Treatment of Elderly Patients with Head and Neck Cancer

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Introduction

In 1981, when the first conference addressing the topics of cancer in the elderly was held by the US National Institute of Aging, the history of geriatric oncology began to unfold. Following this event, several literature reviews pointed out the apparent underrepresentation of older individuals in clinical trials. As a result, studies funded by the US National Cancer Institute no more considered advanced age automatically as an exclusion criterion, and new trials focusing specifically on the elderly population were initiated. It has become clear that despite being more vulnerable to complications of cytotoxic chemotherapy, senior persons may derive the same benefit as their younger counterparts if biological and not chronological age is taken into account [1]. In fact, about half of patients over 70 years of age can be treated with standard oncologic approaches, while the other half will require more extensive measures [2–5]. Still, for numerous reasons including disqualifying medical conditions, logistical issues, long-established institutional practices, and personal physicians' attitudes, the needs of elderly individuals remain largely unmet. They have been underrepresented in prospective trials, undertreated in routine practices, and refrained from a proper geriatric assessment. The former remains to be a continuing issue despite the fact that their willingness to participate in clinical research does not seem to pose a barrier [6]. Here, the ensuing lack of evidence-based data hampers effective implementation of novel drugs and development of clinical practice guidelines.

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Focusing mainly on systemic therapy, this chapter details cancer care in the elderly with squamous cell carcinoma of the head and neck (SCCHN), both in the locoregionally advanced and the recurrent and/or metastatic settings. It sets out to briefly review the answers to the following two fundamental questions: "How to select an appropriate approach to an elderly person?" and "What is the current state of clinical evidence in these patients?" Usually amenable to single-modality surgery or radiotherapy, the early disease setting will not be addressed here.

Cancer and Ageing

As documented in many epidemiological studies, there is a marked association between tumour development and ageing. Advanced age is indeed the major risk factor for cancer, which in turn represents the second most common cause of death for persons 65 years and over in Europe [7, 8]. In accordance with demographic projections clearly showing the steadily growing number of elderly people, the global cancer burden will nearly double in the near future. By 2030, up to 22 million new cases (12 million in those 65 years or older) and 13 million cancer deaths (8.4 million in those 65 years or older) are to be expected worldwide each year. Of note, these figures exclude non-melanoma skin cancers, which are frequent and generally well curable [9]. However, the biological landscape of malignant transformation in older adults is far from being straightforward. Besides the dominant role of somatic mutations accumulating over lifetime, other age-related processes promote but also hinder tumorigenesis. Vascular ageing and a decline in circulating levels of various hormones probably counteract neoplastic progression, while it may be fostered by chronic low-grade inflammation and an increased fraction of senescent cells [7]. Interestingly, cancer incidence and mortality were reported to decrease or plateau in the oldest population (over 90 years) owing partly to the selection of less vulnerable individuals [10].

With an annual incidence reaching almost 700,000 cases worldwide, SCCHN follows the same epidemiologic trends as outlined above [11]. According to the 2010 cancer incidence projections for the United States, 54% of malignant head and neck cancer cases occurred in patients 65 years and older. By 2030, the proportion is expected to rise to 66% [12]. Considering that at present the median age at diagnosis of laryngeal carcinoma is 65 years, and of oral cavity and pharynx cancers 63 years, such estimates are certainly understandable [13]. Although major risk factors for SCCHN in the elderly are still tobacco and alcohol consumption, their prevalence is lower than in an unselected population (40% versus 70%) underscoring age alone as an important risk factor. Compared to younger patients, older age groups have a higher ratio of female cases and are more likely to have primary tumours located in the oral cavity and larynx but less in the hypopharynx. Metastatic spread to the regional lymph nodes and human papillomavirus-associated (HPV) oropharyngeal cancer also appear to be less frequent in the elderly [14]. More importantly, however, there is an increase in non-cancer-related mortality responsible for about one third of deaths within the first 5 years after SCCHN diagnosis in senior patients [15].

Chronological Versus Biological Age

But how to define old age? This is one of the key questions; unfortunately, no universally accepted criteria exist that would facilitate clinical decision-making. The elderly are usually classified into young old (65–75 years), old old (76–85) and oldest old (>85) [1]. This categorisation has been adopted by the National Institute on Aging and the National Institutes of Health, whereas most clinical studies use the age of 70 (or even 75) as a cut-off defining the elderly [16]. In fact, the latter cut-off point may better capture the reality in terms of biological alterations occurring with advancing age, because aging is associated with a progressive loss of functional reserve of multiple organ systems, increased prevalence of chronic diseases, enhanced susceptibility to stress, and fluctuations in social support and economic resources [1]. These age-related changes occur at different rates in different individuals, and we already begin to recognize and actively pursue ways to delay them. Owing to the progress in medical care and improvements in the quality of our everyday life, senior people nowadays are distinct from their ancestors' generations. In 2011, the first wave of the Baby Boom generation, born after the Second World War between 1946 and 1964, reached the pension age of 65. The so-called Boomers demand more involvement and competence in their health care, seek social engagement and healthy lifestyle, continue to have physical and intellectual activity, and use the Internet and modern information technologies [17]. Interestingly, the positive impact of a more active and healthier lifestyle in elderly people on the development of dementia has recently been reported in the United States [18].

Thus, it has become clear that chronological age does not sufficiently correlate with biological parameters and provides only limited information for personalized management. In the elderly, progressively declining organ functions and associated metabolic changes are responsible for higher prevalence of comorbidities and deterioration in cognition, functional and nutritional status, and psychological state. For this reason, biological age represents a more suitable parameter to express the heterogeneity of the geriatric population. Such diversity is reflected by individual life expectancy, functional reserve, and even the risk of treatment side effects [19]. In clinical practice, the crucial step is to distinguish a fit-old individual, who will likely withstand a radical treatment with curative intent, from a frail-old patient, who will probably not tolerate such approach. So, coming back to the topic of chronological age, is there any point in using landmarks for defining the elderly? Actually, there is. It should instigate us to evaluate the patients for their biological age by applying geriatric assessment as will be discussed later in the text [20].

