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CLINICAL REVIEW

The role of age in treatment-related adverse events in head and neck cancer patients: a systematic review

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Abstract

Head and neck squamous cell carcinoma (HNSCC) is often diagnosed in advanced stage and therefore requires aggressive, multimodal treatment. Elderly patients are often excluded from standard therapy regimens purely based on age. This clinical review aims to collect all published data in the literature on treatment modality selection in elderly patients and on age-related adverse events following treatment of HNSCC. We performed a literature search for articles on the treatment of HNSCC in elderly patients. Most of the articles were retrospective studies with the consequent limitations. It can be concluded that age is not an absolute contraindication for intensive treatment and comorbidity is an important predictor of outcome, but not the only one. Despite the existence of multiple tools for pretreatment evaluation, there are not consistent data on their use.

Key words: adverse events, head and neck cancer, elderly, comorbidity, postoperative complications, prognosis, toxicity.

1. Introduction

Despite the increase of a subpopulation of relatively younger head and neck squamous cell cancer (HNSCC) patients with human papillomavirus (HPV) related oropharyngeal cancer patients, HNSCC remains primarily a cancer of an older population. According to the Surveillance, Epidemiology, and End Results (SEER) database, approximately 64% of all patients diagnosed with HNSCC in the U.S. between 1975 and 2014 were ≥ 65 years[1]. It has been estimated that 24% of newly diagnosed HNSCC patients are older than 70 years[2,3] and the larynx, oropharynx and oral cavity are the three tumor sites most common affected[4]. The definition of "elderly" is not uniform and different cut-points are used for this purpose. However, the National Institute on Aging suggest categories of "young old" (65-74 years), "older old" (75-85 years), and "oldest old" (>85 years)[5]. The majority of patients with HNSCC present with advanced stage disease which usually requires extensive combined treatment, i.e. surgery and postoperative radiotherapy (RT) with or without chemotherapy (CT) or primary RT with or without systemic therapy (CT or cetuximab) with salvage surgery, when needed and possible[6]. These intensive multimodality treatments harbor a high risk of associated acute and long-term toxicity, which in many cases is demonstrated by poor adherence to treatments, inferior quality of life (QoL), treatment-induced death and limited life expectancy[7]. In elderly patients, medical comorbidities are common. As such, these patients are considered poor candidates for intensive multimodal therapy and frequently they receive less effective but better tolerated treatments regimens, often with a poorer response[8]. The selection of patients for either standard or non-standard therapy

is not clearly defined, and a comprehensive geriatric evaluation is rarely conducted. Fear of adverse events in these elderly patients often results in different treatment of elderly as compared to younger patients. An adverse event can be defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure[9], thus, subjective factors frequently influence the decision on treatment[10]. In the last years, the concept of frailty has been developed. The term frailty refers to a state of decreased physiological reserves, arising from cumulative deficits in several physiological systems and resulting in a diminished resistance to stressors[11,12]. Research has been conducted to find screening methods to identify fit older patients who are able to receive standard cancer treatment, and vulnerable patients who should subsequently receive a geriatric assessment to guide tailoring of their treatment[13]. Moreover, elderly patients are frequently not included in prospective clinical trials. These trials often accrue younger and healthier patients, as described by Siddiqui and Gwede[14]. They found that the median age of the patients enrolled was between 53 and 62 years old and most studies lack data on comorbidities. Therefore, recommendations derived from these trials and guidelines based on their results are not directly applicable to older patients. Another factor is the reluctance of physicians to offer the best available therapy, based on the belief that older people are not fit to receive complex surgical procedures or intense chemoradiotherapy (CRT)[15].

The purpose of this article is to review the currently available literature with focus on (1) the importance of age in the treatment selection for HNSCC, (2) if these

patients legitimately receive nonstandard treatment regimens, (3) if elderly HNSCC patients more often face treatment-related adverse events and worse survival in contrast to their younger counterparts and finally, (4) if in the published articles any screening method is used to assess if older patients are candidates for standard treatment.

For this purpose, the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) were used to conduct a systematic review of the current literature[16]. The search strategy aimed to include all articles concerning the treatment of HNSCC in elderly patients. A PubMed internet search updated to July 24, 2018 was performed for English language publications between the years 1980-2018 using the following search criteria in the title or abstract: “head and neck cancer,” coupled with “older”, “elderly” or “age”, and “radiotherapy”, “chemotherapy”, “systemic therapy”, “targeted therapy”, “surgery” and “adverse event”. The search results were reviewed for potentially eligible studies. When there was reference in the abstract that the study includes patients over 65 years old, the full text article was searched; all review articles were also checked in full. References from any full text articles were cross-checked to ensure inclusion all relevant publications in this review (Figure 1). Studies were selected if they met the following inclusion criteria: 1) patients treated for HNSCC, 2) age of the patients ≥65 years, 3) type of treatment that the patients received, 4) data about the primary site of the tumor, 5) if the study included also younger patients, data should be analyzed by age group (e.g. >65 years, <65 years). Studies involving patients of all ages, without age differentiation, were excluded.

According to our search criteria, 2543 papers were initially identified. After sorting and removal of duplicates, 82 papers that fully fit our inclusion criteria were retrieved, reviewed in detail and summarized in tables 1-4[4,15,17-96] according to the modality of treatment used: RT, systemic therapy (CT or targeted therapy), surgery or multimodal therapy.

2. Adverse events and survival after different treatment modalities in elderly

2.1. Radiotherapy

2.1.1. Toxicity

Most studies find no age-specific differences in the efficacy of radiation therapy[4,17], and note comparable survival outcome. However, the data on treatment related toxicity differ among studies. For instance, Pignon et al.[4] found more severe but not more frequent acute toxicities in aged patients, and contradictory to this, Schofield et al.[21] found no differences. The study by Allal et al.[20], indicates lack of compliance of elderly patients to accelerated radiotherapy.

2.1.2. Specific RT techniques

Specific RT techniques and protocols, such as intensity modulated radiotherapy (IMRT)[22,25], intensity modulated radiotherapy/image guided radiotherapy simultaneous integrated boost (IMRT/IGRT SIB)[23], and hypofractionation[24] seems to be feasible and well-tolerated in elderly. Based on the published literature, age itself seems not to be a limiting factor in curative radical RT, even in the octo-[18] and nonagenarians[19]. However, data on efficacy, toxicity and compliance in the very old patients is based on small

study populations. In addition, the proportion of older patients in these trials is lower compared to the fraction they represent among all HNSCC patients, which implies a significant selection bias. Despite only apparently "fit elderly" (individuals, over 65 years of age, living independently at home or in sheltered accommodation[97]) patients are recruited to curative-intent radiotherapy programs, the meta-analysis of prospective randomized trials comparing conventional and altered fractionated radiotherapy showed a decreasing effect (worse overall survival, but not the disease specific survival) of intensified radiotherapy regimens with increasing[98,99]. Increase in non-cancer related deaths, and lower compliance and tolerance were recognized as possible factors for this observation[100,101]. However, the difference between chronological and biological age of the patients, the parameter that was not addressed in the meta-analysis, could also play a role[10].

Based on the presented data, it appears that altered fractionated radiotherapy has a decreased benefit in older patients and in patients with poor performance status. It could be due to an excess of non-cancer related deaths but also by lower compliance and tolerance in older patients; although late toxicity and outcomes are not different, asking for careful selection of elderly patients for curative intent radiotherapy regimens.

2.2. Chemotherapy and other systemic therapy

2.2.1. Chemoradiation, bioradiation

Adding CT to radiation therapy for the treatment of HNSCC in elderly patients is often discarded from treatment protocols, based on a meta-analysis of Pignon et al. in

2009 (MACH-HN)[102]. This study concluded that adding CT to conventional RT has no beneficial effect in patients over 70. There are several points of criticisms on this conclusion; one of these is the fact, that non-cancer related deaths were more common in the elderly and significantly altered the analysis. A similar observation was made by Machtay et al.[57] who analyzed three RTOG chemoradiation trials (12% of patients were over 70) for the factors influencing the occurrence of severe (grade 3-4) late toxicities with potential detrimental effect to survival: the risk of their development was significantly increased with higher age (hazard ration 1.05 per year). Another weakness of the MACH-HN study is the small number (356 patients) of elderly patients who received CRT, compared to the whole study population, which was over 17.000 patients.

A more recent addition to systemic HNSCC treatment is Cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor (EGFR), approved in 2006 for concurrent use with radiation in locally or regionally advanced disease[81]not was demonstrated not to increase common acute radiation-associated toxicity or a decline of patient's quality of life[103]. However, in older patients (≥65 years) no overall survival benefit was reported when used in combination with RT[104].

