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AHNS Series: Do you know your guidelines? Principles of Treatment for Locally Advanced or Unresectable Head and Neck Squamous Cell Carcinoma

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Abstract

This article is a continuation of the “Do You Know Your Guidelines” series, initiated by the Education committee of the American Head and Neck Society. Treatment guidelines for advanced head and neck squamous cell carcinoma are reviewed here, including the critical roles of radiation, chemotherapy and the recent application of immunotherapy agents. We will be limiting this discussion to include cancers of the oral cavity, oropharynx, hypopharynx, and larynx. It should be noted that much of the article pertains to HPV-negative oropharynx cancer where applicable, as HPV-positive oropharyngeal squamous carcinoma carries a different natural history, different prognosis, and now different staging criteria. Additionally, the article will not include information on nasopharyngeal or sinus cancers, as these latter topics are covered in separate “Do You Know Your Guidelines?” installments and these diagnoses carry somewhat different approaches to diagnosis and management that diverge from the focus of this paper.

INDEXING KEY WORDS

head and neck cancer; advanced head and neck cancer; National Comprehensive Cancer Network; management; guidelines as topic

Introduction

Approximately two-thirds of patients with head and neck squamous cell carcinoma (HNSCC) present with advanced stage disease. It is therefore essential to follow current

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treatment guidelines for patients with advanced or unresectable disease to optimize patient outcomes¹. This review will outline the latest National Comprehensive Cancer Network (NCCN) guidelines versions 1.2017² regarding advanced HNSCC and, where appropriate, will provide a brief summary of the current literature supporting these guidelines, detailing recent advances in therapy. Although this discussion focuses on advanced disease in most sites of HNSCC and general treatment principles are applicable in most cases, it should be noted that Human Papillomavirus (HPV) associated oropharyngeal cancers have a more favorable prognosis^{3–6} and will be staged differently compared to HPV-negative cancers in accordance with the American Joint Committee of Cancer (AJCC) 8th edition^{7–9}. Nevertheless, treatment strategies remain the same despite HPV status. Further research is necessary to determine the safety and efficacy of altering the management for patients with HPV positive HNSCC with respect to the new staging. The following article discusses current guidelines for management of advanced HNSCC.

How is “Advanced Disease” Defined in HNSCC?

“Advanced disease” as it relates to HNSCC can be defined several ways, depending on the context. This review focuses on four clinical settings where HNSCC disease progression can be considered ‘advanced’ – (1) postoperative “high-risk” HNSCC, (2) potentially resectable locoregional disease, (3) locoregionally unresectable disease, and (4) distant-metastatic HNSCC. The management of recurrent HNSCC will also be discussed briefly, though this subject is a topic of a separate article in the series. Two clinical features have been generally agreed upon to define ‘high-risk, resected disease’: when extranodal extension (ENE) is present, and second, the presence of disease at the surgical margins of resection^{10–20}. Newly diagnosed unresectable disease is defined generally as T4b classified (stage group IVB) tumors according to AJCC TNM staging system²¹. “Unresectable” tumors are typically those that cannot be removed without causing unacceptable morbidity, such as tumors with dense involvement of the cervical vertebrae, brachial plexus, deep muscles of the neck, base of skull or carotid artery. Subsequently, we will discuss treatment of patients with distant metastatic HNSCC and finally, we will review guidelines for treatment of HNSCC tumors that persist or recur following attempted primary treatment.

What Are the Guidelines for Treatment of High-Risk Resectable HNSCC?

After surgical resection with curative intent, adjuvant therapy with postoperative radiation (PORT) to the local and regional sites of disease is the standard of care for patients with AJCC stage III or IV HNSCC - that is for patients with T3 or T4 local disease and/or for patients with stage N2a or greater nodal metastases². As stated above, the presence of ENE and positive surgical margins are generally accepted as indicators of disease that is at “high-risk” of recurring both locoregionally or distantly. After resection, additional treatment is indicated for this high-risk group to reduce these risks. Moreover, adjuvant radiation is also recommended if patients have significant perineural or lymphovascular invasion identified on pathologic evaluation².

For patients with positive surgical margins, if additional resection can be carried out with a high likelihood of achieving a complete surgical resection without long-term complications,

then re-resection is recommended². For patients with positive margins that cannot be cleared surgically, and/or for patients with ENE, postoperative adjuvant radiation (POCRT) with concurrent cisplatin treatment is indicated². The evidence for the use of POCRT compared to radiotherapy (RT) alone derives from two large phase III trials, the Radiation Therapy Oncology Group (RTOG (#9501)) study¹⁷ and the European Organisation for Research and Treatment of Cancer (EORTC (#22931)) study¹⁸, detailed below.

