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# TUMOR BOARD REVIEW

Guideline and Case  
Reviews in Oncology

**Second Edition**



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# *Tumor Board Review*



# *Tumor Board Review*

## Guideline and Case Reviews in Oncology

SECOND EDITION

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# *Preface to the Second Edition*

Thankfully, medical oncology is a rapidly evolving field, and significant progress has been made in the diagnosis and management of several forms of cancer in the 3 years since the publication of the first edition. In the second edition of *Tumor Board Review: Guideline and Case Reviews in Oncology*, we have maintained the same case-based format introduced in the first edition, but have updated the “Evidence-Based Case Discussion” of each case to include the most recent advances in diagnosis and treatment that have emerged from recently published clinical trials. Most prominent among the diagnostic advances is the further identification of genetic mutations that point to selective anticancer drug sensitivity (e.g., Braf mutations in melanoma). Similarly, the results of several phase III clinical trials have demonstrated the efficacy of a growing number of “targeted agents” in the treatment of several solid tumors and hematological malignancies. Accordingly, the content of the second edition represents our best effort to incorporate and highlight the latest, clinically relevant knowledge in our field.

The second edition continues to represent a joint effort between oncology faculty and subspecialty fellows based

at the Baylor College of Medicine (Houston, Texas) and the University of Michigan Medical School (Ann Arbor, Michigan). Both institutions are the homes of NCI-designated Cancer Centers: the Dan L. Duncan Cancer Center and the University of Michigan Comprehensive Cancer Center, and contributors to the second edition were selected based on their interest and expertise in the relevant cancers. The editors gratefully acknowledge the contributions of our trainee and faculty authors, as well as the support staff who assisted in the preparation of each chapter. We also thank the editorial staff of Demos Medical Publishing, particularly Richard Winters, executive editor (who originated the tumor board concept), and Joseph Stubenrauch, managing editor.

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# *Preface to the First Edition*

As physicians, we generally practice medicine on one patient at a time, focusing our knowledge base on the specific problems of each individual. As trainees, we are urged to learn as much as we can from each patient who provides a case-specific context for applying the broader body of information derived from textbooks, lectures, and other didactic materials. In the academic practice of oncology, we encourage our trainees to attend tumor boards, which, by applying the knowledge and expertise of relevant oncology specialists to the problems of individual patients, serve as a wonderful venue for learning the practice of oncology. The tumor board as a venue for learning was the concept we applied to the design of *Tumor Board Review: Guideline and Case Reviews in Oncology*. Each of the 32 chapters follows a uniform format: a concise summary of the epidemiology, risk factors, natural history, and pathology of each major organ-specific tumor type; an abbreviated display of the relevant staging (generally based on the *American Joint Commission on Cancer [AJCC] Staging Manual, 7th edition*); and several “tumor board-style” illustrative patient case summaries (representative of major stage categories of each tumor), each followed by an evidence-based case discussion that reviews the current guidelines and rationale for the diagnostic and therapeutic steps taken. Clearly, it was our intention to make the case summaries and accompanying evidence-based discussion (the latter including helpful management algorithms) the dominant focal point of the book. The authors of each chapter have endeavored to provide the most up-to-date evidence on which treatment decisions are based, including the latest advances in targeted cancer therapy.

We are hopeful that several categories of readers will find *Tumor Board Review* particularly useful, including oncology subspecialty trainees and practitioners who are preparing for subspecialty certification or recertification, respectively; trainees at all levels (e.g., medical students, residents, and subspecialty fellows) who are seeking a readable, case-based review of the relevant oncology literature; and oncologists in practice who are looking for a concise opportunity to refresh their knowledge across the broad field of medical oncology.

The development of *Tumor Board Review* was made possible by the combined efforts of selected subspecialty fellows and expert faculty of two academic institutions, the Baylor College of Medicine (Houston, Texas) and the University of Michigan Medical School (Ann Arbor, Michigan). The editors gratefully acknowledge the dedicated participation of our trainee and faculty authors, and the support staff of both academic centers, the latter including the invaluable editorial support of Ms. Leneva Moore at Baylor. The successful completion of this project was made possible by the editorial and publishing staff of Demos Medical Publishing, especially Richard Winters, executive editor (who originated the tumor board concept), and Dana Bigelow, production editor.

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# 1

## *Head and Neck Cancer*

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ASSUNTINA G. SACCO, IRINA Y. DOBROSOTSKAYA, AND FRANCIS P. WORDEN

### **EPIDEMIOLOGY, RISK FACTORS, NATURAL HISTORY, AND PATHOLOGY**

Squamous cell carcinoma of the head and neck (SCCHN) accounts for about 3% of new cancers diagnosed in the United States each year, with roughly 3-fold higher incidence in men compared to women. The American Cancer Society estimated that about 55,000 Americans were diagnosed with SCCHN in 2014, and approximately 12,000 patients died of this disease in that year.

