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ORIGINAL ARTICLE

Negative prognostic factors for head and neck cancer in the young

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Summary

Purpose: *To evaluate the prognosis of head and neck (HN) squamous cell carcinoma (SCC) diagnosed in young people (≤40 years), and to compare it with the typical older patients.*

Methods: *The study population comprised 69 HN cancer patients below the age of 40 years. An equal-sized control group of older patients was pair-matched with the young cases. Cases and controls were compared for type and frequency of recurrence, in addition to survival. Tongue tumor specimens from 12 women of the study group (6 young and 6 old) were included in a pilot immunohistochemical analysis of estrogen receptors (ER) expression.*

Results: *Young patients with early (T1,T2) tongue cancer had shorter overall survival (OS) than their matched controls, but the finding was marginally non-significant (p=0.056). In the young population, late neck metastasis was a particularly aggravating factor for survival (p=0.004). In the case of tongue SCCs, young women were at the greatest risk of recurrence than any other gender-age combination (p=0.006). However, only 8.3% of tumors expressed ER.*

Conclusion: *Early-stage tongue cancer, regional recurrence, and tongue SCCs in women are negative prognostic factors for young HN cancer patients. Treatment modifications targeting these subgroups might be beneficial.*

Key words: *estrogen receptors, head and neck cancer, prognosis, young*

Introduction

Classically, talking about HN cancer, one has in mind a male patient, usually above the age of 60, with chronic tobacco and alcohol abuse, and sometimes of low socioeconomic status [1]. In the background of such cases lies an active subclinical carcinogenic course, characterized by sustained irritation of the normal mucosa by the typical risk factors. HN carcinogenesis is considered a chronic disease process, and time is the key element, as a window of a few decades is customarily required for the accumulation of events leading to malignant transformation [2]. This temporal pattern of pathogenesis is reflected in the epidemics of the disease: in oral cancer, the mean age at diagnosis is 60 years, and the reported incidence in adults younger than 40 years it is only between 0.4 and 5.5% [3,4]. Alarmingly, the rate of tongue SCC has doubled in the young population over the past decade [5]. Moreover, the traditional male sex prevalence and the positive history for excessive smoking and alcohol drinking do not seem to apply to this particular age group [6]. In addition, oral tongue cancer displays a more aggressive natural course in the young, characterized by frequent locoregional recurrences and worse survival [7,8]. Altogether, the above features suggest that early-onset HN cancer might be a distinct entity with different pathogenesis, clinical behavior, and possibly, biology.

Several studies have addressed the uniqueness of this form of neoplasia, focusing on prognosis. One of them reviewed SCC cases of the oral tongue, which is, excepting the nasopharynx, the most frequent site of occurrence in this age group [9].

The present study compared the clinical progression of HN SCCs of all sites in patients below and over the age of 40. We aimed to isolate the

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prognostic effect of a number of clinicopathological factors, so as to unmask their possible significance. A standard epidemiological observation for HN cancer over the gender (male to female ratio 7:3) has always been a matter of discrepancy [9]. In an attempt to explain this, Lukits et al. suggested implications of sex hormones [10]. As the endocrine milieu of tumors is markedly affected by age [11], we also performed a limited pilot study, evaluating immunohistochemically the differential expression of ER in tongue tumors of young and old women.

Methods

Patient characteristics

A retrospective database of all patients ≤40 years old, who were diagnosed with HN SCC at the Kansas University Medical Center between 1995 and 2009, was created. Sixty-nine patients were included, with a mean age of 35 years (range 18-40). Their clinicopathological characteristics are presented in Table 1. To assess the prognostic significance of young age at diagnosis, we conducted a case-control analysis. For each young case, a patient over 40 years was selected from the Department's database. Young cases were matched with old controls for gender, site of the primary, tobacco and alcohol habits, grade and TNM clinical stage, as well as for treatment received. All female patients belonging to the old cohort were post-menopausal. The study design was approved by the institution's review board.

