Case report

Dose coverage comparison between "interstitial catheter-only" and "hybrid intracavitary-interstitial brachytherapy" for early stage squamous cell carcinoma of the buccal mucosa

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Abstract

Purpose: When squamous cell carcinoma of the buccal mucosa (BSCC) extends surrounding anatomical sites such as gingiva, retromolar triangle, or hard palate, it might be challenging to ensure adequate tumor coverage by sole interstitial brachytherapy due to the complexity of catheter implantation. By combining interstitial catheters with an enoral placed, individually assembled "oral spacer plus embedded catheters" device (hybrid of intracavitary-interstitial brachytherapy), it should be easier to deliver the necessary tumoricidal dose to irregular-shaped tumor volumes (clinical target volume – CTV) with improved conformity. The purpose of this analysis was to compare the dose distribution created by the hybrid of intracavitary-interstitial brachytherapy (HBT) with the dose distribution of an interstitial catheter only-approach, based on the interstitial catheters used for HBT (ISBT-only) by evaluating respective treatment plans (HBT plan vs. ISBT-only plan) for the treatment of early stage BSCC.

Material and methods: A retrospective analysis was performed for patients with localized BSCC treated between April 2013 and October 2017. All patients received sole HBT without additional external beam radiation therapy or planned neck dissection. Dosimetric parameters taken into account for comparison between actual HBT and virtual ISBT-only were CTV D_{90}, CTV V_{100}, CTV V_{150}, CTV V_{200}, mandible D_{2cc}, and mucosal surface D_{2cc}.

Results: Dosimetrically, HBT showed a trend toward better CTV D_{90} compared to ISBT-only. In addition, HBT demonstrated statistically better CTV V_{100} coverage compared to ISBT-only. There was no statistically significant difference with respect to CTV V_{150}, CTV V_{200}, and mucosal surface D_{2cc}, while a trend was seen in better mandible $D_{0.1cc}$ between HBT and ISBT-only.

Conclusions: The HBT approach appears to enable improved dose coverage of irregular-shaped enoral tumor volumes compared to ISBT-only for patients with early stage BSCC.

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Key words: brachytherapy, buccal mucosa, hybrid, interstitial brachytherapy, squamous cell carcinoma.

Purpose

According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, standard treatment for T1-2 N0 squamous cell carcinoma of the buccal mucosa (BSCC) is surgical resection or definitive radiation therapy [1]. Favorable long-term local control (LC) in early stage disease was reported by several authors with oncosurgical treatment [2,3]. However, cosmetic and/or functional impairment is regularly associated with otolaryngologic surgery, supporting the quest for additional treatment options. If surgery is not an option, irradiation with simultaneous chemotherapy utilizing external beam radiotherapy (EBRT) is associated with satisfying long-term LC [4,5,6,7]. Nevertheless, when using dose-escalated EBRT for BSCC, normal tissue

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toxicity can be significant, thus affecting quality of life strongly. From this perspective, image-based brachytherapy (BRT) has proven to be an effective alternative for early stage BSCC by escalating the biologically effective dose to the treatment target whilst ameliorating conformity. Three-dimensional treatment planning in high-dose-rate (HDR) BRT enables for anatomy-oriented dose optimization, while the versatility of intratarget dose modulation inherent to BRT can be controlled and directed to deliver higher doses to gross disease or to selectively reduce the dose to organs at risk (OARs). A number of publications have reported good LC associated with acceptable complication rates in the treatment of early stage BSCC [8,9,10,11,12,13].

In the attempt of OARs protection in head and neck BRT, the use of oral spacers can increase the distance between buccal mucosa and gingiva, mandible, or the tongue, therefore minimizing the risk of higher-grade adverse events. The hypothesis of this study was that when BRT catheters are mounted inside of a spacer, which works per se as a mold device, the combination of interstitial catheters and the mold itself could improve the conformity of the dose distribution covering the clinical target volume (CTV) to be treated. Moreover, when the CTV extends surrounding anatomical sites, in which it is difficult to insert interstitial catheters such as gingiva, retromolar triangle, or hard palate, the mold could facilitate the delivery of adequate doses to those regions. As such, the purpose of this study was to compare the dose distribution created by the hybrid of intracavitary (mold-based) and interstitial BRT (defined as HBT plan) with the dosimetry of an interstitial catheter only treatment plan (defined as ISBT-only plan) in the management of early stage BSCC.

