA-4 antibodies than with PD-1 antibodies)

(56), while the localization and the entity of the tumor do not seem to influence the probability. It should be noted here that the symptoms of enterocolitis, such as diarrhea, also occur nonspecifically in the population, and even the clinical picture of pathological enterocolitis can be caused by multiple pathogens. Therefore, an etiologic assignment, such as irAE, is particularly difficult. The fact that the patients in our collective showed rapid clinical improvement after pausing CPI therapy and cortisone administration is not conclusive for an irAE, but from a retrospective perspective, it seems likely.

Vasculitis and hepatitis

In our study, vasculitis and hepatitis occurred in only one patient. Therefore, a statistical evaluation of possible correlations and associations was not possible. Hepatic irAE manifests primarily in a laboratory-detectable elevation of the transaminases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (57). They occur more frequently in patients who are being treated with CPI due to hepatocellular carcinoma and who already have limited organ functions due to chronic hepatitis or liver cirrhosis (58). Patients are usually asymptomatic, and when symptoms do occur, they are often nonspecific and are therefore frequently not referred to therapy by patients (59). It is of high importance to regularly check liver enzymes during CPI therapy. As with other forms of irAE, other possible causes of liver enzyme elevation must be investigated and ruled out. These include infectious hepatitis and cholestasis.

Vasculitis as an irAE can occur in many forms due to its ubiquitous vascular supply. However, it is a rare subtype compared to the rest of the irAEs. In our patients, vasculitis manifestations were mainly found on the forearms and hands, with rapid regression under systemic cortisone therapy.

Alcohol and nicotine consumption

There was no statistically significant association between the consumption of noxious substances by the patients and the occurrence of irAEs, nor was there any association with the outcome of the first re-staging. However, there were differences in the blood counts before the start of therapy, with increased leukocytes and neutrophil granulocytes and simultaneously lower levels of lymphocytes in the patients with toxicant consumption. Increased leukocytes, with a shift to increased formation of neutrophil granulocytes and decreased formation of lymphocytes, represent a systemic inflammation marker, as they can be increasingly detected with typical noxae, such as nicotine (60). Furthermore, patients with classical noxious consumption were found to have a greater tumor size at the onset of therapy. On one hand, it can be assumed that classical noxae (alcohol and tobacco) have a synergetic carcinogenic effect and thus explain the larger tumor sizes compared to abstinent patients. On the other hand, this could also be explained by the consideration that patients with increased use of noxious substances, on average, have rather low medical adherence and therefore consult a physician only at an advanced stage of the disease. The fact that the incidence of HPV-positive tumors seems to be lower in the subgroup with toxin use than in the subgroup without use is consistent with published studies in larger study cohorts (61).

p16 status

In addition to classic noxae like alcohol and nicotine, infection with HPV, more specifically high-risk types 16 and 18, is a relevant risk and etiological factor in HNC (62). Therefore, histopathological determination of the expression of the surface marker p16 was performed in a large proportion of cases to assess whether HPV association of the tumor was present (63). However, it is important to emphasize that p16 is only a surrogate marker for HPV infection. Up to 23% of p16-overexpressing HNCs are not associated with HPV (64).

It seems conceivable that viral surface markers, which are also discussed as a cause for the better prognosis of HPV-positive vs. HPV-negative HNC (65), allow better recognition of tumor cells by immune cells infiltrating the tumor. Therefore, HPV- (or p16-) positive tumors could be expected to have a stronger immune response due to higher immunogenicity and are associated with both a higher risk for irAEs and a better outcome due to the stronger antitumor effect of CPI therapy. In our cohort, however, there was no significant difference between the p16-positive and p16-negative groups, either with regard to the frequency of irAEs or the outcome of the first re-staging. Early efficacy studies of pembrolizumab (66) and nivolumab (67) in R/M-HNC also showed no significant differences in outcome depending on HPV status. Recently, reviews and meta-analyses have demonstrated an improved outcome of p16-positive R/M-HNC under CPI. However, the study participants were treated with PD-1 inhibitors, as well as PD-L1 inhibitors, and no retrospective differentiation was possible (68). Some meta-analyses discovered that the superior outcome of p16-positive R/M-HNC was limited to oropharyngeal cancers only and was undetectable outside the oropharynx (69). This contrasts with other meta-analyses that also demonstrated the improved response of p16-positive R/M-HNC outside the oropharynx but without a distinction between PD-1 and PD-L1 inhibitors (70). It should be noted, however, that our study examined the outcome of the first re-staging, not the overall survival defined as an endpoint in most studies. By considering the first re-staging instead of overall survival as an endpoint, we hoped for a more specific assessment of the CPI response. Even though overall survival is considered one of the most relevant endpoints in oncologic research, it is unspecific in its assessment of treatment response because a variety of other factors are involved (e.g., comorbidities). Overall, the significance of HPV/p16 status as a prognostic parameter for CPI therapy in R/M-HNC does not appear to be as conclusively assessable as in conventional radio(chemo)therapy, where the more favorable outcome of p16-positive tumors is generally accepted (71).

irAE as a predictive factor for re-staging

Among other antitumor drugs in the HNC field, namely the epidermal growth factor receptor (EGFR) antibody cetuximab, an

association between the adverse drug effect in the sense of acne-like skin changes and the therapy response is known (72, 73). Thus far, it remains unclear whether a clinically visible autoimmune complication could also be a favorable predictive factor for treatment response, as it demonstrates a systemic activation of the immune system. In retrospective studies of HNC patients, the relationship between overall survival (OS) and progression-free survival (PFS) was investigated (74, 75). These authors describe the occurrence of autoimmune complications as an independent prognostic factor for favorable OS and PFS. Other studies and meta-analyses of this type confirm the association of autoimmune complications and later OS and PFS in other tumor entities, such as non-small cell lung cancer, melanoma, gastric cancer, renal cell carcinoma, and urothelial carcinoma (76). However, the authors criticize various sources of error, such as the guarantee (or immortal) time bias, which may feign this association due to the retrospective study design (77, 78). Responders to treatment with CPI survive longer, receive more CPI therapy, and thus have a cumulative increased risk of irAE over time. A retrospective evaluation demonstrated a spurious association between the occurrence of irAEs and a favorable outcome. To avoid this bias, we evaluated the treatment response at the first re-staging at a defined time point. Patients from our collective were re-staged after the first cycle (four administrations) of CPI using cross-sectional imaging (CT neck-thorax, possibly with CT abdomen in case of metastases), and the images were radiologically evaluated according to the RECIST criteria (79). Subsequently, patients were presented to our interdisciplinary head and neck tumor board, and a decision was made regarding the continuation of CPI therapy. In the case of PR, SD, and MR, CPI therapy was continued; the re-staging results were designated as "favorable" for this study. In patients with PD, the therapy regimen was changed; these re-staging results were designated as "unfavorable" for this study.

