

Clinical and Therapeutic Considerations for Older Adults with Head and Neck Cancer

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Abstract: Approximately 30% of patients with head and neck squamous cell carcinoma (HNSCC) are at least 70 years of age, and this percentage is expected to increase as the population increases and lives longer. Elderly patients are underrepresented in head and neck oncology clinical trials, and there is minimal evidence on the management of HNSCC for this population. Subsequently, despite their best intentions, physicians may unknowingly recommend an ill-suited course of therapy, which may result in suboptimal oncological or functional outcomes or adverse events. Surgical approaches have the potential to carry a higher risk of morbidity and mortality in older adults, especially in patients with multiple comorbidities. Definitive radiation therapy treatment in patients with HNSCC frequently involves 7 weeks of daily radiation, sometimes with concurrent chemotherapy, and this demanding treatment can be difficult for older adult patients, which may lead to treatment interruptions, potential removal of concurrent systemic therapy, compromised outcomes, and diminished quality of life. There are clinical trials currently underway investigating altered fractionation regimens and novel, less toxic systemic treatments in this population. This review provides an overview of how best to approach an older adult with HNSCC, from initial work-up to treatment selection.

Keywords: elderly, older adult, geriatric, head and neck squamous cell carcinoma, oropharynx, hypofractionation

Introduction

The global cancer burden is projected to increase in the elderly population, given increasing life expectancy and continued population growth. The head and neck squamous cell carcinoma (HNSCC) patient population is expected to mirror this global trend. HNSCC is the sixth most common malignancy worldwide, with approximately 30% of all patients diagnosed with HNSCC over the age of 70 years old.^{1–3} Between 2012 and 2016, the highest incidence of oral cavity and pharyngeal cancers was among those aged at least 70 years.⁴ Moreover, one of the most rapidly increasing populations with HNSCC is the human papillomavirus (HPV)-mediated HNSCC patient population, and while it is thought that this disease primarily affects a younger patient population, with initial diagnosis in the fifth or sixth decade of life, there are increasing numbers of elderly patients impacted by HPV-mediated HNSCC.^{5–8} Thus, a significant portion of the HNSCC population falls into the category of older adults or elderly people (age >70 years).

The elderly HNSCC population has grown significantly, but this demographic still represents <5% of enrolled participants in HNSCC clinical trials, as demonstrated in the MARCH-NC and MACH-NC meta-analyses.^{9–11} As such, the data extrapolated from HNSCC clinical trials, which inform clinical practice guidelines, may lack validity in older adults.

Concerns such as treatment-related toxicity may be more relevant for the elderly versus the broader patient population, given elderly people's higher risk of this complication and their potential prioritization of quality of life over quantity of life.¹² A multimodal approach to treating HNSCC is typical, often combining surgery, radiation therapy (RT), and systemic therapy with chemotherapy (and, in some circumstances, immunotherapy). Over the past several

decades, there have been significant improvements in oncological outcomes, as well as the toxicity profile, with the aforementioned treatments. However, treatment-related side effects may diminish quality of life, with the most common implications affecting speech, swallowing, mastication, salivation, pain, and taste.

Side effects from HNSCC treatment are concerning for the elderly population, who are more likely to have other medical comorbidities. In addition, age-related physiological changes, including sarcopenia, decreased pulmonary function, cognitive changes, and reduced immune function, place elderly patients at risk for delayed recovery and adverse events. Acute and subacute side effects of HNSCC treatment include dermatitis, dysphagia, dysgeusia, mucositis, chronic pain, and xerostomia. Malnutrition and subsequent weight loss may result from side effects in the upper aerodigestive tract. In turn, this may lead to treatment interruptions and may require the use of a gastrostomy tube (G-tube) for short-term and potentially long-term nutritional sustenance. Cavities, trismus, osteoradionecrosis, and fibrosis are among the chronic side effects of RT or chemoradiotherapy (CRT).^{13,14} Despite the propensity of this patient population to develop treatment-related toxicity and morbidity, sufficient evidence-based guidelines for how to best treat older adults with HNSCC are not readily available.