Material and methods

This single-institution retrospective analysis included T1-2 N0, early stage BMCC patients who refused or were considered medically unfit for primary surgical resection and were treated by HBT between April 2013 and October 2017. Staging work up included examination of the oral cavity, computed tomography (CT), and/or magnet resonance imaging (MRI) of the neck. Before BRT, all patients underwent a general dental check-up, and a customized oral spacer was manufactured to increase the distance between macroscopic tumors and the mandible, the gingiva, or the tongue. After the individual preparation of the oral spacer, multiple plastic catheters were incorporated inside the spacer in order to enable its use as a mold applicator for image-based BRT (Figure 1).

Brachytherapy

For the interventional procedure, metallic markers were inserted around the primary tumor under local anesthesia and sedation in order to enhance CTV demarcation in plain CT imaging used for BRT treatment planning. Subsequently, interstitial plastic catheters were inserted percutaneously near the labial commissure under finger guidance. For single plane insertion, catheters were inserted parallel 3-5 mm under the surface of the mucosa.

After completion of free-hand catheter insertion, the customized oral spacer with embedded catheters was positioned and CT imaging for anatomy-oriented planning (1 mm slice thickness) was performed. No planning target volume margin was added around the CTV. BRT dose calculation was performed using Oncentra® Brachy version 4.5.1 (Nucletron, an ELEKTA company, ELEKTA AB, Stockholm, Sweden). Prescribed dose per fraction was 6 Gy in all patients for typically 9 fractions, up to a total physical dose of 54 Gy. The dosimetric goal was to cover the CTV with the prescribed reference dose, while avoiding more than 150% of the prescribed reference dose on the mucosa surface as well as the mandible. Irradiation was performed twice-daily, with an interfractional interval of at least 6 hours. All treatments were carried out by a ^{192}Ir remote after loading system (RALS, MicroSelectron V2r® HDR Ir-192 source, Nucletron, an ELEKTA company, ELEKTA AB, Stockholm, Sweden).

Follow-up

After HBT, oral examination once per 1-2 weeks was performed until acute mucositis subsided. CT and/or MRI was performed 3 months after radiotherapy to evaluate initial response and was repeated every 3-6 months up to the first 5 years after treatment.

Dosimetric analysis

In order to evaluate the dosimetric contribution of the catheters mounted inside the oral spacer, the virtual dose distribution considering only free-hand implanted interstitial catheters was calculated (ISBT-only plan) and doses to the CTV, mucosal surface, and the mandible were compared to the actual HBT plan. The dosimetric parameters taken into account for analysis were CTV D_{90}, CTV V_{100}, CTV V_{150}, CTV V_{200}, mandible D_{2cc}, and mucosal surface D_{2cc}, which were the dose covering 90% of

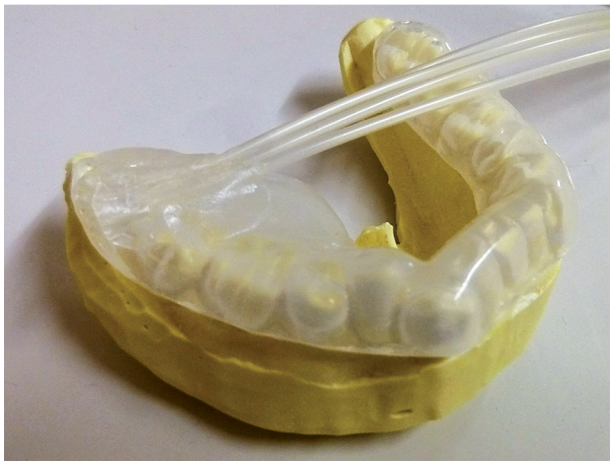

Fig. 1. The spacer is crafted by dental plastic to create additional space between the high-dose region and the tongue. Four catheters are mounted in the spacer to improve the dose coverage of the tumor through intracavitary brachytherapy together with the interstitial irradiation through the interstitial catheters

Table 1. Patients' characteristics (n = 4)

Factors	
Median age (years)	77 (range: 63-82)
Sex	
Male	2
Female	2
T	
T1	0
T2	3
rT2*	1
N	
0	4
1	0
Tumor diameter (mm)	27 (range: 25-38)
Clinical target volume (ml)	2.5 (range: 1.1-3.8)
Location of the tumor	
Posterior part	4
Anterior part	0
Tumor extending surrounding site	
Hard palate	1
Soft palate	1
Gingiva	1
None	1

