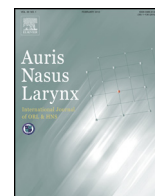




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## Management of advanced hypopharyngeal and laryngeal cancer with and without cartilage invasion

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### ABSTRACT

**Objective:** To compare efficacy, in terms of disease control/survival in advanced hypopharyngeal and laryngeal lesions, according to treatment strategy (primary surgery, PS or primary chemoradiotherapy, CRT) and invasion pattern (cartilage, CAI or soft tissue involvement, STI).  
**Methods:** Records from 463 patients with T3 and T4a carcinoma with CAI ( $n = 221$ ) or STI ( $n = 242$ ) treated at a university clinic over 18 years were retrospectively reviewed.

**Results:** Disease-specific survival (DSS) for the CAI group was 70.1% (PS) and 38.4% (CRT), and 76.6% and 46% for the STI group, respectively. Overall survival (OS) for STI was 56.4% (PS) and 30.6% (CRT), and for CAI 51.1% (PS) and 28.5% (CRT) respectively. Positive resection margins and regional neck metastases reduced survival. T3 lesions treated non-operatively still had significantly improved survival versus T4a by >20%.

**Conclusion:** Surgery remains an indispensable part of treatment in local advanced hypopharyngeal and laryngeal cancer with high survival results. It should be part of a concept that includes adjuvant (C)RT. For T3 lesions, primary CRT is also acceptable and CAI is not a contraindication for primary CRT. Regional disease is a strong prognostic factor. In spite of adjuvant treatment, DSS deteriorates by about 20% in cases with positive resection margins.

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## 1. Introduction

Until the 1990s, the standard treatment for advanced hypopharyngeal and laryngeal carcinoma was surgery, often including laryngectomy. A primary organ preservation approach with chemoradiation therapy (CRT) started in the aftermath of the landmark trial conducted by the

U.S. Department of Veteran Affairs Laryngeal Study Group [1]. Patients with T4 disease and cartilage invasion had poorer survival rates when treated with CRT [2]. As a result, the subsequent Radiation Therapy Oncology Group (RTOG) 91-11 trial excluded cases with cartilage invasion into the base of the tongue or high volume >1 cm [3]. Advanced-stage tumors, especially those with bone and cartilage invasion, harbor a hypoxic microenvironment that causes resistance to CRT [4]. A retrospective analysis of the RTOG 91-11 suggests that salvage laryngectomy after organ preservation adversely affects survival compared with no salvage laryngectomy [5]. The findings of the aforementioned studies on tumors with cartilage

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invasion and high volume led the American Society of Clinical Oncology to recommend abandoning the larynx-preservation approach in patients with tumor penetration through the cartilage [6]. Despite this guideline, it is claimed that modern CRT modalities can be used to control such diseases using an organ preservation approach [7,8]. The choice between surgical therapy and the alternative CRT remains controversial. The purpose of this study was to analyze efficacy and survival depending on treatment management in patients with advanced lesions, in particular patients with soft tissue invasion (STI)/high volume tumors or cartilage invasion (CAI) and to compare the latter two groups. To our knowledge, there are no studies available that have evaluated the survival of patients with CAI in comparison to STI depending on treatment options in a cohort of more than 400 cases.

## 2. Material and methods

### 2.1. Patients

This retrospective study was conducted at an academic tertiary referral center. Relevant approval from the institutional review board of the hospital was obtained. The records for all patients treated with primary surgery (PS) or CRT for T3 and T4a laryngeal and hypopharyngeal carcinomas over a period of 18 years were evaluated. Patients with distant metastases at the time of diagnosis, second primary tumors, histologic findings other than squamous cell carcinoma, T4b, induction chemotherapy, premature discontinuation of therapy including adjuvant CRT, and insufficient data were excluded from the study. To prevent selection bias, all non-surgical files were carefully reassessed. Cases that had been assigned to primary CRT because of inoperability according to imaging or panendoscopy results were excluded. The carcinomas were classified in accordance with the International Union Against Cancer using the seventh edition [9]. Due to the subdivision of T4 into T4a and T4b in 2002, the files of patients with T4 carcinoma prior to 2002 were reassessed. The cases were grouped into PS  $\pm$  adjuvant (C)RT (Group A) or primary CRT  $\pm$  salvage surgery (Group B).