Immunohistochemistry

Archival paraffin-embedded tissue sections were deparaffinized and heat-treated for estrogen receptor-alpha antigenic retrieval. Estrogen receptor-alpha antibody, clone SP1 (Neomarkers, Fremont, CA, USA), and the Envision+ labeled polymer (Dako, Glostrup, Denmark) were used. Staining was evaluated at x100 magnification in up to 10 microscopic fields, and at least 5% of cells ought to demonstrate immunoreactivity for a case to be considered positive.

Statistics

Age groups were compared with the rate of disease recurrence, but also within subgroups defined by gender, tumor site, and clinical stage. The different types of recurrence (local, regional, distant) were also assessed separately. The purpose of such stratification was to uncover any potential clinicopathological determining factors. The significance of correlations was investigated using the Fisher's exact test and x2 test. Kaplan-Meier method was used to analyze OS, disease-free (DFS), and disease-specific survival (DSS), and differences were evaluated using the log-rank test. Survival was estimated in the total number of cases, and in smaller stratified samples. A p value <0.05 was considered as statistically significant. Data were processed using SPSS software, version 13.0.

Table 1. Clinicopathological features and treatments of the "young" group

Clinicopathological and treatment data	*N (%)*
Gender	
Male	47 (68.1)
Female	22 (31.9)
Site	
Oral tongue	30 (43.5)
Floor of mouth	6 (8.7)
Buccal mucosa	3 (4.3)
Tonsil	9 (13)
Hypopharynx	1 (1.4)
Larynx	15 (21.7)
Nasal cavity & sinuses	2 (2.9)
Nasopharynx	3 (4.3)
Grade	
I	11 (15.9)
II	33 (47.8)
III	25 (36.2)
T stage	
T1-2	46 (66.7)
T3-4	23 (33.3)
N stage	
N0	34 (49.3)
N1-2	34 (49.3)
N3-4	1 (1.4)
Metastasis	
M0	60 (86.9)
M1	9 (13.1)
Treatment	
None	5 (7.2)
Surgery	21 (30.4)
Surgery+radiotherapy	10 (14.5)
Chemoradiotherapy	7 (10.1)
Surgery+chemoradiotherapy	26 (37.7)

Results

Survival

Survival analysis did not demonstrate any substantial differences between the two age groups. The outcome was similar for all tested types of survival (OS, DFS, DSS). Nonetheless, the comparison among subgroups defined by combination of both site and size of the primary neoplasm, detected shorter OS of young patients with