**This patient received surgery as an initial treatment and received brachytherapy for her local recurrence.*

the CTV, the volume of the CTV covered by 100%, 150%, 200% of the reference dose, the highest dose on 2 cc of the mandible, and the highest dose on 2 cc of the mucosal surface, respectively. The comparison of dosimetric parameters was performed by the Shapiro-Wilk test and the Mann-Whitney test, with a p-value of < 0.05 considered as statistically significant. All analyses were performed using IBM SPSS Statistics (version 18.0; SPSS, Inc., Chicago, IL).

Results

Between April 2013 and October 2017, four consecutive BSCC patients were treated with definitive radiotherapy by means of HBT. All of them either refused surgery or were medically inoperable. One patient was salvaged by BRT for local recurrence after initial surgical resection. Patient's demographics are summarized in Table 1. Median tumor diameter at initial presentation measured by oral examination was 27 mm (range: 25-38 mm). Prescription dose per fraction was 6 Gy with three patients receiving 9 and one patient receiving 8 treatment fractions. Median volume of CTV measured by planning CT imaging was 2.5 ml (range: 1.1-3.8 ml).

Median follow-up for patients still alive at the last follow-up visit was 6 months (range: 1-55 months). One patient experienced ipsilateral neck lymph node metastasis 3 months after BRT, which was effectively salvaged by neck dissection without disease recurrence being reported thereafter. Another patient experienced invasive oral squamous cell carcinoma of the contralateral lower gingiva without local recurrence in the BRT site. At the time of reporting, three patients were alive and free of disease progression.

The dosimetric comparison between treatment plans of HBT (HBT plan) and ISBT only (ISBT-only plan) are summarized in Table 2. Because not all patients received the same number of fractions, dose parameters were expressed with regard to a single fraction. Dosimetrically, HBT showed a trend toward better CTV D_{90} compared to ISBT-only (7.07 Gy vs. 5.44 Gy, respectively; p = 0.083). In addition, HBT demonstrated statistically better CTV V_{100} coverage compared to ISBT-only (96.8% vs. 84.2%, respectively; p = 0.021). There was no statistically significant difference with respect to CTV V_{150}, CTV V_{200}, and mucosal surface D_{2cc} between HBT and ISBT-only. HBT showed a trend toward better mandible $D_{0.1cc}$ compared to ISBT-only (5.99 Gy vs. 8.99 Gy, respectively; p = 0.096).

Table 2. Comparison of dose parameters between HBT and ISBT plan (n = 4)

	HBT plan	ISBT plan	p value
Median dose of CTV D_{90} (Gy)	7.07 (range: 6.52-7.59)	5.44 (range: 4.38-7.08)	0.083
Median % of CTV V_{100}	96.8 (range: 96.4-99.9)	84.2 (range: 70.3-96.2)	0.021*
Median % of CTV V_{150}	52.0 (range: 22.9-68.7)	49.4 (range: 25.6-70.2)	0.773
Median % of CTV V_{200}	18.7 (range: 3.0-33.7)	22.7 (range: 8.7-47.4)	0.773
Median dose of mandible D_{2cc} (Gy)	3.41 (range: 2.57-3.98)	4.08 (range: 2.74-4.53)	0.248
Median dose of mandible D_{1cc} (Gy)	4.11 (range: 3.16-4.83)	5.22 (range: 3.40-5.95)	0.101
Median dose of mandible $D_{0.1cc}$ (Gy)	5.99 (range: 4.50-6.83)	899.5 (range: 4.88-11.43)	0.096
Median dose of buccal mucosa D_{2cc} (Gy)	8.57 (range: 7.31-9.93)	9.39 (range: 5.90-9.54)	0.773

HBT – hybrid of intracavitary and interstitial bracytherapy, ISBT – interstitial brachytherapy, CTV – clinical target volume
Because not all the patients received the same number of fractions, dose parameters were expressed in single fraction.
$V_{100\%}$, $V_{150\%}$, $V_{200\%}$ – volume of the anatomic volume receiving 100%, 150%, 200% of the prescribed dose
D_{90} – percent of the prescription dose covering 90% of the CTV
$D_{0.1cc}$, D_{1cc}, D_{2cc} – minimum dose to the most exposed 0.1 cm^3, 1 cm^3, 2 cm^3