### 2.2. Therapy

Surgery was performed either as total laryngectomy or as partial or total pharyngectomy with or without flap reconstruction. Definitive CRT consisted of normofractionated or hyperfractionated/accelerated radiotherapy at a dose of 66–72 Gy in combination with platinum-based chemotherapy. Chemotherapeutic agents were mostly Cisplatin 20 mg/m<sup>2</sup>, d1-5 in combination with 5-Fluorouracil 800 mg/m<sup>2</sup> d1-5, q28. The respective primary treatment approach had been decided by an interdisciplinary tumor board oriented to patient preferences, functional status of the larynx, comorbidities, or other subtle clinical factors. The decision on adjuvant (C)RT after PS was also made by the board according to oncological criteria such as nodal status, tumor size, localization, grading, and resection margins. At our institution, CAI or high volume tumors with or without CAI are not a contraindication for primary CRT. Many

patients have been assigned to it and received an individualized treatment regimen. The non-surgical treatment protocol has been subject to changes over the years due to technical developments and scientific standards. In case of local or regional disease, salvage surgery was performed.

### 2.3. Endpoints of study and statistics

Comparisons of five-year OS (overall survival), DSS (disease-specific survival), and local disease control estimates (LC) were made using the Kaplan–Meier estimate between the patient groups with CAI (Group A<sub>CAI</sub> or B<sub>CAI</sub>) or STI (Group A<sub>STI</sub> or B<sub>STI</sub>) according to treatment modality: PS  $\pm$  (C)RT (Group A) and primary CRT  $\pm$  salvage surgery (Group B). OS was measured from the time of initial diagnosis to the death of the patient or last follow-up. DSS was calculated from the initial diagnosis to tumor- or treatment-related death or to the last follow-up. LC was calculated from the time of initial diagnosis to the first local recurrence, or to the last follow-up. Variables that appeared to have prognostic potential as suggested by the univariate analysis were further analyzed to assess whether they matched the proportional assumption of the Cox regression. In this multivariable analysis, survival estimation was evaluated using the log-rank test with 95% confidence intervals and the chi-square test (significance:  $p \leq 0.05$ ). The computer software SPSS version 21 for Windows (IBM Corporation, Armonk, New York, USA) was used.

## 3. Results

### 3.1. Patient characteristics

A total of 463 patients – 405 men and 58 women – who fulfilled the inclusion criteria were investigated. The mean age was 58 years (range 27–88). The mean follow-up period was 3.97 years (range 0.00–17.62). When classified by anatomical site, 252 patients (54.6%) had a hypopharyngeal carcinoma and 211 (45.3%) a laryngeal carcinoma. All patients had either laryngeal CAI or STI based on CT imaging or on pathological results qualifying as T3 or T4a tumor staging of the primary site. In the surgical group evaluation of the state of cartilage involvement was done exclusively by using excised specimen in every case. In the group of primary CRT, specimen of cartilage was not available. Only in this group assessment procedure of cartilage invasion was carried out by CT. In this group, only patients with very clear radiological evidence of cartilage invasion, erosion or definitely no cartilage involvement were included in the study. Thus, the difference in diagnostic accuracy between the surgical group (histopathological determination of cartilage involvement) and the non-surgical group was minimized. The patients were divided into the two major groups: carcinoma with CAI (Group A<sub>CAI</sub> or B<sub>CAI</sub>) versus STI (Group A<sub>STI</sub> or B<sub>STI</sub>) and were subdivided according to treatment modality (PS  $\pm$  (C)RT (Group A) and primary CRT  $\pm$  salvage surgery (Group B)). The cartilage involvement group (CAI) was defined as an invasion of the INNER CORTEX of thyroid cartilage (T3, hypopharynx

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