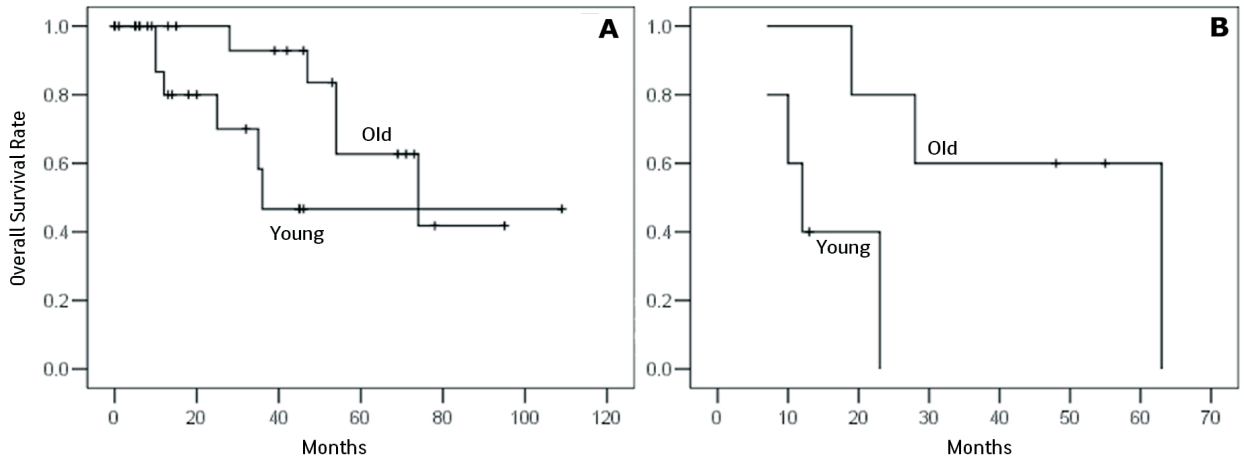

Figure 1. Kaplan-Meier plots of overall survival for the young and old group. **A:** Subgroup with early-stage (T1,T2) SCC of the tongue (p=0.056). **B:** Head and neck cancer patients who had neck relapse (p=0.004).

early (T1,T2) tongue carcinoma (Figure 1A). This finding was marginally non-significant (p=0.056), which seems understandable, as the test was conducted in a small group, limited by two factors, and its statistical power was low.

Prognosis

Prognosis was investigated specifically in cases that developed post-treatment neck disease, regardless of the primary tumor site. None of these patients had signs of local recurrence, besides the cervical disease. In 2/8 (25%) of young and 2/6 (33.3%) of old patients (p=0.59), the neck tumor was a recurrence of a previously treated metastasis. For the late cervical metastases, 3/8 (37.5%) in the young group of patients underwent neck dissection, 3/8 (37.5%) received radiation therapy, while 2/8 (25%) were treated with a combination of external radiation and chemotherapy. These three different approaches were utilized in 2/6 (33.3%), 3/6 (50%), and 1/6 (16.7%) of the older patients, respectively. On x2 testing, distributions of the patient gender and the treatment modality, as well as of the primary SCC site, stage, and grade, did not vary significantly between the two age groups. Young age was significantly associated with worse prognosis after a relapse in the neck, in terms of both OS (p=0.004) and DSS (p=0.023) (Figure 1B). Characteristically, 7/8 (87.5%) of young patients who had developed neck disease post-treatment died within 4 years after the initial diagnosis, whereas half (3/6) of the older patients survived.

Apart from survival assessment, our approach to the prognostic importance of the patient age also included correlations with rates of recurrence. Comparisons between groups of similar clinicopathological profile did not reveal any significant differences in relapse rates, except when the gender and site were considered in addition to the patient age. Specifically for tongue SCC, among the 4 gender/age combinations, young women stand out clearly (Figure 2) as the group with the highest rate of recurrence (p=0.006). This was also the case when young women were compared with their exactly-matched older female controls (p=0.025). Yet, this finding was not reflected on their survival.

Immunohistochemical findings

ER were expressed only in 1/12 cases (8.3%). The positive specimen was a recurrent tongue SCC, with aggressive features (extracapsular spread of a neck lymph node), in a 52-year-old perimenopausal patient (Figure 3). The pattern of immunostaining was nuclear and confined to tu-

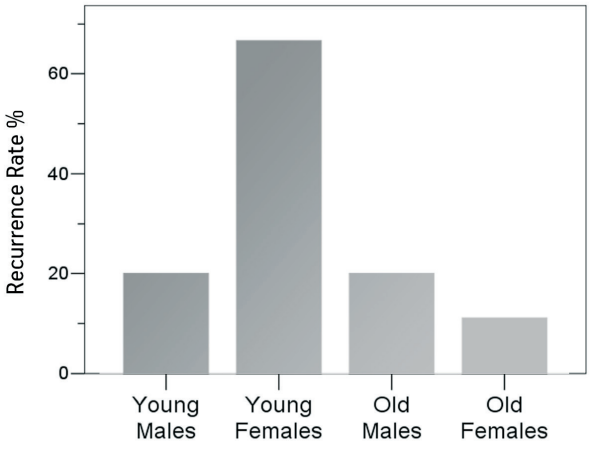

Figure 2. Recurrence rates of tongue SCC for the 4 gender/age combination subgroups.

