Chapter 1
Trends in Head and Neck Cancer

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Etiology

The most common cancer of the head and neck after cutaneous malignancies of the skin is squamous cell carcinoma of the oral cavity and pharynx. Worldwide, there are over 550,000 new cases of head and neck squamous cell carcinoma (HNSCC) diagnosed and 380,000 deaths each year [1]. There is great heterogeneity in rates of HNSCC by geographic distribution. In some developing countries such as India, HNSCC can be one of the leading causes of death, whereas in developed countries such as the USA, it is rare (<10 per 100,000 individuals) [2]. According to the National Cancer Database, in the USA between 1990 and 2004, there were reported 821,779 head and neck tumors (approximately 55,000 per year) which accounted for 6.5% of all tumors [3]. In the USA, according to the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Result (SEER) database between 2009 and 2015, the 5-year survival rate for oral cavity and pharynx cancers combined was 65.3% with an estimated 53,000 new cases and 10,860 deaths projected for the year 2019 [4].

Traditionally, tobacco and alcohol have been the most important risk factors for HNSCC with heavy smokers experiencing a 5- to 25-fold increased risk of developing HNSCC when compared to nonsmokers [5, 6]. Alcohol has both an independent

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and multiplicative effect on the risk for HNSCC, with a more than 35-fold increase in those who smoke more than two packs of cigarettes and consume more than four alcoholic beverages daily [5]. Cessation of smoking for more than 10 years reduces the risk of cancer development [5]. Other risk factors, such as radiation exposure, immunosuppression, chewing betel nut quid, and poor oral hygiene, have also been reported [7–10]. A minority of patients are predisposed to HNSCC as a result of inherited genomic instability, for example, in Fanconi anemia.

Over the last 20 years, the epidemiology of HNSCC has changed significantly due to the rapidly increasing incidence of human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) [11]. Even after adjustment for multiple patient-specific factors, patients with HPV-associated OPSCC have improved overall and disease-free survival compared to HPV-negative tumors [12]. Treatment de-escalation trials are therefore currently being conducted to assess whether the survival advantage can be maintained with less therapy since individuals may live many decades with the toxicities associated with radiation treatment [2].

Recurrence of HNSCC and disease-specific deaths often occur within 3 years of diagnosis [13, 14], and patients are often considered cured after 5 years of disease-free survival with only very rare recurrence occurring after this time. However, subsequent malignancies may occur in survivors for a number of reasons including genetic susceptibilities (e.g., cancer syndromes), shared etiologic exposures (smoking, alcohol, and environmental exposures), and mutagenic effects of cancer treatment. The overall cancer rate in head and neck cancer survivors is higher than the general population. After treatment, smoking remains a critical determinant of outcomes, as smokers are at higher risk for treatment failure, disease recurrence, and development of second primaries [15–17].

Staging of Head and Neck Cancer

Assigning the appropriate clinical and pathologic stage is one of the most important initial tasks for clinicians who diagnose and treat cancer patients. Staging forms the basis for understanding the extent of disease at initial presentation and the long-term prognosis for the patient. It allows for a standardized lexicon to be used when describing malignancies and as such is a useful system for understanding the changing incidence and prevalence of these malignancies on a population level. The American Joint Committee on Cancer (AJCC) has led the efforts to define and revise the staging system in the USA and collaborates with the Union for International Cancer Control (UICC) to maintain a system that is used worldwide. This follows the traditional tumor, lymph node, metastases (TNM) staging paradigm.

