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Review

Squamous cell carcinoma of the head and neck in the elderly

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ABSTRACT

The incidence of head and neck squamous cell carcinoma (HNSCC) peaks between the fifth and seventh decades of life. With prolongation of life expectancy, however, the proportion of elderly HNSCC patients is also increasing, which makes HNSCC in this life period an important issue for healthcare providers. With features characteristic to the older patient groups coupled with the inherent complexity of the disease, HNSCC in the elderly represents a considerable challenge to clinicians. Indeed, to expedite the progress and improve the healthcare system to meet the needs of this unique population of patients, several essential issues related to the clinical profile, diagnostics, optimal treatment and support are of concern and should be addressed in properly conducted clinical trials.

In the present review, we analyzed a literature series comparing different age groups with regard to their clinical characteristics, therapy, outcome and quality of life in an attempt to determine their implications on treatment-decision-making for elderly patients with HNSCC.

1. Background

The population in developed countries is aging rapidly, which is associated with a significant increase in the total cancer burden over the last decades and, specifically, also with an increase in the incidence of the head and neck squamous cell carcinoma (HNSCC) after 50 years of age[1,2] (Table 1). Although the age of most of the HNSCC patients ranges between 50 and 70 years, the occurrence of this tumor type in older patients is not rare. Muir et al. estimated that as many as 24% of the HNSCCs are found in patients older than 70 years,[3] whereas Sikora reported for the period 1992–1999, establishing that patients >74 years of age made up 19.5% of new cases in the SEER database.[1] In Slovenia, the Cancer Registry data has shown a continuous increase in the percentage of new HNSCC cases diagnosed in the age group of ≥70 years: 17.9% in 1981–1990; 16.5% in 1991–2000; and 22.3% in 2001–2008[2] (Table 1).

2. Aim

The aim of this review is to present the characteristics of HNSCC in the elderly and to describe their implications on treatment-decision-making.

3. Who is actually old?

The medical literature provides no clear definition of an elderly person. According to the National Institute on Aging and the National Institutes of Health, elderly persons can be classified into three categories: young old – aged 65–75; old – aged 76–85; and oldest old – older than 85 years.[4] However,

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Table 1 – Incidence trends of the head and neck squamous cell carcinoma in Slovenia, 1981–2008.

HNSCC[a]	1981–1990	1991–2000	2001–2008
All, per 100,000	19.3	21.3	21.4
≥50 years, %	81.5	79.1	83.3
≥70 years, %	17.9	16.5	22.3
≥75 years, %	9.5	8.3	12.2

HNSCC, head and neck squamous cell carcinoma.
[a] Primary tumor sites included: C00-C14, C32.

most studies use the age of 70 years or 75 years as a cut-off point[5–9] (Table 2).

Because aging is a highly individualized process and the elderly population is very heterogeneous, chronological age alone is an inappropriate parameter for treatment selection. More important is functional age, which should be defined individually for each patient based on the functional status, comorbidities and presence of geriatric syndromes.[10,11]

Several authors concluded that traditional oncology measures of functional status alone (e.g. Karnofsky performance status score) do not appear to reflect the comorbidity burden and its prognostic potential in elderly patients. A long-lasting history of tobacco and alcohol abuse that is characteristic for a substantial proportion of HNSCC patients, an advanced age per se, and the history of other factors or events increase the probability for severe comorbidity. According to a literature review by Paleri et al., the prevalence of comorbidity in the general population of HNSCC patients is approximately 60%, whereas the rate of moderate and severe comorbid burden is in the range of 20%.[12] As may be expected, these figures rise with age, impacting the prognosis of the patients significantly and independently from other factors. In the study of Sanabria et al. conducted among 310 HNSCC patients aged over 70 years, 75.1% had at least one comorbid illness, which was assessed as severe in 13.9% of these patients.[13] In another study, the figures reported by Peters et al. for a group of 139 laryngeal carcinoma patients aged ≥75 years were 80% and 7%, respectively.[14]

