Multidisciplinary approach of head and neck cancer in the elderly: an update

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Abstract

Squamous-cell carcinoma of the head and neck (SCCHN) represents the sixth most common malignancy and accounts for approximately 6% of new cancer cases annually worldwide. Although the majority of cases occur between the fifth and sixth decades of life, their onset in patients older than 60 years is not rare, and up to one-fourth of SCCHN cases are diagnosed in patients older than 70 years. As the elderly population with SCCHN is constantly growing and as elderly cancer patients are severely under-represented in clinical trials, there is a clear need to address the particular aspects of this specific patient group, especially in the context of novel multidisciplinary cancer approaches. The frailty of elderly patients with SCCHN is further exacerbated by the high incidence of smoking and alcohol abuse and the presence of substantial cardiovascular, respiratory or metabolic co-morbidities that may hamper optimal therapeutic strategies. Herein, we review current and emerging treatment approaches, including improved surgical techniques attempting to improve the radicality of excision while preserving functionality, the incorporation of sophisticated techniques in radiotherapy and the implementation of novel chemotherapeutic regimens and molecular targeted agents in an effort to reduce toxicity without compromising efficacy. We also discuss the particular characteristics that render this patient population a unique entity, and we emphasize on the need for a multidisciplinary approach to optimize therapeutic outcome while preserving the quality of life in this frail subgroup of SCCHN patients.

Introduction

In Western countries, cancer-related incidence and mortality increase progressively with age. As life expectancy increases, the challenge of treating elderly patients with cancer is upfront in daily oncology clinical practice. It is estimated that by year 2030, 20% of the European Union population will be ≥65 years of age. This expansion of the aged population and its inherent increased risk for cancer is anticipated to ultimately increase the burden of cancer.

Squamous-cell carcinoma of the head and neck (SCCHN) represents the sixth most common malignancy and accounts for 6% of all cancer cases. Approximately, 650,000 new cases and 350,000 SCCHN-related deaths are reported worldwide annually. Although the majority of cases occur between the fifth and sixth decade of life, their onset in patients older than 60 years is not rare. It has been estimated that up to 24% of SCCHN cases are diagnosed in patients older than 70 years. Almost half of the approximately 40,000 new cases diagnosed annually in the United States of America (USA) occur in patients >65 years. In Finland, between 2006 and 2007, the percentage of new SCCHN cases diagnosed in the age group over 70 years was 31% for laryngeal cancer both in males and females and 30% and 48% for cancers of the oral cavity and pharynx in males and females, respectively.

As the elderly population with SCCHN is constantly growing and as elderly cancer patients are severely under-represented in clinical trials, there is a clear need to address the particular aspects of this specific patient group. In the current review, we summarize all available evidence on current treatment approaches of SCCHN in the elderly population, we discuss the particular characteristics that render this patient population a unique entity and we emphasize on the need for a multidisciplinary approach of the disease to optimize the therapeutic outcome while preserving the quality of life (QOL) in this frail, yet constantly increasing subgroup of patients.

Definition of the elderly SCCHN patient

The borderline of 65 years has been used by the European Organization for Research and Treatment of Cancer (EORTC) in trials of radical radiotherapy (RT) in SCCHN. Nowadays, this borderline is under re-evaluation. The National Institute on Ageing and the National Institute of Health of the USA have refined the term ‘elderly’ as the chronological group ≥65 years, which covers three subcategories: the ‘young old’ for those aged between 65 and 74 years, the ‘older old’ for those aged 75–85 years and the ‘oldest old’ for patients aged >85 years. The presence of substantial co-morbidities in this frail group of patients that often have a heavy history of smoking and/or alcohol addiction complicates therapeutic decisions, suggesting that the biological rather than the chronological age should be taken into account when designing and implementing the therapeutic modalities. To go even further, along with the physiological age, it is important to know the life...
Expectancy of a patient when deciding which treatment modality should be followed. For example, in Western countries, the estimated life expectancy in the general population is up to 84.2 years for a 70-year-old man and 5.4 years for an 85-year-old man.

**Characteristics of the disease in the elderly**

**Patient characteristics and risk factors**

SCCHN represents a heterogeneous group of tumors requiring multimodal treatment approaches, implicating both locoregional and systemic treatments with respectable toxicity rates. The management of such tumors in a geriatric context is challenging due to the concurrent geriatric syndromes such as dementia or depression that might have a detrimental effect on a patient’s ability to tolerate cancer treatment or polypharmacy that complicates the administered chemotherapy regimens through unexpected drug interactions. Moreover, ageing is associated with a variety of declining physiological functions and co-morbidities. Co-morbidity has been referred to as one of the factors accounting for treatment modifications, as coexisting cardiovascular, pulmonary or hepatic disease could affect treatment tolerance and clinicians often have to modify the treatment schedule in order to decrease therapy-related toxicity. Sanabria et al. found a high frequency of co-morbidities (75%) in a large series of elderly patients with SCCHN. Ferrier et al. found at least one co-morbidity in 59% of 117 patients, in a series where 28% of patients were >70 years of age. In an analysis of 7131 patients reviewed from the Surveillance, Epidemiology and End Results (SEER) database, Piccirillo et al. found up to 59% of co-morbidities, including approximately 52% of patients older than 70 years. The most frequent situations reported were cardiovascular diseases (hypertension, congestive heart failure, arrhythmia, myocardial infarct), respiratory diseases, alcohol abuse and diabetes mellitus, which were closely related to chronic tobacco and alcohol intoxication, but which were also common in the geriatric population. The prognostic significance of co-morbidities in the survival of elderly patients with SCCHN was established by a study using data from the SEER Program in 9386 subjects. To make things worse, elderly patients are generally excluded from prospective clinical trials, resulting in a lack of evidence-based data regarding efficacy and safety of available treatment modalities. In the literature, few studies have focused on treatment modalities in SCCHN patients aged ≥75 years. Finally, socioeconomic issues such as access to medical centres and availability of caregivers may influence therapeutic strategy.

