Squamous Cell Carcinoma of the Head and Neck in the Elderly

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Abstract: *Background:* Increasing life expectancy and incidence of head and neck carcinomas, including some types of head and neck malignancies, lead to a constantly higher proportion of old oncologic patients. Previous reports regarding the outcome for elderly patients with head and neck carcinomas squamous cell carcinoma (HNSCC) are controversial. For further insight, a large single-institution material has been analysed.

Material: Prospective recording of demographic details, continuous follow-up and determining exact cause of deaths of patients with carcinoma of the head and neck have been in progress over a period of 14 years. Having excluded 154 patients (7.3%), who did not follow-up, who had distant metastases at diagnosis, or who had received extensive treatment for a previous head and neck carcinoma or who refused treatment, or for medical or mental reasons, were unable to receive curative treatments. The material includes 1944 patients, of whom 37% received combined treatment, 58% radiotherapy alone and 6% surgery alone. The mean age was 65 years with a mean follow-up of 3.8 years. The material was divided into two groups; ≤65 and >65 years of age and analysed by means of X^2 tests and log-rank X^2 tests.

Results: Early stage primary tumours and a more advantageous N- classification were more conspicuous among the older patients ($p = 0.2406$ and $p<0.0002$). The group of patients ≤65 years had a significantly better disease-specific survival rate compared to the older patients ($p = 0.145$). However, 40 % of the older patients were alive with no evidence of disease. By comparing 65-74 patients with patients' ≥ 76 years of age, a p-value of 0.0105 was obtained in favour of the younger group, but still an appreciable number of the older patients escaped their HNSCC.

Conclusion: Given a satisfactory mental and physical condition, patients older than 65 years had a reasonable disease-specific survival. It is therefore no reason to withhold appropriate treatment for the elderly, fit patients which could prevent or delay the misery and devastating situation, as well as a reduction in the heavy expenditures that patients with persistent or recurrent head and neck tumours represent.

Keywords: Head and neck carcinoma, geriatrics, oncology prognosis, survival, treatment.

INTRODUCTION

Squamous cell carcinoma of the head and neck (SCCHN) is generally considered a disease of the late middle- aged and elderly people. The literature abounds with bewildering reports of the effect of advanced age on survival and other tumour parameters [1]. Because this group of people is the fastest growing population segment in Europe and North America, a steadly increasing incidence of malignant tumours, including in some sites within the head and neck region, an increasing number of older patients with SCCHN is anticipated. In light of this and the escalating expenditures connected to medical care, it is important to determine the impact of appropriate treatment on the disease-specific survival in elderly patients.

Based on continuous prospective recording of relevant clinical information and complete follow-up collected over a period of 14 years, the disease specific- survival for SCCHN of the upper aero- digestive tract was analysed in relation to age at the diagnosis.

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PATIENTS AND METHODS

From 1983 through 1997, the author has, in prospective manner, collected relevant clinical information, follow-up and the exact cause of death for all patients with malignant disease of the head and neck admitted to our institution. Classification was initially performed according to the 3rd edition (1982) of the International Union against Cancer (UICC). The database has recently been updated to the 1997 (4th) edition of UICC. The registration has through the years been equivalent to certainty factor 2 (UICC, 6th Ed).

The database comprises of a total of 2096 patients with histologically verified squamous cell carcinoma of the upper aero-digestive tract (lips and salivary glands not included) treated at the Department of Otolaryngology, Rikshospitalet, in close collaboration with the Norwegian Radiumhospital, a tertiary referral centre that recruits patients from the South-Eastern part of Norway, with approximately 1.5 million people. Excluded from this evaluation were 154 patients (7.3 %) who did not receive any treatment with curative intent. The reasons for abstaining from treatment were either distant metastases of the actual tumour, a refusal of treatment, or other serious diseases corresponding to the ASA physical indexing (American Society of Anaesthesiology), an ASA index exceeding ≥4 (life threatening diseases, not necessarily related to the primary disease) [2], or mental disorders that

