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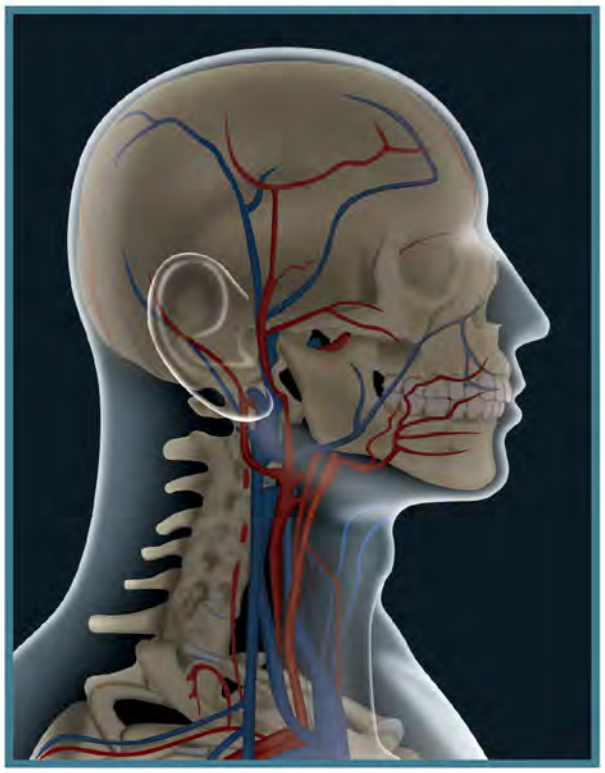
Sataloff's Comprehensive Textbook of
Otolaryngology
Head & Neck Surgery

Head and Neck Surgery

Series Editor
Robert T Sataloff



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CHAPTER

3

Principles of Medical Oncology

Cristina P Rodriguez, David J Adelstein

INTRODUCTION

Malignant tumors of the head and neck are remarkable in the diversity of their anatomic sites of origin, histology, disease behavior, and in the range of available therapeutic options. Contemporary management now routinely involves multiple disciplines, including the medical oncologist, whose role in treating these malignancies continues to expand.

Squamous cell carcinoma is the most common malignancy in the head and neck, and the use of systemic therapy has been most extensively investigated in this disease. In the 1960s, with the introduction of the earliest generation chemotherapy agents, a surprising sensitivity to chemotherapy was demonstrated.[1] Today, the role of systemic therapy is no longer limited to the management of squamous cell carcinoma, but extends to the less frequently occurring histologic subtypes, including the sinus and salivary gland cancers, and advanced cancers of the thyroid. This primarily reflects an increasing understanding of the underlying molecular mechanisms influencing tumor biology, and the subsequent identification of active systemically administered agents that modify these mechanisms. Unlike locoregional treatments like surgery and radiation, the use of systemic therapy is influenced more by histology and biologic behavior than by anatomic subsite. Scientific investigation has led to defined roles for conventional chemotherapeutic agents in curative and palliative management strategies as well as to the identification of newer, targetable molecular markers, resulting in the development, approval, and clinical availability of several novel agents for the treatment of these malignancies.

This chapter will provide the reader with a foundation for understanding the basic tenets behind the use and selection of systemic therapeutic agents in the treatment of head and neck carcinomas, with a major emphasis on squamous cell carcinomas. The specifics of the regimens used and approved for curative and palliative treatment approaches will be discussed elsewhere in this book.

THE MOLECULAR BASIS FOR SYSTEMIC THERAPY

It is well documented that many epithelial malignancies represent the sequela of accumulated molecular changes that begin during the gradual progression from normal mucosa to dysplasia and to invasive carcinoma. In head and neck malignancies, this is best illustrated by the tobacco-related squamous cell carcinomas of the oral cavity, oropharynx, larynx, and hypopharynx. Alterations at the molecular level initiated by continued carcinogen exposure involve oncogenes and proto-oncogene, and result in genomic instability, impairment of DNA repair mechanisms, and loss of apoptosis.[2] For example, chromosome 9p and 3p deletions and p53 mutations have been reproducibly demonstrated in dysplastic epithelia and are felt to be mutations that occur early in the process of carcinogenesis. On the other hand, 18q deletions are more commonly found in severely dysplastic epithelium and/or frankly invasive carcinoma. These genetic changes can also be detected in the surrounding nonmalignant mucosa, supporting the theory of a "field defect" shared by carcinogen-exposed epithelia, and the frequent observation of second primary upper aerodigestive malignancies

in this population.[3] The resulting dysregulated cellular growth and inability to repair genetic damage are processes that are commonly exploited by systemic chemotherapeutic agents.

