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Geriatric Oncology

Treatment of Older Patients With Head and Neck Cancer: A Review

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Learning Objectives

Compare survival and toxicity outcomes of older patients with head and neck cancer with those of their younger cohorts.

Describe the role played by comorbidity, quality of life, and supportive care in the treatment decision and treatment process of older patients with head and neck cancer.

Abstract

The incidence of head and neck cancer (HNC) in the elderly is increasing. The treatment of HNC often includes multimodality therapy that can be quite morbid. Older patients (herein, defined as ≥65 years) with HNC often have significant comorbidity and impaired functional status that may hinder their ability to receive and tolerate combined modality therapy. They have often been excluded from clinical trials that have defined standards of care. Therefore, tailoring cancer therapy for older patients with HNC can be quite challenging. In this paper, we performed a comprehensive literature review to better understand and discuss issues related to therapeutic recommendations that are particular to patients 65 years and older. Evidence suggests that older patients have similar survival outcomes compared with their younger peers; however, they may experience worse toxicity, especially with treatment intensification. Similarly, older patients may require more supportive care throughout the treatment process. Future studies incorporating geriatric tools for predictive and interventional purposes will potentially allow for improved patient selection and tolerance to intensive treatment. ***The Oncologist*** 2013;18:568–578

Implications for Practice: Tailoring therapy for older patients with head and neck cancer (HNC) is challenging. This review article provides physicians with evidence on how older patients may differ from their younger peers. In addition, we offer clinical recommendations to guide oncologists on treatment recommendations and management of older HNC patients.

Introduction

Head and neck cancers (HNC) occur within the paranasal sinuses, nasal cavity, oral cavity, pharynx, and larynx. In 2012, there were an estimated 52,610 new cases of HNC and 11,500 related deaths in the U.S. [1]. Despite the increasing trend of cancer related to human papillomavirus, which primarily affects younger patients [2, 3], HNC remains primarily a cancer of an older population. According to the Surveillance, Epidemiology, and End Results database, approximately 47% of all patients diagnosed with HNC in the U.S. between 1973 and 2008 were ≥65 [4]. In addition, the incidence of newly diagnosed HNC cases among the elderly is expected to increase by more than 60% by the year 2030 [5].

Treatment paradigms for older patients with HNC are not well defined. The majority of patients with HNC will present with advanced (stage III and IV) disease requiring multimodality therapy [6]. Combined surgery, radiation, and chemotherapy cause significant acute toxicity and long-term morbidity, thus reducing compliance to therapy, quality of life, and life expectancy. These morbidities can be profound in older patients, secondary to comorbid medical conditions and impaired functional status. Hence, older patients are often considered poor candidates for multimodality treatment and are subsequently less likely to receive standard of care therapy compared with younger patients [7, 8]. This bias against optimal treatment may jeopardize their chance of cure. In addition, older patients are often ineligible for the large prospective randomized trials on which treatment paradigms are based (Table 1) [9–27]. For example, in a recent meta-analysis of 93 clinical trials, only 692 of 17,346 patients (4%) were >70 years of age [28]. Thus, the outcomes of these trials may not be applicable to older patients. Despite recommendations not to include age limits in large prospective trials, many ongoing trials continue to have upper age limits in their inclusion criteria. For these reasons, many are concerned that older patients with HNC have a smaller therapeutic benefit with treatment intensification compared with their younger peers (Fig. 1) [29].

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Table 1. Median age in important multimodality randomized trials on head and neck cancer

Trial	Randomization	Results	No. of patients	Median age, yrs (range)
Larynx preservation studies				
Department of Veterans Affairs (VA) Larynx [11]	Definitive sequential chemotherapy + radiation vs. surgery + postoperative radiation	OS: no difference; larynx preserved in 64%	322	62 (24–79)
Radiation Therapy Oncology Group (RTOG) 91-11 [12]	Sequential chemotherapy + radiation vs. concurrent chemoradiation vs. radiation alone	Larynx preservation; LC: better with concurrent chemoradiotherapy	547	59 (26–79)
European Organization for Research and Treatment of Cancer (EORTC) 24954 [13]	Sequential chemotherapy + radiation vs. alternating chemotherapy and radiation	No differences	450	55 (35–76)
Definitive chemoradiation with standard fractionation studies				
Groupe Oncologie Radiotherapie Tete Et Cou. (GORTEC) [14]	Radiotherapy with concurrent chemotherapy (carboplatin + 5-FU) vs. radiotherapy alone	OS, DFS, and LC were all improved with chemotherapy	226	55 (32–74)[a]
Intergroup trial [15]	Radiation alone vs. radiation with bolus cisplatin vs. split course RT with bolus cisplatin and infusional 5-FU	Did not meet accrual; OS was improved with RT and bolus cisplatin	295	57 (25–80)[a]
RTOG 97-03 [16]	RT with daily cisplatin and 5-FU vs. RT with daily hydroxyurea with 5-FU vs. RT with weekly cisplatin and paclitaxel	Phase II: All three regimens feasible	241	56 (21–83)
Hellenic Cooperative Oncology Group (COG) [17]	RT alone vs. RT with cisplatin vs. RT with carboplatin	OS improved with concurrent chemotherapy; cisplatin with best median OS and TTP	128	57 (31–78)
United Kingdom Head and Neck Trialsts Group 1 (UKHAN1) Trial (nonsurgery arms) [18]	RT alone vs. RT with concurrent chemotherapy (VBMF or M alone) vs. RT with adjuvant chemo vs. RT with concurrent and adjuvant chemotherapy	Improvement in EFS with RT + concurrent chemotherapy	713	60 (17–84)
Bonner trial [19]	RT + concurrent cetuximab vs. RT alone	LC and OS improved with cetuximab	424	57 (34–83)
Definitive chemoradiation with hyperfractionation studies				
Brizel trial [20]	Hyperfractionated RT alone vs. hyperfractionated RT + cisplatin and 5-FU	Improvement in LC with chemotherapy and trend in OS, RFS	122	59[a]
Jeremic trial [21]	Hyperfractionated RT alone vs. Hyperfractionated RT + daily cisplatin	OS, LRPFS, and DMFS improvement with concurrent chemotherapy	130	61 (39–70)
German trial [22]	Hyperfractionated RT alone vs. hyperfractionated RT + carboplatin and 5-FU	1-yr survival with local control benefit for concurrent chemotherapy	263	57 (28–73)
Swiss trial [23]	Hyperfractionated RT alone vs. hyperfractionated RT + cisplatin	LC and DFS improved with cisplatin; no difference in OS or time to failure	224	~55 (33–74)
GORTEC 99-02 [24]	Standard fractionated RT + concurrent carboplatin and 5-FU vs. accelerated hyperfractionated RT + concurrent carboplatin and 5-FU vs. very accelerated hyperfractionated RT alone	Most favorable outcomes in conventional chemoradiotherapy arm	840	56.5 (34–75)[a]
Postoperative chemoradiation studies				
RTOG 9501 [25]	RT alone vs. RT with concurrent cisplatin	LC and DFS benefit with chemotherapy	459	~56 (24–80)[b]
EORTC 22931 [26]	RT alone vs. RT with concurrent cisplatin	LC, PFS, and OS improved with chemotherapy	167	54
French trial [27]	RT alone vs. RT with concurrent carboplatin	No difference	144	55.5[a]
UKHAN1 trial (surgery arms) [18]	RT alone vs. RT with concurrent VBMF	No difference	253	~58 (32–81)