In older patients with cancer, a full onco-geriatric evaluation is warranted prior to any treatment-decision-making to avoid overlooking any relevant information about the ability of an older patient to cope with the proposed treatment. This assessment is probably the most critical step, as its results have a profound effects on all down-stream decisions (i.e. the aim of treatment – palliation vs. curative, the extent of diagnostics and mode(s) of therapy employed) and, thus, also on the prognosis. Numerous tools have been developed for a comprehensive assessment of older patients and the best example seems to be the Comprehensive Geriatric Assessment (CGA) (Fig. 1).[11,15,16] Unlike other evaluation instruments, which are mostly focused on some specific issues, the CGA uses standardized instruments to employ a multidimensional and interdisciplinary approach. The CGA encompasses a spectrum of important clinical domains, namely an evaluation of different aspects of patient functioning, comorbidity, polypharmacy, nutritional status, cognitive function, socioeconomic issues and geriatric syndromes, thus allowing for the identification of patient groups with different frailty levels and selection of the appropriate therapeutic strategy.[11,15,16] Chaibi et al. reported on the results of the CGA of 161 patients aged 73–97 years with different types of cancer. After the CGA, geriatric intervention was proposed for 76% of patients and the initial proposed anti-cancer treatment was changed in 49% of cases.[17] A report provided by the Curie Institute showed that the treatment plan was modified in 38.7% of 93 cancer patients after this assessment.[18] Recently, a phase II prospective study has demonstrated that a CGA-based stratification of elderly cancer patients is also of predictive value. It was found to be a useful and cost-effective tool for an appropriate assignment of patients to different treatment programs to achieve an optimal balance between the effectiveness and toxicity of the proposed therapy.[19]

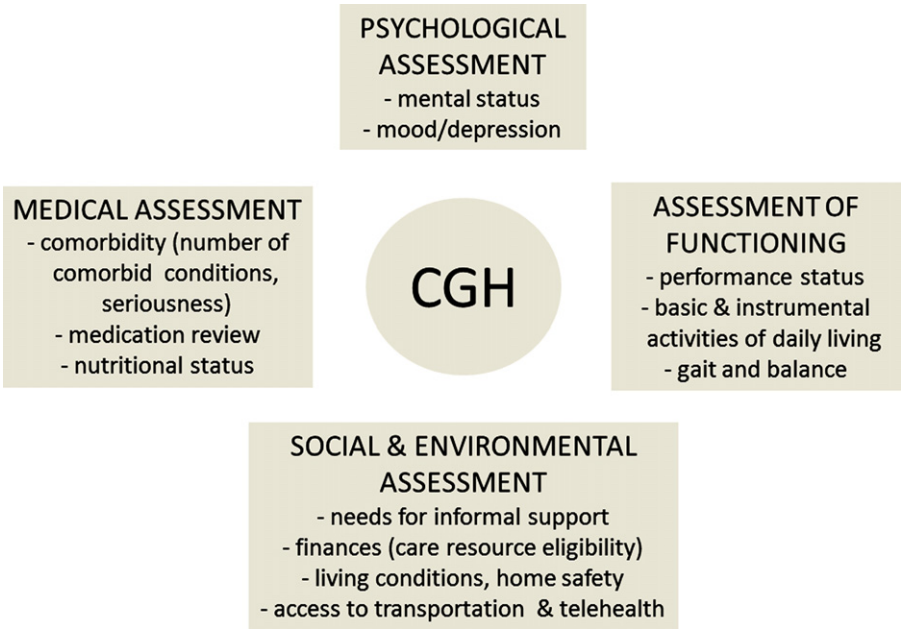

Fig. 1 – Comprehensive Geriatric Assessment – CGA.

Table 2 – Clinical characteristics of HNSCC: comparison between elderly patients and younger age groups (only studies on different primary tumor sites and with >100 patients included in the elderly study group are presented).