2.2.2. Systemic therapy for recurrent/metastatic (RM) disease

In the Extreme trial, which stated the superiority of cetuximab added to platinum and 5-fluorouracil (PF) in comparison to PF alone in first line setting for RM HNSCC, only 18% of the patients were 65 years and older[28]. The highest benefit in survival for

the 3-drug regimen was observed in patients with less than 65 years (HR 0.74; 0.59–0.94), whereas it was not significant in older patients (HR 1.07; 0.65–1.77). Gebbia et al.[26] showed that fit elderly can receive CT without major age-related toxicity, underlining the importance of screening. The outcome of a phase III, open-label trial was consistent with this study, and the results showed that advanced age does not adversely affect toxicity and oncologic outcome in patients treated in a second-line setting with afatinib or methotrexate[29]. In contrast to these two studies, Argiris et al.[27] found significantly higher toxicity rates and also higher CT-related deaths in elderly; however, global survival data of elderly were comparable to the younger patients. These data are based on analysis of two phase III ECOG studies on palliative cisplatin-based studies with only 13% of the patients from ≥70 age group. Observed differences are very likely due to the differences in eligibility for receiving CT across different age groups, indicating a need for more effective strategies for decreasing toxicities in elderly patients.

Nakano et al.[30] compared the efficacy of two cetuximab-containing regimens (weekly paclitaxel and cetuximab vs 5-Fluorouracil, platinum and Cetuximab). They found that male gender, older age (≥ 70 years), good performance status, no history of platinum chemotherapy and the presence of a tracheostomy were favorable factors within the cohort treated with weekly paclitaxel and cetuximab.

Obviously, age-related changes in physiology of different organs alter pharmacokinetics and pharmacodynamics of systemic drugs, which increase susceptibility of normal tissues to toxicity. Changes in toxicity profile observed in older

patients reduce tolerability to systemic therapies and require more effective supportive care measures; in this regard, the importance of tools for prediction of the risk of toxicity and the probability of response before administering systemic therapies should be underlined[27].

2.3.Surgery

The literature on the effect of age on treatment related adverse events in patients undergoing major head and neck surgery is very consistent. However, all available literature data is based on retrospective studies; which very likely introduces selection bias in the inclusion of patients in these studies. Surgical candidates are usually thoroughly screened before major oncological head and neck surgery and only fit elderly patients are selected for these complex procedures. Usually, patients who are excluded are not analyzed, and their outcome is unknown. Therefore, these studies have to be carefully interpreted.

Roughly, two types of studies can be identified in this topic; studies comparing young versus elderly and studies including only aged patients. All studies that compare complication rates[31–35,37,40–43,105] conclude that complication rate is comparable in elderly and young patients, except the study of Morgan et al.[31]. Despite the fact that the latter study finds slightly more frequent complications in elderly patients (32% vs 21%), the authors concluded that age alone should not be a factor to exclude patients from extensive surgery[31]. Retrospective studies with cohorts of elderly patients that lack a control group[34,36,38,39,44,45] draw the same conclusions; surgical treatment can be safely

performed in elderly HNSCC patients and selection should be based on medical assessment, and not on age. While most of the studies focused on complication rates, a small subset do report survival data[35]. Interestingly, Clayman et al.[35] found lower local control and disease-specific survival in octogenarians when compared with group of similar patients aged up to 65 years.

2.4.Multimodality treatment

The literature on age specific treatment outcome after multimodality treatment is not very consistent. Several studies confirm no age-related differences after multimodal treatment of HNSCC in terms of treatment-related adverse events[46,47,49,60,62–64,68,77,106]. In contrast, other studies identified more adverse events in the elderly[54,57,58,66,67,69,72,75,78,79,87]. Since all of these studies are retrospective; the selection bias, may have had an effect on the outcome. This problem is highlighted in the study of Hirano and Mori[48]. These authors found significant differences between young and old patients regarding the choice of the modalities of curative treatment, due to significantly more common concomitant comorbidities in elderly. In the study of Derks et al.[53], the proportion of patients aged 45-60 years, 70-79 years and ≥80 year that received standard treatment was 89%, 75% and 35%, respectively; whereas no treatment was given to 4%, 13% and 18% of the patients from respective groups.

Comparing survival between cohorts of different age categories is difficult due to expected differences in life expectancy. Some studies confirm poorer survival in the elderly after multimodality treatment[50,51,62,69,93,94], others report comparable survival in

the elderly to the younger cohorts[46,47,66,75,87]. Concerning the rate of treatment-related death, Sarini et al.[49] did not find any age-specific differences.

In the past, elderly patients were clearly underrepresented in non-age-related clinical trials. However, the number of studies, on the eligibility of elderly for intensive multimodal treatment is exponentially increasing. It seems that the old dogma, that elderly patients should be excluded from standard treatment protocols, purely based on their chronological age does not stand any longer. This is also reflected in the outcome of a recent study on the SEER database, confirming the increased use of chemoradiation and particularly cetuximab, in older patients over the past decades[81].

3. Factors influencing adverse events

3.1.Comorbidity, advanced stage, use of CT

One of the key factors in the decision on treatment of a patient with HNSCC is comorbidity. Comorbidity is defined as one or more unrelated diseases present at the time of cancer diagnosis[10]. In elderly patients, comorbidity is more frequent, and these patients sometimes receive non-standard treatments due to the fear of complications, that intensive standard treatments entail. For this reason, these patients are often offered non-surgical treatments or surgical treatment without postoperative RT[49,53,107]. Peters et al.[63] reported on a cohort of elderly oropharyngeal cancer patients, and no difference in post-treatment complications between young and old patients was found, despite the higher incidence of comorbidity in elderly patients. T-classification was the only factor associated with the frequency of complications in multivariate analysis. This

observation was confirmed by Zabrodsky et al.[38]. They reported that surgical and medical complications were influenced by advanced comorbidity, long operative times and advanced stage at diagnosis. Sanabria et al[39] observed that advanced stage was associated with postoperative complications as well, and identified additional factors that contributed: male gender, bilateral neck dissection and presence of two or more comorbidities. Advanced stage at diagnosis is often considered a predictor for postoperative complications[41,42,63,64]. One of the factors studied as influential in the incidence of adverse effects in the elderly is the addition of CT to RT. For example, in the study by O'Neill et al.[78], a higher rate of hospitalization and acute toxicity with emergency room visit was found in patients receiving CRT versus RT treatment. The group also reported a higher rate of acute treatment-related toxicity, feeding tube placement, and long-term feeding tube dependence among these older patients treated with combined modality therapy. Similar results were reported by Strom et al.[108]. This report evaluated patients by age, rather than by treatment modality, and found an increased rate of hospital admission and a late percutaneous endoscopic gastrostomy (PEG) dependence among older patients treated with CRT. Michal et al.[66] confirmed these observations as well.

3.2.Other prognosticators

Other factors possibly related to adverse events during treatment of the elderly patients with HNSCC have also been studied. Besides comparing young and elderly patients, a significant proportion of these studies attempted to identify predictors of outcome other than age. Comorbidity, performance status, frailty and advanced tumor stage all seem to

correlate with clinical outcome[39,56,59,63,64,67,80,83,85–87,93,95,96,106]. Beside the known general prognosticators for surgical complications, like advanced stage and previous RT, also the duration of the surgery plays a role. In fact, prolonged surgery time was found to be a significant independent predictor for surgical complication in these studies[38,41,44,105]. However, the ability of older patients to cope with the proposed treatment goes beyond the comorbidity status and includes other aspect of patient functioning with assessment of the nutritional status, polypharmacy, cognitive function, socioeconomic issues, and geriatric syndromes[109].

3.3.Coordination of care

Apart from these observations, the majority of the authors agree that older patients can receive the same treatment as younger ones, with comparable or higher complication rates. A higher chance on complications as such does not imply not to give treatment, but calls for better planning, better preoperative evaluation, and optimal multidisciplinary team coordination, including supportive care, to minimize treatment-related complications, maximize postoperative or post-(chemo)radiotherapy support and decrease the impact on survival and QoL. Introduction of enhanced recovery after surgery (ERAS) strategy in other oncologic procedures can be considered a demonstration of this philosophy. The ERAS programs have been applied successfully in the last two decades to offer a faster recovery, reducing hospital stay and thus, fostering early return to daily activities after hospital discharge[110].

Other factors that are important for optimal recovery and quality of life after treatment are social and family support, caregivers' availability and resilience and financial support. Studies have demonstrated that living alone[111], lack of psychological support[112] and lack of social support[113] are prognostic factors of QOL decline after treatment.