[a]Mean age.
[b]Total of 25 patients who were >70 years old (5%).
Abbreviations: DMFS, distant metastases-free survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FU, fluorouracil; LC, local control; LRPFS, local recurrence progression-free survival; M, Methotrexate; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; RT, radiation therapy; TTP, time to progression; VBMF, vincristine, bleomycine, methotrexate, and fluorouracil.

The purpose of this paper is to review the published literature to attempt to answer the following questions with regard to HNC, with an objective to better equip oncologists to manage older patients with HNC:

1. Do older patients have worse survival rates?
2. Do older patients experience worse toxicities?
3. Should comorbidity influence treatment recommendations?
4. Do older patients have worse quality of life after treatment?
5. Do older patients require more supportive care during treatment?

Methods

For each subsection of this review, we performed a PubMed search using the terms "head and neck cancer,"

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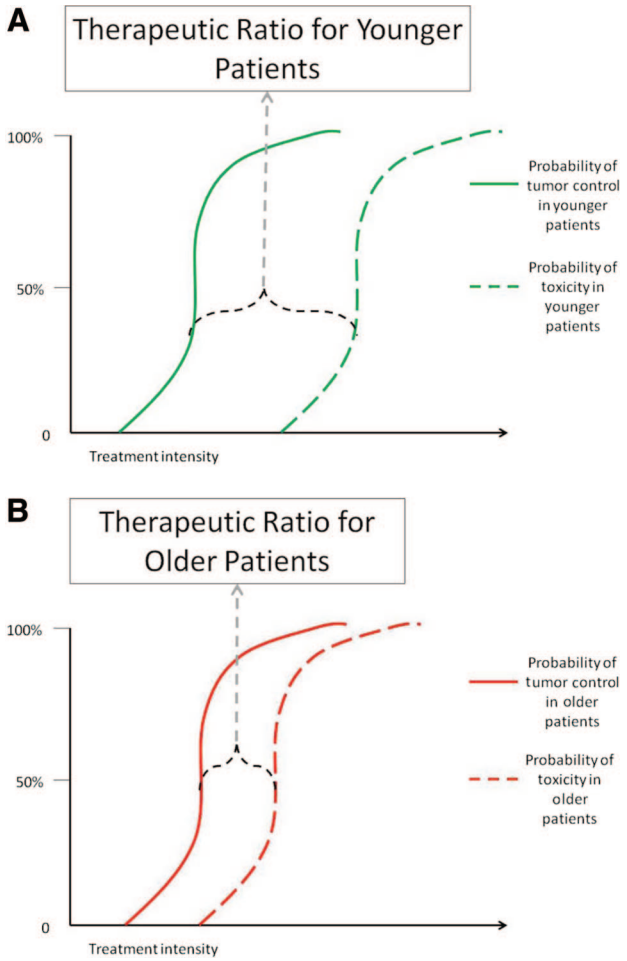

Figure 1. Theoretical therapeutic ratio for head and neck cancer treatment. **(A):** Younger patients. **(B):** Older patients.

"older" or "elderly," and the topic of each subsection. Relevant prospective and retrospective studies published from 1980 to 2012 were included. Studies published in languages other than English or not involving human subjects were not reviewed. There was no definitive age cutoff used for defining older patients.

Results

Survival Rates

In the majority of studies comparing treatment modalities between older and younger cohorts with HNC, older patients did not appear to have worse survival than their younger peers. The data are summarized in Table 2 by modality and are discussed below.

Surgery

Limited data suggest that selected older patients have survival outcomes similar to younger patients when treated primarily with surgery. In particular, a number of retrospective studies have matched older patients to a younger cohort and have shown no difference in survival outcome [30–32]. Kowalski et al. matched 115 patients who were ≥70 years of age by tumor type and stage to 115 patients <70 years of age and found no difference in 5-year survival rate [30]. In addition, multiple nonmatched retrospective studies have shown similar results [33, 34].