There are numerous considerations that must be taken into account when determining an HNSCC treatment plan for an individual patient, including tumor-related factors such as subsite, stage, and histopathological features, and patient-related factors such as age, baseline functional status, and comorbidities. While some studies have demonstrated poorer tolerability of treatments such as chemotherapy in patients over the age of 70, it is unclear whether age is a confounder or a true independent risk factor. When determining a treatment plan for an older adult with HNSCC, it is important to recognize that older individuals represent a heterogeneous cohort and chronological age alone is often a poor surrogate for treatment-related outcomes. Patient age and functional status may have an impact on treatment planning; however, there is a gap in how to define standard therapy for the elderly demographic, given a lack of established guidelines for elderly HNSCC patient treatment.¹⁵ When making treatment recommendations, factors such as medical comorbidities, and functional and performance status must be taken into account.^{16–18}

Treatment paradigms in HNSCC typically involve a surgical-based approach with adjuvant radiation or chemoradiation as necessary, or a non-surgical-based approach with radiation or chemoradiation. Surgery risks increase morbidity and mortality in elderly patients with significant comorbidities, which may yield an assessment of poor surgical candidacy. In addition, the ability to recover from surgery or the acute functional deficit caused by surgery may leave these patients with poorer outcomes. Non-surgical therapy typically involves definitive CRT over 7 weeks, which can be especially cumbersome on an older adult's time, resources, and body, and result in treatment interruptions and worse outcomes.¹⁹ The elderly population has a higher risk of treatment interruptions, which are particularly concerning in patients with HNSCC, given that treatment interruptions have been associated with worse overall survival,¹⁹ but, interestingly, not with disease-specific outcomes.^{20–24} Thus, the etiology and impact of treatment interruptions in the elderly population is multifactorial and may serve as a substitute for other specific issues that contribute directly to poor outcomes.^{22,24–27}

In order to optimize outcomes for this unique, albeit heterogeneous, population, comprehensive geriatric assessments (CGAs) are increasingly being used to assist with clinical decision making in elderly patients in most fields of medicine. However, there is still no formal recommendation for inclusion of these assessments in treating elderly HNSCC patients to help guide treatment. In addition, providers must acknowledge potential barriers to care by adequately assessing socioeconomic and psychosocial status, especially given the high rates of financial toxicity associated with HNSCC treatment for patients in the USA. Here, we review the clinical and therapeutic considerations for HNSCC treatment in elderly patients, highlighting key aspects of the work-up (geriatric assessments, medical comorbidities, barriers to care, polypharmacy, etc) and treatment.

Work-Up

Psychosocial and Socioeconomic Status

Psychosocial factors play an important role in head and neck cancer outcomes, and this is no exception for the elderly population. Specifically, socioeconomic status, insurance status, and race have been demonstrated to impact both treatments received and outcomes. A SEER-Medicare database study, published in 2021, found that socioeconomic

status is a key prognosticator in older adults, and that Black, non-Hispanic older adults have worse HNSCC prognosis compared to older adults of other races and ethnicities.²⁸ The authors postulate that this may be secondary to a lack of access and barriers to healthcare and prevention measures (eg smoking cessation resources). Another SEER-Medicaid study, assessing outcomes based on insurance status, found that uninsured patients and Medicaid patients are more likely to present with metastatic disease (adjusted odds ratio 1.60; $p < 0.001$) and to have higher rates of head and neck cancer-related mortality, and are less likely to receive definitive therapy.²⁹ HNSCC treatment is also associated with high rates of financial toxicity for patients residing in the USA,³⁰ which can have significant implications, especially for elderly patients, who are more likely to be retired and without wages. A cross-sectional study of 104 HNSCC survivors found that up to 40% of patients experienced high financial toxicity and up to 60% of patients ultimately had to use savings and/or take out loans in order to help finance treatment. Patients at highest risk for financial toxicity were patients who were not married, had lower levels of education, and had primary tumors of the larynx/hypopharynx.³¹ While little is published on financial toxicity specifically in the elderly HNSCC population, it is an important to identify at risk patients and discuss potential financial toxicity concerns with patients and their caregivers.³⁰

Medical Comorbidities

Medical comorbidities tend to be more common among elderly HNSCC patients, and some of these comorbidities may interfere with treatment tolerability and recovery. Assessments such as the Charlson Comorbidity Index (CCI), Adult Comorbidity Evaluation-27 (ACE-27), and Kaplan–Feinstein Comorbidity Index (KFI) are helpful in quantifying the implications of comorbid conditions on outcomes.^{32–34} While these tools were not specifically developed for cancer patients or the elderly population, they can be very informative and can be used to quantify the burden of comorbid conditions more accurately. The CCI is a predictor of 10-year survival and incorporates comorbidities such as neurological, cardiac, pulmonary, and gastrointestinal conditions into its scoring system. Reid et al demonstrated that overall comorbidity, quantified by the CCI, is an independent predictor of survival in elderly patients with HNSCC.³⁵ Similarly, Datema et al showed that comorbidity is an independent prognostic factor and impacts both the short-term mortality of HNSCC patients and overall survival.³⁶ It is worth noting that there are three neurological components/comorbidities included in the CCI: cerebrovascular accident (CVA), transient ischemic attack (TIA), and dementia. All three of these factors have the potential to lead to cognitive decline, but research is lacking into the potential effect on outcomes of cognitive impairment in older adult HNSCC populations. That considered, van Deudekom et al demonstrated that cognitive impairment in older HNSCC patients correlates with postoperative delirium in patients undergoing surgery.³⁷ Still, the impact of cognitive delirium on non-surgical HNSCC therapy has been poorly studied to date.

