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Glottic carcinoma

Pattern of failure in 5001 patients treated for glottic squamous cell carcinoma with curative intent – A population based study from the DAHANCA group

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ABSTRACT

Purpose: To describe the pattern of failure in a national consecutive cohort of patients with glottic squamous cell carcinomas (SCC) treated with primary radiotherapy (RT) with curative intent over a 41-year period.

Materials and methods: All patients undergoing curative treatment for a glottic SCC diagnosed in Denmark between 1971 and 2011 were included and followed from the first contact with the oncology center to death or February 15, 2015.

Results: 5001 patients were identified of whom 98% had primary RT. The median follow-up was 9.1 years/5.7 years (patients alive/patients who died). Ten patients were lost to follow-up. In total 1511 failures were observed; of these 93%, 11% and 5% included T site, N site, and M site, respectively. For patients diagnosed in the 70s and the 00s, respectively, the five-year incidences were: local failure (32% vs 19%), loco-regional failure (34% vs 21%), laryngectomy (26% vs 10%), laryngectomy-free survival (48% vs 62%), disease-free survival (62% vs 68%), and overall survival (62% vs 68%). The five-year incidence of ultimate failure (13–16%) remained statistically unchanged.

Conclusion: From the 70s to the 00s a continually improving primary disease-control was observed with a concurrent decrease in the incidence of laryngectomy. The survival rate was significantly higher in the 00s compared to the previous three decades.

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The treatment of glottic cancer is local, being either surgery or radiotherapy (RT). The choice between primary surgery or radiotherapy depends largely on tradition [1] since no consensus exists as to which treatment provides optimal disease control and survival with preservation of laryngeal function [2–4]. In early glottic cancer (Stages I–II), endolaryngeal surgery, with or without laser, and RT offer comparable outcomes [5,6], while the voice function might be slightly better after RT [6–8] and the laryngeal preservation seems to be higher after surgery [9–15]. Considering advanced (Stages III–IV) disease, studies comparing surgery and RT include all laryngeal sites and not only glottic. Comparable survival rates after primary surgery (laryngectomy) vs induction chemotherapy plus RT (CRT) was observed in a randomized trial by The U.S. Department of Veterans Affairs [16], favoring the RT-arm due to higher voice box preservation. Concomitant CRT was later found superior concerning primary disease control and survival compared to induction CRT or RT alone [17–19]. The equivalence of primary surgery and CRT has been debated, since a decrease in the survival of patients with laryngeal cancer was observed in the U. S. simultaneously with an increased use of CRT and a decrease in primary surgery [20].

For several decades, the treatment strategy in Denmark has been primary radiotherapy, reserving laryngectomy for salvage. The DAHANCA group continuously aimed at improving the cancer treatment by conducting national clinical trials [21–25] and we hypothesize that the disease control after glottic SCC improved over time as a result of this strategy.

Previously, we reported the incidence of glottic SCC and the disease-specific mortality and overall survival for all patients diagnosed with glottic SCC in Denmark between 1971 and 2011 [26]. For the present paper, only patients who started treatment with curative intent were included.

The aim of this study was to describe the pattern of failure, treatment outcome, laryngeal preservation, and survival in a

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national ethnical homogenous cohort of patients diagnosed with glottic SCC and treated with curative intent in Denmark over a 41-year period.

Materials and methods

Patients

Since 1971, all Danish patients with glottic SCC were registered in a database by the Danish Head and Neck Cancer Group (DAHANCA), with the following inclusion criteria: (1) biopsy-proven invasive SCC; (2) diagnosed alive; (3) treatment given in Denmark; (4) no previous tumor expected to influence the treatment or obstructing the outcome evaluation.

The coverage of glottic SCC patients in the DAHANCA-database approximates 100%, as described earlier [26]. The DAHANCA-database contains information about patient characteristics, tumor characteristics, treatment, treatment outcome, treatment morbidity, salvage procedures, vital status, and cause of death. For the present analysis, patients diagnosed with primary glottic SCC Stages I–IV, who started curatively intended treatment, were included. Patients were followed from the first consultation at an oncological treatment center to the date of death or to February 15, 2015, except for 10 patients who were lost to follow-up. In case of missing or conflicting data in the DAHANCA-database, information was investigated by linkage to the Pathology Registry (failure/laryngectomy), the Cause of Death Registry, and by extensive national chart reviews. All tumors were classified or re-classified according to the UICC 1987 classification [27].

