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TUMOUR REVIEW

Head and neck cancer in the elderly: An overview on the treatment modalities

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SUMMARY

The percentage of elderly people with head and neck cancers (HNC) is rising due to increasing average lifespan. As with younger patients, elderly patients require a multidisciplinary approach in order to optimise treatment results. The biological, not the chronological, age should be defined individually based on co-morbidities and performance status. A comprehensive geriatric assessment represents the first and essential step for selecting further treatment options. Major improvements have been accomplished in surgical techniques and radiotherapy delivery. Several chemotherapeutic agents and targeted therapies with different toxicity profile are also available. However, the randomised studies that defined the nature of these improvements included only a small proportion of patients older than 65 years. In deciding which treatment strategy would be suitable for an individual elderly patient, we review the literature regarding surgery, radiotherapy, and chemotherapy or their various combinations.

Introduction

In western societies, the percentage of elderly people within the population is increasing as a result of increased average lifespan. Consistently, the issue of what is the cut-off point for the definition of "elderly" remains unresolved. Until recently, the borderline between middle and old age was 65 years. This age limit was used by the European Organization for Research and Treatment of Cancer (EORTC) in trials of radical radiotherapy in head and neck cancers.[1] However, this borderline is no longer considered valid. The National Institute on Aging and the National Institutes of Health have redefined the term "elderly" as the age group greater or equal to 65 years, which covers three subcategories, namely: 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 subjects aged more than 85 years old.[2] In parallel with the physiological age, it is important to know the life expectancy of a subject when deciding which treatment schedule should be followed. For example, in western countries, the estimated life expectancy in the general population is about 14.2 years for a 70 year-old man and 5.4 years for an 85 year-old.[3] In contrast, Socinski et al.[4] offered a different definition for an old oncology patient: "old is when his health status begins to interfere with oncological decision-making guidelines".[4]

Tumours of the head and neck region represent the sixth most common malignancy and account for 6% of all cancer cases. Approximately 650,000 new head and neck cancer (HNC) cases and 350,000 cancer deaths are reported worldwide every year.[5] Although the majority of HNC occur between the fifth and sixth decade, their onset in patients older than 60 years is not a rare event.[6] It has been estimated that as many as 24% of HNC are found in patients older than 70 years.[7] HNC is a broad term that encompasses epithelial malignancies that arise in the paranasal sinuses, nasal cavity, oral cavity, pharynx and larynx. In western countries, no marked age-related differences were noticed in the distribution of tumor sites. The larynx, oropharynx and oral cavity are the three tumor sites usually affected in elderly patients.[8,9] The most common histological type is squamous cell carcinoma (95%), while other less common types include salivary gland tumors, lymphomas and sarcomas.[10]

Historically, HNC is a predominantly male disease with the usual male to female ratio varying between 8:1 and 15:1.[8,11] This proportion does not appear to be valid for older patient groups. Sarini et al. found a relatively higher proportion of females among older compared with younger patients (male: female ratio = 6:1 vs.

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23.1; $p < 0.001$).[12] Similarly, Lusinchi et al. found an unusual male:female ratio of 5:4 in 331 patients treated with radiotherapy for an upper aerodigestive tract carcinoma in France.[13]

About two-thirds of head and neck squamous cell carcinoma (HNSCC) patients present with locoregionally advanced disease, commonly involving cervical lymph nodes. Metastatic disease at initial presentation is reported in about 10% of patients.[10] Elderly groups were found to develop more locally advanced disease (T4, in TNM staging) but fewer neck node metastases.[9,13,14] Overall, distributions of disease stage and tumor differentiation present no major differences between older and younger patients.[13–15]

The major risk factors for HNC are the use of tobacco (85%) and the frequent and heavy consumption of alcohol. People who use tobacco and alcohol are at greater risk than people who use alcohol or tobacco alone. Other risk factors include sun exposure, age, gender, race, previous radiation to the head and neck region, occupational inhalant industrial exposures (wood or nickel dust), human papilloma virus (HPV) infection, Epstein-Barr virus (EBV) infection, Plummer–Vinson syndrome, poor oral hygiene and poor dietary vitamin intake.[16] Due to the fact that elderly populations with HNSCC have a lower rate of exposure to known risk factors, advanced age itself has been proposed as a main contributing factor in the development of this malignancy. Advanced aged may interfere with accumulation of mutations, decreased efficiency in DNA repair mechanisms and reduced immune surveillance. Koch et al.[9] in a study which included 81 patients older than 75 years and 102 patients aged between 40 and 70 years, showed that elderly people with HNSCC are more likely to have second primary cancers, particularly outside the head and neck region. Thirty-one percent of older patients had second cancers while 20% of younger patients had two primary cancers.[9]

This review aims to address controversies in the multidisciplinary management of elderly patients with head and neck cancers.

