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BRACHYTHERAPY

Feasibility of accelerated image-guided high-dose-rate interstitial brachytherapy with inverse planning simulated annealing (IPSA-HDRBT) for post-operative treatment of pathologically node-negative squamous cell carcinomas of the oral tongue

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ABSTRACT

PURPOSE: Inverse planning simulated annealing (IPSA) produces highly conformal dose distributions and quick optimizations for high-dose-rate interstitial brachytherapy (HDRBT). We report our dosimetry and overall outcomes using this approach for the accelerated post-operative treatment of pathologically node-negative squamous cell carcinomas of the oral tongue (OTSCC) with high risk of local recurrence.

METHODS: Patients with newly diagnosed pN0 OTSCC treated with partial glossectomy, neck dissection, and post-operative HDRBT alone from 2007 to 2021 were retrospectively reviewed. Patients received 30 Gy in 5 fractions over 2.5 days. Target volume and mandible dosimetry are reported. Actuarial rates of local control, regional control, disease-specific survival, and overall survival were estimated using the Kaplan-Meier method. Toxicity was categorized using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

RESULTS: 19 consecutive patients were reviewed. Median follow-up was 3.2 years (IQR 1.4–8.2 years) with a 3-year estimated local control rate of 81%. Target volumes were generally small, as the median volume was 12.66 cc. Median V150% and V200% were 52% and 24%, respectively. D1cc and D2cc to the mandible were 17.31 Gy and 14.42 Gy, respectively.

CONCLUSIONS: IPSA-HDRBT is feasible and highly efficient for post-operative treatment of the primary tumor bed in patients with pathologically node-negative squamous cell carcinomas of the oral tongue. Further technical optimization and prospective clinical evaluation in a larger patient cohort are planned.

Keywords: Head and neck cancer; Brachytherapy; High-dose-rate; Inverse planning; Oral tongue cancer

Introduction

Inverse planning simulated annealing (IPSA) is a treatment planning technique that utilizes an automated algorithm to rapidly determine optimal dwell time combinations satisfying prespecified dose prescriptions and constraints. Optimization of high-dose-rate interstitial brachytherapy (HDRBT) with an IPSA algorithm offers numerous technical advantages including conformal dose distributions, protection of organs at risk, and quick optimization. These advantages have enabled the safe delivery of high doses per fraction in HDRBT treatment of various

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cancers. However, to date, dosimetric and clinical results of IPSA-optimization for head and neck HDRBT have not been reported.

HDRBT is used in the treatment of both primary and recurrent HNSCC allowing for the delivery of high-doses of radiation over a short period of time to very specific target areas with the head and neck. Dose optimization with IPSA may allow for the use of larger doses per fraction than previously recommended in standard guidelines. Accelerated HDRBT offers a higher level of resource efficiency and decreased hospitalization. In this study, we report our experience with accelerated IPSA-optimized HDRBT in patients with pN0 OTSCC and risk factors for local recurrence treated with a post-operative dose of 30 Gy in 5 fractions, given twice daily over 2.5 days.

Methods and materials

Patients

Patients with newly diagnosed pN0 squamous cell carcinomas of the oral tongue at a single institution between 2007 and 2021 were reviewed. All patients underwent partial glossectomy, unilateral or bilateral neck dissection, and post-operative HDRBT alone to the primary tumor site without external beam radiotherapy or chemotherapy as part of adjuvant therapy. Patients were selected for HDRBT if at least 1 risk factor for local recurrence was present (perineural invasion, lymphovascular invasion, close surgical margins) and they were considered by a multidisciplinary tumor board to be appropriate candidates for omission of adjuvant radiotherapy to the pN0 neck.