Cancers of the head and neck are staged according to their site of origin with seven major sites identified: (1) oral cavity, (2) pharynx, (3) larynx, (4) nasal cavity and paranasal sinuses, (5) thyroid gland, (6) salivary glands, and (7) skin cancers including melanoma. In 2018, the eighth edition of the *AJCC Cancer Staging*

Manual was published and the Head and Neck Section introduced significant modifications to the prior edition. The most significant update to the staging system includes the creation of a separate staging algorithm for HPV-associated cancers of the oropharynx which also includes differentiating pathologic staging of high-risk HPV oropharyngeal cancers from clinical staging by exclusively using node number. This separation and different staging criteria distinguishes it from classical OPCSCC and emphasizes the improved prognosis of these cancers [18]. Other major updates include division of cancer of the pharynx into three separate chapters (nasopharynx, oropharynx, and hypopharynx) and the creation of a separate chapter for cutaneous malignancies of the head and neck (non-melanoma and non-Merkel cell). In the new edition, oral cavity cancers have the additional criteria of depth of invasion rather than only size criteria for staging of the primary tumor. Additionally, all sites except nasopharyngeal carcinoma and high-risk HPV-associated OPCSCC include the important parameter of extranodal extension in staging of cervical nodal metastases [18, 19].

Trends in the USA

In 2009 Cooper et al. published a 10-year update on the trends in head and neck cancers within the National Cancer Database (NCDB) [3]. They found that between 1990 and 2004, 821,779 head and neck tumors (approximately 55,000 per year) were reported to the NCDB and accounted for 6.5% of all tumors [3]. The mucosally derived head and neck cancers were more commonly associated with lower income, whereas thyroid gland carcinomas had the opposite association. Cooper et al. identified a major shift in the distribution of anatomic sites between 1990 and 2004 such that carcinomas arising in the thyroid gland now constitute the largest group of tumors increasing from 17% to 30% and the relative proportion of non-thyroid malignancies has decreased for every anatomic subsite except carcinomas of the oropharynx (which have increased) and carcinomas of the major salivary glands (which have remained stable) [3]. In terms of cancer subtype, Cooper et al. found that squamous cell carcinoma (SCC) continues to constitute the largest histologic group, but the proportion of SCC relative to others has decreased over time [3]. This decrease in SCC correlated with the increase in thyroid carcinoma. The vast majority (89%) of cancers arising from mucosal surfaces of the upper aerodigestive tract (lip, oral cavity, pharynx, and larynx) were SCC [3]. Squamous cell carcinomas accounted for 90.8% of the common head and neck cancers in men and 83.6% in women [3].

Despite changes in staging systems, Cooper et al. found stage I tumors have become more common over time, and they identified associations between the degree of histologic differentiation, histologic type, and stage, specifically noting an association of undifferentiated and poorly differentiated tumors with higher stage at presentation and well-differentiated tumors most frequently associated with stage I

disease [3]. When looking at treatment strategies, Cooper et al. found that the most common initial management between 1990 and 2004 continued to be surgery alone (28.3%), surgery combined with irradiation (22.0%), and irradiation alone (15.2%) [3]. They observed a continuing trend toward an increasing use of combined radiotherapy and chemotherapy (increasing from 6.1% of patients treated between 1990 and 1994 to 11.7% between 2000 and 2004) and a corresponding decrease in the use of radiation therapy alone for initial management [3]. This trend was especially evident for laryngeal tumors as part of organ preservation where the use of surgery alone decreased (21.4–17.5%), the use of surgery and radiation therapy decreased (28.9–20.2%), while the use of concurrent radiation therapy with chemotherapy increased (4.4–15.0%) [3].

Head and Neck Cancer Subsites

Oral Cavity

The oral cavity is comprised of the lips, alveolar ridge, buccal mucosa, retromolar trigone, floor of mouth, and oral tongue. The most common cancer of the oral cavity is SCC, associated mostly with risk factors of alcohol, tobacco, and betel nut quid use. Chaturvedi et al. all reviewed the SEER registry from 1973 to 2004 and found the US incidence of oral cancer was stable until 1982 and has been on the decline since 1983–2004 [20]. Despite this decline there has been an increase in a subset of patients – white women less than 45 years of age. These cases also tend to have a more aggressive cancer [21]. These cancers are often more common populations that are underserved in terms of medical and dental coverage, and in these populations they are difficult to detect and treat at earlier stages [22]. LeHew et al. point out the importance of early detection and intervention for the US population, especially in underserved areas, however early detection has proven to be a difficult parameter to measure in these areas and is largely dependent on access to primary care providers [22]. Treatment for oral cavity cancers, like all head and neck cancers, requires a multimodal approach. The mainstay of treatment for resectable disease involves primary surgery and sometimes postoperative radiation. Spiotto's group in Chicago investigated primary chemoradiation vs surgery followed by radiation and found that for resectable disease surgery should still be the first goal of treatment [23].