This model by no means fully encompasses the tremendous complexity underlying carcinogenesis and tumor behavior among head and neck malignancies. Viral infections and immune factors also appear to be involved in specific subsets of head and neck squamous cell carcinomas. Epstei–Barr viral DNA is a marker of endemic nasopharyngeal carcinoma, which has a unique geographic and demographic distribution, as well as a distinct biology compared with squamous cell carcinomas of the oral cavity, oropharynx, larynx, and hypopharynx.[4] Loss of serologic evidence of Epstein–Barr viral infection after completion of therapy appears to predict treatment outcome.[5] Among oropharynx squamous cell carcinomas, the human papillomavirus (HPV) has been established as an important etiologic agent[6-8] The incidence of HPV-initiated squamous cell carcinomas of the oropharynx continues to increase, and this disease appears to be biologically, demographically, and prognostically distinct from its HPV negative counterpart.[9,10]

Further insight into the drivers of malignant transformation and behavior has led to the identification of tumor-specific targets for therapy. Certain malignancies appear to rely heavily on cellular pathways that are abnormally activated by mutated, amplified, or over-expressed receptors or protein kinases. Relatively new to the systemic therapy armamentarium are agents with the ability to inhibit specific proteins involved in these pathways. One example is the epidermal growth factor receptor (EGFR), which is frequently overexpressed in the mucosal head and neck squamous cell carcinomas.[11] EGFR belongs to a family of transmembrane cellular receptors Ligand binding and activation of these receptors result in downstream intracellular events, which lead to invasion, dedifferentiation, and loss of apoptosis. Several EGFR inhibitors have been developed and studied in squamous cell carcinomas of the head and neck, including the monoclonal antibody EGFR inhibitor, cetuximab, which has demonstrated efficacy, and Food and Drug Administration approval when used in combination with radiation therapy in locoregionally advanced head and neck squamous cell carcinoma, and in combination with conventional chemotherapy in patients with metastatic disease.[12,13] Prognostic and predictive molecular markers are actively being studied in other head and neck cancer malignancies. For example, Her2neu, C-kit, and vascular endothelial growth factor (VEGF) are targets of interest among the salivary gland cancers; RET appears important in medullary thyroid cancer, as does BRAF in differentiated thyroid malignancies.[14,15]

Overall, this underscores the inherent molecular heterogeneity among the head and neck malignancies Identification of these molecular markers makes targeted therapy the intuitive direction for future scientific inquiry and for improving treatment outcomes.

GENERAL PRINCIPLES IN SYSTEMIC THERAPY ADMINISTRATION

Defining Treatment Goals

The therapeutic goals of treatment for any malignancy can be considered either curative or palliative in intent. Patients with head and neck malignancies who have locally or locoregionally confined disease can usually be approached with curative intent. The cornerstone of their treatment will be locoregional therapies, including surgical resection and/or radiation therapy. It must be emphasized that to date, systemic therapy as a single modality is not a curative intent approach for malignancies of the head and neck and is largely utilized to augment local tumor control and/or modify the risk of distant metastatic recurrence. In situations where a cure is attainable, the administration of planned local and systemic therapy with minimal or no interruptions and maximal dose intensity is a treatment priority. Acute toxicities of treatment are often more acceptable to these patients and their physicians when the curative potential of therapy outweighs the morbidity and potentially mortality associated with the treatment approach. Consequently, aggressive supportive care is fundamental to successful completion of treatment. These curative intent regimens involve significant pretreatment planning and are often logistically challenging for patients. Appropriate patient selection is essential, with specific attention to those somewhat unique factors relevant to the head and neck cancer population, including comorbidity, compliance, and social support. When long-term survival is anticipated, late toxicities and long-term side effects of therapy must also be taken into consideration during treatment planning.

