Head and Neck Squamous Cell Carcinoma: A Review Article

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ABSTRACT

Head and Neck Squamous Cell Cancer (HNSCC) is one of the major health related burdens worldwide, causing high morbidities and significant number of mortalities, accounting for more than 800,000 new cases every year. HNSCC usually develops in males in the 6th and 7th decade. Major risk factors of HNSCC are the consumption of tobacco and alcohol and infection with high-risk types of human papillomavirus. HNSCC often develops from preexisting dysplastic lesions. Particular chromosomal alterations appear to be associated with distinct stages of tumor progression. Management of head and neck cancers is complex and involves multiple modalities therefore a multidisciplinary approach is mandatory. Surgery, radiation and chemotherapy are the backbones of the treatment. Majorities of the patients present in the locoregionally advanced disease. Similarly, almost 10% of newly diagnosed patients present with distant metastatic disease. Almost 60% of these patients even after aggressive, site-specific multimodality therapy, fail locally and up to a 30% develop distant metastases. Targeted therapy and Immunotherapy are recent advances in the management of refractory HNSCC to conventional treatments.

KEY WORDS: Chemotherapy, Head and Neck Squamous Cell Carcinoma, Immunotherapy, Radiation therapy, Surgery.

INTRODUCTION

Head and Neck Squamous Cell Carcinomas (HNSCC) are the epithelial cancers derived from the mucosal lining of lip, oral cavity, nasal cavity, pharynx, larynx and paranasal sinuses. The most common sites of HNSCC are oral cavity and larynx. According to the GLOBOCAN (Global Cancer Incidence, Mortality and Prevalence) 2018, more than 800,000 new HNSCC cases are diagnosed annually worldwide comprising the 6th most common cancer leading to more than 400,000 deaths annually. HNSCC are more frequent in men than in women with a ratio of 3:1, and the incidence increases with age. There is a large variation in geographic distribution of the head and neck cancers. The incidences are relatively low in Western Europe and USA whereas the high incidence regions include the countries of South East Asia, parts of Africa and South America. The management of HNSCC remained static for a long time. However, in the recent years, new findings and diagnostic tools have emerged and more treatment options are available. This review article aims at comprehensive compilation of the gradual advancements in the line of management of HNSCC.

ETIOLOGY

Carcinogen exposure, diet, oral hygiene, infectious agents, family history, and preexisting medical conditions all play a role, individually or in combination, in the development of HNSCC. The most important risk factors for developing HNSCC are tobacco smoking and alcohol consumption. Smoking...
habits that increase the risk of developing HNSCC are smoking black tobacco (commonly found in pipes, cigar and hand rolled) compared to blond tobacco (commonly found in cigarettes), smoking at a young age, long duration, high number of cigarettes per day, and deep smoke inhalation. Heavy tobacco users have a very high risk (5 to 25 folds) of developing cancer in comparison to non-tobacco users. Chewing tobacco is a major cause of oral and oropharyngeal squamous cell carcinoma (SCC) in the Indian subcontinent and parts of South-East Asia. In India, chewing accounts for nearly 50% of oral and oropharyngeal tumors in men and over 90% in women. Heavy alcohol consumption is also recognized as an independent risk factor for HNSCC, particularly for cancers of the hypopharynx. Alcohol consumption, however, is most relevant for its ability to magnify the effects of tobacco smoke in a synergistic manner. The risk of cancer development among heavy smokers and drinkers is much higher than expected based on the additive effects of the individual risks. Avoiding cigarettes and alcohol could prevent about 90% of HNSCC, especially laryngeal and hypopharyngeal tumors.

The role of alcohol and tobacco in tumorigenesis of the oropharynx is much less consequential. Instead, oncogenic human papilloma virus (HPV), particularly type 16, has been established as a causative agent in up to 70% of oropharyngeal cancers particularly in non-smoker, non-alcohol consumers young patients. HPV-associated HNSCC is strongly associated with oral HPV infection and certain sexual practices such as early age of sexual debut, a high number of sexual partners, frequent oral-genital and oral-anal contact, and infrequent use of barriers during sexual activity. Although the patients associated with HPV tend to be younger, the rates of HPV associated oropharyngeal cancer are increasing in older adults.