4. The selection of patients for therapy

4.1.Comprehensive Geriatric Assessment (CGA) and frailty tests

Attempting to predict adverse events of a given treatment in elderly patients is much more difficult than in young patients. It is preferable in elderly patients to evaluate the potential impacts of treatment on the QoL, survival and the potential for adverse events. With this knowledge, older patients who may benefit from intensified treatment can be better selected for the most appropriate treatment. One of the available options for this assessment is the Comprehensive Geriatric Assessment (CGA) which is defined as a "multidimensional interdisciplinary diagnostic process focused on determining a frail older person's medical, psychological and functional capability in order to develop a coordinated and integrated plan for treatment and long term follow up"[114]. CGA is therefore both a diagnostic and therapeutic tool. It seeks to ensure that problems are identified, quantified, and managed appropriately. A CGA is now considered as the gold standard by some authors to assess whether individual patients can undergo a certain (radical) treatment, or not, based on their vulnerability seems mandatory. However, as suggested by Neve et al.[86], to avoid over-use of this complex an time consuming assessment instrument the most feasible option is to use a

"screening" tool first, in order to identify patients who are truly "vulnerable" and therefore require further examination by a CGA (two-step approach). Other patients recognized in the screening phase as "fit" do not require further examination. In order to identify frail patients several tools are available, like the Geriatric 8 (G8), the Flemish version of the Triage Risk Screening Tool (fTRST), the Groningen Frailty Indicator (GFI), the Vulnerable Elders Survey-13 (VES-13), and an abbreviated CGA[115].

4.2.Predictive value of CGA items and frailty tests

As described by Hamaker et al.[11] in a recent systematic review the predictive value of these frailty tests can be questioned as some tests are highly sensitive for frailty but their specificity and negative predictive value are rather poor. In HNSCC, the G8 appears to be the diagnostic screening tool with a greater ability to select vulnerable patients, who should need a full CGA[116]. In our review, only two studies use some kind of geriatric, QoL or functional assessments among the RT trials[24,25], two studies of the trial on systemic therapy[26,29], four in surgical studies[38,41,42,44] and seventeen in papers on results of multimodal treatment [15,53,55,59,63,64,67,80,83,85–87,93,95,96,106,117]. Most of them did not use a specific geriatric tool. Since it is known that the selection of a substandard treatment for an elderly patient decreases overall and a cancer-specific survival, this decision must be based on the results of the available screening tools and eventual CGA, not simply on chronological age.

5. Conclusions and recommendations.

This is the first comprehensive review which systematically assesses age-related adverse events and treatment selection in elderly HNSCC patients and associated survival outcomes. Most of the studies agree that chronological age itself should not to be a reason to exclude patients from standard therapy. However, these data are mostly based on retrospective studies, which might introduce selection bias. Furthermore, the quality of the studies is diverse, and some data are controversial. When selecting treatment modalities, biological age is clearly more important than chronological age. However, there is no gold standard to assess it. Comorbidity and performance status of the patients are frequently analyzed and are certainly important factors, but as such seem to be insufficient to predict treatment outcome. In fact, tolerance to treatment is multi-factorial and also depends on psychological status and various socioeconomic issues, in addition to medical condition and the level of functioning. Pretreatment assessment remains a crucial issue in treatment selection. However, choosing the proper therapy remains challenging. This process is even more complex, as patients' preferences also need to be considered in the context of the shared decision making and elderly are known to have other priorities that their younger counterparts. Using frailty screening instruments, only selected candidate patients may be directed to more complex CGA evaluation (two-step approach). Other promising screening tools need further investigation of their impact in guiding the treatment decision making and in predicting toxicities, in the framework of HNSCC prospective trials. Large scale, prospective, multicenter studies are also needed to explore the possibility of including

more elderly HNSCC patients in guideline-based, (intensive) treatment protocols, and to select appropriate de-intensified approaches for non-fit patients.

Figure 1: Flow chart showing the process of the study selection for the systematic review.

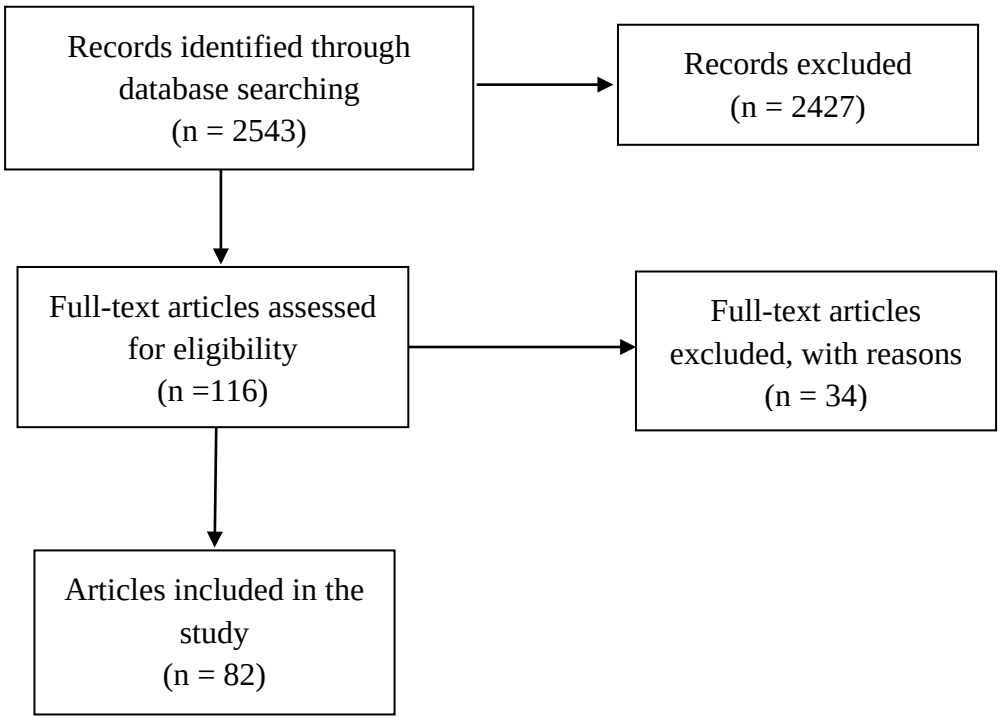

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Table 1: Results of Radiotherapy Clinical Trials

Author [Ref]	Year	Cohort	Type of study	Primary tumor site	Adverse events
Huguenin et al.[17]	1996	75	Retrospective study	Multiple	30% of the patien required treatmen interruption (unknown reasons 1 case of late bon necrosis
Pignon et al.[4]	1996	1589	Secondary analysis	Multiple	An increase in grade III-IV mucosal toxicity among the aged
Zachariah et al.[18]	1997	50	Retrospective study	Multiple (include other locations)	No differences
Mitsuhashi et al.[19]	1999	14	Retrospective study	Multiple	No differences

Allal et al.[20]	2000	119	39 patients ≥ 70 years	Retrospective study	Multiple	No differences
			80 patients < 70 years			
Schofield et al.[21]	2003		98	Retrospective study	Multiple	No differences. 98% completed RT; severe late toxicity occurred 3.1%
Yu et al.[22]	2012	1613 patients	≥ 65 years	Retrospective study	Multiple	NA

Straube et al.[23]	2016	27	Retrospective study	Multiple	Acute toxicities were seen on mos patients, however no severe acute side effects > CTCAE grade 4 (Life-threatening consequences; urgent intervention indicated) were observed
Bonomo et al.[24]	2017	36 patients with advanced HNSCC deemed unsuitable for CRT	Observational prospective study	Multiple	The most commo treatment-related toxicities were grade 1 oral mucositis and grade 1 dysphagia both with an incidence of 36.1%
De Felice et al.[25]	2017	15 patients ≥ 70 years	Retrospective study	Multiple	Incidence rate of any severe acute toxicity was 37%.

IMRT: Intensity Modulated Radiotherapy. IGRT SIB: Image Guided Radiotherapy Simultaneous Integrated Boost. RT: Radiotherapy. CTCAE: Common Terminology Criteria for Adverse Events. HNSCC: Head and Neck Squamous Cell Cancer. CRT: Chemoradiotherapy.

Table 2: Results of Chemotherapy and/or Targeted Therapy Clinical Trials.

Author [Ref]	**Year**	**Cohort**	**Type of study**	**Primary Tumor site**	**Adverse events**
Gebbia et al.[26]	2003	45 patients >70 years	Prospective study	Multiple	Mucositis grade 3 in 34% rhEpo) - 36% (with rhEpo Mild grade 1 renal and liv toxicities were occasionall observed. Grades 3–4 leuk 20 and 25% of patients, respectively. Grade 3 thrombocytopenia was not influenced by rhEpo treatm

						12% of patients reported thrombocytopenia in both the study.
Argiris et al.[27]	2004	399 (53 patients≥70 years)		Review data from two consecutive phase III randomized trials	Multiple	Elderly patients had a sign higher incidence of severe nephrotoxicity, diarrhea, a thrombocytopenia. A high toxic deaths was noted in t but did not reach statistica significance (13% v 8%; P
Vermorken et al. [28]	2008	442 (77 patients≥65 years)		Randomized trial	Multiple	9 cases of sepsis in the cet group, as compared with 1 the chemotherapy-alone group
Clement et al.[29]	2016	483	355 patients ≤65 years 128 patients ≥65 years	Phase III, open-label trial	Multiple	No differences
Nakano et al. [30]	2017	86 (20 patients>70 years)		Retrospective study	Multiple	Different toxicity pattern h seen between the "5-Fluo platinum and cetuximab" a "weekly paclitaxel and cet cohort

CT: Chemotherapy.