Author (year)[Ref.]	Time span	N	M:F ratio	Primary tumor site, %	Stage, %	Treatment, %	Outcome, %	New PTs, %
Barzan et al. (1990)[5]	1981–1984	438		OC vs. OPh vs. HPh vs. Lx vs. others	I vs. II vs. III vs. IV	S/contraindications for S	5-Year OS[a,b]	
<70 years		331	8.9:1	13 vs. 26 vs. 13 vs. 38 vs. 10	22 vs. 18 vs. 25 vs. 35	78/9	86	27
≥70 years		107	7.9:1	16 vs. 22 vs. 6 vs. 37 vs. 19	29 vs. 20 vs. 21 vs. 31	57/23	83	28
Sarini et al. (2001)[6]	1974–1983	4610		OC vs. OPh vs. HPh vs. Lx	I + II vs. III + IV/N0/M1	S_T vs. S_N vs. S + RT vs. RT + ChT vs. ChT	5-Year OS[c]	
<75 years		4337	25:1	33.8 vs. 29.4 vs. 14.5 vs. 22.3	29.8 vs. 37/52.1/2.8	27.4 vs. 35.6 vs. 22.3 vs. 14.1 vs. 17.6	25.1	17.5
≥75 years		273	0.2:1	39.9. vs. 26.7 vs. 8.8 vs. 24.6	31.1 vs. 37.9/59.7/0.7	13.9 vs. 15.4 vs. 9.7 vs. 0.2 vs. 5.5	16.5	8
Vaccher et al. (2002)[7]	1975–1998	2143		OC vs. OPh vs. HPh vs. Lx	I + II vs. III + IV/T3 + 4/N0/M1	Curative vs. palliative/S + RT vs. RT + ChT	5-Year OS[c]/CSS[b]	
<75 years		1962	10.3:1	28 vs. 19 vs. 13 vs. 39 vs.	39 vs. 16/41/54/2	71 vs. 21/29 vs. 10	44/59	n.r.
≥75 years		181	7.2:1	23 vs. 17 vs. 10 vs. 49	52 vs. 47/39/72/2	69 vs. 31 vs. 11 vs. 6	31/55	n.r.
Derks et al. (2005)[8]	1998–2001	266		OC vs. Ph vs. Lx	II vs. III vs. IV	Standard vs. w/o TH	5-Year OS[b,d]	
45–60 years		148	2.6:1	38 vs. 52 vs.10	18 vs. 20 vs. 63	89 vs. 4	38%	n.r.
≥70 years		118	1.6:1	49 vs. 26 vs. 25	25 vs. 26 vs. 48	62 vs. 14	32%	n.r.
Huang et al. (2011)[9]	2003–2007	2312		OC vs. OPh vs. HPh vs. Lx	0–II vs. III + IV/T3 + 4/N0	Curative vs. palliative vs. w/o TH	5-Year CSS[c,e]	
<75 years		1860	2.7:1	19 vs. 26 vs. 5 vs. 21	30 vs. 64/43/42	93 vs. 5 vs. 2	75.4	n.r.
≥75 years		452	1.8:1	25 vs. 15 vs. 7 vs. 30	35 vs. 57/47/56	79 vs. 10 vs. 11	64.9	n.r.

Ref., reference; N, number of patients; M, male; F, female; PT, primary tumor; OC, oral cavity; OPh, oropharynx; HPh, hypopharynx; Lx, larynx; S, surgery; OS, overall survival; S_T, surgery for the primary; S_N, surgery for the neck; RT, radiotherapy; ChT, chemotherapy; CSS, cause-specific survival; Ph, pharynx (oro- and hypo-); n.r., not reported; w/o TH, without therapy.

[a] Estimated from the Fig. 2 in the Ref. 5.

[b] $P > 0.05$.

[c] $P < 0.05$.

[d] Estimated from Ref. 32, Fig. 1.

[e] For patients who received definitive radiotherapy ($N = 1487$).

Table 3 – Head and neck squamous cell carcinoma in the elderly: clinical profile.

Parameter	In elderly[a]
Sex ratio	Females > males
History of tobacco and alcohol abuse	↓
New primary tumors	↓
Primary tumor site	Oral cavity and/or larynx, ↑ Hypopharynx, ↓
Disease stage	T-stage, ↓ or comparable N-stage, ↓
Survival (overall)	↓ or comparable
HPV-status	↓

↓, less frequent; ↑, more frequent; HPV, human papillomavirus.
[a] Compared to younger age groups.

While the CGA can be extremely helpful for physicians dealing with elderly cancer patients, its value has not been assessed specifically for HNSCC. Moreover, the CGA is time-consuming and, consequently, impractical for a routine clinical use. Shortened forms of CGA were proposed, although their validation in a routine clinical setting is needed.[11,19,20]

4. Clinical profile of HNSCC in the elderly

There are features distinctive for HNSCC patients of older age groups (Table 3). First of all, in the elderly, there is a significantly higher proportion of female patients compared to the younger population[21] (Table 2). The reason for this is most probably longer life expectancy among females. In addition, a history of alcohol abuse and smoking is less frequently reported in the advanced age groups than in the general population of HNSCC patients. In the latter, the prevalence of tobacco and alcohol consumption is over 70%,[22,23] whereas among elderly patients it is in the range of 40%.[21,24–26] The same was reported by Barzan et al. for life-style related diseases (e.g. chronic hepatitis, gastric and duodenal ulcer; 41% vs. 33%).[5] This observation supports the theory that age alone is a risk factor for HNSCC: the presence of risk factors resulted in an earlier occurrence of malignancy, although it may also appear spontaneously in patients who have not been exposed to any of these factors as time passes. The possible mechanism for age-related cancer is the accumulation of mutations: the efficiency of DNA repair mechanisms may decrease with age, as may that of the immune system, resulting in a reduced immune surveillance against cancer cells. Due to a shorter life expectancy after the completion of treatment, the occurrence of secondary cancers is lower in elderly HNSCC patients as compared with their younger counterparts,[6] although the opposite has also been reported in the literature.[24]