Treatment

RT was the standard treatment for glottic cancer in Denmark throughout the study-period (Supplementary Table 1). The treatment, though changing over time, was homogeneous nationwide owing to the national collaboration within the DAHANCA-group. From 1992 the DAHANCA-group provided official national treatment guidelines. High voltage RT was delivered as lateral opposing fields using Cobalt-60 until the early 1980s and 4–6 MV linear accelerator later on. From 2005 IMRT was gradually used for larger tumors. In the early 1970s the standard regimen was 60 Gy, 30 fractions, 5 fractions per week (60 Gy, 30 fx, 5 fx/w). In 1977 the dose was escalated to minimum 62–64 Gy with larger tumors (>2 cm) receiving the largest dose. From 1978 to 1985 split-course treatment was used mainly as a part of the nation-wide DAHANCA 2 trial (see below) [22]. In 1986, this was abandoned in favor of minimum 66–68 Gy, 33–34 fx, 5 fx/w (for <4 cm vs $\geqslant$4 cm, respectively), except from well differentiated T1a tumors for which 62 Gy was optional until 2000. Accelerated RT (accRT: 66–68 Gy, 33–34 fx, 6 fx/w) became the standard treatment from 2002 [23]. For T2–4 tumors, elective lymph node irradiation was recommended since 2002, and in 2006 concomitant CRT was introduced as standard for Stages III–IV patients [25]. A gentle curative intended schedule (52 Gy, 13 fx, 2 fx/w) was used for patients not considered suitable for the prevailing standard schedule.

Patients were continuously included in national clinical trials by the DAHANCA-group. Among these a few patients were treated with induction CRT in the 1970s (DAHANCA 1) [21], concomitant CRT in the 2000s (DAHANCA 18) [25] and hyperfractionation in the 2000s (DAHANCA 9) [24]. The DAHANCA 6 trial randomized 694 glottic cancer patients between either conventional fractionation with 5 fx/w or accelerated fractionation with 6 fx/w to the same total dose between 1992 and 1999 [23]. The DAHANCA 2 trial (1978–1985) randomized 365 patients between a hypo-fractionated split-course regimen of 65–67 Gy or a normo-fractionated split-course regimen of 66–72 Gy (Supplementary Table 1) [22]. This trial also investigated the effect of hypoxic modification with misonidazole, but did not show a significant benefit in patients with glottic SCC. These patients were consequently omitted from the subsequent studies of hypoxic modification with nimorazole [28,29]. Still, since 2001, hypoxic modification has been recommended for T2–T4 glottic tumors in Denmark.

Primary surgery was endoscopic resection (n = 74) or laryngectomy (n = 11), the latter in patients who rejected RT or who were considered unfit for RT.

Statistics and endpoints

The competing risk method was used to calculate the cumulative incidence of local failure (LF), loco-regional failure (LRF), any failure (F), laryngectomy (LG), ultimate failure (UF), and disease-specific mortality (DSM). Competing risks were: LF (N/M/NM failures and death), LRF (M failures and death), F (death), LG (death), UF (death), and DSM (death from non-glottic SCC cause). The proportion of laryngectomy-free survival (LFS), disease-free survival (DFS) and overall survival (OS) was estimated using Kaplan–Meier (Supplementary Table 2 for description of time-to-event endpoints). The probability of equal hazard rates was tested using the cox proportional hazard method in univariate analysis and multivariate analysis. The Chi^2 test was used to test for difference in proportions. A significance level of 1% was used to avoid significance due to multiple comparison. All tests were two-sided. When describing changes over time, the calendar-periods were referred to as the 70s (1971–1980), 80s (1981–1990), 90s (1991–2000) and 00s (2001–2011).

Results

The cohort

5001 patients with glottic SCC were treated with curative intent in Denmark between 1971 and 2011 (Table1). The median age was 65.7 years and 90% were males. Most patients were diagnosed with early Stage disease (Stage I 54%, Stage II 27%), and very few had lymphnode positive (N+) disease (4%), or distant metastases (<1%). Tumor characteristics significantly differed over time. N+ disease increased a little in the 00s, as did the proportion of Stage I and IV tumors whereas the proportion of Stage II tumors decreased.

Primary treatment was RT (96%), CRT (2%), and surgery (2%). (Supplementary Table 1). The increase in primary surgery over time was due to more T1 tumors treated with endoscopic resection.

Median follow-up for patients still alive at assessment was 9.1 years (inter quartile range 5.7–15.3 years) and for patients who died 5.7 years (inter quartile range 2.1–11.5).

Failure pattern

In total 1511/5001 patients (30%) had a treatment failure, of whom 106 never achieved primary control (Supplementary Fig. 1). Overall, 91% (n = 1372) of the failures occurred within five years after the first visit, with 84% (n = 1262) being observed within the first 3 years (Supplementary Table 3, Supplementary Fig. 2). The proportion of late (>5 years) failures was correlated to T-classification with a decreasing proportion of late failures with higher T classification; T1 = 15%, T2 = 8%, T3 = 4%, T4 = 0% (p < 0.01). The primary tumor site (T site) was included in 93% (n = 1408) of failures and 85% (n = 1279) were solitary T site failures. Regional lymphnodes (N site) and distant metastasis (M site) were included in 11% (n = 172) and 5% (n = 79) of failures, respectively. The failure pattern of the late failures (>5 years) was