A typical case is shown in Figure 2 and Figure 3. This patient was presented with right sided BSCC, which extended onto the retromolar triangle. The dose distribution of HBT and ISBT-only are shown in Figure 3. On that point, the volume of the hyper-dose-sleeve, representing 200% of the prescribed reference dose, was larger in ISBT-only attempting to cover the posterior part of the CTV, which included the gingiva of the wisdom tooth. However, the posterior part was also not covered by the 100% isodose adequately (Figure 3c). This patient experienced pericoronitis of wisdom tooth, which was treated conservatively. No further severe acute morbidity or late adverse events were noted in relation to the interventional procedure or the radiotherapy treatment.

Discussion

Compared to oral tongue, lip, oropharynx, floor of mouth, or nasopharynx, reports of BSCC BRT are scarce [9,10]. Literature review concerning technique and clinical results of BRT for BSCC was well performed by the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) handbook of brachytherapy [14]. Local control ranging between 64-88% with BRT was reported for BSCC [8,9,10,11,12,13,15]. Inserting parallel interstitial needles anteroposterior direction spacing 12-15 mm in between 3-5 mm under the buccal mucosa is the general principle of needle insertion. Buccal mucosa is a subsite of the oral cavity, which is surrounded by many anatomically complex components such as gingiva, intermaxillary commissure, retromolar trigone, hard palate, or soft palate. Relative contraindications for BRT of BSCC are extension to the retromolar trigone, the intermaxillary commissure, and the gingiva [8]. Pernot *et al*. emphasized the importance of the loop technique in the management of posterior situated BSCC with low-dose-rate BRT as only parallel interstitial catheters cannot always cover the posterior part of these tumors adequately [8]. However, this loop technique might result in extreme cathe-