Several studies have suggested that older patients with SCCHN are less likely to receive treatment with curative intent when compared with the younger age population. In all series, a lower prevalence of radical treatments, in particular surgery and combined modality of surgery and radiation therapy or chemotherapy and radiation therapy, was evident among the elderly patients as compared with younger patients (30%–74% vs. 67%–91%). Overall survival is significantly lower in elderly patients compared with their younger counterparts, with an actuarial rate at 5 years of 17%–31% vs. 30%–44%, in the same case series. Finally, other studies have proven that radical surgical or RT treatment can be performed safely in elderly patients without an increase in the overall complication rate, as long as the patients do not have severe co-morbidities.

SCCHN is a predominantly male disease; the usual male-to-female ratio ranges from 8:1 to 15:1. Many studies have suggested that women are over-represented in the elderly SCCHN population, with a sex ratio close to 1:1. Sarini et al. found a significantly higher proportion of females among the elderly patient population compared with the younger patient population (15.8 vs. 4.4%, p < 0.001). Similarly, Lusinchi et al. reported an unusual male-to-female ratio of 5:4 in 331 patients treated with RT for SCCHN. Reasons for this shift in sex representation remain unknown but may be related to the longer life expectancy of elderly women compared with their male counterparts.

The major risk factors for SCCHN are the use of tobacco (85%) and alcohol consumption. Other risk factors include sun exposure, age, race, gender, occupational inhalant industrial exposures (wood or nickel dust), previous radiation to the head and neck region, Epstein–Barr virus infection, human papilloma virus (HPV) infection, Plummer–Vinson syndrome, poor oral hygiene and poor dietary vitamin intake. A history of alcohol or tobacco intoxication is reported in up to 70% of SCCHN patients. However, the elderly patients have a significantly lower prevalence of alcohol and tobacco exposure as compared with the younger patients. This finding is in accordance with the perception that malignant tumours occur earlier under the influence of risk factors, but are also likely to occur without them as time passes by. In a French series of 270 patients aged ≥80 years treated for oral cavity cancer, tobacco or alcohol intoxication was the main risk factor among male individuals, whereas a history of chronic oral traumatic or lichen planus (or leukoplakia) was found in half of the women. It has also been implied that HPV infection could play a marginal role in SCCHN carcinogenesis of elderly patients.

**Geriatric assessment of a patient with SCCHN**

A Comprehensive Geriatric Assessment (CGA) is very helpful in geriatric oncology as it provides a reasonably accurate estimation of life expectancy.
allows the clinical team to identify factors—including situations such as early dementia, malnutrition and inadequate caregiver support that may compromise the effectiveness of treatment—and apply preventative measures when they are not addressed. It also provides a common language for measuring the health status before cancer treatment in clinical trials and helps predict the risks of complications from chemotherapy. Various instruments have been developed to assess the effect of co-morbidities on survival. The National Cancer Institute (NCI) co-morbidity index includes the number of diseases, but does not evaluate severity for each one of them. On the contrary, the Charlson co-morbidity index and the Adult Co-morbidity Evaluation 27 (ACE-27) incorporate measures of severity. The ACE-27, a modification of the Kaplan–Feinstein Co-morbidity Index, has been validated in patients with head and neck cancer. In 2002, Piccirillo et al. described a new co-morbidity index, the Washington University Head and Neck Co-morbidity Index (WUHNCI), derived from the ACE-27, which has similar predictive characteristics, but possesses the advantage of fewer items to be assessed. Recently, more extensive, precise and sophisticated indexes have emerged and are under evaluation. Preoperative assessment of cancer in the elderly (PACE) was evaluated in 460 patients aged ≥70 prior to elective surgery. PACE incorporates multiple instruments including activities of daily living (ADL), mini-mental state inventory (MMS), geriatric depression scale (GDS), brief fatigue inventory (BFI), instrumental activities of daily living (IADL), American society for anaesthesiologists scale (ASA), ECOG performance status (PS) and Satariano’s index of co-morbidities (SIC). Poor health as assessed by disability, which in turn is assessed using IADL, fatigue and PS, was associated with a 50% increase in the relative risk of postoperative complications. The most significant independent prognostic factors of post-surgical complications were moderate/severe fatigue, a dependent IADL and an abnormal PS.