In addition, sarcopenia, age-related involuntary loss of skeletal muscle mass and strength, has been shown to be an independent prognostic factor for elderly HNSCC patients and a predictor of chemotherapy dose-limiting toxicity.^{38–43} Depending on a patient's comorbidities, patients may tolerate treatments differently. Thus, a patient's comorbidities should be carefully evaluated before making treatment decisions to understand the risks and the patient's ability to undergo treatment.

Medication Management

Polypharmacy, the simultaneous use of multiple medications, is common in the elderly population and may be another contributor to worse outcomes in this population. Polypharmacy is common in the USA and is an indirect measure of the medical comorbidity burden. Approximately 90% of elderly adults (age >65 years) take at least one prescription medication in a typical month, 66% take at least three medications, and 42% take at least five medications.⁴⁴ A systematic review analyzing elderly cancer patients showed an association between polypharmacy and chemotherapy-induced toxicities in addition to postoperative complications.⁴⁵ In addition, there are medications that may not be appropriate for elderly adults: the American Geriatrics Society (AGS) maintains the Beers Criteria medication list, which is a list of potentially inappropriate or harmful medications for older adults that should be avoided in the elderly population.⁴⁶ Another systematic review and meta-analysis showed that potentially inappropriate medication use is associated with worse mortality in elderly patients.⁴⁷ A retrospective study of elderly patients, defined as age greater than 70 years, with oropharyngeal squamous cell carcinoma (OPSCC) evaluated the effects of polypharmacy, potentially

inappropriate medication use, and comorbidities, and found that a comorbidity–polypharmacy score, and not the comorbidity score alone, was associated with worse overall survival.⁴⁸ These studies illustrate that is essential to consider potential medication interactions and minimizing polypharmacy when appropriate in elderly patients with HNSCC and to educate patients and/or caregivers accordingly.

Geriatric Assessments

It is essential to consider an older adult patient's functional status and social support network during the initial work-up. Patient age, medical comorbidities, and functional status may affect treatment planning, as well as the patient's priorities and goals of care. Several methods have emerged to systematically assess frailty and functional status to identify which patients are at increased risk for adverse outcomes, including the CGA and Geriatric 8 (G8).^{49–53} The CGA is a very thorough assessment developed by the International Society of Geriatric Oncology (SIOG), and can be impractical to complete in the clinical setting, potentially limiting its use.⁵⁴ Since publication of the CGA, subsequent abbreviated versions of this survey, such as the G8 questionnaire, have been efficacious in predicting the survival of elderly cancer patients.^{49,55} The G8 panel incorporates eight items, comprising food intake, weight loss, mobility, neurological and psychological problems, body mass index (BMI), polypharmacy, self-reported health status, and age. The G8 is accurate in risk stratifying overall survival and quality-adjusted survival for elderly patients with HNSCC, and can accurately identify vulnerable patients who may have lengthened postoperative courses and prematurely terminated radiotherapy courses.^{56,57} In addition to geriatric assessments, there are predictive algorithms that can be incorporated to estimate treatment risks or identify patients at risk for treatment-related adverse effects. For example, the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) is a scoring system that identifies patients at risk for chemotherapy-related side effects.⁵⁸ Risk assessments, such as CRASH and other geriatric assessments, should be incorporated to help guide HNSCC management in this special population. A more aggressive, standard therapy may be selected for a fit older adult and a less aggressive treatment may be more appropriate for a more frail older adult. A prospective trial evaluating the use of geriatric assessment for HNSCC, utilizing the G8 screening tool and CGA to guide treatment planning, found that after the use of a geriatric assessment, the proposed therapy changed from what the physician was originally going to recommend in 12% of patients. The researchers also found that specific supportive needs, including nutritional, psychological, and chronic medication support, were altered after the use of the geriatric assessment. This study placed patients with locally advanced HNSCC into one of three categories: fit, vulnerable, and frail, as defined by the assessments.⁵⁹ Despite emerging evidence regarding the utility of the CGA, assessments currently do not seem to be routinely incorporated in routine practice. In a survey study published in 2020, only 10% of the HNSCC radiation oncologists in Italy stated that they performed a CGA in older adult patients.⁶⁰