Oropharynx

Oropharyngeal carcinoma includes cancers that arise in the palatine tonsils, tongue base (lingual tonsils), soft palate, and pharyngeal walls. The base of the tongue is functionally and anatomically distinct from the oral tongue (anterior 2/3) in that the

muscles of the base of the tongue are more involved with swallowing than speech. Base of the tongue dysfunction resulting from tumor, postsurgical resection, or radiation-related effects may result in transient or permanent dysphagia and aspiration. Resection or irradiation of the soft palate may result in velopharyngeal insufficiency, hyper-nasal speech, and Eustachian tube dysfunction. Squamous cell carcinoma is the most common tumor type in this area and makes up over 98% of oropharyngeal cancers (OPSCC). Traditionally, the development of these tumors was most closely related to tobacco and alcohol exposures, but as mentioned previously, over the last 20 years, the epidemiology of OPSCC has changed significantly due to the rapidly increasing incidence of human papillomavirus (HPV)-associated OPSCC [11]. These patients often present with early primary tumor stage, but advanced nodal stage. HPV-associated OPSCC continues to affect men more often than women, and the risk increases with increasing number of sexual partners. In contrast to traditional HNSCC patients, those with HPV-associated OPSCC are more likely to be younger, nonsmokers, of higher socioeconomic status, and Caucasian [24–26]. Even after adjustment for these factors, patients with HPV-associated OPSCC have improved overall and disease-free survival compared to HPV-negative tumors [12]. Treatment de-escalation trials are therefore currently being conducted to assess whether the survival advantage can be maintained with less therapy since individuals may live many decades with the toxicities associated with radiation treatment [2].

Louie et al. found that the most common HNC in 1995 was from the larynx, in 2011 the oral cavity, and their group projects that in 2025 the oropharynx, accounting for 35% of the new HNC cases [27]. They also point out that of those, 50% will likely be under the age of 60 [27]. Therefore, the long-term morbidities and treatment-related side effects are important to consider, especially when it comes to dysphagia and aspiration. Studies point out that despite increased stage of these patients at time of diagnosis, their prognosis with treatment was much better [28]. Therefore, it has been proposed and investigated to de-intensify treatment in order to decrease the long-term side effects. The De-ESCALaTE HPV trial was completed from 2012 to 2016 using immunotherapy (cetuximab) over standard platinum-based chemotherapy (cisplatin). While it showed that the overall side effect profile was similar for both arms, the overall locoregional control and 2-year overall survival was decreased for the cetuximab group. Therefore, it continues to be recommended that treatment include radiotherapy and platinum-based chemotherapy [29].

Another recent advancement in the treatment of OPSCC is the development of transoral robotic surgery (TORS). Prior to TORS, surgical intervention for the oropharynx presented significant morbidity, often requiring jaw-split, tracheostomy, severe dysphagia necessitating a gastrotomy tube, as well as prolonged operative length [30, 31]. TORS offers a standardized en bloc resection for oropharyngeal malignancies. The outcomes for patients that have undergone TORS result in decreased postoperative radiation and decreased gastrostomy tube dependence [32].