Table 3: Results of Retrospective Cohorts Undergoing Surgery for HNSCC

Author [Ref]	Year	Cohort		Type of study	Primary tumor site	Adverse events	Geriatr quality and fu assessn
Morgan et al.[31]	1982	1773	810 patients ≥65 years 963 patients <65 years	Retrospective study	Multiple	Nonlethal complications: 32% for patients >65 years; 21% for patients <65 years	No
Bridger et al.[32]	1994	117	26 patients ≥70 years 91 patients <70 years	Retrospective study	Multiple	No differences	No
Kowalski et al.[33]	1994	230	115 patients ≥70 years 115 patients <70 years	Retrospective study	Multiple	No differences in complications or postoperative deaths	No
McGuirt and Davis[34]	1995	217		Retrospective study	Multiple	No differences	No
Clayman et al.[35]	1998	122	43 patients ≥80 years 79 patients ≤65 years	Retrospective study	Multiple	No differences in postoperative complications	No
Laccourreye et al.[36]	1998	69		Retrospective study	Larynx	No differences	No

Shaari et al.[37]	1998	87	52 patients >70 years 35 patients <70 years	Retrospective study	Multiple	No differences	No
Zabrodsky et al.[38]	2004	24		Retrospective study	Multiple	Presence of advanced comorbidity, longer operative times and advanced stage of disease seemed to influence the development of surgical or medical complications	Comorb Data Co Form
Sanabria et al.[39]	2008	242 patients>70 years		Retrospective study	Multiple	Male sex, bilateral neck dissection, presence of 2 or more comorbidities, reconstruction, and clinical stage IV were associated with postoperative complications	No
Milet et al.[40]	2010	261	29 patients ≥70 years 232 patients <70 years	Retrospective study	Multiple	No differences	No

Peters et al.[41]	2014	1201	205 patients ≤49 years 359 patients:50-60 years 341 patients:60-70 years 214 patients:70-80 years 82 patients >80 years	Retrospective study	Multiple	Age was only associated with the risk of cardiopulmonary/ neurologic complications in patients aged > 80 years (p = 0.033). Higher complications rates were found in elderly and patients with preexisting comorbidities. Advanced tumor stage and prolonged surgery time were associated with surgical complications.	Adult Comorb Evaluat index/C Dindo classifi
Petters et al.[42]	2015	202	169 patients <70 years 33 patients ≥70 years	Retrospective study	Multiple	Age was not a predictor of complications in patients treated with free-flap surgery. Only disease stage was a significant predictor of recipient site complications, and comorbidity was	Adult Comorb Evaluat index/C Dindo classifi

						the only significant predictor of medical complications	
Goh et al.[43]	2017	234	60 patients ≥65 years 174 patients <65 years	Retrospective study	Multiple	Age alone, tobacco use and preoperative radiation treatment did not independently increase the risk of postoperative complications.	No
L´Esperance et al.[44]	2017	219 patients ≥80 years		Retrospective study	Multiple	74 patients experienced serious complications within 30 days and 25 died within 90 days of surgery.	Adult Comorb Evaluat index
Wu et al.[45]	2018	637 patients >65 years		Retrospective study	Multiple	Age not predictive of complications	No

	or mortality. Flap reconstruction surgery had no significant association with necrosis, hemorrhage, infection, need for rescue treatment, or length of intensive care unit stay.

Table 4: Multimodal Therapy of HNSCC

Author [Ref]	Year	Cohort		Type of study	Type of treatment	Primary tumor site	Adverse events
Barzan et al.[46]	1990	438	196 patients ≤59 years 135 patients: 60-69 years 107 patients ≥70 years	Retrospective study	Surgery/CT/ RT	Multiple	The percentage of local and general post-operative complications were similar in the three ages groups
Lusinchi et al.[47]	1990	331 patients >70 years		Retrospective study	Surgery/RT	Multiple	No differences
Hirano et al.[48]	1998	679	560 patients <75 years 119 patients ≥75 years	Retrospective study	Surgery/RT	Multiple	Concomitant health problems were significant more common i the older group

Sarini et al.[49]	2001	4610 (273 patients ≥75 years)		Retrospective study	Surgery/RT/ CT/CRT	Multiple	No significantly more treatment related deaths in elderly
Vaccher et al.[50]	2002	2143	1962 patients <75 years	Retrospective study	Surgery/RT/ CT/CRT	Multiple	NA
			181 patients ≥75 years				
Bhattacharyya[51]	2003	5016	2508 patients ≥70 years	Matched controlled study on SEER database	Surgery/RT	Multiple	NA
			2508 patients <70 years				

Airoldi et al.[52]	2004	40 patients >70 years		Prospective study	CRT	Multiple	Grade 3 toxicity included mucos (10 patients), neutropenia (6 patients), dermatitis (2 patients), and thrombocytoper (1 patient)
Derks et al.[53]	2005	183	105 patients:45-60 years 78 patients ≥70 years	Prospective stydy	Surgery/RT/ CRT	Multiple	NA
van den Broek et al.[54]	2006	125		Prospective study	CRT	Multiple	Severe acute toxicity (grade 3 4), mainly mucositis and dysphagia was recorded in 51% of patients. Leukopenia (gra 3-4, 39%) and aspiration pneumonia in 20%.

							Tracheotomy (12%). Neurological complications (2%) patients. Severe late toxicity (34%)
Sanabria et al.[15]	2007	312 patients ≥70 years		Retrospective study	Surgery/RT/ CRT	Multiple	NA
Sanabria et al.[55]	2007	310 patients >70 years		Retrospective study	Surgery/RT/ CRT	Multiple	NA
Koussis et al.[56]	2008	35	16 patients ≥70 years	Phase II study	CRT	Multiple	Haematological toxicity was gra 3-4 in 13 patien while gastrointestinal toxicity was gra 3-4 in 20 patien
			19 patients <70 years				

Machtay et al.[57]	2008	230	27 patients >70 years 203 patients ≤70years	Secondary analysis	CRT	Multiple	Severe late toxicity was related with advanced age
Palazzi et al.[58]	2008	149		Prospective study	RT/CRT	Multiple	Severe (Grade 3 4) adverse even were recorded i 28% (mucositis 33% (dysphagia 40% (pain), and 12% (skin) of patients
Fesinmeyer et al.[59]	2009	5086 patients ≥66 years		Retrospective study of SEER database	Surgery/RT/ CRT	Multiple	NA

Tsukuda et al.[60]	2009	50	13 patients >75 years 37 patients <75 years	Prospective study	CRT	Multiple	Grade 3 mucosi occurred in 20% of the patients. Grade 3 neutropenia occurred in 12% and leukocytopenia occurred in 6% the cases
Boscolo-Rizzo et al.[61]	2011	44 patients >65 years		Retrospective study	Surgery/CRT	Multiple	66% developed severe toxicities 11% required permanent feed tubes
Huang et al.[62]	2011	2312	452 patients ≥75 years 1860 patients <75 years	Retrospective study	Surgery/RT/CT	Multiple	No differences

Peters et al.[63]	2011	126	84 patients ≤64 years 42 patients ≥75 years	Retrospective study	Surgery/RT	Pharynx	Complication ra was not significantly different. Only stage was significant independent predictor of complications
Peters et al.[64]	2011	428	139 patients ≥75 years 289 patients ≤65 years	Retrospective study	Surgery/RT	Larynx	Co-morbidity a age were not predictors of complications. Radiation therap (vs. total laryngectomy) a tumor stage wer predictors. Ther was correlation between co-morbidity and complication, b not in the elderl group
Jilani et al.[65]	2012	73 patients ≥65 years		Retrospective study	RT/CRT	Multiple	Most common toxicities includ dermatitis, mucositis, dysphagia and xerostomia. Thr patients develop grade 4 (4%) toxicities including fistula esophageal stricture, tracheostomy dependence

Michal et al.[66]	2012	181	44 patients ≥70 years 137 patients <70 years	Retrospective study	CRT	Multiple	The elderly was less likely to receive both CT courses, experienced mo myelosuppressi required more unplanned hospitalization, and were feedin tube dependent longer
Merlano et al.[67]	2012	317	93 patients ≥65 years 224 patients <65 years	Retrospective study	CRT/BRT	Multiple	Infections (p=0.011) and pneumonias (p=0.002) were significantly mo represented in elderly patients
Nguyen et al.[68]	2012	112	27 patients ≥70 years 85 patients <70 years	Retrospective study	CRT	Multiple	No differences grade 3-4 toxici weight loss and treatment break
Maggiore et al.[69]	2013	89 patients ≥70 years		Retrospective study	CRT	Multiple	The majority (86.5%) could complete all planned treatme cycles. A significant proportion of patients require gastrostomy tub (62%) and

						developed aspiration durin swallowing evaluation post- treatment (44%) Several patients required hospic (9%) or skilled nursing facility (13%) referrals during treatmen
Camilon et al.[70]	2014	14909 (4406 patients ≥65years)	Retrospective study on SEER database	Surgery/Rt/ CRT	Orophary nx	NA
O´Neill et al.[71]	2014	759 patients ≥66 years	Retrospective study on SEER database	Surgery/ CRT	Larynx	Almost 20% of the CRT patient had a tracheostomy following treatment, and 57% had a feed tube