The most prevalent primary tumor sites in the head and neck region in elderly patients seem to be – depending on the series – the oral cavity or the larynx, each comprising up to one half of all primaries, with the tendency to overcome their incidence among younger-aged patients. A trend of fewer hypopharyngeal cancer cases in the elderly patient group was also observed (Table 2).[21,24] Considering the tumor stage at presentation, it appears that the occurrence of an advanced disease (T3, T4) at the primary site is comparable to or even reduced when matched with that observed in younger age groups, but the regional lymphatics are primarily less frequently infiltrated by cancer cells in older patients (Table 2). Apparently, an increase in the disease severity that would be expected from the usual delay in diagnosis in older people, probably reflecting age-related inequalities in access to health care due to a variety of social and behavioral factors,[27] is successfully compensated by a less aggressive biology of the disease in the elderly.[28]

There is no specific data on the role of the human papillomavirus (HPV) in the HNSCC carcinogenesis of elderly patients. However, summarizing the results from the published studies that describe the HPV-positivity status in the general population with HNSCC, it appears that HPV is not an important factor or has only marginal significance in the etiology of HNSCC in elderly patients. Among other, the HPV tumor positivity is typically associated with a clinical profile of a middle-aged white male having a higher socioeconomic status and the oropharyngeal origin of the primary but no or only low smoking history.[29]

5. Treatment concepts for the elderly

The cornerstones in the treatment of patients with HNSCC are surgery and radiotherapy (RT), often given in combination with one another and additionally intensified with chemotherapy (ChT), recently also with targeted therapy agents. Over the last decades, the treatment protocols for HNSCC have become more complex and aggressive with the implementation of larger surgical resections requiring reconstructions and a high-dose RT that employs altered fractionation regimens and is administered in different combinations with systemic agents.

In several studies, age alone was found to be an important factor for treatment selection. When compared with the younger population with HNSCC, it was observed that elderly patients are less likely to receive standard or curative treatment (Table 2). As reported by Derks et al., after subdividing the elderly group into two sets (aged 70–79 years and ≥80 years), the proportions of patients receiving standard treatment in the 45–60 years group and the other two groups were 89%, 75% and 36%, respectively, whereas no treatment was given to 4%, 13% and 18% of cases from the respective groups.[8] Age itself was listed specifically as a reason for not undergoing the indicated therapy (surgery, RT or ChT) in the study by Italiano et al.[30] To continue, according to Ortholan et al., as much as 59% of 200 patients aged ≥80 years and treated with curative intent (surgery and/or RT) received aged-adapted curative treatment.[25]

On the other hand, many studies showed that standard treatment with curative intent can be safely performed in elderly patients with a good performance status and without severe comorbidities. Huang et al. reported no differences in respect to unplanned RT interruptions, premature termination of the RT regimen or treatment-related deaths between younger (aged <75 years) and older (aged ≥75 years) patients on definitive RT.[9] Analyzing the data of 1307 patients included in the EORTC trials with RT, Pignon et al. found that the age profiles of patients with and without toxicity were similar, and neither locoregional control nor

survival were affected by age.[31] A similar observation regarding treatment-related complications was described in several surgical series and for systemic therapy.[5,32–35] As reported by Peters et al., age was not recognized as an independent prognosticator for treatment-related complications in a group of 428 patients (aged ≥75 years, 32%) with laryngeal cancer after curative RT or surgery,[14] as was the case in the study by Milet et al. involving 261 patients (aged ≥70 years, 11%) with different primaries treated with upfront surgery.[21]

Anyhow, elderly patients are underrepresented in non-age-related clinical trials, and there is no sufficient data from high-quality phase III studies to guide the treatment decision-making process for these patients. As outlined above, a comprehensive oncogeriatric initial assessment of their functional status and psychological profile is crucial for the selection of the most appropriate therapy or treatment combinations for the individual patient. Age alone should not be used as a criterion to limit therapy. However, only elderly patients in a good general condition following the initial assessment should be considered candidates for curative interventions. Bearing in mind that treatment could be harmful, adequate supportive care must be provided in order to improve patients' compliance.

