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LETTER TO THE EDITOR

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Subglottic squamous cell carcinoma in Denmark 1971–2015 – a national population-based cohort study from DAHANCA, the Danish Head and Neck Cancer group

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Introduction

Cancers arising in the larynx are divided into supraglottic, glottic and subglottic tumors. Primary subglottic cancer constitutes less than 5% of all laryngeal malignancies [1–6], and are histologically dominated by squamous cell carcinomas (SCCs) [2,7]. The treatment strategies include radiotherapy (RT) and surgery alone or combined [2,3,8,9]. In Denmark, RT is the primary choice of treatment, leaving surgery for salvage [1]. The treatment strategy has been described in the national Danish Head and Neck Cancer group (DAHANCA) guidelines since 1991 [1].

Since primary subglottic SCC is a rare disease, knowledge regarding the clinical course of the disease and treatment outcome is sparse [10]. Except from one American study based on the SEER database (Surveillance, Epidemiology, and End Results Program) [2], therapeutic studies on subglottic cancers are small including less than 60 patients [3–5,8,9,11,12] and based on single institution populations. The aim of the present study was to describe the clinical course of a complete national cohort of consecutive patients diagnosed with subglottic SCC in Denmark between 1971 and 2015.

Material and methods

Study setting and population

The study population included all Danish patients diagnosed with subglottic SCC between 1971 and 2015. Patients were identified using the DAHANCA database [1] in which all Danish citizens diagnosed with head and neck SCC are prospectively registered. To identify potential missing patients, the database population is regularly compared with the Danish Cancer Registery [1,13] population. Hence, the DAHANCA database approximates a 100% national patient coverage. Patients were followed from the first day at the oncology treatment center to death or January 16, 2018. In Denmark, each resident is assigned a unique civil registration number permitting unambiguous record linkage across registries. Therefore, missing information regarding patient and tumor characteristics, treatment, treatment outcome, vital status and cause of death were retrospectively updated using extensive national patient chart reviews, the Danish Pathology Registry, the Danish Civil Registration System, and the Cause of Death Registry, as previously described [1,13,14].

The subglottic space was defined according to the UICC TNM classification 4th edition, the superior boundary being 5 mm below the vocal cords and the inferior boundary as the bottom of the of the cricoid cartilage. Several updated editions of the UICC TNM classification have been used throughout the study period, but the definition has not changed over time.

From 1971 to 2015, the treatment dose was increased and the treatment was accelerated. In the early 70s, the recommended dose was 60 Gy, 5 weekly fractions, 2 Gy/fraction. This was increased to 62–64 GY in 1977 – with larger tumors receiving larger dose. From 1978 to 1985, split-course treatment was used for some patients, mainly as a part of the nationwide DAHANCA 2 trial [15]. In 1986, the recommended dose was escalated further to 66–68 GY as part of the DAHANCA 5 trial [16] which also introduced elective nodal irradiation and hypoxic modification. Elective lymph node irradiation including the first non-involved lymph node region and hypoxic modification was recommended in the national guidelines from 1991. In 1992, accelerated RT using 6 weekly fractions instead of 5 was introduced in the DAHANCA 7 trial [17]. Accelerated RT became the standard treatment from 2003 [18]. Accelerated hyperfractionated RT (76 GY/56 fractions, 10 fractions/week) was introduced in the DAHANCA 9 trial [19] in 2000 and became optional from 2007. Radiotherapy was the primary treatment during the entire period.

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Statistical analysis

STATA 13th edition was used for all calculations. The 5-year survival estimates were calculated using the Kaplan Meier method. The Cox proportional hazard method was used for calculating hazard rate (HR) estimates. All tests were two-sided and presented with 95% confidence intervals (CI).

Failure was defined as either persistent or recurrent disease. Local failure (LF) and loco-regional failure (LRF) was defined as failure in T-site, and T- and/or N-site, respectively. Disease-specific mortality (DSM) was defined as patients who died from or with subglottic SCC, or due to treatment complications. In laryngectomy-free survival (LFS), an event was defined as death or laryngectomy regardless of cause.

The probability of equal hazard rates was tested using the cox proportional hazard method in univariate and multivariate analysis. In the analysis, modern-RT was defined as curatively intended treatment with accelerated or accelerated hyperfractionated RT (±chemotherapy) provided with a dose ≥66 GY. Other curatively intended RT-regimens were called old-RT. In the multivariate analysis, the effect of modern-RT compared to old-RT was adjusted for age, disease stage and differentiation.