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made curative treatment impossible, previous extensive treatment for a malignant head and neck tumour, for whom the treatment options were exhausted and one patient lost to follow-up. Age alone has never been a reason to abstain from treatment. For obvious reasons, the number of patients not receiving treatment was highest in the group of patients older than 65 years (Table **1**). Some of the patients excluded received some kind of palliative treatment. All these patients died either from their HNSCC or co-morbidity within 2 years. The material (Table **1**) thus comprises of 1944 eligible patients with squamous cell carcinoma of the oral cavity, oro-, epi- and hypopharynx, sino-nasal cavity, larynx and neck metastases with unknown primary tumour (ICD9; 141,143,144 146 147, 148, 149,160, 161 and 196).

Table 1. Material According to Age Groups

Patients	Age Groups		Total Sum	Statistics
	≤65 y	>65 y		
No of pat. withHNSCC	1087	1009	2096	p = 0.1865
M+ at diagnosis	1	1	2	
Lost to follow-up		1		
previous head and neck				
carcinoma; no treatment.	15	55	70	p<0.001
Unfit for treatment;				
(ASA≥3)	30	51	81	p = 0.0018
No. of pat. excluded	46	108	154	
No. of pat. treated				
with curative intent.	1043	901	1944	p = 0.1895

The mean age was 65 years (from 20 to 92 years). A cut-off age of 65 years was therefore chosen, resulting in two age groups of approximately equal size (≤65 and >65years), enabling comparison and statistical analysis. Information regarding tobacco and alcohol abuse has not been recorded.

Complete follow-up and accurate cause of death were obtained by, review of outpatient and hospital charts, autopsy findings (when performed), direct contact with the local hospitals, family physicians, direct contact with patients or next to kin. The mean follow-up time was 3.8 years, but never less than 3 years [3].

Since 1983 the author holds an authorization from the Norwegian Data Inspectorate to collect and evaluate data from patients admitted to our department. The local Ethical Committee and the Ministry of Health and Welfare have approved the study. There is no conflict of interest.

Treatment was planned in a joint, clinical meeting with radiation oncologist, head and neck surgeons, pathologists and a nurse specialized in oncology. Initially the patients were treated with radiotherapy alone, or radiotherapy followed by surgery, when this was planned, or in cases of residual loco-regional tumor manifestations 6 weeks after completion of radiotherapy. In 1991 we revised our treatment policy, and since then surgery has played an increasingly grater role. Whenever possible, we now prefer surgery, followed by radiotherapy, for most tumours, decided by primary tumour size, unfavourable histological spread, such as violated resection margins or an infiltration depth of the primary tumour exceeding 3 mm or a spread to cervical glands. The neck has, as a rule, been treated together with the primary tumour. Neo-adjuvant chemotherapy with cisplatin and 5-fluorouracil, according to a Nordic protocol [4] was administered to 53 patients. Tumours of advanced stage were otherwise treated by radiotherapy alone. Radiotherapy was generally given in fractions of 2 Gy/day 5 days a week from a high voltage source. The primary site received 60-70 Gy and the neck 50-60 Gy over a period of 5-7 weeks.

Statistics

The data were stored and analysed by means of SAS software (SAS Institute, Cary, NC). X^2 tests were performed for categorical data. Kaplan-Meyer plots were used to illustrate the disease-specific survival and the log-rank procedure, to test the effect of age on the disease-specific survival. A case was censored if death resulted from diseases other than the original tumour, or if the patient was alive with no evidence of the original tumour at the last follow-up contact/consultation. P-values <0.05 were considered statistically significant.

RESULTS

Table **2** presents the clinical data and treatment. Men outnumbered women in both age groups (p<0.001).