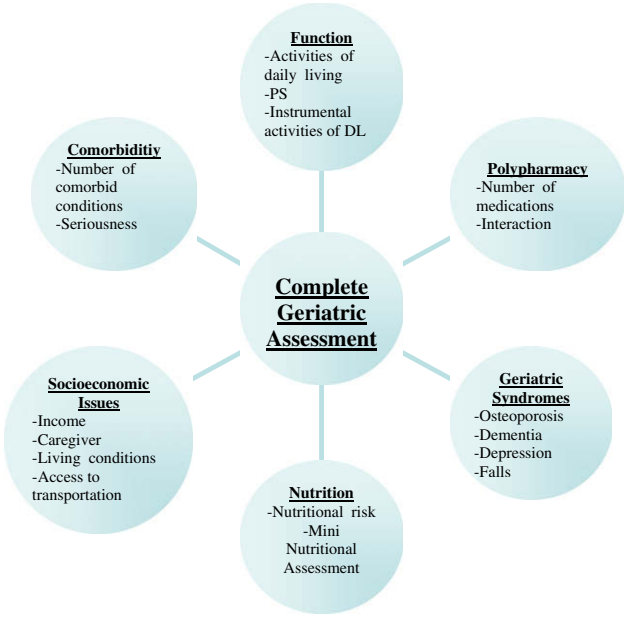
Geriatric assessment

Elderly patients are characterized by age-specific problems such as multi-organ functional decline, depression, alterations of mental status, reduced nutritional status and absence of social support, all of which have the potential to interfere with the diagnosis and treatment of their cancer. These problems are seen with different grades of severity in this subpopulation and, for this reason, chronological age by itself cannot be the only criterion for treatment planning. The biological age of each patient is one of the most important parameters and should be defined individually, based on co-morbidities and performance status.[17,18] The role of co-morbidities as a predictor of survival for patients older than 65 years with HNC was established by a study using data from the Surveillance, Epidemiology and End Results (SEER) Program in 9386 subjects.[19] A clinical study in 203 cancer patients with a median age of 75 years using the Cumulative Illness Rating Scale – Geriatric (CIRS-G) and the Charlson score scale showed that co-morbidity should be assessed independently from functional status.[20] This issue was further explored in a large retrospective study including 11.558 patients with breast, lung, colon and prostate cancer. The important finding of this study was that the prognostic importance of overall co-morbidity for these patients is relative to the mortality burden of the index cancer. Concurrent co-morbidities have the greatest prognostic impact among groups with the highest survival rate and the least impact in groups with the lowest survival rate.[21] Based on these studies performance status as well as co-morbidities play a major role in pre-treatment assessment of geriatric oncologic patients.

A Comprehensive Geriatric Assessment (CGA) is very helpful in geriatric oncology for the following reasons:

- It provides a reasonably accurate estimate of life expectancy.
- It allows the clinical team to identify factors-including illness 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 provides a common language for measuring health status before cancer treatment in clinical trials, as well as in retrospective evaluation of treatment outcome in older patients.
- It helps to predict the risks of complications from chemotherapy.[20,22–25]
- It helps to consent elderly cancer patients.

A general principle of geriatric medicine interventions is to achieve a "compression of morbidity". Current clinical trials in older individuals with cancer focus on preservation of functional independence and quality of life, in addition to prolongation of survival and reduction of tumor progression.[26] The management of elderly patients with HNC includes the use of radiotherapy, surgery and chemotherapy. The cornerstone treatment modalities are radiation therapy and surgery, or both combined, while chemotherapy is sometimes used as an additional or adjuvant treatment. Furthermore, the Complete Geriatric Assessment (Fig. 1) and a multidisciplinary approach (Table 1) are crucial points in classifying patients with functional limitations and may assist the oncologist in making the most appropriate therapeutic decision for each patient.[27,28] Recently, more extensive, precise and sophisticated instruments are under evaluation. Preoperative assessment of cancer in the elderly (PACE) was evaluated in 460 consecutively recruited patients aged 70 or more prior to elective surgery. PACE incorporates validated instruments including mini-mental state inventory (MMS), activities of daily living (ADL), instrumental activities of daily living (IADL), geriatric depression scale (GDS), brief fatigue inventory (BFI), ECOG performance status (PS), American society for anaesthesiologists scale (ASA) and Satariano's index of co-morbidities (SIC). Poor health in relation to disability assessed using IADL, fatigue and PS were associated with a 50% increase in the relative risk



PS: Performance Status

DL: Daily Living

Fig. 1. Multidisciplinary approach of elderly patients.

Table 1
Multidisciplinary approach (NCCN Practice Guidelines in Oncology – Senior Adult Oncology v.2.2007).

Head and neck surgery	Pain and symptom management
Radiation oncology	Nutritional support
Medical oncology	Enteral feeding
Plastic and reconstructive surgery	Dental care for RT effects
Specialized nursing care	Oral supplements
Dentistry/prosthodontics	Xerostomia management
Physical medicine and rehabilitation	Smoking cessation
Speech and swallowing therapy	Tracheotomy care
Clinical Social work	Social work and case management
Nutrition support	Supportive care
Pathology	
Diagnostic radiology	

of post-operative complications. The most important independent predictors of post-surgical complications were moderate/severe fatigue, a dependent IADL and an abnormal PS.[29]

Surgery

Surgery may be the treatment of choice if the primary tumor can be excised with an appropriate margin of normal tissue without causing major functional compromise. This treatment modality can be as effective in elderly patients as in younger patients without a significant increase in mortality and complications. An aggressive approach to HNC with adoption of a curative intent can also be considered in elderly patients with advanced cancer.[30] The choice of definitive local therapy must take into account:

- The likely functional outcome of treatment.
- The resectability of the tumor.
- The comprehensive geriatric assessment.
- The patient's wishes.