Statistical analysis showed a significant association between the occurrence of pneumonitis as an irAE and a favorable re-staging outcome ($p = 0.038$, Somer's $d = 0.24$). For the remaining individual irAEs and the occurrence of irAEs in general, there were no statistically significant associations with subsequent re-staging outcomes. In contrast, previous meta-analyses that did not include HNC patients partially demonstrated an association between the occurrence of endocrine, dermatological, and low-grade irAEs and the better efficacy of CPI therapy (80). Meta-analyses have shown that the occurrence of high-grade irAEs is associated with a better response to therapy but with worse overall survival (81), which makes clear that the occurrence of irAEs should not only be interpreted as a positive predictive factor, if at all, but also as a potential threat to the patient. However, data regarding R/M-HNC are still too limited to draw valid conclusions about the association between irAE and the response to CPI therapy and patient outcomes.

PD-L1 scores

A special interest in the selection of CPI therapy is given to the PD-L1 score, which indicates the expression of PD-L1 on tumor cells by specifying TPS (percentage of PD-L1-positive tumor cells from all vital tumor cells), IC (percentage of area of PD-L1-positive immune cells from area of vital tumor cells), and CPS (combination of TPS and IC, percentage of PD-L1-positive cells, including lymphocytes and macrophages from all vital tumor cells) quantified in the expression of PD-L1 on the tumor cells and the immune cells infiltrating them. There were no correlations between PD-L1 scores and the occurrence of irAEs. Similarly, there were no correlations between PD-L1 scores and the outcome of the first re-staging. Other studies have described a statistically significant association between tumors scored as "PD-L1-positive" and "PD-L1-negative" with respect to patient outcome (82), but correlation analyses showed no significant association once the PD-L1 score exceeded the positivity level (83). In the literature, studies of a possible predictive/prognostic value of PD-L1 scores beyond a positive/negative assessment can be found mainly in entities other than HNC, such as NSCLC (84). In patients receiving first-line CPI therapy, a positive correlation between high TPS scores and the occurrence of irAE could be demonstrated. In contrast, a correlation of high TPS scores and a favorable outcome was only found in patients who received CPI therapy as second- or third-line therapy, but not in first-line therapy. It should be noted that, depending on the study, the threshold for the evaluation of the PD-L1 score as positive or negative was chosen differently, which makes comparative considerations difficult. Overall, the determination of the PD-L1 score in the therapy of HNC is important for the assignment of the appropriate CPI agent, but beyond that, prognostic/predictive evaluation seems to be very limited.

Concomitant cortisone therapy

In studies evaluating the efficacy of nivolumab in recurrent brain tumors against bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, the outcome of patients treated with cortisone in addition to nivolumab was found to be worse than in patients treated with nivolumab without cortisone (85). This effect was not found in the bevacizumab group, so it can be assumed that immunoinhibitory drugs, such as cortisone, limit the immunogenic antitumor effect of CPI. This seems comprehensible, as cortisone is also used for autoimmune complications with CPI therapy in HNC as a counter-regulation to disinhibit the immune system therapeutically (86). Similar results were also found in patients receiving CPI therapy for non-small cell lung cancer, with a worse outcome after high-dose cortisone therapy (87). However, the authors specifically note that the indication of cortisone therapy also reflects the advanced, more symptomatic tumor status of patients and therefore cannot necessarily be considered an independent factor. We reviewed the continuous medication of the patients in our study for any comedications with immunosuppressive agents they were receiving for other indications. Two patients were found to be on cortisone therapy for another indication prior to the possible occurrence of irAE. Both patients showed progressive diseases in the first re-staging but did not develop irAEs. This supports the idea that the antitumor effects of CPI therapy and potential irAEs are suppressed under continuous immunosuppressive medication. However, a potential statistical

conclusion cannot be drawn, as the pattern described above comprises only a very small number of patients in our cohort (n = 2).

Furthermore, studies from other entities also exist in which no negative influence was demonstrated by immunosuppressive cortisone administration during CPI therapy. Nevertheless, these data refer to cortisone therapies initiated only during ongoing CPI therapy for the treatment of irAEs (i.e., in which an activated immune system is obviously present) (88, 89). In conclusion, it seems reasonable to check the patient's existing permanent medication for potential immunosuppressants when starting CPI therapy and to critically evaluate the indications for this. At the same time, if irAEs occur that necessitate low-dose cortisone therapy, it should not be omitted out of false fear of the immunosuppressive effect on CPI therapy.

Limitations

The limitations of this study are mainly the modest size of the study population. Since CPI is a relatively new treatment modality in HNC, clinical expertise is still limited compared to other entities in which CPI has been used for a longer time period. Furthermore, the retrospective evaluation cannot exclude influencing factors that were not documented. The patient population was also rather heterogeneous. On one hand, patients who are in recurrent or residual situations receive CPI therapy and no longer have surgical therapy options due to their multimorbidity. These patients are likely to succumb to their illness at an earlier stage before autoimmune complications occur.

On the other hand, patients with remote metastases and a likely poorer outcome who receive CPI over a long period of time show stable diseases throughout. Thus, the observation periods differed between the two groups due to the different dropout rates, which also resulted in limited comparability of the patient cases in the cohort. In addition, the guarantee-time bias mentioned above should not be neglected. It can also be assumed that irAEs with mild symptoms were not considered relevant by the patients and were not recorded, even despite specific inquiries at each examination. Thus, a certain underestimation of the occurrence of irAEs in general can be assumed, but not of clinically relevant irAEs.

Conclusion

Our data show how difficult it is to predict autoimmune complications under CPI therapy. We were able to identify some parameters associated with the occurrence of irAEs in the retrospective evaluation. However, neither demographic, histopathological, nor laboratory chemistry values seem to be able to generate a sound and reliable risk profile for this type of complication.

There are only a few available studies on this topic regarding HNC patients, and few meta-analyses include HNC patients. While some of the data from our collective are consistent with findings from certain other tumor entities, others differ. Future multicenter studies must be designed prospectively to achieve robust data from ideally larger collectives.

Until then, it is all the more important to inform patients in detail about possible complications at the start of CPI therapy, to enquire regularly and specifically about corresponding symptoms, and to monitor organ functions by means of laboratory chemistry. By combining these precautions, autoimmune complications during CPI therapy can be detected at an early stage, and appropriate therapeutic measures can be initiated.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethikkommission II, Heidelberg university. The studies 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

FJ: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. AA: Writing – review & editing. CB: Writing – review & editing. AL: Writing – review & editing. SL: Writing – review & editing. KM: Writing – review & editing. NR: Writing – review & editing. LH: Supervision, Writing – original draft.

Funding

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

Conflict of interest

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

Publisher's note

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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 05 March 2024
DOI 10.3389/fonc.2024.1336577

OPEN ACCESS

EDITED BY
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RECEIVED 10 November 2023
ACCEPTED 25 January 2024
PUBLISHED 05 March 2024

CITATION
Guo T, Zamuner F, Ting S, Chen L, Rooper L, Tamayo P, Fakhry C, Gaykalova D and Mehra R (2024) Clinical and genomic characterization of chemoradiation-resistant HPV-positive oropharyngeal squamous cell carcinoma.
Front. Oncol. 14:1336577.
doi: 10.3389/fonc.2024.1336577

Clinical and genomic characterization of chemoradiation-resistant HPV-positive oropharyngeal squamous cell carcinoma

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Introduction: Most patients with HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) have an excellent response to chemoradiation, and trials are now investigating de-escalated treatment. However, up to 25% of patients with HPV-positive OPSCC will experience recurrence, and up to 5% will even progress through primary treatment. Currently, there are no molecular markers to identify patients with poor prognosis who would be harmed by de-escalation. Herein we report the clinical and genomic characteristics of persistent HPV-positive OPSCC after definitive platinum-based chemoradiation therapy.

