

## High-dose-rate brachytherapy in early oral cancer with close or positive margins

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### ABSTRACT

**PURPOSE:** Retrospective evaluation of high-dose-rate brachytherapy (HDR BT) in early oral cancer and factors influencing tumor control.

**METHODS AND MATERIALS:** A total of 30 patients with T1–T3N0 tongue and floor of mouth cancer were treated with tumor excision ± elective neck dissection and HDR BT 18 × 3 Gy b.i.d. The Kaplan–Meier model was used for survival analyses, and the log-rank test and Cox regression analyses were used to evaluate the influence of T-stage, histologic grade, resection margin, depth of invasion, and vascular endothelial growth factor (VEGF) intensity on local control (LC), nodal control (NC), disease-free survival (DFS), and overall survival (OS). Median followup was 40 months (6–145).

**RESULTS:** Actuarial 3-year LC, NC, DFS, DFS after salvage treatment, and OS were 85.4%, 69.2%, 65.4%, 75.6%, and 73.0%, respectively. The log-rank test and univariate Cox regression analysis revealed the following correlations, namely tumor grade correlated with LC, DFS, and OS; T-stage with NC and DFS; depth of invasion and VEGF intensity with NC, DFS, and OS. Associations detected on the multivariate analysis were as follows: tumor grade with LC, depth of invasion with NC, depth of invasion and tumor grade with DFS, and VEGF intensity with DFS after salvage treatment. Only one case of osteoradionecrosis and two cases of soft tissue necrosis occurred.

**CONCLUSION:** The HDR BT 18 × 3 Gy b.i.d. is a safe treatment of early oral cancer with a good LC. The T-stage, tumor grade, depth of invasion, and intensity of VEGF were significant predictors of locoregional control. © 2015 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

### Keywords:

Oral cancer; High-dose-rate brachytherapy; Locoregional control; Prognostic factors; VEGF

### Introduction

Surgery, brachytherapy (BT), and external beam radiotherapy (EBRT) are all commonly used treatments for early-stage oral cancer (cT1–2cN0M0). Surgery yields 5-year local control (LC) rates ranging from 81% to 85% for T1 tumors and 77% to 85% for T2 tumors (1, 2). Compromised surgical resection margins (<5 mm from the inked surface of the specimen), presence of lymphovascular space invasion, perineural invasion, poor tumor cell differentiation, and tumor thickness greater than 5 mm are

associated with higher recurrence rate and worse survival after surgery alone; in these patients, postoperative radiotherapy is recommended (3). However, EBRT is associated with numerous acute and late side effects, including mucositis, dysphagia, xerostomia, neck fibrosis, and mandibular necrosis.

Low-dose-rate (LDR) BT has long been used to treat oral cancer with good results. It can be applied as a definitive treatment or in postoperative setting. The BT treatment alone could be used for tumors smaller than 3 cm located at least 5 mm from the mandible. This modality has a 5-year LC rate at least comparable with surgery, with the added benefit of better functional outcome, particularly less dysphagia and articulation impairment (4, 5). Postoperative BT could be offered in presence of unfavorable pathologic features as an alternative to EBRT with excellent results (6). The main advantage of BT in comparison with EBRT is

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delivery of higher dose of radiation in shorter time, with reduced volume of irradiated healthy tissues, reduced treatment toxicity, and improved quality of life.

Combined EBRT and BT is indicated for tumors larger than 3–4 cm and node positive status. There is a good evidence that LC for early tongue cancer is superior when BT is administered with smaller doses of EBRT or without any EBRT (7).

Although various BT modalities have been used to treat oral cancer, the approach with the longest history is LDR BT. Since the 1990s, many radiotherapy departments—including all BT departments in the Czech Republic—have been gradually replacing manual afterloading and LDR BT with high-dose-rate (HDR) BT with remote afterloading devices. Compared with LDR BT, HDR BT has a greater biological effect on normal late-reacting tissues than on the tumor. The consequence is a less beneficial therapeutic ratio and the need for fractionation. However, the important advantage of HDR remote afterloaders is the potential to improve dose distribution by means of computer optimization. The HDR BT treatment has proven to be equal to or better than LDR BT in a variety of clinical situations including intraluminal and intracavitary BT for cervical cancer. Nevertheless, in general, a move from LDR to HDR involves a higher likelihood of side effects for a given level of tumor control, particularly in interstitial applications (8). Therefore, it is essential to select the correct number of fractions and total dose of HDR BT to match the effects of LDR BT on the tumor and normal tissues.

Numerous studies of HDR BT in oral cancer have been published (9–13). However, most of those studies contained a limited number of patients with highly variable fractionation schedules. Despite these studies, our knowledge about which variables best predict local and nodal recurrence remains limited. Although it is well known that the main clinical risk factors for nodal recurrence are tumor thickness and ulcerative-type growth, other predictors of nodal recurrence have received less attention. In a previous study, our group found that vascular endothelial growth factor (VEGF) expression may have predictive value; although VEGF expression was only marginally significant as a predictor for regional and locoregional control, it was a strong predictor of worse disease-free survival (DFS) (14).

Given this context, we carried out a retrospective study to evaluate tumor control and complications of HDR BT alone at 3 Gy dose per fraction administered twice daily in patients with oral cancer after tumor excision. We also analyzed the predictive value of clinical factors (stage, grade, depth of invasion, and resection margins) and VEGF expression for local and nodal recurrence.

## Patients and methods

The treatment strategy (surgery, radiotherapy, or combined treatment) in patients with oral cancer at the

University Hospital Hradec Kralove is determined by the multidisciplinary committee. Some patients are referred from other hospitals after surgery for radiotherapy consideration. The treatment decision is based on the *National Comprehensive Cancer Network* guidelines, and individualized considering the patients preference. Patients with T1–T2N0 tongue and floor of mouth cancer are treated usually by surgery alone. Postoperative BT is considered in case of close or positive margins, presence of lymphovascular space invasion or perineural invasion, poor differentiation, or tumor thickness greater than 5 mm.

Between years 2002 and 2013, 49 patients with oral cancer were treated by HDR BT alone or EBRT plus HDR BT; of these 49 patients, 30 were treated by HDR BT alone for mobile tongue or floor of mouth cancer. All patients underwent baseline clinical examination, neck ultrasound, chest X-ray, and CT scans of the head and neck and lungs before the start of the treatment. Patient characteristics are presented in Table 1. Surgery was limited to excision of the tumor; no flap or skin grafts were used. At our center, neck dissection was performed only for nodal recurrences until the year 2010; since that time, elective neck dissection is performed in cases with invasion beyond 5 mm and/or tumor ulceration. The median interval between surgery and BT was 56 days (29–92). The BT started the next or the second day after implant.

## BT technique

The BT implant was performed under general anesthesia. The plastic catheter technique with 1-cm spacing

Table 1  
Patient characteristics

Parameters	N/range
Localization	
Tongue	29
Floor of mouth	1
Sex	
Male	15
Female	15
Age (y)	
Median	60 (43–74)
Stage	
T1N0M0	22
T2N0M0	7
T3N0M0	1
Grading	
1	10
2	17
3	3
Depth of invasion (mm)	
Median	4 (1–20)
Resection margin	
Close (<3 mm)	7
R1	21
R2	2
Elective neck dissection	12
Follow up to the last control or death (mo)	
Median	40 (6–145)

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