

Image guided high-dose-rate brachytherapy versus volumetric modulated arc therapy for head and neck cancer: A comparative analysis of dosimetry for target volume and organs at risk

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Background. The aim of the study was to present dosimetric comparison of image guided high-dose-rate brachytherapy (IGBT) with volumetric modulated arc therapy (VMAT) for head and neck cancer regarding conformity of dose distribution to planning target volume (PTV) and doses to organs at risk (OARs).

Patients and methods. Thirty-eight consecutive patients with T1-4 mobile tongue, floor of mouth and base of tongue cancer treated with IGBT were selected. For these patients additional VMAT treatment plans were also prepared using identical computed tomography data. OARs and PTV related parameters (e.g. V98, D0.1cm³, Dmean, etc.) were compared.

Results. Mean V98 of the PTV was 90.2% vs. 90.4% ($p > 0.05$) for IGBT and VMAT, respectively. Mean D0.1cm³ to the mandible was 77.0% vs. 85.4% ($p < 0.05$). Dmean to ipsilateral and contralateral parotid glands was 4.6% vs. 4.6% and 3.0% vs. 3.9% ($p > 0.05$). Dmean to ipsilateral and contralateral submandibular glands was 16.4% vs. 21.9% ($p > 0.05$) and 8.2% vs. 16.9% ($p < 0.05$), respectively.

Conclusions. Both techniques showed excellent target coverage. With IGBT dose to normal tissues was lower than with VMAT. The results prove the superiority of IGBT in the protection of OARs and the important role of this invasive method in the era of new external beam techniques.

Key words: head and neck cancers; image guided high-dose-rate brachytherapy; volumetric modulated arc therapy; dosimetric comparison

Introduction

Head and neck (H&N) cancer is an excellent indication for radiation therapy (RT) which is an organ preserving method maintaining the quality of life of patients. Brachytherapy (BT) with or without external beam RT (EBRT) can play an essential role in the treatment of certain tumor localizations in the H&N

area except cases with bone invasion or proximity of large vessels, delivering an ablative dose to the target volume while sparing the critical and normal tissues - due to the rapid dose fall-off - which is not safely feasible with EBRT alone.¹⁻³ Image guided high-dose-rate BT (IGBT) with computed tomography (CT) and/or magnetic resonance imaging (MRI) has been implemented improving the effica-

cy of BT.⁴ IGBT decreases irradiated doses to critical structures without compromising target coverage.⁵ However, IGBT is an invasive procedure requiring special skills and interdisciplinary co-operation with a H&N surgeon, as well as patience on the part of patients who have to endure the insertion of catheters.^{6,7} Recently, intensity modulated RT (IMRT) has been introduced in clinical practice and achieved higher dose conformity with better organs at risk (OARs) sparing compared to 3-dimensional conformal radiation therapy.⁸ Volumetric modulated arc therapy (VMAT), an improved technique of IMRT offers reduced irradiation time compared to IMRT.⁹ Nowadays IGBT meets the challenge of high precision EBRT such as VMAT, which is a non-invasive modality and does not require special skills to deliver a high conformal dose to the target volume while saving critical normal structures. To our knowledge no detailed dosimetric comparisons of IGBT with VMAT have so far been reported in the H&N region, such publications are available only for breast and cervical cancer.^{10,11}

The purpose of this study is to present a dosimetric analysis regarding planning target volume (PTV) and OARs with the comparison of IGBT and VMAT for localized H&N cancer using identical CT data and contours.

Patients and methods

Patients' characteristics

Thirty-eight consecutive patients with T1-4 mobile tongue (n = 17), floor of mouth (n = 9) and base of tongue (n = 12) cancer treated between January 2013 and March 2017 at the National Institute of Oncology, Budapest, Hungary were selected for this study (Table 1). Primary lesions or tumor bed were treated with CT image based IGBT alone (n = 22) or after EBRT as a boost (n = 16). All T3-4

cases (n = 12) were base of tongue cancer treated exclusively with radiotherapy (EBRT + BT boost). The T4 tumors invaded the deep muscles of the tongue, without invasion into the mandible or other regions. Tumor excision was carried out in 18 patients. Ipsi- and contralateral submandibular glands (15 and 1) (iSMGs, cSMGs) were removed during surgery.