SCCHN is related to several environmental and lifestyle risk factors. Of these, tobacco exposure and alcohol consumption are the 2 main causes, and when combined, they increase the risk by about 100-fold compared to nonusers. Epstein-Barr virus (EBV) is present in a significant proportion of nasopharyngeal cancers, while carcinogenic strains of human papillomavirus (HPV) have been recognized as a major contributor to carcinogenesis, especially within the oropharynx (about 70% of squamous cell cancer [SCC] of tonsils and base of tongue). HPV-related cancers of the head and neck are more prevalent in younger patients (aged 40–60 years), whereas traditional smoking- and alcohol-related SCCHN is diagnosed more frequently in patients older than 60 years. HPV-associated oropharynx cancers tend to have a better prognosis for reasons that are not completely understood. This may reflect a difference in tumor biology or simply more favorable host factors such as younger age and fewer comorbidities (and therefore better tolerance of treatments).

Significant advances in the treatment of SCCHN have been possible due to progressive improvement in surgical techniques, radiation modalities, and chemotherapeutic regimens. The multimodality approach allows cure even in locally advanced, unresectable cancers. Furthermore, organ preservation is achievable in a considerable number

of these patients. This is due to the good results that can be achieved with definitive chemoradiation in patients with locally advanced tumors. Patients with early-stage disease (stage I or II) without high-risk features are treated with a single-modality approach, either surgery or radiation, depending on which technique allows for better function preservation. Positive margins necessitate re-excision or radiation treatment in most cases. Adverse features such as extracapsular extension, vascular embolism, and perineural invasion should prompt consideration for adjuvant therapy.

Patients with locally advanced, curable disease are treated with surgery followed by radiation with or without chemotherapy, or with definitive chemoradiation. The latter is used for inoperable tumors or for organ-preservation purposes. Adjuvant chemoradiation is preferred over adjuvant radiation alone in patients with >2 positive lymph nodes (LNs), positive surgical margins, or nodal disease with extracapsular extension.

Induction chemotherapy followed by definitive locoregional treatment may be considered in a subset of patients with advanced nodal disease. Patients with metastatic or incurable, recurrent disease may benefit from palliative chemotherapy, depending on their functional status.

Because of the great heterogeneity among SCCHNs, treatment is based on the primary site of origin (see Table 1.1). For example, oral cavity tumors are treated primarily with surgery because advances in reconstruction using microvascular techniques have led to improved functional outcomes. Locally advanced oropharynx and nasopharynx SCC, on the other hand, are invariably treated with combined chemoradiation, and locally advanced larynx and hypopharynx cancers can be treated either with organ preservation approaches or total laryngectomy followed by radiation with or without chemotherapy.

**Table 1.1** Primary Sites of Origin for SCCHN

Area	Components
Oral cavity	Lips, alveolar ridge, hard palate, buccal mucosa, anterior 2/3 tongue, floor of mouth, retromolar trigone
Oropharynx	Palatine tonsils, posterior 1/3 tongue, vallecula, lingual tonsil, midportion of posterior pharyngeal wall, inferior surface of soft palate, uvula
Nasal cavity	Nasal septum; mucosa of floor of nasal cavity; superior, middle, and inferior turbinates
Nasopharynx	Superior surface of soft palate, upper portion of posterior pharyngeal wall above the level of uvula
Hypopharynx	Postcricoid area, pyriform sinuses
Larynx	<i>Supraglottis</i> : Supra and infrahyoid epiglottis, aryepiglottic folds, arytenoids, false cords <i>Glottis</i> : True vocal cords, anterior and posterior commissures, region 1 cm below plane of true cords <i>Subglottis</i> : Region from 1 cm below true cords to the cervical trachea

SCCHN, squamous cell cancer of the head and neck.

## STAGING

### Overview of Staging

The most useful classification subdivides SCCHN into early-stage (I–II), advanced but potentially curable (stage III–IVB), and incurable (stage IVC) disease, because the treatment differs significantly among these groups. Early-stage disease generally indicates primary tumor not >4 cm in size with no LN involvement. The exception is nasal cavity and ethmoid sinus (stage I or II allows invasion of some regional bony structures) and nasopharynx (stage II allows LN involvement). Advanced but potentially curable disease implies extensive local involvement and/or progressively more bulky LN disease. Incurable disease implies the presence of distant metastases.

### Site-Specific Staging for SCCHN

Table 1.2 provides staging of head and neck cancers (HNCs; derived from *National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Treatment of Head and Neck Cancers*, v.2.2014) (1).