Despite these arguments, many physicians concerned about excessive toxicity still tend to use chronological age as a sole discriminator and opt for non-standard or less aggressive therapies in otherwise healthy elderly persons [21]. Retrospective data indicate that only half of these patients are managed according to institutional policies [22–24]. The resulting suboptimal treatment has been hypothesized as one of the reasons for shorter survival. In oral cavity and pharynx cancers, Surveillance, Epidemiology, and End Results (SEER) data from 2007 to 2013 revealed 5-year

overall survival of 56% and 69% for older (≥65 years) and younger patients, respectively [13]. Further factors contributing to such a difference in the outcomes include serious age-related comorbidities and individual patient decisions to avoid receiving full-dose regimens [25]. This is in line with the results of a long-term prospective observational study of 266 individuals showing that chronological age has no independent prognostic value as opposed to comorbidities and non-standard treatment [26].

One possible solution of how to address the complexity in delivering patient care at an individual level is a team approach in treatment planning represented by multidisciplinary tumour boards. These meetings should offer a collaborative review of each case with a special attention to disease factors (site, stage, biology, and risk factors for locoregional or distant relapse), patient factors (age, sex, performance and nutritional status, comorbid conditions, oral health, life-style habits, and socio-economic background), treatment options, and patient preferences. A geriatrician is not always available, so to tailor cancer care for older patients, practicing oncologists should familiarize themselves with some of the assessment tools described below.

Geriatric Evaluation in Oncology

Although often used as traditional oncology measures, performance status scores alone (e.g. Karnofsky or Eastern Cooperative Oncology Group [ECOG]) do not convey sufficiently accurate information about functional status, comorbidities, and physiological reserves. However, these characteristics are crucial to differentiating between fit and frail persons of the same chronological age. Functional status evaluated by a geriatrician comprises an assessment of the patient's ability to complete activities of daily living (ADLs) such as bathing, dressing, feeding oneself, maintaining continence, and transferring from a bed or chair without assistance and instrumental activities of daily living (IADLs) like doing housework, using transportation, shopping, and taking medications. Both ECOG and functional status assessed by IADL predict postoperative morbidity, toxicity to chemotherapy, and survival [19].

Comorbidities are defined as additional concurrent diseases unrelated to cancer. They should be evaluated independently from functional status, because in a large prospective study, the relationship between these two variables was found to be low or absent [27]. Due to worsening pulmonary functions with reduced vital capacities and gas exchange, weaker cardiac output, decreasing renal blood flow, and changes in hepatic metabolism, the prevalence of comorbid conditions increases with growing age [4]. About 60% of SCCHN patients suffer from at least one co-existing illness and this percentage is estimated to approach 75% in the population over 70 years old [28, 29]. Among various comorbidity scores, Charlson Comorbidity Scale and Adult Comorbidity Evaluation 27 (ACE-27) were shown to have independent prognostic value for overall survival in retrospective analyses of SCCHN cases with primary or recurrent disease [30, 31]. In oropharyngeal squamous cell

carcinoma, the inclusion of a comorbidity score measured by ACE-27 led to a further refinement of a prognostic model described earlier by Ang et al. In the new model, the ensuing factors were involved: age, gender, tumour and nodal stages, pack-years of tobacco smoking, alcohol consumption measured by unit years, comorbidity, and HPV status. As expected, HPV status was the principal determinant of overall survival, while the second place was reserved for comorbidity and nodal stage in HPV-positive and -negative subgroups, respectively [32, 33].

In addition to functional status and comorbidities, further factors linked to survival include cognition, nutritional status, social support, and psychological state (depression) [19]. In an outpatient oncology setting, the following health issues and their prevalence were reported in older cancer patients: comorbidity (>90%, severe in 30–40%), IADL dependence (50–60%), nutritional compromise (30–50%), depression (20–40%), cognitive impairment (25–35%), ADL dependence (about 20%), and ECOG ≥2 (about 20%) [34]. Moreover, with prevalence reaching up to almost 50%, falls and problems with balance and/or walking are significantly more frequent in some elderly cancer survivors compared with the pre-diagnosis period. These difficulties are associated with poor quality of life, dependence in ADLs, increased mortality, and higher costs of health care [35].

To address the complexity of geriatric assessment, certain scales and tools were developed for use in clinical practice.

Comprehensive Geriatric Assessment

Comprehensive geriatric assessment (CGA) was introduced by geriatricians to estimate overall health status of an individual, detect unknown deficits, predict survival, and anticipate on adverse effects of chemotherapy. It includes validated tests for evaluation of functional status, comorbid conditions, cognition, nutritional status, social support, psychological state, and polypharmacy [14, 36] (Table 1). Information about life expectancy may help guide treatment decisions. A CGA can predict morbidity and mortality not only in the general geriatric population but also in elderly patients with cancer, where it was shown to modify the initially proposed treatment plan in as much as 49% of patients [2, 3, 19]. This multidimensional interdisciplinary process is thus both a diagnostic and therapeutic tool aiming at improving quality of life, compliance to therapy, and overall survival. With a notable remark that results from randomized trials are available mostly for non-malignant diseases, a CGA has been recommended by the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), the European Organisation for Research and Treatment of Cancer (EORTC), and the International Society of Geriatric Oncology (SIOG) [37–40]. The first randomized controlled study of a CGA in elderly SCCHN patients is the EGeSOR trial currently recruiting participants in France. In the experimental group, GCAs are performed by geriatricians at predefined time points. The primary endpoint is a composite of death, ADL,