The incidence of metastases found on histological examination of neck specimens after RND in patients with clinically node negative necks is shown in Table 2. It is suggested that prophylactic treatment of the neck is required if the risk for occult nodal metastases rises above 20%.[31]

The literature demonstrates that individualized surgical management of elderly HNC patients can be effective, well tolerated, and clinically indicated. The first positive results for aggressive surgical therapy in elderly patients was provided by a study which reviewed 162 elderly patients with operable HNC and compared them to 552 younger patients receiving similar treatment procedures.[32] In another study that reviewed the perioperative mortality in 810 cancer patients over the age of 65 years who had undergone major head and neck resections under general anesthesia, the mortality rate was as low as 3.5 percent.[33] A later study compared 43 HNSCC patients, aged 80 years and older, with 79 similar patients, aged 65 years or younger. The median overall survival for the older age group was significantly lower than that for the controls ($P = 0.001$). However, their overall survival was similar to the actuarial survival for the general population of the same age. Advanced age also adversely affected local control ($p < 0.001$) and disease-specific survival ($P = 0.041$). Although the older age group had a higher frequency of morbid preoperative conditions, there were no significant differences in perioperative or post-operative complications between the two groups.[14] This issue has been addressed in another study in which 24 consecutive HNSCC patients, aged 70 years and over, underwent extensive surgical resections and reconstruction. The outcome data were judged to be very good and complication rates were deemed acceptable.[34] According to a study by Laccourreye et al. surgery is feasible and well tolerated in elderly patients with carcinoma of the glottic and supraglottic larynx. Although these surgical procedures pose a higher risk of aspiration pneumonia, only 22% of the 69 treated patients presented pulmonary complications in the first 6 months of follow-up.[35]

Table 2
Nodal status in node negative neck after elective surgery (Scottish Intercollegiate Guidelines Network "Diagnosis and Management of Head and Neck Cancer", October 2006)

Subsite	Percentage of metastases in Prophylactically treated necks
Oral cavity	>20%
Glottic	0–15%
Supraglottic	8–30%
Oropharyngeal	>50%
Hypopharyngeal	>50%

Due to the presence of degenerative conditions and co-morbidities, reconstructive surgery with free flaps in the elderly is a controversial area. Several retrospective studies show that microvascular free tissue transfer is a safe and reliable option in the great majority of elderly patients. The risk of medical and surgical complications following reconstruction is directly related to the presence of concurrent illness in individual patients, rather than to age and duration of the operation.[36–40] On the other hand, a small study in 13 octogenarians who underwent free flap reconstruction of defects resulting from HNC surgery concluded that microvascular reconstruction in the very old subpopulation is reliable but the incidence of medical complications and the monetary cost are significantly increased.[41]

The presence of co-morbidities in the elderly population represents the key indicator for a patient selected for surgical management since they influence not only the administration of anesthesia but also the incidence of post-operative complications. The administration of anesthesia must be individually planned in older patients, because the pharmacokinetics and pharmacodynamics of anesthetic agents are not the same as in younger patients. Elderly patients with HNC have unique airway issues that must be addressed preoperatively. Likewise, thorough planning for perioperative management is imperative to reduce morbidity and mortality.[42,43] It has been proved that time under general anesthesia showed a statistically significant relationship with complication rate and hospital length of stay. Data analysis from 157 medical chart review cases revealed that time under general anesthesia was the only factor consistently related to complications ($p < 0.006$), and it was the only factor consistently related to length of stay ($p < 0.001$). Analysis of major complications (6% incidence) as an outcome using univariate analysis resulted in a strong positive correlation with both co-morbidity indexes: adult co-morbidity evaluation 27 ($P = 0.002$) and Charlson Co-morbidity Index ($P = 0.005$). Multiple logistic regression showed no significant relationship between age 70 years or older (20% of patients) and either complications or length of hospital stay.[44] Consequently, a precise and extensive pre-operative assessment is crucial. For example, as depression is a prognosticator for longer hospital stay, a course of anti-depressants should be prescribed before surgery, or well-controlled glucose levels should be maintained pre-operative in patients with diabetes mellitus.

Co-morbidity, measured with ACE-27 (Adult Co-morbidity Evaluation-27) in a small study, is a prognostic factor for overall survival in patients older than 70 years with HNC. In addition, Karnofsky performance index, mental condition, quality of life and the existence of systemic diseases have been assessed in several studies.[45] In one study, 121 patients (83 men and 38 women from 70 to 94 years old) who were treated for HNC were classified into two groups by age – the "aged" at 70–79 years and the "very old" at 80 years and older. A younger group aged 50–59 years was

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also evaluated. The frequency of post-operative complications correlated significantly with the American Society of Anesthesiologists (ASA) classification of physical status and preoperative performance status (PS). Complications of surgery, including pneumonia, dehydration, and feeding disturbance occurred in 53% of the very old. Cures were achieved in 83.9% of controls, 81.5% of the aged, and 65.0% of the very old. Tumor-specific 5-year survival rates were 85.2% for controls, 84.5% for the aged, and 80.0% for the very old. Median survival in those not cured was 4 months in controls, 9.6 months in the aged, and 5 months in the very old. OoL was similarly deranged after surgery both in the young and elderly age-groups.[46] Besides, two more studies have shown that PS and ASA are marginally specific for the elderly.[29,43]

According to a large study of 242 patients who were aged more than 70 years who underwent surgery for HNC, co-morbidities were present in 87.6% and 56.6% had some type of complication (44.6% local and 28.5% systemic). Post-operative complications were associated with male sex, bilateral neck dissection, presence of two or more co-morbidities, reconstructive surgery and clinical stage IV disease. The major study finding is a remarkable probability (ROC curve of 69%) of predicting post-operative complications in older patients with head and neck tumours who underwent oncologic surgery using clinical preoperative variables.[47]