Though each trial had similar aims, the definition of high-risk disease and inclusion criteria differed between these two studies. The EORTC (#22931) trial included not only patients with T1/T2 and N0/N1 disease with the above noted high-risk features, but also enrolled patients without high-risk pathological findings¹⁸. Patients were included if they had T3/T4 tumors regardless of nodal involvement (except T3N0 of the larynx) with negative margins, or T1/T2 tumors with N2/N3 disease. For this trial, high-risk features comprised of the following: ENE, positive resection margins, perineural involvement, or vascular tumor embolism. The RTOG (#9501) trial selectively included patients with defined high-risk features, including histologic evidence of invasion of two or more regional lymph nodes, ENE, and microscopically involved mucosal margins of resection¹⁷. Both studies concluded that the addition of cisplatin to postoperative radiation benefited patients with high-risk HNSCC. The EORTC (#22931) study demonstrated significant improvement in both progression-free survival and overall survival (OS) in the combined-therapy group. In the RTOG (#9501) study, locoregional control was improved and disease-free survival was significantly longer after combined-therapy; however, OS did not differ significantly between the two study groups.

Post-operative chemoradiation carries a high burden of toxicity and potential morbidity to patients. Therefore, to determine which patients would maximally benefit from receiving POCRT, a meta-analysis of EORTC (#22931) and RTOG (#9501) was published¹⁹. This meta-analysis concluded that patients with nodal ENE and/or positive surgical margins derived a significant OS benefit from combined therapy over radiation alone. When neither of these risk factors was present, there was no significant survival advantage observed as a result of POCRT compared to PORT alone. Furthermore, in a long-term follow-up to RTOG (#9501), at a median time of 9.4 years, the only significant difference in locoregional control and disease-free progression was detected in the subgroup of patients with ENE and/or positive surgical margins²⁰. Therefore, current guidelines recommend POCRT for patients with ENE or positive surgical margins².

What are the Treatment Guidelines for Newly Diagnosed T4b, Unresectable Disease?

Locoregionally advanced unresectable HNSCC carries an unfavorable prognosis, and effective treatment options often carry high toxicity and morbidity. Management of this disease is best provided by an interdisciplinary team which includes individuals from the disciplines of head and neck surgical oncology, radiation oncology, medical oncology, nutrition support, speech and language pathology, physical medicine and rehabilitation, and palliative care. It is imperative to have quality of life discussions with the patient while

establishing realistic expectations. Generally, enrollment in clinical trials is preferred, if possible². The NCCN guidelines base treatment options on an individual's performance status (PS) as defined by the Eastern Cooperative Oncology Group (ECOG, Table 1).

For patients with an ECOG PS of 0 or 1 the recommendations include concurrent systemic therapy (cisplatin is the preferred agent) and radiation, or induction chemotherapy followed by either RT alone or RT and additional systemic therapy. The controversy regarding the additional benefit that induction chemotherapy offers to these patients is discussed below. Patients with an ECOG PS of 2 should undergo definitive RT with or without concurrent systemic therapy, depending on the perceived ability of the patient to tolerate chemotherapy. With an ECOG PS of 3, goals shift toward palliative treatment either with RT, single agent systemic therapy, or supportive care alone to manage symptoms and provide comfort². Such patients with severe functional decline are treated in a comparable manner as those with incurable recurrent or metastatic disease, which is discussed later in this review.

Concurrent cisplatin-based chemoradiotherapy remains one of the more substantially supported options for managing unresectable advanced HNSCC or for patients who cannot tolerate surgery. A standard treatment approach uses high-dose cisplatin on days 1, 22, and 43 during RT and has been found to be effective and easy to administer, and a low dose, weekly administration schedule of cisplatin is also employed². Limited information is available regarding outcome differences between alternative chemotherapy regimens. Cetuximab, as a single agent with RT, is a recommended alternative².

Cetuximab, a recombinant chimeric anti-EGFR (epidermal growth factor receptor) monoclonal antibody, has been shown to be effective in the treatment of HNSCC^{2,22}. EGFR is expressed in roughly 90% of all HNSCC tumors and elevated levels of EGFR protein expression is associated with decreased survival^{23–27}. Results from several clinical trials have established the activity of cetuximab in the treatment of HNSCC, including in combination with cisplatin and cisplatin/5-fluorouracil^{22,28–35}. The landmark phase III trial by Bonner et al.²⁹ supporting cetuximab, demonstrated increased disease-free survival and OS for patients with locoregionally advanced HNSCC treated with cetuximab plus RT versus RT alone.

