



## Complications of Treatment

## Multimodal treatment strategies for elderly patients with head and neck cancer

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## ABSTRACT

The population in developed countries is growing older and the number of elderly people annually diagnosed with head and neck cancers is expected to rapidly increase within the following decades, since these types of tumors are age-dependent. The vast majority of older head and neck cancer patients present with locally advanced disease and multimodality treatment, including surgery, radiation and/or chemotherapy, is considered the best therapeutic option for these patients. However, several factors, including comorbidities, disabilities, frailty, and impaired functional status are considered to be more relevant criteria than chronological age per se for treatment planning. Therapeutic decisions are often complicated and demand the participation of many specialists. Advances in surgical and radiation techniques, along with the use of conventional chemotherapy and molecularly targeted agents, have improved treatment outcomes. The best-tailored individualized therapeutic option should be selected for these patients in order to avoid high toxicity and major functional deterioration. Still, more older-specific studies are needed in order to produce more definitive and applicable results. The aim of this review article is to investigate the multimodal treatment approaches for elderly patients with head and neck cancer.

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## Introduction

Head and neck cancers (HNC) represent the sixth most common malignancy worldwide and account for approximately 650,000 new cases and 350,000 deaths every year [1]. It was estimated that in the United States alone, approximately 45,660 new cases and 11,210 deaths occurred due to HNC in 2007 [2]. Although the majority of HNC occur between the fifth and sixth decade, almost one-fourth of patients belong in the “elderly” population [3–5]. Especially in developed countries, population is aging and life expectancy is rapidly growing, thus leading to a significant increase in the number of people annually diagnosed with cancer since most types of tumors are age-dependent. Consequently, the incidence of HNC increases with age and geriatric HNC population is expected to rapidly increase within the following decades [6]. In Finland, the percentage of new laryngeal cancer cases diagnosed in patients over 70 years of age in 2006–2007 was 31% both for males and females and for cancers of the mouth and pharynx, 30% and 48% for males and females respectively [7].

HNC is a heterogeneous group of aggressive epithelial malignancies that develop in the paranasal sinuses, nasal cavity, oral cavity, pharynx and larynx. The vast majority of HNC are squamous cell carcinomas (SCCHN), for which several risk factors have been identified. Tobacco and alcohol consumption are considered the most important risk factors, although strong evidence exist to support the significant role of human papillomavirus (HPV) as a causal factor in specific subsets of SCCHN. Other risk factors include age, gender, race, previous radiation to the head and neck region, occupational exposure and poor oral hygiene/dental status [8]. Surgery and radiotherapy have long been the cornerstone treatment modalities. Improved surgical and radiation techniques along with the use of systemic agents have improved clinical outcomes in curative therapy. However, approximately two-thirds of HNC patients present with locoregionally advanced disease, while 10% of patients have already metastatic disease at the time of initial presentation [9]. For these patients, a multimodality therapy is required, including surgery, radiation and/or chemotherapy. Treatment decisions are often complicated, and demand the participation of many specialists, including head and neck surgeons, medical oncologists, radiation oncologists, radiologists, plastic surgeons, and dentists.

In the literature, the definition of “elderly” is variable. A chronological landmark is considered the age of 70. After this age, an

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increased incidence of age-related physiological changes is observed, which leads to alterations in pharmacokinetics and pharmacodynamics, resulting in potentially increased treatment-related toxicity [10]. The National Institute of Aging and the National Institutes of Health are currently using three categories to define aged patients: 65–74 years as “young old”, 75–84 years as “older old” and 85 and over as “oldest old” [11]. Although aging is associated with a variety of declining physiological functions which might affect patient’s ability to withstand cancer treatment, due to the fact that biological age may differ greatly from chronological age, thorough evaluation and risk assessment are needed for decision making. In addition, it is important to estimate the life expectancy of the patient when treatment strategies are planned. In the western societies, the age adjusted life expectancy is about 13.6 years for a 70 year-old male and 16.4 years for a 70 year-old female [10].

Older patients are generally underrepresented, relative to their incidence rates, in most cancer treatment trials [12], while many studies use as exclusion criteria disorders or characteristics that are more common in the elderly (hematologic, renal, cardiac, etc. disorders, functional status limitations, life expectancy, etc.) [13]. This underrepresentation has also been demonstrated in head and neck cancer trials, specifically [13]. Thus, most studies concerning cancer treatment in the elderly are retrospective and subjected to significant selection bias. There are only few Phase III studies having sufficient data for the elderly and they do not always demonstrate beneficial effects for this subgroup of patients. The result is a lack of evidence-based data with regard to the most appropriate treatment, thus depriving them from potential new therapy that may improve their care. Therefore, there is an imperative need for individualized management of the elderly HNC patients in a multidimensional and multidisciplinary way.