Shapiro et al.[72]	2014	360	317 patients <71 years 43 patients ≥71 years	Retrospective study	CRT	Multiple	Age over 70 an pre-treatment tracheostomy al correlated with significantly higher rate of la toxicity
Sharma et al.[73]	2014	47 patients ≥65 years		Retrospective study	Surgery/RT/ CRT	Multiple	NA
VanderWalde et al.[74]	2014	10599 patients ≥66 years		Retrospective study on SEER database	CRT/RT	Multiple	NA
Chang et al.[75]	2015	126	21 patients >65 years 105 patients ≤65 years	Retrospective study	CRT	Multiple	Elderly were les likely to tolerate cisplatin, experienced mo weight loss, required more feeding tube support and tended to have >grade 3 hematological toxicities and to develop sepsis during the perio of CRT

Kataria et al.[76]	2015	32 patients ≥65 years		Prospective study	CRT	Multiple	Fourteen (45.2% patients experienced gra 3 mucositis. No one developed grade 3 or abov hematological toxicity
Moye et al.[77]	2015	1598	1166 patients <70 years 281 patients ≥70 years	Retrospective study	Surgery/RT/ CRT/CT	Multiple	NA
O´Neill et al.[78]	2015	1502 patients ≥66 years		Retrospective study on SEER database	CRT/RT	Multiple	Patients receivi CRT had more acute toxicities and prolonged u of feeding tubes
Sachdev et al.[79]	2015	100		Retrospective study	RT/CRT	Multiple	NA

Amini et al.[80]	2016	4042 patients >70 years	Retrospective study on NCDB	RT/CRT	Multiple	NA
Baxi et al.[81]	2016	3705 patients ≥65 years	Retrospective study on SEER database	Surgery/RT/ CRT	Multiple	NA
Chalissery et al.[82]	2016	47 patients ≥65 years	Prospective study	CRT	Multiple	Grade III skin reaction and mucositis in 24 and 47% respectively. No grade III neutropenia observed.
Chen et al.[83]	2016	2257(523 patients ≥70 years)	Retrospective study on NCDB	Surgery/RT	Oral cavity and oropharyn x	NA

Doi et al.[84]	2016	14 patients ≥75 years	Retrospective study	CRT	Paranasal	Grade 3 mucosi in 3 patients.
Kwon et al.[85]	2016	165 patients ≥65 years	Prospective study	Surgery/CT/ RT/CRT	Multiple	Respiratory complications such as aspirati pneumonia or dyspnea were th most common reasons for hospitalization, and dysphagia v another major cause of severe post-treatment morbidity
Neve et al.[86]	2016	35 patients ≥65 years	Prospective study	Surgery/RT/ CRT	Multiple	NA

Teymoortash et al.[87]	2016	58	28 patients <65 years	Retrospective study	Surgery/RT/ CRT/CT	Larynx	Surgical complication ra was significantl increased in elderly (p = 0.0
			30 patients ≥65 years				
Ward et al.[88]	2016	4165 patients ≥71 years		Retrospective study on NCDB	RT/CRT	Multiple	NA
Falk et al.[89]	2017	35 patients ≥70 years		Retrospective study	CRT	Multiple	RT was interrupted in 9 of patients and t dose of cetuxim was reduced in 29%.
Lai et al.[90]	2017	70 patients ≥75 years		Retrospective study	CRT/RT	Multiple	CRT group had more adverse events such as neutropenia, febrile neutropenia and thrombocytoper than RT group.

Juarez et al.[91]	2017	421 patients >50 years	118 patients: 50-59 years 152 patients: 60-69 years 151 patients: ≥70 years	Retrospective study	Surgery/CRT/RT	Multiple	NA
Pollom et al.[92]	2017	25829 (7823 patients >70 years)		Retrospective study on NCDB	Surgery/CRT/RT	Oral cavity	NA
Sommers et al.[93]	2017	674 (168 patients ≥ 70 years)		Retrospective analysis of prospectively collected data	RT/CRT	Multiple	NA

Spiotto et al.[94]	2017	6900 (1541 patients >70 years)	Retrospective study on NCDB	Surgery/RT/ CRT	Oral cavity	NA
Zumsteg et al.[95]	2017	74 patients ≥70 years	Retrospective study	CRT	Orophary nx	RT interruption of > 1 day were needed in 4% o patients receivi cisplatin, 20% o patients receivi CARB, and 15% of patients receiving cetuximab (P = .19). Unplanned hospitalizations during CRT occurred in 25% 55%, and 58%, respectively, of patients receivi cisplatin, CARB and cetuximab (P = .03). There were 2 treatmen related deaths, both of which occurred among

						the patients who were treated wi cetuximab
Yoshida et al.[96]	2018	1199 patients ≥70 years	Retrospective study on NCDB	Surgery/RT/ CRT	Multiple	NA

CARB: Carboplatin with either 5-fluorouracil or paclitaxel. EORTC QLQ-C30 and H&N35: European Organisation for Research and Treatment of Cancer. Head and Neck Cancer Quality of Life Questionnaire. CES-D: Centre for Epidemiological Studies Depression Scale. RSS12-I: Social Support List-Interactions. QQ: Quality-Quantity questionnaire. BRT: Bioradiotherapy. SEER: Surveillance, Epidemiology and End Results program. NCDB: National Cancer Data Base. BDI-II: Beck Depression Inventory.

Table 1: Results of Radiotherapy Clinical Trials

Author [Ref]	Year	Cohort	Type of study	Primary tumor site	Adverse events	Geriatric, quality of life and functional assessments	Conclusions
Huguenin et al.[17]	1996	75	Retrospective study	Multiple	30% of the patients required treatment interruption (unknown reasons), 1 case of late bone necrosis	No	Outcome in elderly patients HNSCC is comparable to the outcome in younger patients
Pignon et al.[4]	1996	1589	Secondary analysis	Multiple	An increase in grade III-IV mucosal toxicity among the aged	No	Differences in toxicity but not in overall survival between older and younger patients
Zachariah et al.[18]	1997	50	Retrospective study	Multiple (include other locations)	No differences	No	RT is highly effective and well tolerated by patients over 80 years. Age is not a contraindicatio n for

								aggressive RT
Mitsuhashi et al.[19]	1999		14	Retrospective study	Multiple	No differences	No	Age of 90 years or older is not a limiting factor for RT
Allal et al.[20]	2000	119	39 patients ≥ 70 years	Retrospective study	Multiple	No differences	No	Acute and late toxicities and treatment outcomes were similar in younger and older patients. More patients in the ≥70-yr group required unplanned treatment breaks (3 patients due to acute toxicity and lack of compliance)
			80 patients < 70 years					
Schofield et al.[21]	2003		98	Retrospective study	Multiple	No differences. 98% completed RT; severe late	No	Cancer-specific survival was

					toxicity occurred in 3.1%		59% and overall local control was 70% at 5 years. Cancer-specific survival was comparable in patients over and under 80 years
Yu et al.[22]	2012	1613 patients ≥ 65 years	Retrospective study	Multiple	NA	No	Equivalent survival was observed between IMRT and standard RT. Use of IMRT had no adverse impact on survival in older patients
Straube et al.[23]	2016	27	Retrospective study	Multiple	Acute toxicities were seen on most patients, however no severe acute side effects > CTCAE grade 4 (Life-	No	The IMRT/IGRT SIB concept is feasible by and reduces the total treatment time to 4

					threatening consequences; urgent intervention indicated) were observed		weeks. By limiting treatment to gross disease, this approach should be considered for patients that are not able or not willing to undergo radical treatment
Bonomo et al.[24]	2017	36 patients with advanced HNSCC deemed unsuitable for CRT	Observational prospective study	Multiple	The most common treatment-related toxicities were grade 1 oral mucositis and grade 1 dysphagia, both with an incidence of 36.1%	Geriatric 8 and Charlson comorbidity index	Hypofractionated radiation provides clinical benefit with low toxicity in frail, elderly patients affected by locally advanced HNSCC
De Felice et al.[25]	2017	15 patients ≥ 70 years	Retrospective study	Multiple	Incidence rate of any severe acute toxicity was 37%.	Adult Comorbidity Evaluation-27 (ACE-27)	A high degree of locoregional and distant

									control can be achieved with definitive sequential IMRT, with high compliance and tolerable toxicity. IMRT should be considered a valid option in old patients.