Radiation

Multiple retrospective single-institution studies all indicate that the oncologic outcomes among older patients receiving radiotherapy alone are similar to their younger cohorts [35–41]. However, only three studies directly compared outcomes among different age groups [35, 40, 42]. The first, a secondary analysis of four prospective European Organization for Research and Treatment of Cancer HNC trials, found no difference in overall survival among four different age groups, including patients >75 years [35]. The second study performed a comparison of 39 patients ≥70 years receiving accelerated concomitant boost radiation with 80 patients <70 years receiving the same radiation regimen [40]. There was no observed difference in 3-year overall survival or local control between the two groups. The third study showed that age, as a continuous variable, had a statistically significant detriment to cause specific survival; however, the effect was modest (relative risk: 1.03) [42].

Chemoradiation

Evidence suggests that older patients may not have a survival benefit from the addition of chemotherapy to radiation. In a meta-analysis of 93 clinical trials, Pignon et al. demonstrated that although there appeared to be an overall survival benefit of 4.5% at 5 years with the addition of chemotherapy, this benefit was not evident among older patients [28]. Specifically, patients age 71 and older had no statistical benefit in 5-year survival rates with the addition of chemotherapy. The authors suggest that this may be due to the increased rate of noncancer deaths among this cohort of older patients, but it may also be due to the small number of evaluable patients [28].

We identified three prospective studies that treated older patients with chemoradiotherapy to identify the tolerability of different chemoradiation regimens [43–45]. Although these studies showed relatively good short-term survival results, they did not study their regimens in younger cohorts and thus do not answer our question. Two retrospective studies directly compared older cohorts with their younger peers and suggested no difference in overall survival (OS), disease-specific survival, or recurrence-free survival among patients ≥70 years [46, 47]. However, an additional retrospective study suggests a statistically significant decrease in OS among patients ≥65 years [48]. It is important to note that it is difficult to compare outcomes among different studies because many of these studies used different chemotherapy regimens even within the same study. For example, Merlano et al. had a higher percentage of the older patients receiving cetuximab and radiation with a higher percentage of younger patients receiving platinum-based chemoradiation [48]. Therefore, although the existing data supports that older patients have oncologic outcomes to chemoradiation similar to younger patients, the quality of the data limits the confidence of this assertion.

Conclusion

Surgery, radiation, and chemoradiation appear to be equally efficacious in older and younger patients. Treatment recommendations should not be influenced by a perception that one modality may not be efficacious in older patients.

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Table 2. Outcomes and toxicity in elderly specific studies for head and neck cancer