Methods: Patients with HPV-positive OPSCC treated with curative intent platinum-based chemoradiation between 2007 and 2017 at two institutions and with a persistent locoregional disease were included. We evaluated clinical characteristics, including smoking status, age, stage, treatment, and overall survival. A subset of five patients had tissue available for targeted exome DNA sequencing and RNA sequencing. Genomic analysis was compared to a previously published cohort of 47 treatment-responsive HPV+ OPSCC tumors after batch correction. Mutational landscape, pathway activation, and OncoGPS tumor states were employed to characterize these tumors.

Results: Ten patients met the inclusion criteria. The tumor and nodal stages ranged from T1 to T4 and N1 to N2 by AJCC 8th edition staging. All patients were p16-positive by immunohistochemistry, and eight with available *in situ* hybridization were confirmed to be HPV-positive. The 1-year overall survival from the time of diagnosis was 57%, and the 2-year overall survival was 17%. *TP53* mutations were present in three of five (60%) persistent tumors compared to 2% (one of 47) of treatment-responsive HPV-positive tumors (p = 0.008). Other

genes with recurrent mutations in persistent HPV-positive OPSCC tumors were *NF1*, *KMT2D*, *PIK3C2B*, and *TFGBR2*. Compared to treatment-responsive HPV-positive tumors, persistent tumors demonstrated activation of DNA Repair and p53, EMT, MYC, SRC, and TGF-beta signaling pathways, with post-treatment samples demonstrating significant activation of the PI3K-EMT-Stem pathways compared to pretreatment samples.

Conclusion: Chemoradiation-resistant HPV-positive OPSCC occurs infrequently but portends a poor prognosis. These tumors demonstrate higher rates of p53 mutation and activation of MYC, SRC, and TGF-beta pathways. A comparison of tumors before and after treatment demonstrates PI3K-EMT-Stem pathways post-treatment in HPV-positive tumors with persistent disease after platinum-based chemoradiation.

KEYWORDS

HPV, oropharyngeal squamous cell carcinoma, platinum resistance, treatment resistance, persistent disease, genomics

Introduction

In recent years, the prevalence of HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) has increased significantly, and the incidence of OPSCC has now surpassed that of cervical cancer in both the US and the UK (1, 2). Currently, over 70% of all oropharynx tumors are HPV-positive (1). In addition, it is now recognized that a HPV-positive tumor status is associated with a good prognosis and improved response to chemoradiation (3, 4). Accordingly, the new AJCC staging system has incorporated HPV tumor status, and a HPV-positive status significantly downstages a tumor (4). Several trials are actively investigating the de-escalation of therapy for HPV-positive OPSCC, given significantly improved overall prognosis (5, 6).

However, in contrast to this paradigm, up to 25% of patients with HPV-positive OPSCC will experience recurrence, and up to 5% will demonstrate a lack of response to primary treatment, representing a persistent disease (3, 4). These patients have tumors that do not respond to standard chemoradiation and are without a disease-free interval. By the first post-treatment evaluation at 12 weeks, they demonstrate a persistent or progressive disease. This atypical aggressive clinical behavior is distinct in patients who experience a recurrent disease with a disease-free interval, often years after the definitive treatment. Similar to other patients with a HPV-positive disease, some of these disease-persistent patients may not even have a history of smoking or alcohol use and may be relatively young. In short, the biology of their disease is inconsistent with what we understand about HPV-related tumors. Those with treatment resistance are rare but portend dire prognosis and have not been well characterized. There are currently no biomarkers to identify patients who will not respond to treatment or would potentially be harmed by de-escalation.

Therefore, the goal of this study is to characterize HPV-positive tumors that demonstrate persistence and a lack of treatment response to standard platinum-based chemoradiation treatment through targeted DNA sequencing and RNA sequencing. These tumors were then compared to previously sequenced cohorts: HPV-positive tumors with good prognosis (no progression with 3 years follow-up) and from The Caner Genome Atlas (TCGA). A comparison of the mutational landscape and gene expression profiles for these cohorts will seek to identify potential biomarkers and key oncogenic pathways for HPV-positive tumors with poor prognosis. While these cases are rare, the ability to identify patients with this aggressive disease would inform which patients are not candidates for de-escalation of therapy and provide insight into the biomarkers of poor prognosis in a HPV-positive disease.

Methods

Patient cohort

This study was approved as a part of IRB protocol NA_00036235 through Johns Hopkins Medicine IRB. Patients were included if they completed platinum-based chemoradiation with curative intent for HPV-positive oropharyngeal squamous cell carcinoma between 2007 and 2017 at two institutions, Johns Hopkins Hospital and Greater Baltimore Medical Center, and demonstrated a locoregional persistent disease or progression after treatment. Clinical characteristics, including smoking status, age, stage, primary treatment, and overall survival, were abstracted from the medical record. Patients were excluded if they did not complete the standard-of-care curative intent treatment, were not

treated with concurrent platinum-based treatment, had out-of-field or metastatic recurrence without a locoregional disease, or were lost to follow-up.

Patient samples

Patient samples were obtained from archived paraffin-embedded tissue from a biopsy or surgical specimens. Only a subset of patients had available archival biopsy or resection tissue for DNA/RNA extraction and subsequent sequencing. Patients with original biopsies performed outside of our institution did not have tissue available for additional sequencing analysis. The diagnosis of squamous cell carcinoma was confirmed by pathology, and HPV tumor status was evaluated with p16 immunohistochemistry with >70% staining. In eight out of 10 patients, HPV *in situ* hybridization was also available to confirm HPV positivity. Pre-treatment specimens and additional post-treatment samples of a persistent disease were also obtained when available. Two patients had paired pre- and post-treatment tissue samples that were available for analysis. Additional comparisons were performed with a previously published HPV-positive cohort with 47 tumors and 25 normal samples (7). Data from the Cancer Genome Atlas (TCGA) was utilized for a comparative mutational analysis. A total of 497 head and neck squamous cell carcinoma (HNSCC) tumors from The Cancer Genome Atlas (TCGA) were also utilized for tumor state analysis, including 44 HPV-positive oropharyngeal tumors (8).

Sample preparation and sequencing

Next-generation sequencing was performed as part of routine clinical care for three patients. Targeted exome data was obtained from FoundationOne (Cambridge, MA, USA) for two patients and PGDx (Personal Genome Diagnostics, Baltimore, MD, USA) for one patient. These analyses included the targeted sequencing of 125–315 cancer-related genes. Remaining available tissue was obtained in these patients from unstained paraffin-embedded slides from biopsy or surgical specimens. The tissue slides were reviewed by a pathologist, and tumor tissue was defined on each slide to enrich the tumor collection on tumor slides. Matched adjacent normal tissue from cancer patients was obtained from two patients to include for normal comparison and for somatic mutation analysis. Five slides per patient sample were utilized for tissue collection. The tissue from slides was then collected, and combined DNA and RNA extraction was performed using the AllPrep DNA/RNA extraction kit (Qiagen). All tumor samples were processed in a single batch with two matched normal controls (adjacent normal tissue from two cohort patients with persistent disease) and tissue from three previously sequenced tumors in patients with no evidence of a recurrent disease to be used for batch correction with the previously published cohort (7). Due to the small size of the biopsy tissue, one patient with targeted DNA exome sequencing did not have any remaining tissue available for RNA extraction and sequencing.