IMRT: Intensity Modulated Radiotherapy. IGRT SIB: Image Guided Radiotherapy Simultaneous Integrated Boost. RT: Radiotherapy. CTCAE: Common Terminology Criteria for Adverse Events. HNSCC: Head and Neck Squamous Cell Cancer. CRT: Chemoradiotherapy.

Table 2: Results of Chemotherapy and/or Targeted Therapy Clinical Trials.

Author [Ref]	Year	Cohort	Type of study	Primary Tumor site	Adverse events	Geriatric, quality of life and functional assessments	Conclusions
Gebbia et al.[26]	2003	45 patients >70 years	Prospective study	Multiple	Mucositis grade 3 in 34% (without rhEpo) - 36% (with rhEpo). Mild grade 1 renal and liver toxicities were occasionally observed. Grades 3–4 leukopenia in 20 and 25% of patients, respectively. Grade 3 thrombocytopenia was not influenced by rhEpo treatment: 12% of patients reported thrombocytopenia in both arms of the study.	Visual linear-analog scales for energy, activity, and global QoL	Fit elderly patients with HNSCC may receive CT without major age-related toxicity
Argiris et al.[27]	2004	399 (53 patients≥70 years)	Review data from two consecutive phase III randomized trials	Multiple	Elderly patients had a significantly higher incidence of severe nephrotoxicity, diarrhea, and thrombocytopenia. A higher rate of toxic deaths was noted in the elderly but did not reach statistical significance (13% v 8%; P =.29).	No	Fit elderly patients with recurrent or metastatic HNSCC sustained increased toxicities with cisplatin-based treatments but had comparable survival outcomes

								compared with younger patients
Vermorken et al. [28]	2008	442 (77 patients≥65 years)		Randomized trial	Multiple	9 cases of sepsis in the cetuximab group, as compared with 1 case in the chemotherapy-alone group	No	Compared with platinum-based chemotherapy plus fluorouracil alone, cetuximab plus platinum–fluorouracil chemotherapy improved overall survival
Clement et al.[29]	2016	483	355 patients ≤65 years 128 patients ≥65 years	Phase III, open-label trial	Multiple	No differences	ECOG performance status	Advanced age (≥65 years) did not adversely affect clinical outcomes or safety with afatinib versus methotrexate in second-line recurrent or metastatic tumors.
Nakano et al. [30]	2017	86 (20 patients>70 years)		Retrospective study	Multiple	Different toxicity pattern has been seen between the "5-Fluorouracil, platinum and cetuximab" and the "weekly paclitaxel and cetuximab" cohort	No	Older patients might be good candidates for weekly paclitaxel and cetuximab.

CT: Chemotherapy.

Table 3: Results of Retrospective Cohorts Undergoing Surgery for HNSCC

Author [Ref]	Year	Cohort		Type of study	Primary tumor site	Adverse events	Geriatric, quality of life and functional assessments	Conclusions
Morgan et al.[31]	1982	1773	810 patients ≥65 years 963 patients <65 years	Retrospective study	Multiple	Nonlethal complications: 32% for patients >65 years; 21% for patients <65 years	No	Differences in complications were reported but no data was presented regarding survival differences. Advanced age alone should not exclude patients from aggressive surgical therapy
Bridger et al.[32]	1994	117	26 patients ≥70 years 91 patients <70 years	Retrospective study	Multiple	No differences	No	No differences in complications, no data about survival differences. Age alone should not exclude a patient from radical surgery for HNSCC with free-flap reconstruction
Kowalski et al.[33]	1994	230	115 patients ≥70 years 115 patients <70 years	Retrospective study	Multiple	No differences in complications or postoperative deaths	No	The main causes of death in the elderly patients were not related to cancer or treatment complications
McGuirt and	1995	217		Retrospective	Multiple	No differences	No	No significant difference

Davis[34]				study				in survival or complications in oldest patients (≥81 years) compared with youngest old patients (65–71 years)
Clayman et al.[35]	1998	122	43 patients ≥80 years 79 patients ≤65 years	Retrospective study	Multiple	No differences in postoperative complications	No	Although median survival was different among groups, when patients ≥80 years were compared with expected survival, there was no difference
Laccourreye et al.[36]	1998	69		Retrospective study	Larynx	No differences	No	Age was not correlated with mortality or morbidity
Shaari et al.[37]	1998	87	52 patients >70 years 35 patients <70 years	Retrospective study	Multiple	No differences	No	No differences in complications, no data about survival differences. Age older than 70 years did not increase the rate of surgical complications.
Zabrodsky et al.[38]	2004	24		Retrospective study	Multiple	Presence of advanced comorbidity, longer operative times and advanced stage of disease seemed to	Comorbidity Data Collection Form	In cases with clinically important comorbidities the extent and duration of surgery should be reduced to minimum

						influence the development of surgical or medical complications		
Sanabria et al.[39]	2008	242 patients>70 years		Retrospective study	Multiple	Male sex, bilateral neck dissection, presence of 2 or more comorbidities, reconstruction, and clinical stage IV were associated with postoperative complications	No	No differences in complications, no data about survival differences
Milet et al.[40]	2010	261	29 patients ≥70 years 232 patients <70 years	Retrospective study	Multiple	No differences	No	No differences in complications, no data about survival differences. The postoperative course in elderly patients is not significantly different from that of younger patients

Peters et al.[41]	2014	1201	205 patients ≤49 years 359 patients:50-60 years 341 patients:60-70 years 214 patients:70-80 years 82 patients >80 years	Retrospective study	Multiple	Age was only associated with the risk of cardiopulmonary/ neurologic complications in patients aged > 80 years (p = 0.033). Higher complications rates were found in elderly and patients with preexisting comorbidities. Advanced tumor stage and prolonged surgery time were associated with surgical	Adult Comorbidity Evaluation-27 index/Clavien-Dindo classification	Elderly have more comorbidities than young; however, surgical complication is not more common. Age itself seems not to be a contraindication for major head and neck surgery.

						complications.		
Petters et al.[42]	2015	202	169 patients <70 years 33 patients ≥70 years	Retrospective study	Multiple	Age was not a predictor of complications in patients treated with free-flap surgery. Only disease stage was a significant predictor of recipient site complications, and comorbidity was the only significant predictor of medical complications	Adult Comorbidity Evaluation-27 index/Clavien-Dindo classification	Optimal patient selection for free flap surgery is essential by thorough pre-operative assessmen. Patients' biological age, and not chronological age, should be individually determined to assess feasibility of major surgery. Optimal patient selection requires a thorough pre-operative assessment, including analysis of comorbidity in all patients
Goh et al.[43]	2017	234	60 patients ≥65 years 174 patients <65 years	Retrospective study	Multiple	Age alone, tobacco use and preoperative radiation treatment did not independently increase the risk of postoperative complications.	No	Advanced age itself does not predict poor outcome following head and neck free flap reconstruction

L´Esperance et al.[44]	2017	219 patients ≥80 years	Retrospective study	Multiple	74 patients experienced serious complications within 30 days and 25 died within 90 days of surgery.	Adult Comorbidity Evaluation-27 index	Patient and surgical factors predict risk of serious complications and mortality in patients aged 80 years and older undergoing ablative head and neck surgery. ASA score ≥4, and surgeries longer than 6 hours are associated with increased risk of serious complications. Age ≥90 years, severe comorbid disease, presence of dysphagia, and large resections are associated with increased 90-day mortality
Wu et al.[45]	2018	637 patients >65 years	Retrospective study	Multiple	Age not predictive of complications or mortality. Flap reconstruction	No	The treatment choice for elderly patients with HNSCC should be based on medical

	surgery had no significant association with necrosis, hemorrhage, infection, need for rescue treatment, or length of intensive care unit stay.	assessments but not on age. Age is not a risk factor for surgical treatment or flap reconstruction

Table 4: Multimodal Therapy of HNSCC

Author [Ref]	Year	Cohort		Type of study	Type of treatment	Primary tumor site	Adverse events	Geriatric, quality of life and functional assessments	Conclusions
Barzan et al.[46]	1990	438	196 patients ≤59 years 135 patients: 60-69 years 107 patients ≥70 years	Retrospective study	Surgery/CT/ RT	Multiple	The percentage of local and general post-operative complications were similar in the three ages groups	No	Age is not an independent prognostic factor for local control and survival
Lusinchi et al.[47]	1990	331 patients >70 years		Retrospective study	Surgery/RT	Multiple	No differences	No	No differences in survival nor toxicity. No significant relationship between age, general status, and the carcinologic

									outcome could be observed
Hirano et al.[48]	1998	679	560 patients <75 years 119 patients ≥75 years	Retrospective study	Surgery/RT	Multiple	Concomitant health problems were significantly more common in the older group	No	The frequency with which curative treatment could not be executed was 8.8% in the younger group and 26.1% in the older group
Sarini et al.[49]	2001	4610 (273 patients ≥75 years)		Retrospective study	Surgery/RT/ CT/CRT	Multiple	No significantly more treatment related deaths in elderly	No	HNSCC in elderly patients did not have a significantly different outcome when compared with younger patients. When properly monitored, therapies according to guidelines are feasible in older patients