In addition to geriatric assessments, there are several predictive models to calculate probabilities of cancer-related events. The Generalized Competing Event (GCE) model is a way of risk-stratifying patients by weighing the relative hazard of cancer- and non-cancer-related events.^{61–66} The GCE is also known as the omega (ω) score, and is a ratio that was developed for all cancer patients. The ratio is a proportion of the risk of cancer recurrence to non-cancer mortality, such that the closer the ratio is to 1, the higher the risk of cancer progression relative to mortality from other causes, while a value closer to 0 designates a higher likelihood of mortality from other causes. Variables incorporated in the GCE model include age, Eastern Cooperative Oncology Group (ECOG) status, BMI, primary tumor site, N stage, and p16 status. This model has been validated in patients with locally advanced HNSCC in the Meta-Analysis of Radiotherapy in HNSCC (MARCH)^{11,67} and Meta-Analysis of Chemotherapy in HNSCC (MACH-NC) studies.^{9,11} Furthermore, the GCE has been validated in a SEER database cohort study especially for elderly patients with HNSCC, which showed that this model is a more reliable way to risk stratify elderly patients and risk of HNSCC-related mortality than other existing models.⁶² Table 1 and an online, open-access nomogram tool⁶⁸ outline the numerous predictive tools available, including GCE, G8, CCI, Cancer and Aging Research Group (CARG), ACE-27, and the Cumulative Illness Rating Scale – Geriatric (CIRS-G). These resources are referenced and utilized in an ongoing clinical trial (NCT: 03258554: Radiation Therapy With Durvalumab or Cetuximab in Treating Patients with Stage III–IVB Head and Neck Cancer Who Cannot Take Cisplatin), which investigates the efficacy of durvalumab or cetuximab in patients with HNSCC unable to tolerate cisplatin, which includes many elderly patients.⁶⁵

Table 1 Validated Assessments and Nomograms That Are Available to Guide Treatment Planning and Predict Treatment-Related Toxicity and Help Guide Clinicians in Informing Patients on Their Specific Expected Disease Course and Treatment Course

Assessments and Nomograms
Assessments and Criteria for Geriatric Patients: • Comprehensive Geriatric Assessment (CGA) • Geriatric 8 (G8) • Beers Criteria for potentially inappropriate medications Comorbidity Assessments: • Charlson Comorbidity Index (CCI) • Kaplan–Feinstein Comorbidity Index (KFI) • Charlson–Deyo Comorbidity score • Adult Comorbidity Evaluation (ACE-27) Treatment Nomograms: • Generalized Competing Event (GCE) model • Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) • Hearing loss prediction tool for cisplatin chemotherapy and radiation in head and neck cancer treatment

Developing a standard comprehensive assessment tool for HNSCC patients would be beneficial to personalize care for this population. Predictive nomograms specific to elderly patients with HNSCC are continuing to be developed and refined. One example is a predictive nomogram specific to elderly patients with HNSCC that was developed using data from 284 patients at least 65 years of age, which incorporated Karnofsky Performance Status (KPS), CCI, and baseline serum CRP, published in 2021. Long-term data are needed, but this predictive nomogram has the potential to help guide treatment decisions for the elderly population in the future.⁶⁹ In 2022, Zhou et al published a predictive nomogram utilizing different clinical variables, including BMI, nodal status, hemoglobin level, and neutrophil–lymphocyte ratio (NLR), to prognosticate elderly patients with oral cavity squamous cell carcinoma (OCSCC), with the intention of specifically guiding treatment for elderly patients.⁷⁰ A similar model developed by another group, using retrospective data from 583 patients and including variables such as EBV viral load, tumor and nodal stage, and albumin level, was created to characterize elderly patients with nasopharyngeal SCC.⁷¹ The aforementioned predictive models are limited given that they have yet to be validated in the prospective setting; however, these predictive nomograms offer useful information and can serve as a guide for clinical discussions with elderly patients. An assessment of frailty in tandem with relevant biomarkers, not just chronological age, should be conducted for elderly patients with HNSCC in the future. Table 1 lists the most commonly referenced assessment nomograms currently in use.

Treatment

Surgical Management

Surgical outcomes of HNSCC have significantly improved, especially with regard to the functional morbidity associated with the surgery for HNSCC patients. This has been enhanced by a critical appraisal and review of surgeons' functional outcomes, as well as the use of more advanced surgical techniques, such as the use of free flap reconstruction and minimally invasive techniques such as transoral robotic surgery (TORS) and transoral laser microsurgery (TLM). Surgery can still carry significant risks, despite the substantial advances in surgical techniques, improvements in perioperative care, and anesthesia.⁷² Data on postoperative complications in elderly patients with HNSCC are heterogeneous and contradictory, with some studies reporting increased risks associated with surgery for HNSCC in the elderly population based on age alone,^{73,74} and others demonstrating that frailty, higher rate of pre-existing comorbidities, advanced tumor stage, surgery time, poor G8 score, and smoking are correlated with perioperative complications independent of age.^{75–82} Free flap reconstructive surgery has become the standard of care for larger ablative defects to restore form and function. Despite being associated with longer operative times, studies have demonstrated that elderly patients (even in patients ≥ 90 years of age) who undergo free flap reconstruction experience similar outcomes to their younger counterparts;