There was no evident difference in the T-classification. An advantageous N-classification favouring the older patients resulted in a significant stage distribution. It should, however, be noted that the material includes 145 patients with T1a glottic carcinoma (all N0), who since 1996 have preferably were treated with CO_2 laser surgery. As T1a glottic squamous cell carcinomas rarely metastasize, there is a distinct skew towards early T-stage and N0 in both age groups. Having excluded these carcinomas, the T-distribution turned out to be statistically significant due to a relative high incidence of early carcinomas of the oral cavity among the oldest patients (Table **2**).

The change in our treatment policy resulted in an apparent skew towards either surgery or radiotherapy alone, in the group of older patients (p = 0.0011, Table **2**). Radiotherapy alone, or combined with neo-adjuvant chemotherapy, was for several years the preferred treatment in advanced disease, especially for the group≤65 years [4]. There was no difference in peri- and postoperative deaths or in serious complications between the two age- groups.

The incidence of residual loco-regional disease following completion of treatment was significantly higher in the group of the older patients (Table **3**). Recurrences, on the other hand, were more frequently observed among the patients ≤ 65 years of age (p = <0.001). Salvage treatment, both locally and regionally, was successful in 94 patients. There was no pronounced difference in loco-regional recurrences or salvagere when T1a glottic carcinoma were left out. This observation strongly suggests that early glottic carcinoma rarely recur, and thus have prognosis.

Table 2. Clinical Data According to Age Groups

Variables	Age Groups		Sum	Statistics[3]
	≤65 y	>65 y		
Gender				
Male	832	678	1510	
Female	211	223	434	
Eligible patients	1043	901	901	p = 0.170 (p = 0.170)
Tumor sites[1]				
Sino-nasal (160)	40	43	83	
Larynx(161)	373	359	661	
Oral cavity (141)	332	318	650	
Oropharynx(146)	164	82	246	
Nasopharynx(147)	27	11	38	
Hypopharynx(148)	74	73	147	
Unknown primary(196)	33	15	48	
				p<0.001
primary tumor				(p = 0.1343)
classification				
T1	306	246	552	
T2	272	230	502	
T3	113	108	221	
T4	319	302	621	
Tx	33	15	48	
				p = 0.1343
Neck node				p = 0.0002
classification				
N0	650	636	1286	
N1	129	110	239	
N2	202	117	319	
N3	62	38	100	
				p = 0.0002
Stage distribution				(p = 0.0002)
I	251	234	485	
II	212	173	385	
III	123	113	236	
IV	457	381	838	
				p = 0.6826
Treatment				p < 0.0001
Surgery alone	74	83	157	
Surgery+ irradiation	172	135	307	
Irradiation + surgery	154	101	255	
chemotherapy[2]+irradiation	85	45	130	
chemotherapy+irradiation+ surgery	15	8	23	
Irradiation alone	543	529	1072	p = 0.0011 (p = 0.0012)

1. (): ICD9 classification

2. Chemotherapy with cisplatin+ 5-Fluorouracil[4].

3.() p-values where T1a glottic laryngeal carcinoma are left out.

Table 3. Failures (Recidual Disease Following Treatment and Recurrences) According to Age Groups

Failures	Age Groups		Sum	Statistics[4]
	≤65 y	>65 y		
Residual tumor[1]	100	265	365	p = 001
Locally	121	144	265	p = 0.0051
Regionally	66	70	136	p = 0.2141
Recurrences[2]	324(321)	208(205)	0	p<00001 (p<0.0001)
Locally	212(210	1338(131)	0	p = 0.0014 (p = 0.0016)
Regionally	72(79)	54(53)	0	p = 0.1686 (= 0.1537)
Distant	45	36	81	p = 7257
Salvage[3]	73 (71)	22 (22)	94(94)	0.5810 (p = 0.5784)
Locally	61 (60)	17 (17)	78(77)	p = 0.04999 (p = 0.51804)
Regionally	10 (10	4 (4)	14 (14)	p = 0.6031 (p = 0.6206)
Distant	2(2)	1 (1)	3(3)	p = 0.6031

1. 13 patients had residual disease both locally and regionally

2. 11 patients had recurrences at more than one site simultaneously

3. Alive with no evidence of disease.

4.() figures and p-values where T1a glottic squamous cell carcinoma are left out.