Vaccher et al.[50]	2002	2143	1962 patients <75 years 181 patients ≥75 years	Retrospective study	Surgery/RT/ CT/CRT	Multiple	NA	No	Chronological age may be an unreliable parameter for decision making. Cancer-specific overall survival of elderly with laryngeal and hypopharyngeal carcinoma was significantly poorer than in younger.
Bhattacharyya[51]	2003	5016	2508 patients ≥70 years 2508 patients <70 years	Matched controlled study on SEER database	Surgery/RT	Multiple	NA	No	Overall Survival and Disease Specific Survival are significantly worse in elderly tongue and glottis laryngeal cancer and not different in tonsil cancer. However, survival does not differ after stage stratification
Airoldi et	2004	40 patients >70		Prospective	CRT	Multiple	Grade 3 toxicity	No	The results of

al.[52]			years		study			included mucositis (10 patients), neutropenia (6 patients), dermatitis (2 patients), and thrombocytopenia (1 patient)		adjuvant CRT were better than those observed in a comparable group treated with RT alone and were like those observed in a younger group with the same poor prognostic factors treated with adjuvant carboplatin plus RT
Derks et al.[53]	2005	183	105 patients:45-60 years 78 patients ≥70 years	Prospective stydy	Surgery/RT/CRT	Multiple		NA	EORTC QLQ-C30, H&N35, CES-D, RSS12-I, QQ	Non-standard treatment is predicted by: marital status (widowed), advanced tumor stage, comorbidity, less pain, considering the length of life less important than its quality and old age

van den Broek et al.[54]	2006	125	Prospective study	CRT	Multiple	Severe acute toxicity (grade 3-4), mainly mucositis and dysphagia was recorded in 51% of patients. Leukopenia (grade 3-4, 39%) and aspiration pneumonia in 20%. Tracheotomy (12%). Neurological complications (2%) patients. Severe late toxicity (34%)	No	A statistically significant, association was observed with advanced age and severe xerostomia, p = 0.004. Older patients were more likely to developing xerostomia, ascompared to younger patients
Sanabria et al.[15]	2007	312 patients ≥70 years	Retrospective study	Surgery/RT/ CRT	Multiple	NA	Adult Comorbidity Evaluation-27 index	Selecting substandard treatment for reasons such as chronologic age, tumor site, or moderate or mild comorbidities worsen patient prognosis

Sanabria et al.[55]	2007	310 patients >70 years		Retrospective study	Surgery/RT/ CRT	Multiple	NA	Adult Comorbidity Evaluation-27 index	Comorbidity measured with ACE-27 was a prognostic factor for overall survival in patients older than 70 years with HNSCC
Koussis et al.[56]	2008	35	16 patients ≥70 years	Phase II study	CRT	Multiple	Haematological toxicity was grade 3-4 in 13 patients, while gastrointestinal toxicity was grade 3-4 in 20 patients	No	The regimen of neo-adjuvant carboplatin and vinorelbine followed by CRT is feasible and active in older (> or =70 years) or low performance status (Karnofsky 70-80) patients, although toxicity is not negligible and long-term outcome remains poor
			19 patients <70 years						
Machtay et al.[57]	2008	230	27 patients	Secondary analysis	CRT	Multiple	Severe late toxicity was	No	Older age, advanced T-

			>70 years 203 patients ≤70years				related with advanced age		stage, and larynx / hypopharynx primary site were strong independent risk factors
Palazzi et al.[58]	2008	149		Prospective study	RT/CRT	Multiple	Severe (Grade 3-4) adverse events were recorded in 28% (mucositis), 33% (dysphagia), 40% (pain), and 12% (skin) of patients	No	CT is the most relevant factor independently predicting for worse toxicity (mucositis, dysphagia, weight loss, salivary changes). RT acceleration and older age predicted for a worse outcome of weight loss.
Fesinmeyer et al.[59]	2009	5086 patients ≥66 years		Retrospective study of SEER database	Surgery/RT/ CRT	Multiple	NA	Charlson score	Surgery before RT is associated with an increased likelihood of completing RT. At a subset of

									sites (oral cavity, pharynx and larynx) CT is associated with a decreased likelihood of completing RT
Tsukuda et al.[60]	2009	50	13 patients >75 years 37 patients <75 years	Prospective study	CRT	Multiple	Grade 3 mucositis occurred in 20% of the patients. Grade 3 neutropenia occurred in 12% and leukocytopenia occurred in 6% of the cases	No	Concurrent CRT is a safe, well-tolerated and effective regimen for locally advanced HNSCC in elderly cases and/or cases with comorbidity
Boscolo-Rizzo et al.[61]	2011	44 patients >65 years		Retrospective study	Surgery/CRT	Multiple	66% developed severe toxicities, 11% required permanent feeding tubes	No	In selected medically fit elderly patients with loco-regionally advanced HNSCC, cis-platinum-based CRT can be successfully applied, with

									moderate adverse events, in attempt to preserve a functional upper aerodigestive tract
Huang et al.[62]	2011	2312	452 patients ≥75 years 1860 patients <75 years	Retrospective study	Surgery/RT/ CT	Multiple	No differences	No	Differences in survival (2-year cancer-specific survival: 72% for patients ≥75 years; 86% for patients<75 years; p<.01). Elderly patients selected for definitive RT or intensified RT showed no evidence of impaired treatment tolerance
Peters et al.[63]	2011	126	84 patients ≤64 years	Retrospective study	Surgery/RT	Pharynx	Complication rate was not significantly different. Only	Adult Comorbidity Evaluation-27 index	No evidence has been found to treat elderly pharyngeal

			42 patients ≥75 years				stage was significant independent predictor of complications		cancer patients differently than younger ones
Peters et al.[64]	2011	428	139 patients ≥75 years	Retrospective study	Surgery/RT	Larynx	Co-morbidity and age were not predictors of complications. Radiation therapy (vs. total laryngectomy) and tumor stage were predictors. There was correlation between co-morbidity and complication, but not in the elderly group	Adult Comorbidity Evaluation-27 index	There is no reason to treat elderly laryngeal cancer patients differently from guidelines
			289 patients ≤65 years						
Jilani et al.[65]	2012	73 patients ≥65 years		Retrospective study	RT/CRT	Multiple	Most common toxicities included dermatitis, mucositis, dysphagia and xerostomia. Three patients developed grade 4 (4%)	No	Elderly patients have a high response rates to RT with excellent local control and limited toxicity

							toxicities including fistula, esophageal stricture, tracheostomy dependence		
Michal et al.[66]	2012	181	44 patients ≥70 years 137 patients <70 years	Retrospective study	CRT	Multiple	The elderly was less likely to receive both CT courses, experienced more myelosuppression, required more unplanned hospitalization, and were feeding-tube dependent longer	No	Outcomes were the same as in younger patients. Age alone should not be considered a contraindication to aggressive CRT for this disease
Merlano et al.[67]	2012	317	93 patients ≥65 years 224 patients <65 years	Retrospective study	CRT/BRT	Multiple	Infections (p=0.011) and pneumonias (p=0.002) were significantly more represented in elderly patients	ECOG performance status	Age alone does not justify exclusion from treatment

Nguyen et al.[68]	2012	112	27 patients ≥70 years 85 patients <70 years	Retrospective study	CRT	Multiple	No differences in grade 3-4 toxicity, weight loss and treatment breaks	No	No significant differences in protocol schedule violations and survival were found between the two groups
Maggiore et al.[69]	2013	89 patients ≥70 years		Retrospective study	CRT	Multiple	The majority (86.5%) could complete all planned treatment cycles. A significant proportion of patients required gastrostomy tube (62%) and developed aspiration during swallowing evaluation post-treatment (44%). Several patients required hospice (9%) or skilled	No	Older patients have lower 5-year survival rates than younger and with higher risk for acute toxicities

						nursing facility (13%) referrals during treatment		
Camilon et al.[70]	2014	14909 (4406 patients ≥65years)	Retrospective study on SEER database	Surgery/Rt/ CRT	Orophary nx	NA	No	Proportionally fewer elderly patients with oropharyngeal cancer receive treatment (surgery, RT, or CRT) than younger individuals. These patients can have significant benefits from aggressive treatments despite their older age as shown by the survival analysis
O´Neill et al.[71]	2014	759 patients ≥66 years	Retrospective study on SEER database	Surgery/ CRT	Larynx	Almost 20% of the CRT patients had a tracheostomy following	No	Total laryngectomy remains an important treatment option

							treatment, and 57% had a feeding tube		in well selected older patients
Shapiro et al.[72]	2014	360	317 patients <71 years 43 patients ≥71 years	Retrospective study	CRT	Multiple	Age over 70 and pre-treatment tracheostomy also correlated with a significantly higher rate of late toxicity	No	Concurrent IMRT and platinum-based chemotherapy resulted in significantly superior overall survival than cetuximab
Sharma et al.[73]	2014	47 patients ≥65 years		Retrospective study	Surgery/RT/ CRT	Multiple	NA	No	Nearly two-thirds of elderly HNSCC patients were compliant to cancer-directed therapy
VanderWalde et al.[74]	2014	10599 patients ≥66 years		Retrospective study on SEER database	CRT/RT	Multiple	NA	No	The addition of CT to RT may be less effective in an older patient population treated outside of a controlled trial setting