Table 1 Components of comprehensive geriatric assessment and how to measure them, adapted from [14, 36]

Assessment of functioning	Social assessment
Definition: ability to live independently at home and in the community, physical performance (mobility, balance, fall risk) Measurement: ADLs, IADLs, history of falls, timed up and go, short physical performance battery, handgrip testing	Definition: adequate social support to undergo treatment Measurement: needs assessment of financial capabilities, transportation, and caregiver status; Medical Outcomes Survey Social Support
Medical assessment	Psychological assessment
Comorbidity and medication Measurement: Charlson comorbidity scale, adult comorbidity evaluation 27, cumulative illness rating scale-geriatrics, comorbidity count and severity, medication count, Beers criteria[a] *Nutritional status* Measurement: mini-nutritional assessment, weight loss, body mass index	*Cognition* Measurement: mini-mental status examination, blessed orientation memory scale, short portable mental status questionnaire, montreal cognitive assessment *Depression and anxiety* Measurement: geriatric depression scale, hospital anxiety and depression scale

[a]Beers criteria for potentially inappropriate medication use in older adults
ADLs activities of daily living, *IADLs* instrumental activities of daily living

and weight loss ≥10%. The investigators expect at least a 10% decrease in the primary endpoint to be achieved by the intervention [25].

Notwithstanding its importance, a CGA is rarely performed in oncology practices. It is time-consuming, not necessary for all patients, and requires skilled professionals. Consequently, a two-step approach has been developed furnishing clinicians with geriatric screening tools to decide: (1) which patients will need a full assessment, (2) who will benefit from a specific examination, and (3) in which cases no further testing is required.

Geriatric Screening Tools

Several geriatric screening tests have been used in oncology including the G8, Flemish version of the Triage Risk Screening Tool (fTRST), Groningen Frailty Indicator, Vulnerable Elders Survey-13 (VES-13), and abbreviated Comprehensive Geriatric Assessment. The G8 and fTRST were prospectively validated in a non-interventional, multicentre study (Tables 2 and 3). Both instruments demonstrated high sensitivity and moderate negative predictive value to identify patients with a geriatric risk profile. Moreover, they were prognostic for overall survival, especially the G8 [41]. In a recent update of the SIOG recommendations, a systematic review of 44 studies on the use of 17 different screening tools was reported. The G8 proved to be more or at least equally sensitive compared to other tests. Although the screening tools should not replace a full assessment, the authors concluded that a busy practice setting entitles the physicians to use them for triage decisions prior to a CGA [42].

Table 2 G8 screening questionnaire in elderly patients [41]

Items	Score
1. Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = Severe reduction in food intake 1 = Moderate reduction in food intake 2 = Normal food intake
2. Weight loss during the last 3 months	0 = Weight loss more than 3 kg 1 = Does not know 2 = Weight loss between 1 and 3 kg 3 = No weight loss
3. Mobility	0 = Bed or chair bound 1 = Able to get out of bed/chair but does not go out 2 = Goes out
4. Neuropsychological problems	0 = Severe dementia or depression 1 = Mild dementia or depression 2 = No psychological problems
5. Body mass index (BMI) = weight in kg/height in m^2	0 = BMI < 19 1 = 19 ≤ BMI < 21 2 = 21 ≤ BMI < 23 3 = BMI ≥ 23
6. Takes more than 3 medications per day	0 = Yes 1 = No
7. In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = Not as good 0.5 = Does not know 1.0 = As good 2.0 = Better
8. Age	0 = Over 85 years 1 = 80–85 years 2 = Under 80 years
Total score	0–17 (abnormal if ≤14)

Table 3 Flemish version of the triage risk screening tool [41]

	Score	
Items	Yes	No
1. Presence of cognitive impairment (disorientation, diagnosis of dementia, or delirium)	2	0
2. Lives alone or no caregiver available, willing, or able	1	0
3. Difficulty with walking or transfers or fall(s) in the past 6 months	1	0
4. Hospitalized in the last 3 months	1	0
5. Polypharmacy: 5 medications	1	0
Total score	0–6	

Abnormal if ≥2 within the geriatric population and ≥1 within the oncologic population

Stratifying elderly head and neck cancer patients according to the VES-13 test into frail, vulnerable, and fit cohorts, Perri et al. proposed possible approaches for their management. Frail (VES-13 score = 3) and vulnerable (score = 1–2) groups should undergo a CGA, while standard therapy is advised for the remaining patients. Importantly, physicians should respect physiological changes in the elderly

concerning drug metabolism as well as limited bone marrow reserve reflected in guidelines for growth factor prophylaxis. Where indicated, a CGA tailors planned interventions, so that frail persons receive best supportive care only, whereas patients designated as vulnerable are treated with anticancer modalities. However, in the latter category, doses are often reduced, drugs substituted, and regimens switched in order to prevent excessive toxicity [43].