RNA sequencing and DNA sequencing were performed at the Johns Hopkins Genetic Resource Core Facility (GRCF). Targeted exome sequencing was performed on two patients with paired normal tissue to allow for mutation calling on a panel of 434 cancer-associated genes in the curated solid tumor panel (Supplementary Table S1). Sequencing was conducted using NovaSeq system (Illumina) as previously described (9). Library preparation was performed using SureSelect-XT Target Enrichment System (Agilent Technologies) with a curated cancer-related solid tumor gene panel. The read depth ranged from 100 to 500×. Reads were aligned to the human genome (GrCh37/hg19) using Burrows–Wheeler alignment. Variant calling was performed using in-house variant caller algorithm (MDLVC v5.0) and HaplotypeCaller (Genome Analysis Tool Kit 3.3). These were reviewed using Integrated Genomics Viewer (Broad Institute). Variants with strand bias, low coverage (<300), or consistent with artifact after review were removed. As mentioned above, the remaining exome sequencing was obtained from clinical genomic testing. Mutational profiles of each sample are available in Supplementary Table S2.

For RNA sequencing, samples were required to achieve an RNA Integrity Number (RIN) of at least 7.0. Barcoded and stranded libraries from ribosomal RNA depleted RNA were prepared using Takara SMARTer Total RNA-Seq Kit v2. Sequencing was performed using Illumina NovaSeq 6000 platform. Alignment was performed to GRCH37/hg19 genome assembly using the salmon aligner (10), and gene expression profiles were extracted. A similar pipeline was used to realign 47 HPV+ OPSCC tumors and 25 oropharyngeal mucosae from normal controls from our previously published patient cohort (7), including four patients with a recurrent disease at a median follow-up of 31 months to allow for batch correction and gene expression comparison.

Gene expression analysis

Batch correction and gene expression analysis were performed using DESeq in R (11), version 4.0.4. Batch correction then allowed integrated gene expression analysis between persistent tumors and the previously published cohort (7). Batch corrected gene abundances are included in Supplementary Table S3. Gene Set Enrichment Analysis (GSEA) was performed to compare differentially expressed genes between cohorts (12). Pathway activation was scored utilizing the Denoising Algorithm based on Relevance network Topology (DART) (13) and published pathway activation signatures. PD1 (PDCD1) and PDL1 (CD274) expressions were directly compared after batch correction. Deconvolution of the estimated immune infiltrates was evaluated using xCell (14). The estimated cell type enrichment scores were compared after batch correction, and multiple testing correction was performed using the Benjamini–Hochberg method.

OncoGPS tumor states

Additional genomic modeling was performed by projecting gene expression profiles onto an archetype map of head and neck

squamous cell carcinoma using Onco-GPS methods (15). Briefly, the characteristic cancer pathways characteristic of head and neck squamous cell carcinoma were selected *a priori*: NfkB-SRC-JUN pathway, TCA Cycle, DNA Repair-MYC-E2F, PI3K-EMT-Stem, WNT-BCAT-AKT, NFkB-IRF-KLF5, EGFR-p63, EMT-ZEB1, and NRF2-PPP pathways (Supplementary Figure S1). Utilizing projections of these gene set pathways, nine tumor states were defined within head and neck squamous cell carcinoma by utilizing 497 head and neck squamous cell carcinoma tumors from The Cancer Genome Atlas (TCGA). TCGA tumors were then categorized into these nine states based on master transcriptional components, and tumor characteristics were described within each state including tumor subsite, HPV status, *TP53* mutation status, and smoking history. Lastly, non-recurrent and persistent HPV-positive tumors were projected and defined onto these tumor states based on the pathway activation of nine master transcriptional components, and pre- and post-treatment tumor states were compared for patients for which biopsy samples were available before and after chemoradiation.

Survival analysis

A survival analysis was performed using the "survival" package from CRAN, version 3.3-1, using R version 4.0.4. The survival data was compared between groups using Kaplan–Meier and log rank statistics. Similar methods were utilized for the evaluation of our clinical cohort patients and TCGA patients. Additional survival analyses were performed to compare overall survival based on mutational status.

Results

Clinical characteristics and outcomes

Of 18 patients identified with persistent or progressive HPV-positive oropharyngeal squamous cell carcinoma, 10 patients who completed curative intent chemoradiation with treatment to 70 Gy and concurrent platinum-based chemotherapy (cisplatin or carboplatin) met the inclusion criteria (Table 1). Patients were excluded if they received cetuximab (n = 1), did not complete recommended chemotherapy or radiation course due to side effects (n = 2), only had metastatic recurrence without locoregional persistence (n = 3), had out-of-field recurrence (n = 1), or were lost to follow up (n = 1). All patients were male, with a median age of 58 years. The patients included 30% of never smokers and 40% of former smokers. The tumor and nodal stages ranged from T1 to T4 and N1 to N2 by AJCC 8th edition staging. All patients were p16-positive by immunohistochemistry, and eight patients with available HPV *in situ* hybridization (ISH) were confirmed to be HPV-positive. All patients were treated with definitive chemoradiation with evidence of locoregional persistence after treatment.

All patients demonstrated a persistent locoregional disease after completion of primary therapy, assessed within 4 months of treatment by the first post-treatment imaging study or sooner if clinically evident persistence was present. All patients demonstrated no disease-free interval. In addition, four patients (40%) developed new distant metastases upon follow-up imaging at the time of first post-treatment evaluation at 4 months, including lung, bone, and liver metastases. Median overall survival was 12.4 months. The 1-year overall survival from the time of diagnosis was 57%, and the 2-year survival was 17% (Figure 1). Median survival in patients with locoregional persistence was 13.9 months compared to 9.6 months in those with concurrent metastatic disease.

Two patients were enrolled in hospice care following the diagnosis of a persistent disease, and survival for both patients was less than 6 months from the initial oncologic diagnosis. Four patients underwent salvage surgery for the persistent locoregional disease, and four patients underwent treatment with systemic therapy with chemotherapy and/or immunotherapy. Overall survival in this small cohort differed for patients based on salvage treatment received; patients receiving hospice (median, 5.16 months) had lower overall survival compared to those receiving systemic therapy (9.73 months) and salvage surgery (20.96 months) (Figure 1, p = 0.002).

Mutational analysis

TCGA showed that HPV-negative tumors have a high rate of *TP53* mutation, while these mutations are quite rare in HPV-positive tumors. DNA sequencing demonstrated that *TP53* mutations were present in three of five (60%) persistent HPV-positive tumors compared to 2% of treatment-responsive HPV-positive tumors from the previously published cohort (p = 0.008). This is consistent with the *TP53* mutation rate in TCGA of 2.2% of 45 HPV-positive tumors. The identified *TP53* mutations in persistent tumors were D228H, R123X, and R181C. These mutations were all within the DNA binding domain of p53, but they were not identified in known mutational hotspots (16).