Chang et al.[75]	2015	126	21 patients >65 years 105 patients ≤65 years	Retrospective study	CRT	Multiple	Elderly were less likely to tolerate cisplatin, experienced more weight loss, required more feeding tube support and tended to have >grade 3 hematological toxicities and to develop sepsis during the period of CRT	No	1- and 2-year disease-free survival and disease-specific survival rates were nearly identical. With an intensive nutritional support program, age alone should not be considered a contraindication to aggressive CRT for advanced head and neck cancer
Kataria et al.[76]	2015	32 patients ≥65 years		Prospective study	CRT	Multiple	Fourteen (45.2%) patients experienced grade 3 mucositis. No one developed grade 3 or above hematological toxicity	No	CRT in elderly patients with IMRT is a feasible option

Moye et al.[77]	2015	1598	1166 patients <70 years 281 patients ≥70 years	Retrospective study	Surgery/RT/ CRT/CT	Multiple	NA	No	Older patients receiving stage-appropriate treatment had oncologic outcomes equivalent to those of their younger counterparts
O´Neill et al.[78]	2015	1502 patients ≥66 years		Retrospective study on SEER database	CRT/RT	Multiple	Patients receiving CRT had more acute toxicities and prolonged use of feeding tubes	No	For certain older patients, the potential benefit of adding CT to RT does not outweigh the harm of combined modality therapy
Sachdev et al.[79]	2015	100		Retrospective study	RT/CRT	Multiple	NA	No	Older age was found to be the most significant risk factor for needing enteral feeding in patients with locally advanced HNSCC treated

								with multimodal treatment
Amini et al.[80]	2016	4042 patients >70 years	Retrospective study on NCDB	RT/CRT	Multiple	NA	Charlson-Deyo score	Patients older than 70 years should not be denied concurrent CT solely on the basis of age; additional factors, including the performance status and the tumor stage, should be taken into account
Baxi et al.[81]	2016	3705 patients ≥65 years	Retrospective study on SEER database	Surgery/RT/ CRT	Multiple	NA	No	The use of CRT has increased substantially from 2001 to 2009 and cetuximab may have increased CRT use, especially in older and sicker patients

Chalissery et al.[82]	2016	47 patients ≥65 years	Prospective study	CRT	Multiple	Grade III skin reaction and mucositis in 24% and 47% respectively. No grade III neutropenia observed.	No	Radical CRT with IMRT in elderly patients is a feasible option
Chen et al.[83]	2016	2257(523 patients ≥70 years)	Retrospective study on NCDB	Surgery/RT	Oral cavity and oropharynx	NA	Charlson-Deyo score	Postoperative RT may be associated with improved survival in patients with pN1 oral cavity and oropharyngeal cancer, especially in those younger than 70 years or those with pT2 disease
Doi et al.[84]	2016	14 patients ≥75 years	Retrospective study	CRT	Paranasal	Grade 3 mucositis in 3 patients.	No	>60 Gy of RT in IMRT led to improved survival outcomes in

								elderly paranasal sinus carcinoma patients
Kwon et al.[85]	2016	165 patients ≥65 years	Prospective study	Surgery/CT/ RT/CRT	Multiple	Respiratory complications such as aspiration pneumonia or dyspnea were the most common reasons for hospitalization, and dysphagia was another major cause of severe post-treatment morbidity	Charlson comorbidity index, ECOG score, BDI-II	Pretreatment functional disabilities related to respiration and swallowing were significantly associated with early morbidity and mortality
Neve et al.[86]	2016	35 patients ≥65 years	Prospective study	Surgery/RT/ CRT	Multiple	NA	G8 score	There was a trend towards longer postoperative stay and lower RT completion rates in patients deemed vulnerable by Geriatric 8 scores

Teymoortash et al.[87]	2016	58	28 patients <65 years	Retrospective study	Surgery/RT/ CRT/CT	Larynx	Surgical complication rate was significantly increased in elderly (p = 0.04)	Charlson comorbidity index, Clavien-Dindo Classification	Locoregional and distant control did not significantly differ by age. Disease-free and overall survival showed no significant differences for the two age groups by the Kaplan-Meier analysis (p = 0.66 and 0.08, respectively)
			30 patients ≥65 years						
Ward et al.[88]	2016	4165 patients ≥71 years		Retrospective study on NCDB	RT/CRT	Multiple	NA	No	A threshold age eliminating the need for systemic therapy could not be identified, and the decision to administer systemic therapy should be patient-specific
Falk et al.[89]	2017	35 patients ≥70 years		Retrospective study	CRT	Multiple	RT was interrupted in 94%	No	Concomitant RT and cetuximab

							of patients and the dose of cetuximab was reduced in 29%.		seem to be an effective therapy in the elderly population
Lai et al.[90]	2017	70 patients ≥75 years		Retrospective study	CRT/RT	Multiple	CRT group had more adverse events such as neutropenia, febrile neutropenia and thrombocytopenia than RT group.	No	Definitive RT with or without systemic CT did not significantly influence disease-specific survival and overall survival in elderly patients. Therefore, for elderly patients aged ≥75 years, conservative RT might be sufficient for treatment purposes
Juarez et al.[91]	2017	421 patients >50 years	118 patients: 50-59 years 152 patients:	Retrospective study	Surgery/CRT/RT	Multiple	NA	No	Patients aged ≥70 years were more commonly treated with less-aggressive strategies,

		60-69 years 151 patients: ≥70 years						including RT alone
Pollom et al.[92]	2017	25829 (7823 patients >70 years)	Retrospective study on NCDB	Surgery/CRT/RT	Oral cavity	NA	No	Greater patient distance from reporting facility, in addition to older age, was associated with lower odds of receiving both adjuvant RT and adjuvant CRT. Elderly patients were disproportionally offered less aggressive treatment
Sommers et al.[93]	2017	674 (168 patients ≥ 70 years)	Retrospective analysis of prospectively collected data	RT/CRT	Multiple	NA	WHO performance status	Elderly HNSCC patients have poorer survival outcomes than younger patients. Age is an independent

								prognostic factor for overall survival, mainly due to an increase in non-cancer-related mortality and comorbid diseases
Spiotto et al.[94]	2017	6900 (1541 patients >70 years)	Retrospective study on NCDB	Surgery/RT/ CRT	Oral cavity	NA	No	On multivariate analysis, worse survival was associated with increasing age
Zumsteg et al.[95]	2017	74 patients ≥70 years	Retrospective study	CRT	Orophary nx	RT interruptions of > 1 day were needed in 4% of patients receiving cisplatin, 20% of patients receiving CARB, and 15% of patients receiving cetuximab (P = .19). Unplanned hospitalizations	Charlson Comorbidity Index	Toxicity from concomitant CRT remains a challenge for older adults. No evidence that this toxicity was mitigated by treatment with cetuximab. Nevertheless, a subset of patients aged ≥70 years

						during CRT occurred in 25%, 55%, and 58%, respectively, of patients receiving cisplatin, CARB, and cetuximab (P = .03). There were 2 treatment-related deaths, both of which occurred among the patients who were treated with cetuximab		appear to tolerate cisplatin-based treatment with acceptable toxicity and survival rate
Yoshida et al.[96]	2018	1199 patients ≥70 years	Retrospective study on NCDB	Surgery/RT/ CRT	Multiple	NA	Charlson-Deyo comorbidity	CRT improved survival in N2 or N3 disease but not in earlier stage disease

CARB: Carboplatin with either 5-fluorouracil or paclitaxel. EORTC QLQ-C30 and H&N35: European Organisation for Research and Treatment of Cancer. Head and Neck Cancer Quality of Life Questionnaire. CES-D: Centre for Epidemiological Studies Depression Scale. RSS12-I: Social Support List-Interactions. QQ: Quality-Quantity questionnaire. BRT: Bioradiotherapy. SEER: Surveillance, Epidemiology and End Results program. NCDB: National Cancer Data Base. BDI-II: Beck Depression Inventory.