Frailty

Given the wide range of available anti-cancer approaches, the ultimate goal of geriatric assessment is to select which elderly patients are fit enough to receive such a treatment. However, it seems more practical to define the opposite quality, i.e. frailty, declaring at the same time that those who are not frail are candidates for a systemic and/or locoregional treatment with or without individualized modifications. Frailty can be regarded as a physiologic phenotype highly vulnerable to impaired homeostasis after an exposure to minimal stress. The negative health-related outcomes are reflected by physical disability, high-risk of falls, hospitalization, and mortality [44]. In the 65 years and over population, prevalence of frailty may reach almost 60%, increasing with age. Frailty also appears to occur more frequently in women and in those with poorer self-assessed health, more comorbidities, lower education, and lower income [5, 44]. Being considered a clinical syndrome, its wide symptomatology includes weight loss, fatigue, decreased muscle mass, gait disturbance, mild changes in cognition, and social withdrawal [45]. However, clinically silent frailty with no symptoms may be present in apparently healthy people, where it evolves into an overt form under destabilizing conditions. In 2001, Fried and colleagues defined frailty based on the presence of at least three of the following five criteria: muscle weakness, poor endurance, weight loss, low physical activity, and slow gait speed [44]. This concept was later validated in a cohort of 4735 participants enrolled in the Cardiovascular Health Study, which was a population-based, longitudinal trial aimed at finding etiological factors of coronary heart disease and stroke [46]. In addition, several other validated instruments to measure frailty have been described in literature, and interested readers are advised to refer to the review article by Buckinx et al. [5].

As already emphasized, not all senior patients are frail. Many of them are actually in a very good general condition. Acknowledging the unique characteristics of every individual in the real-world setting, fitness and frailness represent the very two ends of an imaginary scale with various intermediate stages which often pose challenges to clinical judgement in routine practice. Consequently, with the aim of creating the basis for treatment decisions, various assessment tools have been established for a proper patient categorisation. This is not only relevant for senior patients, but of importance for their younger counterparts as well. The most commonly used measures involve organ functions, usually defined by hematologic, renal, and hepatic parameters, and performance status (e.g., Karnofsky or ECOG score).

Although these may be sufficient for younger patients and are routinely incorporated in clinical trial protocols, older patients require a different approach consisting of geriatric assessment and a specific trial design. In the latter respect, it is not only the inclusion criteria but also study endpoints which are at stake. In spite of an increased risk of death from non-cancer-related causes in the elderly, disease-specific survival has been rarely reported in trials dedicated to this population. Similarly, the use of clinically meaningful objectives like functional status or Patient Reported Outcomes remains limited [47].

Two Continuums of Care

We explained the differences between chronological and biological age and between fit and frail persons. We also illustrated that the boundaries are not rigid and definitions not absolute, creating space for interdisciplinary discussions, flexible reassessment, and individualized management. To visualize this perception we constructed a model of two continuums presented in Fig. 1. The vertical continuum implies a transition from chronological to biological age during the process of pretreatment evaluation. Containing all intermediate stages, the horizontal continuum

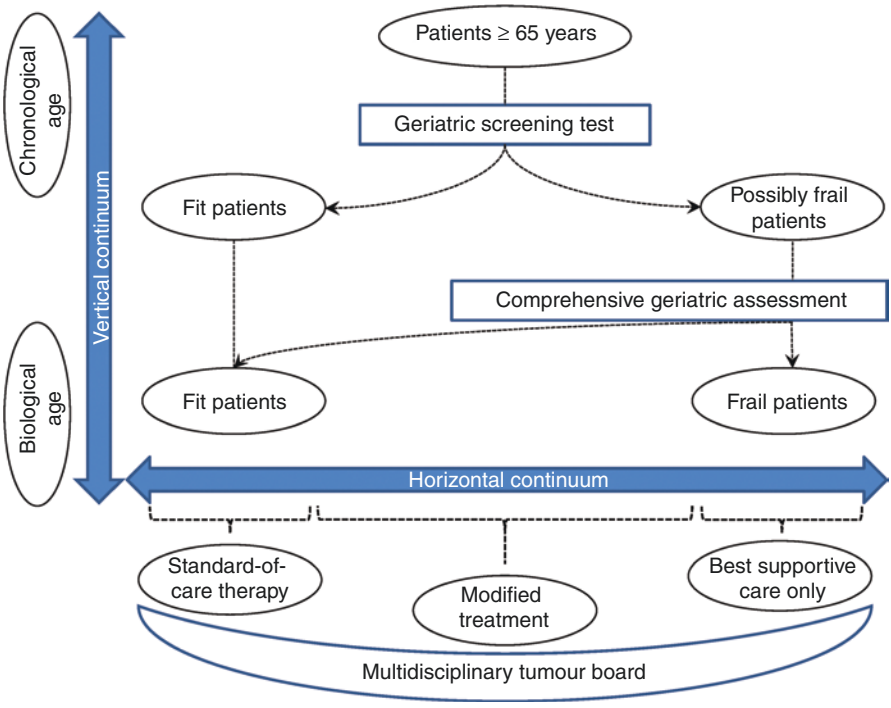

Fig. 1 Two continuums of cancer care in the elderly

leads from fitness to frailness and vice versa. The whole algorithm starts at the top, where patients whose age surpasses 64 years are indicated for some kind of geriatric testing. Performed by any professional competent in internal medicine, a basic screening helps to categorise patients by selecting those who are almost certainly fit and can proceed directly to the therapy-decision phase. In the other patients, who are possibly frail, a detailed assessment by a geriatrician is warranted, equipping the treating physician with information on the presence or absence of frailty and its severity. Based on the outcomes, a multidisciplinary tumour board provides decisive recommendations for clinical practice.

Locally Advanced Head and Neck Cancer

In this setting, according to the ESMO guidelines, there are two principal approaches with level I evidence and grade A recommendation. Either patients undergo surgery with adjuvant radiotherapy which is complemented by single-agent cisplatin in case of positive surgical margins and/or extracapsular nodal extension. Or if surgery is deemed too mutilating or the disease is unresectable or patients are not operable for medical reasons, physicians may opt for definitive platinum-based concurrent chemoradiation. Alternatively, radiotherapy with curative intent may be combined with cetuximab (level II, grade B). Organ preservation approaches with concurrent chemoradiotherapy or by induction chemotherapy followed by radiation can be considered in patients with locoregionally advanced resectable larynx and hypopharynx cancer (level II, grade A). Other procedures like sequential treatment (induction chemotherapy followed by chemo- or bioradiation) are still under evaluation [48]. Herein, only the former two standard-of-care strategies will be addressed.