Patients considered medically unfit for curative intent therapy, and those with systemic metastases at presentation, or recurrent disease not amenable to local therapy,

have incurable disease and are treated with palliative intent. Therapeutic intervention in these circumstances is directed towars improving quality of life, amelioration of symptoms related to tumor burden, and survival prolongation, and chemotherapy can often be of significant, albeit temporary benefit. When systemic therapy is used in these settings, however, regimens with high rates of acute toxicity and cumbersome administration schedules fall out of favor. Because of the importance of quality of life and minimizing toxicities, the use of novel targeted agents in this group is particularly attractive.

Chemotherapy Administration

Systemically administered chemotherapeutic agents achieve cell death by targeting cellular processes that, although present in normal tissues, may be amplified in the malignant cell. This is responsible for the narrow therapeutic window of these drugs. Remaining within this therapeutic window, and avoiding severe morbidity and patient mortality, is therefore key to the successful administration of chemotherapy.

Most chemotherapeutic agents are cleared through either a renal or hepatobiliary route. Patients with compromised renal or hepatic function will have prolonged drug half lives, extended drug exposure, and therefore magnified drug-related toxicity. Patient selection with these factors in mind is routine. Myelosuppression is often a dose-limiting toxicity of chemotherapeutic agents, due to the potentially fatal complication of enteric bacteremia that can develop during neutropenia. The necessity for bone marrow recovery after chemotherapy treatment in avoiding this risk dictates the intermittent administration of chemotherapy. The typical chemotherapy administration "cycle" includes the drug administration, followed by a period of no drug exposure, to allow for normal tissue recovery.

Supportive care is an equally critical component to the successful administration of chemotherapy. Very effective antiemetics have entered routine practice and have been instrumental in mitigating the toxicities of highly emetogenic agents such as cisplatin. Growth factors that stimulate bone marrow stem cells have also been approved for use after chemotherapy, to shorten the duration of myelosuppression and prevent the infectious complications of chemotherapy-induced neutropenia. An cillary supportive services including nutritional support, physical and occupational rehabilitation, speech pathology, and dentistry all play important roles in patient care.

Efficacy Measurement

Approving a new drug with promising preclinical activity in the laboratory for use in the clinic typically requires a rigid stepwise process, which begins with phase I clinical trials. These human studies aim to define the safety and toxicity profile of the agent under study and provide additional insight into its pharmacokinetic and pharmacodynamic properties. Once the maximum tolerated dose of drug is determined, testing its activity in specific tumor types is usually done through phase II clinical trials. Promising activity in phase II studies often leads to phase III studies, which are comparisons of the promising drug or drug regimen with the current treatment standard of care.

The gold standard measure of benefit from a cancer therapy is an improvement in overall survival.[16] Survival is an unequivocal endpoint in reporting clinical trial results. Among certain patient populations, however, such as those tobacco-related head and neck malignancies, overall survival may not entirely reflect the success of a treatment regimen, due to competing causes of mortality including comorbidity and second primary malignancies.[17]

Objective response or tumor shrinkage after exposure to systemic therapy is another endpoint used in measuring treatment efficacy and has been repeatedly demonstrated to be a predictor of superior outcome in patients with squamous cell carcinomas of the head and neck.[18-20] Whether this correlation between objective tumor response and survival relates to drug efficacy or to patient and tumor biology is often challenging to distinguish. The subjectivity and inherent inter observer variability in physical examination findings and imaging study interpretation have necessitated the standardization of response criteria for reporting in clinical trial results. For the majority of solid tumors including head and neck cancers, the Response Evaluation Criteria in Solid Tumors definitions for complete, partial, stable, and progressive disease are employed in describing responses to systemic therapy.[21]

