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# Outcome of multimodal treatment for oropharyngeal carcinoma: A single institution experience

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**Summary** The clinical management of patients with primary oropharyngeal squamous cell carcinoma remains controversial. The results of a combined approach involving surgery for the primary tumor, neck dissection, and postoperative radiotherapy were reviewed. A retrospective review was carried out for 211 patients meeting the inclusion criteria of resectable squamous cell carcinoma of the oropharynx. Overall survival and disease-free survival rates were calculated using the Kaplan–Meier method. Univariate (Log-rank test) and multivariate (Cox proportional hazards models) statistical analyses were carried out to investigate the role of clinical factors as significant prognostic markers. The 2- and 5-year disease-free survival rates were 79.8% and 68.8%, respectively. In univariate and multivariate analyses, positive resection margins were the only and independent significant prognostic markers for impaired disease-free survival (Log-rank: $p = 0.0238$; Cox model: $p = 0.045$; hazard ratio 2.48 [95% confidence interval 1.02–6.05]). In univariate analysis, male sex was the only significant negative prognostic factor for overall survival (Log-rank: $p = 0.0453$), whereas Cox multivariate analysis identified extracapsular spread as an independent prognostics marker ($p = 0.049$; hazard ratio 1.86 [95% confidence interval 1.00–3.43]). We conclude that the presented multimodal approach of surgery for the primary tumor and the neck followed by postoperative radio(chemo)therapy seems to be superior to non-surgical treatment protocols, as it results in better disease-free and overall survival. To assess this multimodal treatment approach, morbidity and economic considerations need to be further analyzed.


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## Introduction

Oropharyngeal carcinoma is usually of squamous cell origin, and is often referred to as oropharyngeal squamous cell carcinoma (OSCC). OSCC is strongly related to smoking and alcohol ingestion. Another, more recently identified risk factor, is infection of the oropharyngeal mucosa with oncogenic human papilloma virus (HPV) (high risk).[1] This risk factor seems to define a separate tumor entity with a different biological behavior.[2]

In the West, oropharyngeal carcinomas account for about 5% of all cancers. Between 1992 and 2001, cancer of the oral cavity and pharynx was the seventh most common cancer among men in the USA, with an incidence rate of 16.7 per 100,000.[3] An estimated rate of 28,260 new cases of OSCC was expected in the USA in 2004, and about 7230 of these patients were expected to die from the disease.[4] In other parts of the world, particularly India and southern China, cancers of the head and neck are the most common cancers. The incidence of OSCC in younger adults has increased remarkably. The incidence of HPV has also been increasing in recent years; this increase may be due to an association with OSCC and HPV infection in younger adults.[5]

The clinical management of patients with primary OSCC remains controversial.[6–16] It is often reported that radiotherapy and surgery are equally effective in treating patients with early stage disease.[17–19] For some institutions, a combination of these two modalities is standard care for patients with advanced disease. This is based on the assumption that two radical treatment modalities are more effective than one. However, randomized data comparing radiotherapy alone with combined-modality treatments are insufficient. The only randomized trial, conducted by the Radiation Therapy Oncology Group,[17] reported no significant differences in survival results of the two different treatment modalities.

For treatments with curative intent, tumor control and survival are the most important measures of treatment efficacy. Furthermore, treatments for patients with OSCC are assessed by the complications and morbidity they induce. The purpose of this study was to review our experience and findings of a combined approach involving surgery for the primary tumor, neck dissection and postoperative radiotherapy.

## Patients and methods

Two hundred and eleven patients were selected for inclusion in our study. These patients attended our institution with previously untreated oropharyngeal carcinoma between 1992 and 2005. They fulfilled the following inclusion criteria: a histological confirmed diagnosis of squamous cell carcinoma and an extended tumor suitable for curative surgical treatment. The tumor stage was classified according to the American Joint Committee on Cancer (AJCC) 2002 staging system.[20] In general, a tumor was defined as non-resectable when clinical or radiological signs pointed to infiltration of the vertebra, skull base, or infiltration of the carotid artery. Carcinomas of the base of the tongue that crossed the midline were also considered as non-resectable. Patients with distant metastases were excluded from the study. A standardized oncological protocol was applied, and remained the same during the study period. All patients underwent major surgery for the primary tumor using a transoral or transcervical approach. All patients were additionally considered for a neck dissection. In patients without clinical evidence pf lymph-node metastasis (cN0), an elective ipsilateral neck dissection was regularly carried out. A bilateral elective neck dissection was carried out in cases of primary tumors crossing the midline. In all patients with clinical evidence of lymph-node metastasis (cN+), a selective or modified radical neck dissection was carried out. Patients with histologically confirmed positive neck nodes (pN+) underwent either an incomplete resection of the primary tumor (R1/R2) and pT3/T4 stage, postoperative radiotherapy or, more recently, radiochemotherapy. The average, overall dose delivered was 59.6 Gy (range 28.8—70.2 Gy). The median time from surgery to postoperative radiotherapy was 44 days (SD = 29 days). Follow-up data were collected at periodic visits in 4—6-month intervals at the outpatient department. Follow-up time was defined as the time from the date of the first tumor operation until the date of the last visit or date of death.

Statistical analyses of the data were carried out using SPSS software for medical statistics. Overall- and disease-free survival were calculated using the Kaplan—Meier method. The statistical relationship between the following variables on overall- and disease-free survival were analyzed: age, sex, tobacco and alcohol intake, and localization of the primary tumor, T stage and N stage, histological grading, lymphangiosis carcinomatosa, extracapsular spread of neck metastases, tumor stage according to the AJCC 2002, surgical approach to the primary tumor, use of laser for surgery of the primary tumor, neck dissection and postoperative radio(chemo)therapy. For univariate analysis, the Log-rank statistic was used to detect the differences between the strata and corresponding survival data. Multivariate survival analysis was carried out with the Cox proportional hazards method, including all parameters with $p$ values less than 0.1 resulting from the Log-rank test. For all tests, two-sided $p$ values of less than 0.05 were considered statistically significant.

## Results

The demographic details of the 211 participants are listed in Table 1. Most patients were active smokers (74%) and reported daily alcohol consumption (66%). We found a high rate of positive neck nodes (pN+) at early stages of primary tumors: about two-thirds of all patients with pT1 and pT2 tumors initially presented with neck metastases (Table 2). Tonsilar carcinomas and carcinomas of the base of the tongue were most frequent in the present series (54% and 20%, respectively). More details of the localization of the primary tumors, the TNM-classification and the disease stage are given in Tables 2 and 3. Seventy-four percent of all patients received postoperative radio(chemo)therapy, and almost all (97%) of the patients received a neck dissection. More details of the treatment modalities are provided in Table 4.

The mean follow-up time was 38.6 months, with a minimum of 0.2 months and a maximum of 142.9 months. The 2-year overall survival estimate was 79.8% and the 5-year