In the following sections, the main treatment modalities used in HNSCC are discussed within the context of their relevance to elderly patients.

5.1. *Surgery*

The first studies on aggressive surgical management of HNSCC in elderly patients with a favorable outcome date back to the 1970s and 1980s. Mortality rates reported in these studies were 3.5% (aged >65 years) and 7.4% (aged >70 years) for elderly patients vs. 0.8% and 1.4% for younger patients.[36,37] The authors urged that advanced age alone should not be a deterrent to performing aggressive surgical therapy for HNSCC; careful preoperative evaluation of comorbidity and skillful perioperative and postoperative management are mandatory. The same conclusion was reached later by Clayman et al., who reviewed the results of individualized surgical management in a group of 43 HNSCC patients aged 80 years and older.[38] Comparison was made with patients younger than 65 years. Although the elderly patients had a higher frequency of chronic diseases, complication rates were comparable (23.2% vs. 20.2% for major; 27.7% vs. 22.6% for minor complications). The elderly were more likely to have systemic, i.e. pulmonary and cardiovascular complications, whereas younger patients more frequently experienced local complications. There was one postoperative death in the whole series, which occurred in the group of elderly patients. Advanced age seemed to have adversely affected local control, disease-specific survival and overall survival. However, when compared with actuarial survival for the general population of the same age group, the overall survival rates of elderly patients were similar. Results of other smaller series support these observations.[31,39]

Reconstructive surgery using microvascular free tissue transfer was also found to be feasible and safe in elderly patients, but a higher incidence of perioperative complications, especially medical, was observed, which can be attributed mainly to a higher prevalence of comorbidity among older patients.[40–45]

Obviously, elderly patients have a higher perioperative morbidity and mortality rates due to underlying coexisting illnesses and often a poor performance status. Careful perioperative management is essential in order to reduce the incidence of perioperative complications. Other important parameters of concern when planning a major head and neck surgery in elderly patients were identified as follows: male gender (did worse), duration of the operative procedure and extent of the procedure, which could be assessed through disease stage or the need for, e.g. bilateral neck dissection or reconstruction surgery.[31,39,46] One option to minimize the operative time is to adapt the surgical procedure by omitting either reconstruction or (extensive) neck dissection. However, both approaches must be weighed against the expected functional and cosmetic outcome and the likelihood to achieve a complete removal of the tumor. Definitive RT as an alternative to major surgery in high-risk patients should also be considered.

5.2. *Radiotherapy*

Preclinical studies evaluating the in vitro radiosensitivity of human cells failed to show any age-associated differences.[47] In the clinical setting, Pignon et al. reached the same conclusion. The authors reviewed acute and late toxicity in 1589 patients with HNSCC treated with RT alone, 26% of whom were over 65 years old, enrolled in five EORTC phase III trials.[31] The locoregional control and overall survival were comparable across different age groups, which was also the case for objective mucosal reactions and weight loss. There was a statistical difference in the distribution of functional mucosal reactions (i.e. symptoms as experienced by the patient, directly related to pain due to mucositis) with regard to age; this difference existed for grade 3 and 4 side effects but not for grade 1 or 2 toxicities, which were more frequent in older age groups. However, after adjusting for the WHO performance status (elderly patients scored significantly higher), the occurrence of objective and functional mucosal reactions was quite similar for all patients. The observed discrepancy in the distribution of acute mucosal damage, which was independent of age, and severe age-dependent functional reactions pointed to a decreased tolerance for acute toxicity in the elderly. The occurrence of late toxicity was independent of age. This study clearly demonstrated that the effectiveness and toxicity of RT were similar for all patients; as older patients tolerate less acute toxicity compared to the younger ones, an appropriate selection of patients for radical and palliative RT regimens is of utmost importance.