Surgery

Under the condition of a careful preoperative evaluation of comorbidities and appropriate perioperative management, advanced calendar age does not seem to be an independent determinant of eligibility for limited or extensive surgical treatment. One of the first reports on the risks of major head and neck surgery dates back to the late 1970s, when McGuirt and co-workers reviewed medical records of 714 cases undergoing radical neck dissection. About one quarter of patients were over 70 years old. Major surgical complications comprised operative mortality, cutaneous fistula, carotid blowout, and haemorrhage, while minor complications were defined as wound infections, necrosis, seroma, chyle fistula, and flap elevation from hematoma formation. The incidence of both major and minor surgical complications was comparable between those aged above and below 70 years. However, medical complications, mostly of cardiovascular and pulmonary origin, were higher by 8% in the elderly cohort. Perioperative mortality rates, defined as death within 30 days of

intervention, were 7.4 and 1.4% in older and younger subjects, respectively [49]. Perioperative mortality was also addressed in a large retrospective study of 810 patients over 64 years, and reported to be 3.5% [50].

Smaller series published later by other investigators showed similar findings even in the oldest old category. Clayman et al. compared 79 patients younger than 65 years with 43 who were 80 years of age or older. Even though median overall survival was significantly lower in the older age group, it was similar to the actuarial survival of the general octogenarian population. Furthermore, despite a higher rate of preoperative comorbid conditions in the older age group, the investigators did not observe significant differences in terms of perioperative or postoperative complications between the two study groups [51]. Recently, L'Esperance et al. looked at postoperative complications and mortality in 219 octo- and nonagenarians. Independently associated with American Society of Anesthesiologists (ASA) score of 4 or greater and operating room time of 6 h or longer, serious complications within 30 days of surgery were noted in about one third of study population. About 11% of participants died within 90 days of surgery with an increased risk observed in nonagenarians, in case of a high comorbidity score measured by the ACE-27, and in the presence of preoperative dysphagia and/or a large extent of resection [52].

Although preferred by patients and treating physicians, conservative, non-destructive surgical procedures are not always feasible. Therefore, reconstructive surgery with microvascular free tissue transfer has become an integral part of aggressive surgical interventions in locally advanced SCCHN. The procedure can be used safely and effectively even in the elderly population. The higher rate of perioperative complications was reported to be more likely a result of an increased prevalence of comorbid conditions than advanced chronological age [53, 54]. Apart from comorbidities, which have indeed been identified as the main predictive factor for postoperative complications, several other factors such as type of surgery and disease stage merit attention. Among them, case volume at treatment centres has often been mentioned in relation with quality of care, albeit published data are still scarce. In a cross-sectional study by Jalisi et al., a total of 4544 elderly patients treated in 93 US hospitals were included. According to the number of performed surgical cases, the institutions were arbitrarily categorized into tertiles, i.e. high- ($\geq$50 cases), moderate (22–49), and low-volume ($\leq$21) hospitals. After performing multiple analyses, the authors concluded that high-volume academic centres showed a significantly shorter intensive care unit stay ($p = 0.0144$) and a marginally lower mortality ($p = 0.4699$) [55].

Chemoradiotherapy

High-dose three-weekly cisplatin (100 mg/m^2 on days 1, 22, and 43) given concurrently with conventionally fractionated external beam radiotherapy represents the standard of care in the postoperative setting of patients with high-risk features in the pathology specimen and in patients with locoregionally advanced SCCHN in whom

a non-surgical definitive approach is preferred. The benefit of adding cisplatin to the radiation was shown in four large phase III studies showing a significantly better locoregional control and/or overall survival [56–59]. The downside of this approach is an increase in acute toxicity, notably in mucositis, myelosuppression, and gastrointestinal side effects, and an increase in late toxicity [60]. Three of the four above mentioned studies focused on survival or locoregional control as the primary endpoint. Compared with radiotherapy alone, the absolute benefit in overall survival at 5-years ranged between 8% and 13% [56–58]. In the fourth trial, with larynx preservation as the primary end point, the 5-year overall survival was numerically worse with concurrent chemoradiotherapy (54% versus 55% versus 56% for concurrent chemoradiotherapy versus induction chemotherapy followed by radiotherapy versus radiotherapy alone, respectively). The difference between concurrent chemoradiotherapy and radiation alone became more evident with longer follow-up, but could not be attributed to larynx cancer or the treatment itself suggesting an unexplained higher incidence of competing causes of deaths in the concurrent arm which warrants further investigation [59–61].

So a question has been raised as to whether concurrent chemoradiation with high-dose cisplatin is a suitable approach for the elderly. In the four pivotal phase III studies, no restrictions were put on the upper age limit. Consequently, the recommendations are valid for the whole adult patient population. Nonetheless, in all these four trials, the median age at randomisation was in the fifth decade, and no geriatric screening or assessment of comorbid conditions or functional status were undertaken. Therefore, taking into account the substantial toxicity and only a limited long-term survival benefit (about 10% or less), many practicing physicians have been hesitating to use high-dose cisplatin during radiotherapy in the older population. This notion has been nourished by an imprecise interpretation of a large individual patient-based meta-analysis, which will be discussed later in the text.

