2 Novel Multidisciplinary Paradigms: Surgery/Radiation, Immunotherapy, Organ Preservation

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Background

Head and neck cancer (HNC) treatment has evolved with advances in surgery, radiotherapy, and systemic therapies aimed to maximize oncologic control and organ preservation. In addition to chemotherapy, immunotherapy and targeted agents have grown a larger role in systemic therapeutics. All treatment paradigms must carefully consider functional consequences. Given the complex interactions between multimodality therapies, multidisciplinary care is always evolving. The oncologist has the responsibility to provide patients with treatment options, both curative and palliative, and provide understanding of the advantages and disadvantages inherent to each approach.

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Over the last 30 years, there has been an overall decrease in the incidence of HNC, attributable to a decline in tobacco consumption. Over the same period, there has been a substantial increase in high-risk human papillomavirus (HPV)-associated oropharyngeal squamous cell cancers (OPSCC) [1]. In the last three decades, survival rates of HNC overall have improved from 54.7% in 1992–1996 to 65.9% in 2002–2006. This statistic has been driven largely by the high rate of cure in HPV-associated oropharyngeal squamous cell carcinoma (HPV-OPSCC).

The various sites of head and neck squamous cell carcinomas (HNSCC) are labeled in Fig. 2.1. Each site within the head and neck confers different anatomic and physiologic constraints. A squamous cell carcinoma (SCC) in the nasopharynx, for example, behaves in a very different fashion than one in the adjacent oropharynx. Treatment algorithms, therefore, vary highly dependent on site.

Given the complexity of head and neck anatomy and tumor biology, multidisciplinary approaches to treatment confer enormous benefit to patients. Surgical, systemic, and radiotherapeutic technologies and techniques have made large improvements of late. Some of the most important advances are detailed in this chapter.

In contrast to 20 years ago, HPV-OPSCC now makes up the majority of oropharyngeal cancer diagnoses [1]. Combination chemotherapy and radiation (CRT) demonstrated excellent oncologic control for HPV-OPSCC and became gold

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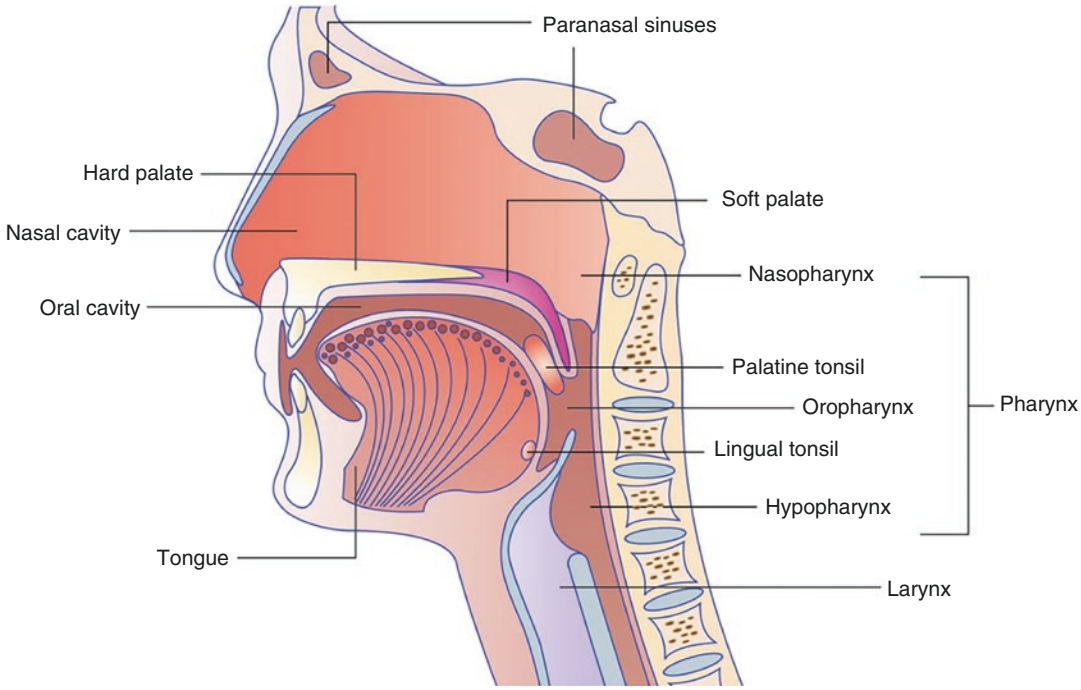