however, elderly patients are more likely to have longer hospital stays and longer length of intensive care unit stays when treated at lower volume head and neck cancer centers.^{83–86} Similarly to free flap reconstruction, TORS is generally well tolerated in the elderly population, with the exception of elderly patients with severe comorbidity, as demonstrated in a multi-institutional retrospective review of patients greater than 70 years of age with HPV-positive OPSCC.⁸⁷ Similarly to TORS, TLM for early-stage laryngeal surgery has been shown to be safe and effective in patients with laryngeal cancer, regardless of age.^{88,89} Surgical options for early-stage laryngeal cancer include TLM and partial laryngectomy; however, despite similar overall survival rates between the two surgical options, TLM is favored given the improved functional outcomes.^{90–92} Minimally invasive and major head and neck surgeries have been shown to be generally well tolerated in the elderly population.

Radiation Therapy

A main trend in HNSCC RT is de-escalation therapy, which involves minimizing any of the following variables: radiation target volumes, fractions, and/or dosage, in order to minimize treatment toxicity. De-escalation trials have not been thoroughly studied in the HNSCC elderly population. Hypofractionation is a salient component of de-escalation therapy, and involves reducing total dosage by reducing the number of fractions. Hypofractionation is critical to study given that standard regimens of RT for HNSCC can cause significant toxicity. Active areas of HNSCC de-escalation research involve investigating radiation dose reduction in HNSCC to better delineate the balance between treatment efficacy and minimizing toxicity. Alternative fractionation regimens and hypofractionation are based on foundational research by Withers et al, which determined that there is a relationship between radiation treatment time and total dose needed for adequate tumor control in patients with HNSCC. This sentinel study demonstrated that a greater dose of radiation is needed to achieve the same tumor control after 4 weeks of radiation given because of tumor repopulation. This study provided proof of concept for alternative fractionation regimens for HNSCC treatment.⁹³ Radiobiological modeling has demonstrated that 3 Gy per fraction or accelerated hyperfractionation (1.8 Gy given twice daily) is effective in achieving tumor control for HNSCC patients and was determined to reduce late effects compared to the standard 2 Gy per fraction standard of care regimen.⁹⁴ Hypofractionation with curative intent in patients with HNSCC is a new and emerging area of research, and the elderly population is an ideal cohort set to benefit from this area of research.

Hypofractionation, shortening total treatment time, and decreasing total dose have been shown to decrease malignancy-associated burden in the palliative care setting; however, the primary objectives of several studies involved assessing for improvement in symptoms rather than local disease control.^{95–101} During the COVID-19 pandemic, the American Society of Radiation Oncology and European Society of Radiation Oncology released a statement promoting a hypofractionated treatment regimen for appropriate patients with HNSCC.¹⁰²

There are a small series of published studies assessing the efficacy of hypofractionation specifically in the older adult HNSCC population. One such example is a study conducted by Ortholan et al investigating a split-course, hypofractionated plan in elderly and vulnerable populations with HNSCC (the ELAN study), which is one of the first prospective trials designed specifically for elderly patients. In this study, patients are stratified into one of three arms based on fitness, using different geriatric assessments, and disease stage: unfit non-metastatic, fit metastatic, and unfit metastatic disease. Unfit patients with non-metastatic HNSCC receive a hypofractionated split course of 30 Gy in 10 fractions over the course of 2 weeks followed by a 2-week break, subsequently followed by 25 Gy in 10 fractions for a total of 6 weeks. This study aims to show that split-course therapy may achieve good local control tumor response rates at 6 months for those patients who are unfit to tolerate continuous therapy, and may be better tolerated, with decreased side effects.¹⁰³ Appropriate patient selection is critical, given that split-course therapy carries the potential risk of rapid repopulation typical for head and neck cancers after 4 weeks of treatment initiation.¹⁰⁴ It is worth noting that a split course in combination with hypofractionation may cause more long-term side effects, and further studies are needed to determine the long-term effects of hypofractionation regimens in the elderly population.¹⁰⁵