Study	Type of study	No. of patients	Survival outcomes	Toxicity outcomes	Comments	Difference between young and old patients
Surgical studies						
Kowalski et al. [30]	Retrospective single institution	115 pts age ≥70 yr; 115 pts age <70 yr (matched)	5-yr survival: 43% for pts ≥70 yr, 55.6% for pts <70 yr; $p = .1$	No difference in local/systemic complications or postoperative deaths	Majority of deaths in both cohorts were not related to cancer	Survival: no; toxicity: no
Clayman et al. [31]	Retrospective single institution	43 pts age ≥80 yr; 79 pts age ≤65 yr (matched)	Median survival: 34.3 mo for pts ≥80 yr, 42.7 mo for pts ≤65 yr; $p = .001$	No differences in postoperative complications between two groups	Although median survival was different among groups, when patients ≥80 yr were compared with expected survival, there was no difference	Survival: yes; toxicity: no
McGuirt et al. [32]	Retrospective single institution	217 pts age ≥65 yr, split into four age groups (65–71 yr, 72–72 yr, 75–80 yr, ≥81 yr)	5-yr survival rates: 65–71 yr: 53.4%, 72–74 yr: 58.9%, 75–80 yr: 55.1%, ≥81 yr: 46.3%; not significant	Major complications: 65–71 yr: 10%, 72–74 yr: 9%, 75–80 yr: 14%, ≥81 yr: 19%	No significant difference in survival or complications in oldest patients (≥ 81 yr) compared with youngest old patients (65–71 yr)	Survival: no; toxicity: No
Laccourreye et al. [33]	Retrospective single institution	69 pts age >65 yr	5-yr actuarial survival: 68%; 5-yr local control: 93.9%	Early surgical: 13.1%; early medical: 10.1%; late surgical: 4.3%	Univariate analysis; age was not correlated with mortality or morbidity	NA
Morgan et al. [49]	Retrospective single institution	810 pts age ≥65 yr; 963 pts age <65 yr	NA	30-day mortality: 3.5% for pts ≥65 yr, 0.8% for pts <65 yr; nonlethal complications: 32% for pts ≥65 yr; 21% for pts <65 yr	Although there was a statistical difference in mortality, this was a nonmatched cohort that did not account for stage, type of cancer, baseline health, or type of surgical procedure	Survival: NA; toxicity: yes
Bridger et al. [51]	Retrospective single institution (free flap reconstruction)	26 pts age ≥70 yr; 91 pts age <70 yr (matched)	NA	Surgical complications: 42% for pts ≥70 yr, 37% for pts <70 yr; postoperative medical complications: 54% for pts ≥70 yr, 29% for pts <70 yr	No statistical difference between two groups	Survival: NA; toxicity: no
Shaari et al. [52]	Retrospective single institution (microvascular free tissue transfers)	52 pts age >70 yr; 35 pts age <70 yr (matched)	NA	Major surgical complications: 13% for pts ≥70 yr, 23% for pts <70 yr; minor surgical complications: 24% for pts ≥70 yr, 34% for pts <70 yr; major medical complications: 4% for pts ≥70 yr, 0% for pts <70 yr; minor medical complications: 7% for pts ≥70 yr, 6% for pts <70 yr	No statistical significance was shown between the groups, even after controlling for site, ASA classification, and method of reconstruction; >50% of pts in each group underwent preoperative radiation therapy	Survival: NA; toxicity: no
Milet et al. [50]	Retrospective review of prospectively accrued patients at single institution	29 pts age ≥70 yr; 232 pts age <70 yr	NA	Length of stay (median): 29 days for pts ≥70 yr, 21 days for pts <70 yr; all postoperative complications: 51% for pts ≥70 yr, 59% for pts <70 yr	No statistical differences; age was predictive on univariate analysis of postoperative death, but not on multivariate analysis controlling for gender, alcohol, cancer type, and comorbidities	Survival: NA; toxicity: no
Zabrodsky et al. [54]	Retrospective single institution	24 pts age ≥70 yr	NA	Overall complication rate: 63%; clinically important complication rate: 54%	Advanced comorbidity, longer operative times, and advanced-stage disease influenced complications	NA
Sanabria et al. [55]	Retrospective single institution	242 pts age >70 yr	NA	Local complications: 45%; systemic complications: 29%	Age was not correlated with complications on univariate analysis and was not incorporated into predictive model	NA
Radiation-alone studies						
Pignon et al. [35]	Secondary analysis of patients with head and neck cancer	1,589 pts total; 408 pts (25%) age >65 yr	No difference in overall survival between age groups	No difference in objective mucosal reaction, weight loss, or long-term toxicity, but there was a difference in functional mucosal reaction, with an increase in grade 3–4 toxicity among the older groups	The only difference found was for functional mucosal toxicity; however, when performance status was controlled for, this became no longer significant	Survival: no; toxicity: yes
Lusinchi et al. [36]	Retrospective single institution	331 pts age >70 yr; 249 pts had RT alone with curative intent (30% had contraindication to surgery)	Pts treated with curative intent had 71% local control; 5-yr survival rate for all patients: 33%	Severe mucositis in 17% of cases; no correlation with age or KPS; 9% unable to complete prescribed curative dose	No statistical correlation between cancer outcome and age was observed	Survival: no; toxicity: no
Schofield et al. [37]	Retrospective single institution	98 pts age 80–92 yr; curative intent radiotherapy (high dose per fraction)	5-yr OS: 28%; 5-yr CSS: 59%; 5-yr LC: 70%; 5-yr nodal control: 87%	98% completed RT; severe late toxicity occurred in 3.1%	Age did not affect cancer or toxicity outcomes	NA
Zachariah et al. [38]	Retrospective single institution	50 pts with HNC age 80–94 yr (35 curative intent)	Complete response: 66%; complete or partial response: 83%	97% completion rate; 66% grade 2–4 mucositis among curative intent pts	Radiation is a safe treatment for oldest old patients	NA
Mitsuhashi et al. [39]	Retrospective single institution	14 pts with HNC age 90–98 yr; 11 of 14 treated with curative intent	90% response rate; 60% complete response rate	90% completion rate among those treated with curative intent; 4 of 11 pts required 2- to 3-week break	Age >90 yr not a contraindication to radiation treatment	NA
Allal et al. [40]	Retrospective single institution; accelerated concomitant boost RT	39 pts age ≥70 yr; 80 pts age <70 yr	3-yr OS: 68% for pts ≥70 yr; 62% for pts <70 yr; LC: 73% for pts ≥70 yr, 68% for pts <70 yr	100% completion rate in both groups; unplanned breaks: 8% in older group, 0% in younger group; $p = .03$; no difference in other acute toxicities	No difference in cancer outcomes or acute toxicity, although more patients in the ≥70-yr group required unplanned treatment breaks	Survival: no; toxicity: yes

(continued)

Table 2. (continued)