Other retrospective studies have also confirmed that, considering the ultimate outcome of treatment with RT and the related toxicity, elderly patients are comparable to their younger counterparts. Patients included in these studies were aged 70 years and older[9,48–50] and were irradiated mainly with conventional fractionated schedules, although altered fractionated RT regimens were also employed.[51] RT was found feasible also for the "oldest old" patients aged >85 years,[25,30,52–55] although only a part of these patients (41%)

were to receive treatment delivered according to the institution's policy, being age-adapted in 59% of them.[25] It is also necessary to take note that postoperative RT could be applied to only 58% of patients with indications for adjuvant irradiation.[30] The multivariate analysis with a cut-off point of 84 years of age clearly distinguished between patients with more (aged 80–84 years) and less (aged <80 years) favorable outcome.[25]

In elderly patients, conventional fractionation (5 weekly fractions of 1.8–2 Gy per day) seems to improve the most optimal balance between efficacy and toxicity. This is in line with the results of the meta-analysis of 15 randomized trails comparing conventional RT and altered fractionated RT with 6515 patients included.[56] A significant benefit in the overall survival (3.4% at 5 years, hazard ratio of 0.92) was observed with altered fractionation, and the overall benefit was due to the effect on death related to cancer. Higher age influenced the patients' survival significantly and adversely (hazard ratios of 0.78 for those under 50 years old; 0.95 for 51–60 years old; 0.92 for 61–70 years old; and 1.08 for over 70 years old), which could be attributed to an excess of deaths not related to cancer in patients aged ≥71 years and a lower compliance and tolerance to aggressive RT regimens in elderly patients.

In regard to the extent of irradiate volumes and dose for elderly patients, no other recommendations could be made beside those used in younger patients. Eventual adaptation of these two parameters in order to reduce radiotherapy-related side-effects should base on the results of a well-designed clinical trial which have not been conducted yet. Retrospective series on age-adapted treatment with curative intent of 118 patients aged 80 years or more with oral cavity SCC was reported by Ortholan et al.[25] An "adapted" treatment of operable tumors included definitive radiotherapy instead of surgery, omission of postoperative irradiation in high-risk patients, no neck dissection or irradiation when required, and implementation of unconventional fractionation regimens and reduced radiotherapy doses. Although treatment adapted to age was not associated with reduced disease-specific survival or overall survival in this study, the omission of elective lymph node treatment in stage I–II tumors increased the rate of regional recurrence from 6% to 36% ($P = 0.01$). Again, proper selection of patients for curative treatment, including radiotherapy, appears to be the most critical step in the management of elderly patients with HNSCC.

Considering the fact that elderly patients have a lower ability to tolerate the acute toxicity of irradiation, active support is mandatory, including mucosal hygiene measures, pain control and early nutrition intervention. Recent technological developments in the field of RT are also expected to exert a positive effect on the toxicity profile in irradiated patients.[57,58] The ability of sophisticated RT techniques, primarily the intensity-modulated RT, to shape the high-dose volume according to the 3-dimensional outline of the target(s) and to improve the control of dose deposition in nearby structures, which are not infiltrated with cancer cells, allows a better preservation of their function. Recently reported clinical results on the use of IMRT planning aimed to spare parotid glands and the non-involved parts of the swallowing apparatus during the optimization process can be considered as a proof of the principle.[59,60]

Elderly patients who were considered in the pre-therapy assessment to be too fragile to cope with a lasting and intensive curative RT should be directed to shorter and less aggressive palliative regimens. Several different palliative schedules are in use for HNSCC patients, all reporting high rates of locoregional responses and symptom relief as well as a favorable compliance.[61–64] If the tumor responses favorably and the patient's general status has improved significantly after palliative irradiation, additional fractions of RT could be given to convert the palliative intended treatment into a curative one to increase the likelihood for obtaining local control of the disease.

5.3. *Chemotherapy*

Prospectively collected data on the toxicity and efficacy of ChT in elderly patients is limited. With regard to the proportions of older patients (aged >70 years) in larger phase III ChT trials, they are either not recruited at all[65,66] or their number is not presented[67,68] or is negligible (<10%, Ref. 69), as was the case in a recently updated meta-analysis of ChT in HNSCC (RT alone vs. concomitant RT + ChT, 7% vs. 8%).[70] It is necessary to stress that in the latter the age was the only patient characteristic affecting survival: the benefit of concomitant ChT was smaller in older patients. The authors tried to explain this observation with a higher tendency of older patients to die from other causes that their HNSCC; the ChT-related increase in non-cancer deaths in this group might be another reason. An argument for this explanation was given by Machtay et al. who analyzed three previous RTOG trials on concurrent radiochemotherapy for factors associated with the occurrence of late toxicity. Out of 230 assessable patients (12% of them in the age group of 71–78 years), 43% suffered from a severe late toxicity; older age was recognized as a significant variable correlated with its development on multivariate analysis with the odd ratio of 1.05 per year.[71] Also, in a combined analysis of two phase III ECOG trials on palliative cisplatine-based chemotherapy with a total of 13% patients aged ≥70 years, Argiris et al. found no difference in the objective response rate (28% vs. 33%) and the median time to progression (5.25 vs. 4.8 months) between elderly and younger patients. However, there was a trend of a poorer survival outcome at 1 year (26% vs. 33%) and a higher rate of toxic deaths (13% vs. 8%) in the older group with a significantly higher incidence of grade 3–5 nephrotoxicity, diarrhea, and thrombocytopenia.[72]