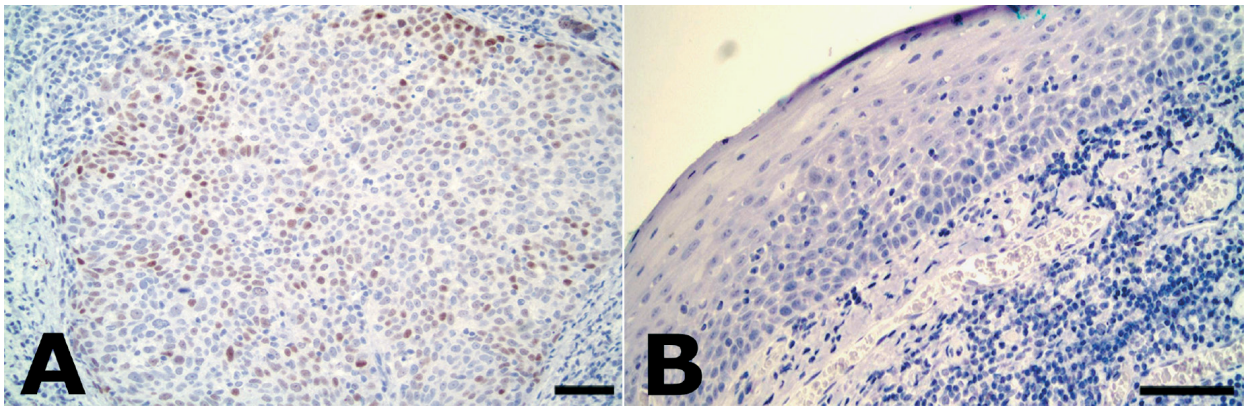

Figure 3. Immunohistochemistry photomicrographs. **A:** Moderate nuclear expression of estrogen receptor-alpha in a tongue SCC of a peri-menopausal female patient. **B:** Normal epithelial cells are not immunostained (original magnification x100, scale bar=20μm).

mor areas only, without any positivity of the normal mucosa.

Discussion

Unlike lymphoma or thyroid cancer, HN SCCs traditionally do not occur before the fourth decade of life [12]. The present study attempted to determine whether this rare, yet increasing in frequency condition, deviates from the standard clinical behavior and biology of HN cancer.

According to our results, three observations indicate that a 20-year-old patient with HN cancer might have worse prognosis than a 70-year-old with a neoplasm of the same grade and stage, and who had received the same treatment. At first, we have shown that young patients with low-stage tongue cancer seem to have shorter OS (Figure 1A), although this finding was marginally non-significant. Oral tongue in particular has been studied more than any other tumor site with regard to patient age, and both locoregional [7] as well as distant [13] failures have been reported to occur preferably in the young cases. In contrast, Pitman et al. found that disease outcomes are independent of age at diagnosis [14]. Nevertheless, poorer prognosis specifically for tumors of small size (T1,T2) has not been reported previously.

As far as disease recurrence in the neck is concerned, irrespective whether the patient had presented initially with regional metastasis or not, our data indicate (for the first time to our knowledge) dismal prognosis in the young cohort. In our analysis we did not discriminate between the different primary tumor sites, as all the subjects included were diagnosed with late neck metastasis alone, and never developed local recurrence of their initial carcinoma. We acknowledge the influence of the primary site on the natural history and behavior of the lymph node disease, particularly in regard to the neck level that is affected. In that sense, our sample was not homogeneous. Nonetheless, as a general rule in HN cancer, regional failure becomes the main predictor of prognosis [15]. A large-scale study, with no pair-matching between cases and controls, documented cervical metastasis at presentation as a more ominous sign for patients under 45 years [16].