Inverse-planned HDRBT technique

Interstitial brachytherapy catheters were implanted freehand without the use of a template in the operating room with patients under general anesthesia. A single implant was used for each patient and the median number of catheters was 4 (3–8). Catheters were spaced by 1 cm intervals to cover the tumor bed based on intraoperative exam and correlation with preoperative imaging. For all cases, the prescription dose was 30 Gy in 5 fractions with two fractions delivered per day. The target volume and mandible were delineated on CT scans using the Oncentra treatment planning system v4.5 (Elekta, Stockholm, Sweden). Based on these contours, a treatment plan was generated using volumetric and surface dose constraints with an IPSA algorithm as shown in Fig. 1. Dose hotspots were mitigated by setting a maximum dose penalty to the inside of the target volume. A small weight was applied to this penalty to avoid compromising target coverage. Planning objectives included $\geq$90% target coverage and avoiding overlap of the 100% isodose line with the mandible, which was the only organ at risk delineated. We minimized high dose (>100%) outside of the target volume using inverse planning. Brachytherapy catheters were removed in clinic following completion of HDRBT treatment. Tracheostomy was not required for any patient. Patients were kept as inpatients for 48 h.

Toxicity and disease outcomes

Following completion of HDRBT, patients were followed to evaluate for toxicity and disease status at 3–6 months intervals for up to 5 years. A retrospective review of patient records was performed to assess for toxicity, local control, regional control, distant control, disease-specific survival, and overall survival after HDRBT treatment. Toxicity was categorized using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Local control was defined as no evidence of disease at the treatment site. Regional control was defined as no evidence of disease in the neck. Acute and late toxicities were assessed before and after 90 days of completing HDRBT. Follow-up time was calculated from the last day of HDRBT treatment to the date of death or last follow-up.

Statistical analysis

The dosimetric indices of interest for target volume included D90, D1cc, V100%, V150%, and V200%. The mandible dosimetric indices of interest included D2cc, D1cc, and D1%. Actuarial rates of local control, disease-specific survival, and overall survival were estimated using the Kaplan-Meier method. Statistical analyses were performed with R version 3.4.4 (R Core Team, Vienna, Austria).

Results

Patient and tumor characteristics

19 consecutive patients with OTSCC treated with partial glossectomy and neck dissection who were pN0 and offered post-operative HDRBT to the primary site alone were retrospectively reviewed. Baseline patient and tumor characteristics are reported in Table 1. The median age at HDRBT treatment was 61. 18 (95%) patients underwent elective unilateral neck dissections and one patient underwent a bilateral neck dissection; a median of 27 nodes were dissected (IQR 22–48). 18 (95%) patients were selected for HDRBT due to being deemed at high risk of local recurrence and appropriate for omission of adjuvant radiotherapy to the pN0 neck. One (5%) additional patient with a 4.8 cm tumor with depth of invasion (DOI) of 10 mm was given HDRBT due to advanced age (82), poor performance status, and inability to complete a standard course of external beam radiotherapy. The median tumor size was 2.5 cm (IQR 1.7–2.8) and median DOI was 6 mm (IQR 5.3–11.0 mm). 14 (74%) tumors had perineural