Study	Type of study	No. of patients	Survival outcomes	Toxicity outcomes	Comments	Difference between young and old patients
Huguenin et al. [41]	Retrospective single institution	75 pts age ≥75 yr; 17 pts postoperative, 58 pts with RT alone	5-yr OS: 30% (with curve following age-matched normal population after rapid dropoff)	30% of the patients required treatment interruption (unknown reasons), 1 case of late bone necrosis	No comparison to younger group and no acute toxicity mentioned	NA
Huang et al. [42]	Retrospective single institution	238 pts age ≥75 yr; 1,249 pts age <75 yr; 16% of pts age ≥75 yr and 58% of pts <75 yr received intensified RT (hyperfractionated or chemoradiation)	2-yr CSS: 72% for pts ≥75 yr; 86% for pts <75 yr; $p < .01$; RR: 1.03 (per year)	No difference in treatment interruptions, RT completion, treatment-related deaths, or late toxicities	Modest effect of age at diagnosis on CSS	Survival: yes; toxicity: no
Chemoradiation studies						
Tsukuda et al. [43]	Prospective feasibility study	50 cases: 13 pts age >75 yr; 37 cases with comorbidity treated with concurrent S-1 (Tegafur)	Complete response rate: 93% for stage III and 54% for stage IV	36% required nutritional support and GI tube; 20% had grade 3 mucositis, 12% had neutropenia, and 6% had leukocytopenia	Well-tolerated regimen; no attempt was made to compare patients with older age to those with younger age and severe comorbidity	NA
Koussis et al. [44]	Prospective phase II study	35 pts total; 16 pts age ≥70 yr, 19 pts with KPS 70–80; treated with 3 cycles of induction chemotherapy followed by CRT (weekly carboplatin)	77% had some response to neoadjuvant chemotherapy; 2-yr OS: 31.5 mo	During neoadjuvant chemotherapy, 37% had grade 3–4 hematologic toxicity and 57% had grade 3–4 GI toxicity; 8.5% had both grade 4 mucositis and febrile neutropenia	No difference in hematologic toxicity between older patients and those with poor KPS; concluded that this regimen is feasible in older populations	NA
Airoldi et al. [45]	Prospective study	40 pts age ≥70 yr, with at least one pathological risk factor for postoperative chemoradiation (carboplatin)	3-yr OS: 64%; 3-yr DFS: 58%; LC: 79%	25% had grade 3 mucositis; 15% had grade 3 neutropenia; no grade 4 toxicities; no patient required hospitalization; 80% of patients received all 3 courses of chemotherapy	In comparison to similar prospective study in younger cohort, they found similar oncologic outcome results; in comparison with older cohort receiving radiotherapy alone, chemoradiation cohort had better results	NA
Machtay et al. [56]	Retrospective analysis of 3 prospective studies (RTOG 91-11, RTOG 97-03, RTOG 99-14)	230 evaluable pts; 27 pts age >70 yr; 203 pts age ≤70 yr	NA	Age as a continuous variable was significantly associated with late toxicities (OR: 1.05)	Age was a strong independent risk factor for developing severe late toxicities	Survival: NA; toxicity (late): yes
Boscolo-Rizzo et al. [57]	Retrospective single institution	44 pts age >65 yr; treated with induction chemotherapy followed by CRT (cisplatin and 5-FU)	3-yr OS: 71%; 3-yr PFS: 67%; 3-yr functional PFS: 57%	84% completed induction, RT, and at least 80% of concurrent chemotherapy; 66% developed severe toxicities; 11% required permanent feeding tubes	Good oncologic outcomes but moderate to severe toxicity; no comparison to younger cohort, although increasing age was not correlated with death	NA
Michal et al. [46]	Retrospective single institution	44 pts age ≥70 yr; 137 pts age <70 yr; RT with 2 cycles of Cisplatin and continuous 5-FU; 72% of younger cohort treated with b.i.d. RT; only 30% of older patients treated with b.i.d. RT	5-yr DSS: 71% for pts ≥70 yr; 74% for pts <70 yr; recurrence-free survival: 69% for pts ≥70 yr; 71% for pts <70 yr	Older patients less likely to receive full-dose chemotherapy, increased myelosuppression, more unplanned hospitalizations, and longer period of feeding tube dependence	Oncologic outcomes were the same, but more supportive care required among older patients	Survival: no; toxicity: yes
Nguyen et al. [47]	Retrospective single institution	112 total pts; 27 pts age ≥70 yr; 85 pts age <70 yr; all treated with chemoradiation (different types)	2-yr OS: 68% for pts ≥70 yr; 74% for pts <70 yr	No difference in grade 3–4 toxicity; no difference in treatment breaks or early cessation of treatment	No differences found in oncological or toxicity outcomes between two groups	Survival: no; toxicity: no
Merlano et al. [48]	Retrospective single institution	317 total patients; 93 pts age ≥65 yr; 224 pts age <65 yr (higher rate of older pts treated with cetuximab)	OS was worse in elderly (28 mo vs. 46 mo; HR: 1.51 on multivariate analysis; no difference in response rates	Higher rate of infections (28% vs. 16%) and pneumonia (11% vs. 2%) in elderly; otherwise no toxicity difference	Worse overall survival but this was felt not to necessarily reflect lower effectiveness of treatment in that group (relative survival not used)	Survival: yes; toxicity: yes

Abbreviations: ASA, American Society of Anesthesiologists; CRT, chemoradiotherapy; CSS, cancer-specific survival; DSS, disease-specific survival; FU, fluorouracil; GI, gastrointestinal; HNC, head and neck cancer; HR, hazard ratio; KPS, Karnofsky Performance Status; LC, local control; NA, not available; OR, odds ratio; OS, overall survival; PFS, progression-free survival; pts, patients; RR, relative risk; RT, radiotherapy.

Toxicity

It stands to reason that patients with medical comorbidities and poorer functional reserve (common issues in older patients with HNC) would experience more and/or worse treatment-related toxicity. Treatment modality-specific toxicity is reviewed and summarized in Table 2. The results of these studies appear to be mixed in their conclusions.

Surgery

Two surgical retrospective series suggested an increased risk of postoperative mortality in older patients [49, 50]. Morgan et al. [49] observed an increase in 30-day mortality in older patients (3.5% mortality) as compared with that in a younger cohort (0.8%). This study did not match the cohorts by tumor, stage, comorbidity, or any other risk factors. The authors concluded that, given the relatively low rate of perioperative mortality, age alone should not be a contraindication to aggressive surgery. Milet et al. observed age to be associated with postoperative mortality on univariate but not multivariate analysis [50]. However, an additional six retrospective matched cohort reviews [30–32, 51–53] and three unmatched retrospective reviews [33, 54, 55] show no correlation between age alone and postoperative complications (Table 2).

Radiation

Two retrospective studies that compare older patients with younger patients suggest an increase in mucositis [35] and/or unplanned treatment breaks [40] among the older cohorts. However, other comparative studies appear to show no difference in acute toxicities or treatment interruptions [36, 42].

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In their retrospective study comparing 238 patients ≥75 years to 1,249 patients <75 years, Huang et al. demonstrated no difference in treatment interruptions, radiotherapy completion, treatment-related deaths, or late toxicities [42]. In addition, three additional studies retrospectively analyzed their outcomes in their oldest patients (≥80 years) and demonstrated acceptable rates of toxicities [37–39].