Fig. 2.1 Anatomic regions of the head and neck [2]

standard primary treatment for advanced disease [3, 4]. However, the short- and long-term adverse effects of CRT for OPSCC are significant [4, 5]. These concerns in part led to two separate and intersecting advances within the multidisciplinary treatment of OPSCC: clinical trials aimed at dose de-escalation for CRT protocols (detailed in the Chap. 1) and the reemergence of primary surgical treatment, detailed below.

The treatment of oligometastatic disease provides a new setting through which we can effectively intervene in a patient's cancer progression. Oligometastatic is disease distant from the primary site but in limited quantity. The nascent literature on this currently describes oligometastases as less than or equal to 5 metastatic lesions [6]. This differs from oligoprogression wherein a majority of disseminated disease sites respond to systemic therapy; however, specific lesions progress through treatment [7]. New data demonstrates the value of stereotactic body radiation therapy (SBRT) in select cases to slow or halt progression in select sites of distant metastatic disease. In head and neck cancer, this provides a modality for potential control of a small number of distant metastases when locoregional control has been achieved. Furthermore, this modality can be useful in the setting of recurrent disease.

Many improvements continue to be made at the outer reaches of what is currently considered treatable disease. Multimodality organ preservation techniques continue to be explored in areas where traditional methods would cause intolerable morbidity. Examples include sparing the eye during sinonasal tumor treatment and maximizing the preservation of function for oral cavity cancers [8–10].

Oral cavity squamous cell carcinomas (OSCC) today are predominantly treated with surgery, with adjuvant radiation and systemic therapy as indicated. Unfortunately, the morbidity of surgical treatment for advanced T-stage tongue tumors is debilitating especially for speech and swallow function. In addition, the poor prognosis for very advanced OSCC patients invited reinvestigation of neoadjuvant systemic therapy, with or without radiotherapy, for further prognostication and consideration for definitive nonsurgical manage-

ment. While definitive CRT protocols have been widely adopted for the treatment of laryngeal, hypopharyngeal, nasopharyngeal, and oropharyngeal primaries, only a limited number of institutions have updated CRT treatment protocols with the intent of improving organ preservation in the treatment of OSCC [10, 11].

Induction chemotherapy has also become an important approach in sinonasal malignancies. We discuss below the implications of this treatment modality on surgical morbidity, mainly orbital preservation [8, 10].

Finally, this chapter will explore the quickly advancing field of immunotherapy and targeted therapies. Early research on targeted therapies in head and neck cancer focused primarily on using cetuximab in place of platinum-based chemotherapy as a de-escalation strategy. While cetuximab ultimately did not demonstrate equivalent oncologic efficacy [5, 12], other promising targeted therapies are emerging. Newer generations of targeted therapies have focused on combined regimens, treating metastatic and locally advanced cancers in the palliative setting. Several of these agents have had good results and factor heavily into decision-making in planning multidisciplinary care for HNC patients. While immunotherapy will be more thoroughly covered in another chapter, we will explore its value in multimodal care here.