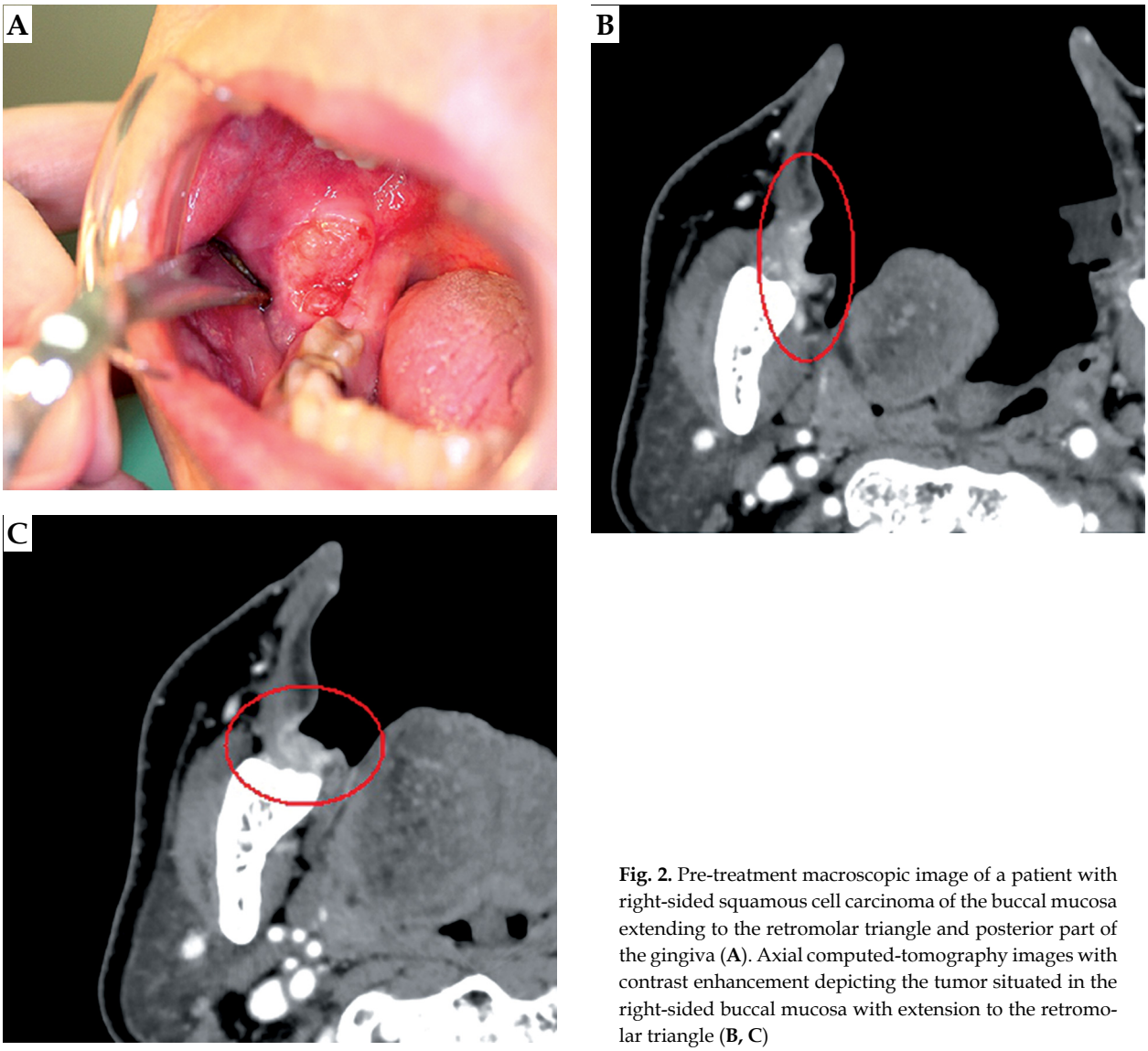

Fig. 2. Pre-treatment macroscopic image of a patient with right-sided squamous cell carcinoma of the buccal mucosa extending to the retromolar triangle and posterior part of the gingiva (**A**). Axial computed-tomography images with contrast enhancement depicting the tumor situated in the right-sided buccal mucosa with extension to the retromolar triangle (**B, C**)