**TUMORIGENESIS**

HNSCC is considered to be the final stage of a multi-step process evolving from normal histology to hyperplasia, mild dysplasia, moderate dysplasia, severe dysplasia, carcinoma in situ, to invasive carcinoma. Particular chromosomal alterations appear to be associated with distinct stages of tumor progression. Underlying genetic instabilities including the loss of heterozygosity (LOH) of certain chromosomes (3p14, 9p21, 17p13, 8p, 11q, 13q, 14q, 6p, 4q27 and 10q23) and amplification, deletion, up-regulation or down-regulation of certain oncogenes or tumor-suppressor genes, including epidermal growth factor receptor (EGFR), p53, Retinoblastoma (Rb), p65, cyclooxygenase 2 (COX-2), p16, cyclin D1 and phosphatase and tensin homolog (PTEN) have been identified as genetic alterations in each of the pathological stages of this disease. supercript15 Cyclin D1 (CCND1) is an oncogene which is amplified in 30% to 50% of patients with head and neck cancer and is associated with more advanced disease, early recurrence, and shortened survival. TP53 is a tumor suppressor gene which is mutated in 40% to 60% of patients with head and neck cancer, and this mutation is associated with the progression from premalignancy to invasive disease. Tumors with TP53 mutations are likely to recur early and there is a strong direct correlation between smoking and alcohol consumption and TP53 mutation. Unlike HPV-negative HNSCC, HPV-positive HNSCC is caused by two viral oncogenes encoding for early viral proteins, E6 and E7, those bind and inactivate the tumor suppressor genes p53 and pRb leading to malignant transformation of the squamous epithelium. p16 is a surrogate marker of HPV infection. HPV-negative and HPV-positive cancers truly represent two different diseases each with a distinct biology, clinical presentation, and prognosis.

EGFR expression is highly expressed in more than 95% of HNSCCs. Increased protein expression of EGFR and its ligand, transforming growth factor α, is associated with poor prognosis. EGFR has been associated with increased resistance to radiation. Similarly, it has been demonstrated that HNSCC is an immunosuppressive disease associated with low absolute lymphocyte count, altered natural killer cell function and impairment of tumor-infiltrating T lymphocytes.

**ANATOMY**

HNSCCs are commonly located in the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx. The oral cavity includes the buccal mucosa, upper and lower alveolar ridge, retromolar trigone, floor of mouth, hard palate, and anterior two-thirds of the tongue. The oropharynx includes the base of the tongue, tonsils, soft palate, uvula, posterior pharyngeal wall, and lateral pharyngeal wall. The nasopharynx is situated behind the nasal cavity and has a vault, posterior wall, and lateral walls that include the fossa of Rosenmüller.
and the mucosa covering the torus tubarius forming the orifice of the eustachian tube. The hypopharynx is located between the oropharynx and the cervical esophagus. The hypopharynx is divided into 3 parts: the pyriform sinus, the lateral and posterior hypopharyngeal walls, and the postcricoid area. The larynx is divided into 3 regions: the supraglottic, glottic, and subglottic larynx.\(^1\)

The most important route in the dissemination of HNSCC is through lymphatic pathways towards regional lymph nodes thus knowledge of the nodal classification is of utmost important for surgeons and radiation oncologist for treatment planning. The American Joint Committee on Cancer (AJCC) staging classifies the lymph nodes as level I through level VII. Level I refers to nodes in the submandibular and submental region. Levels II, III, and IV refer to lymph nodes along the anterior cervical chain. Level V includes nodes in the posterior compartment. Level VI nodes are in the visceral compartment of the neck, whereas level VII nodes are in the superior mediastinum.\(^2\) This classification is based mainly on the surgical point of view and does not level the other mediastinum. There is another system of leveling neck nodes based on axial CT sections useful to radiation oncologists to delineate the nodes which includes all the neck nodes in a numerical system.\(^2^2\) This system divides neck nodes into 10 levels. All the groups up to the level VI is same as in the AJCC classification. The level VII is prevertebral compartment group (VIIA - retropharyngeal and VIIIB - retro-styloid nodes), level VIII is parotid group, level IX is bucco-facial group and the level X is posterior skull group (XA – retro-auricular & sub-auricular nodes XB - occipital nodes).\(^2^2\)