Results

A total of 183 patients were registered in the DAHANCA database with subglottic cancer, but 14 patients were excluded due to non-SCC histology ($n = 13$) or other primary T-site ($n = 1$) (Figure 1). Hence, 169 patients were diagnosed with a subglottic SCC in Denmark between 1971 and 2015. The median follow-up (FU (25%; 75% percentiles)) was 2.2 years (0.7;7.1) for all patients and 6.8 years (5.3;10.3) for patients still alive at assessment time. No patients were lost to FU. Patient and tumor characteristics (Table 1) show a strong male predominance (83%) and a median age of 67 years. Half of the patients (54%) were diagnosed with advanced tumor stage (stage III and IV). Of the 126 tumors with known differentiation, 39 (31%) were poorly differentiated or undifferentiated. The number of patients diagnosed per year ranged between none and eight, and the mean number of patients diagnosed per year was 70s: 3.4, 80s: 3.2, 90s: 2.8, and from 00 to 2015 4.8 patients. Lymph node positive disease was observed in 32 (19%) of the patients. The proportion of patients with N+ disease was 15% before 2000 and 23% after 2000. This difference was not statistically significant.

The treatment was curative in 146 patients, palliative in nine patients and 14 patients did not receive any treatment. Of the 146 patients treated with curative intent, 134 (92%) were treated with primary RT, two (1%) with primary surgery

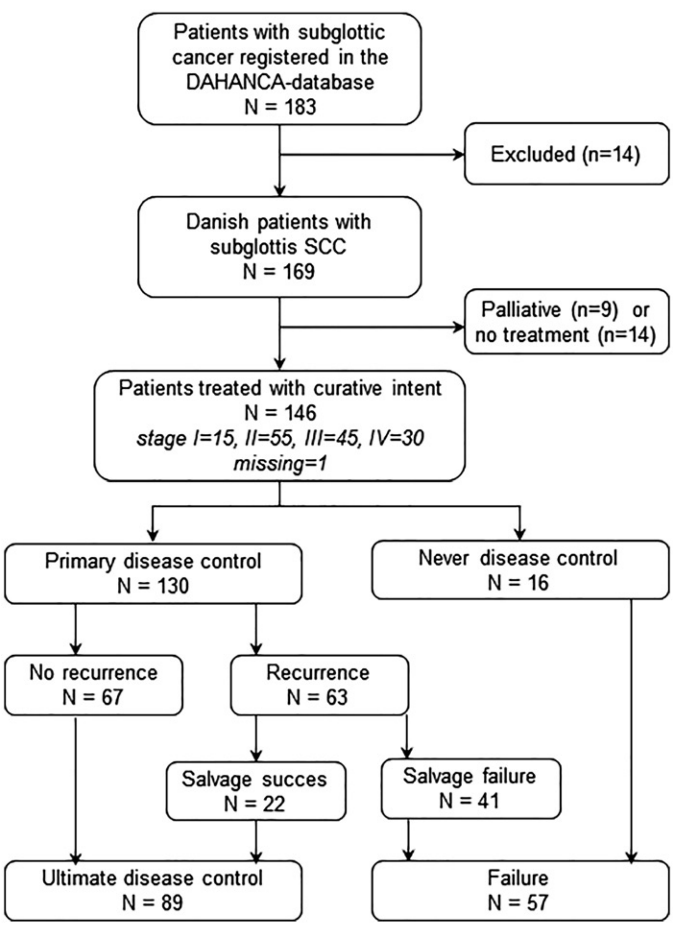

Figure 1. Overview of the clinical course of patients diagnosed with glottic SCC in Denmark in 1971–2015.

Table 1. Patient- and tumor characteristics for all patients and for the patients treated with curative intent.