Within the entire TCGA HNSCC cohort (n = 506 with available mutation data) including both HPV-positive and HPV-negative cohorts, p53 mutations were identified in 71% of patients. The presence of *TP53* mutation was associated with worse overall survival (median OS, 45.8 vs. 65.8 months, p = 0.009). This was even more pronounced among HPV-positive TCGA patients (median OS, 12.2 vs. 68.4 months, p < 0.001; p53 mutation rate 2.2%, Supplementary Figure S2). As has been previously published (17), p53 mutations were associated with smoking; mutations were identified in 79% of current smokers compared to 65% of non-smokers (p = 0.009). HPV-positive patients within control cohorts that harbored p53 mutations included both a current smoker (TCGA) and non-smoker (previously published cohort) (18). The mutation in *TP53* was associated with worse overall survival in smokers (p = 0.01) but not in never smokers (p = 0.3).

Other genes harboring mutations among 40% (n = 2) of persistent HPV-positive OPSCC tumors were *NF1*, *KMT2D*, *PIK3C2B*, and *TGFBR2*. The mean tumor mutational burden was 12.96 Mut/Mb (range, 2–36.05). The prevalence of other recurrent mutations, respectively, was less than 20% in the full TCGA cohort:

10.3389/fonc.2024.1336577

TABLE 1 Patient cohort.

		Smoker	AJCC 8th edition staging	Primary treatment	Response and treatment	Follow-up, months	Alive at FU	TMB	p53	RNA		DNA	
										Pre	Post	Pre	Post
1	59, M	Never	T1N1M0	CRT with cisplatin	LR persistence, new spinal mets: hospice care	5.65	N	9	WT	X		X	
2	43, M	Never	T1N1M0	CRT with cisplatin	LR persistence: salvage surgery	13.94	N	5	WT		X		X
3[a]	55, M	Former (15 pky)	T3N2M0	CRT with cisplatin	LR persistence: hospice care	4.66	N	36	D228H	X	X	X	
4	87, M	Former (7.5 pky)	T2N2M0	CRT with carboplatin	LR persistence: immunotherapy, carboplatin	8.12	Y	–	R123X			X	
5[a]	49, M	Current (30 pky)	T4N2M0	CRT with carboplatin/ paclitaxel	LR persistence, new liver mets: immunotherapy trial	9.73	N	2	R181C	X	X		X
6	75, M	Former (10 pky)	T3N1M0	CRT with cisplatin	LR persistence, new lung mets: carbo/taxol	9.47	N						
7	58, M	Never	T2N1M0	CRT with cisplatin	LR persistence: salvage surgery	15.85	Y						
8	54, M	Former (15 pky)	T2N1M0	CRT with cisplatin	LR persistence: salvage surgery	12.39	N						
9	58, M	Former (27 pky)	T4N2M0	CRT with cisplatin, cetuximab, and paclitaxel	LR persistence, new lung mets: cis/ cetux/paclitaxel	20.25	N						
10	64, M	Current (45 pky)	T3N2M0	CRT with cisplatin	LR persistance: salvage surgery	27.98	N						

pky, pack years; CRT, chemoradiation; LR, locoregional; FU, follow-up; TMB, tumor mutation burden in mut/Mb.
[a]Patients with paired pre- and post-treatment biopsies.

NF1 (2.8%), KMT2D (16.2%), PIK3C2B (1.4%), and TGFBR2 (4.7%). Mutations in KMT2D and PIK3C2B were also associated with trends toward worse overall survival in TCGA HNSCC patients compared to WT (KMT2D, p = 0.10, PIK3C2B, p = 0.08), but mutations in the NF1 and TGFBR2 were not significantly associated with prognosis in TCGA (p = 0.8 for both, Supplementary Figure S3).

In HPV-positive tumors from the TCGA cohort, mutations were not found in NF1, PIK3C2B, or TGFBR2, and KMT2D mutations were seen in 13.3% of tumors. The frequency of

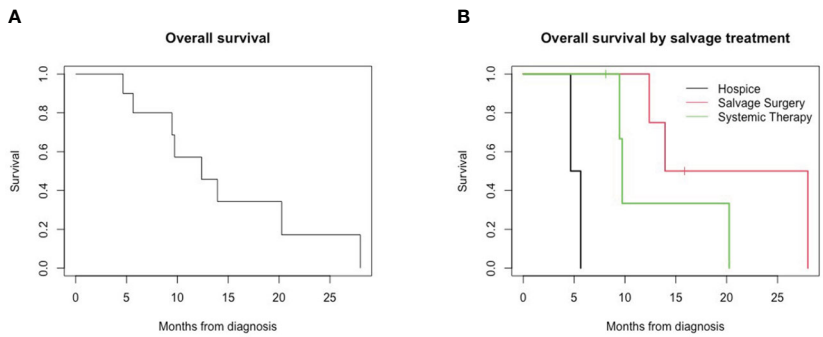

FIGURE 1
Overall survival for patients with persistent HPV-positive oropharyngeal squamous cell carcinoma. **(A)** Overall survival of all patients. **(B)** Overall survival by salvage treatment.

KMT2D mutations in TCGA was not significantly different from the treatment-resistant cohort (13.3% vs. 40%, $p = 0.12$). Among HPV-positive tumors, KMT2D mutations were not associated with overall survival ($p = 0.6$, Supplementary Figure S3).

Gene expression analysis

Evaluation of gene expression through RNA sequencing revealed alterations in specific pathways enriched in persistent tumors. Differential gene expression analysis was performed between persistent and non-persistent tumors (Figure 2A). The initial analysis was performed only in FFPE specimens (three non-persistent and four persistent tumors). Gene set enrichment analysis (GSEA) of hallmark pathways demonstrated a significant differential expression in the following major pathways: hypoxia (padj = 0.013), MYC targets (padj = 0.013), epithelial–mesenchymal transition (padj = 0.013), TGF-beta signaling (padj = 0.026), DNA Repair (padj = 0.026), interferon alpha response (padj = 0.026), IL2 STAT5 signaling (padj = 0.038), and p53 pathway (padj = 0.039).

Persistent tumors were then compared to non-recurrent HPV tumors from the previously published cohort, including 47 treatment-responsive tumors, of which four patients experienced a subsequent recurrence. Pathway activation analysis was performed in three groups: HPV-positive treatment-responsive tumors without recurrence ($n = 43$), treatment-responsive tumors with recurrence ($n = 4$), and persistent tumors ($n = 4$). Using DART pathway activation scoring and previously published pathways, gene expression profiling demonstrated a significant activation of MYC, SRC, and TGF-beta signaling pathways in persistent tumors compared to tumors with good prognoses, without recurrence (Figure 2B). Tumors with response to treatment but with a subsequent recurrence trended toward the intermediate activation of the MYC, SRC, RAS, and TGF-beta signaling pathways.