A total of 199 secondary primary tumours (including 9 synchronous tumours) within the aero-digestive tract were observed (Table **4**). The upper aero-digestive tract, especially the oral cavity, was the dominant site of a secondary primary tumour. The annual incidence of such tumours was 2.3 and 4.3 for patients ≤ 65 years and >65 years, respectively. Secondary lung carcinomas increased to 66 with approximately equal annual incidence. A majority of the secondary lung carcinomas was diagnosed after the 70th birthday. Secondary tumours as cause of death were equal when comparing the two age groups.

Table **5** presents the outcome, according to site and age. Patients with laryngeal cancer represents the largest group of patients, and these patients experienced the most advantageous course, which might be an effect of likely is a relatively high number of T1 tumours. For pharyngeal tumours, the older patients were in the worst situation. Fig. (**1**) shows that patients ≤65 had a significantly better disease-free survival than the group with the older patients (p=0.105). When comparing the outcome for patients 65-75

Table 4. Second Primary Tumors According to Age Groups

Sitesec. prim.	Age-Groups				Sum/Mean
	≤65 y		>65 y		
	No.	Mean No. /Year (Range)	No. (%)	Mean No. Annually (Range	
Head and		2,3		4,3	3,3
Neck	78	(0-17.8)	37	(0-12.9)	115
Oesophagus	12	3,3	6	1,5	18
		(0-10,7)		(0.2-2.3)	
Lung	45	2,3	21	1,5	1,9
		(0,1-12,5		(0,1-9.7)	66
No., mean/year	135	2,6	64	3,2	199
(range)		(0-17.8)		(0-12.9)	(0-17.8)
Patients dead sec. prim.	89		41		130
(%)	(6.6)		(6.4)		(6.5)

years of age with those older than 76, the older had the poorest survival (Fig. **2**), but still there was an appreciable number of the older patients who escaped their HNCC.

Combined treatment, irrespectively of whether radiotherapy was given pre- or postoperatively, showed the best results, when compared to monotherapy, principally radiotherapy. For radiotherapy alone, the disease- specific survival was 44% and 28 % for patients ≤65 and >65 years respectively. The disease-specific survival was independent of gender.

DISCUSSION

This study focuses on the disease -specific survival of elderly patients with SCCHN, considered physically and mentally fit for the treatment with curative intent. Several recent studies have established co-morbidity as an independent predictor of survival in elderly patients (age ≥65 years) [5, 6] A malignant disease may aggravate co-morbidity illnesses or vice versa. There are certainly in this, as in comparable materials, patients with significant concomitant illnesses who did not preclude treatment, but that might have affected survival unfavourably. There is, however, no way to identify these patients with certainty, and/or to judge the impact of their comorbidity on survival. As most patients in this study had surgery as part of the treatment, the ASA index, which since the 1960s has been used as a simple prognostical description of a patient's physical state as an exclusion criterion, has been used [2]. Patients with an ASA index of ≥ 4 (life threatening diseases, not necessarily related to the primary disease) were considered unfit for the treatment and consequently were excluded from this study. Roughly seen, the ASA classification emphasizes the same disadvantageous conditions as does the co-morbidity indices in use [6]. Likewise, treatment was withheld when patients were considered mentally unfit for treatment. The percentage of patients excluded (7.9%) from treatment in this study is similar to that previously reported from a comparable institution in Canada [7].