### CLINICAL PRESENTATION

The classical presenting symptoms of head and neck cancers are mainly site specific. Patients with early-stage disease usually come with vague symptoms and physical findings are minimal. Patients with cancer of the oral cavity generally come with nonhealing ulcers accompanied by pain. Patients of oropharyngeal cancer present with symptoms of sore throat, chronic dysphagia or persistent odynphagia lasting more than 6 weeks, and otalgia whereas patients of hypopharyngeal cancer present late in the course of disease with dysphagia, otalgia, hoarseness, and often with cervical adenopathy. The presentation of cancer of the larynx depends on the involvement of specific subsite. Patients of cancers of glottis present with persistent hoarseness and are usually diagnosed at an early stage and the cure rate is high, whereas patients with supraglottic tumors present with more advanced disease and usually have a neck mass. Cancers of the nasal cavity and paranasal sinuses are associated with symptoms of sinusitis, unilateral nasal airway obstruction, and epistaxis. Classic symptoms of nasopharyngeal carcinoma (NPC) include otitis media that is unresponsive to antibiotics, nasal obstruction, epistaxis, and cranial nerve palsies.\(^2^3\) HPV positive oropharyngeal cancer usually has a different presentation and is characterized by small primary lesion (T1-T2) with early painless neck node metastasis. Patients are usually 5-10 years younger than HPV negative HNSCC. Often, the metastatic nodes are cystic in consistency. Pathologically, HPV oropharynx cancer is likely to be poorly differentiated and to have basaloid features.\(^2^4\)

#### Neck node metastasis: The incidence of metastatic dissemination to neck node is influenced by the size of the tumor. T1 may show a regional spread in 10 to 20% of cases, T2 lesions in 25 to 30% of cases and T3 to T4 tumors in 50 to 75%.\(^2^5\) The presence of nodal metastasis has poor prognosis reducing the 5-year survival rate by 50%. Moreover, the contralateral nodal metastasis further reduces the survival rate by 25%.\(^2^6\)

The mucosa of the upper aerodigestive tract drains to the cervical lymph nodes in the lateral aspect of the neck. Tumors of the pharynx may drain to the parapharyngeal and retropharyngeal lymph nodes. The Delphian lymph node is present in the central compartment of the neck and drains the larynx and perithyroid lymph nodes adjacent to the thyroid gland. Lymph nodes in the tracheoesophageal groove provide primary drain from the thyroid gland, the hypopharynx, subglottic larynx and cervical esophagus. Each anatomic subgroup of lymph nodes described above specifically serve as primary echelon lymph nodes, draining a specific site in the head and neck region. Thus, the location of a palpable metastatic lymph node may often indicate the source of a primary tumor.\(^2^7\)

### IMAGING

Imaging is an integral part of management of patients with HNSCC. Imaging provides information for accurate staging, therapy selection, therapy
assessment, detection of recurrence, and predicting survival outcomes. Interventional radiology helps in establishing diagnosis by guided aspiration or trucut biopsy. Modern imaging modalities, including ultrasound (USG), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and radionuclide scans, have dramatically enhanced the process of diagnosis and staging as well as the evaluation for tumor recurrence in HNSCC. PET scan is potentially helpful in contouring and planning in radiation oncology. In different cancers and in specific situations, certain imaging modalities are superior to others. Individual modalities have their own pros and cons. STAGING

The stage of disease, which determines the prognosis, is determined using AJCC tumor node metastasis (TNM) staging system. Cancer staging is largely an anatomically based description of patient tumor burden. In the AJCC/Union for International Cancer Control (UICC) cancer staging manuals, staging is described by the primary tumor, nodal disease, and distant (metastatic) spread, which are designated as T, N, and M, respectively. The final clinical stage, cTNM, is designated after combining information from the physical examination, radiological findings, cytology, biopsy and other diagnostic tests. Following tumor resection, the clinical c is replaced with the prefix p using T and/or N information from the final pathologic examination pTNM and at recurrence rTNM. Staging stratifies patients into various prognostic groups. Based on the stage of the disease, it is possible to select best treatment option, plan the treatment, and estimate prognosis. The latest AJCC Cancer Staging Manual is the 8th edition which has been effective since 1st January 2018. The major modifications in the 8th edition were changes in the T category for oral cavity cancer by incorporating depth of invasion of the primary tumor; inclusion of extranodal extension (ENE) in N staging except in p16+ oropharynx cancer and nasopharynx cancer; the division of the pharynx chapter into one chapter for oropharynx (p16−) and hypopharynx, a separate chapter describing the staging system for human papillomavirus related (p16+) oropharyngeal cancer, and a third separate chapter for nasopharynx. In general, stage I or II disease defines a relatively small primary tumor with no nodal involvement. Stage III or IV disease generally includes larger primary tumors, which may invade underlying structures and/or spread to regional nodes.