In the USA there are currently three FDA-approved vaccines available against HPV: a bivalent HPV-16/HPV-18 vaccine (Cervarix®, GlaxoSmithKline Biologicals), a quadrivalent HPV-6/HPV-11/HPV-16/HPV-18 vaccine (Gardasil™, Merck Sharp and Dohme), and a nanovalent HPV-6/HPV-11/HPV-16/HPV-18/HPV-31/HPV-33/HPV-45/HPV-52/HPV-58 (Gardasil™). With reference to cervical cancer, prospective clinical trials have demonstrated that premalignant lesions can be prevented by HPV vaccination and detected by screening for HPV infection. Given the success of these vaccines in cervical cancer prevention, it is postulated that vaccination may be similarly successful in preventing head and neck cancer. A double-blinded study by Herrero found 93.3% vaccine efficacy against oral infections with HPV-16/HPV-18 in women in Costa Rica 4 years after receiving vaccination [33, 34]. Another study demonstrated that vaccination with the quadrivalent vaccine induced HPV antibodies in the oral cavity of males that correlated with the level of circulating antibodies [35]. Using the National Health and Nutrition Examination Survey (NHANES), vaccinated adults (age 18–30 years) were found to have a lower prevalence of HPV-6, HPV-11, HPV-16, and HPV-18 compared to unvaccinated adults [36]. Gillison has demonstrated that the prevalence of oral HPV-16/HPV-18/HPV-6/HPV-11 was significantly reduced in vaccinated versus unvaccinated individuals (0.11% vs 1.61%) [20]. It has yet to be determined whether HPV vaccination and decreased oral HPV infections will prevent the development of OPSCC or other HNSCC; however, in response to mounting evidence, in 2016 the American Head and Neck Society published a position statement which concludes, "based on the observed link between HPV infection and the majority of OPSCC and the safety and efficacy shown of the currently available HPV vaccines in preventing HPV infection, The American Head and Neck Society strongly encourages HPV vaccination of both boys and girls for prevention of OPSCC and anogenital cancers" [37].

Larynx and Hypopharynx

Hypopharyngeal and laryngeal cancers commonly present with symptoms of hoarseness, dysphagia, dyspnea, and swallowing dysfunction. They are more common in men versus women. The most significant risk factors for development of laryngeal cancer are tobacco and alcohol usage which work synergistically [38]. With the decline in tobacco use, there has been a decline in incidence of laryngeal cancers; however the full effects of the increasingly popular marijuana and vaping are still to be determined. Rates for new laryngeal cancer cases have been falling on average 2.4% each year over the last 10 years with 4.7 cases per 100,000 persons in 1992 to 2.4 cases per 100,000 persons in 2016 in the USA [39]. Death rates have been falling on average 2.2% each year over 2007–2016. Five-year survival rate for patients presenting with localized disease is 77%, but significantly worse for those presenting with regional nodal metastases (44.7%) or distant metastases (33.3%) [39]. Multidisciplinary workup and treatment is pivotal, and for laryngeal cancer in

particular, the input from speech pathologists and dietitian is helpful in guiding treatment option and posttreatment rehabilitation.

For all stages of laryngeal cancer, the function and preservation of laryngeal functions is paramount in determining the treatment. Early-stage tumors are usually treated with transoral laser microsurgery/endoscopic resections or very narrow field radiation. There are also open laryngeal conservation options that depend on the integrity of the cricoid cartilage. These are the supraglottic, supracricoid, and vertical partial laryngectomies [40–42]. The success of these surgeries is dependent on well-planned preoperative workup (including pulmonary function) and counseling [43, 44].

For advanced-stage laryngeal cancers, data from the VA and RTOG 91-11 studied induction chemotherapy followed by concurrent chemoradiation versus concurrent chemoradiation alone [45]. For many years since these studies in the 1990s, concurrent chemotherapy and radiation had become the mainstay of treatment with the option for salvage laryngectomy in case of locoregional recurrence [46]. Given the decrease in overall survival for patients with laryngeal cancer, institutions have begun to show benefit of primary laryngectomy again [47].

Sinonasal Malignancies

Malignancies of the nasal cavity and paranasal sinuses account for less than 3% of all cancers of the upper aerodigestive tract. The incidence has remained stable over time, and tumors of epithelial origin predominate, most commonly squamous cell carcinoma followed by adenocarcinoma. Less frequent pathologies include esthesioneuroblastoma, mucosal melanoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, and sinonasal undifferentiated carcinoma (SNUC) [48]. Unlike other cancers of the head and neck, sinonasal malignancies are not associated with tobacco or alcohol use. Instead, wood dust and nickel are known risk factors, and HPV has recently been suggested to play a role in the malignant transformation of inverted papillomas.