**Table 1.2** Site-Specific Staging of Head and Neck Cancer

<b>Oral Cavity</b>	
Stage I	Tumor ≤2 cm, no LN involvement
Stage II	Tumor >2 cm but ≤4 cm, no LN involvement
Stage III	Tumor >4 cm with or without a single, ipsilateral LN ≤3 cm <i>or</i> A smaller tumor with involvement of a single, ipsilateral LN ≤3 cm
Stage IVA	Tumor may invade skin of face, cortical bone of the face but not the skull, may invade extrinsic tongue muscles, maxillary sinus, with or without LN involvement ≤6 cm <i>or</i> A smaller tumor with LN involvement ≥3 cm but ≤6 cm
Stage IVB	Tumor invades very deep such as masticator space, pterygoid plates, base of skull, encases carotid artery, with or without LN involvement (any size) <i>or</i> A smaller tumor with LN involvement >6 cm
Stage IVC	Distant metastases are present, irrespective of tumor size or LN involvement
<b>Oropharynx</b>	
Stage I	Tumor ≤2 cm, no LN involvement
Stage II	Tumor >2 cm but ≤4 cm, no LN involvement
Stage III	Tumor >4 cm or involves lingual surface of epiglottis with or without a single, ipsilateral LN ≤3 cm <i>or</i> A smaller tumor with involvement of a single, ipsilateral LN ≤3 cm
Stage IVA	Tumor may invade larynx, hard palate, mandible, medial pterygoid space or extrinsic tongue muscles, with or without LN involvement ≤6 cm <i>or</i> A smaller tumor with LN involvement ≥3 cm but ≤6 cm
Stage IVB	Tumor may invade base of skull, pterygoid plates, lateral pterygoid muscle, extend to lateral nasopharynx or encase carotid arteries, with or without LN involvement (any size) <i>or</i> A smaller tumor with LN involvement >6 cm
Stage IVC	Distant metastases are present, irrespective of tumor size or LN involvement

(continued)

**Table 1.2** Site-Specific Staging of Head and Neck Cancer (*continued*)**Nasopharynx**

Stage I	Tumor is limited to nasopharynx, nasal cavity, or oropharynx, no LN involvement
Stage II	Tumor may involve parapharyngeal space or be less extensive, unilateral involvement of cervical LN, or uni- or bilateral involvement of retropharyngeal LNs $\leq 6$ cm
Stage III	Tumor extends into base of skull or paranasal sinuses and/or there is bilateral involvement of cervical or retropharyngeal LNs $\leq 6$ cm
Stage IVA	Tumor may involve intracranial structures, cranial nerves, orbit, infratemporal fossa, masticator space, or hypopharynx and there may be bilateral involvement of cervical or retropharyngeal LNs $\leq 6$ cm
Stage IVB	Any tumor size as above with LN $>6$ cm or involvement of LNs in supraclavicular fossa
Stage IVC	Distant metastases are present, irrespective of tumor size or LN involvement

**Hypopharynx**

Stage I	Tumor $\leq 2$ cm and is limited to 1 subsite in hypopharynx, no LN involvement
Stage II	Tumor $>2$ cm but $\leq 4$ cm and may extend to $>1$ subsite of hypopharynx, no LN involvement
Stage III	Tumor $>4$ cm or involves esophagus or causes fixation of hemilarynx with or without a single, ipsilateral LN $\leq 3$ cm <i>or</i> A smaller tumor with involvement of a single, ipsilateral LN $\leq 3$ cm
Stage IVA	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus or central compartment, with or without LN involvement $\leq 6$ cm <i>or</i> A smaller tumor with LN involvement $\geq 3$ cm but $\leq 6$ cm
Stage IVB	Tumor may invade prevertebral fascia, encase carotid artery, involve mediastinal structures, with or without LN involvement (any size) <i>or</i> A smaller tumor with LN involvement $>6$ cm
Stage IVC	Distant metastases are present, irrespective of tumor size or LN involvement

**Larynx**

Stage I	Tumor is confined to 1 larynx site, normal vocal cord mobility, no LN involvement
Stage II	Tumor extends to include other larynx site, and/or with impaired vocal cord mobility, no LN involvement
Stage III	Tumor is limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (inner cortex), with or without a single, ipsilateral LN $\leq 3$ cm <i>or</i> A smaller tumor with involvement of a single, ipsilateral LN $\leq 3$ cm
Stage IVA	Tumor invades cricoid or thyroid cartilage and/or invades extralaryngeal tissues (trachea, soft tissues of neck, deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus), with or without LN involvement $\leq 6$ cm <i>or</i> A smaller tumor with LN involvement $\geq 3$ cm but $\leq 6$ cm
Stage IVB	Tumor invades prevertebral space, encases the carotid artery, or invades mediastinal structures, with or without LN involvement (any size) <i>or</i> A smaller tumor with LN involvement $>6$ cm
Stage IVC	Distant metastases are present, irrespective of tumor size or LN involvement

LN, lymph node.

**CASE SUMMARIES****Locoregionally Advanced Disease**

J.S. is a 56-year-old male who initially presented to his primary care physician 3 months after noticing a small, pea-sized right neck mass that subsequently started to grow. Treatment with antibiotics and steroids brought initial, short-lived relief, but then the neck mass further increased in size. He underwent fine-needle aspiration of his neck

mass, which revealed undifferentiated SCC. A CT scan of his neck demonstrated multiple enlarged, necrotic LNs in the right cervical chain. J.S. deferred further medical and surgical management and pursued alternative treatment with herbal medications. His neck mass remained stable until 5 months after his initial presentation when it increased in size. He sought medical care after developing dysarthria, difficulty chewing, and a sensation of airway narrowing. J.S. had no other medical problem and did not take any medications. He had a 60-pack-year smoking

history and a history of excessive alcohol consumption. His family history was noncontributory.