TREATMENT

The management of HNSCC is complex and depends on a number of factors including the exact location of the tumor, stage, age, performance status and the general medical condition of the patient. Treatment can include surgery, radiotherapy (radiation therapy, RT), chemotherapy, targeted therapy, immunotherapy or a combination from these options. Almost 30-40% of the newly diagnosed patients present in early stage disease (stage I-II). They are generally treated with single modality either surgery or radiotherapy which results in similar survival and have excellent prognosis. Most of the patients (60-70%) present with locally and or regionally advanced disease (stage III-IVB). They are managed with combined modality treatment comprising surgery, radiation therapy and or chemotherapy. In comparison to other cancers, the incidence of systemic metastasis in HNSCC is low and depends on the location of the primary tumor, initial tumor size, involvement of nodes and disease control above the clavicle; with higher incidence of stage IV disease if nodal involvement is present.

Also, despite aggressive, site-specific multimodality therapy, a significant proportion of patients develop disease recurrence, with up to a 60% risk of local failure and up to a 30% risk of distant failure. These patients are offered palliative therapy, which could be symptomatic, analgesics, chemotherapy, radiotherapy, targeted therapy, immunotherapy or sometimes salvage surgery. If patient’s performance status permits, generally chemotherapy becomes the initial palliative treatment.

Because of the complexities of the management of head and neck cancers, the initial evaluation, development of a plan for treating and managing the sequelae of the treatment requires a multidisciplinary team of health care providers with expertise in caring for these patients. Depending upon the situation, the multidisciplinary team can involve head and neck surgeons, radiation oncologists, medical oncologists, radiologists, pathologists, palliative care specialists, psychiatrists/psychologists, plastic and/or reconstructive surgeons, dentists with particular interest and expertise in head and neck cancer, nurse specialists, speech therapists, physiotherapists...
managing lymphedema, nutritionists and social workers.\textsuperscript{30, 31}

SURGERY is one of the most important treatment modalities of the HNSCC and has come a long way since the removal of tongue for cancer in 1664 described by Maschette. Classical radical neck dissection (RND) was described and performed by Crile in 1906. With the development of reconstructive surgery and publications of use of different flaps in 1960s, the head and neck surgery took another height. The forehead flap and deltopectoral flap were the standard reconstructive options until the advent of the free flap with its own vasculature in late 1970s. These flaps along with microsurgery are commonly used to reconstruct defects in the oral cavity. The modified radical neck dissection (MRND) was described in 1963 by Suarez and was popularized by Bocca who demonstrated that MRND is not only as equally effective as RND, but the functional outcome is superior too.\textsuperscript{1}

For paranasal sinuses cancers limited to the sinuses, radical surgery is the treatment of choice. For locally and regionally advanced disease, surgery followed by radiotherapy with or without chemotherapy is recommended. The same principle is applied in the oral cavity squamous cell cancers. Radiation therapy is the mainstay of treatment of nasopharyngeal cancer with or without chemotherapy depending on the stage. For the treatment of oropharyngeal, hypopharyngeal and laryngeal cancers, the principle of organ preservation is followed as far as possible to avoid the dysfunction and morbidities created by surgery. For early stage I and stage II oral cancers, both surgery and radiation therapy can offer cure rates in the 60% to 90% range, depending on the specifics of the individual tumor. Patients with advanced T3 and T4 lesions of the oral cavity benefit from a multimodality approach using both surgery and postoperative radiation therapy. Regarding oropharynx, except for early tonsil cancer, wide local excisions cause significant defect in functionally important tissues of oropharynx and moreover, surgery cannot remove retropharyngeal nodes. Thus, radiation is the treatment of choice for the early stage cancers of palate, base of tongue and pharyngeal walls. Locally or regionally advanced cancers of oropharynx are treated with chemoradiotherapy, preserving surgery for residual or recurrent disease.\textsuperscript{32}