Most patients present with nonspecific symptoms that mimic inflammatory sinus disease, such as nasal obstruction, epistaxis, or facial pain, often leading to a delay in diagnosis and advanced stage of disease. Despite this, the rate of regional or distant metastasis at the time of diagnosis is less than 10%. The most commonly involved subsite is the nasal cavity, followed by the maxillary sinus. More advanced disease at presentation leads to potential difficulty in determining the exact site of origin or attachment point. A unified staging system was not developed until 2003 by the American Joint Committee on Cancer (AJCC), and currently the ethmoid sinus and nasal cavity are bundled together, while the maxillary sinus is staged separately. In the most recent eighth edition guidelines, the T staging remains unchanged, but the modification for nodal staging also applies to cancers of the sinonasal tract.

Given the infrequency and diverse pathology of nasal tumors, survival and treatment analyses are limited. However, multimodality therapy is the standard approach. Surgical excision is the mainstay, with postoperative radiotherapy often considered. High-grade pathologies, such as esthesioneuroblastoma and sinonasal undifferentiated carcinoma, will require adjuvant treatment even after a successful resection. The development of the endoscopic technique has resulted in a shift of the surgical approach from the standard open craniofacial method. Several studies have found that disease control was at least equal comparing endoscopic to open but that endoscopic had better overall functional and cosmetic outcomes [49].

The anatomy of the sinonasal cavity is unique in its proximity to vital structures like the orbit and skull base, both of which are frequently involved by sinonasal malignancies. The main objective with skull base involvement is reconstruction and restoration of the water-tight seal between the intracranial and sinonasal cavity. The nasoseptal flap was discovered in 2006 and has become the vascularized tissue of choice since. The challenge with the orbit is whether to preserve the eye or not. While orbital exenteration results in functional, aesthetic, and psychological losses, radiation toxicity to the globe is not benign either. A recent trend toward orbital preservation in cases of periorbita or fat invasion has shown similar survival and local control compared to exenteration [50]. Induction chemotherapy has also been employed to reduce tumor volume and help preserve the eye; however it has not been shown to improve overall survival [51]. Advances in targeted immunotherapy are promising, especially for squamous cell carcinoma of the head and neck as well as mucosal melanoma. The preliminary data is encouraging, and it is likely that targeted therapy will gain widespread use in sinonasal malignancies [52].

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) has distinct epidemiologic and biologic factors that differentiate it from other head and neck cancers. It is endemic to areas of Southeast Asia and Northern Africa, as high as 25 cases per 100,000, compared to only 1 case per 100,000 in North America and Europe. Over the past few decades, the incidence has decreased worldwide but most significantly in those endemic locations. This is thought to be attributed to the reduced consumption of salt-preserved fish in the Chinese diet, a known risk factor for the development of NPC [53]. Epstein-Barr virus (EBV) is also a known etiologic cause of NPC. The pathogenesis is thought to be related to a latent infection that combined with a genetic predisposition leads to malignant transformation. EBV is not only useful for initial diagnosis, especially for an unknown primary tumor, but can also be employed as a biomarker for monitoring recurrence [54]. HPV has recently been suggested to play a role in NPC that is EBV-negative and is associated with a poorer prognosis; however the data on this is scarce.

The World Health Organization (WHO) revised the classification of NPC in 2005, defined by the following histologic subtypes: (1) keratinizing squamous cell

carcinoma, (2a) non-keratinizing differentiated carcinoma, (2b) non-keratinizing undifferentiated carcinoma, and (3) basaloid squamous cell carcinoma. Group 2 is predominately EBV-positive, and specifically 2b is the most common subtype, found primarily in endemic areas. NPC can also be characterized by TNM staging, of which it is important to note that the N staging differs from other head and neck sites. N1 represents any unilateral cervical metastasis less than 6 cm and above the supraclavicular fossa, N2 is the same but bilateral, N3a is greater than 6 cm, and N3b is within or below the supraclavicular fossa.