A relatively new endpoint in determining drug activity is the concept of "clinical benefit", the sum of the rates of objective responses and stable (nonprogressive) disease. This endpoint holds particular relevance in the era of targeted agents, which, when used as single agents, often halt disease growth but generally produce low rates of objective tumor shrinkage. Contemporary clinical trials describing the activity of targeted agents often report the "clinical benefit" as the outcome of interest. This

Table 3.1: Commonly used chemotherapy agents in head and neck malignancies

Agents	*Class*	*Mechanism of action*	*Common adverse effects*
Cisplatin Carboplatin Oxaliplatin	Platinum compounds	DNA adduct formation	Nausea Nephro- and neurotoxicity Myelosuppression
Methotrexate	Antifolates	Depletion of intracellular reduced folate required for purine and pyrimidine synthesis	Myelosuppression Gastrointestinal toxicity Renal insufficiency
5-Fluorouracil Capecitabine	Antimetabolites	Depletion of thymidine precursors	Gastrointestinal toxicity Myelosuppression
Paclitaxel Docetaxel	Taxanes	Microtubule stabilization	Hypersensitivity Peripheral neuropathy Myelosuppression

can be misleading, however. Among the more indolent malignancies of the head and neck such as differentiated thyroid cancer, or adenoid cystic salivary gland carcinomas, disease progression may take place very slowly over a period of many months. When clinical trials in these diseases report clinical benefit rates, this may only reflect the natural history of the disease.

Somewhat unique to the management of head and neck malignancies is the importance of preserving local anatomic structures involved in speech, eating, swallowing, sight, and airway patency. Locoregional disease control and its impact on function and cosmesis are of particular concern to the patient and physician. Provocative data havs been published suggesting that patients may be willing to accept some decrement in the success of curative intent therapy in exchange for preserving functional anatomy in the head and neck.[22] Prior to the use of concurrent chemoradiotherapy approaches in squamous cell carcinomas, the standard of care was often surgical ablation. The development of surgical and nonsurgical interventions that successfully avoid radical resection of critical structures (most studied in laryngeal squamous cell carcinomas) hae made organ preservation an important endpoint in the head and neck cancer management.[23,24]

Some of the more challenging endpoints to measure in this disease group, and arguably some of the most important to patients, are those involving functional outcomes and long-term quality of life. Although feeding tube dependence and the presence of a tracheostomy are easily recorded, these are often gross and imperfect indicators of intact organ function. The repercussions of head and neck cancer treatment encompass a wide spectrum of measures of well-being, which also include mood, diet, taste, and social integration. An increasing number of validated instruments to measure patient-reported quality of life are now available and are being routinely incorporated into clinical trial design.[25,26]

CHEMOTHERAPY AGENTS

There are numerous drugs with demonstrated cytotoxic activity in head and neck malignancies. Some of the earliest and most frequently used agents in systemic therapy of head and neck malignancies are the platinum compounds, the antifolate methotrexate, the antimetabolite 5-fluorouracil, and the taxanes (Table 3.1).

Platinum Compounds

The most extensively used platinum agent is cisplatin. It is a compound that appears to exert its cytotoxic effects by forming adducts with DNA resulting in disruption of its helical structure and subsequent cell death.[27] The major acute toxicities of cisplatin administration are its emetogenicity and the potential for renal toxicity. These toxicities are often prevented and managed by aggressive antiemetic administration and intravenous hydration. Neurotoxicity, including ototoxicity, can be a consequence of cumulative exposure to the drug. Carboplatin is an analoe of cisplatin with a more stable chemical structure.[28] Emetogenicity, nephro- and neurotoxicity are less pronounced than with cisplati ; however, the drug produces more myelosuppression. Oxaliplatin is a newer platinum analog, which has neurotoxicity as its predominant dose-limiting side effect.[29] Compared to carboplatin and cisplatin, drug-related ototoxicity and myelosuppression are less common.

Methotrexate

Methotrexate is an antifolate chemotherapy agent first introduced in the 1950s. This drug can be given both orally and parenterally. Its mechanism of action lies in its competitive inhibition of dihydrofolate reductase, an enzyme critical for folate synthesis.[30] This ultimately results in the malignant cells' inability to produce purine and pyrimidine precursors. Methotrexate is renally excreted. The adverse effects of methotrexate range widely and can include a variety of organ system toxicities, depending on the dose and the treatment schedule used. Oral mucositis, diarrhea, myelosuppression, and renal insufficiency from tubular damag, are some of the more common side effects of drug administration.