Alternative radiosensitizing chemotherapeutic combinations recommended for treatment of unresectable disease include carboplatin/5-fluorouracil^{36,37}, 5-fluorouracil/hydroxyurea³⁸, cisplatin/paclitaxel³⁸, cisplatin/5-fluorouracil³⁹, or carboplatin/paclitaxel⁴⁰. Unfortunately, there is a lack of quality studies comparing differences between these individual systemic therapies plus RT with respect to one another, and therefore, there is no established superiority of one regimen over others.

Evidence behind the recommendation for use of concurrent chemotherapy and radiation derives from many randomized trials^{41–47} and several meta-analyses^{48–52}. The more significant of these, the large Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC), was recently updated in 2016^{49–52}. The recent update in 2016⁵² analyzed 94 trials (18,934 patients) comparing local RT alone to RT plus concurrent/alternating chemotherapy, or induction chemotherapy followed by concurrent chemoradiotherapy

(CRT). The addition of chemotherapy to RT led to improved OS versus RT alone, but this benefit was limited to concomitant CRT, but not induction chemotherapy, translating into a 5-year and 10-year absolute survival benefit of 6.5% and 3.5%, respectively.

Nevertheless, potential benefits of induction chemotherapy remain unclear. Induction chemotherapy may allow for significant reduction in the rate of distant metastasis according to results of the 2009 MACH-NC update⁵¹. Additional rationale behind induction chemotherapy include possible increase in the efficacy of subsequent chemoradiotherapy resulting from its down-staging effects on the gross tumor volume and that it may act as a test of tumor radiosensitivity⁵³. These potential advantages have driven continued active research focusing on the utility of induction chemotherapy in HNSCC^{53–57}. A triplet chemotherapy regimen (cisplatin plus, 5-fluorouracil, and a taxane - TPF) revealed improved responses over cisplatin/5-fluorouracil^{58–64}, and for docetaxel containing regimens⁵⁹, improved overall survival, which has led to USFDA approval of docetaxel for HNSCC and further exploration of TPF as an induction regimen.

Despite this recent emphasis on triplet chemotherapy as an induction strategy, the current literature has not yielded consistent results in favor of this approach. If induction chemotherapy followed by CRT is used, evidence is in favor of the addition of a docetaxel to cisplatin/5-fluorouracil². Due to high toxicity, it is not recommended to follow cisplatin-based induction with cisplatin-based CRT^{2,65,66}. Recommended agents for CRT after induction include weekly carboplatin or cetuximab^{63,67,68}.

What Are the Considerations for Patients Who Have Distant Metastatic Disease at Initial Presentation?

The standard treatment of patients with HNSCC who are determined to have distant metastases at first diagnosis should be largely dictated by the patient's performance status, personal goals, co-morbidities, potential cost, and consideration of toxicities and prognosis. Treatment options for these patients include combination systemic chemotherapy, single agent chemotherapy, palliative RT or best supportive care². Enrollment in clinical trials is preferred, if possible². Many of the regimens employed to treat unresectable disease are similarly recommended for patients with distant metastasis, as many of the studies in support of these regimens included patients with unresectable and/or distant metastatic disease for inclusion.

Acceptable regimens include cisplatin or carboplatin in combination with 5-fluorouracil/cetuximab^{69,70}, cisplatin or carboplatin/docetaxel (or paclitaxel)^{71,72}, cisplatin/cetuximab⁷³, cisplatin/5-fluorouracil^{72,74,75} or cisplatin or carboplatin in combination with docetaxel (or paclitaxel)/cetuximab^{76–78}. Drug options for single agent therapy include cisplatin^{73,75}, carboplatin⁷⁹, paclitaxel⁸⁰, docetaxel^{81,82}, 5-fluorouracil⁷⁵, methotrexate^{74,83} cetuximab⁸⁴, afatinib^{85,86} or capecitabine^{87,88}.