The nasopharynx is a difficult location to access surgically, and clear margins are often difficult to obtain. For this reason, surgery is often reserved for salvage or recurrent cases. Nasopharyngeal carcinoma is radiosensitive and thus, the primary modality of treatment is radiation. Early-stage disease can often be treated with radiotherapy alone and survival rates remain high, around 90%. Locally advanced disease (i.e., stages II–IV) requires chemotherapy, most commonly in the form of concurrent chemoradiotherapy with or without adjuvant chemotherapy. Cervical metastases are common and have been reported to be present at the time of diagnosis 80–90% of the time. Neck disease is often treated with radiation as well, with a neck dissection performed only for persistent disease. Immunotherapy directed against EBV has recently been explored and the results of early clinical trials are promising; however further studies are needed to determine their exact role [55].

Thyroid Cancer

Thyroid cancer is generally grouped separately from head and neck cancer in epidemiologic studies and represents 3.1% of all new cancer cases in the USA. The diagnosis of thyroid cancer has increased dramatically over the past 40 years with incidence rising on average 3% per year for the last 10 years making it now the 12th most common cancer in the USA [56]. Unlike many other cancers in the head and neck region, thyroid cancer is more common in women and among those with a family history of thyroid cancer. The number of new cases of thyroid cancer was 14.5 per 100,000 men and women per year based on 2011–2015 cases with a median age at diagnosis of 51 years [56]. Overall 5-year survival for thyroid cancer is excellent at 98.2% and is highest for patients with localized disease (99.9% 5-year survival) and those with only regional metastases (98.2% 5-year survival) [56]. The 5-year survival rate for those with distant metastases (all types) is 56.2%, and the percent of thyroid cancer deaths is highest among people aged 75–84 [56].

There are six types of thyroid carcinoma: papillary (84%), follicular (2%), Hürthle cell (2%), medullary (4%), poorly differentiated (6%), and anaplastic (1%) [57]. The behaviors of these different types are drastically varied, ranging from quite indolent papillary thyroid cancers to rapidly fatal anaplastic thyroid cancers. Staging for differentiated thyroid cancer is the only staging system for a head and neck cancer which incorporates patient age. While the basic TNM staging system was retained, the eighth edition downstages a significant number of patients by

raising the age cutoff from 45 years to 55 years of age at diagnosis and by removing regional nodal metastases and microscopic extrathyroidal extension from T3 disease [58].

Fine needle biopsy and cytopathological testing is used to discriminate between benign and malignant tumors; however it is inconclusive in approximately 20–30% of cases [59]. Multiple molecular diagnostic methods have therefore arisen within the past two decades with the intent of narrowing the differential diagnosis. Afirma, a proprietary gene-expression classifier with a high negative predictive value, is designed to identify benign nodules among those with inconclusive results on cytopathological testing (a rule-out test) [60, 61]. Alternatively, next-generation sequencing of a panel of oncogenes and tumor-suppressor genes identifies nodules with mutations that have been associated with thyroid cancer, with high positive and negative predictive values (a rule-in test) [62]. Other tests using microRNA have more recently become available. These tests aim to reduce unnecessary surgery, although their reliability in various clinical-practice settings remains to be definitively established.

The majority of the apparent increase in thyroid cancer has been in papillary thyroid carcinoma (PTC) and is generally accepted to be largely due to greater detection of <1 cm papillary thyroid microcarcinomas (PTMCs) [57, 63, 64]. However, there has also been an observed rise in larger PTC, indicating a true increase in incidence (1.1% annually since 1994 and 2.9% annually for patients with advanced-stage PTC) [65, 63]. Additionally, while overall mortality from PTC remains very low, there has been an increase in mortality rates over the past 30 years [56]. Some authors have suggested that attribution bias and treatment-related deaths may explain this slight increase in mortality [64]. However, treatment-related deaths remain extremely rare (<1%), and attribution bias may not explain why mortality has only increased among patients with PTC, rather than medullary, poorly differentiated, or anaplastic thyroid cancers which are more aggressive [65, 66, 7]. Despite the increasing incidence of small (T1) primary tumors, >25% of PTC patients nevertheless present with regional metastasis at the time of their diagnosis, including PTMC [67]. Although in younger patients (<55 years old) nodal metastasis does not portend a worsened survival, greater numbers of lymph node metastases do entail greater risks of both locoregional tumor persistence and recurrence in PTC [67, 68].