On the other hand, the results from retrospective studies suggest that the ability of older patients to cope with ChT is comparable to younger ones, particularly when adequate supportive care is provided.[34,35] Due to a selection bias regarding patients' recruitment into retrospective studies, these results can hardly be applied to the general population. The physiological changes associated with the process of aging resulted in alterations in the pharmacodynamics and pharmacokinetics of the drugs applied. Together with the increased susceptibility of the normal tissue to their activity, they may significantly increase the rate of toxic complications and have a detrimental effect on the patient's ability to tolerate ChT.[73] The idea to circumvent a diminished tolerance of elderly patients to ChT by reducing its dose intensity was tested by Schnider et al.[74] The authors grouped 71 patients with HNSCC

by their age into three cohorts: 54 patients aged 70–79 were treated with a standard dose of cisplatin (100 mg/m^2/day 1) and 5-FU (1000 mg/m^2/day administered in continuous infusion for 5 days), whereas in those aged 80–84 the ChT dose was reduced by 20% and by 30% in patients older than 85 years (17 patients in total). The objective response rate was 79% (52% of complete responses) for the first cohort and only 31% (6% of complete responses) for those aged 80 years and older. This study clearly demonstrated that reduction in the ChT dose seriously compromises the efficacy of treatment.

5.4. *Target therapy*

At the moment, cetuximab is the only molecular targeting agent routinely used to treat HNSCC. In registration studies, it was found effective and well tolerated, both in the concomitant setting with RT in patients with a locoregionally advanced HNSCC[75] and in combination with platinum-based ChT as a first line treatment in patients with a recurrent or metastatic HNSCC.[76] Considering its use in elderly patients, several points should be noted. Firstly, older patients (aged ≥65 years) represented only a small proportion of those included in the experimental arm in either of the two studies: 19% in Bonner's study and 21% in Vermorken's study.[75,76] Furthermore, with the accumulation of clinical experience with the drug in a routine setting, it seems that its toxicity, particularly when combined with RT, is more pronounced than reported in the above mentioned studies. Bonner et al. reported no difference in grade 3–5 radiation mucositis (52% vs. 56%) or dermatitis (18% vs. 23%) between the RT alone arm and the RT-cetuximab arm.[75] Giro et al. who conducted a survey on the use of cetuximab and concurrent RT in EORTC centers reported a 49% incidence rate of grade 3–4 radiation dermatitis.[77] The Australian experience with concurrent cetuximab and RT in 13 elderly HNSCC patients (median age 68 years, range 52–82 years) is even more alarming: the authors observed a high rate of toxicity (both grade 3–4 radiation mucositis and dermatitis in 10 out of 13 patients), low treatment compliance and delays in completing RT. Only 4 out of 12 patients (33%) managed to complete the planned 8 cycles of cetuximab.[78] Finally, updating the original data, Bonner et al. found the combination of RT and cetuximab beneficial only in distinct sub-groups: in patients aged less than 65 years, with a high Karnofsky performance status (90–100) and a prominent skin rush. In less fit and/or elderly patients or in those without or with a mild skin reaction, the effect of combined treatment was comparable to RT alone.[79] Also in the randomized study on metastatic/recurrent HNSCC, older patients (aged ≥65 years) and those with a low Karnofsky index (<80) did not benefit from the addition of cetuximab to platinum–fluorouracil ChT.[76] Although the patient numbers in these subgroups were small and the results might represent spurious findings, they are highly provocative and require further investigation.

More encouraging data was presented by Jensen et al. (73 patients, median age 69 years) and Alongi et al. (22 patients, median age 73 years), who found concomitant administration of cetuximab with RT feasible, with manageable toxicity and of promising activity.[80,81] At the moment, the limited data regarding the use of cetuximab in elderly patients, especially when administered with RT, do not allow a firm conclusion to be drawn.