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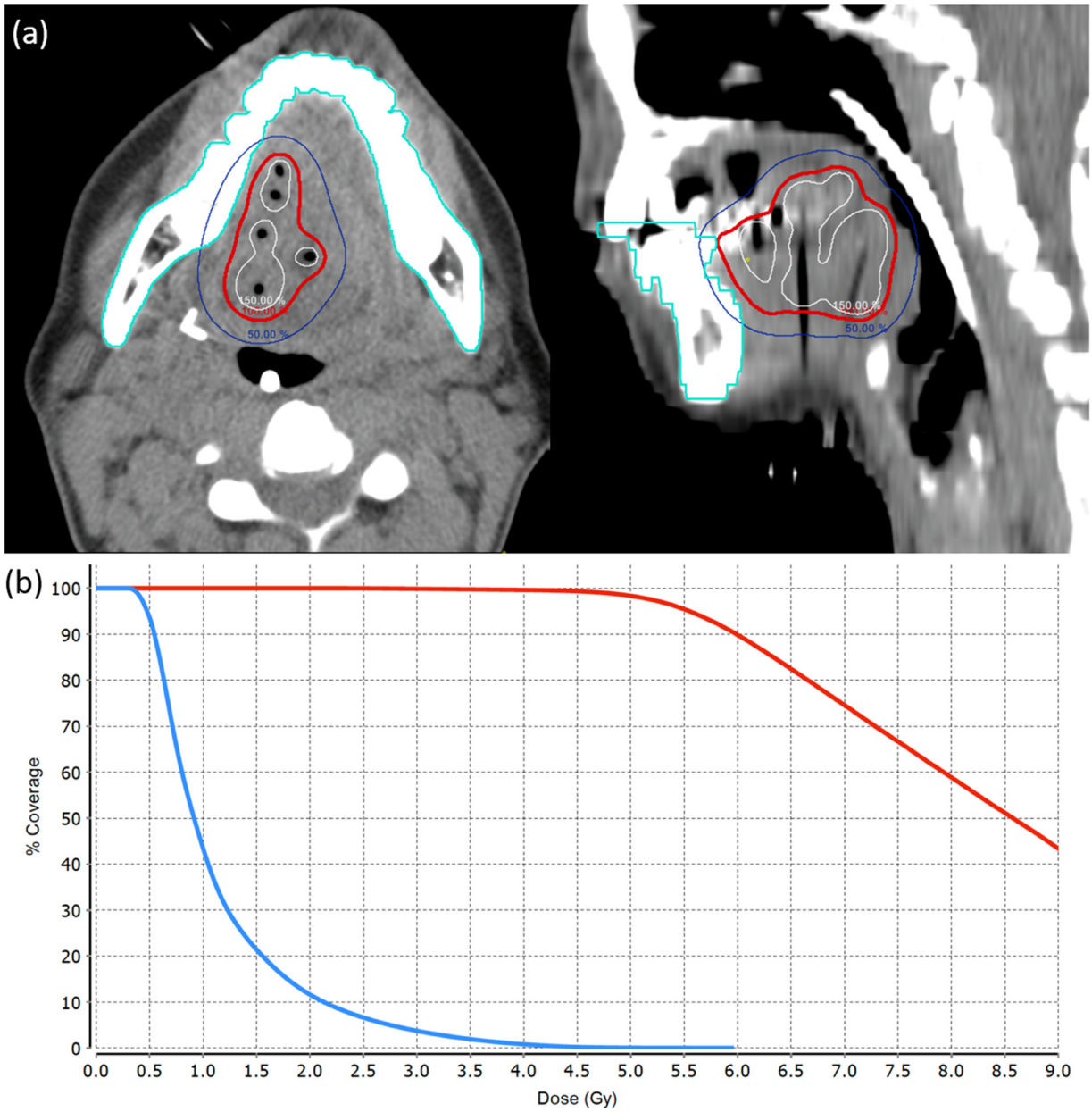

Fig. 1. A representative oral tongue case planned with IPSA. (a) The 50% (blue), 100% (red), 150% (white) isodose lines are shown. (b) The dose-volume histogram shows 90% coverage of the target (red) by the per fraction prescription dose of 6 Gy and 0 cc of the mandible (blue) overlapping with the prescription dose. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

invasion. Main specimen close margins (≤5 mm) were observed in 18 (95%) of the 19 cases and the remaining case was reported as "negative" margins at an outside facility and the specimen was not available for review. 18 (95%) patients had separately submitted margins of which two contained severe dysplasia and none contained invasive or *in situ* carcinoma.

IPSA-HDRBT dosimetry

In all cases, the prescription dose was 30 Gy in 5 fractions with two fractions delivered per day, at least 6 h apart following a single implant, and no unplanned treatment breaks were observed. A representative implant and treatment plan is shown in Fig. 1. In all cases only a target volume and the mandible were contoured. Target delineation and inverse planning was generally completed within 30–60 min and the first fraction was delivered on the same day as the implant for all patients. Target and mandible dosimetry are summarized in Table 2. Target volumes were generally small, as the median volume was 12.66 cc. Median V150% and V200% were 52% and 24%, respectively. D1cc and D2cc to the mandible were 17.31 Gy and 14.42 Gy, respectively.

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Table 1
Patient and disease characteristics.