To understand the potential role of immune infiltrates, gene signature-based immunoprofiling was inferred from bulk sequencing. PD1 and PDL1 expression did not significantly differ in the persistent tumor cohort ($p > 0.3$). Overall immune score, stroma score, and microenvironment scores did not differ in the persistent tumor cohorts ($p > 0.1$). After multiple testing correction, three of 64 cell types were noted to have a significantly altered enrichment in persistent tumors: basophils (padj = 0.01) and Th2 cells (padj = 0.024), and pro B-cells showed increased enrichment (padj = 0.006).

OncoGPS analysis and shift of genomic markers during treatment

A model of HNSCC tumors was then defined using Onco-GPS methods (15) with 497 head and neck squamous cell carcinoma (HNSCC) tumors from The Cancer Genome Atlas (8). In order to test the hypothesis that persistent HPV-positive tumors match a phenotype that is more similar to HPV-negative disease, both HPV-positive and HPV-negative tumors were used to build a full Onco-GPS model. The tumors were defined by nine tumor states (Figure 3A), each characterized by the differential activity of nine key pathways: NRF2-PPP, NFkB-SRC-JUN, TCA Cycle, DNA Repair-MYC-E2F, PI3K-EMT-Stem, WNT-BCAT-AKT, NFkB-IRF-KLF5, EGFR-p63, and EMT-ZEB1. These pathways were selected using a cancer archetype methodology based on differential expression pathways that characterized head and neck cancers through GSEA analyses (Supplementary Figure S1). TCGA HNSCC tumors were then mapped to each subtype. HPV-positive and oropharynx tumors were clustered in states T2 and T7 (Figures 3B, C). Both states are characterized by the upregulation of EGFR-p63 and TCA Cycle pathways and the downregulation of EMT-ZEB1 and DNA Repair pathways. Interestingly, most laryngeal tumors were characterized as state T8 and additionally demonstrated NRF2-PPP and PI3K-EMT-Stem pathway activation. *TP53* mutations were most dominant in states T0, T4, and T8. State T4 was primarily comprised of current smokers, and states T4, T5, and T8 had the fewest never smokers.

When sequenced FFPE tumors were projected onto tumor states and archetypes, tumors responsive to treatment (purple)

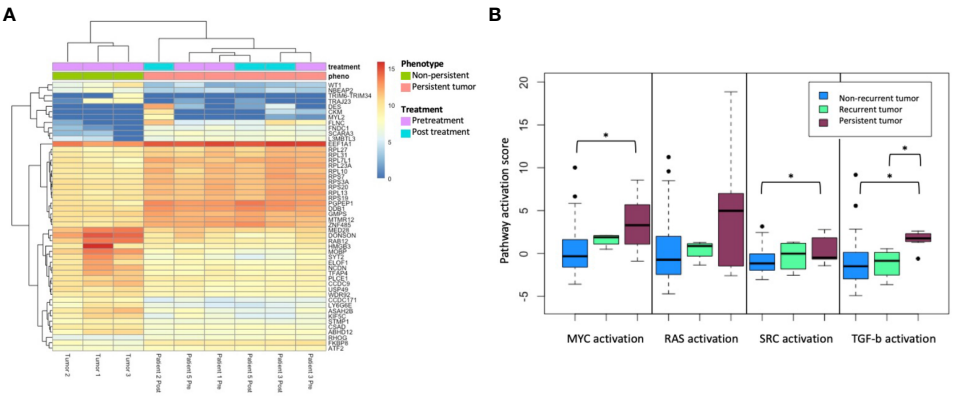

FIGURE 2
(A) Top 50 differentially expressed genes' hierarchical clustering from between persistent tumors (red) and non-persistent tumors (green), FFPE only. **(B)** Pathway activation score for MYC, RAS, SRC, and TGF-b activation between non-recurrent tumors (n = 43), recurrent tumors (n = 4), and persistent tumors (n = 5). The asterisk (*) denotes p < 0.05 on paired t-test.

10.3389/fonc.2024.1336577

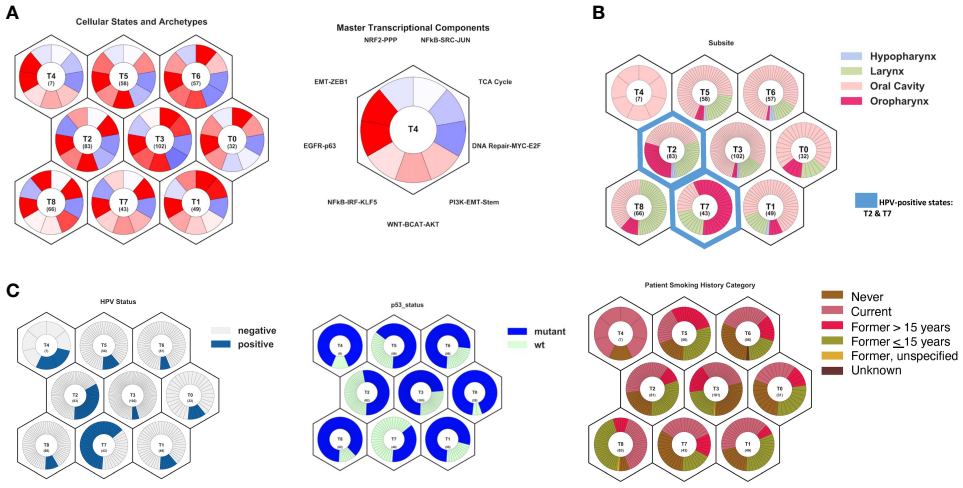

FIGURE 3
Model of head and neck squamous cell carcinoma tumor states and archetypes developed from The Caner Genome Atlas using Onco-GPS methods. **(A)** Summary of cellular states and archetypes, showing nine distinct cellular types, and transcriptional components used to build the cellular states, showing the key pathways to differentiate states. **(B)** Projection of tumor subsite onto cellular states, showing oropharyngeal tumors primarily in T2 and T7 states and larynx tumors in T8 state. **(C)** Projection of HPV status, TP53 mutation status, and smoking history onto cellular states, showing majority of the HPV-positive tumors in states T2 and T7. TP53 mutations were most dominant in states T0, T4, and T8. State T4 comprised primarily current smokers, and states T4, T5, and T8 had the fewest never smokers.

clustered in state T2, characterized by EGFR-p63/WNT and downregulation of EMT-ZEB1 and DNA Repair-MYC-E2F, and associated with HPV-positive oropharyngeal tumors (Figure 4). Two persistent tumors (green) were defined by T7 state (upregulation EGFR-p63 and TCA Cycle pathways and the downregulation of EMT-ZEB1 and DNA Repair pathways), an oropharyngeal/HPV-positive state. However, several persistent tumors were characterized by HPV-negative non-oropharyngeal states, including T0 and T3 states (predominantly the oral cavity, characterized by the upregulation of EGFR-p63 and NFkB-SRC-JUN pathways and the downregulation of DNA Repair-MYC-E2F) and T8 (predominantly larynx cancer and current/former smokers, characterized by the upregulation of NRF2-PPP and PI3K-EMT pathways).