Tumour distribution
SCCHN is a broad term encompassing epithelial malignancies that arise in the paranasal sinuses, nasal and oral cavity, pharynx and larynx. According to the World Health Organization classification, tumour distribution over all age groups is as follows: 43% in the oral and nasal cavity, 31% in the pharynx and 26% in the larynx. In Western countries, no significant age-related differences have been reported in the distribution of tumour location. The larynx, oropharynx and oral cavity are the three tumour sites usually affected in the elderly patients. In a recent study evaluating 316 patients aged ≥80 years, Italiano et al. reported that 46% of the tumours were located in the oral cavity, 23% in the laryngeal, 19% in oropharyngeal and 4% in hypopharyngeal sites whereas in 8% of the patients, another site was also involved. Kruse et al. have described in an epidemiological study of 99 patients (aged >70 years), a significant prevalence of oral cavity cancers, while in the study by Sarini et al., there were fewer cases of cancer of the hypopharynx and more cases of cancer of the oral cavity in older patients than in younger patients (8.8% vs. 14.5% and 39.9% vs. 33.8%, respectively). Similarly, Jun et al. reported a series of 159 patients aged ≥80 years in whom 53% of tumours were located in the oral cavity, 10.9% in the larynx and only 5.8% in the pharyngolaryngeal area. Finally, a higher proportion of maxillary carcinomas in elderly patients has been reported in some studies.

The most common histological type of head and neck cancer is squamous cell carcinoma (95%), while other less common types include salivary gland tumours, lymphomas and sarcomas. Yet, in the study by Kruse et al., four patients had a verrucous type of SCCHN, a type of well-differentiated squamous cell carcinoma that is well known in elderly patients.

Stage
Approximately two-thirds of SCCHN patients present with locally advanced disease (commonly involving cervical lymph nodes), whereas metastatic disease at diagnosis is documented in approximately 10% of patients. Elderly groups have been reported to present more often with locally advanced disease (T3 or T4 in TNM staging) but fewer neck lymph node metastases. Overall, distributions of disease stage and tumour differentiation present no major differences among different age groups. For example, in the study by Sarini et al., cancer stage grouping was equally distributed between the older patients and the younger ones—31.1% vs. 29.8% for those with stages I and II, 37.9% vs. 37% for those with stage III and 31% vs. 33.2% for those with stage IV, respectively.

In elderly patients, the length of their symptomatic history is of special clinical interest, since a median duration of complaints dating up to 15.5 weeks until the patient seeks medical advice has been reported. Ageing patients consider several symptoms as normal in the ageing process, or relate them to common colds; thus, symptoms are not interpreted correctly as early-warning signals. This encourages adoption of initial ‘watch-and-wait’ strategies and thus a significant loss of time before consulting medical practitioners. Moreover, problems of the elderly such as social isolation due to the loss of a partner or friends, the distance to children or other relatives, limited mobility, hearing or visual loss, other physical handicaps, or already existing diseases occupy more space in the awareness of the patients than cancerous diseases which they are not used to discuss openly. Thus, an eventual newly developed malignant disease is
likely to be neglected, as long as the symptoms do not influence daily routine\textsuperscript{13}.

**Therapeutic approaches**

Management of SCCHN is challenging mainly from aspects of treatment-related toxicity. Local treatments may be associated with significant acute iatrogenic morbidities in the elderly, with a high risk of functional deterioration even in patients with pre-therapeutic good general condition. However, the natural history of untreated SCCHN could also lead to severe symptoms, characterized by rapid deterioration of functional status. On that frail ground, clinicians are often obliged to make compromises and apply suboptimal treatments that are less toxic than standard treatment; however, these treatments may also be less efficient. Sarini et al.\textsuperscript{20} reported that the issues in their study were therapeutic decisions governed by the patient’s age. Surgery was less often used for older patients: 13.9\% vs. 27.4\% for the primary site and 15.4\% vs. 35.6\% for neck lesions. Irradiation was equally used but combined modalities including surgery and irradiation or chemo-RT were less frequently administered in the elderly patient population than in the younger patient population: 22.3\% vs. 9.7\% and 14.1\% vs. 0.2\%, respectively. Chemotherapy was less frequently administered in the elderly and irradiation or chemo-RT were less frequently administered in the elderly patient population than in the younger patient population: 22.3\% vs. 9.7\% and 14.1\% vs. 0.2\%, respectively. Chemotherapy was less frequently administered in the elderly and irradiation or chemo-RT were less frequently administered in the elderly patient population than in the younger patient population: 22.3\% vs. 9.7\% and 14.1\% vs. 0.2\%, respectively.

For a long time, under-treatment was attributed to assumed poor tolerance and compliance in older patients. The available data currently suggest that curative therapy should be attempted in ageing SCCHN patients, not only because of the reversible nature of therapy-associated toxicities but also because of the comparatively good prognosis\textsuperscript{51}. The treatment of choice should be based on a medical assessment and the preferences of the patient, not on chronological age alone\textsuperscript{22}. In order to deliver the best-tailored treatment, physicians have to determine the primary goal of local treatment—to cure or to relieve/prevent tumour symptoms.

According to Linn et al.\textsuperscript{52}, the nutritional profile was a definitive and relevant factor evaluated during the selection of the elderly patients in whom radical treatments were administered. The prevalence of malnutrition is dramatically high in patients with SCCHN cancer\textsuperscript{53}. Moreover, SCCHN patients are usually symptomatic, thus inducing a rapid functional decline that may be reversible with intensive nutritional support and local treatment of the tumour.

**Surgery**

Surgery accommodates as the treatment of choice if the primary tumour can be excised with clear margins without causing major functional compromise. Such an aggressive approach with a curative intent can also be considered for the elderly SCCHN patients\textsuperscript{54}. The choice of radical local therapy must take into account the likely functional outcome of treatment, the resectability of the tumour; the CGA, the life expectancy and finally the patient’s wishes.