5-Fluorouracil

5-Fluorouracil is an antimetabolite that acts primarily through inhibition of the enzyme thymidilate synthetase, which catalyzes the conversion of deoxyuridine monophostphate (dUMP) into thymidine monophosphate (dTMP) a critical step in intracellular thymidine production.[31] The thymidine deficient cellular environment produced in the presence of the drug results in cell cycle arrest and eventual apoptosis. This drug is deactivated in the liver, and its inactive form is renally excreted. The toxicities observed are typically mucosal (stomatitis, mucositis, diarrhea) and myelosuppression. 5-Fluorouracil is administered intravenously, whereae its prodrug capecitabine is an orally administered drug.

Taxanes

The taxanes are a group of systemic agents whose mechanism of action is related to the stabilization of the cellular microtubule structure, resulting in mitotic arrest and cell death.[32] The earliest taxane introduced in the management of head and neck malignancies was paclitaxel, a derivative of the pacific yew tree. Docetaxe is a synthetic counterpart that is also approved for use in head and neck malignancies. Both of these drugs are hepatically metabolized and excreted through the biliary system. The toxicities of this class of agents are predominantly neurologic (peripheral neuropathy) and myelosuppression.

MOLECULAR TARGETING

Spurred by the paradigm shifting success of the drug imatinib, an oral tyrosine kinase inhibitor of the mutant BCR/ABL protein in chronic myelogenous leukemia,[33] and trastuzumab, a monoclonal antibody targeting the Her2 receptor in breast cancer,[34] there has been tremendous interest in identifying molecular markers and developing novel therapeutics targeted toward these markers in epithelial malignancies. Targeted agents or biological therapies differ from traditional chemotherapy drugs due to their specificity for one or more molecular markers that are overexpressed, amplified, or mutated in the malignant cell.[35] This in theory will result in relative sparing of normal tissues from drug-related toxicities and is consistent with the more favorable side effect profiles of these drugs when compared with traditional chemotherapy. These targeted agents, when used alone in solid tumors, also tend to produce lower rates of objective response than conventional chemotherapeutics and appear to have a cytostatic rather than cytotoxic antitumor effect. Currently available targeted agents fall into two broad categories, intravenously administered monoclonal antibodies and oral tyrosine kinase inhibitors.[35]

The monoclonal antibodies in clinical use today are typically chimeric, humanized, or fully humanized with their variable regions specific to an epitope directed toward extracellular targets on the malignant cell. The specificity of these antibodies to the target of choice and their clearance by nonrenal or hepatic means, allows them to be better tolerated even when administered in the setting of organ dysfunction. The mechanisms of action of monoclonal antibodies are incompletely understood, but they are not believed to be solely related to binding and inhibition of a cellular receptor expressed on the malignant cell surface. Specific host immune factors are also likely involved by either recruitment of cytotoxic cellular immune responses to the target or complement activation.

In contrast, the tyrosine kinase inhibitors are a class of small molecule orally bioavailable targeted agents. These drugs modulate enzymes catalyzing the transfer of the terminal phosphate to adenosine triphosphate in tyrosine residues of cellular proteins involved in signal transduction-mediating cellular proliferation, invasion, and immortalization. These drugs can act on extracellular, transmembrane, or intracellular targets and generally exert their inhibitory action on protein kinases by competitive inhibition or by producing a conformational change at the kinase ATP binding site.