Two patients (#3 and #5) had both pre- and post-treatment paired tumors for which RNA sequencing was performed. These paired tumor samples were projected onto tumor states. Both patients had tumors characterized by p53 mutations and had a prior smoking history. Pre- and post-treatment states and state pathway activation were evaluated for those patients (Figure 4). Patient #3 initially presented in state T3, shifting to T0 after treatment, characterized by the upregulation of the EMT-ZEB1 and PI3K-EMT-Stem pathways. Patient #5 initially presented in the HPV-positive T7 state but, during treatment, shifted to a post-treatment state dominated by larynx/smoking SCC type T8, with a significant upregulation of the NRF2-PPP and PI3K-EMT-Stem pathways. Thus, both persistent tumors demonstrated an upregulation of the PI3K-EMT pathway after platinum-based chemoradiation treatment. These state shifts suggest that the inhibition of PI3K and EMT pathways represent an opportunity to target treatment resistance in these tumors.

Discussion

In the past two decades, our understanding of the impact of HPV-positive tumor status on clinical outcomes in oropharyngeal disease has expanded dramatically. The Ang et al. landmark study described the improved outcomes in HPV-positive disease (4), and we have continued to see an increasing incidence of HPV-positive oropharyngeal SCC (1). While most of these HPV-positive patients have an excellent response to therapy and remain disease-free, this disease continues to have a spectrum of patients who harbor an aggressive disease despite favorable biology. Within the RTOG 0522 cohort, locoregional failure was 17.3% and distant metastatic disease was 6.5% at 3 years for HPV-positive patients. Herein we described an even rarer phenomenon of patients who present with the persistent disease despite treatment with curative intent, which may occur in up to 5% of patients (3, 4).

Given this relatively infrequent disease phenotype, we were motivated to better understand the clinical characteristic as well as the genomic features of a treatment-resistant HPV-positive oropharyngeal disease. Within this rare clinical entity, we report a case series of patients and include the genomic analysis of this disease phenotype that has not previously been published. Notably, this patient cohort with treatment resistance included 30% never smokers. The patient age range was wide (43 to 87 years at the time of diagnosis), spanning the range of typical ages for the diagnosis of OPSCC. Most notably, the poor overall survival is highlighted in treatment-resistant diseases, with a median overall survival of 12.4 months. These patients have significantly worse prognosis compared to most HPV-positive patients with a 3-year OS of 82.4% (4) and even compared to HPV-positive patients who present with a recurrent disease, whose median OS after

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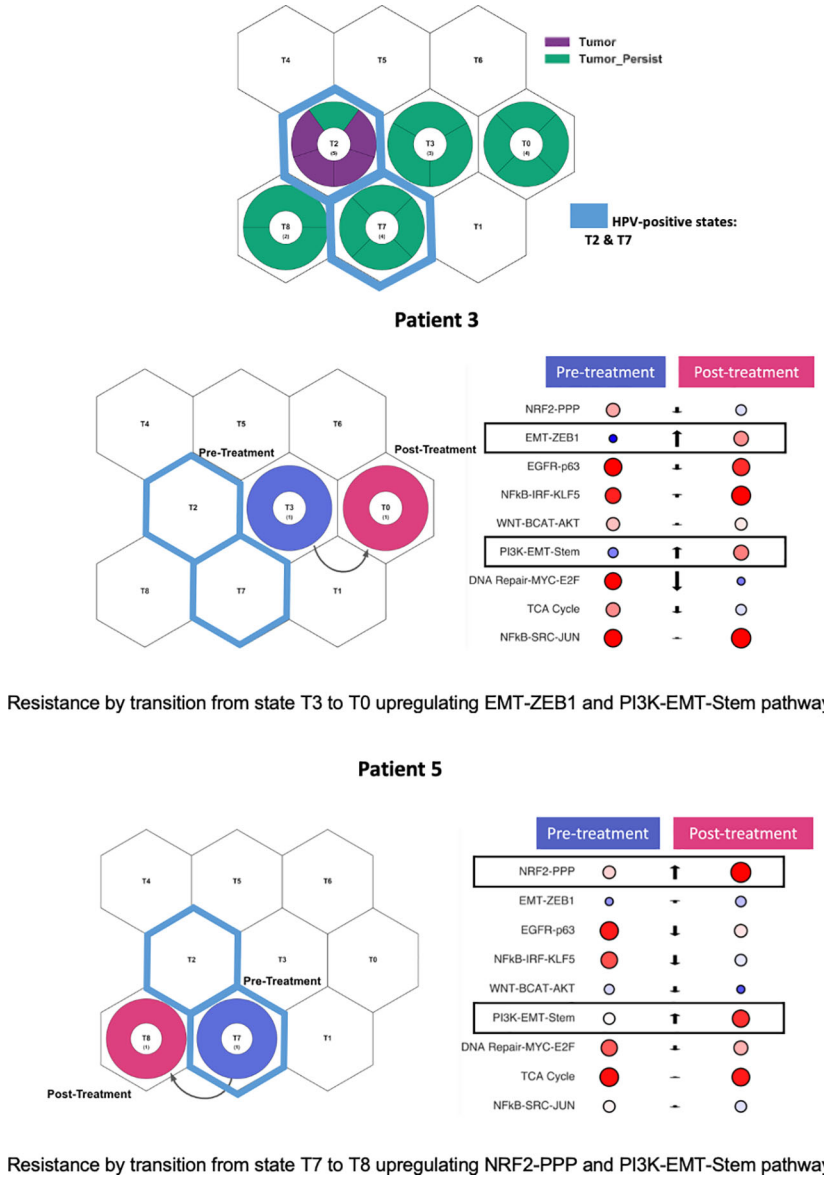

FIGURE 4
Persistent tumors projected onto tumor states and archetypes. Persistent tumors projected into both HPV-positive and HPV-negative states. Two patients with paired pretreatment and post-treatment samples. Patient 3 demonstrated cellular state shift from state T3 to T0. Patient 5 demonstrated cellular state shift from state T7 to T8. Both patients demonstrated upregulation of the PI3K-EMT-Stem pathway post-treatment.

progression is 2.6 years (3). Treatment with salvage therapy was associated with some benefits, particularly salvage surgery, increasing the median OS to 21 months.

Mutational analysis in this cohort of treatment-resistant HPV-positive tumors demonstrated a much higher rate (60%) of p53 mutation compared to other published rates in the literature. In our previously published cohort, the p53 mutation rate was 2% in HPV-positive tumors (18), and the TCGA cohort demonstrated a similar rate of 2.2% (8). Another report detected up to 6.7% rate of p53 mutations in HPV-positive oropharyngeal cancer in a Japanese population (19). *TP53* mutations are a well-established risk factor for worse overall survival in HNSCC (20). Still its impact in the setting of HPV-positive diseases is not well described as these mutations rarely co-exist with HPV-mediated diseases. One study evaluating recurrent HPV-positive tumors demonstrated higher rates of p53 alterations in recurrent HPV-positive tumors (21). In the TCGA cohort, one HPV-positive patient demonstrated p53 mutation, and the overall survival was 12 months, similar to the median survival of the treatment-resistant cohort. Our data suggest that p53 mutation in the setting of HPV-positive OPSCC may portend a worse prognosis and may be a predictor of chemoradiation resistance. This may represent one biomarker to select patients for primary surgical therapy if treatment resistance is predicted.