The multi-drug regimens included above generally improve response rates over single agents, but until the addition of cetuximab, have never been shown to improve survival over single agent approaches². Response rates for single agent chemotherapeutics for recurrent or

metastatic disease is about 10-20% with a modest increase in response (30-40%) when platinum-based combination regimens are selected⁸⁹. Only a few studies have described differences between using multiple cytotoxic agents and single agents. One such study by Jacobs et al.⁷⁵ reported a phase III study involving patients with recurrent or metastatic HNSCC randomized to cisplatin alone, 5-fluorouracil only, or the combination once every three weeks. The ORR improved with the combination; however, the median survival remained 5.7 months for all groups. The Southwest Oncology Group conducted a similar phase III trial⁷⁴ treating patients with cisplatin and 5-fluorouracil, carboplatin and 5-fluorouracil, or methotrexate. The response rate of cisplatin and 5-fluorouracil was greater than methotrexate. The difference in response rate was not significant for the combination of carboplatin and 5-fluorouracil versus methotrexate. Further, the median OS was not significantly different across all three arms.

Based on literature comparing different combinational approaches, there is no straightforward consensus for choosing between various platinum regimens. A trial (E1395) by the Eastern Cooperative Oncology Group⁷² compared cisplatin and 5-fluorouracil to cisplatin and paclitaxel in patients with recurrent or metastatic HNSCC. At one year there was no difference in OS between the treatment groups. Nevertheless, taxane combinations with platinum agents offer an advantage in terms of ease of administration and schedule and obviates the need for an indwelling catheter or port.

The addition of cetuximab in first line treatment of metastatic disease in combination with chemotherapy and as a single agent in patients with platinum resistant disease has been well documented. The EXTREME trial by Vermoken et al.⁶⁹ was the first phase III trial to show improvement in OS with the addition of cetuximab to previous standard agents. This study enrolled patients with untreated recurrent or metastatic HNSCC and randomized them to chemotherapy (with either cisplatin or carboplatin plus 5-fluorouracil every 3 weeks) with or without cetuximab. The addition of cetuximab significantly improved OS from 7.4 months in the chemotherapy alone arm (either cisplatin or carboplatin plus 5-fluorouracil) to 10.1 months for the chemotherapy plus cetuximab group. Progression free survival was also improved from 3.3 months to 5.6 months, respectively. The phase III study by Burtneß et al.⁷³ randomized patients with recurrent or metastatic HNSCC to receive cisplatin with either cetuximab or placebo. The addition of cetuximab to cisplatin improved the ORR from 10% to 26% over cisplatin/placebo but did not demonstrate a statistically significant improvement in either progression free survival or OS.

Recently developed drugs under investigation for use in metastatic HNSCC include capecitabine and afatinib. Afatinib is an irreversible inhibitor of EGFR, HER 2 and HER4⁸⁵. Capecitabine is a prodrug that is converted to its only active metabolite, fluorouracil, by thymidine phosphorylase⁸⁷. Higher levels of this enzyme are found in several tumors and the liver, compared with normal healthy tissue. Both of these drugs have low level recommendations by the NCCN for use in recurrent or metastatic disease in patients who have had disease progression on platinum-based therapy². Afatinib has more robust data with a published phase III study⁸⁶, while use of capecitabine is advised based on evidence from phase II studies^{87,88}. Research toward the utility of these agents in the setting of failure after more substantiated regimens is ongoing.

How Do the Guidelines Change for Recurrent/Persistent Disease? What if the Patient Has Had Prior Radiotherapy?

If disease-extent allows, patients with recurrent or persistent disease should have surgery, regardless of radiation history. High-risk pathological features after salvage surgery should be managed by PORT or POCRT as detailed in the high-risk disease section above. For patients with recurrent or persistent disease who had previous RT and have resectable disease, surgery with possible reirradiation (with or without concurrent chemotherapy) is indicated. Alternatively, if the disease is resectable but surgery is not performed, similar schedules of CRT that are used for treatment-naïve disease, as mentioned in a preceding section, are indicated².

The rationale supporting salvage surgery for patients with resectable recurrent or persistent disease is a complex topic and exceeds the scope of this article; but, it is important to address a few aspects. Salvage surgery may offer a high chance of long-term disease control and a possible cure to select patients, yet morbidity from surgery in this setting can result in significant suffering and cost with marginal benefit in survival⁸⁹. Salvage procedures often result in reduction or permanent loss of function of important head and neck structures (ie. the larynx, pharynx, oral cavity, etc.), leading to significant cosmetic detriments, high economic burden, and even death. One of the most difficult, but critical, questions is determining which patients will maximally benefit from salvage surgery while reducing potential harms as much as possible.