Chronic age alone should not be a contraindication to adequate oncological surgery and, thus, aggressive surgical approach is recommended when risk assessment is favourable. Radical surgical treatment was assessed in an old study that evaluated 162 elderly patients with operable SCCHN and compared them with 552 younger patients with favourable outcomes, suggesting that radical surgery should be attempted in the elderly, when feasible\textsuperscript{55}. In 810 patients, >65 years, who had undergone major head and neck resections, Morgan et al. reported a mortality rate of 3.5\%\textsuperscript{56}. Italiano et al. reported a postoperative 30-day mortality of 3\%, when 61\% of elderly patients who were amenable to be cured by surgery underwent potentially curative resection\textsuperscript{14}. These results were challenged by a later study that compared 43 SCCHN patients, aged >80 years, with 79 controls, aged <65 years and a significantly lower median overall survival was evident for the older age group. However, even in this group, overall survival was similar to the actuarial survival for the general population adjusted for the same age. No significant differences in perioperative or postoperative complications between the two groups were demonstrated, although the older age group had a higher frequency of morbid preoperative conditions\textsuperscript{52}. Finally, Laccourreye et al. evaluated the surgical outcome for carcinoma of the glottic and supraglottic larynx, and although these surgical procedures pose a higher risk of aspiration pneumonia, a moderate 22\% of the 69 recruited patients presented pulmonary complications in the first 6 months of follow-up\textsuperscript{57}.

There is a wide range of available surgical techniques, with various degrees of resectability involving either limited excision under local anaesthesia or extensive resection requiring reconstruction that may provoke functional impairments. The estimated duration of operative time, the need for reconstruction, the need for postoperative functional rehabilitation and for postoperative irradiation that could compromise functional results are factors that should be taken into account before the multi-disciplinary team reaches a decision regarding the appropriate surgical approach.

Preoperative risk assessment is predictive for the development of postoperative morbidity\textsuperscript{58,71}. The prognostic factors for postoperative complications after wide SCCHN surgery are: age\textsuperscript{59}, preoperative co-morbidities evaluated with the Charlson or the ACE-27 co-morbidity index and duration of anaesthesia\textsuperscript{60}. According to Serletti et al.\textsuperscript{23}, prolonged surgical time longer than 10 h serves as a predictive factor for the development of postoperative surgical complications. From another
study assessing 121 patients treated for SCCHN, after stratification according to their age, the frequency of postoperative complications correlated significantly with the American Society of Anaesthesiologists (ASA) classification of physical status and preoperative PS. Complications of surgery, including pneumonia, dehydration and feeding disturbance occurred in 53% of the very old patient group. Tumour-specific 5-year survival rates were 85.2% for controls, 84.5% for the aged and 80.0% for the very old.62 According to a large study63 in 242 patients >70 years of age who underwent surgery for SCCHN, co-morbidities were present in 87.6% of the patients and 56.6% had some type of postoperative complication (44.6% local and 28.5% systemic). Postoperative complications were associated with male sex, bilateral neck dissection, presence of two or more co-morbidities, reconstructive surgery and clinical stage IV disease. In accordance with these data, clinical preoperative variables assessed could predict postoperative complications in older patients with head and neck tumours who underwent oncological surgery with a remarkable probability (receiver-operator characteristic curve of 69%).64

Regarding QOL assessment following surgical management of SCCHN, no significant differences were observed between the elderly and younger patients. In the series by Dhivakar et al., patients completed questionnaires about QOL (EORTC QLQ-C30 and QLQ-H&N35) and depression (CES-D) before and 3 months after surgery. Both the elderly and younger patients scored worse on most QOL aspects 3 months after treatment, but there were no significant differences among them. In another study,65 several QOL domains were evaluated in elderly patients undergoing major head and neck surgery when compared with younger patients. With the Short Form-12 (SF-12) questionnaire, physical and emotional pain was decreased by the surgical intervention, while physical function was affected by age alone. With the University of Washington (UW) Questionnaire, overall QOL was preserved. ‘Appearance’ and ‘Leisure’ subscales were affected by both surgical intervention and older age. ‘Chewing’ and ‘Activity’ were decreased by surgical intervention only in the older patients, and ‘Speech’ was affected by surgical intervention alone. The ‘sense of burden’ was alleviated by surgery in the elderly patients.66

For early disease, resection of the primary tumour is often limited, with acceptable functional outcome64,65. Adaptation of surgical techniques for elderly patients with early SCCHN should consider omitting neck dissection. Indeed, in cT1-T2 N0 oral cavity cancers, prophylactic neck dissection may be considered in younger patients, whereas it is often omitted in the elderly.66-68

For locally advanced disease, surgical procedure involves longer operative time, higher risk of postoperative complications and major functional deterioration. When elderly patients are unsuitable for the standard surgical procedure, two approaches could be proposed. The first one is to adapt the surgical procedure to minimize the operative time and therefore the risk of postoperative complications. Complete removal of the tumour and a satisfactory postoperative function with minimal complications should be ensured. The alternative approach is to propose definitive RT. Nevertheless, in a study including resectable stage III/IV oral cavity cancers in patients aged ≥80 years, who received surgery or RT (upon refusal of surgery), the disease-free and the overall survival were significantly better in the surgical group.69 In another recent study, which compared toxicity of RT vs. laryngectomy, RT was more toxic than surgery, irrespective of the patient’s age.70