	All patients ($N = 169$)		Curative intent ($N = 146$)	
	n	%	*n*	%
Gender				
Male	140	83	123	84
Female	29	17	23	16
Age				
Median years (range)	67 (35–93)		66 (35–92)	
T-classification				
T1	19[a]	11	19[e]	13
T2	67[b]	40	61[f]	42
T3	47[c]	28	41[g]	28
T4	33[d]	19	24[h]	16
Unknown	3	2	1	1
N-classification				
N0	137	81	123	84
N+	32	19	23	16
M-classification				
M0	164	97	144	99
M+	5	3	2	1
Stage				
I	15	9	15	10
II	59	35	55	38
III	48	28	45	31
IV	44	26	30	20
Unknown	3	2	1	1
Size (largest diameter, cm)				
<2	36	21	34	23
2–<4	95	57	84	58
≥4	31	18	24	16
Unknown	7	4	4	3
Differentiation				
Moderate/ well	87	52	76	52
Poor/undiff	39	23	33	23
Unknown	43	25	37	25

[a]N+ = 3.
[b]N+ = 8, N+M+ = 1.
[c]N+ = 7, M+ = 2.
[d]N+ = 9, N+M+ = 2.
[e]N+ = 3.
[f]N+ = 7.
[g]N+ = 5, M+ = 1.
[h]N+ = 7, N+M+ = 1.

Table 2. Patients treated with RT with curative intent ($N = 144$).

	70th	80th	90th	00-15	Total
<56 Gy	2[a]	4	2	5	13
56–65 Gy	22[b]	16[c]	3	0	41
>65 Gy	3	11	18[d]	57[e]	89

[a]Hereof two pt had surgery + RT.
[b]Hereof four pt had surgery + RT, three pt had chemoRT, and one pt had surgery + chemoRT.
[c]Hereof one pt had surgery + RT.
[d]Hereof nine had modern-RT.
[e]Hereof one pt had surgery + Rt. Fifty-two had modern-RT, hereof 5 had chemoRT.
The dose was unknown for one patient.

and 10 (7%) with RT and surgery in combination. In coherence with the dose escalation outlined in the changing Danish guidelines, the provided RT dose increased over the study period as shown in Table 2. Of the 134 patients treated with curatively intended (chemo)RT, in total 61 patients received Modern-RT, being accelerated (chemo)RT in 55 patients and accelerated hyperfractionated RT in 6 patients, the latter all treated after year 2000. The clinical course for the patients treated with curative intent is illustrated in Figure 1. In total, 130 of the 146 patients achieved primary disease control. Of these, 63 patients had recurrence, and 22 of the 63 patients suffering a recurrence achieved secondary tumor control due to salvage procedures. Ultimate disease control defined as no signs or suspicion of tumor after treatment including salvage procedures was achieved for 89 of 146 (61%) patients treated with curative intent. The remaining 57 patients (39%) did not achieve ultimate disease control.

At the time of assessment, 143 of the 169 patients had died. Seventy-nine (55%) died of subglottic SCC, hereof two patients died of complications to the radiotherapy treatment. The remaining deaths were due to another head and neck cancer ($n = 4$), lung cancer ($n = 10$), other cancers ($n = 13$) and other disease ($n = 37$). Within two years of diagnosis, 64 (83%) of the 79 subglottic SCC-specific deaths had occurred.

Laryngectomy was part of the primary treatment in four cases, and 17 laryngectomies were performed as salvage treatment, of which 10 patients achieved secondary tumor control.

For the whole cohort, the median survival was 2.3 years. The 5-year overall survival (OS) was 38% (CI: 30–45). For disease-specific mortality, loco-regional failure and local failure, the 5-year estimates were as follows: DSM 49% (CI: 42–58), LRF 58% (50–66) and LF 56% (48–64). For the 146 patients treated with curative intent, the median survival was 3.2 years, and the 5-year estimates were OS: 43% (CI: 35–51), DSM: 43% (CI: 35–52), LRF: 53% (CI: 45–62) and LF: 50% (CI: 42–59) (Figure 2).

For the 146 patients treated with curative intent including RT, surgery and chemotherapy in any given combination, the univariate HR ratio of DSM was male vs female: 0.7 (0.3–1.3), poor/undifferentiated tumor vs moderate-well differentiated: 1.2 (0.7–2.3), Stage III–IV vs I–II: 3.4 (1.9–6.0), tumor size >3 cm vs ≤3 cm: 2.2 (1.3–3.7) and treatment before vs after 1990: 1.1 (0.6–1.8). For the 134 patients treated with curatively intended (chemo)RT, the univariate HR ratio of DSM was: Modern-RT vs Old-RT: 0.6 (0.3–1.1) (Figure 2). The multivariate HR ratio of DSM adjusted for age, stage and differentiation was Modern-RT vs Old-RT: 0.6 (0.4–1.1).