Table 5. Outcome According to Age Groups

Site	Age-Groups								Total No.
	≤65 y				>65 y				
	Aned	Dfd	Dod	Sum	Aned	Dfd	Dod	Sum	
Sino-nasal	13	23	4	40	6	17	20	43	83
Larynx	181	65	127	373	142	66	151	359	661
Oral cavity	132	121	79	332	79	126	113	318	650
Nasopharynx	8	11	8	27	2	2	7	11	38
Oropharynx	60	59	45	164	13	42	27	82	246
Hypopharynx	14	42	18	74	8	44	21	73	147
Unknown primary	13	9	11	33	4	6	5	15	48
All	421	330		1043	254	303	344	901	1944

Abbrevations: Aned: Alive no evidence of disease, Dfd: Dead from disease, Dod: Dead other disease.

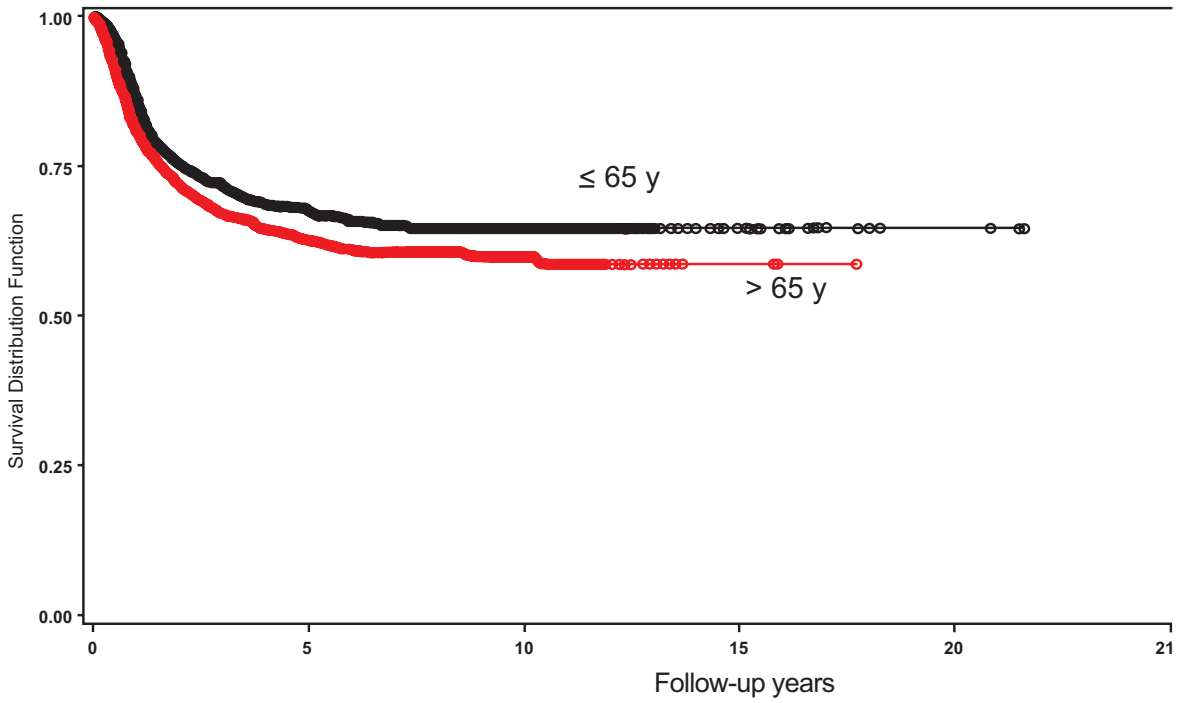

Fig. (1). Disease-specific survival for patients ≤65 *vs* >65years of age (failed/total: 330/1049 *vs* 303/901; (p<0.143).