Chemoradiation

As treatment intensity increases, the potential for greater toxicity also increases. In a retrospective analysis of three prospective Radiation Therapy Oncology Group (RTOG) studies, Machtay et al. demonstrated that age as a continuous variable was significantly associated with developing severe late toxicities (odds ratio: 1.05, $p = .001$) [56]. Two retrospective studies that directly compared toxicity outcomes among older cohorts with those of younger cohorts demonstrated worse tolerability and toxicity to treatment. Specifically, they identified worse compliance with chemotherapy, more unplanned hospitalizations, increased myelosuppresion, increased infections/pneumonia rates, and longer periods of feeding tube dependence among the older cohorts [46, 48]. Additional noncomparative retrospective studies demonstrated high rates of severe toxicities among older cohorts [57].

Unfortunately, the three prospective trials that analyzed feasibility of multimodality treatment regimens in older patient populations do not directly answer our question of whether older patients experience worse toxicity. Although they all report relatively similar toxicity profiles to the larger randomized trials, including younger cohorts [43–45], they include highly selected patient populations and do not report all relevant toxicities. In particular, one study only reported toxicities during the induction portion of the treatment regimen [44].

Cisplatin is the standard chemotherapy to give concurrently with radiation. It is common practice to substitute cetuximab with cisplatin in older patients because of perceived lower toxicity profile as observed in the Bonner trial [19]. However, there are now multiple published retrospective studies that demonstrate either similar or increased rates of mucositis in patients who receive cetuximab compared with those who receive cisplatin concurrent with radiation [58, 59]. Additionally, a randomized trial undertaken by the Gruppo di Studio sui Tumori della Testa (GSTTC) Italian Study Group compared concurrent cetuximab radiation with concurrent cisplatin radiation with or without induction in a 2×2 design [60]. Preliminary toxicity results demonstrated similar rates of mucositis (76% with cetuximab vs. 78% with cisplatin; $p = .63$). More patients were able to complete concurrent cisplatin compared with cetuximab (93% vs. 81%; $p < .01$) without dose modifications (75% vs. 50%; $p < .01$). Furthermore, median duration of concurrent radiation was 1 week longer in the cetuximab arm (7 weeks cisplatin versus 8 weeks cetuximab; $p < .01$). Thus, concurrent cetuximab may not result in less acute toxicity [60].

Locally recurrent disease in the setting of previous radiation is a challenge in the older patient with HNC. Currently, adjuvant chemotherapy alone is considered standard of care [61]. Older patients in this setting have worse toxicity from platinum-based chemotherapy compared with their younger peers [62]. Prospective clinical trials have shown that reirradiation with chemotherapy in carefully selected patients results in poor survival rates and high rates of major toxicities. The RTOG has conducted two phase II trials evaluating the efficacy of reirradiation and chemotherapy: RTOG 9610 [63] and 9911 [64]. The median age of patients in these trials were 62 and 60 years. In RTOG 9610, the incidence of severe acute toxicity was 17.7% (grade 4) and 7.6% (grade 5) [63]. The 2-year overall survival estimate was 15.2% and the cumulative incidence of grade 3–4 late toxicity was 9.4% [63]. The follow-up phase II study RTOG 9911 (60 Gy with concurrent cisplatin and paclitaxel) had higher 2-year overall survival rate (25.9%) but comparable acute grade 4 or worse (28%) and grade 5 (8%) toxicities [64]. Late toxicities were also significant (34% grade 3–4, 4% grade 5) [64]. Local regional recurrences after radiotherapy can sometimes be salvaged with surgery. The efficacy of reirradiation with chemotherapy after salvage surgery has been evaluated in a randomized trial from France [65]. The median age of patients in this study was not reported. Patients were randomized to either salvage surgery alone versus salvage surgery and postoperative chemoradiotherapy. The addition of reirradiation with chemotherapy after salvage surgery improved disease-free survival but not overall survival rates. Furthermore, 39% of patients in the chemoradiation arm experienced grade 3–4 late toxicity (compared with 10% in the surgery-alone arm) [65]. In the above trials, highly selected patients (i.e., excellent performance status, minimal comorbidities) were enrolled; despite careful selection, outcomes were poor and severe toxicities were excessive. In older patients with HNC, it is likely that toxicities will be worse. Our practice is to avoid reirradiation whenever possible and advocate salvage surgery alone. Reirradiation is only attempted in the most carefully selected patients.

Conclusion

Older patients experience greater acute and late toxicity as the intensity of treatment increases. Specifically, the addition of chemotherapy to radiation increases toxicity and reduces tolerance to therapy. The belief that cetuximab (when given concurrently with radiation) is less toxic than cisplatin may not be true. Re-irradiation with/without concurrent chemotherapy in the recurrent/previously irradiated setting should be avoided.

Comorbidities and Treatment Recommendations

Patients with HNC often have a history of tobacco and alcohol use and multiple other chronic illnesses related to these habits. In a study of patients with laryngeal cancer, 65% of patients had some form of comorbid illness and 25% had multiple comorbidities [66]. In patients >70 years old, the incidence of comorbidities was as high as 75% [67]. There are multiple indices that measure comorbidity and attempt to grade the burden of particular comorbidities. Two of the most well-known indices are the Adult Comorbidity Evaluation 27 [68] and the Charlson Comorbidity Index [69].