Patients, *n*	19
Age at diagnosis	61 (IQR 46–73)
Sex	
Male	8 (42%)
Female	11 (58%)
T stage (AJCC 7)	
T1	7 (37%)
T2	11 (58%)
T3	1 (5%)
T stage (AJCC 8)	
T1	5 (26%)
T2	7 (37%)
T3	6 (32%)
T4	1 (5%)
Grade	
Well-differentiated	4 (21%)
Moderately-differentiated	12 (63%)
Poorly-differentiated	3 (16%)
Main specimen margins	
<1 mm	2 (11%)
1–5 mm	16 (84%)
Unknown	1 (5%)
Perineural invasion	14 (74%)
Lymphovascular invasion	1 (5%)
Worst pattern of invasion 5	8 (42%)
Size (cm)	2.5 (IQR 1.7–2.8)
Depth of invasion (mm)	7.0 (IQR 5.3–11.0)
Free flap reconstruction	5 (26%)
Nodes recovered from dissection	27 (IQR 22–48)
Weeks from surgery to HDRBT start	9.9 (IQR 8.9–13.9)

Table 2
High-dose-rate brachytherapy number of catheters used and dosimetry.

	Median (IQR)
Catheters	4 (4–5)
Prescription	30 Gy in 5 fractions
Target	
Volume (cc)	12.66 (10.26–16.05)
D90%	30.66 Gy (29.80–31.82 Gy)
D1cc	98.12 Gy (89.72–108.67 Gy)
V100%	91% (90–94%)
V150%	52% (49–55%)
V200%	24% (23–30%)
Mandible	
D2cc	14.42 Gy (13.80–15.06 Gy)
D1cc	17.31 Gy (15.82–17.79 Gy)
D1%	19.55 Gy (16.44–21.07 Gy)

Tumor control and toxicity

Median follow-up was 3.1 years (IQR 1.4–8.2 years), during which 6 (32%) patients experienced disease progression at a median time of 1.5 years from the end of HDRBT. There was 1 local only recurrence (5%), one regional only recurrence (5%), two local and regional recurrences (11%), and one neck and distant recurrence (5%). 3-year estimates of local control, regional control, disease-free survival, and overall survival were 95%, 81%, 76%, and 75%, respectively (Fig. 2). No complications were observed during the HDRBT implant, hospitalization, or implant removal. Acute toxicities included grade 2 intra-oral catheter-site pain (16%) and grade two mucositis (11%). Late toxicities included grade two xerostomia (5%), grade two dysgeusia (5%), and grade three soft tissue necrosis (5%). The single case of a grade three soft tissue necrosis occurred 6 months after completion of HDRBT and improved with hyperbaric oxygen treatments. There were no cases of osteoradionecrosis. The 5 patients underwent soft tissue free flap reconstructions at the time of initial surgery, and there were no cases of free flap necrosis or failure.

Discussion

IPSA for HDRBT was developed at our institution in 2000 and since then more than 1200 licenses have been issued. In HDRBT of non-head and neck tumors, the combination of highly customized, freehand catheter placement with IPSA optimization has enabled the safe delivery of high doses per fraction with sparing of organs at risk (1–4). The ability to complete adjuvant radiotherapy in a short period of time could be advantageous in the adjuvant treatment of oral tongue squamous cell carcinomas where a delay between surgery and completion of radiotherapy is a known risk factor for locoregional recurrence (5–7). The toxicity profile of adjuvant HDRBT alone for OTSCC has not been reported in the literature, as most series of image-guided HDRBT include multiple head and neck cancer types and include patients who have also received external beam radiotherapy as part of either a prior or the same treatment course (8–13). This study is the first report of IPSA-optimized head and neck HDRBT with this accelerated fractionation scheme, and specific to only oral cavity cancer patients. Our results show that this technique is feasible, effective, and highly efficient when used to treat relatively small targets in the post-operative setting of pN0 OTSCC without EBRT.

No established guidelines regarding total dose, number of fractions, and dose per fraction exist for the treatment of OTSCC with HDRBT alone due to a lack of large, long-term studies (14–16). However, per fraction doses between 3 and 4 Gy have generally been studied in the past due to concern for injury to surrounding normal tissues and resultant toxicity (Table 3). In comparison, the dose per fraction used with IPSA-optimization in our study was higher, and the overall treatment course was accelerated at 6 Gy per fraction given twice daily over 2.5 days. This accelerated regimen is in part attributed to the rapid treatment planning with IPSA, where optimization is achieved within 1 min whereas manual forward planning techniques can require more than 45 min (4). We have found clinically acceptable dose homogeneity using IPSA alone and without manual adjustment of dwell times after optimization or imposing any restriction on dwell time variance (17). Furthermore, this approach allowed for compensation of tissue deforma-