6. Survival of elderly patients with HNSCC

As in other types of cancer, the prognosis of HNSCC patients is age-related and is poorer in the elderly[82] (Table 2). Analyzing the joint French Cancer Registry database, Colonna et al. found an excess mortality rate in HNSCC patients aged >75 at the time of diagnosis compared to younger age groups.[83] This may be attributed to frailty of older patients with impaired ability of the immune system to generate an efficient response against tumors and a poorer tolerance to the applied therapies, which are often less aggressive and, consequently, less effective. A more advanced disease at presentation is probably not the reason for the observed differences in age-related survival of HNSCC patients (Table 2). It is necessary to take note that excess mortality was observed mainly at the beginning of a follow-up, whereas no effect of age was seen in the period between 1 and 3 years after the diagnosis (but re-appeared later). The decline in excess mortality over time could be explained by patient selection that occurs earlier in elderly patients than in younger ones, most probably due to the initial frailty of the former.

The survival difference between age groups is significantly reduced or even eliminated with a more balanced comparison (Table 2). For example, Bhattacharyya analyzed the SEER database for the years 1988–1998 using random matching of each case from the elderly cohort (aged ≥70 years) with younger cases (aged <70 years) on gender, year of diagnosis, cancer stage, the extent of surgery and RT to create a reference group.[84] With a controlled analysis, the author eliminated the potential bias that elderly patients under consideration were treated with a less aggressive surgical or radiation therapy compared to younger patients. Three distinctive primary sites were analyzed: glottis larynx, oral tongue and palatine tonsil. A significant difference in the overall mean survival and a disease-specific survival (although small in magnitude) were recorded for glottis and tongue carcinomas but not for tonsil carcinoma. After stage stratification, however, the overall and disease-specific survivals were comparable between the two age cohorts for all three tumor sites. Similarly, no independent prognostic value of age was found by van der Schroeff et al. for mortality after making an adjustment for the tumor stage, comorbidity burden and treatment intent.[33]

7. Quality of life issue in the elderly

Several studies confirmed that the quality of life (QoL) in elderly patients with HNSCC suitable for curative treatment programs appeared to be at least comparable to the one of younger patients when a global health-related QoL is considered.[33,85–88] Opposite results were also reported,[89] which could be explained in part by the influence of gender (female scored worse) and/or tumor site (patients with laryngeal tumors described more significant problems) on QoL perceptions.[87]

A positive effect on QoL is probably not influenced only by the general view of older patients that they have less to lose as a consequence of their cancer and the related treatment; also, their expectations might be less comparable to the ones of the younger counterparts. For example, when Rogers et al. compared the results of a QoL survey undertaken in surgical patients with oral and oropharyngeal cancer to the national reference data, the young patients cohort (aged <60 years) feared significantly more than expected for their age, which was not the case with older patients.[90] Recently, Laraway et al. reported QoL data for 638 patients obtained one year after curative treatment for oral SCC.[88] In many domains, the health-related QoL scores were higher among older patients (aged ≥65 years) compared to those of younger patients.

Investigating prospectively the coping and locus of control strategies in HNSCC patients, Derks et al. recognized that there were differences in the coping styles and locus of control mechanisms used by older and younger patients.[91] However, these variances did not result in differences in the QoL and depressive symptoms after treatment, which confirms that elderly patients can cope and adapt to a disease and therapy surprisingly well.

Finally, technological advances could also be expected to provide positive effect on the QoL. As shown by Huang et al., who conducted a QoL survey among 307 HNSCC survivors treated with two-dimensional RT, three-dimensional RT or intensity-modulated RT, more advanced RT techniques resulted in a better QoL outcome, especially on swallowing-related QoL scales.[92]

8. Conclusion

The burden of cancer in the elderly population is high and will increase further, especially in developed countries. There is a considerable body of evidence that older patients cope well with and adjust successfully to the disease and therapy; thus, chronological age alone should not be the only factor considered in the treatment decision-making process. Other parameters are also important, namely the functional status, comorbidity burden, polypharmacy, nutritional status, cognitive function, socio-economic issues and geriatric syndromes, which should be evaluated in a multidisciplinary setting before initiating any treatment. According to the available data, surgery and RT are feasible, effective and well tolerated also in elderly patients in a good performance status and without severe comorbidities. Further investigations are warranted to determine the role of ChT, target therapies and combined modality therapies in patients of advanced age groups.

Conflict of interest

None declared.

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