Thorough anaesthesiological planning for perioperative management is imperative to reduce the morbidity and mortality in the elderly patients.70 The administration of anaesthesia must be individually planned and meticulously monitored, because the pharmacokinetics and pharmacodynamics of anaesthetic agents are not the same as in younger patients. Disturbed renal function and impaired hepatic metabolism influence drug distribution in elderly patients. Moreover, elderly patients with SCCHN have unique airway issues that must be addressed preoperatively. As mentioned above, time under general anaesthesia correlates with complication rate and hospital length of stay. Further factors that have been associated with postoperative morbidity are large fluid shifts and significant blood loss. Moreover, increased myocardial stiffness, increased aortic impedance, increased left atrium size and increased vascular stiffness, in addition to decreased β-adrenoceptor responsiveness, must be considered before anaesthesia is administered to the elderly patients.70 Postoperative delirium is a common complication, with the overall incidence estimated up to 10% in elderly patients following major elective non-cardiac surgery.71 It usually presents around 24 h postoperatively, resolving in most patients within 48 h, but episodes can last for months.72

**RT**

RT can be delivered in patients with SCCHN with a curative intent (radical RT), to improve local control following surgery (adjuvant RT) or to provide symptomatic relief (palliative RT). Anatomic, tumour and clinical factors determine the use of radiation as primary treatment or as an adjuvant to surgery in combination with chemotherapy. Radiation monotherapy results in high local tumour control and improves cure rates for early stage glottic, base of tongue and tonsillar cancer. In addition, it represents the treatment of choice for those who are considered unfit for surgery or in...
whom surgery results in an unacceptable functional outcome. The advantages of RT involve preservation of the organ concerned and, at least partially, of its function. In the elderly patients, modern radiation techniques, facilitating the irradiation of a limited target with increased doses, have been applied in order to improve the tolerance and QOL. As a general rule, the primary tumour and gross lymphadenopathy require a total dose of 70 Gy at a dose fractionation of 2 Gy/day, while radiation to suspected unresected microscopic disease in nodal levels requires a total of 50 Gy or more at 2 Gy/day. Higher dosages (60–65 Gy) are required for node-positive tumours in an effort to reduce the locoregional recurrence rate. In the postoperative setting, higher prescription doses are required due to the interruption of the normal vasculature, scarring and relative hypoxia in the tumour bed. The presence of co-morbidities, multifocal malignancies, poor PS, limited supportive care and/or impaired mental status often necessitate deviations from the established standards of care regarding radiation therapy in the elderly patient population. Delineation of the irradiation volume is a complex task in SCCHN RT. In elderly patients, an open question is whether the reduction of the clinical target volume (CTV) in order to minimize the adverse events is acceptable. As mentioned above, Ortholan et al. reported that the omission of node treatment for T1–T2 N0 oral cavity cancer in patients aged >80 years induces a high risk of node recurrence. Several studies have shown that RT is effective and well tolerated in an ageing patient population and that advanced age alone does not represent a contraindication for RT. Importantly, it has been noted that elderly patients recruited in clinical trials had a better PS compared with those who were deemed not eligible; therefore, the results from clinical trials might be biased and not generalizable to the general aged SCCHN population. Of note, two large meta-analyses found that the benefit of intensified RT regimens was diminished in the elderly patients enrolled in chemoradiotherapy (RT) or accelerated RT trials, probably owing to competing risks from co-morbidities. Barzan et al. reported a tendency towards less aggressive RT for the elderly patients. Nevertheless, in a recent, large, single-centre cohort study, among 1487 patients who received definitive RT for SCCHN, no differences were found between the elderly and younger patients in terms of treatment interruption, completion and treatment-related death. Within the subset of 760 patients who received intensified treatment (concurrent chemo-RT or hyperfractionated accelerated RT), no difference was seen between the elderly and younger patients with respect to the outcome. After a median follow-up of 2.5 years, the 2-year cause-specific survival rate after definitive RT for the elderly and for the younger patients was 72% and 86%, respectively. Similar results were reported by other smaller case series studies, overall suggesting that older patients with locoregional SCCHN, or at least a subset of them, appear to be able to tolerate radical courses of RT and to have outcomes that are similar to those in younger patients. In the series from Italiano et al. evaluating 180 SCCHN patients aged >80 years, who received definitive RT, 81% of them completed their prescribed RT course.