On physical examination, there was a palpable 8-cm firm, fixed conglomerate of LNs at levels I through V in his right neck, which were adherent to the sternocleidomastoid muscle. The remainder of his physical examination was unremarkable.

On fiberoptic examination, the right tonsil was enlarged, and there was a 4.5-cm area of fullness in the right glossotonsillar sulcus, tonsillar fossa, and the tongue base. This was biopsied and revealed an invasive, poorly differentiated non-keratinizing SCC. A full-body PET/CT and contrast CT scan of his neck revealed a 4-cm,  $^{18}\text{F}$ -fluorodeoxyglucose (FDG)-avid mass emanating from the right glossotonsillar sulcus that invaded tongue muscles and encased the right carotid artery. Multiple, enlarged, FDG-avid right neck LNs forming a 7-cm conglomerate mass were also noted. There was no evidence of distant disease.

## Evidence-Based Case Discussion

### Combined Chemoradiation

The aforementioned patient has T4b, N3, and M0 (stage IVB) SCC of the right tonsil. Given the nature of its carotid involvement, the tumor is unresectable, but still may be curable in 10–15% of patients. The current standard of care for such a tumor is definitive, concurrent chemoradiation, which employs a platinum-containing regimen. There is stronger evidence supporting the use of cisplatin versus carboplatin, and cisplatin ( $100\text{ mg/m}^2$ ) every 21 days with radiation, which is generally recommended. A carboplatin-based combination regimen (such as carboplatin–paclitaxel or carboplatin–FU) may be considered if toxicities of cisplatin are prohibitive. Cisplatin is more likely than carboplatin to cause neuropathy, hearing loss, and renal failure, whereas carboplatin has a higher risk of cytopenias, especially thrombocytopenia. Cisplatin is also more emetogenic when given in high doses ( $>80\text{ mg/m}^2$ ). Unlike cisplatin, carboplatin is generally used in combination with other drugs in the setting of concurrent chemoradiation. The most efficacious combinations include carboplatin with 5-FU or carboplatin with a taxane. In patients who are not candidates for platinum-based therapies (i.e., poor renal function or severe sensory neuropathy), cetuximab alone may be given as a radiosensitizing agent, although the efficacy of this targeted agent has not been compared directly to that of cisplatin with radiation. Recently, there has been a renewed interest in the addition of induction chemotherapy prior to definitive chemoradiation in an effort to improve survival outcomes.

### Induction Chemotherapy

The interest in induction chemotherapy for locally advanced HNC has undergone a revival. The rationale for its use is related to the possibility for better delivery

of chemotherapy to the tumor tissue not yet affected by radiation and improved distant control. Historically, the treatment of such locally advanced SCCHN used to be confined to surgery and radiation therapy. Local control was difficult, and the pattern of recurrence was more frequently local than systemic. Furthermore, the site-specific differences in prognosis and treatment were not clear. More recently, better radiation techniques and surgical approaches improved local control and survival in such patients. However, there is still room for improvement in both local and distant disease control.

The earlier trials performed before the 1990s included mostly laryngeal cancer patients and showed that induction chemotherapy, when added to local control measures (either surgery or radiation), did not adversely affect survival and allowed superior organ preservation outcomes by reducing the need for extensive surgery (e.g., Veterans Affairs Laryngeal Cancer Study Group (2) study published in 1991). Similar results were seen in the RTOG 91–11 trial published in 2003. Of note, radiation therapy was not given concurrently with chemotherapy; this concept was introduced later. The earliest meta-analysis of the role of chemotherapy in HNC by the Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) group evaluated 63 trials, including 10,741 previously untreated patients with various head and neck SCC locations treated between 1965 and 1993 (3). It showed improved survival with the addition of chemotherapy to local treatment (surgery or radiation or both) with absolute benefit of 4% at 2 and 5 years. The analysis of timing of chemotherapy showed that overall survival (OS) was better with concomitant, but not neoadjuvant or adjuvant chemotherapy versus local therapy alone. Subgroup analysis showed better survival with chemotherapy in patients younger than 61 years, males, Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1, stage IV disease, with tumors of oral cavity, and marginally of hypopharynx. This contributed to the subsequent shift in treatment paradigm from radiation to chemoradiation, both as a definitive treatment in inoperable patients and part of adjuvant treatment after surgery. The overall analysis of induction chemotherapy did not show a survival benefit, except for platinum and 5-fluorouracil (5-FU)-based regimens (hazard ratio [HR] = 0.88, 0.79–0.97). An update to the aforementioned meta-analysis by the MACH-NC group was recently published (4). It analyzed an additional 24 new trials, to bring the total number of trials to 87 and number of patients to 16,485. It included analysis of 31 induction chemotherapy trials including 5311 patients. There was no survival advantage to induction chemotherapy (HR of death = 0.96, 0.9–1.02,  $P = .18$ ), although the FU–platinum-based therapies once again proved to be better than other analyzed regimens (HR of death = 0.9, 0.82–0.99), and there was significant benefit for prevention of distant metastases (HR = 0.73, 0.61–0.88,  $P = .001$ ). Subsequent phase III studies of advanced curable disease