A new surgical technique, the transoral endoscopic head and neck surgery (eHNS), using either laser or robotic methodologies, has emerged as an option for the surgical management of oropharyngeal cancers. eHNS has many advantages over the conventional methods such as the lack of external incisions and significant ease and good visualization of oropharyngeal tumors which results in less scarring and disfigurement which ultimately causes significant reduction in the impairment of speech and swallowing. In large and complex cancers, robotic surgery can resect lesions, avoiding a lip-splitting approach, reducing the length of hospital stay with a superimposable rate of tracheostomy decannulation time, operative time, surgical margin status, and postoperative complications.\textsuperscript{33}

In the hypopharynx, most T2 and larger tumors are associated with cervical metastases and large tumor volumes. Because of these conditions and the unique anatomy of the hypopharynx, the surgery usually involves partial laryngopharyngectomy (if amenable to larynx preservation) with neck dissection for early stage (T1-T2N0) tumors. If larynx is not amenable to preservation, T2 tumors require removal of tumor with total laryngectomy. For the more advanced tumors total laryngectomy plus partial pharyngectomy with flap closure remains the standard of care. Because of the high morbidities associated with these procedures most of the patients of hypopharyngeal cancers are treated with radiation with or without chemotherapy or induction chemotherapy followed by concurrent chemoradiation (CCRT).\textsuperscript{30}

There are many options available for the treatment of cancer of larynx. For early stage laryngeal cancer, single modality treatment either radiation therapy or limited surgery is the option. For advanced one, concurrent chemoradiotherapy or surgical procedures are the options. Different surgical procedures in laryngeal cancers are laser resection of supra/glottic cancer, supraglottic laryngectomy, vertical partial laryngectomy, near total laryngectomy, supracricoid larynectomy and total laryngectomy. There are specific indications and contraindications for each of these procedures.\textsuperscript{32}

RADIATION THERAPY is one of the two curative modalities of treatment of HNSCC. The major goal of radiotherapy is the local and regional control of cancer with organ preservation with minimal damage
to the surrounding normal tissues and critical organs. Because of the complexities of the structures of head and neck region, radiotherapy to this region is also very complex. The extent of the primary tumor, involvement of regional lymph nodes and the histopathological findings guide the appropriate radiation fields, dose and fractionation. Generally, local primary cancer and regional metastatic lymph nodes require a total of 70 Gy or more, with a daily fraction of 2 Gy. Low-risk regional neck nodes require a total of 50 Gy or more. In the postoperative radiotherapy (PORT) set-up, microscopic disease requires minimum of 60 Gy to decrease the risk of locoregional failure resulting from interruption of the normal vasculature, scarring, and relative hypoxia in the postoperative tumor bed.

Though there are many fractionation schedules practiced, no single fractionation schedule has proved to be optimal. The conventional fractionation schedule, the most commonly practiced one, consists of daily fractions of 1.8 to 2 Gy, five treatments per week. The hyperfractionation schedule delivers two or more small dose fractions on each treatment day and keeps the overall treatment time the same or slightly reduced (1.2 Gy twice daily; 81.6 Gy over the course of 7 weeks). The use of smaller-dose fractions allows a higher biologically effective dose to be delivered to the tumors and increases the tolerance of late-responding normal tissues. Accelerated fractionation refers to a schedule in which the overall treatment time is reduced, but the number of dose fractions, total dose, and size of dose per fraction are unchanged or somewhat reduced (1.6 Gy twice daily; 67.2 Gy over the course of 6 weeks). The basic rationale for accelerated fractionation is that reduction in overall treatment time decreases the opportunity for tumor cell regeneration during the treatment course. Considering the normal tissue effect, these schedules are associated with more severe acute mucositis, but the incidence of late complications are within the range observed with conventional fractionation schedules. For both hyperfractionation and accelerated fractionation schedules, an interval of 4.5-6 hours or more between fractions is required for normal tissue repair of sublethal radiation injuries. In comparison to the surgery, radiotherapy imparted on certain primary localized cancers of head and neck region (as mentioned above) results in better functional outcomes and is preferred over surgery. Early stage (stage I and II) tumors involving oral commissure, oropharyngeal, hypopharyngeal and laryngeal cancers are treated definitely with radiotherapy. Radiotherapy with or without chemotherapy is the treatment of any stage of nasopharynx. Nearly all patients with advanced disease require postoperative adjuvant radiotherapy with or without concurrent chemotherapy.

Postoperative irradiation is recommended based on stage, histology, and surgical-pathologic findings. In general, postoperative RT is recommended for selected risk factors, including advanced T stage (T3-T4), depth of invasion, multiple positive nodes (without extranodal extension), or perineural/lymphatic/vascular invasion. Higher doses of postoperative RT (60–66 Gy) with systemic therapy, unless contraindicated are recommended for the high-risk features of extranodal extension and/or positive margins. The preferred interval is 6 weeks or less, between resection and commencement of postoperative RT. Dosing schedules are the same regardless of whether or not systemic therapy is administered concurrently with postoperative RT.

Palliative radiation therapy to distant metastatic sites can be effective for symptomatic relief. Select patients with recurrent disease confined to the head and neck may be candidates for re-irradiation which can result in long-term disease control in 10–20% of patients.

Nearly all patients receiving curative radiotherapy to head and neck region develop some degree of acute or late complications. Acute skin reaction, mucositis, pain (generally secondary to mucositis) are common acute and subacute complications. Xerostomia is the most common late complication. Other complications are osteoradionecrosis, trismus, subcutaneous fibrosis, laryngeal edema. Neck irradiation can cause hypothyroidism. Radiation fields encompassing the sphenoid sinus, base of skull, and cavernous sinus can result in hypopituitarism. Chronic otitis media and hearing impairment can occur in patients whose middle and inner ears were irradiated. With modern Three-dimensional conformal radiotherapy (3-D CRT) techniques, radiation-related complication rates can be reduced. An advanced form of RT delivery in 3-D CRT fashion is intensity modulated radiotherapy (IMRT), which allows delivery of high doses of RT to clinical target volumes while preserving critical normal structures and, even more importantly, salivary gland function.
CHEMOTHERAPY, though generally not indicated for the treatment of early stage (stage I and II) HNSCC, plays a crucial role in the management of advanced diseases. Chemotherapy is strongly indicated in the postoperative patients with locally advanced head and neck cancers with high risk factors, extranodal extension and positive surgical margins.35, 36

Chemotherapy is an integral part of the management of surgically inoperable locally and or regionally advanced HNSCC which when given concurrently with radiotherapy improves disease free and overall survival. Cisplatin is the preferred chemotherapeutic agent to be given along with radiotherapy in advanced HNSCC.37 One of the approaches of chemotherapy administration in locally advanced (LA) HNSCC is induction (sequential) chemotherapy, which is given prior to definitive treatment (i.e. radiotherapy, concurrent chemoradiotherapy or sometime surgery). The main objectives of the implementation of this strategy could be tumor shrinkage, organ preservation, to arrest the cancer while waiting for the starting of radiotherapy or surgery (after dental prophylaxis, or if there is a long queue for radiotherapy or surgery), and to reduce the rate of locoregional relapse and distant metastases. For laryngeal and hypopharyngeal cancers this strategy is strongly suggested with the aim of maximizing organ preservation without compromising survival.38 When induction chemotherapy is chosen the combination of taxane, cisplatin and 5-fluorouracil (TPF) is considered the gold standard regimen. Addition of taxane with PF has resulted in improved overall and progression free survival (OS, PFS), head and neck cancer mortality, and locoregional and distant failure compared with PF, which has been confirmed in a meta-analysis by Blanchard.39

Chemotherapy remains the standard therapeutic option for most of the patients presenting with a recurrent and or metastatic disease (r/m HNSCC). Depending on the situation patients are offered single or double agent chemotherapy. Cisplatin is the preferred chemotherapeutic agent. Other single agents with activity in head and neck cancers are paclitaxel, docetaxel, 5-fluorouracil (5-FU), methotrexate and pemetrexed. Gemcitabine is indicated in nasopharyngeal carcinoma. Though overall survival is not improved, doublet platinum-based regimens are generally used as first line which has shown better response rate, and is useful in patients having symptoms such as pain, difficulty in speech, eating or breathing. Cisplatin with 5-FU and cisplatin with a taxane are commonly used doublet regimens.40 Triplet cytotoxic regimens have been less extensively studied and no benefit in median or overall survival were seen in phase II trials.41

Besides chemotherapy, biologic therapy and immunotherapy have shown promising results in the management of LA and r/m HNSCC. Cetuximab is a chimeric monoclonal antibody of the immunoglobulin G1 class, which binds with high affinity to the extracellular domain of the human EGFR. Cetuximab is indicated in patients with LA HNSCC with RT when cisplatin and carboplatin are contraindicated. Cetuximab has modest palliative activity in platinum-refractory LA HNSCC and has been tested in few phase II trials.42, 43 The landmark Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer (EXTREME) trial is the first phase III trial to show a significant improvement in overall survival in r/, HNSCC by adding cetuximab to chemotherapy, from 7.4 months with chemotherapy alone to 10.1 months with chemotherapy plus cetuximab.44 Thus, EXTREME trial has established the role of triplet regimen of cisplatin, 5-FU and cetuximab in symptomatic patients with a good performance status. Currently, this regimen is the first line of treatment recommended by guidelines in fit patients.45

Efficacy of immune check point inhibitors in HNSCC have been shown by many studies. Two monoclonal programmed cell death-1 (PD-1) antibodies, pembrolizumab and nivolumab were approved by U.S. Food and Drug Administration (USFDA) in 2016 for the treatment of patients with r/m HNSCC with disease progression on or after a platinum-based therapy. Pembrolizumab is a highly selective humanized monoclonal antibody that binds to programmed cell death-1 (PD-1) receptor and inhibits the interaction between PD-1 and its ligands programmed death ligand (PD-L1) and PD-L2.18 Recently, USFDA has approved pembrolizumab as first-line treatment for recurrent, unresectable, or metastatic HNSCC when combined with platinum and 5 fluorouracil(5-FU), or as a monotherapy option in patients with PD-L1 expressed tumors. This recommendation is based on the results of the trial KEYNOTE-048.44 KEYNOTE-048 was a randomized, phase 3 trial which evaluated
pembrolizumab as a first-line systemic therapy option for r/m HNSCC. Participants were stratified by PD-L1 expression, p16 status, and performance status and total 882 patients were randomly allocated (1:1:1) to pembrolizumab alone, pembrolizumab plus platinum and 5-fluorouracil (pembrolizumab with chemotherapy), or cetuximab plus platinum and 5-fluorouracil (the EXTREME regimen). There was an OS benefit in the pembrolizumab and chemotherapy arm, compared to the EXTREME arm (median 13 months vs. median 10.7 months).46

Nivolumab is a fully human immunoglobulin G4 immune checkpoint inhibitor antibody. It is considered to be the new standard of second-line treatment.42 Its efficacy was approved in a Phase III trial called Checkmate 141. Out of 361 patients enrolled, 141 patients received nivolumab as a second-line therapy. Survival rate at 1 year was 36% vs 16% in the standard therapy (as selected by the investigator). Similarly, it was associated with an improvement in quality of life (QoL).47

CONCLUSION

HNSCC is a heterogeneous group of tumors which when diagnosed in early stage is curable. Unfortunately, most of the cases are diagnosed in advanced stage. The management of advanced HNSCC requires a dedicated expert multidisciplinary team and the financial expenditure is huge. Lamentably, the major burden of this disease is mainly in the developing and underdeveloped world where the resources for combating advanced HNSCC is very limited. On the other hand, the treatment of HNSCC was unchanged for a long time. Surgery or radiotherapy for early stage disease is still the current standard. Surgery followed by radiotherapy with or without chemotherapy for resectable advanced cancers, chemo-radiotherapy for unresectable cancers and chemotherapy or best supportive care for recurrent or metastatic cancers have been the treatment for more than two decades. Even with all these modalities the survival was not encouraging. However, the inventions of new surgical techniques, advanced radiation modalities, systemic therapies such as targeted and immunotherapy are widening the possibilities of promising enhanced quality of life and improved progression free and overall survival of patients with head and neck squamous cell carcinomas.

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