Brachytherapy planning

The process of BT planning was described in details in our previous publication.¹² Under general anesthesia in the operating theatre plastic catheters (median 7, range 3–12) were implanted into the target volume located in 17 patients on the left, in 18 on the right side, and in 3 in the central region of the tongue/ floor of mouth/base of tongue. After implantation, all patients underwent CT imaging with 3 mm slice thickness including the primary tumor or tumor bed, the spinal cord, parotid glands (PAGs) on both sides and SMGs. The images were transferred to the Oncentra Brachy v4.3 (Elekta, Brachytherapy, Veenendaal, The Netherlands) treatment planning system. Gross tumor volume (GTV), clinical target volume (CTV) and PTV were contoured on CT images as follows. In non-surgical cases (definitive) palpation, visual inspection and MR images without CT-MRI fusion were used to determine GTV in the patients. CTV was defined as GTV + 5mm limited to mandible. In postoperative cases CTV was directly defined similarly to definitive cases using the preoperative MRI. For all cases PTV was the same as CTV without using any margin. Based on CT image sets, the mandible, the spinal cord, PAGs on both sides and SMGs - as OARs - were delineated. Mandible was not part of the PTV. After catheter reconstruction, treatment plans were made with geometrical optimization, complemented with graphical optimization by adjusting the isodose line in order to appropriately cover the PTV by the prescribed dose (PD) and keep the doses to OARs as low as possible.¹³ Our aim was to obtain less than 0.40 for the dose non-uniformity ratio (DNR), the ratio of volumes receiving 1.5 times the PD and those receiving the PD, (V_{150}/V_{100}). At our institute the fractionation schedule was 15 x 3 Gy (45 Gy) for IGBT alone and 7 x 3 Gy (21 Gy) for IGBT after 50 Gy EBRT.

VMAT planning

For VMAT plans the same CT images and structure set were used as for IGBT. The contours applied for

TABLE 1. Dosimetry of PTV

Parameters	IGBT n=38		VMAT n=38		p-value
	mean	S.D.	mean	S.D.	
V95 (%)	92.1	3.0	98.4	0.9	<0.05
V98 (%)	90.2	3.2	90.4	3.7	>0.05
V100 (%)	89.0	3.4	76.7	8.9	<0.05
D90 (%)	98.6	4.7	98.2	0.8	<0.05
D100 (%)	58.6	9.0	87.0	3.2	<0.05

DX = minimum relative dose of the planning dose delivered to X% of the PTV; IGBT = image guided high-dose-rate brachytherapy; n = number of patients for analysis; PTV = planning target volume; S.D. = standard deviation; VMAT = volumetric modulated arc therapy; VX = relative volume of the PTV receiving at least X% of the planning dose

IGBT plans were transferred from the Oncentra Brachy to the Eclipse v11 (Varian Medical Systems, Palo Alto, CA) treatment planning system using DICOM RT protocol. Due to this process, all contours of PTV and OARs were identical in both planning systems. In case of IGBT alone patients VMAT was set up for a total dose of 70 Gy (35 x 2 Gy), and for EBRT+IGBT patients a total dose of 20 Gy (10 x 2 Gy) was planned as a boost. VMAT plans were created with 6 MV photon energy beams using double partial arcs from gantry angle 110° to 250° to ensure the homogeneity of PTV dose coverage. As regards the dose constraints for OARs and target volume coverage, VMAT plans were optimized using the Varian RapidArc progressive resolution optimization algorithm (PRO) and AAA dose calculation algorithm. The objective for PTV was to deliver a dose of 95–107% of the PD. The dose constraints for PTV70Gy were as follows: V98% > 90%, V95% > 95%, V50% = 100%, V2% < 107%, for the spinal cord V2% < 45 Gy, for parotid glands Dmean < 24 Gy, for mandible V0.03cc < 70 Gy.