showed better survival with neoadjuvant cisplatin and 5-FU as well as improved locoregional control compared to local therapy alone (5–7). In a study by Paccagnella et al. (8), the induction chemotherapy group ( $n = 118$ ) received 4 cycles of cisplatin plus 5-FU followed by locoregional treatment: surgery followed by radiation in operable patients or radiation alone in inoperable patients. The comparison group ( $n = 119$ ) received locoregional treatment alone. There was a significantly lower rate of distant metastases in the induction chemo group for both operable and inoperable patients. However, the OS benefit from induction chemotherapy was limited to inoperable patients (at 3 years, OS was 24% vs. 10%,  $P = .04$ ). In this study, the majority of patients had oropharyngeal cancer (54–59%); they were younger than 70 years, most had stage IVA or B disease (63–64%), and most patients were inoperable (71–73%). A later update by Zorat et al. (9) confirmed these findings: The OS benefit was limited to inoperable patients (10-year survival = 16% vs. 6%,  $P = .04$ ). In a similar phase III study by Domenge et al. (10), only younger patients (aged 69 years or younger) with curable oropharyngeal disease were included. The chemotherapy group ( $n = 157$ ) received a similar induction chemotherapy with cisplatin and 5-FU, followed by surgery and/or radiation therapy. The nonchemotherapy group ( $n = 161$ ) received only locoregional treatment. This study demonstrated an OS benefit, which was conferred by neoadjuvant chemotherapy in both resectable and unresectable patients (median survival = 5.1 years vs. 3.3 years,  $P = .03$ ).

### TPF-Induction Chemotherapy

In an effort to capitalize on the potential survival benefit of induction chemotherapy, taxanes have been added to platinum and 5-FU. The combination of docetaxel, cisplatin, and 5-fluorouracil (TPF) has recently emerged as the standard induction chemotherapy regimen if induction chemotherapy is to be considered. TPF was shown to improve OS when compared to treatment with neoadjuvant cisplatin and 5-FU followed by radiation (5,11). These findings set the stage for the investigation of induction chemotherapy followed by chemoradiation in locally advanced SCCHN. Posner et al. demonstrated an improvement in OS and progression-free survival (PFS) when TPF was compared to cisplatin/5-fluorouracil (PF) as induction chemotherapy followed by treatment with weekly carboplatin combined with radiation (6).

Subsequent randomized trials were performed to directly compare TPF induction followed by concurrent chemoradiation to definitive chemoradiation alone. A Spanish randomized phase III trial comparing 3 treatment arms (definitive chemoradiation vs. induction with PF followed by chemoradiation vs. induction with TPF followed by chemoradiation) included 439 patients with locally advanced, nonmetastatic stage III/IV SCCHN (12). While there were concerns related to study methodology,

an intention-to-treat analysis demonstrated no advantage of an induction approach over concurrent chemoradiation with respect to locoregional control, time-to-treatment failure, PFS, and OS.

The Docetaxel Based Chemoradiotherapy Plus or Minus Induction Chemotherapy to Decrease Events in Head and Neck Cancer (DeCIDE) study was a phase III, multinational trial of 280 patients randomized to receive either definitive chemoradiation alone or 2 cycles of induction with TPF followed by the same chemoradiation as the control arm (13). Patients with previously untreated SCCHN with N2/N3 disease and no distant metastases were included. Fifty-eight percent of patients had oropharyngeal primaries and 88% had N2 disease. Poor accrual led to modification of the sample size and statistical plan; however, the 280 subjects accrued were still able to provide 80% power to detect an HR of 0.5 for OS ( $\alpha = 0.05$ ). The primary end point was OS. Results presented at the American Society of Clinical Oncology (ASCO) 2012 meeting showed no statistically significant difference between the 2 arms for OS (HR = 0.91, confidence interval [CI] [0.59–1.41],  $P = .68$ ). While the rate of distant recurrence (with preserved locoregional control) was improved in the induction arm ( $P = .043$ ), there were no significant differences in recurrence-free or distant failure-free survival. Both treatment arms were able to successfully deliver the prescribed chemotherapy and radiation; however, the induction arm was associated with increased toxicity. Specifically, grade 3–4 neutropenia rates during subsequent chemoradiation were significantly higher in the induction arm ( $P = .02$ ). More concerning was the observation that induction led to an increased rate of early treatment-related deaths (4 deaths during induction [3.5%] and 9 deaths [10%] during subsequent chemoradiation) as compared to 4 deaths (3.8%) in the chemoradiation-alone arm, undoubtedly contributing to the study outcomes.

The PARADIGM study was a phase III, multi-institutional trial of 145 patients randomized to receive either TPF induction followed by chemoradiation versus chemoradiation alone (14). The induction arm received 3 cycles of TPF and was further stratified to concurrent chemoradiation based on tumor response. Similar to the DeCIDE trial, the study was halted midcourse secondary to poor accrual with only 145 of the 300 planned patients accrued. Patients with previously untreated, stage III or IV SCCHN were eligible. The majority (55%) had oropharyngeal primaries and 86% had stage IV disease. The primary end point was OS. After a median follow-up of 49 months, 3-year survival was better than expected in the chemoradiation arm (78%). Neither PFS nor OS favored the use of induction ( $P = .82$  and  $.77$ , respectively). Furthermore, there was no improvement in the rate of distant recurrence with induction. In terms of toxicity, patient deaths were again higher in the induction arm (4 patients died during the first year of treatment [2 during induction]) compared to those in the chemoradiation arm (1 death).