As regards the quality of life (QOL) following surgical management of HNC, no significant differences were observed between elderly and younger patients. Dhiwakar et al.[48] reported a study in which patients completed questionnaires about QOL (EORTC QLQ-C30 and QLQ-H&N35) and depression (CES-D) before and 3 months after surgery. Before treatment, elderly and younger patients did not differ in QOL parameters. Three months after treatment, both groups scored worse on most QOL aspects, but there were no significant differences between the elderly and the younger patients.[48] In another study, several QOL domains were evaluated in elderly patients undergoing major head and neck surgery when compared with younger patients. With the SF-12 (Short Form-12), physical, emotional, and bodily pain were decreased by the surgical intervention, while physical function was affected by age alone. With the UW-QOL (University of Washington- Quality of Life) Questionnaire, overall QOL was preserved. ‘‘Appearance” and ‘‘Leisure” subscales were affected by the surgical intervention and old age. ‘‘Chewing” and ‘‘Activity” were decreased by the surgical intervention in the older patients, and ‘‘Speech” was affected by the surgical intervention alone. The ‘‘sense of burden” was alleviated by surgery in the elderly patients.[49]

Conclusively, the majority of retrospective studies support appropriate surgical management of resectable HNC in elderly people. Careful pre-operative staging and evaluation of associated medical illnesses, as well as skillful peri- and post-operative management, are essential for reducing operative morbidity and mortality in the elderly. Successful outcomes depend on appropriate surgical management, treatment of concurrent illnesses, and minimization of post-operative complications.

Radiotherapy

Radiotherapy (RT) for HNC can be delivered with curative intent (radical RT), in order to improve local control following surgery (adjuvant RT) or to provide symptomatic relief (palliative RT). RT for HNC is extremely complex. Anatomic, tumor and clinical circumstances govern the use of radiation as primary treatment or as an adjuvant to surgery in combination with chemotherapy for HNC. The prescribed radiation dose depends on the tumor and neck node size, the location of the tumor and clinical circumstances.

RT conserves the organ concerned and, at least partially, its function. Modern radiation techniques make it possible to irradiate a limited target with increased doses. In elderly patients this may be very important in terms of tolerance and improved quality of life.[50] RT alone results in high tumor control and cures rates for early stage glottic, base of tongue and tonsillar cancer. In addition, by default it represents the treatment of choice for those who are considered unfit for surgery or in whom surgery leads to an unacceptable functional outcome. As a general rule, the primary tumor and gross lymphadenopathy require a total of 70 Gy or more at a dose fractionation of 2 Gy/day, while radiation to suspected microscopic disease in nodal levels that have not undergone surgical excision requires a total of 50 Gy or more at 2 Gy/day. Higher dosages (60–65 Gy) are required for node positive patients, in order to reduce the locoregional reoccurrence rate. The reason for the higher prescription dose in the post-operative setting is because of interruption of the normal vasculature, scarring and relative hypoxia in the tumor bed.

The most widely used RT fractionation in elderly patients with HNC is conventional fractionation of 1.8–2.0 Gy/fraction, 5 days a week over 7 weeks up to a total dose of 70 Gy. Hyperfractionation was designed to improve effectiveness by delivering more than one fraction per day with a reduced dose per fraction but 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 to deliver a dose of more than 10 Gy per week. By keeping the same total dose of radiation as conventional RT, accelerated RT ensures that treatment is completed more rapidly (e.g. in 5.5 to 6 weeks).[51] Accelerated schedules attempt to compensate for rapid tumor proliferation by compressing the time – dose schedule. Accelerated RT and hyperfractionation RT, which are often used in combination, represent a promising method to improve the treatment outcome in HNC. No single fractionation has proven to be best for all tumors of the head and neck.[27] However, two large randomized clinical trials, the EORTC protocols 22791 and 22851, have reported improved locoregional control using altered fractionation. The EORTC 22851 trial studied 512 patients with a median age of 57 years. Patients up to 75 years and with PS $\leqslant 2$ were eligible. Precise percentages for the different age groups are not available. Interestingly, 20% of patients presented with co-morbidities. In the EORTC 22791 trial, 325 patients aged up to 75 years were evaluated but there was no stratification by age and detailed data on age distributions were not provided.

In the United States, the Radiation Therapy Oncology Group (RTOG) conducted a large phase III clinical trial (protocol 90-03), comparing hyperfractionation with two variants of accelerated fractionation. Half of the eligible patients were aged over 60 years. The results showed a locoregional tumor control advantage and marginal survival benefit at a cost of slightly increased acute and late side effects for both accelerated and hyperfractionated regimens compared with conventional radiotherapy.[52] Consensus regarding altered fractionation schedules with concomitant boost or hyperfractionation for stage III or IV oral cavity, oropharynx, supraglottic larynx and hypopharyngeal squamous cell cancers has not yet emerged among NCCN member institutions. A meta-analysis of 15 randomised trials with 6515 patients was recently published. Trials with a curative intent comparing conventional radiotherapy with hyperfractionated or accelerated radiotherapy were included. The main analysis conclusion was that altered fractionated radiotherapy is better than conventional radiotherapy for overall survival and primary tumor control. It was also suggested that hyperfractionation presents a more consistent survival advantage than accelerated radiotherapy. However, an increased risk of late toxicities was observed with accelerated fractionation without total dose reduction. Focusing on elderly patients, there is a suggestion of a decreasing effect of altered fractionated radiotherapy with increasing age and poor PS. Elderly patients and individuals with poor performance status showed lower compliance and

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tolerance, besides there being an excess in non-cancer related deaths in patients over 71 years.[53]