In squamous cell carcinomas of the head and neck, the EGFR is frequently overexpressed and makes intuitive sense to target. Cetuximab, a chimeric monoclonal

antibody, which binds to the EGFR and competitively inhibits ligand binding, has been the most extensively studied targeted agent in this disease.[36] In clinical trials, it produces modest response rates when used as a single agent. However, phase III clinical trials that have investigated cetuximab given concurrent with radiation therapy for locally advanced disease, or in combination with chemotherapy for recurrent/metastatic disease, have demonstrated survival benefit, and have led to approval of cetuximab for both indications.[37] Oral tyrosine kinase inhibitors directed against the EGFR have, to date, not proven as effective.[38,39]

The identification of molecular targets has also proven successful in the management of advanced thyroid malignancies. The oral drugs vandetanib and cabozantinib, both inhibitors of RET (as well as other targets) have recently been approved for use in metastatic medullary thyroid carcinoma.[40,41] Iodine-refractory-differentiated thyroid cancers have been successfully targeted by sorafenib, a multikinase inhibitor of VEGF and BRAF, and a recently completed large phase III clinical trial demonstrated a progression-free survival benefit from this agent.[42] Salivary gland cancer subtypes can overexpress markers such as Her2, c-kit, EGFR, and VEGF. However, clinical trials of targeted agents in this disease have not yet yielded promising results.[43-45] Table 3.2 summarizes selected molecular targets of interest in head and neck malignancies.

Table 3.2: Molecular targets of possible interest in head and neck malignancies

Disease	*Molecular marker*
Squamous cell carcinoma	EGFR VEGF
Salivary gland carcinoma	Her2 EGFR VEGF C-kit Androgen receptors
Papillary thyroid cancer	RET/PTC BRAF RAS
Follicular thyroid cancer	RAS PAX8/PPAR gamma
Medullary thyroid cancer	RET

(EGFR: Epidermal growth factor receptor; VEGF: Vascular endothelial growth factor).

INTEGRATION OF SYSTEMIC THERAPY INTO CURATIVE INTENT TREATMENT

The integration of systemic therapy into curative intent treatment approaches has been extensively studied in locoregionally advanced squamous cell carcinomas of the larynx, hypopharynx, oral cavity, and oropharynx. Table 3.3 provides a summary of the standard nomenclature for multimodality treatment approaches incorporating systemic therapy. The rationale is to both decrease the risk of systemic metastases, and, based on its known synergism with radiation therapy, improve locoregional control. Numerous clinical trials completed over the past 3 decades have studied the use of chemotherapy prior to, during, or after locoregional therapy. A meta-analysis of these studies revealed that only the concurrent administration of chemotherapy with radiation therapy conferred a survival benefit.[46,47] The use of chemotherapy prior to locoregional treatment (also referred to as induction or neoadjuvant chemotherapy) decreased the risk of distant metastases without an appreciable improvement in locoregional control or overall survival. It did, however, appear to have a benefit in organ preservation strategies. Adjuvant single modality postoperative chemotherapy was of no benefit, although postoperative adjuvant concurrent chemoradiotherapy with single-agent cisplatin conferred a survival advantage in high-risk patients with positive margins of resection or extracapsular nodal extension.[48]

The use of induction chemotherapy prior to definitive concurrent chemoradiotherapy (termed "sequential therapy or sequential chemoradiotherapy") has generated some enthusiasm in recent years. The rationale is based on an anticipated improvement in distant metastatic disease control from induction, when it is added to the effective locoregional control achieved by the concurrent treatment. Randomized trials to date, however, have not demonstrated a benefit from this approach.[49,50] Table 3.4 outlines the results of a meta-analysis of clinical trials examining systemic therapy in the induction, concurrent, and adjuvant settings.

The applicability of these multimodality treatment approaches to the other less common head and neck cancer malignancies has not yet been established, primarily due to the rarity of these diseases, although multi-institutional clinical trials are currently ongoing.