RT may be beneficial even in the ‘oldest old’ subgroup. A study, which included 23 patients aged between 90 and 96 years, reported that age does not affect the effectiveness of RT or patient tolerance. There were no treatment discontinuations for those patients who were planned to receive definitive RT, and 62% of them obtained local control. A total of 63% of patients who received RT with a palliative intent completed their treatment, with 81% of them achieving palliation. Hyperfractionation was designed to improve effectiveness by delivering more than one fraction per day with a reduced dose per fraction and an increased total dose. Accelerated fractionation was designed to increase radiation dose intensity by using fractions of 1.5–1.8 Gy more than once daily in order to deliver a dose of more than 10 Gy per week. By keeping the same total dose of radiation as conventional RT, accelerated RT ensured that treatment was completed more rapidly (e.g. in 5.5–6 weeks). From a large phase III Radiation Therapy Oncology Group (RTOG) clinical trial (protocol 90-03), comparing hyperfractionation with two variants of accelerated fractionation with half of the eligible patients aged >60 years, a locoregional tumour control advantage and marginal survival benefit at a cost of slightly increased acute and late side effects were demonstrated for both accelerated and hyperfractionated regimens compared with conventional RT. ‘Split course’ accelerated protocols, which include a planned radiation break, have been proposed as an alternative strategy in an effort to improve radiation tolerance and increase the QOL by reducing mucositis and its consequences. On this ground, to allow unplanned interruption in standard treatment, data from the Danish Head and Neck group randomized trial showed that the combination of accelerated RT with a break does not affect local control of the tumour. A further issue in the elderly is the number of daily transportations required for RT, which, in standard fractionation, necessitates approximately 35 daily transportations for more than 7 weeks, a process that may be associated with increased fatigue over time. Thus, standard fractionation could be difficult to deliver and treatment interruption due to fatigue or socioeconomic reasons is frequent in such patients. Hypofractionated treatments that involve increased dose per fraction...
and decreased total number of fractions seem to facilitate geriatric patients on that ground. Many hypofractionated palliative schedules for SCCHN have been proposed including 20 Gy in five fractions91, 30 Gy in five fractions92, 14 Gy in four fractions93 and 50 Gy in 16 fractions94. In an effort to limit acute toxicity, these protocols are delivered in a split-course manner that facilitates wound healing of mucositis and limit pain, malnutrition and functional deterioration. Two series of 30 Gy in 10 fractions for more than 2 weeks with a planned interruption of 2 or 3 weeks between the series or three series of 20 Gy in five fractions with the same planned interruption are commonly administered100–103. Such adapted regimes may represent a favourable compromise between a biologically effective dose and an acceptable tolerance in elderly patients. Yet, increased late toxicity rates were still reported for those patients who were treated using a hypofractionated schedule95.

Intensity-modulated radiation therapy (IMRT) is an advanced, computer-generated beam modulation that permits exquisite radiation dose sculpting around complex target volumes, thus protecting normal tissues (e.g. salivary glands, spinal cord) from late normal tissue damage96 and facilitating radiation dose escalation in the tumour97. Preliminary clinical results of IMRT are encouraging for the treatment of SCCHN98,99, but data regarding the elderly patient population are missing. Data from other solid tumours that show a good tolerance of RT in the elderly population, with up to 80% of patients completing treatment and only 36% breaks, are not always transposable to SCCHN RT, in which unplanned treatment breaks are frequent irrespective of the age of the patients100,101, thereby compromising the local control of the disease102.

Some researchers argue against delivering palliative RT in elderly patients with SCCHN due to the disproportionately high toxicity induced in order to achieve a clinical benefit103. The elderly are often treated with less aggressive adapted treatment schedules in an attempt to preserve their QOL with regard to toxicity. However, there exists little data regarding acute and late toxicity of palliative RT in elderly patients. Regarding the tolerance of RT, in a series of 1589 patients included in the EORTC trials between 1980 and 1995 with 20% of patients aged >65 years and 2% aged >75 years, Pignon et al.17 concluded that acute functional mucosal reaction rates increased with the age of the patients, with 8% of grade 4 in patients aged <50 years and 31% in patients aged >70 years. However, there was no statistically significant difference in survival or acute objective mucosal reactions and in weight loss rates more than 10% among different age groups. Similar supporting data has been reported by the Italian Geriatric Radiation Oncology Group, which prospectively evaluated 2060 patients aged >70 years, who received RT alone or in combination with surgery and/or chemotherapy104.

The management of radiation-induced toxicities in the elderly should follow the same protocols as those for the younger patients. Xerostomia is often permanent and causes discomfort, eating and articulating difficulties, taste alteration and a high risk of accelerated dental caries. A specific intervention for the prevention of radiation-induced xerostomia is not indicated by available data, although amifostine has been investigated for the treatment of acute and late xerostomia105. There is no evidence to justify any other intervention for prevention or treatment of radiation mucositis. A patient’s mucosa should be inspected regularly and analgesia and antimicrobial/antifungal agents to treat infection should be applied accordingly on clinical indications. Specific interventions for the prevention or treatment of radiation skin toxicity are not recommended other than the routine use of topical moisturizing agents before the onset of moist desquamation.

Chemotherapy
The role of chemotherapy in SCCHN is expanding and its utility is recognized both in patients with metastatic or incurable locoregional disease, as palliative therapy, but also in patients with potentially curable locoregional disease where it is an integral component of the multimodality approach, especially when organ preservation is attempted. Chemotherapy is administered in combination with locoregional therapy (surgery or RT) in patients with locally advanced SCCHN as neoadjuvant/induction when it is delivered before surgery or radical RT, as adjuvant when it is delivered following RT or surgery or as concomitant when it is delivered during a course of RT.

The current standard chemotherapy regimen for SCCHN is a sequential combination of cisplatin and infusional 5-fluorouracil (5-FU). In the treatment of metastatic or recurrent disease, this combination achieves response rates of up to 40%–50%, whereas in the induction setting attempted for organ preservation, this regimen yields responses of up to 70%–80% (including complete remissions in 30%–40%)106. The addition of chemotherapy to locoregional treatment for patients with non-metastatic SCCHN significantly improves survival, with absolute survival benefit of 8% at 2 and 5 years107. However, the size of benefit with concurrent chemo-RT is age dependent, with the largest benefit in those aged <60 and at the expense of increased acute toxicity (mucosal and haematological) and possibly late toxicity127.