Based on these negative trials, concurrent chemoradiation remains the standard of care for locally advanced SCCHN, and the role of induction within the treatment paradigm remains investigational. Furthermore, TPF sequential regimens have primarily been studied in patients with SCC of the oropharynx, hypopharynx, or larynx. Additional studies are needed to determine if induction chemotherapy could benefit other head and neck tumor types.

### Adjuvant Chemotherapy

Adjuvant chemotherapy is not typically given in HNC, except for nasopharyngeal carcinoma because this tumor type is exquisitely sensitive to the effects of chemotherapy as well as radiation. The evidence for this is largely represented by several studies conducted in late 1990 to early 2000s. In the Intergroup Trial 0099, Al-Sarraf et al. compared radiation alone versus chemoradiation (including adjuvant chemotherapy) in 193 patients with advanced nasopharyngeal cancer (15). This study showed both a PFS and an OS advantage for patients in the chemoradiation arm, which included 3 cycles of adjuvant cisplatin–FU. The 3-year PFS was 69% versus 24% in the chemoradiation versus radiation-alone groups, respectively ( $P < .001$ ). The 3-year OS was 78% versus 47% ( $P = .005$ ). A conceptually similar trial was reported by Wee et al. in 221 patients with stage III–IV nasopharyngeal carcinoma (16). Disease-free survival (DFS) was better in chemotherapy-treated patients versus radiation-alone (HR for DFS was 0.57,  $P = .0093$ ). The OS was also better in this group: HR for OS was 0.51 ( $P = .0061$ ). The question that remains unanswered is the timing of chemotherapy in this setting: whether concurrent chemoradiation confers the observed benefit or the adjuvant chemotherapy explains the difference in outcomes, or a combination of both. Indeed, Chan et al. reported a trial of 350 patients with various stages of nasopharyngeal carcinoma and showed a similar benefit of concurrent-only chemoradiation versus radiation therapy alone in patients with stage III–IV disease (17). Similarly, OS was improved to a comparable extent by concurrent chemoradiation as compared to radiation alone in another trial reported by Lin et al. (18).

### Recurrent/Metastatic SCCHN

D.C. is a 63-year-old male who was diagnosed with a T2N2bM0 (stage IVA) SCC of the floor of the mouth 1 year prior to presentation. At that time, he underwent surgical extirpation including a unilateral neck dissection. Surgical margins were negative, but extracapsular extension and perineural invasion were noted. He then received adjuvant chemoradiation. Seven months following definitive therapy, he developed a cough. A CT scan of the chest revealed multiple, new pulmonary nodules. A biopsy was performed and confirmed SCC, consistent with metastatic disease.

D.C.'s medical history was otherwise positive for hypertension well controlled with lisinopril. He had

developed mild neuropathy after treatment with cisplatin, manifesting as numbness in bilateral fingertips and toes. He had an 80-pack-year history of smoking and a remote history of excessive drinking (he quit both 2 years prior to his initial diagnosis). His family history was noncontributory. His physical examination was unremarkable with the exception of the stigmata related to his previous surgery and radiation therapy.

### Evidence-Based Case Discussion

#### Single-Agent Chemotherapy

The aforementioned patient has metastatic cancer of the oral cavity. The extracapsular extension in his neck nodes attests to the aggressive nature of his cancer, portending a poor prognosis, despite aggressive surgery and chemoradiation. Survival in patients with recurrent or metastatic (R/M) SCCHN is approximately 6 months. Median survival rates, however, can be extended to 9–11 months with systemic chemotherapy.

Single-agent chemotherapy has been studied in metastatic HNC, but response rates are low, generally on the order of 10–30%. Traditional cytotoxic agents, including cisplatin, carboplatin, 5-FU, low-dose methotrexate, paclitaxel, docetaxel, ifosfamide, and bleomycin, have been tested as single agents in this setting. Given the improved tolerability of single-agent chemotherapy, such regimens are best suited for patients with a marginal performance status (i.e., ECOG PS 2). Combination regimens, on the other hand, improve response rates and are usually reserved for patients with an ECOG PS of 0–1.

#### Targeted Therapies

Newer targeted therapies have also been tested as single-agent regimens for R/M SCCHN. Inhibition of the epidermal growth factor receptor (EGFR) pathway has been extensively studied due to the virtual overexpression of EGFR in >90% of SCCHN, as well as its strong correlation with poor prognostic outcomes (19,20). Cetuximab, a chimeric mouse–human monoclonal antibody against EGFR, is the only Food and Drug Administration (FDA)-approved molecularly targeted agent for HNC. In the R/M setting, it is approved as second-line therapy for patients with platinum-refractory disease, with a toxicity profile that is more tolerable compared to conventional, cytotoxic chemotherapy drugs. Vermorken et al. noted a response rate of 13%, and a disease stabilization rate of 46% (21).