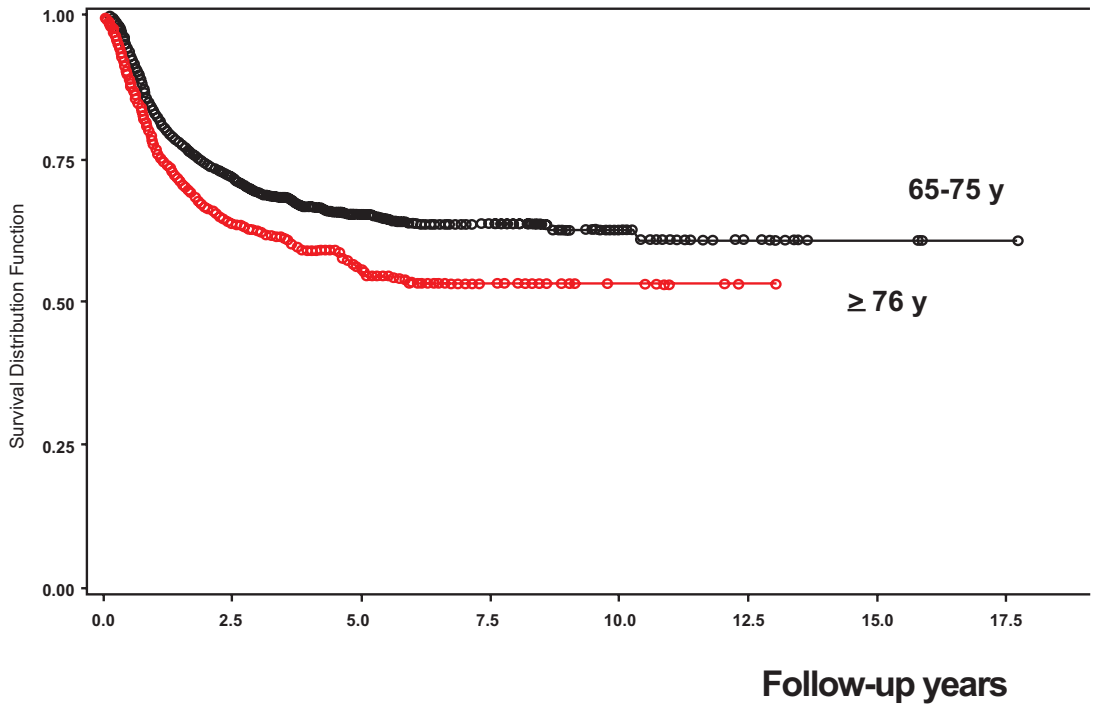

Fig. (2). Disease-spesific survival for patients 65-75 *vs* ≥76years of age (failed/total: 192 /603 *vs* 111/603; p<0.105).

As life expectancy increases, clinicians increasingly face the challenge of treating elderly patients with cancer, including some types of head and neck carcinomas [8]. It has been estimated that in Norway the number of persons older than 70 will be increased by 40% by 2020 (Source: Ministry of Health and Welfare). This increase in the number of old patients with cancer, combined with increasing costs related to medical management, force clinicians to concern themselves with the effect of age on survival.

Paucity of well controlled materials and conflicting reports limit our knowledge of the disease- specific survival of the older patients with SCCHN [1, 8]. Several factors may

explain the lack of attention to this topic and the contradicting results, the major limitations probably being that it has been difficult to accumulate a sufficiently large number of patients with long follow-up, and that most studies presented are retrospective [9,10]. Other methodological issues, such as unequivocal criteria for tumour sites, stage, histology, inclusion and exclusion, are also some features that should be accurately accounted for.

The classification of age, with a cut-off at 65 years that coincides with the average age is similar to that used in several other studies [5-7]. This age cut- off might also contribute to a reduction of the impact of co-morbidity in the group of the older patients. This material thus satisfies the strict and compulsory criteria for evaluation, proposed by Lacy and co-workers for this kind of studies [9].

In contrast to some reports [9-11], it was our observation, as well as that of others [12, 13] that the older patients in general had less advanced disease. This distribution of stage in favour of the older patients was accentuated after exclusion of the early stage glottic carcinomas. There was no difference in extent of the disease, when comparing those excluded from the treatment with those included and thus no selection bias.