Fortunately, considering the complexity of geriatric care and the discrepancy between chronological and biological age, some research groups made an effort to clarify the utility of chemoradiation in geronto-oncology. At present, besides numerous retrospective observations and subset analyses of prospective trials, several meta-analyses of controlled clinical trials and reports of population-based registries are available. In this chapter, we will concentrate on the latter two sources. Despite the fact that both represent the strongest currently available evidence in this field, there are several limitations to address in the first place. Registry reports are retrospective in nature, some critical details including treatment specifications are often lacking, and available patient data might not always be complete. On the other hand, many trials have been criticised for the limited representativeness of the study population and the ensuing poor generalisability of the results to the real-world practice. Furthermore, the inclusion period of some trials started more than 20 years ago or even earlier, and older people nowadays (Boomers) are different from their parents' generation (see above). Finally, oncologic care recently experienced a rapid evolution marked by refinements in treatment and supportive care protocols along with a number of new drugs on the market, which all have contributed to changing paradigms in clinical medicine.

Meta-Analyses

Combining data from 87 randomized trials performed between 1965 and 2000, a large individual patient-based meta-analysis demonstrated an absolute survival benefit of 6.5% at 5-years when adding concomitant chemotherapy to loco-regional treatment in locoregionally advanced SCCHN. However, the magnitude of the survival advantage conveyed by concomitant chemoradiotherapy was smaller in older than in younger adults. The declining effect of chemotherapy with age ($p = 0.003$, test for trend) has often been cited to contradict such treatment in those over 70. In this respect, we advocate more caution when interpreting the outcomes. Trials performed after 1994 exhibited a progressively growing proportion of non-cancer related deaths with advancing age (15% in those under 50, 39% in those over 70). This might have been a consequence of comorbidities, frailty, and a higher susceptibility to chemotherapy toxicity. Thus, a question remains as to whether a proper selection of fit patients could have had a more favourable impact on the results [62].

Second, a subset analysis of three Radiation Therapy Oncology Group (RTOG) trials (RTOG 91-11, 97-03, and 99-14), exploring different radiation and chemoradiation regimens, found that apart from advanced T-stage and larynx/hypopharynx primary site, older age is an independent risk factor for the development of severe late toxicity after concurrent chemoradiation (odds ratio 1.05 per year; $p = 0.001$) [60].

The third meta-analysis was presented only as an abstract at an international conference, and a full-text publication is still pending. It also involved three phase III RTOG trials exploring radiotherapy with or without concurrent chemotherapy, but these were different from the previous ones (RTOG 9003, 0129, and 0522). Here, patients aged 70 years or older were more likely to be female with a poorer performance status, heavier smoking history, and a negative p16 status ($p < 0.001$ for each parameter). After adjusting for covariates, elderly patients had worse overall survival (hazard ratio [HR] for death, 1.55; 95% confidence interval [CI], 1.35–1.77; $p < 0.001$), regardless of smoking history or p16 status. The relationship was more pronounced in the combined modality trials with cisplatin (RTOG 0129 and 0522), in which senior individuals experienced, in addition, significantly more grade 3–5 thrombocytopenia ($p = 0.02$), anaemia ($p = 0.03$), nephrotoxicity ($p = 0.01$), and ototoxicity (borderline significant; $p = 0.06$) than their younger counterparts, which was surprisingly not the case of severe mucositis exhibiting an opposite correlation ($p = 0.04$). In RTOG 9003, comparing two types of radiotherapy (standard versus altered fractionation) without chemotherapy, toxicities were similar by age [63].

Registries

In none of the three above mentioned meta-analyses, details on the proportion of frail and polymorbid patients were provided. It should be kept in mind that the number of older people enrolled in prospective trials has traditionally been low (8–12% in the three meta-analyses), while the frailty represents a common

phenomenon (up to almost 60%, see above). Therefore, the outcomes of such clinical investigations are not appropriate for concluding on the management in the elderly. Until age-specific prospective trials supply high-quality evidence, retrospective reviews of population-based cross-sectional registries will remain the reference source of information. We refer to five registry reports on the use of chemoradiation (versus radiation alone) in elderly patients with locoregionally advanced SCCHN. They all used the National Cancer Data Base of the US as source, from which records of Charlson-Deyo comorbidity scores could be obtained. The growing interest of healthcare professionals in this topic reflects the fact that all five papers were published in the last 2 years (Table 4) [64–68].

Amini et al. reported an overall survival gain achieved by adding chemotherapy concurrently to definitive irradiation in SCCHN patients older than 70 years. Five-year overall survival was 30.3% and 15.2% in those who received concurrent chemoradiation and radiotherapy alone, respectively. According to a recursive partitioning analysis, the survival benefit was limited to patients not older than 81 years, with low comorbidity scores, and either T1-2/N2-3 or T3-4/N0-3 disease [64]. Definitive treatment setting was also a subject of interest to researchers from the Cleveland Clinic, who confirmed an improved overall survival in those receiving concurrent chemoradiation. In a complex propensity score-adjusted multivariate model, controlled for age, insurance status, income, comorbidity, tumour site, differentiation, tumour and nodal stages, and different radiotherapy variables, the association remained statistically significant. Importantly, the authors did not find any age threshold for this correlation between 56 and 90 years, as measured by three-year overall survival gains. Additionally, an increase in the use of systemic therapy in the elderly was noticed from 64% in 2004 to 86% in 2012 [65].