There are multiple articles establishing the relationship between comorbidity and prognosis for older patients with HNC (Table 3) [70–78]. The association between comorbidity and overall survival found in all of these articles is understandable. The greater the severity of the comorbidity, the more likely a patient is to die of disease unrelated to cancer. However, multiple studies have also demonstrated worse disease-specific survival rates or higher odds of disease re-

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Table 3. Impact of comorbidity on prognosis for head and neck cancer

Study	No. of patients	Comorbidity index	Median age (yrs)	Hazard ratio (95% CI) for survival[a]
Reid et al. [70]	9,386	CCI	Not stated (62% age 66–74 yr)	1.83 (1.64–2.05)
Datema et al. [71]	1,371	ACE-27	Not stated (49% age ≥60 yr)	2.23 (1.73–2.87)
Piccirillo et al. [72]	1,086	ACE-27	Not stated (43% age ≥65 yr)	2.48 (1.77–3.47)
Alho et al. [73]	221	CCI	63	2.1 (1.2–3.7)
Liu et al. [74]	214	CCI	51	2.7 (1.7–4.2)
Chen et al. [75]	182	ACE-27	59.5	2.3 (1.4–3.6)
Paleri et al. [76]	180	ACE-27	65.5	13.55 (4.81–38.15)
Sabin et al. [77]	152	Age-adjusted CCI	Not stated	1.57 (1.18–2.08)
Montero et al. [78]	99	WUHNCI	Not stated	1.55 (1.09–2.21)

[a]Comparing highest score to lowest.
Abbreviations: ACE-27, Adult Comorbidity Evaluation 27; CCI, Charlson Comorbidity Index; CI, confidence interval; WUHNCI, Washington University Head and Neck Comorbidity Index.

currence among patients with worse comorbidity [72, 76, 79]. It is possible that deaths unrelated to cancer are being misattributed to cancer. Alternatively, patients with more comorbidities may receive less intensive treatment (i.e., physician recommendation or patient preference), leading to worse disease-related outcomes, or they may receive more intensive therapy then they can tolerate, leading to treatment alterations that result in less effective treatment. This may explain the results of the Pignon et al. [28] meta-analysis, which observed less benefit from intensive treatment in the elderly.

Conclusion

Older patients with more comorbidities experience more treatment-related toxicity and poorer outcomes. Intensification of treatment (i.e., adding chemotherapy to radiation) should only be in carefully selected patients and done when absolutely necessary.

Quality of Life

Quality of life is a multidimensional concept that includes evaluation of positive and negative aspects of life [80]. Quality of life refers to "a patient's appraisal of and satisfaction with their current level of functioning compared with what they perceive to be possible or ideal" [81]. The subjective evaluation of patients' perceptions of their quality of life (as measured by validated questionnaires) may be especially challenging in older patients.

Limited data exists on the quality of life of older patients with any cancer. Many believe that older patients suffer more side effects and toxicities from treatment and therefore have more difficulty adjusting to their cancer diagnosis. However, at least one study has shown that physicians tend to overestimate the problems of their older patients with cancers.

Limited data exists on the quality of life of older patients with any cancer. Many believe that older patients suffer more side effects and toxicities from treatment and therefore have more difficulty adjusting to their cancer diagnosis. However, at least one study has shown that physicians tend to overestimate the problems of their older patients with cancers [82]. The same study indicated that it was younger patients who reported more quality-of-life difficulties through treatment. In a prospective study on 78 older patients and 105 younger patients with HNC undergoing surgery, Derks et al. demonstrated that although older patients had worse physical functioning prior to treatment, the difference remained constant throughout treatment, indicating that the older patients did not have a higher relative decrease in physical functioning compared with younger patients. In addition, they found that younger patients reported more pain at 6 months than older patients [83]. In a retrospective study of 638 patients, Laraway et al. demonstrated that patients older than 65 had better physical and emotional functioning 1 year after surgery than younger patients [84].

These findings may suggest that older patients experience less quality-of-life difficulties than their younger peers. Alternatively, they may suggest that older patients are less likely to report changes in quality of life due to differences in perceived expectations. A 45-year-old patient who missed a month of work due to posttreatment pain may score changes in quality of life worse than a retired 70-year-old patient with the same pain. Although the current data suggests that older patients do not have worse quality of life following treatment, the subjective nature of quality-of-life endpoints makes it difficult for clinicians to interpret this data for their individual older patients.

Conclusion

The available data suggest that patient-reported quality of life is not significantly reduced after treatment in older patients with HNC. However, we do not recommend using these data to inform patient counseling and treatment decisions.

Supportive Care During Treatment

HNC and its therapy are associated with marked symptom burden and functional impairment [85]. Supportive care is crucial to enable patients to complete their prescribed treatment course without breaks in treatment and to recover safely from toxicities. Although the term "palliative care" is often used interchangeably with "supportive care," we use the term "supportive care" to mean care that helps patients and their families cope with cancer and its treatment [86].

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A myriad of symptoms such as constipation, nausea/vomiting, pain, mucositis, and xerostomia affect those undergoing treatment for HNC. Each symptom can have a unique presentation and treatment in the older patient. There is sparse literature specific to the supportive care needs of older patients undergoing chemoradiation. Michal et al. [46] compared toxicities in patients older and younger than 70 years who were receiving concurrent chemoradiation. Patients older than 70 years required more supportive care, with 89% requiring feeding tube placement, as compared with 69% in the younger cohort. In a secondary analysis of five cross-sectional studies of patients with HNC, a statistical correlation between age and overall symptom burden and nutritional dysfunction during therapy was reported [85]. Although not specific to patients with HNC, in a prospective multicenter study, 53% of older adults experienced at least one grade 3–5 toxicity [88]. The authors correctly pointed out that even grade 2 toxicities, which were not looked at in this study, can dramatically affect the older patient. Grade 2 diarrhea, for example, could be enough to compromise an older patient's volume and electrolyte status, whereas the younger patient could more easily compensate.