Our institution treats a high volume of HNSCC patients, and our experience with unfit, frail, elderly patients is consistent with the published literature in terms of challenges in receiving treatment.^{105–107} For elderly patients with HNSCC who cannot or do not want to receive standard RT, a new hypofractionation regimen is being investigated, with shortening of adjuvant and definitive standard treatment regimens. The study aims to evaluate the efficacy of

hypofractionated RT without chemotherapy with curative intent in elderly patients with HNSCC. Inclusion criteria for the definitive arm include patients unfit for standard of care, and the adjuvant arm includes patients with adverse features on pathology following definitive resection. Patients with HNSCC at least 70 years old and at least ECOG grade 1 can be enrolled to receive definitive RT (45 Gy in 15 fractions over 3 weeks) or adjuvant RT (40.5 Gy in 15 fractions over 3 weeks). Similarly to Ortholan et al, the primary endpoint of our study is locoregional control at 6 months (NCT04284540: Hypofractionated Radiotherapy in Elderly Patients With Head and Neck Squamous Cell Carcinoma). Our investigators hypothesize that this hypofractionated regimen will significantly improve treatment tolerance, with no change in disease control efficacy at 6 months.^{108,109}

There are conflicting data regarding RT-related toxicity in the elderly population, with studies reporting either increased or similar RT-induced toxicity in elderly patients compared to a younger cohort;^{10,19,110–112} however, the association between increased RT toxicity and the addition of chemotherapy in the elderly population is well established.^{10,110} A review of Radiation Therapy Oncology Group (RTOG) CRT trials for HNSCC demonstrated significantly higher rates of severe late toxicity (defined as chronic grade 3+ pharyngeal/laryngeal toxicity and/or requirement for a feeding tube ≥ 2 years after registration and/or potential treatment-related death within 3 years) in the elderly cohort.¹¹¹ A retrospective study of HNSCC patients compared elderly patients, 70 years of age or older, with a younger cohort who underwent surgery followed by adjuvant CRT, and determined that chronic nephrotoxicity was the only toxicity that was significantly increased in the elderly cohort.¹¹² A retrospective study assessing patients greater than or equal to 70 years of age with HNSCC treated with curative intent demonstrated that comorbidity (measured with the CCI) did not predict treatment toxicity; however, there was a higher G-tube placement than expected (24% prophylactic and 18% reactive), which is consistent with other studies suggesting that G-tubes are more frequently placed in older adult patients with HNSCC.^{19,113} Treatment-related toxicity can be a barrier for novel hypofractionation regimens. De Felice et al published a trial investigating a hypofractionated RT course treating with 60 Gy over 4 weeks (3 Gy/fraction) with concurrent cetuximab (400 mg/m² given a week before radiation followed by 250 mg/m² during treatment), with a primary endpoint of partial or complete objective response at 3 months. The median age was 77.5 years and the trial included only six patients in total owing to premature closure from treatment-related toxicity. These toxicities included grade 3+ oral mucositis, acneiform eruption, dermatitis, and nausea.¹¹⁴ All patients completed the radiation schedule; however, only two of the patients successfully completed the concurrent cetuximab course. A partial response was observed in three patients, the remaining three patients had progressive disease, and none of the patients had a complete response. Providers should be cautious when considering hypofractionation regimens in combination with radiosensitizing chemotherapy.

Systemic Therapy

Numerous studies have raised concerns about the use of chemotherapeutics in elderly patients with HNSCC, as chemotherapy can incur severe toxicities that outweigh its benefits in tumor control. Special considerations need to be made when treating the elderly population, as several physiological differences differentiate them from the younger adult population, which has the potential to alter the response to systemic chemotherapeutics. For example, older patients often have reduced glomerular filtration rate (GFR) and hepatic metabolism, which can affect the distribution of chemotherapeutics.¹¹⁵ In addition, polypharmacy and potentially inappropriate medications are an ongoing area of concern in the elderly population and could potentially interfere with systemic therapy.¹¹⁶

The benefit of chemotherapy in the treatment of HNSCC has been well established, with the most benefit seen with concomitant chemotherapy as opposed to induction, adjuvant, or neoadjuvant chemotherapy.^{9,117,118} It is worth noting that the efficacy of chemotherapy appears to decline with increasing age.¹¹⁹ The 2009 MACH-NC patient-based meta-analysis of 16,485 patients found that patients older than 70 years of age received no significant survival benefit in 5 years with the addition of chemotherapy; this was in stark contrast to the younger cohort, which experienced a 4.5% 5-year survival benefit.⁹ The updated 2021 MACH-NC large study with 18,951 patients reinforced this notion of decreasing efficacy of concomitant chemotherapy with increasing age and cautioned providers to carefully consider the use of systemic therapy in the elderly HNSCC population.¹²⁰ Other studies have similarly reported on the toxicity and drawbacks of chemotherapeutics in the elderly HNSCC population. A subset analysis of three RTOG trials with 230 patients reported a significant correlation of older age with severe late toxicity from CRT.¹¹¹ A retrospective study of