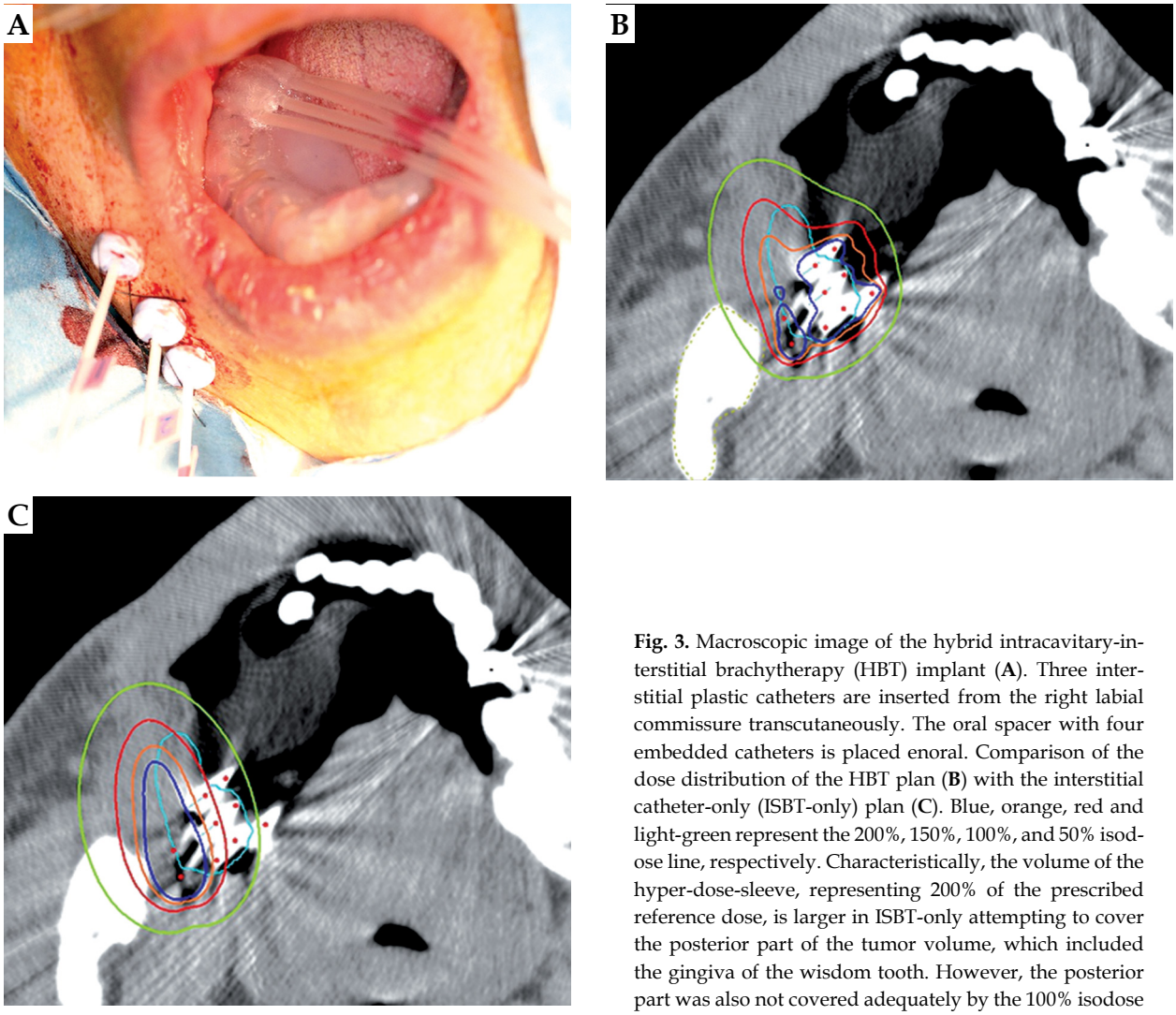

Fig. 3. Macroscopic image of the hybrid intracavitary-interstitial brachytherapy (HBT) implant (**A**). Three interstitial plastic catheters are inserted from the right labial commissure transcutaneously. The oral spacer with four embedded catheters is placed enoral. Comparison of the dose distribution of the HBT plan (**B**) with the interstitial catheter-only (ISBT-only) plan (**C**). Blue, orange, red and light-green represent the 200%, 150%, 100%, and 50% isodose line, respectively. Characteristically, the volume of the hyper-dose-sleeve, representing 200% of the prescribed reference dose, is larger in ISBT-only attempting to cover the posterior part of the tumor volume, which included the gingiva of the wisdom tooth. However, the posterior part was also not covered adequately by the 100% isodose

ter curvatures prohibiting the access of calculated dwell positions as part of the afterloading irradiation procedure. Therefore, the loop technique might not always be realizable in non-coplanar HDR BRT. Against this background, our hypothesis was that when BRT catheters are mounted inside the oral spacer as integral device of our hybrid approach, the combination of free-hand implanted interstitial catheters and the mold will ameliorate the conformity of CTV coverage even when the macroscopic tumor extends to anatomical sites, where it is very challenging to perform an implantation such as gingiva, retromolar triangle, or hard palate. Although the number of patients included in this experience is limited, we could demonstrate that HBT can generate improved CTV V_{100} coverage compared to ISBT-only (Table 2, Figure 3). Therefore, we consider the introduced hybrid technique a meaningful approach, which has the potential to improve OARs sparing through enhanced conformity of CTV coverage. Its implementation and general rationale are obvious to the radiation oncologist. The used mold component can be individually assembled for various clinical settings and this flexibility extends its safe applicability. It might though also be an expenditure of time, although without relevance when considering its potential merits.

None of our patients received prophylactic neck treatment. From an oncological point of view, a disagreement exists whether neck dissection in the management of clinically node-negative, early-stage BSCC is necessary or not [2,16,17]. However, it is reported that regional neck-node recurrence can be safely salvaged by post hoc dissection, while only a minority of patients experience neck failure in early-stage BSCC. Concerning our small cohort, prophylactic neck dissection was considered overtreatment given the absence of pathologically enlarged nodes in local staging by CT/MRI. Another point of potential criticism could be the fact that no quality of life assessment was performed using standard tools with context-specific scales. Given, however, the nature of our study, the functional and cosmetic superiority of BRT over surgical resection may be better assessed through future prospective trials. In contrast to time consuming and expensive randomized clinical trials, an effort to collect clinical data, a Consortium for Brachytherapy data analysis [18] was

created, presenting possibly suitable methodology for rare applications such as BRT for BSCC.

Conclusions

The HBT approach appears to enable improved dose coverage of irregular-shaped enoral tumor volumes compared to ISBT-only for patients with early stage BSCC.

Acknowledgements

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Ethical approval

All procedures performed in the study involving human participants were approved and in according with the ethical standards of the institutional research committee (approval number is 2017-091) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants in the study.

Disclosure

Authors report no conflict of interest.

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