Contrary to the two analyses mentioned above, which concerned elderly SCCHN patients who had been treated with definitive chemoradiotherapy, the next three retrospective analyses focused on patients who had been treated with chemoradiotherapy or radiation alone after surgery of tumours which showed high-risk features (positive surgical margins and/or extracapsular extension) on pathology review. All three analyses revealed a prolonged 3-year overall survival with the combined approach (53.8% versus 44.6%, 50.7% versus 44.4%, and 52.4% versus 43.4%, respectively), although this was less apparent on multivariate analysis in the study by Giacalone et al. [66–68]. This author group demonstrated a reduction in the risk of death with the use of chemoradiotherapy which was non-significant but could be considered as potentially important (50.7% versus 44.4%; HR, 0.88; 95% CI, 0.73–1.06; $p = 0.17$), particularly in a subgroup with a low Charlson-Deyo score (HR, 0.84; 95% CI, 0.69–1.02; $p = 0.08$). No meaningful difference was shown on propensity score matching ($p = 0.839$) [67]. Also in the adjuvant setting, as noted in two of the studies, the percentage of elderly patients that received concurrent chemoradiation increased over time [66, 67].

Table 4 Retrospective reviews of population-based cross-sectional registries exploring concurrent chemoradiotherapy in elderly patients with SCCHN

First author, year	Clinical setting	Inclusion period	Definition of elderly (years)	Proportion of elderly pts.	Elderly pts. receiving		Overall survival benefit on multivariate analysis	
					CCRT	RT	CCRT group (elderly vs. younger pts.)	Elderly group (CCRT over RT)
Amini, 2016 [64]	Definitive	1998–2011	>70	100% (4042)	2538	1504	N/A	Yes (HR, 0.63; $p < 0.001$)
Ward, 2016 [65]	Definitive	2004–2012	>70	14% (4165/30,399)	3028	818	Sustained benefit from 56–90 years	Yes (HR, 1.46; $p < 0.001$)[a]
Woody, 2017 [66]	Post-operative	2004–2012	>70	100% (445)	187	258	N/A	Yes (HR, 0.74; $p = 0.04$)
Giacalone, 2017 [67]	Post-operative	1998–2011	≥70	100% (1686)	491	1195	N/A	Maybe (HR, 0.88; $p = 0.17$)
Yoshida, 2018 [68]	Post-operative	2004–2013	≥70	100% (1199)	531	668	N/A	Yes (HR, 0.75; $p = 0.001$)

[a]Pertaining to larger cohort of 3347 patients comprising also those who received induction chemotherapy (n = 91) and where the type of systemic treatment was unclear (n = 228)

SCCHN squamous cell carcinoma of the head and neck, *pts.* patients, *CCRT* concurrent chemoradiotherapy, *RT* radiotherapy alone, *N/A* not available, *HR* hazard ratio for death

Recurrent and/or Metastatic Head and Neck Cancer

With an expected overall survival usually not exceeding 1 year, recurrent and/or metastatic SCCHN is a devastating disease qualifying most of the patients for palliative measures. At present, evidence from the literature is insufficient to draw firm conclusions regarding the management of the elderly population. In cases without distant metastases, locoregional treatment options should be considered [14]. However, only a minority of locoregional recurrences can be successfully salvaged by complete resection or irradiation [69]. As was recently reported, carefully selected cases with metachronous pulmonary metastases may also be considered for surgical intervention [70]. In the remainder, irrespective of age, treatment goals focus primarily on symptom control and improvement of quality of life. A single-drug regimen or best supportive care alone are offered to frail patients with poor functional status and comorbidities. In first line, however, fit patients may benefit from multi-drug chemotherapy with or without the targeted agent cetuximab (epidermal growth factor receptor [EGFR] inhibitor) [69].

Cytotoxic Chemotherapy

As a result of age-related changes in pharmacokinetics and pharmacodynamics, chemotherapy administration carries safety concerns in the elderly. In a combined analysis of two phase III trials conducted by ECOG (1393 and 1395), Argiris et al. compared the toxicity, response rates, and survival of elderly recurrent and/or metastatic SCCHN patients (70 years or older) with their younger counterparts. The ECOG 1393 trial randomized participants to receive a cisplatin/paclitaxel doublet at two dose levels, while treatment arms in the ECOG 1395 trial consisted of cisplatin plus either 5-fluorouracil or paclitaxel. Altogether, 53 older patients were compared with 346 younger ones. No statistical difference was observed in terms of objective response rate (28% versus 33%), median time to progression (5.25 versus 4.8 months), median overall survival (5.3 versus 8 months), or 1-year survival (26% versus 33%) between these two subgroups, respectively. However, the authors noted a significantly higher incidence of severe nephrotoxicity, diarrhoea, and thrombocytopenia in the elderly population, which was paralleled by a trend towards a higher toxic death rate (13% versus 8%). In conclusion, cisplatin-based doublets yielded comparable survival outcomes among fit elderly and younger patients, yet at the cost of increased side effects in the former group [16].

Targeted Treatment

The landmark EXTREME (Erbitux in first-line treatment of recurrent or metastatic head and neck cancer) trial found significant overall survival improvement with the platinum (cisplatin or carboplatin)/5-fluorouracil/cetuximab combination over the

chemotherapy doublet alone. It is the only approved standard first-line systemic treatment in platinum-sensitive recurrent/metastatic SCCHN today. Population aged 65 years or older made up 17% of the total number of enrolled patients (77/442) and was equally distributed between both treatment arms. Subgroup analysis of this cohort revealed that the survival benefit conferred by adding cetuximab to platinum/5-fluorouracil chemotherapy fell short of statistical significance, in contrast to younger adults and the whole intention-to-treat population. Median progression-free survival was 4.2 and 3.2 months (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.38–1.12) and median overall survival 9.1 and 7.8 months (HR, 1.07; 95% CI, 0.65–1.77), in the cetuximab and control arms of the elderly subpopulation, respectively [71].