4042 patients aged 71 years or older from the National Cancer Data Base (NCDB) directly disputed the claims from the 2009 MACH-NC study; specifically, they found a 5-year survival difference of 8% with CRT from propensity score matching for older adults with HNSCC. While not all cohorts in their study experienced a longer median overall survival, they found that patients aged greater than 70 years with a low Charlson–Deyo comorbidity score and T1–2/N2–3 or T3–4/N0–3 disease had a significantly longer median overall survival with CRT compared to RT alone. The authors speculated that the MACH-NC study did not find a longer median overall survival with CRT compared to RT alone since only 4% of their population were in the over-70 age category, which limited the statistical power.¹²¹ These results were supported by another review of patients from the NCDB, which found increased systemic chemotherapy use in elderly patients from 2004 to 2012 and noted that it was significantly associated with improved overall survival in a multivariate model.¹²² Furthering this controversy, there is no consensus regarding the optimal systemic treatment regimen for older adults with HNSCC. Cisplatin is the standard cytotoxic agent that has been used for decades to treat a wide spectrum of malignancies, including HNSCC, and has been shown to be effective for older adults if they are able to tolerate it.^{123–125} The regimen of cisplatin and 5-fluorouracil has been widely used as therapy in older adults with HNSCC; however, owing to the toxicity of cisplatin and the advent of more targeted biologics, such as the epidermal growth factor receptor (EGFR) inhibitor cetuximab, there is ongoing debate on the optimal systemic therapy in this patient population.

Even though the immune system wanes with increasing age, immunotherapy appears to be efficacious in the older adult population; however, it is worth noting that the elderly population has been excluded from many immunotherapy trials.^{126–131} Currently, there are conflicting data in the literature regarding immunotherapy toxicity in the elderly population – some studies report similar rates of toxicities between older and younger patients and others report higher rates of toxicity in the older adult cohort.^{132,133} A trial published in 2021, assessing single-modality immunotherapy and immunotherapy combination therapy in the HNSCC population (average age of 60 years), demonstrated immunotherapy to be well tolerated, with approximately 15% of patients experiencing serious treatment-related adverse events.¹³⁴ To date, no specific study has been conducted assessing immunotherapy toxicity rates specifically in the elderly HNSCC population.

Both RT and chemotherapy, notably cisplatin, can cause permanent sensorineural hearing loss (SNHL), principally by causing degeneration of outer hair cells in the organ of Corti.^{135–137} This has major implications for older adults, who are more likely to have presbycusis at baseline, and can negatively affect quality of life. RT-induced ototoxicity is directly proportional to the radiation dose (typically >45 cGy) and type of radiation, while cisplatin-induced ototoxicity is related to both dose and schedule.^{138–140} It is worth noting that the ototoxic radiation dose in patients undergoing concomitant chemotherapy with cisplatin is lowered.¹⁴¹ There is a validated predictive nomogram for assessing who is at highest risk for developing HNSCC treatment-related SNHL, with high sensitivity and specificity, 80% and 75%, respectively,^{142,143} and at-risk patients should be counseled accordingly.

Conclusion

How to best treat HNSCC in the older adult population varies depending on several factors, including subsite, comorbidities, performance status, frailty, and social support. There is no established standard of care specifically for older adults with HNSCC. [Figure 1](#) demonstrates a proposed work flow for the therapeutic considerations for elderly patients with HNSCC. To determine the best treatment approach for older adult patients with HNSCC, it is strongly recommended to administer a geriatric assessment (paying special attention to medical comorbidities, socioeconomic status, psychosocial status, and polypharmacy) in combination with a predictive treatment nomogram to help predict treatment toxicity. Geriatric assessments and the involvement of a geriatrician in multidisciplinary care will afford the patient more accurate information and enable them to make the most informed decision regarding their treatment plan. Treatment modalities for HNSCC may involve monotherapy or multimodal therapy, and include surgery, RT, chemotherapy, and, in some instances, immunotherapy. Surgical considerations for older adults center around anesthetic risk. Elderly patients tend to tolerate major HNSCC reconstructive surgery generally well; however, they may have longer hospital stays compared to younger patients. RT and chemotherapy are often used in combination and can lead to treatment-related toxicity. Hypofractionated trials and de-escalation therapy, especially for HPV-positive OPSCC, are currently being investigated to minimize treatment-related toxicity and increase quality of life while maximizing