Intensity-modulated radiation therapy (IMRT) is an advanced computer generated beam modulation that permits exquisite radiation dose sculpting around complex target volumes. It has been used in treating HNC with twin goals: (i) to protect normal tissues (eg. salivary glands, spinal cord) from late normal tissue damage **[54] and (ii) to attempt radiation dose escalation in the tumour.[55] Besides, this technique allows for delivery of a synchronous integrated boost in which treatment field modifications, such as matching, are no longer needed. Preliminary clinical results of IMRT are encouraging for the treatment of SCCHN.[54,56,57]

Several studies have shown that RT is effective and well tolerated in an ageing population and age does not represent a limiting factor for radiation therapy.[8,58–62] Two decades ago, a large retrospective study reviewed 249 elderly patients treated with radical irradiation for cancers of the upper aerodigestive tract and 59 elderly patients who received radiation therapy with a palliative intent. The immediate and long-term tolerance was good. The local control was 71% for patients treated with a curative intent and 19% for the palliatively irradiated patients. Five-year survival of the population was 33%. No significant relationship between age, general status, and the cancer-specific outcome could be observed.[13] In another study, 75 patients aged 75 years or more (median 78.5 years) were treated with curative intent for carcinomas of the head and neck excluding the nasopharynx, paranasal sinuses, salivary glands and lips. Seventeen patients received post-operative radiotherapy while 58 were treated with radiotherapy alone. The survival curve of the patients followed the curve of the normal population after a rapid drop in survival within the first 2 years. Median times to local relapse were 3 and 4 months, respectively, for early and advanced stages, and 6 months for glottic carcinomas. Although retrospective, the results suggest that the ultimate outcome in elderly patients with carcinomas of the head and neck is comparable to the course of the disease in younger patients.[63] In a cohort of 203 patients older than 80 years who received radiation therapy for any kind of malignancy, fifty patients were treated for HNC in different sites and stages. The objective response rate was 86%, with 66% complete remissions in the radically treated group, while palliation of the symptoms of the disease was achieved in 67% of patients.[64] A further study reviewed 98 patients aged 80–92 who received radiotherapy for carcinoma of the head and neck. All patients received beam directed radiotherapy with radical intent using an immobilisation shell. Cancer specific survival was 59% and overall local control was 70% at 5 years, both were significantly affected by T stage and site of disease. Cancer specific survival was comparable to that of patients aged below 80 years. Seven patients died within 6 months of completion of treatment. Three patients developed severe late toxicity and metastatic disease occurred in eight patients.[65] Similar results were obtained in another study in which 88 patients received radical radiotherapy and 16 palliative radiotherapy for oropharyngeal cancers. Treatment intent, radical or palliative, did not appear to be related to age, before ($P = 0.42$) or after adjusting for other factors ($P = 0.34$). Older patients were prescribed and received lower doses of radiation. However, older age was not related to the risk of loco-regional recurrence ($P = 0.96$) or shorter survival ($P = 0.67$), and was not associated with duration of treatment interruption or severity of toxicity after adjustment for prognostic factors. There was some suggestion of a higher risk of recurrence with increasing age for patients under 70 years, but the risk for patients over 70 was at least equal to that of the youngest group. Older patients with loco-regional oropharyngeal cancer, or at least a subset of them, appear to be able to tolerate radical courses of radiotherapy, and to have outcomes that are similar to younger patients.[62]

Radiotherapy may be beneficial even in the "oldest old" subpopulation. A study which included 23 patients whose ages ranged from 90 to 96 years (median 93) reported that age over 90 years does not affect the effectiveness of RT or patient tolerance. RT was individually planned, depending on the stage of the disease and PS of the patient. All the patients who received definitive radiation therapy completed their treatment with 62% of them obtaining local control. Seven of 11 patients who received palliative radiation therapy completed their treatment with 81% of them achieving palliation. Radiation-induced acute dermatitis, mucositis, pharyngitis and esophagitis of grade 2-3 were tolerable for patients with good PS.[66] An additional study examined the results of radiotherapy in patients older than 90 years. Thirty-two patients (14 patients with HNC) underwent radiation therapy. This study concluded that age did not represent a limiting factor for radiation therapy.[58] Definitive conventional radiation therapy should be considered, when applicable, even for patients older than 90 years with good PS while these patients present increased response rates at acceptable toxicity. Elderly patients should be considered for treatment with accelerated concomitant boost schedules, so long as they are physically healthy enough to undergo curative treatment. One such study enrolled 39 patients aged >70 years (mean, 75 ± 6 years) who presented with carcinomas of the oral cavity, pharynx, or larynx. They were treated radically with a modified concomitant boost RT schedule (planned dose of 69.9 Gy over 38 days). The planned RT schedule was completed in all cases. According to the Radiation Therapy Oncology group grading system, Grade 3–4 acute reactions were observed in 66% of elderly patients and in 71% of younger patients. Grade 3–4 late complications were observed in 3% of the elderly patients and 10% of the younger patients ($P = 0.43$). Both elderly and younger patients had similar results with regard to 3-year actuarial overall survival (68% vs. 62%; $P = 0.48$) and locoregional control (73% vs. 68%; $P = 0.31$). The acute and late toxicities appeared to be similar to those observed in younger patients, and treatment outcomes appeared to be comparable.[67]

Both acute and late complications induced by RT can be very severe when treating HNC. The side effects of RT are caused by unavoidable irradiation of normal tissues adjacent to the tumour. They can be described as "acute", those that occur during or immediately after radiotherapy or "late", those that occur months or years after treatment has been completed. In patients with HNC, common side effects that are likely to cause patient discomfort are: mucositis and xerostomia (dry mouth) caused by irradiation of the salivary glands, particularly the parotid glands and consequent reduction in salivary flow. Skin included in the irradiated volume may also suffer from acute and late toxicity from radiotherapy. Some researchers support the idea of not delivering palliative RT in HNC elderly patients due to the disproportionately high toxicity induced in order to achieve a clinical response.[50]