Discussion

This study represents the only national cohort of consecutive patients diagnosed with subglottic SCC published to date. The data validity is high due to the systematic national registration strategy in Denmark, and no patients were lost to follow-up. As all the patients registered with subglottic SCC were included, there was no registration bias except from patients never diagnosed. This contribution was believed to be only a few cases since all citizens in Denmark have universal access to free tax-supported health care.

Other published studies on subglottic SCC presents small, retrospective single institution cohorts ($N = 10$–89) [10,20] except from one study by Marchiano et al. [2] including more than 889 cases extracted from the SEER database. In the study by Marchiano, the primary treatment was RT (34%), surgery (17%), combination of RT and surgery (39%), and no treatment (10%). Hence, more patients received surgery than in our study where the majority of patients were treated with RT only. The 5-year overall survival was 42% and DSS was 57% compared to OS 38% and DSM 49% in our study.

Marchiano et al. also found no significant difference in the 5-year OS or DSS among treatment modalities [2]. This is in contrast with Santoro et al. [11] who presents 49 cases treated with RT (12%), surgery (35%), combination of RT and surgery (37%), and other treatments (14%). The overall 5-year disease-free survival was 56% and significantly higher among patients treated with combination therapy (83%), compared to surgery (47%) and RT (0%). The comparison of the treatment strategies in these retrospective studies is of cause highly susceptible to selection bias, since specific criteria for selection of patients to the different treatment cohorts are not given. All patients treated with surgery in the study by Santoro et al. [11] had a total laryngectomy with partial thyroidectomy and ablation of up to three tracheal rings. Most of the patients were also treated with a neck dissection. This type of extensive surgery might leave the patients with significant sequelae and hence a deteriorated quality of life despite of longer survival. In contrast, no difference in survival was observed for patients treated with primary laryngectomy compared with patients treated with primary RT [20] in a recently published study by MacNeil et al., including 89 patients in total. These results encourage the recommendation of a laryngeal preservation therapy as an option for primary treatment in suitable patients.

The DSM for patients treated with curative intent in our study was significantly associated with tumor stage, showing lower hazard rates of DSM for stage I–II compared to stage III–IV. Marchiano et al. [2] and Haylock et al. [9] also observed this association. We also observed DSM to be significantly influenced by tumor size. This is not surprising since tumor size and stage are associated parameters. The gender, tumor differentiation and treatment before/after 1991 (the time periods are substituting for low and high dose treatment