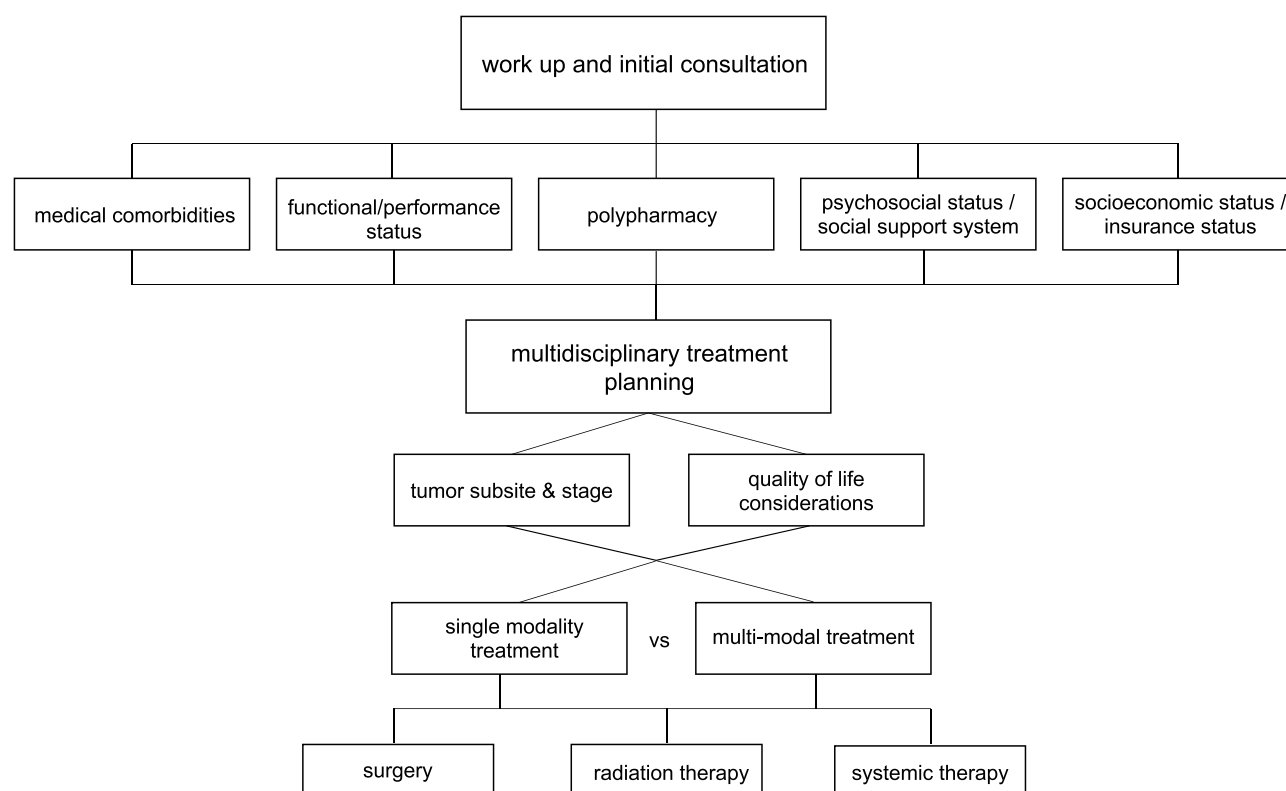


Figure 1 Proposed work flow for therapeutic considerations for elderly patients with HNSCC.

treatment efficacy. As new studies are being developed, the elderly HNSCC population is the ideal group to benefit from these initiatives.

It is essential to optimize treatment for the elderly population, which is particularly vulnerable to treatment-related toxicity. This review should serve to guide clinical decision making for elderly patients with HNSCC. In addition, this review emphasizes that clinical considerations and treatment decisions for older adults with HNSCC should be approached holistically and go beyond chronological age alone.

Abbreviations

HNSCC, head and neck squamous cell carcinoma, RT, radiation therapy, CRT, chemoradiotherapy, CGA, comprehensive geriatric assessment, G8, geriatric 8, SIOG, society of geriatric oncology, CRASH, chemotherapy risk assessment scale for high age patients, GCE, generalized competing event, MARCH, meta-analysis of radiotherapy in HNSCC, CCI, Charleston comorbidity index, KFI, Kaplan Feinstein comorbidity index, ACE-27, adult comorbidity evaluation-27, AGS, American geriatrics society, TORS, transoral robotic surgery, TLM, transoral laser microsurgery, ECOG performance status, Eastern Cooperative Oncology Group performance status, CD, Charlson-deyo index, 5FU, 5-fluorouracil, SNHL, sensorineural hearing loss, OCSS, oral cavity squamous cell carcinoma.

Acknowledgments

The authors would like to express deep gratitude to Lynda Rath for her enthusiastic assistance in clinical research and data management related to older adults at our institution. Daniel R Dickstein and Ann E Powers are co-first authors for this study.

Disclosure

The authors report no conflicts of interest in this work.

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