The elderly are often treated less aggressively in an attempt to preserve their quality of life with regards to toxicity. However, there are few data regarding the acute and late toxicity of radiotherapy (RT) in elderly patients. From February 1980 to March 1995, 1589 patients with head and neck cancers who enrolled in EORTC trials received RT and were available for analysis on RT toxicity. Patients over 65 years of age were in excess of 20%. Data regarding age and acute objective mucosal reactions were available for 1307 patients, from which 1288 had toxicity of grade 1 or more. Age and acute functional mucosal reactions were registered for 838 patients and 824 patients had toxicity of grade 1 or more. Data on body weight alteration during treatment was available in 1252 patients; it increased in 153 patients and decreased in 1099 patients. Late toxicities were examined only if they occurred before an eventual tumour failure in order to avoid confusion between effects of first- and second-line treatments. Seven hundred and forty nine

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patients were available for analysis of whom 646 had late toxicity of grade 1 or more. Survival and toxicity were examined in different age ranges from 50 to 75 years and over. There was no significant difference in survival between each age group. A *t*-test was performed to assess any correlation between age and the acute toxicity. There was no significant difference in acute objective mucosal reactions ($P = 0.1$) and in weight loss more than 10% ($P = 0.441$). In contrast, older patients had more severe (grade 3 and 4) functional acute toxicity ($p < 0.001$) than younger patients. The probability of the occurrence of late toxicity in relation to time was evaluated with the Kaplan-Meier method and the log rank test in each age group. Eighteen per cent of patients were free of late effects at 5 years, the log rank test showing no significant difference between ages ($P = 0.84$). In conclusion, chronological age is irrelevant for therapeutic decisions. Supporting data come from the Italian "Geriatric Radiation Oncology Group" (GROG) which performed a prospective study in 2060 patients aged 70 and over who received radiotherapy alone or in combination with surgery and/or chemotherapy for any cancer. Most patients had grade 1 acute toxicity.[68]

The management of acute and late RT-induced toxicities in the elderly should follow the same protocols as for younger patients. Some degree of xerostomia is often permanent and results in discomfort, eating difficulties, taste alteration and high risk of accelerated dental caries. The evidence does not support a specific intervention for the prevention of radiation-induced xerostomia but some researchers explore the role of amifostine in the rate of acute and late xerostomia.[69] There is no evidence to support any other intervention for prevention or treatment of radiation mucositis. A patient's mucosa should be inspected regularly during treatment and analgesia and antimicrobial/antifungal agents to treat infection should be made available. Specific interventions for the prevention or treatment of radiation skin toxicity are not recommended other than routine use of topical moisturising agents before the onset of moist desquamation.

Finally, the indications for RT in elderly cancer patients should take into account multiple parameters and be based on a thorough geriatric assessment. Chronological age itself is seldom a contraindication for radiation therapy. Radiation therapy can be safely administered to an elderly population aged 80 years and older with both curative and palliative intent with the expectation of completion in more than 80% of patients.[70] Regarding the available data in the literature, there is no indication for a dose reduction because of age, especially in the curative setting. Extensive atherosclerotic vessel damage should be a factor of discussing the radiation dose intensity. It has been reported that older patients suffer more functional mucositis after radiation therapy to the head and neck and they may suffer increased weight loss. Elderly patients should be monitored closely during therapy, since the loss of electrolytes or fluid is often not well tolerated.[71] If the patient is in a good general condition following a complete evaluation of the cancer, physicians should have no qualms about proposing curative treatment with radiotherapy.

Chemotherapy

The role of chemotherapy in HNC is expanding and its utility varies with the stage of the disease. For patients with metastatic or incurable locoregional disease, chemotherapy is palliative. In contrast, for patients with potentially curable locoregional HNC, chemotherapy is an integral component of the multimodality approach, particularly when the disease is unresectable or organ preservation is one of the goals of therapy. The administration of chemotherapy in patients with HNC in combination with locoregional therapy (surgery or radiotherapy) may be:

- Neoadjuvant/induction: delivered in the weeks before surgery or radiotherapy.
- Adjuvant: delivered following radiotherapy or surgery.
- Concomitant: delivered during a course of radiotherapy.

Standard chemotherapy for HNC is a sequential combination of cisplatin and infusional 5 fluorouracil (5FU). In the treatment of locoregional recurrence or distant metastases, this combination achieves a response rate of 40–50% (CR 5–10%). In the induction setting (e.g. chemotherapy before definitive chemoradiotherapy) for organ preservation, this regimen yields response rates of 70–88% (CR 40–60%).[72]

The addition of chemotherapy to locoregional treatment for patients with non-metastatic squamous carcinoma of head and neck significantly improves survival, with absolute survival benefit of 8% at two and five years.[73] Induction cisplatin-5FU chemotherapy followed by concurrent chemoradiation results in excellent locoregional control and lower distant reoccurrence rates. In this study patients up to 78 years were included.[72] Recently published studies have shown that the addition of cisplatin in adjuvant radiotherapy after surgery is beneficial when extracapsular spread or positive margins are present.[74] However, the size of benefit with concurrent chemoradiotherapy is age dependent, with the largest benefit in those aged 60 or less (Table 3). The survival benefits associated with concurrent chemoradiotherapy are at the expense of increased acute toxicity (mucosal and haematological) and possibly late toxicity, particularly dental problems.[73]