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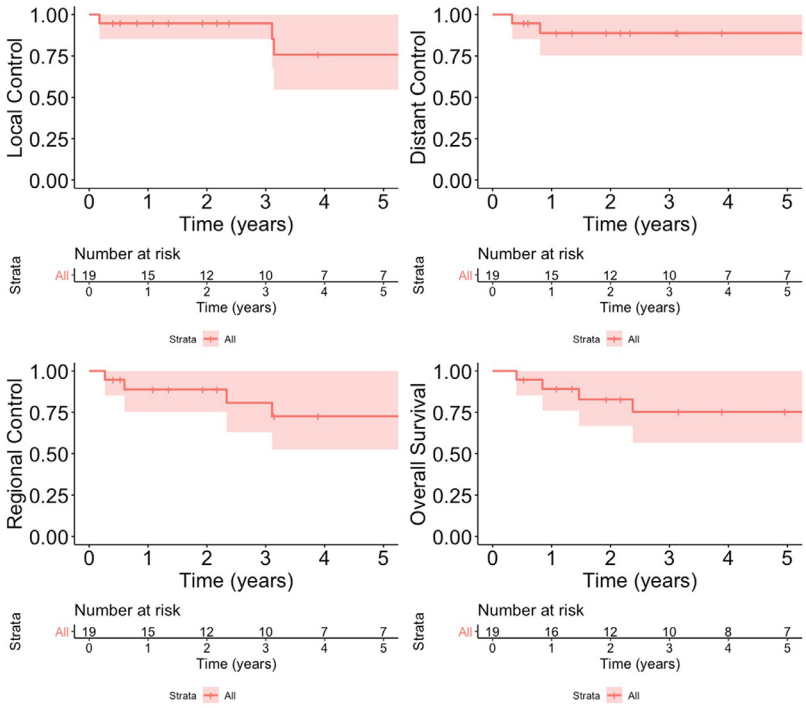

Fig. 2. Outcomes of high-dose-rate brachytherapy in the adjuvant treatment of pN0 OTSCC.

Table 3
Studies of high-dose-rate brachytherapy for the adjuvant treatment of oral tongue squamous cell carcinomas.

Reference	Post-operative HDR alone, *n*	Total Dose (Gy), Average or Range	Dose per fraction (Gy, Schedule)	EQD2(Gy, $a/b=10$)	EQD2(Gy, $a/b=3$)	Late toxicity (≥Grade 3) for entire series (including patients receiving EBRT)
Guinot *et al.*	17	44	4 BID	51	62	20%
Martinez-Monge *et al.*	46	32–40	4 BID	37–47	45–56	20%
Petera *et al.*	29	54	3 BID	70	108	10% (moderate-severe)
Cheung *et al.*	19	30	6 BID	48	90	5%

Patients who did not receive external beam radiotherapy in the same or prior course are shown below. Toxicity rates reflect the entire series including patients receiving EBRT

tions between the implant and treatments. In spite of relatively heterogeneous dosimetry with V150% and V200% of roughly 50% and 24%, respectively, the toxicity profile we observed seemed acceptable in comparison to external beam radiotherapy (18,19) with only one case of grade three soft tissue necrosis (5% in our series. However, given the retrospective nature of toxicity scoring in this report, grade 1 and 2 acute and late toxicities are likely underestimated. This dosimetric profile may not be appropriate for larger OTSCC than those in this report where the median target volume was only 12.66 cc.

Taken together, these findings suggest that IPSA optimization allows for HDRBT with delivery of higher doses per fraction than previously reported with rates of major toxicities in our cohort being similar to those previously reported in the literature. To our knowledge, this study represents the first clinical investigation of inverse-planned HDRBT for OTSCC with the potential advantages of this technique being its high efficiency for patients and providers. The main limitations of this study are its single institution setting, retrospective nature, highly selected cohort, and small sample size and lack of patient reported outcome measures. We plan further investigation of technical optimization and prospective clinical evaluation of IPSA-HDRBRT in the post-operative treatment of OTSCC.

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