New chemotherapeutic regimens are under evaluation for locally advanced SCCHN. Patients with locoregionally advanced disease, including the elderly, who received the taxanedocetaxel plus cisplatin and fluorouracil as induction chemotherapy plus carboplatin-based chemo-RT had a 12% absolute survival benefit when compared with patients.
who received cisplatin and fluorouracil induction chemotherapy\textsuperscript{108}. Furthermore, in another study with 10\% of the patients aged between 65 and 71 years, induction chemotherapy with the addition of docetaxel to the standard regimen of cisplatin and fluorouracil significantly improved progression-free and overall survival in patients with inoperable/advanced SCCHN\textsuperscript{109}. Combination chemotherapy with either cisplatin/5-FU or a platinum/taxane combination has become the standard of care in patients with incurable or recurrent SCCHN, including the elderly\textsuperscript{110}.

A theoretical background exists for the increased rates of chemotherapy-related toxicity in the elderly; however, clinical studies, aimed at evaluating the relationship between toxicity from chemotherapy and age, are scarce\textsuperscript{111}. Elderly patients are often excluded from chemotherapy clinical trials, because they are considered subjects at high risk for toxicity from cytotoxic agents\textsuperscript{112}. Age has been associated with pharmacokinetic and pharmacodynamic changes and with increased susceptibility of normal tissues to toxic complications or reduced capacity of healthy tissues to recuperate. Chemotherapy complications such as neutropenia, anaemia, bleeding, mucositis, cardiac toxicity and neurotoxicity are more frequently observed in the elderly and may affect individual functional independence\textsuperscript{113}. Besides, chemotherapy and agents used to prevent its toxicities may affect cognition, balance, vision, continence and mood. Moreover, polypharmacy, frequently encountered in elderly patients, may lead to interactions with cytotoxic chemotherapeutic agents. Co-morbidities also increase the risk of toxicity due to delayed renal excretion or hepatic metabolism. For example, a well-described change with age is the decline in the glomerular filtration rate\textsuperscript{114}, which may potentially increase toxicities of cisplatin-based chemotherapy in the elderly. In addition, the hematopoietic reserve is reduced in the elderly, which renders them more susceptible to chemotherapy-induced myelotoxicity\textsuperscript{115}. In general, chemotherapy seems to be feasible in elderly patients with SCCHN, although its toxic effects may be exaggerated. However, a reduction in the administered dosage based purely on chronological age may adversely affect efficacy of treatment, thus the effective management of chemotherapy-associated toxicity with appropriate supportive care is crucial in the elderly population\textsuperscript{116}.

Older age has been recognized as a barrier for recruitment in clinical trials and for the delivery of cancer treatment in general. Analyses of two databases, the SWOG trials from 1993 to 1996 and the cooperative group phase II and III trials from 1997 through 2000, have found that the proportion of elderly participants, defined as 65 years or older, in head and neck cancer clinical trials was 24\%–29\% compared with the proportion of elderly of 48\%–49\% in the U.S. population of patients with cancer\textsuperscript{117,118}. A number of reasons may explain the under-representation of the elderly in clinical trials\textsuperscript{119,120}, including a therapeutic-restrained attitude towards the elderly, lack of social and financial support and co-morbidities that result in ineligibility.

The tolerability of chemotherapy by the elderly has been a matter of controversy in the literature\textsuperscript{121–126}. The intensity of treatment and the toxicity profile of the chemotherapy regimens used have been identified as differentiating factors. In a combined analysis\textsuperscript{147} from two large phase III randomized trials conducted by the Eastern Cooperative Oncology Group (ECOG; trial E1393, which compared cisplatin plus paclitaxel at two dose levels, and trial E1395, which compared cisplatin plus fluorouracil to cisplatin plus paclitaxel) that evaluated the toxicity, objective response rates, and survival of patients with advanced SCCHN 70 years or older vs. their younger counterparts, both trials demonstrated that elderly patients had similar objective response rate [28\% vs. 33\%, \(P = \text{non-significant (NS)}\)] and median time to progression (5.25 vs. 4.8 months, \(P = \text{NS}\)) compared with the younger ones. The median survival was 5.3 vs. 8 months (log-rank \(P = 0.17\)) and the 1-year survival was 26\% vs. 33\% for the elderly and younger patients, respectively. However, elderly patients had a significantly higher incidence of severe nephrotoxicity, diarrhoea, and thrombocytopenia. A higher rate of toxic deaths was noted in the elderly but did not reach statistical significance (13\% vs. 8\%, \(P = 0.29\)). Another striking observation of the analysis was the small percentage of elderly participants (30\% were 65 years or older and 13\% were 70 years or older)\textsuperscript{127}.