Table 3.3: Multimodality treatment approaches incorporating chemotherapy

Nomenclature	*Definition*	*Rationale*
Induction chemotherapy	Administration of chemotherapy prior to surgery and/or radiation	Decrease risk of distant metastases Organ preservation
Adjuvant chemotherapy	Administration of chemotherapy after surgery and/or radiation	Decrease risk of distant metastases
Definitive concurrent chemoradiotherapy	Simultaneous administration of chemotherapy with radiation therapy	Improve locoregional control through radiation sensitization Decrease risk of distant metastases Organ preservation
Adjuvant chemoradiotherapy	Simultaneous administration of chemotherapy with radiation therapy after resection	Improve locoregional control through radiation sensitization Decrease risk of distant metastases
Sequential therapy/sequential chemoradiotherapy	Induction chemotherapy administration prior to definitive concurrent chemoradiotherapy	Decrease risk of distant metastases Improve locoregional control through radiation sensitization Organ preservation

Table 3.4: Meta-analysis of the effect of chemotherapy timing on overall survival in head and neck squamous cell cancer[47]

Timing	*No. of trials*	*No. of patients*	*Hazard ratio (95% confidence interval)*	*p value*	*5-year survival benefit*
Induction	31	5311	0.96 (0.90–1.02)	NS	2.4 %
Adjuvant	12	2567	1.06 (0.95–1.18)	NS	–1.0%
Concurrent	50	9615	0.81 (0.78–0.86)	<0.0001	6.5%

SYSTEMIC THERAPY FOR PALLIATION

Evidence for the use of systemic therapy in advanced incurable malignancies of the head and neck is most robust for the squamous cell carcinomas. When left untreated, patients with incurable squamous cell carcinomas of the head and neck have a dismal prognosis and a median survival expectation of 6–9 months. There are only limited prospective data, however, suggesting a survival advantage from systemic chemotherapy compared with best supportive care alone.[51] The surprising sensitivity of the disease, especially in previously untreated patients, nonetheless makes systemic therapy an attractive palliative option, particularly since a reduction in local tumor volume may have important symptomatic benefit.

Despite extensive prior treatment and an often declining performance status, limited single-agent activity has been seen in patients with incurable disease. Multiple clinical trials have compared these single agents (usually platinum compounds) to chemotherapy combinations.[52,53] Although the drug combinations have reproducibly produced an increase in response rates, little or no impact on survival has been identified. In general, these trials have only shown increased toxicity when chemotherapy combinations are used, leading to the observation that any incremental tumor shrinkage only came at the cost of higher treatment-related morbidity. The integration of targeted agents into palliative therapy may change this bleak outlook. A recently published phase III clinical trial comparing combination chemotherapy to the same chemotherapy with the EGFR inhibitor cetuximab demonstrated, for the first time, a clear survival advantage from a systemic treatment combination.[13]

The identification of active systemic agents in advanced incurable disease has now expanded to the less common malignancies of the head and neck. Previously mentioned examples include sorafenib in radioactive iodine-resistant-differentiated thyroid cancer as well as vandetanib and cabozantinib in advanced medullary thyroid cancer. The enthusiasm generated by this progress must be tempered by the challenges posed by appropriate patient selection for these often costly agents, which, although better tolerated than chemotherapy, still produce nontrivial toxicities. Attention to multiple endpoints, including disease progression and survival, toxicity, quality

of life, and patient-reported outcomes, will be critical in evaluating the benefit of these newer agents in these patient populations.

FUTURE DIRECTIONS

There are several avenues of investigation likely to shape the future of clinical investigation in this group of diseases. One of these is the increasing recognition of important prognostic and predictive biomarkers that may aid appropriate patient selection for curative and palliative intent therapies. Among squamous cell carcinomas of the head and neck, this issue is best exemplified by the recognition of HPV-initiated oropharynx squamous cell carcinoma. Nonsmoking patients with this disease are a distinct population with a superior prognosis compared with those patients with tobacco-related cancers.[54] Given the significant acute and late toxicities of multimodality treatments, and the excellent outcomes achieved in this good risk patient population, clinical investigations are exploring the possibility of "deintensifying" current curative intent treatment schedules. The RTOG 1016 phase III clinical trial comparing standard of care chemoradiotherapy to cetuximab and radiation is one such biomarker-driven effort.

Appropriate patient selection for targeted agents in both curative and palliative intent treatments has become an increasingly urgent question. The urgency stems from the escalating costs and toxicities of therapy for what is often only a marginal benefit when these drugs are used in an unselected patient population. Among other epithelial malignancies, for example, molecular markers for response to EGFR inhibitors have been identified; EGFR mutations in adenocarcinomas of the lung, and Kras status in adenocarcinomas of the colon.[55,56] These molecular determinants of benefit remain undefined among squamous cell carcinomas of the head and neck but would be tremendously helpful in identifying those individuals likely to benefit from drugs like cetuximab.