Advances in Surgery and Radiation

Oropharynx Cancer

Open surgical management of oropharyngeal cancer historically carried high treatment morbidity with difficult operative exposure. Taking this into account, a majority of the initial treatment algorithms for oropharynx cancers preferentially favored concurrent chemotherapy and radiation as the primary modality for treatment. Early pioneering work to develop transoral robotic surgery (TORS) for the treatment of oropharyngeal cancer catalyzed present-day adoption in many head and neck cancer programs [13, 14]. TORS offered a new technique with the potential lower functional morbidity in select HNC cases due to reduced disruption of neural and muscular soft tissues relative to open pharyngotomy approaches. The surgical robot delivered visualization and wristed instrumentation to tumor sites where the human hand was unable to reach. An endoscope provided a high-definition three-dimensional view of the tumor for resection. The newest iteration of the surgical robot by Intuitive Surgical Inc. (Sunnyvale), the da Vinci Single Port (SP) surgical system, is depicted in Fig. 2.2. The system includes the patient cart with the robotic arms and endoscope, the vision cart, and the surgeon console. The SP was originally

Fig. 2.2 The Intuitive da Vinci Surgical System [15]

developed to be able to introduce the camera and all instruments into the abdomen using a single trocar port, and these same mechanics benefit the head and neck surgeon operating in the narrow corridor of the oropharynx.

For carefully selected tumors, high local control rates are achievable when utilizing TORS. The original description of the TORS radical tonsillectomy reported a series of 27 patients with 93% achieving negative margins. A subsequent study reported a similar rate of negative margins (98%) and observed that positive margins were predictive of poorer local control and survival [16]. A later retrospective multi-institutional study of 410 patients undergoing TORS resection of oropharyngeal malignancies reported 2-year and 3-year locoregional control rates of 91.8% and 88.8%, and overall survival rates of 91% and 87.1%, respectively [17]. The proportions of HPV-positive disease are often not known in these study populations, complicating the evaluation of results. This obscures the expected natural history of the disease in the study populations and clouds the utility of recorded markers of surgical success, such as close margins.

While robotic oropharyngectomy was being established, concurrent chemotherapy and radiotherapy (CRT) continued to be a mainstay of OPSCC treatment with excellent oncologic outcomes in the HPV-OPSCC group. CRT was an effective means of treating local disease and provided a high overall survival in HPV-OPSCC disease [3]. A subset analysis of Radiation Therapy Oncology Group (RTOG) 0129 evaluated and detailed the effect of CRT on HPV-OPSCC. The study evaluated 743 patients with Stage III or IV OPSCC (American Joint Committee on Cancer [AJCC] version 7), enrolled over 3 years, and followed for a median of 4.8 years. Three-year overall survival (OS) in the HPV-positive patients receiving standard CRT was 82.4%, compared to 57.1% for HPV-negative patients [3].

The discovery of HPV as a driver of OPSCC introduced a new tumor biology in a site with anatomic and functional restrictions for both radiotherapy and surgery. The rationale for surgery in part includes obtaining surgical pathology to guide indications for or against adjuvant therapy. In fact, a subset of patients who undergo transoral surgery for OPSCC with neck dissection avoid radiotherapy and systemic therapy altogether [18]. The decision whether to start with surgery followed by adjuvant treatment as necessary, versus definitive CRT, varies highly based upon institutional and patient preference. Ongoing trials are aimed at better defining approaches to deintensification of different treatment modalities (e.g., DART: ClincialTrials.gov identifier NCT02908477, ORATOR 2: NCT01590355, PATHOS: NCT02215265) [19, 20]. The topic of treatment deintensification is discussed at length elsewhere in this text.

Radiotherapy Options for Oligometastatic Disease

The treatment of oligometastastic disease is an area of emerging interest in head and neck cancer. Oligometastases are qualitatively described in the literature as having a few distantly metastatic lesions, rather than widely disseminated disease. This is often described as five or fewer metastatic lesions. The goal in defining oligometastases is the identification of a disease state that is controllable for longer term than a comparison of widely metastatic disease state. Initial research in head and neck cancer has focused on patients with curable local disease that was accompanied with a small number of distant metastases [21].