Oral small tyrosine kinase inhibitors such as erlotinib and gefitinib have also been tested, with phase II trials in heavily pretreated patients with R/M demonstrating good tolerability and disease stabilization (22,23). A phase III study comparing the efficacy of gefitinib versus weekly methotrexate, however, showed no difference in survival outcome, although quality of life was better in the gefitinib arm (24).

Despite cetuximab's approval, its modest success underscores the need to better elucidate resistance mechanisms of EGFR inhibition, and to develop other targeted therapies. One strategy aimed at overcoming EGFR resistance includes the use of irreversible, pan-erythroblastic leukemia viral oncogene homolog (ErbB) receptor tyrosine kinase inhibitors (TKIs) such as afatinib. Phase II results of afatinib demonstrated at least comparable antitumor activity to cetuximab in platinum-refractory metastatic disease, with sequential EGFR/ErbB treatment providing sustained clinical benefit in a subset of patients, suggesting lack of cross-resistance (25).

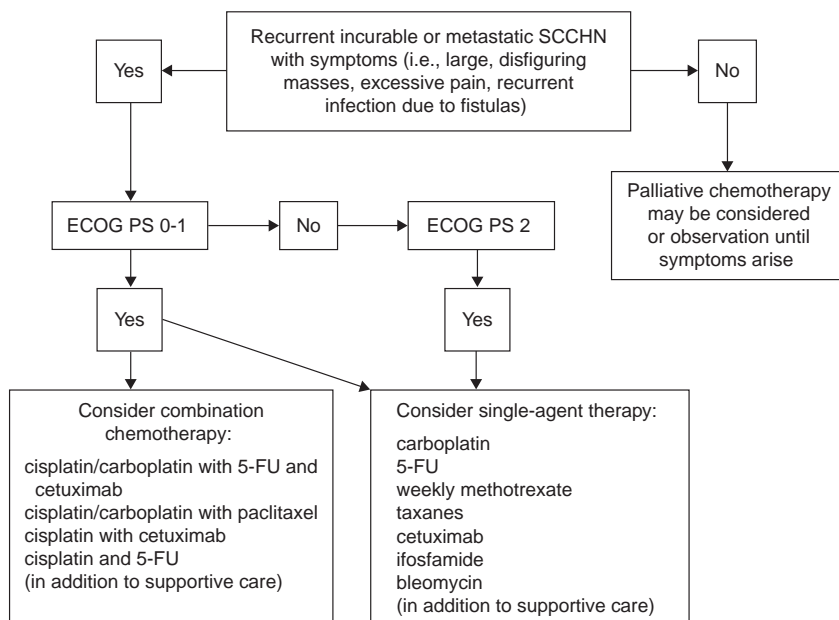
### Combination Chemotherapy

Combination chemotherapy for R/M SCCHN with a platinum-based regimen remains standard of care and provides higher response rates compared to single-agent chemotherapy. A Southwest Oncology Group (SWOG) trial compared outcomes with combinations of cisplatin or carboplatin with 5-FU versus single-agent methotrexate (26). The response rates were higher for the combination regimens (32% for cisplatin plus 5-FU, 21% for carboplatin plus 5-FU, and 10% for methotrexate). There was, however, no significant difference in survival among the 3 treatment arms. Jacobs et al. reported similar results when cisplatin and 5-FU were administered either together or as single agents (27). Again, the response rate was higher in the combination arm, but no OS benefit was noted. Cisplatin in combination with a taxane has been evaluated and does not appear superior to other combination regimens. A phase III trial evaluating cisplatin with 5-FU versus cisplatin and paclitaxel demonstrated no difference in OS, although the quality-of-life scores were higher in the paclitaxel arm (28). Three-drug combinations of conventional cytotoxic agents have also been tested. However, these are more toxic and offer no survival advantage over doublet combinations.

Recently, the introduction of targeted agents with combination chemotherapy regimens has proven to be advantageous in the treatment of R/M SCCHN. Cetuximab was combined with either carboplatin plus 5-FU or cisplatin plus 5-FU in a large phase III trial (EXTREME trial) (29). The control group received a combination of either cisplatin or carboplatin with 5-FU. The patients in the cetuximab arm who attained stable disease continued to receive maintenance weekly cetuximab until disease progression or development of intolerable side effects. This study enrolled 442 previously untreated patients with R/M HNC. The addition of cetuximab increased the response rate from 20% to 36% ( $P < .001$ ) and prolonged the median PFS from 3.3 to 5.6 months ( $P < .001$ ) as well as OS (10.1 vs. 7.4 months, HR of death = 0.8, 0.64–0.99,  $P = .04$ ). Quality of life was not adversely affected by the addition of cetuximab. The combination of platinum, 5-FU, and cetuximab is now considered an accepted, first-line, standard regimen for patients with R/M HNC. One remaining question, however, relates to the benefit of maintenance cetuximab therapy. Given its expense and potential for excessive toxicity, further evaluation of cetuximab in this setting is needed before such treatment is considered standard of care.