Clinicians may be inclined to treat older patients less aggressively than younger. This reluctance toward treating elderly patients may be attributed to a presumed lower tolerance of radiation toxicity and fear of postoperative complications and morbidity in these patients [14]. Although the group of patients older than 65 had the poorest survival rate, the fact that 40% of the patients older than 65 were alive and free of disease at the closure of this study, strongly suggests that treatment is worthwhile in patients at an advanced age, regarding the disease- free survival for SCCHN. This observation concurs with observations in materials similar to the present study [1, 13]. Other reports further substantiate the opinion that age in itself is not an independent prognostic factor, neither is it in itself a decisive factor for survival of SCCHN [9,11,15-17]. On the other hand, Davidson and co-workers [18] showed in a material of oral tongue squamous cell carcinoma matched for age, gender, site, stage and treatment that an increase of 10 years in age was associated with an 18% increase in disease-specific mortality. Both surgery [17, 19, 20], even when combined with free-tissue graft reconstruction [19], and radiotherapy [10, 20-22] offer commendable results in older patients. Moreover, the incidence of peri- and postoperative complications has been reported to be independent of age [14, 20]. Radiotherapy appears to be well tolerated by elderly patients and does not generate drastically different side effects when compared to that experienced by younger patients [14, 21]. Cisplatin based regiments have been widely employed in primary and recurrent treatment of SCCHN. Argiris and co-workers [22] report that elderly fit patients (>70 years) with metastatic or recurrent disease had response rates similar to younger patients, but the older patients suffered a higher rate of toxicity. These authors strongly warn against a therapeutic nihilistic attitude towards chemotherapy in the treatment of elderly patients. Novel chemo-radiation treatment schemes [23] might also become a useful treatment option for elderly patients.

A recent prospective study shows that the impact of treatment on quality of life after one year did not differ when elderly and younger patients with head and neck cancer were compared [14]. However, a large longitudinally prospectively recorded study from Sweden and Norway reveals that the quality of life in patients older than 65 with cancer of the head and neck continue to deteriorate up to 5 years following treatment [24]. The adverse effect of treatment on quality of life varies with the site of the primary tumours, being least pronounced for patients treated for laryngeal carcinoma and worst for those with pharyngeal carcinoma [25, 26].

Contrary to others [10, 11] this study showed the highest incidence of secondary malignancies of the aero- digestive tract among the group with the older patients. This may, to some extent, be an effect of insufficient observation time. Whether the same factors causing the initial tumour, principally alcohol and tobacco consumption [27], are also accountable for the secondary tumours in older patients, is debatable. It has recently been shown that P53 mutations are less common in older patients, and based on this observation, it has been suggested that accumulation of spontaneous mutations during lifetime and defective DNA repair mechanisms may play an important role in the carcinogenesis in elderly patients [10]. In addition to faulty DNA repair, an aging immune surveillance [1] and previous radiotherapy [28] might partly to some extent explain the reduced incidence of secondary malignancies among older patients.

SUMMARY

An assumed prejudiced and erroneous conception of a poor tolerance to treatment of older patients may lead to undertreatment. This should no longer be the case. When properly monitored, conventional therapies seem feasible for older patients.

Although co-morbidity may play an important role regarding the disease-free survival age at diagnosis, is in itself no contraindication for treatment. The site, stage or intrinsic characteristics of the tumour appear to be equally important determinants of the prognosis. Radiotherapy, surgery and chemotherapy have been reported to be well tolerated and with encouraging results in aged patients. Granted a satisfactory physical and mental condition, there is no reason why elderly people should be withheld appropriate treatment that could delay or prevent the misery, suffering and disability that a persistent or progressive head and neck cancer entail. Most likely, treatment of elderly patients might also prove cost favourable. This issue should be an object to further analysis.

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