The use of prophylactic feeding tubes for patients with HNC is controversial. Many argue that prophylactic placements helps avoid significant weight loss and dehydration compared with placement of tubes if/when needed (therapeutic feeding tubes). Others argue that early placement of feeding tubes leads to atrophy of the swallowing mechanism and slower regain of swallowing function after treatment. The data are insufficient to draw definitive conclusions [89]. However, it has been the authors' clinical experience that when older patients require therapeutic feeding tubes, they are often not able to get them in enough time to avoid treatment delay, hospitalizations, or significant weight loss. Therefore, it has been the practice of the authors to place prophylactic feeding tubes in older patients receiving intensive curative chemoradiation.

The clinician must also be astute to physiologic changes that influence the older person's presentation of pain. Pain perception declines with age, is influenced by comorbidities and polypharmacy, and is altered with cognitive impairment or age-related impairments, such as hearing loss [90]. Particularly for the cognitively impaired, more time for evaluation is needed to facilitate adequate evaluation of symptoms.

Conclusion

Older patients with HNC require more supportive care. We recommend prophylactic feeding tubes. We also recommend coordinating care with the patient's other general practitioners and specialists. Specifically, we recommend increased interval of follow-up with patients' other physicians during cancer treatment. Efforts should be made by the oncologist to communicate regularly with other providers.

Discussion

Older patients with HNC may be different from their younger peers. It is generally accepted that age is a poor prognostic factor in the development of HNC [91]. One theory that partially explains the increasing incidence of cancer in the elderly is the prolonged exposure to environmental factors such as tobacco or alcohol in the setting of immunosenescence [92]. This differential in exposures and immunosenescence may lead to biological differences in the solid tumors that develop in older patients compared with their younger peers [93]. These biological differences could lead to differences in the way tumors respond to antineoplastic therapy, possibly leading to worse survival [94]. However, in our comprehensive review of the literature, we found no definitive indication that older patients have worse survival.

The retrospective nature of many of the studies reviewed makes it to difficult to interpret and integrate the findings of these studies. For example, the radiation studies differ from the surgical series in their patient populations. The radiation series included both older [39] and less healthy patients [36]; therefore, the survival outcomes cannot be directly compared with the surgical series. The radiation studies are also hard to compare because they include different patient ages, different tumor sites, and different radiation and chemotherapy regimens. For example, in one study, as many as 16% of the older patients received hyperfractionated (twice a day) treatment [42]. Our review of the literature on toxicity among older patients was also mixed. Many studies had different definitions of acute toxicity or may not have recorded toxicity well. We also have no indication if older patients required increased supportive care during their treatment compared with younger patients. This increased supportive care, if received, may be what allowed older patients to tolerate this often-morbid treatment.

> With current treatment modalities, older patients with HNC do not have worse survival rates but may experience higher treatment-related toxicities than their younger peers, specifically as the intensity of treatment increases. Furthermore, comorbidities and functional age are better predictors of treatment tolerance and development of toxicities compared with chronological age.

To balance the risks and benefits of more effective or toxic treatment among older patients with comorbidities, we require better tools to help predict which patients will tolerate aggressive therapy. There is great interest among geriatric oncologists in the Comprehensive Geriatric Assessment (CGA) as a tool to assess functional age and health of older patients. The CGA is a series of tools and questionnaires used by clinicians to evaluate an older person's functional status, comorbidities, cognition, psychological status, social functioning and support, nutritional status, and medications [95]. Decreases in functional status based on poor scores in activities of daily living or instrumental activities of daily living on CGAs have been shown to predict for increased toxicities to both chemotherapy [88] and surgery [96] and predict for changes in planned treatment regimen [97]. To our knowledge, there are no published prospective studies on the use of the CGA for patients with HNC or patients receiving radiation therapy. However, studies have suggested that the CGA can be used as a tool to help choose appropriate therapy for individual patients [91, 98].

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Better data are needed to answer the question of whether the benefits of intensive therapy truly outweigh the potential risks in selected older patients with HNC. Further, older patients are heterogeneous both in their disease and in their physiologic ability to tolerate therapy. Thus, prospective studies of older patients are needed to define which older patients are likely to tolerate intensive chemoradiotherapy. Pending better data, physicians should counsel older patients, incorporating prognosis of disease and the risks of treatment.

Future research should be directed at developing specific programs for supporting older patients throughout their treatment. These programs should be aimed at decreasing hospitalizations and emergency room visits, reducing treatment breaks or incomplete treatments, and providing better symptom management and satisfaction with treatment. These include assessing how objective measures of independence (e.g., activities of daily living and instrumental activities of daily living) or social support requirements change over different treatments.

Conclusions

Choosing therapy and caring for older patients with HNC is challenging. It is common practice to extrapolate results from clinical trials with few older patients to guide treatment. Evidence suggests that the therapeutic index may shrink as treatment intensity increases. With current treatment modalities, older patients with HNC do not have worse survival rates but may experience higher treatment-related toxicities than their younger peers, specifically as the intensity of treatment increases. Furthermore, comorbidities and functional age are better predictors of treatment tolerance and development of toxicities compared with chronological age. Older patients require careful multidisciplinary assessment for the need for supportive care (e.g., prophylactic feeding tubes) to ensure successful completion of treatment. Ongoing studies exploring the value of geriatric assessments in older patients with HNC may allow clinicians to better choose treatment regimens and address toxicities during treatment. These tools may allow clinicians to better triage older patients with HNC for intensive multimodality treatment.

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