Analogous data are available in the second-line setting. The LUX-Head & Neck 1 trial evaluated the clinical efficacy of afatinib, an irreversible human epidermal growth factor receptor (ERBB) family blocker, matched up to methotrexate in a 2:1 ratio among 483 eligible subjects (128 [27%] aged 65 or more). Although the study was sufficiently powered, no improvement in overall survival was achieved by the ERBB antagonist. However, afatinib induced a marginal but significant improvement in median progression-free survival versus methotrexate in the overall population (2.6 versus 1.7 months; HR, 0.80; 95% CI, 0.65–0.98, p = 0.030) [72]. Moreover, similar progression-free survival benefit with afatinib versus methotrexate was observed in patients 65 years or older (2.8 versus 2.3 months; HR, 0.68; 95% CI, 0.45–1.03, p = 0.061) as well as younger individuals (2.6 versus 1.6 months; HR, 0.79; 95% CI, 0.62–1.01, p = 0.052). Also objective response rates with afatinib versus methotrexate were 10.8% versus 6.7% and 10.0% versus 5.2% and disease control rates were 53.0% versus 37.8% and 47.7% versus 38.8% in older and younger patients, respectively, without an indication of excessive toxicity in the older population [73]. Currently, afatinib is recommended in the NCCN guidelines (category 2B) for patients with recurrent/metastatic who fail on platinum containing chemotherapy [74].

Immunotherapy

Immune checkpoint inhibitors emerged as a ground-breaking discovery in several areas of oncology including head and neck cancer. The mechanism of action resides in restoration of the natural anticancer potential of the host immune system. As an immunosuppressive disease, SCCHN evades immunosurveillance, i.e. recognition and elimination of malignant cells, by manipulating its own immunogenicity, producing immunosuppressive mediators, and promoting immunomodulatory cell types [75]. The process of aging is characterised by a gradual decline in immune functions, referred to as immunosenescence. Although available evidence supports an association of advancing age with decreased immunosurveillance, the tumour-promoting properties of the immune system seem to be compromised as well. Thus, the real impact of immunosenescence on cancer development remains unclear, and chronic inflammation observed in aging tissues may be more important [7].

Contrary to classical cytotoxics and targeted agents aiming therapeutically at tumour cells, immune checkpoint inhibitors are monoclonal antibodies against receptors and ligands found primarily on lymphocytes and myeloid elements. Translated into clinical practice, these new medicines have become known for their potential to induce durable responses even in heavily pre-treated patients at the cost of relatively low incidence of severe adverse events. One of the most studied is the signalling axis between programmed cell death protein-1 (PD-1) and its ligand PD-L1. In SCCHN, drug development has already moved forward to phase III protocols, both in the locoregionally advanced and the first-line recurrent and/or metastatic settings. In the second-line recurrent and/or metastatic setting, final results have been published, bringing important changes to treatment guidelines [76]. Compared with the control arm containing weekly single-agent methotrexate, docetaxel, or cetuximab, the CheckMate-141 trial demonstrated a 30% reduction in risk of death in patients assigned to the experimental arm with nivolumab, an anti-PD-1 inhibitor. Correspondingly, median overall survival rose from 5.1 months to 7.5 months. In a subgroup analysis of patients who recurred within 6 months after chemoradiation, the benefit of nivolumab over standard therapy was also observed. Based on these findings, nivolumab at an intravenous dose of 3 mg/kg every 2 weeks is the current standard in platinum-refractory recurrent and/or metastatic SCCHN. Of the 361 randomized patients, 113 (31%) were 65 years or older. In those aged 65–74, a subgroup analysis fell short of statistical significance (HR, 0.93; 95% CI, 0.56–1.54) [77]. However, in this context, it is important to mention that data from trials exploring immune checkpoint inhibitors in melanoma, non-small cell lung cancer, and renal cell carcinoma revealed that responsiveness and safety are not impaired in the elderly [78]. The tolerance to these agents was recently illustrated in a case report of a 96-year-old woman with SCCHN progressing on cetuximab, showing tumour shrinkage on durvalumab, an anti-PD-L1 blocker, with no serious treatment-related toxicity [79].

Conclusions

Increasing average life expectancy is one of the prosperity indicators, and modern societies have been deliberately undergoing profound multifactorial changes towards maximizing this outcome. However, the aging population exerts enormous strains on health infrastructure. Elderly people deserve the same quality of medical care as their younger counterparts. The situation gets more and more challenging with a widening gap between chronological and biological age driven by the advent of new generations reaching retirement, with novel drugs hitting the market, and with rapidly rising costs in oncology. Practicing physicians have to be prepared for that. However, this will not be possible without collaboration with experienced trialists and other stakeholders involved in clinical research.

To better understand the behaviour of cancer in patients at an advanced age and to offer them a high-quality evidence-based approach, we advocate a strong support

in the development and implementation of elderly-specific prospective trials instead of settling for stratifications based on age. The integration of formal geriatric assessment with co-morbidity scores should take into account a direct applicability to daily clinical practice. The institution of predictive models for chemotherapy toxicity and outcome, examination of tumour genetics, and comparative molecular genomic analysis of elderly patients versus their younger counterparts may further assist us in defining new standards of care in this population [63].

Senior persons derive benefit from intensified treatment approaches but need careful decision making and attentive follow-up. They have shown to develop effective coping strategies and maintain quality of life comparable with their younger counterparts. In fact, elderly patients report even better socioemotional functioning probably because of lower expectations, since they might have less to lose and need fewer adjustments to their lifestyle [80, 81]. Oncologists must be cautious in generalizing results from clinical research to the geriatric population. These patients have often been underrepresented in prospective studies, which were not primarily designed to integrate a population requiring a special diagnostic evaluation. A change has to be made now. We need to abandon the traditional perception of aging and focus on trials that show us how to approach patients we really encounter in our offices.

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