The aim of this review article is to investigate the multimodal treatment strategies for elderly HNC patients with a view to personalized management.

### Head and neck cancer in elderly patients: epidemiological data and geriatric evaluation

Elderly patients with HNC have some specific features, regarding the clinical presentation of the disease that might differ from those found in younger patients. Oral cavity is the most commonly affected tumor site (46%) in patients aged more than or equal to 80 years, as it was reported by Italiano et al. in a single institution study of 316 HNC patients, while other less common sites are the larynx and oropharynx (23% and 19%) [14]. Other epidemiological studies also verify the significant prevalence of oral cavity cancer in HNC patients aged more than or equal to 70 years [4], whereas a decreased incidence of hypopharyngeal cancer was reported by Sarini et al. in a study of 273 HNC patients aged more than or equal to 74 years [15]. In contrast, data from a non age-specific meta-analysis of 17,346 patients from 93 randomized trials presented oropharyngeal cancer as the most frequently observed (36%), followed by laryngeal and oral cavity cancer (21% each) [16].

Even though HNC is considered a predominantly male disease, several studies have reported a higher women proportion in the elderly HNC population, with a sex ratio close to 1 [4,14,16,17]. In addition, elderly patients with HNC present a significantly lower degree of alcohol and tobacco exposure, and higher rates of comorbidities compared with a group of younger patients [4,17–19], which strengthens the role of advanced age as a risk factor in the development of this malignancy. Increasing age is related with reduced immune surveillance, increased mutation rate and deficient DNA repair mechanisms that may potentially lead to increased cancer incidence [16]. Moreover, elderly HNC patients are more

likely to have a second primary cancer compared with younger counterparts (31% vs. 20%) [18]. In a French study of 270 patients with oral cavity cancer aged more than or equal to 80 years, differences in risk factors were also observed between men and women. Tobacco and alcohol consumption were the major risk factors identified in 50% of the male population, whereas chronic oral trauma, leukoplakia and lichen planus were the predominant risk factors found in half of the female population [17]. In addition, HPV infection which is considered a significant causal factor in younger HNC patients seems to have minor effect in the pathogenesis of HNC in the elderly population [20]. However, since HPV status is a significant prognostic factor in the oropharyngeal cancer and HPV positivity is associated with better response to treatment and modality-independent survival benefit [21–23], it should be investigated in any patient with this cancer type, including elderly patients.

The majority of elderly HNC patients has locally advanced tumors at the time of initial presentation with, however, less nodal involvement compared with younger patients [18,24,25]. Multimodality treatment including surgery, radiation and/or chemotherapy is considered the best therapeutic option for these patients. However, numerous studies have shown that older HNC patients are less likely to receive potentially curative treatment compared with younger counterparts based on age alone [15,26–29], and in only half of the older HNC patients, therapeutic strategy complies with institution’s policies [17,20,24], although retrospective and prospective data suggest that survival outcomes between older and younger HNC patients are similar [24,30,31]. In addition, a Surveillance, Epidemiology, and End Results (SEER) database analysis of more than 2500 patients with glottic laryngeal, anterior tongue, and tonsillar cancers failed to show any statistically significant difference in overall survival or disease-specific survival between elderly and younger patients after stage stratification [32]. Thus, other factors, including comorbidities, disabilities, frailty, and impaired functional status are considered to be more relevant criteria than chronological age by itself for decision making [33]. Therefore, treatment decisions regarding the elderly HNC population should be rather based on “functional” and not chronological age.

The “functional” age of each patient is the most significant parameter for treatment planning and should be defined based on comorbidities and functional status [34,35]. However, comorbidity and functional status should be assessed independently as it was reported by a study in 203 cancer patients with a median age of 75 years using the Cumulative Illness Rating Scale – Geriatric (CIRS-G) and the Charlson score scale [36]. Comorbidity is defined as the presence of additional concurrent illnesses and disorders that are unrelated to HNC. Pulmonary function is decreasing with age due to significant deterioration of the lung parenchyma resulting in reduced vital capacities and impaired gas exchange. In addition, heart function becomes less efficient with age, leading to decreased cardiac output, reduced renal blood flow and greater water and electrolyte imbalances during surgery and general anesthesia. Also, changed renal function and hepatic metabolism may result in different drug distribution in elderly patients [37,38]. Therefore, among HNC populations, comorbidity incidence has a tendency to increase with age [4,39,40]. Other factors, such as race, gender and socioeconomic issues are also related to increased incidence and severity of comorbidity. All these parameters should be carefully evaluated when therapy strategies are planned.

Several instruments with the ability to estimate and standardize comorbidity assessment measures, along with quality of life (QOL) measures and symptom assessment tools have been created and validated in HNC [39–41]. Numerous studies have investigated the potential effect of age, comorbidity and/or pre-treatment QOL on prognosis and post-treatment QOL. However, existing data are

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