An extensive informed discussion must occur between the surgeon and patient, particularly assessing prognostic factors which may help guide expectations and choice of suitable surgical candidates. The patient's co-morbidities, life expectancy, performance status, speech and swallowing function, nutritional status and severity of current symptoms need to be evaluated. Significant prognostic factors that should be considered to facilitate management decisions include recurrent stage⁹⁰⁻⁹², recurrent site^{90,91}, disease-free interval, initial treatment by chemoradiation, and locoregional versus limited local recurrence⁹¹. Improved outcomes following salvage surgery have been noted in patients with lower stage disease⁹⁰⁻⁹², disease-free interval greater than 6 months⁹¹, initial treatment with radiation alone compared to CRT⁹¹, and laryngeal recurrence in respect to other subsites^{90,92}.

If previous treatment with radiation was performed, and the disease is unresectable, management includes reirradiation with or without chemotherapy, chemotherapy alone or best supportive care². Regimens for CRT or chemotherapy, are similar to metastatic disease, as noted above. Patients with this level of disease severity should be offered enrollment into clinical trials.

Reirradiation may also be considered in the post-operative setting. The efficacy of reirradiation may be negatively affected by local scarring and fibrosis from previous radiation, as well as, difficulty in achieving adequate dosage because of proximity to vital structures which are already near tissue tolerance. Additionally, recurrence implies a degree of radiation resistance if the initial therapy was properly administered. Reirradiation should be carefully considered because of an increase in acute and late toxicities².

Janot et al.⁹³ reported on 130 patients with HNSCC who previously underwent surgery for a recurrence or a second primary tumor in a previously irradiated area that were randomly assigned to full-dose reirradiation combined with chemotherapy or to observation. Patients in the reirradiation arm received 60 Gy over 11 weeks combined with concomitant fluorouracil and hydroxyurea. A significant difference in locoregional control was found between the two groups, in favor of the reirradiation arm. Disease-free survival was significantly improved in the chemotherapy plus reirradiation arm, but OS was not statistically different. At 24 months, 39% of patients in the RT arm and 10% in the observation arm experienced grade 3 or 4 late toxicity. The main grade 3 and 4 late toxicities were sclerosis, trismus, and osteoradionecrosis. The higher likelihood of increased toxicity should be strongly considered if treating with reirradiation (with or without concurrent chemotherapy) for the potential benefit to locoregional control and disease-free survival.

What are the Recommendations Regarding Follow-Up?

Despite aggressive treatment of advanced disease, locoregional recurrences develop in 30% to 40% of patients and distant metastases occur in 20% to 30% (91,92). These patients also have an elevated risk of developing a second primary cancer if they have pronounced smoking and/or alcohol history. These second primaries more commonly consist of lung or upper aerodigestive tract cancers, but also include head and neck malignancies^{94,95}. Post-treatment surveillance assumes that early recurrence detection can improve outcomes among patients with advanced HNSCC. However, the literature regarding head and neck cancer suggests that regular follow-up is not significantly associated with improved survival outcomes⁹⁶⁻⁹⁹.

Nonetheless, proper follow up is essential for monitoring any recurrence or development of a second primary, assessing treatment results, managing acute and chronic treatment related side effects, providing tobacco education, monitoring for psychosocial well-being, meeting any needs for speech or swallow treatment and offering emotional and morale support. A follow-up schedule must be tailored to the individual patient based on stage of disease at diagnosis, extent of treatment received, the site of the tumor, and patient variables including age and comorbidities.

The NCCN guidelines recommend complete clinical exam and physical, including fiberoptic examination, every 1 to 3 months for the first year, every 2 to 6 months for the second year, every 4 to 8 months between years 3 and 5, and annually thereafter. Thyroid stimulating hormone should be ordered every 6-12 months if irradiation of the neck occurred. For patients 50 years or older with more than a 20 pack-year history of smoking, initial screening recommendations include a low-dose CT scan, followed by annual low-dose CT scans for 2 years². Continued routine imaging may be indicated based on sign/symptoms or desire to assess areas inaccessible to clinical examination. A post-treatment baseline imaging using PET/CT is recommended for patients with T3/T4 or N2/N3 cancers of the oropharynx, hypopharynx, larynx, and nasopharynx. This PET/CT should be within 6 months of treatment, but is ideally performed approximately 12 weeks after the last treatment².