New chemotherapeutic agents and new combinations are under investigation for locally advanced HNC. Patients with locoregionally advanced disease who received docetaxel plus cisplatin and fluorouracil as induction chemotherapy plus carboplatin-based chemoradiotherapy had a 12% absolute survival benefit when compared with patients who received cisplatin and fluorouracil induction chemotherapy plus carboplatin-based chemoradiotherapy. This study enrolled patients up to 82 years old.[75] Furthermore, in another study, induction chemotherapy with the addition of docetaxel significantly improved progression free and overall survival as compared with the standard regimen of cisplatin and fluorouracil in patients with inoperable-advanced head and neck cancer. In this study 10% of the enrolled patients were between 65 and 71 years old.[76]

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.[77]

Combined data from two mature phase III randomised 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) evaluated the toxicity, objective response rates, and survival of patients 70 years or older versus their younger counterparts. Fifty-three elderly patients with HNC were enrolled from a total of 399 eligible participants (13%). Elderly patients had similar objective response rates (28% vs. 33%) and median time to progression (5.25 vs. 4.8 months) compared with younger patients. The median survival was 5.3 vs. 8 months (Wilcoxon $P = 0.06$; log-rank $P = 0.17$) and the 1-year survival was 26%

Table 3
Risk reduction of death after concurrent chemotherapy by age (Scottish Intercollegiate Guideline Network "Diagnosis and Management of Head and Neck Cancer", October 2006).

Age (years)	Percentage reduction in risk of death
60 or less	22–24%
60–70	12%
Over 70	3%

vs. 33% for elderly and younger patients, respectively. 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% vs. 8%; $P = 0.29$). Fit elderly patients with recurrent or metastatic HNC sustained increased toxicities with cisplatin-based doublets, but had comparable survival outcomes compared with younger patients. Strategies to ameliorate toxicities should be pursued in the elderly.[78]

Age has been associated with pharmacokinetic and pharmacodynamic changes and with increased susceptibility of normal tissues to toxic complications. Chemotherapy complications such as neutropenia, anemia, bleeding, mucositis, cardiac toxicity and neurotoxicity are more frequently observed in the elderly and may precipitate individual functional independence.[79] Besides, chemotherapy and agents used to prevent its toxicities interfere with cognition, balance, vision, continence and mood. Moreover, polypharmacy (a frequent situation in the elderly) may lead to interactions with cytotoxic chemotherapeutic agents. All of these conditions may combine to increase the risk of chemotherapy.

In general, chemotherapy seems to be feasible in elderly patients with HNC, although its side effects may be exaggerated. However, a reduction in the administered dosage based purely on chronological age may seriously affect the efficacy of treatment. Effective management of chemotherapy-associated toxicity with appropriate supportive care is crucial in the elderly population to give them the best chance of cure and survival, or to provide palliation.[80]

Co-morbidities also increase the risk of toxicity due to delayed renal excretion or hepatic metabolism. Furthermore, the drugs used to treat co-morbidities may interact with chemotherapeutic drugs, potentially increasing toxicity in elderly patients. Prospective trials in older patients with lymphoma or solid tumours have found that age is a risk factor for chemotherapy-induced neutropenia and its complications.[80]

Nutrition is often deficient in elderly patients, due to several reasons such as depression, poor dentition, functional impairment, cognitive impairment, lack of appetite due to chronic co-morbid disease and lack of caregiver. Elderly patients with cancer may also face additional problems brought on by chemotherapy, such as nausea, diarrhea, vomiting and painful oral ulceration. Correcting malnutrition and establishing a suitable dietary plan can substantially improve the patients' clinical outcome and quality of life.

Bone marrow toxicities must be corrected in older patients with cancer. Anemia is usually present because of the disease or its treatment and, if left uncorrected, it can not only alter drug activity and increase toxicity but also represent a risk factor for decreased distribution of water-soluble drugs, cardiovascular disease, congestive heart failure, coronary death and possibly dementia. Maintenance of haemoglobin concentration at 12 mg/dL or higher is essential for an elderly population.[80] In addition, the EORTC has established recommendations for the prophylactic use of colony stimulating factors (G-CSF) in older patients with cancer in an attempt to combat neutropenia, neutropenic fever and sepsis.

Targeted therapy

Cetuximab is an IgG1 monoclonal antibody against the ligand-binding domain of EGFR. Cetuximab enhances the cytotoxic effects of radiation in squamous cell carcinoma.[81–84] A multicenter randomized controlled trial involving 424 patients has demonstrated that concurrent administration of cetuximab, with radical external beam radiotherapy in locoregionally advanced HNC resulted in an 11% improvement in progression-free survival and a 10% improvement in overall survival compared to external beam RT alone. There was no increase in radiotherapy-related toxicity. Radiother-