In an effort to minimize toxicity without compromising efficacy, age-adjusted dose regimens have been developed. Schneider et al.\textsuperscript{148} reported on 71 patients with advanced SCCHN aged >70 treated with cisplatin and 5-FU, with an age-adjusted dose regimen. Patients aged 70–79 years were treated with standard-dosage of cisplatin 100 mg/m\(^2\) on day 1 and 5-FU 1000 mg/m\(^2\) continuous infusion from day 1 to day 5, while those aged 80–84 years with a reduction of the dosage by 20\% and those older than 85 years with a reduction of the dosage by 30\%. The objective response rate was 79\% among the 54 patients aged 70–79 years, and only 31\% among the 17 patients aged 80 years or older. In the group of patients older than 80 years, patients responsive to chemotherapy were in a better general condition as compared with the non-responsive patients. A low incidence of up to 3\% of cardiotoxicity was documented\textsuperscript{128}.

Regarding drug-specific toxicities, cisplatin is associated with an increase in peripheral neuropathy, anaemia and nephropathy\textsuperscript{129}. In vitro studies have demonstrated that elderly patients have a reduced
capacity to repair cisplatin-induced DNA damage. The inter-chain bindings that are present on the monocytes of young subjects treated with cisplatin are almost completely eliminated after 24–48 h from the exposure to the drug whereas in the elderly patients, the capacity to repair after 48 h is significantly lower and has a higher degree of inter-individual variability\textsuperscript{130}. Treatment with 5-FU, mostly administered in continuous infusion, may provoke in elderly patients a potential increase in cardiotoxicity, mucositis and leukopenia. Mucositis is in general more severe than in younger patients and requires significantly longer time to recuperate. One of the main risk factors is the physiological decline of the intracellular concentration of the dehydropyrimidine decarboxylase, the main enzyme involved in the catabolism of the drug, during ageing\textsuperscript{152}. Leukopenia is mostly determined by a reduction in the bone marrow functional reserve and its severity is strictly age-dependent\textsuperscript{131}.

The elderly patients who are independent on the functional point of view and do not bear severe co-morbidities must be treated in the same manner as younger patients, but during the treatment, immense supportive care is advised. Anaemia is usually present because of the disease or its treatment and, if left uncorrected, it may represent a risk factor for decreased distribution of water-soluble drugs, cardiovascular disease, congestive heart failure, coronary death and possibly dementia. Data concerning the use of recombinant human erythropoietin in the treatment of chemotherapy-related anaemia in early or advanced SCCHN are not extensive\textsuperscript{132–135}, but generally indicate the haemoglobin value of 11 g/dL as the goal of such treatment.

In all patients, particular attention should be paid to maintain an adequate nutritional status, since malnutrition can adversely affect both efficacy of chemotherapy and patients’ survival\textsuperscript{24}. Poor dentition, functional impairment, cognitive impairment, lack of appetite due to chronic co-morbid disease and lack of caregiver are factors contributing to deficient nutrition in elderly patients. Elderly patients with SCCHN may also face additional problems brought out by chemotherapy, such as nausea, diarrhoea, vomiting and painful oral ulceration. Correcting malnutrition and establishing a suitable dietary plan can substantially improve the patients’ clinical outcome and QOL.

\textbf{Figure 1:} Holistic evaluation of an elderly patient with head and neck cancer.
The main concern with respect to emotional conditions in these patients is depression, which is common in both geriatric and oncology populations, and could adversely affect the patient's functional status and the outcome of cancer treatment.24.

Targeted therapy

Cetuximab is a chimeric IgG1 monoclonal antibody against the ligand-binding domain of epidermal growth factor receptor that has been proven to enhance the cytotoxic effects of radiation in SCCHN.25–27, A multicentre randomized-controlled trial involving 424 patients with locally advanced SCCHN has demonstrated that concurrent administration of cetuximab, with radical external beam RT, resulted in an 11% improvement in progression-free survival and a 10% improvement in overall survival compared with external beam RT alone. There was no increase in RT-related toxicity.28 There are no clinical studies assessing the efficacy or tolerability of cetuximab in the elderly patient population. Nevertheless, given the favourable toxicity profile of cetuximab-combined RT, the use of cetuximab with concurrent RT could represent a valid alternative to the combination of platinum compounds with RT in elderly patients unfit for cisplatin administration due to nephrotoxicity, ototoxicity or sensory neuropathy.

Conclusions and clinical recommendations

Elderly patients can cope and adapt remarkably well compared with younger patients, and several studies have shown that the QOL of elderly patients undergoing curative treatment for cancer of the head and neck is at least comparable with that of the younger population.127–129. Despite these notions, elderly patients with SCCHN are less likely to receive standard treatment, including radical surgery or postoperative chemo-RT, which probably contributes to decreased cancer control in such patient populations.

Medical intervention in the elderly is justified when the benefit/risk ratio is favourable as it is estimated by co-evaluation of the expected treatment effect, the life expectancy of the patient, the possible therapy-related toxicities and the patient’s tolerability. The route to optimal management for each geriatric patient with SCCHN lies primarily in a holistic approach to patient assessment and secondarily in provision of high-quality multidisciplinary management and support (Figure 1). The addition of the patient’s wishes to the aforementioned may lead to the best treatment decision. Decision-making in cancer therapy for elderly patients is challenging and fear of the morbidity due to ‘aggressive’ therapeutic regimens often leads to inadequate diagnostic and therapeutic modalities being adapted. Nowadays, there is a complete international consensus that patients suffering from operable SCCHN should be treated with a curative intent, if thorough preoperative assessment of co-morbidities is performed. Optimal medical care of relevant concomitant diseases is indispensable. Age itself should never be the sole factor assessed during the therapeutic decision process.

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locally advanced thyroid cancer: acute

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