A recent study by Mehanna et al.¹⁰⁰ investigated the utility of PET/CT surveillance versus planned neck dissection in 564 patients with nodal stage N2 or N3 HNSCC without metastasis treated with primary chemoradiotherapy. The 2-year OS rate was 84.9% (95% CI 80.7 to 89.1) in the surveillance group and 81.5% (95% CI 76.9 to 86.3) in the planned-surgery group. The HR for death with surveillance as compared with planned surgery was 0.92 (95% CI 0.65 to 1.32). This study suggests that there may be a role for PET/CT in follow-up for patients with severe nodal disease to monitor for recurrence, sparing routine neck dissections for patients. More information on the question of routine surveillance imaging on asymptomatic patients and additional follow-up interventions may be found in the follow-up and surveillance entry in this series¹⁰¹.

What is the Emerging Role of Immunotherapy?

For patients with recurrent/persistent or metastatic HNSCC that have had disease progression despite primary platinum-containing therapy, new immunotherapy agents are now a standard of care option for second-line therapy. Two monoclonal antibodies directed against programmed death receptor-1 (PD-1), pembrolizumab and nivolumab, have received FDA approval for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

Immunotherapy engages and/or enhances immune system function leading to tumor eradication or long-term growth inhibition. Recent advancements in immunotherapy for HNSCC have focused on inhibition of PD-1/PD-L1. PD-1 is a cell membrane receptor expressed on antigen stimulated T cells, B cells, natural killer T cells and dendritic cells^{102–104}. In normal tissues, activation of PD-1 results in inhibition and apoptosis of immune cells, largely utilized to enhance self-tolerance by T cells and prevents autoimmune reactions. Binding of PD-1 to its ligands, PD-L1 and PD-L2, suppresses the immune response by inhibiting T cell proliferation, cytokine release and cytotoxicity^{102,103,105}. Tumor cells with abnormal PD-L1 expression activate the PD-1 receptor, suppressing cytotoxic T cells and avoiding recognition and elimination by the immune system. Anti PD-1 therapies represent a form of reactivating the immune system to attack the tumor by blocking interaction between PD-1 and its ligands. Multiple studies have examined the expression of the programmed death receptor ligand PD-L1 in HNSCC across multiple primary sites revealing expression levels between 46 to 100% depending on staining method, fixation and site^{105–110}.

Pembrolizumab, was given accelerated approval by the FDA in August 2016¹¹¹, based on the work by Seiwert and Chow et al. in the KEYNOTE-012 trial investigating activity of pembrolizumab for patients with recurrent or metastatic HNSCC, published in July 2016¹¹². 104 patients were screened, 81 (78%) were identified to have PD-L1 positive tumors and 60 were treated with pembrolizumab. The ORR by central imaging review (CT or MRI) was 18%. An expansion cohort, including patients with recurrent or metastatic disease, regardless of PD-L1 biomarker status, was published in September 2016¹¹³. 132 patients were enrolled and after a median follow up of 9 months the ORR was 18%.

Similarly, an additional PD-1 monoclonal antibody, nivolumab, gained approval from the FDA in November 2016 for the same indication as pembrolizumab¹¹⁴. Ferris et al. investigated the use of nivolumab in HNSCC in a phase III trial¹¹⁵. In this study, 361 patients with recurrent or metastatic disease were enrolled comparing nivolumab to standard single agent therapy (either cetuximab, methotrexate, or docetaxel). In the nivolumab group, the median OS was improved versus the standard therapy group, 7.5 months and 5.1 months, respectively. Although recent top line data from the Keynote-040 phase III study, released in June 2017, demonstrated that pembrolizumab failed to meet its pre-specified primary specified endpoint of overall survival¹¹⁶, both nivolumab and pembrolizumab are under extensive investigation with multiple ongoing trials assessing their utility in combination with current therapy for HNSCC. Regimens combining immunotherapy with other modalities will likely further improve outcomes.

CONCLUSION

Treatment of advanced HNSCC remains a complex decision process, and thorough understanding of the current management recommendations is essential for providing high quality care to patients burdened by this often grave disease.

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Figure 1.

Treatment Schematic for Recurrent/Persistent Disease. High-risk features: positive surgical margins, extracapsular extension, perineural invasion, lymphovascular invasion.

Abbreviation: RT, radiotherapy; PORT, post-operative radiotherapy; POCRT, post-operative chemoradiotherapy; CRT, chemoradiotherapy. Summarized from the NCCN guidelines².

Table 1

Eastern Cooperative Oncology Group Performance Status

Performance status scale for assessing how disease impacts patients daily living abilities as published by Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology.1982; 5:649-55. In the public domain.

Grade	ECOG Performance Status Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead