Head and Neck Malignancies are Mostly from Dermatological Origin

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ABSTRACT

Head and neck cancer includes epithelial malignancies of the upper aerodigestive tract (UADT), including the paranasal sinuses, nasal cavity, oral cavity, pharynx, and larynx; and, as the sixth most common cancer worldwide, head and neck cancer represents about 6% of solid tumors. Advances in surgery, radiation therapy, and chemotherapy have improved locoregional control, survival, and quality of life. The outcomes of these treatment modalities have shifted the focus of curative efforts from radical ablation to preservation and restoration of function. This evolution has been documented in the pages of Cancer for the past 6 decades. The median age of diagnosis is in the sixth decade of life, and there is a large male-to-female predominance. Although there has been a slight decrease in overall incidence of head and neck cancer over the past two decades, an increase in base of tongue and tonsillar cancer recently has been observed.

Keywords: head and neck cancer, head and neck squamous cell carcinoma, head and neck surgery, chemotherapy.

INTRODUCTION

Head and neck cancer comprises epithelial malignancies of the upper aerodigestive tract, including the paranasal sinuses, nasal cavity, oral cavity, pharynx, and larynx; and, as the sixth most common cancer worldwide, head and neck cancer represents about 6% of solid tumors. Approximately 650,000 new head and neck cancers are diagnosed annually, and there are 350,000 deaths yearly worldwide [1].

Nearly 66% of patients present with advanced-stage disease. The median age of diagnosis is in the sixth decade of life, and there is a large male-to-female predominance. Even though there has been a slight decrease in overall occurrence of head and neck cancer over the past 2 decades [2], an increase in base of tongue and tonsillar cancer recently has been observed [3].

Head and neck squamous cell carcinoma (HNSCC) normally develops in the sixth to seventh decade of life. Since Byers recognized this subset of patients in 1975, clinicians have become gradually more aware of patients who develop HNSCC at a young age, variably defined as age 30 years and younger, 40 years and younger, or 50 years and younger [4].

These patients may represent a distinct cohort with different risk factors and disease behavior. Even though HNSCC normally residues more common in males, even among young patients, some studies have reported a higher relative occurrence in females[5, 6]. Additionally, one report validated a reversal of the typical male-to-female ratio in favor of women within the 35-year-old or younger age group [7]. Moreover, these cohorts of

young women lack the typical related risk factors of alcohol, tobacco, and betel nut exposure and might represent a unique subset even within young HNSCC patients[6-8].

Many of the studies comparing young patients who have HNSCC with old patients with HNSCC use tumor stage as a matching criteria for creating the older, control cohort, consequently limiting the data comparing stage at presentation. Only those studies looking at whole populations can reliably comment on differences in stage at presentation. **Schantz and Yu [(9)]** reviewed the 1973-1997 SEER database and found younger patients to be more expected to present with localized disease than older patients[9]. Correspondingly, Funk's review[(6)] of the 1985-1996 NCDB established younger patients to current at an earlier stage across all types of histology, and a statistically significant higher proportion of stage I disease among young patients when analyzed only for squamous cell carcinoma (SCC). Conflicting to these discoveries, in small single-institution studies, **Verschuur *et al.*[(10)] and Veness *et al.* [(11)]** both found a higher rate of nodal metastases at presentation in younger patients. Nonetheless, **Veness *et al.*[(11)]** likewise found older patients to be more probable to present with

Received: 8/11/2017
Accepted: 18/11/2017

DOI: 10.12816/0043820

a higher T stage compared with younger patients; this latter finding was reverberated by **Sasaki *et al*.**[5] in their single-institution series. In summary, while a tendency for increased nodal metastases amid some young patients might exist, this has so far to be obviously defined, and evidence from the largest databases proposes young patients present at alike or earlier stages than older patients. Head and neck cancer continues to be a overwhelming disease, with high mortality and morbidity rates. Patients might experience incapacitating changes in appearance, talking, and the capability to swallow and breathe. Management of established cancers is difficult, and approaches to avoid these cancers from developing are of great interest.

MATERIALS AND METHODS

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials from January 1, 1985, through July 28, 2017.

- **Data Extraction**

Two reviewers independently reviewed the studies, abstracted data, and resolved disagreements by consensus. Studies were evaluated for quality. A review protocol was followed throughout.

The study was done according to the ethical board of King Abdulaziz university.

Etiology

Nearly 85-90% of all head and neck cancers can be traced to the utilization of tobacco products, the excessive consumption of alcohol, or both. Both can cause changes in the squamous cells of the head and neck aerodigestive tract. In recent years, the number of nonsmokers and nondrinkers diagnosed with head and neck cancers has increased. More than 50% of squamous cell carcinomas (SCCs) that arise in the oropharynx, particularly in the palatine tonsils and the base of the tongue, contain oncogenic human papillomavirus (HPV) DNA[12]. The Epstein-Barr virus (EBV) has been strongly linked to the development of nasopharyngeal carcinoma[13].

Risk factors for head and neck cancer

- Alcohol
- Viruses (EBV [nasopharyngeal], herpes simplex virus, HPV)
- Betel nut, inverted smoking
- Asbestos
- Diet (vitamin A deficiency)
- Systemic immunosuppression
- Mutagen-induced chromosome fragility
- Iron deficiency (Plummer-Vinson syndrome)
- Prior radiotherapy (to mucosa, salivary gland, thyroid, skin)
- Sunlight (cancer of the lower lip and malignant disease of skin)
- Premalignant conditions (oral keratosis with atypia and erythroplakia)
- Tobacco (smoked [ie, cigarettes, cigars, pipes] and smokeless) and marijuana
- Chronic irritation (jagged teeth, luetic lesions, gastroesophageal reflux disease)
- Industrial (metals [nickel, chromium], wood dust, textiles, furniture, leather [nasal cavity and peripheral nervous system]).

Primary cancer

After successful treatment with surgery, radiation, and chemotherapy, patients with head and neck growth are at an expanded danger of metachronous essential tumor, which is assessed to happen at a yearly rate of 3-10%. These tumors are huge dangers to long haul survival [14]. The focal thought that aides head and neck chemoprevention endeavors is the idea of the diffuse damage of epithelium that outcomes from across the board, constant cancer-causing agent presentation. In the 1950s, Slaughter and partners at first portrayed this procedure as field cancerization[15]. Smoking tobacco is a noteworthy hazard factor for head and neck growth, and much previous smokers are at a higher hazard for over 10 years after stopping.

The presentation to cancer-causing substances and cancer-causing promoters in tobacco smoke prompts hereditary changes, called debilitated mucosa disorder, over vast territories of the oral pit and the aviation route epithelium. These progressions result in a field cancerization with potential multifocal unsynchronized premalignant and dangerous sores.

This may clarify the high repeat rate and the advancement of further essential tumors after fruitful treatment of beginning time (I or II) head and neck growths. In this manner, novel ways to deal with controlling diseases of the head and neck locale ought to incorporate treatment of the encompassing denounced aviation route epithelium. Since these malignancies create over a drawn out time of presentation to cancer-causing agents and promoters and in light of the multistep idea of carcinogenesis, an open door exists to mediate in the process with synthetic operators for counteractive action (i.e., chemoprevention).

The inversion of this procedure is the objective of chemoprevention. Different modalities, for example, surgery and light, are utilized to deal with the outrageous articulation of the debilitated mucosa, however not their basic reason. In this way, chemoprevention can and ought to be viewed as the essential treatment.

Treatment & Management

A study by **Murphy *et al.*[17]** using information from the National Cancer Data Base, specified that for patients with head and neck cancer, lengthening the time to treatment initiation (TTI) beyond 46-52 days has a negative effect on overall survival (OS). The study, which involved 51,655 patients, found that when TTI was 46-52 days or less, median OS was 71.9 months, while median OS for a TTI of 53-67 days was 61 months and median OS for a TTI of longer than 67 days was 46.6 months[16, 17].

- **Surgical therapy**

No studies precisely address the extent of surgical resection in young patients. Most young patients with HNSCC do not have an inherently more aggressive disease, and, therefore, do not require a departure from standard treatment for any given stage. However, by the same token, efforts should not be made to perform a more limited or less complete resection simply because of a patient's young age. Additional research may reveal if young women with aggressive disease (Funk's Group I) warrant more aggressive initial treatment, even when offering with early disease (stage I-II)[18].

- **Chemotherapy and radiation therapy**

No examinations have particularly inspected diverse sorts or dosages of chemotherapy or radiation treatment as an element of age. Most investigations utilizing chemotherapy as a methodology for head and neck squamous cell carcinoma (HNSCC) neglect to stratify age in taking a gander at result. Right now, accessible investigations taking a gander at results with respect to quiet age offer practically no information about particular chemotherapeutic specialists or radiation procedures and dosing. Given that under 2% of HNSCC patients are selected in clinical trials across the nation, just future enlistment of all patients into clinical trials can give us information about the part of methodology and result with respect to persistent age. Radiation is utilized as single methodology treatment for the beginning time of infection (arrange I-II) and in multimodality treatment for cutting edge sickness (organize III-IV). Be that as it may, radiation of youthful patients has ramifications given their potential life expectancy. As patients survive longer after radiation treatment for head and neck malignancy, the long haul results of this treatment turn out to be more huge. Troubles with xerostomia, fibrosis, and gulping are huge personal satisfaction issues in long haul survivors of head and neck illumination [19, 20].