Cetuximab has also been combined with docetaxel in a regimen that may be promising for patients with platinum refractory R/M SCCHN. Knoedler et al. reported the results of a multicenter, phase II study of this combination in 84 patients (30). They noted a 12% partial response rate with a disease control rate (partial response plus stable disease) of 39%. The median OS was 7 months, with a satisfactory toxicity profile.

Erlotinib has also shown promising results when combined with cisplatin and docetaxel in a phase II trial in patients with untreated R/M HNC (31). The overall response rate for this study was 67% with a disease control rate of 95%. The median OS was 11 months and median PFS was 6 months.



**Figure 1.1**

Palliative chemotherapy for recurrent/metastatic SCCHN. ECOG PS, Eastern Cooperative Oncology Group performance status; FU, fluorouracil; SCCHN, squamous cell carcinoma of the head and neck.



## SUMMARY

As shown in Figure 1.1, combination chemotherapy consisting of platinum plus 5-FU with or without cetuximab, or platinum combined with a taxane, are considered standard of care for patients with R/M HNC. Combination regimens are best suited for patients with ECOG PS 0–1 who have large bulky, disfiguring tumors or who have distant metastatic disease. Disease that is asymptomatic can be treated with best supportive care until symptoms arise. Patients with a marginal or limited performance status (PS = 2–3) are more likely to tolerate single-agent therapy.

## REVIEW QUESTIONS

- A 69-year-old otherwise healthy male presents with a 4.5-cm lateral tongue mass and multiple bilateral palpable neck nodes, with the largest node measuring 2 cm. Fine needle aspiration confirms squamous cell carcinoma. Imaging reveals no evidence of distant metastases. What would be the optimal treatment approach?

  - Primary surgical approach with adjuvant radiation with/without chemotherapy
  - Surgery alone
  - Radiation alone
  - Definitive chemoradiation
- The patient in Question 1 agrees to proceed with surgery. He undergoes surgical resection of the lateral tongue mass in addition to bilateral neck dissections. Final pathology reveals 5 of 44 lymph nodes positive with the presence of extracapsular extension. What would you recommend now?

  - Adjuvant chemotherapy
  - Adjuvant radiation
  - Adjuvant chemoradiation
  - No additional treatment recommended
- A 67-year-old female presents with a 6-month history of progressive odynophagia and dysphagia, and a 1-month history of a right neck lump. Clinical examination reveals a stage IVB oropharynx cancer. Fine needle aspiration confirms squamous cell carcinoma. Her medical history includes hypertension, diabetes mellitus, stage III chronic kidney disease, and severe painful neuropathy involving both hands and feet. Her status is Eastern Cooperative Oncology Group performance status 1. In addition to definitive radiation, which chemotherapy agent might you consider?

  - High-dose cisplatin
  - High-dose carboplatin
  - Carboplatin and paclitaxel
  - Cetuximab
- A 53-year-old male presents with a several month history of progressive hoarseness. He is diagnosed with a resectable, locally advanced laryngeal cancer. He works full time as a salesman, wishes to preserve his voice, and is not interested in surgery. He has a 60-pack-year smoking history (quit at time of diagnosis). He has no medical comorbidities and an excellent performance status. What would be the optimal treatment approach?

  - Induction with cisplatin, 5-fluorouracil (5-FU) (PF) followed by radiation
  - Induction with docetaxel, cisplatin, and 5-FU (TPF) followed by radiation
  - Induction with TPF followed by chemoradiation
  - Concurrent chemoradiation
- A 42-year-old female is diagnosed with a stage III squamous cell carcinoma of the left tonsil. She is a married homemaker with 2 children. She is a never smoker, only drinks alcohol on special occasions, and has no history of illicit drug use. She is concerned about what may have caused her cancer and asks you about potential etiologies. Which risk factor is most highly associated with cancer of the oropharynx?

  - Epstein-Barr virus
  - Human papillomavirus (HPV)
  - Human immunodeficiency virus
  - Tobacco and alcohol consumption
- A 59-year-old male with a history of squamous cell carcinoma of the floor of mouth status postsurgery and adjuvant radiation completed 9 months ago, now presents with a massive local recurrence that is unresectable and not amenable to further radiation therapy. He has received no prior chemotherapy. His performance status is excellent and he is otherwise healthy. He is interested in pursuing treatment, which may provide him the best chance at prolonged survival. What would be the optimal treatment approach?

  - Single-agent cetuximab
  - Single-agent methotrexate
  - Carboplatin/5-fluorouracil (5-FU) plus cetuximab
  - Carboplatin/5-FU
- A 41-year-old male presents with a 6-month history of nasal congestion, right ear fullness, and bilateral palpable neck masses. Clinicoradiologic assessment and biopsies confirm a stage IVB nasopharynx cancer. He is otherwise healthy with excellent performance status. What would be the optimal treatment approach?

  - Chemoradiation with/without adjuvant chemotherapy
  - Surgery with adjuvant radiation
  - Surgery alone
  - Radiation alone

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