A randomized phase 2 clinical trial comparing stereotactic ablative radiotherapy (SABR) versus standard of care palliative treatment (SABR-COMET) trial evaluated the use of SABR as compared to standard palliative radiotherapy for oligometastatic disease. This was a broad trial, and less than 30% of patients enrolled had head and neck primary tumors. The majority of metastases treated were in the lungs, but the study also included metastases to bone, adrenal glands, and liver. They evaluated 99 patients between 2012 and 2016, 67% of whom were randomized to the intervention arm. These patients had between one and five metastatic lesions. Median survival in the control arm was

28 months (95% CI 19–33) and 41 months (95% CI 26-not reached) in the SABR group. There were higher rates of grade 2 or higher adverse effects in the intervention group. There were also three (4.5%) treatment-related deaths in the SABR group (one from radiation pneumonitis, one from pulmonary abscess, and one from a subdural hemorrhage following surgery to repair a SABR-related perforated gastric ulcer) [22]. Despite the treatment toxicity, the improved survival as compared to standard of care palliative treatment does suggest a role for SABR as treatment of oligometastatic disease. A Phase 3 trial was recommended for further definition of possible benefit from treatment and identification of subgroups that may benefit.

Immunotherapy

Despite innovation and advances in conventional treatment paradigms for head and neck cancer, the overall 5-year survival remains nearly 50% excluding HPV-associated oropharyngeal cancers. Novel treatment methods seek to improve disease control while mitigating toxicity and functional morbidities. The concept of directed molecular marker therapy is gaining ground in all cancer types. This is especially true for high-risk tumors, recurrent disease, and tumors with known mutations. Immunotherapy is a cancer treatment that potentiates a component of a patient's own immune system to target cancer cells. This approach utilizes molecular inhibitors or monoclonal antibodies that are aimed at targeting certain vital processes necessary for tumor survival. This includes affecting the tumor microenvironment or blood supply resulting in tumor death and preventing the spread of metastatic disease. Within the last two decades, improved understanding of the molecular mechanisms behind tumor growth and metastasis has led to the development of targeted agents with specificity for tumor cells. Tumor immunotherapy is in its infancy in the field of head and neck cancers, and there is hope that continued progress can positively impact patient survival with tolerable morbidity.

Multidisciplinary Regimens Including Epidermal Growth Factor Receptor Blockers

The epidermal growth factor receptor (EGFR) has been found to be overly expressed in many head and neck cancers [23]. Disease recurrence and worse patient outcomes have been associated with increased expression of EGFR and its ligand, transforming growth factor-alpha (TGF-α). Cetuximab, an immunoglobulin-G1 chimeric monoclonal antibody, targets the extracellular ligand-binding domain of the EGFR protein. This was the first molecular targeting agent to demonstrate improved survival in patients with HNSCC, and the initial hope was that it could replace platinum-based CRT when given in conjunction with radiotherapy. Unfortunately, two large multicenter trials failed to prove noninferiority of cetuximab with radiotherapy as compared to cisplatin with radiotherapy in oropharynx cancer [5, 12, 24]. Since De-ESCALaTE HPV and NRG Oncology RTOG 1016 trials were published, enthusiasm has waned in the literature for cetuximab except for use in de-escalation for patients unable to tolerate current standard systemic options.

Multidisciplinary Regimens Including Immune Checkpoint Blockers

Some of the most exciting data of late has come with programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1) modulators. Immune checkpoint blockade, targeting the cytotoxic T-lymphocyte antigen 4 (CTLA-4), PD-1, and PD-L1 proteins, has proven to be a fruitful site of oncologic research. PD-1 is an inhibitory receptor expressed on T cells, B cells, regulatory T cells, natural killer cells, and macrophages (Fig. 2.3). Binding to either the PD-1 receptor or the ligand inhibits immune function, and thus inhibitors of these proteins have been targeted as possible immune stimulants to target malignancy [25].

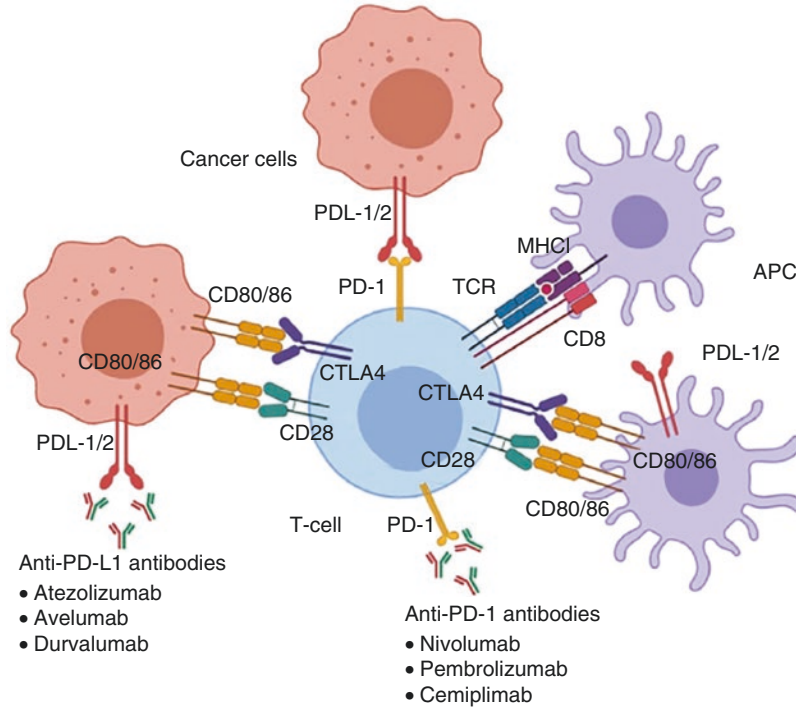

Fig. 2.3 Mechanism of blockade of PD-1 and PDL-1 by targeted therapies [25]

Nivolumab (anti-PD-1 antibody) and ipilimumab (anti-CTLA-4 antibody) have found success in patients with advanced melanoma and other various solid tumors. The multicenter, phase III, randomized clinical trial (CheckMate 067) found that in patients with untreated unresectable stage III or IV melanoma, nivolumab plus ipilimumab or nivolumab alone provided superior survival than ipilimumab alone [26, 27]. CheckMate 141 evaluated nivolumab in unresectable or metastatic HNSCC who progressed on platinum chemotherapy. Nivolumab was found to provide superior OS as compared to the investigator's choice of palliative treatment (16.9% vs. 6.0% alive at 2 years, respectively) with significantly fewer grade 3 or higher adverse effects. Compared to control, the nivolumab intervention group had double the response rate (13% vs. 6%) and double the 1-year overall survival (36% vs. 16.6%) [28, 29]. Importantly, quality of life (QOL) data from this same study showed that the nivolumab group had significantly better QOL outcomes in the first 15 weeks after initiation of treatment [30].

Equal enthusiasm has focused on the PD-1 receptor inhibitor, pembrolizumab. Pembrolizumab has been investigated in recurrent and metastatic HNSCC with good results. KEYNOTE-040, a phase III trial comparing pembrolizumab to methotrexate, docetaxel or cetuximab in patients with recurrent or metastatic HNSCC after a previous platinum containing regimen, showed a median OS of 8.4 months (95% CI 6.4–9.4) compared to 6.9 months (95% CI 5.9–8.0) with standard of care regimens. This was achieved with a significantly better profile of grade III or higher adverse events [31, 32]. With the success of nivolumab and pembrolizumab as second-line treatments, the EAGLE study, a phase III trial investigated employing durvalumab (anti-PD-L1 antibody) with or without tremelimumab (anti-CTLA-4 antibody) as second-line treatment in patients with metastatic or recurrent HNSCC who progressed on prior platinum-based chemotherapy. The intervention groups did not have improved response compared to standard of care chemotherapy (17.9% vs 18.2% vs 17.3%). Survival was also not different between groups [33].

Following these studies, a pivotal phase III comparative study was performed comparing pembrolizumab alone or with chemotherapy to standard of care EXTREME regimen containing cetuximab plus chemotherapy in patients with untreated recurrent or metastatic HNSCC [34]. This study, KEYNOTE-048, is most often cited for providing data to support the use of pembrolizumab monotherapy or in combination with chemotherapy. Pembrolizumab plus cisplatin or carboplatin, and 5-flurouracil, or pembrolizumab monotherapy were all found in the trial to be appropriate first-line treatment for recurrent or metastatic HNSCC. The combination therapy did impart higher levels of adverse effects, but all were found to be noninferior to the control EXTREME regimen [34].

With the landmark KEYNOTE-048 study showing a survival benefit, subsequent trials evaluated immunotherapy as a first-line treatment: CheckMate 651 (nivolumab plus ipilimumab versus EXTREME regimen, presented in ESMO 2021) and KESTREL [35] (durvalumab with or without tremelimumab versus EXTREME regimen, with data announced and awaiting presentation) did not meet the primary endpoint of improving survival. Responses to immunotherapy in patients with recurrent or metastatic HNSCC varied, and different immunotherapies as well as different combination strategies seem to play pivotal roles in augmenting the efficacy of immunotherapy. Mechanistic insight and detailed analysis of the immune contexture in patients with metastatic HNSCC receiving immune checkpoint inhibitors are crucial.

While the checkpoint inhibitors have been used primarily in combination with other forms of systemic therapy, combination radiotherapy and immunotherapy regimens have also been investigated. The safety and tolerability of addition of pembrolizumab to standard chemoradiation with cisplatin were demonstrated in an early phase 1b study [36]. About 85% of HPV-positive and 78% of HPV-negative locally advanced HNSCC achieved complete response at the end of the treatment, and no additional safety concerns were reported. In addition, another phase 2 trial supported the use of pembrolizumab in combination with radiotherapy in patients with locally advanced HNSCC who were platinum ineligible [37]. While preserving a favorable safety profile, 1-year progression free survival (PFS) was 76% (86% in HPV-positive and 67% in HPV-negative) and OS was 86% (93% in HPV-positive versus 80% in HPV-negative). There are many trials employing immunotherapy with radiotherapy that have been launched and are underway; however, results have not been universally positive. A recent phase III study, JAVELIN Head and Neck 100, failed to demonstrate the survival benefit of avelumab plus chemoradiotherapy followed by avelumab maintenance compared to standard chemoradiation in patients with locally advanced HNSCC [38].

Recently, immune checkpoint inhibitors have been explored in the neoadjuvant setting. In a multicenter phase 2 study, the feasibility of neoadjuvant and adjuvant pembrolizumab was studied in patients with locally advanced HPV-negative HNSCC. Although no patients obtained pathological complete response (pCR), 44% of patients had a partial pathologic tumor response (pTR; tumor necrosis, giant cells, and debris in tumor surgery bed). Half of those achieved pTR ≥50% after a single dose of neoadjuvant pembrolizumab, without adversely impacting the surgery or adjuvant therapy [39]. Compared to historical data, patients with high-risk pathology had notably lower 1-year relapse rate (16.7%). Another phase 1b trial explored neoadjuvant PD-1 inhibition with concurrent radiotherapy. This study included 21 patients with locally advanced HNSCC, primarily of the oropharynx, between 2018 and 2019. Patients were treated with 40 Gy in five fractions or 24 Gy in three fractions, with or without concurrent nivolumab. After definitive surgical resection, a major pathological response (mPR) rate of 86% and pCR of 67% was reported. Clinical to pathologic downstaging occurred in 90% of patients. Surgery was followed by adjuvant nivolumab for 3 months. Most of the primary tumors were HPV+ OPSCC (16 of 21, 76.2%). The early results demonstrated proof of concept for immunoradiotherapy strategies, and the literature continues to grow.

Organ Preservation

Neoadjuvant Chemotherapy and Radiation for Advanced Oral Cavity Squamous Cell Carcinoma (OSCC)

Advanced OSCC of the oral tongue and adjacent subsites may necessitate a total or near-total glossectomy for local oncologic control. With a critical role in swallow and speech, loss of oral tongue function is severely debilitating. Free tissue transfer for reconstruction cannot restore the dynamic oral-motor control that is lost by such resection. Quality of life scores have been evaluated at multiple points over the last 30 years for patients who have undergone total glossectomy with laryngeal preservation, and significant deficits remain despite reconstructive surgery [40]. The literature supports what patients know intuitively that the tongue is highly valued for quality of life in ways that are difficult to quantify.

The significant morbidity of total glossectomy has led to the exploration of nonsurgical treatments for OSCC. This is analogous to treatment paradigms for laryngeal cancer. A landmark study demonstrated induction chemotherapy given to patients with advanced laryngeal cancer could select for good responders that may be able to undergo definitive chemoradiotherapy with anatomical preservation of the larynx. Poor responders proceeded with total laryngectomy. Using induction chemotherapy in this way led to exploration of the technique to spare other high-value organs. In one study of advanced oral cavity cancers with induction chemotherapy followed by surgery or definitive chemoradiotherapy based upon response, the surgical group showed a significant survival advantage. The 5-year overall survival (OS) was found to be 32% in the induction chemotherapy cohort and 65% in the surgical cohort [11]. Despite these early findings, there remain significant areas where nonsurgical management can play an important role.

Since that study, several institutions have reported good success with nonsurgical treatment for locally advanced OSCC. A retrospective, single-institution review of definitive chemoradiotherapy management for stage III and IV OSCC patients highlighted both the oncologic outcomes and major morbidity of this approach [41]. Several protocols were utilized including 5-fluorouracil and hydroxyurea along with a third systemic agent, and radiotherapy. Radiotherapy was delivered either once or twice daily, and total dose to the primary site was between 70 and 75 Gy. In total 140 patients with advanced OSCC were treated with these various CRT protocols. Seventy-five percent of these patients had clinical T3 or T4 disease, 68% had N2 or greater disease, and 91.4% were stage IV. Forty-seven percent of the patients had oral tongue primary sites. Median follow-up for this patient group was 5.7 years with a 5-year overall survival of 63.7% and locoregional control survival of 78.6%. They had a 20.7% rate of osteoradionecrosis and a 10.0% rate of long-term feeding tube placement [41].

Another large retrospective series of advanced OSCC patients treated primarily with CRT was reported in 2020 [42]. This cohort included 63% T3–4 patients, 54% stage IV disease. Notably this was a less advanced tumor stage cohort overall as compared to the prior study. In total 1316 OSCC patients were treated with curative intent, and 108 of these were selected for nonsurgical management. They noted that in 49% of these cases, the explicit reason for pursuing nonsurgical treatment was to attempt preservation of oral structure/function. In all nonsurgical cases, definitive radiotherapy with concurrent chemotherapy was planned. Median follow-up was 52 months (range 3–136 months). Their 5-year local control rate was 78%, regional control 92%, disease-free survival (DFS) was 42%, OS was 50%. They reported a Grade 3 or higher rate of osteoradionecrosis of 8%. The studies above are both single arm, retrospective, nonrandomized cohort studies. However, these data show in principle the value of nonsurgical management of advanced OSCC cases that would otherwise require debilitating surgical management. These reports also transparently describe the considerable morbidity inherent to nonsurgical treatment.

Induction Chemotherapy

There are two main roles that induction chemotherapy (IC) is currently used in head and neck cancer therapy. The first is to guide treatment, testing the tumor biology to determine its susceptibility to definitive treatment. The second and overlapping value is reduction of tumor burden that may allow for reduced morbidity of definitive treatment.

Sinonasal undifferentiated carcinoma (SNUC) is a fast-growing sinonasal malignancy that has a well-established treatment algorithm using CRT. A single-arm prospective trial treated 95 patients with SNUC from 2001 to 2018. All underwent IC followed by either consolidation with CRT or surgical extirpation, based on tumor and patient specific factors. The induction chemotherapy regimen in this study was cisplatin (60–80 mg/m^2 on day 1) and etoposide (100–120 mg/m^2 docetaxel (75 mg/m^2 [n = 21]) on days 1–3, administered intravenously every 21 days. When consolidation CRT was performed, it began 4 weeks after the initial dose of IC. In patients who had a partial response (PR) or complete response (CR) to induction chemotherapy, 5-year disease-specific survival (DSS) was 81% in patients who underwent CRT, and 54% in patients who underwent surgery with postoperative radiotherapy or CRT. In patients who did not have a response to induction chemotherapy, the 5-year DSS was 0% in patients who underwent CRT, and 39% in patients who underwent surgery with adjuvant treatment [10].

The same group adopted this protocol for SCC of the sinonasal cavity with promising results. From 1988 to 2017, 123 patients with SCC of the sinonasal cavity were treated with IC followed by definitive CRT or surgery. These were patients with advanced local disease (89% with T4 disease), and 29.3% had regional metastatic disease at the time of presentation. The chemotherapy regimen consisted of platinum-based chemotherapy and taxanes for 88% of patients, but there were some that received additional 5-fluorouracil and cetuximab. After IC, 57.8% of these patients achieved a partial response. Half of these patients underwent definitive surgery, and the other half underwent definitive CRT. The 2-year OS was 61.4% and 5-year OS was 44.2% for the whole population. OS and DFS were significantly worse in the patients who did not achieve partial response; however, many of these patients were censored when lost to follow-up, before the end of the second year. All patients who achieved partial response or better (81% of all patients) were able to preserve their orbital contents. This study showed proof of concept again that IC could be used to assist in organ preservation.

The same group recently published data looking at IC as a possible method of organ preservation in oral cavity SCC (OSCC). They included 120 patients, treated for OSCC from 1995 and 2018. Fifty percent of these patients had T3 or T4 disease. After two cycles of IC, 63.3% of their patients showed at least partial response. Sixty of these patients underwent definitive surgical management. A subgroup of 15 patients were able to undergo a less extensive local resection after tumor shrinkage from IC. Each was able to avoid resection of an oral cavity subsite or avoid a total or subtotal glossectomy. One patient was able to avoid surgery at the primary site entirely and underwent only neck dissection for residual lymph node disease. After surgery was completed, they found that nine patients had achieved pathology-confirmed complete response. They noted that recurrence occurred in 48% of the total patients in the study, but there is no description as to which patients suffered recurrence. Like the above studies, patients who achieved at least a partial response had an improved 5-year DSS (78% vs. 66.9%) and OS (60.1% vs. 51.4%) compared to the whole study population [8]. It should be noted that the current standard of care is that post-IC resection should include the margins of the original tumor regardless of tumor response to the IC therapy. The theory is that the tumor responds nonuniformly to IC at a microscopic level, and thus, clinical examination may not define the true tumor margin post-IC. These data provide support for using IC as a method of preserving more oral-motor function in advanced OSCC.

Conclusion

Much progress has been made in understanding the epidemiology, pathogenesis, and management of head and neck cancers, with the resources of the head and neck oncologist continuing to broaden. Treatment algorithms are modified as scientific advances develop, such as in the implementation of TORS in the primary treatment of oropharynx cancer, or SABR for oligometastatic disease. Even in cases where survival improvements are not currently achievable, efforts to improve the quality of remaining life have value, especially in the context of organ preservation. Finally, the roles of immunotherapy and targeted therapies are rapidly evolving. These have already proven to have substantial value in multidisciplinary cancer care. The combination of various therapies is a nuanced and important resource for patients that require multispecialty collaboration.

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