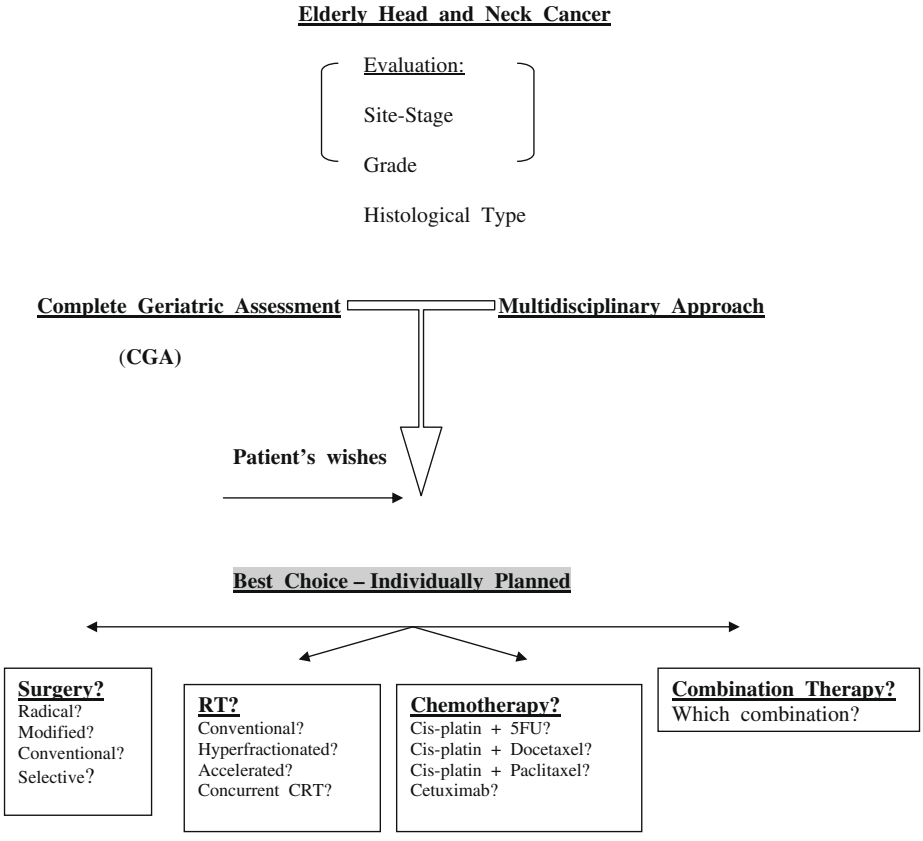

Fig. 2. Individualized treatment plan in elderly with head and neck cancer.

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apy was either conventionally fractionated, hyperfractionated or accelerated.[81] There are no clinical studies of cetuximab with sufficient numbers of elderly patients (65 years old and over) with HNC to determine whether they respond differently from younger subjects. Interestingly, study groups are just starting clinical trials on the use of cetuximab in the elderly. Certainly, the recent UK recommendation by the National Institute for Clinical Excellence (NICE) did not use age as an indication (or contra-indication) for the use of cetuximab therapy.

Combination therapy

It is important to identify appropriate patients for combination therapy. The presence of severe co-morbidities, age-related frailty or underlying severe psychosocial problems may be obstacles for highly intensive treatment plans. Such patients may benefit from less complicated or potentially less toxic treatment plans. The biology of the patient's disease must also be considered in selecting or planning a combined modality approach. Patients with rapidly growing tumours or with advanced nodal presentation are less likely to be cured with surgery or radiation therapy alone and are most likely to benefit from the addition of chemotherapy. The location of the primary tumour is also an important factor in selecting therapy. Small lesions in the larynx, base of tongue and hypopharynx may benefit from an organ preservation approach, while similarly sized lesions in the anterior oral cavity are better treated with direct surgical and radiotherapy approaches. The goals of the addition of chemotherapy in a treatment plan must be considered in determining therapy: appropriate goals in the curative treatment of locally advanced HNC include organ preservation, improved survival, optimization of quality of life and reduction of metastases.

One hundred eighteen patients aged 70 or above with HNC were compared to 148 younger patients (45–60 years) in a follow-up period of up to 6 years. During long-term follow-up, 33 younger and 24 older patients completed the EORTC head and neck quality of life forms (QLQ-C30 and H&N35) and a questionnaire about depression. The survival rate after 3–6 years for younger patients was 36%, as compared to 31% in the older patient group. Higher tumour stages, more co-morbidities and non-standard treatment showed to be independent prognostic factors for mortality. No independent prognostic value of age could be found. The global QOL scores remains roughly comparable. Even up to 6 years after treatment, no significant differences in overall survival or overall QOL were found between older and younger HNC patients.[85]

Conclusion

Medical intervention in the elderly is justified when the potential benefits outweigh the potential risks. Both the older patient and the clinician are faced with four questions before cancer treatment starts:

- Is the patient likely to die directly from the cancer or from another cause? 2. Is the patient going to live long enough to suffer the consequences of cancer?
- Is the patient able to tolerate the treatment?
- What outcome should we expected from the intervention?

Fig. 2 summarizes the initial planning of treatment for elderly with HNC. The route to optimal management for each geriatric patient with HNC lies primarily in an holistic approach to patient assessment (Complete Geriatric Assessment) and secondarily in provision of high quality multidisciplinary team, management/support. The addition of the patient's wishes to the aforementioned may lead to the best treatment plan.

Decision-making in cancer therapy for elderly patients is challenging for medical professionals since this subject is clouded by a high rate of uncertainty. Fear of the morbidity of aggressive therapy regimens often leads to incomplete diagnostic and therapeutic measures being taken. There is almost complete international consensus, that patients suffering from operable squamous cell cancer of the head and neck should be treated with curative intent, if thorough preoperative assessment of co-morbidities is performed. Optimal medical adjustment of relevant concomitant diseases clearly improves the starting point. Age itself should never be the sole factor that decides which treatment is delivered. Exceptions may be made in patients with severe general co-morbidity and exclusion should be based, as for younger subjects, on an individual basis.

Conflict of interest statement

The authors declare no conflict of interest.

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