Along with the observed trends in incidence, there has been significant change in trends with regard to disease treatment. The mainstay of thyroid cancer treatment is surgical thyroidectomy; however the extent of surgery has shifted recently with the option for hemithyroidectomy rather than total thyroidectomy for T1 and T2 differentiated thyroid cancers without extrathyroidal extension [69]. Additionally, prophylactic central neck dissection may be appropriately avoided for noninvasive, node-negative T1 and T2 PTC and for many follicular carcinomas [69]. Total thyroidectomy with resection of involved lymph node compartments is the recommended treatment for tumors larger than 4 cm [69]. According to the literature, as many as 12% of patients who undergo thyroid surgery may have postoperative complications including hematoma, hypoparathyroidism, or recurrent laryngeal nerve

damage [70]. Although it is not yet a common practice across the USA, several centers around the globe have implemented algorithms for active surveillance of selected small PTCs, and recent studies suggest that PTMCs often remain stable for years and can be safely followed with serial ultrasonography every 6–12 months [71, 72]. In landmark Japanese studies establishing the safety of active surveillance for PTMC, only 10–15% of patients experienced tumor growth, usually within 5 years [71]. In the USA, Tuttle et al. had very similar findings for patients undergoing active surveillance for <1.5 cm nodules with Bethesda V or VI cytopathology and no clinical or radiographic evidence of extrathyroidal extension or regional metastases [72]. This study re-demonstrated that only 10–15% of tumors <1.5 cm showed growth greater than 3 mm during 5 years of active surveillance which was independently associated with younger age at diagnosis [72]. It has been reiterated throughout the literature that proper patient selection is the key to successful management of active surveillance protocols.

With the incidence of thyroid cancer on the rise with the potential for a corresponding increase in thyroid surgeries [64, 73–75], it is arguably more important than ever to seek high-volume thyroid surgeons both to reduce the risk of postoperative morbidity and also to engage with a provider knowledgeable about and comfortable with the option of active surveillance for select patients. While it has been recognized for decades that surgeons with a high-volume thyroid caseload have lower incidences of postoperative complications including recurrent laryngeal nerve injury and postoperative hypocalcemia [76–79], in the USA, the majority of thyroid surgery continues to be performed by low-volume thyroid surgeons (three or fewer cases per year) [77, 78, 80]. Recently, this trend may be reversing. Loyo et al. found that from 1993 to 2008, thyroidectomy cases increased and that cases performed by high-volume surgeons increased from 12% between 1993 and 2000 to 25% between 2001and 2008, whereas cases performed by very-low-volume surgeons decreased from 51% to 34% ($P < 0.001$) [81]. The authors also found that high-volume surgeons had a lower incidence of recurrent laryngeal nerve injury (OR 5 0.7, P 5 .024), hypocalcemia (OR 5 0.7, P 5 .002), and in-hospital death (OR 5 0.3, P 5 .004) [81].

Anaplastic thyroid carcinomas (ATCs) are rare (1–2%), highly aggressive, undifferentiated tumors, and patients diagnosed with ATC have a median survival of 5–12 months and a 1-year overall survival of 20–40% [82–84]. They are among the most lethal cancers and all are considered stage IV at diagnosis. Despite multimodality therapy, including surgery, external beam radiation, and systemic chemotherapy, response rates to standard systemic therapies and long-term outcomes remain dismal [85] with no curative options for patients who have exhausted locoregional therapies. Well-differentiated PTC precedes or coexists with approximately 50% of ATCs [86], and recent molecular profiling studies have identified that between 20% and 50% of ATC harbor activating B-Raf kinase (BRAF) V600 mutations, possible therapeutic targets [87–90]. Very recent data suggests that in a subset of ATC with BRAF V600E mutations, the combined use of dabrafenib (BRAF inhibitor) plus trametinib (MEK inhibitor) is demonstrated to have robust clinical activity exceeding any other nonsurgical treatment option to date and the chemotherapy regimen

was well tolerated [91–93]. These findings represent an exciting therapeutic advance for a rare, but devastating, cancer.