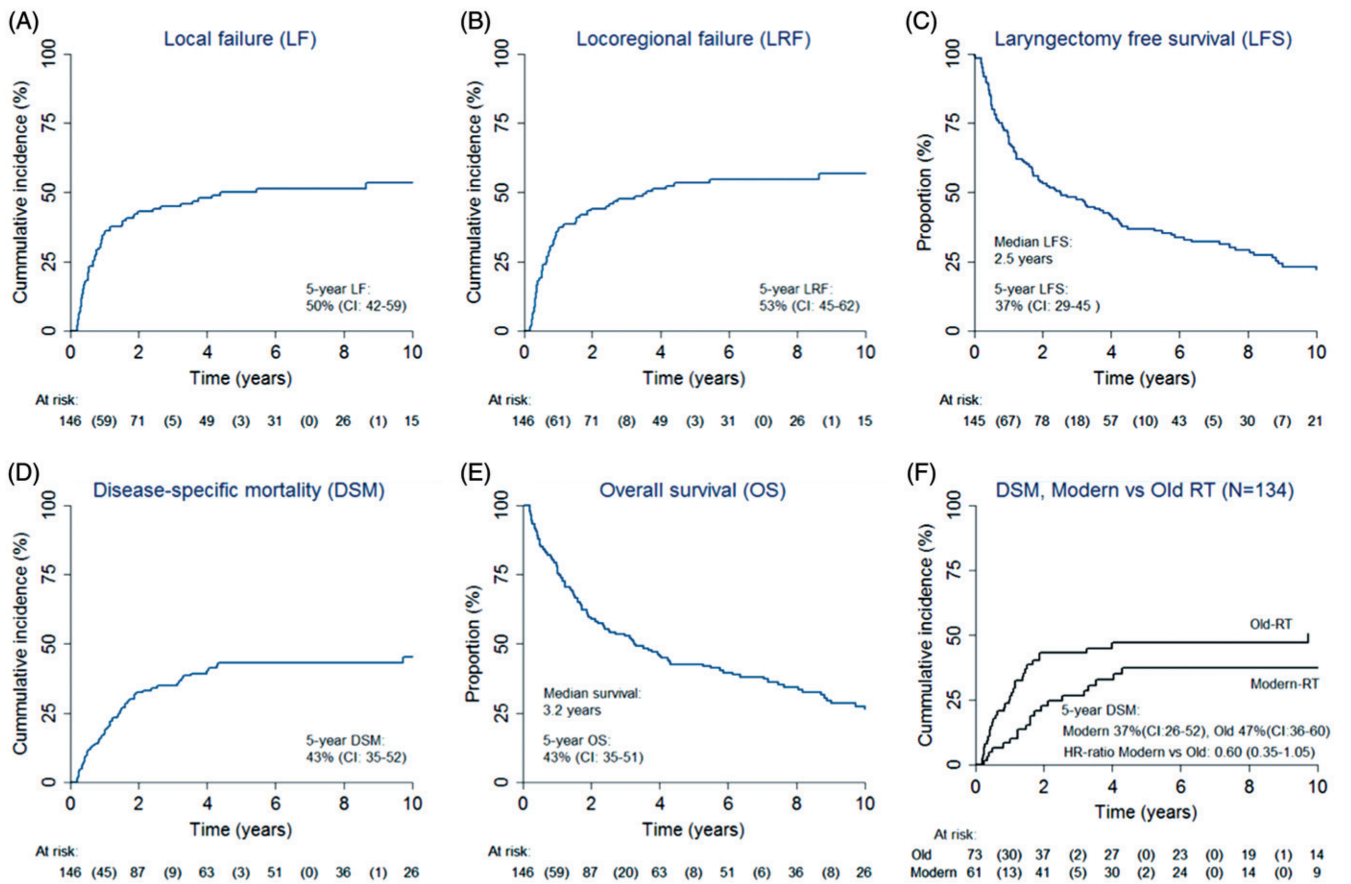

Figure 2. Outcome for the 146 patients treated with curative intent (A–E) and for the 134 patients treated with curative intended (chemo)RT (F).

periods) did not significantly affect the HR of DSM in the present study. Tumor differentiation is known to influence the prognosis for SCC in other subsites of the larynx [13,17]. The lack of association between treatment outcome and tumor differentiation in this study might be due to a different metastatic potential of subglottic tumors compared to other sites in the larynx. More likely the lack of association is due to low statistical power and in line with this, Marchiano et al. [2] was able to show that a significantly lower DSS was associated with low tumor differentiation compared to high differentiation.

Numerous studies [21,22] have shown imaging to be more sensitive in detecting lymph node positive disease compared to clinical evaluation of patients with head and neck cancer. In the current study, we did not observe a significant increase in the proportion of patients diagnosed with lymph node positive disease during the study period. This is somewhat surprising considering the significant increase in imaging used in the diagnostic workup during the study period [23]. The observed lack of difference in the proportion of lymph node positive could be speculated to reflect a low statistical power due to the small number of patients instead of an actual no change in proportion.

In Denmark, the primary treatment is RT leaving surgery for salvage. No significant difference was observed in the DSM in newer time defined as 1990 or later, compared to before 1990 or for patients treated with modern-RT compared to old-RT. None of the published larger studies from centers using other treatment strategies have demonstrated convincingly superior disease control [5,8] compared to our data. Hence, so far a more effective treatment is needed in combination with earlier diagnosis and probably most important, prevention of the disease. Similar to cancer in other laryngeal subsites, it is reasonable to believe that smoking is also the predominant risk factor in subglottic SCC [13,24]. Thus, smoking cessation campaigns are relevant in the prevention strategy for subglottic cancer.

Conclusion

Subglottic SCC is a rare disease with a poor prognosis. More than half of the patients diagnosed with subglottic SCC died of the disease within 5 years. No significant effect of modern RT regimens was observed on the hazard of disease specific mortality. Larger studies are desired in order to explore more effective treatment regimens. Due to the very low disease incidence, this will only be possible in an international setup.

Disclosure statement

No potential conflict of interest was reported by the authors.

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