Lastly, we identified young women as the subgroup at greatest risk for recurrence of tongue SCC, than any other gender/age combination. More than 20 years ago, Robbins addressed the issue of laryngeal cancer prognosis in relation to gender and menopausal status [17]. This pioneer study did not reveal any prognostic variables for this specific tumor site. Since then, controversy exists with regard to gender impact on the disease outcomes, because the prognosis of female patients has been described as similar (tongue) [18], better (all sites) [19], or worse (oropharynx) [20] compared to males. In the latter case, the adverse influence of female gender has been attributed to the low prevalence of human papilloma virus (HPV) infection, which is considered a favorable prognostic factor [20]. One conspicuous difference between the young, pre-menopausal women, and all the other patients is, of course, the high circulating levels of potent estrogens [11]. This prompted us to investigate the expression of ER in 12 tongue tumor specimens from young and old women. Naturally, we acknowledge that this is a preliminary attempt to evaluate the ER tissue positivity, thus not appropriate for safe conclusions. Detection of immunoreactivity in one case only suggests that response of SCCs to estrogens is limited, and should not be considered responsible for variations in prognosis. Our immunohistochemical findings coincide with a study in tumors of the larynx, which is a target organ of sex hormones during puberty [21]. However, PCR analysis of frozen sections

has revealed ER expression in half of HN cases, and interestingly, this was associated with shorter survival [10].

Our study, among others in the literature, proposes a distinct disease profile for HN SCC developing in young people. Classically, this type of neoplasm is associated with prolonged, sustained irritation by carcinogenic factors, until all the protective mechanisms of the cells are overcome [2]. Therefore, in young patients, either the entire process is accelerated, or a different mechanism is responsible. Historically, the early onset of solid tumors is linked to genetic predisposition rather than environmental influences (e.g. BRCA1 gene for breast cancer, MSH2 for colon cancer) [22]. Nevertheless, familial analysis of HN cancer patients under 45 failed to establish a pattern of heredity [23].

As far as environmental hazards are concerned, and in view of the frequent absence of typical risk factors in young patients, HPV-induced carcinogenesis could underlie oropharyngeal SCC of early adulthood, although this has not been established. On the contrary, the favorable prognosis commonly observed in HPV-positive patients is inconsistent with the aggressive course of cancer in the young [24]. Regardless of pathogenesis, the dynamic progression of SCCs in early adulthood remains essentially enigmatic. The invasive and metastatic potential of a neoplasm is also dependent on host factors, age included. Interestingly, in a mouse model of HN cancer, younger animals manifested less necrotic tumors and denser cervical metastases due to their robust vasculature [25].

On the whole, this study strengthens the already postulated hypothesis that HN SCC of young adults is a distinct form of neoplasia which follows an accelerated clinical course. As HN cancer at a young age is highly uncommon, the cohort of this study was small. We acknowledge that statistics in such a limited number of cases are not solid, and merely provide suggestions for larger-scale, multi-institutional studies. That being said, our contribution to the existing data includes three determining factors that signal an aggravated prognosis for patients under 40: early-stage tongue carcinomas (marginally non-significant), regional recurrence, and tongue SCCs in females. On the basis of our findings, several modifications of current clinical practice [26] might be indicated for testing in clinical trials. Small-sized (T1,T2) SCCs of the tongue should be considered advanced tumors per se when diagnosed in the young, and thus neck dissection or radiation therapy could be included in the standard initial management, like for T3 neoplasms, rather than being an option. Likewise, cervical lymph node recurrence is a particularly alarming event for young patients, and either the threshold for prophylactic treatment of N0 neck should be lowered in this population, or the relapse itself might be addressed aggressively by a combination of modalities. Finally, young female patients with cancer of the tongue comprise a high-risk group for treatment failure and surveillance protocols should be intensified in that case. ER may not be involved in the biology of the latter tumor subgroup, but the physiologic impact of other sex hormones (e.g. progesterone, androgens), as well as the variations in the epidemiology of HPV infection require further investigation.

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