New pathways of relevance to head and neck malignancies are also emerging. As examples, inhibition of critical protein kinases in the PI3Kinase–AKT–mtor pathway, and pathways mediated by VEGFR and IGFR are among a few currently under investigation in head and neck squamous cell carcinomas. The refinement and accessibility of whole genome sequencing technology is anticipated to accelerate the identification of common pathways driving malignant transformation and tumor growth and lead to rational drug testing. One such large-scale federally funded effort is The Cancer Genome Atlas, which aims to obtain genomic data from a wide spectrum of malignancies (including head and neck squamous cell carcinomas and thyroid carcinomas) and make these publicly accessible.[57] This technology also has the potential to yield markers of interest in less common malignancies of the head and neck, such as salivary gland malignancies, but efforts at drug testing will require multi-institutional cooperation if clinically meaningful results are to be gleaned.

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Sataloff's Comprehensive Textbook of
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Patrick J Gullane MD FRCSC FACS was born in Ireland and received his medical degree from NUI-Galway, Ireland in 1970. He is a Fellow of the Royal College of Surgeons of Canada and certified by the American Board of Otolaryngology—Head and Neck Surgery. In 1975, he was selected as the McLaughlin Fellow and then pursued advanced Fellowship training in Head and Neck Oncology in Pittsburgh, and New York.

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Dr Gullane is a member of numerous Surgical Societies nationally/internationally and has been invited as a Visiting Professor to over 82 countries, lecturing on all aspects of Head and Neck Oncology. He has delivered over 830 invited and Keynote presentations nationally/internationally including the Eugene Myers International lecture in 2006, the John J Conley lecture in 2012 and the Hayes Martin lecture in 2014. He was one of the six International Faculty leaders who conducted the IFHNOS Head and Neck World Tour Program in 2008. Dr Gullane has published 335 papers in peer-reviewed journals and 94 chapters in textbooks. In addition he has published 10 books on various aspects of Head and Neck Surgery. Currently, he is a member on the Editorial Board of 10 Journals. He has served as President of the American Head and Neck Society, The North American Skull Base Society, President of the Canadian Society of Otolaryngology—Head and Neck Surgery and Vice-President of the Triological Society. In recognition of his distinguished achievements, Dr Gullane was awarded an Honorary Fellowship of the Royal Australasian College of Surgeons in 2006, Honorary Fellowship of the Royal College of Surgeons of England in 2010 and an Honorary Fellowship in the Royal College of Surgeons of Ireland in 2012. He was elected to Fellowship in the Canadian Academy of Health Sciences in 2011 and in 2010 he was appointed as a Member to the Order of Canada by the Governor General of Canada: Cited for his inspiration of young surgeons and his contributions to the field of Head and Neck Surgery. In 2014 an endowed Chair was named in his honor at the University Health Network/University of Toronto. Finally in February 2015, Dr Gullane was invested into the Order of Ontario for his enormous contributions to the field of Head and Neck Surgery.



David P Goldstein MD MSC FRCSC FACS completed his residency in Otolaryngology—Head and Neck Surgery at the University of Toronto. Following residency he completed a one-year American Head and Neck Society Advanced Training in Oncologic Head and Neck Surgery and Microvascular Reconstructive Surgery at the University of Iowa. Subsequently he completed a two-year clinical and research fellowship in head and neck oncology at the University Health Network, University of Toronto followed by a Master's Degree in clinical epidemiology at the University of Toronto. Dr Goldstein is currently a surgeon-investigator at the Princess Margaret Cancer Center, University Health Network in Toronto and an assistant professor in the Department of Otolaryngology—Head and Neck Surgery at the University of Toronto. His current practice is in head and neck oncology and microvascular reconstructive surgery and his research focus includes translational research, clinical outcome studies and population-based studies.

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