Radiation-initiated malignancies, for example, sarcoma or thyroid carcinoma, albeit unprecedented, are likewise a worry in the long haul follow-up of lighted patients. Youthful HNSCC patients effectively treated with radiation have longer post treatment lives in which to possibly build up these malignancies, and this has incited a few creators to propose surgery as the essential methodology for treatment of the youthful patient[21].

On the other hand, late proof proposes that HPV-positive tumors might be more receptive to organ conservation treatment than HPV-negative tumors[22]. This may prompt organ protection treatment being the favored methodology for both youthful and old patients who are HPV positive.

- **Chemoprevention Strategies**

The field of chemoprevention remains an exciting and challenging area of research. Although progress toward chemoprevention of head and neck cancer has been made, this field is still in its earlier stages of development and remains investigational. We are nowhere near the ultimate desired goal of possessing safe and effective preventive agents that can be easily given to the population at high risk for head and neck cancer, as fluoride can be added to drinking water to prevent dental caries. The next generation of chemoprevention trials will involve novel, molecularly targeted agents in patients stratified based on risk factors and clearly defined biomarkers. Future directions in the field of chemoprevention will be proposed that are based on recently acquired mechanistic insight into carcinogenesis.

Table 1. Selected Head and Neck Chemoprevention Trials

Trial	Patients, no	Type of Prevention	Population	Compounds	End Result	Limitation
13cRA in the treatment of oral leukoplakia [23]	44	Oral premalignancy	Leukoplakia chemoprevention	13cRA (1-2 mg/kg)	Positive	High toxicity and significant relapse rate
Comparison of low-dose isotretinoin with beta carotene to prevent oral carcinogenesis [24]	70	Oral premalignancy	Leukoplakia chemoprevention	13cRA (0.5 mg/kg/d)	Positive	...
Fenretinide in the chemoprevention of oral leukoplakia [25]	80	Oral premalignancy	Leukoplakia chemoprevention	Fenretinide (200 mg/d)	Positive	...
Response of oral leukoplakias to the administration of vitamin A[26]	54	Oral premalignancy	SPT development	Vitamin A (200,000 IU/wk)	Positive	...
Prevention of SPTs with isotretinoin in squamous cell carcinoma of the head and neck [23]	103	SPT prevention	HNSCC	13cRA (0.5 mg/kg/d)	Positive	No influence on local recurrence and has high toxicity
Prevention of SPTs with etretinate in squamous cell carcinoma of the oral cavity and oropharynx [27]	316	SPT prevention	HNSCC	Etretinate (50 mg/d)	Negative	...
The effects of isotretinoin in head and neck cancer recurrence and SPTs [28]	1190	SPT prevention	HNSCC	Isotretinoin (30 mg/d)	Negative	...
Supplemental beta carotene to prevent second head and neck cancer [29]	264	SPT prevention	HNSCC or lung cancer	Vitamin A *N* -acetylcysteine	Negative	...
Beta-carotene supplement in cancer chemoprevention [Physician's Health Study]	22,071	SPT prevention	Normal physicians	Beta carotene	Negative	...
Beta carotene and retinol efficacy trial (CARET)	18	Cancer prevention	People who smoke and asbestos workers	Beta carotene	Negative	...
A randomized trial of antioxidant vitamins to prevent second primary cancers in patients with head and neck cancer [30]	540	Cancer prevention (upper airway and lung)	HNSCC	Beta carotene	Negative	...

Medical/legal Pitfalls

- Failure to inform patients of the need for clinical follow-up care.
- Failure to counsel to discontinue the use of all forms of tobacco and to limit consumption of alcohol.
- Failure to inform patients with early-stage head and neck cancers that a study showed that high doses of vitamin E are associated with a greater risk of renewed carcinogenesis.
- Failure to inform patients about the malignant potential of the disease before and after treatment.
- Failure to warn patients with cancer that high doses of antioxidants may interfere with their treatment.
- Failure to remain alert to signs and symptoms of oral cancer and premalignancy in persons who use tobacco or regularly use alcohol.

CONCLUSION

The development of novel chemotherapy regimens and targeted therapeutic agents potentially may improve locoregional control and overall patient survival. Large cooperative groups, like the RTOG, ECOG, SWOG, and EORTC, facilitate patient recruitment into multi institutional prospective randomized trials, which have provided us with the necessary data to define current and future standards of care. Efforts to identify biomarkers that predict disease behavior will continue as individualized therapy evolves. Validated quality-of-life measures additional define treatment results, and intensification of combined treatment likely will require significant attention regarding treatment-induced toxicities. The use of tobacco-related products residues significant worldwide, but additional etiologic factors such as HPV similarly affect HNSCC presentation, behavior, and treatment. Though progress has been made throughout the past 60 years, a great deal remains to be accomplished.

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