Salivary Gland Malignancy

Salivary gland malignancies are comprised of a histologically and pathophysiologically heterogeneous group of cancers. The major salivary glands include the paired parotid glands, submandibular glands, and sublingual glands. There are generally several hundred minor salivary glands which are a few millimeters in size and are located throughout the oral cavity along the hard palate and oral mucosa [94]. The incidence of salivary gland cancer is 1.3 in 100,000 representing less than 9% of all head and neck cancers, and the majority of these present within the parotid gland [95]. The overall 5-year survival is 71.9% [95].

Because the salivary glands are comprised of various cell types, the cancers which arise in the salivary glands are diverse. Using the World Health Organization 2005 classification, Boukheris et al. found the most commonly diagnosed major salivary gland malignancies were mucoepidermoid carcinoma (2.85 per 1,000,000 person years), followed by metastatic squamous cell carcinoma, acinic cell carcinoma, adenoid cystic carcinoma, and adenocarcinoma not otherwise specified [96]. More rare histologic types (less than 1 per 1,000,000 person years) include carcinoma ex pleomorphic adenoma, epithelial-myoepithelial carcinoma, lymphoepithelial carcinoma, salivary duct carcinoma, basal cell carcinoma, oncocytic carcinoma, and other even more rare subtypes. Men are 50% more likely to develop salivary gland cancer than women [96]. These salivary gland carcinomas are not strongly linked to tobacco and alcohol exposure; however exposure to ionizing radiation, including iodine-131, external beam radiation, nuclear event, and dental radiographs, has been shown to increase risk [97–101]. Other risk factors include exposure to silica dust, kerosene, nickel, chromium, asbestos, and cement dust [102, 103].

Staging of salivary gland malignancies is based on primary tumor size, cervical nodal metastases, and distant metastases. Several cancers also will have a pathologic grade which indirectly describes their behavior and therefore is considered in treatment algorithms. In most circumstances, the treatment of salivary gland malignancies is surgical. Extent of surgery for benign parotid tumors is controversial; however for malignant tumors it is more straightforward and is generally dictated by the location and size of the primary tumor. The function of the facial nerve should always be evaluated prior to surgery and preserved if it is not directly involved with the tumor. If facial nerve invasion is suspected prior to surgery, reconstructive options should be discussed with the patient and reconstructive surgeon especially with regard to eye protection. When cancerous pathology is diagnosed by needle biopsy prior to surgery, lymph node dissection will often accompany extirpation of the tumor. There are some authors who have advocated for the use of sentinel lymph node biopsy in clinically and radiographically N0 patients, but this has not yet become a popular practice. In rare circumstances, primary radiation may be in the

best interest of patients who are not good surgical candidates. Adjuvant radiation, however, has been found to significantly decrease risk of recurrence in patients with perineural invasion, lymphovascular invasion, extraparenchymal extension, or positive surgical margins, regional nodal metastases, and advanced T-stage tumors [104].

Conclusion

Despite trends in many developed countries toward decreasing rates of tobacco exposure, recent trends in malignancies of the head and neck region reveal drastic increases in the incidences of HPV-associated oropharyngeal cancer and papillary thyroid cancer. Concurrently, novel treatment strategies have arisen including surgical approaches like TORS for OPSCC that considerably minimize postoperative morbidity and active surveillance for very small PTC. Additionally, the use of adjuvant therapies such as radiation, chemotherapy, and radioactive iodine are being examined to determine if de-escalation of therapy will allow for less treatment-associated morbidity while maintaining excellent survival for select patients. While overall mortality from head and neck cancer is low, there is considerable treatment-associated morbidity which is both cosmetic and functional. The organs with which we communicate both verbally and nonverbally with the world around us and with which we experience the world through taste, smell, and sight can be compromised both by tumors themselves and treatment-related side effects. Mortality is therefore not the only measure upon which we should focus our efforts when treating head and neck cancer patients and developing new treatments.

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