The *TP53* mutations seen in the persistent disease cohort were observed in patients with either current or former smoking history. These mutations could contribute to the worse prognosis seen in HPV-positive smokers (4). Among smokers, indeed p53 mutations

were associated with worse prognosis. However, given the rarity of these mutations in HPV-positive patients, conclusions still remain limited regarding the interplay between p53 and smoking in HPV-positive diseases. Additional investigation will also be needed to understand the mechanisms of disease in non-smokers who harbor an aggressive HPV-positive disease.

Previously published studies of mutational alterations in HPV-positive diseases have described other biomarkers associated with prognosis—for example, the loss of TRAF3 and PI3K pathway alterations has been associated with improved prognosis in HPV-positive tumors, including in a study of distant metastatic lesions (22, 23). *PIK3C2B* mutation was present in two patients in our cohort. Mutations were identified in KMT2D and PIK3C2B within the treatment-resistant cohort, and mutations in these genes demonstrated a trend toward worse overall survival in the TCGA cohort, suggesting possible biomarkers for aggressive diseases.

The genomic analysis demonstrated several key pathways activated in treatment-resistant HPV-positive tumors. GSEA identified MYC, EMT, TGF-beta, and DNA Repair as major pathways of differentially expressed genes compared to treatment-responsive tumors. DNA damage repair pathway enrichment may be associated with p53 mutation and loss. ERCC1 overexpression has also been associated with worse prognosis and treatment resistance in HNSCC (24, 25). Similarly, Hanna et al. described a trend toward greater alterations in DNA Repair proteins in distant metastatic HPV-positive diseases (23). Resistant tumors were also characterized by MYC, SRC, and TGF-beta pathway activation. HPV viral integration has been associated with MYC activation in multiple cancer types (26, 27); however, there have been mixed data on the prognostic significance of HPV integration (28–30). TGF-beta activation may be one mechanism of epithelial-to-mesenchymal transition (EMT), which has been related to treatment resistance with cetuximab (31), recurrent disease (32), as well as poor prognosis (33). Lastly, gene expression data was also utilized to explore differences in immune infiltrates and landscapes, but no significant differences were seen in PD1 expression, PDL1 expression, overall lymphocyte infiltrates, or immune scores. Only one patient demonstrated TMB greater than 10 mut/Mb, who may have derived benefit from immunotherapy (34).

Defining tumor states through OncoGPS archetypes allowed for the distilled characterization of the key pathway activation within each tumor. This demonstrated that treatment-resistant tumors primarily matched the cellular states of non-oropharyngeal HPV-negative tumors. Furthermore, both patients with pre- and post-treatment biopsy samples developed activation of the PI3K-EMT-Stem pathway during treatment. The activation of these pathways may represent an attractive potential target for salvage treatment in the setting of persistent disease after definitive chemoradiation with platinum therapy. Several PI3K pathway inhibitors, particularly mTOR inhibitors, have already been evaluated in clinical trials for HNSCC. While monotherapy with rapamycin and everolimus had limited clinical effect (35–37), dual targets with other inhibitors such as HER3 and MEK may offer more promise for these HPV-positive tumors characterized by PI3K activation (38–40).

This study is limited in scope due to the small patient cohort, limiting specific conclusions regarding both clinical behavior and genetic biologic alterations that may drive treatment-resistant HPV-positive oropharyngeal cancer. Specifically, in the genetic analysis, only half of the patient cohort and available tissue for sequencing analysis and sequencing were performed in archival FFPE samples, which can limit the quality. Tissue was collected when clinically available, resulting in some inconsistency in the use of pretreatment and post-treatment tissue. Specifically for those with clinical genomic testing, DNA sequencing was performed on both pretreatment and post-treatment tissue based on availability and clinician practice. Therefore, the identified alterations in post-treatment tissue could be acquired mutations that would not be as comparable to pretreatment tissue that was collected in the control cohorts. Furthermore, additional tissue validation such as with Sanger sequencing was unfortunately not feasible due to limited tissue availability from archival biopsy tissue. In addition, only two patients had tissue from both pre- and post-treatment available for comparison of change in response to treatment. Therefore, this represents a limited case series for which only preliminary conclusions can be drawn.

To improve the statistical power, treatment-resistant tumors were compared to previously published cohorts, including HPV-positive oropharyngeal cancer (7) and TCGA (8). Comparisons across cohorts can be confounded by significant batch effects. We sought to mitigate this by performing batch correction when performing gene expression analysis with treatment-responsive tumors in the previously published HPV-positive cohort, including three matched samples across cohorts (11). When using TCGA data, we utilized cellular archetype projections to mitigate batch effects when estimating pathway activation.

However, to our knowledge, this is the first published cohort to characterize this unique treatment-resistant phenotype in HPV-positive oropharyngeal disease. While a larger cohort is needed to provide additional validation, this study offers new insight into this rare disease phenotype.

Conclusions

Chemoradiation-resistant HPV-positive OPSCC occurs infrequently but portends a dire prognosis compared to the majority of HPV-positive OPSCC. Specifically, patients with a persistent disease after treatment demonstrate a significantly worse prognosis; however, treatment with salvage surgery or systemic therapy can still increase the overall survival. These tumors demonstrate higher rates of *TP53* mutation, and *TP53* mutation may represent a biomarker for treatment resistance in HPV-positive OPSCC. The gene expression analysis also demonstrates that these resistant tumors demonstrate activation of the MYC, SRC, and TGF-beta pathways. Pathway mapping can further identify specific targeted therapies that may have higher efficacy than traditional platinum-based chemoradiation for tumors with this uniquely aggressive phenotype, such as PI3K pathway inhibition which is under development for the treatment of head and neck cancer.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: GEO repository, accession number GSE256047. The datasets presented in this study can also be found in the Supplementary Material.

Ethics statement

The studies involving humans were approved by Johns Hopkins Institutional Review Board. 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 this is a retrospective review with no more than minimal risk.

Author contributions

TG: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. FZ: Data curation, Methodology, Writing – review & editing. ST: Data curation, Formal analysis, Methodology, Writing – review & editing. LC: Data curation, Formal analysis, Methodology, Writing – review & editing. LR: Data curation, Methodology, Writing – review & editing. PT: Formal analysis, Methodology, Visualization, Writing – review & editing. CF: Data curation, Methodology, Resources, Writing – review & editing. DG: Conceptualization, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. RM: Conceptualization, Formal analysis, Funding acquisition, Resources, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Gleiberman Head & Neck Cancer Early Career Fellowship (TG), 1KL2TR001444 KL2 Training Grant (TG), RSG-21-020-01-MPC from the American Cancer Society (DG), and R01DE027809 from the National Institute of Health (DG).

Conflict of interest

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

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1336577/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Defining tumor cellular states and archetypes in head and neck squamous cell carcinoma.

SUPPLEMENTARY FIGURE 2
Overall survival in months by p53 mutation status in The Caner Genome Atlas (TCGA) head and neck squamous cell carcinoma. **(A)** All TCGA patients [WT n = 144, mutant n = 362]. (B) TCGA HPV-positive patients [WT n = 44, mutant n = 1]. **(C)** TCGA current and former smokers [WT n = 99, mutant n = 275]. (D) TCGA never smokers [WT n = 41, mutant n = 78].

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