Dosimetric analysis

Based on dose-volume-histograms (DVHs), treatment plans of both techniques were dosimetrically analyzed. For evaluating conformity of dose distribution to PTV, the relative volume of the PTV receiving at least 95, 98 and 100% of the PD (V95, V98 and V100) and the minimum relative dose of the PD delivered to 90 and 100% of the PTV (D90 and D100) were calculated. The minimum relative doses of the PD delivered to the most exposed 0.1, 1 and 2 cm³ of the organs (D0.1cm³, D1cm³ and D2cm³) were quantified for the assessment of doses to OARs. The salivary glands were classified as ipsilateral or contralateral based on the tumor location, and were dosimetrically evaluated. For the salivary glands, additional parameters such as the mean relative dose of the PD delivered to the organs (Dmean), D10, D30, D50, V10, V30 and V50 were also quantified. The dosimetric data for the parotid and submandibular glands were not evaluated for all patients, because in some cases the glands were excluded from the field-of-view of the CT scans, the volume was too small (for D1 and D2cm³ calculation), or the target volume (tumor or tumor bed) was centrally located (Tables 4 and 5). The spinal cord was not detected in one case because it was excluded from the field-of-view of the CT scans (Table 3).

The mean value with standard deviation was used to describe dosimetric parameters for both

TABLE 2. Dosimetry of mandible and spinal cord

Parameters	IGBT		VMAT		p-value
	mean	S.D.	mean	S.D.	
Mandible, n=38					
D0.1cm ³ (%)	77.0	17.2	85.4	7.9	<0.05
D1cm ³ (%)	56.9	13.4	74.5	9.6	<0.05
D2cm ³ (%)	48.4	12.2	68.4	9.5	<0.05
Spinal cord, n=37*					
D0.1cm ³ (%)	9.7	2.6	12.3	4.1	<0.05
D1cm ³ (%)	6.8	2.0	10.8	3.7	<0.05
D2cm ³ (%)	5.9	1.9	10.0	3.6	<0.05

DXcm³ = minimum relative dose of the planning dose delivered to most exposed X cm³ of the organs; IGBT = image guided high-dose-rate brachytherapy; n = number of patients for analysis; S.D. = standard deviation; VMAT = volumetric modulated arc therapy.

* in one patient the spinal cord was not detected because it was excluded from the field-of-view of the CT scans

TABLE 3. Dosimetry of parotid gland

Parameters	IGBT		VMAT		p-value
	mean	S.D.	mean	S.D.	
ipsilateral side (n=34')					
Dmean (%)	4.6	1.4	4.6	2.6	>0.05
D0.1cm ³ (%)	11.2	2.8	18.0	7.1	<0.05
D1cm ³ (%)	8.1	2.1	12.9	6.3	<0.05
D2cm ³ (%)	7.0	2.0	10.5	5.7	<0.05
D10 (%)	7.3	2.1	11.2	5.6	<0.05
D30 (%)	5.5	1.6	5.5	4.0	>0.05
D50 (%)	4.5	1.3	3.0	3.1	<0.05
V10 (%)	3.1	4.0	18.0	16.9	<0.05
V30 (%)	0.0	0.0	0.7	3.9	N.A.
V50 (%)	0.0	0.0	0.1	0.5	N.A.
contralateral side (n=35'')					
Dmean (%)	3.0	0.9	3.9	2.1	>0.05
D0.1cm ³ (%)	8.9	2.1	15.3	5.9	<0.05
D1cm ³ (%)	5.9	1.6	10.8	5.9	<0.05
D2cm ³ (%)	4.9	1.5	9.1	5.4	<0.05
D10 (%)	5.4	1.3	9.9	4.4	<0.05
D30 (%)	4.0	1.0	4.9	3.7	>0.05
D50 (%)	3.2	0.8	2.2	2.3	<0.05
V10 (%)	0.5	0.3	14.2	13.2	<0.05
V30 (%)	0.0	0.0	0.8	4.7	N.A.
V50 (%)	0.0	0.0	0.2	1.3	N.A.

Dmean = minimum relative dose of the planning dose delivered to the organs; DX = minimum relative dose of the planning dose delivered to X% of the PTV; DXcm³ = minimum relative dose of the planning dose delivered to most exposed X cm³ of the organs; IGBT = image guided high-dose-rate brachytherapy; n = number of patients for analysis; N.A. = not available; S.D. = standard deviation; VMAT = volumetric modulated arc therapy; VX = relative volume of the PTV receiving at least X% of the planning dose

' in one patient the parotid gland was not detected because it was excluded from the field-of-view of the CT scans, and in three patients parotid glands were not evaluated because of central implantation

'' three patients were not evaluated because of central implantation

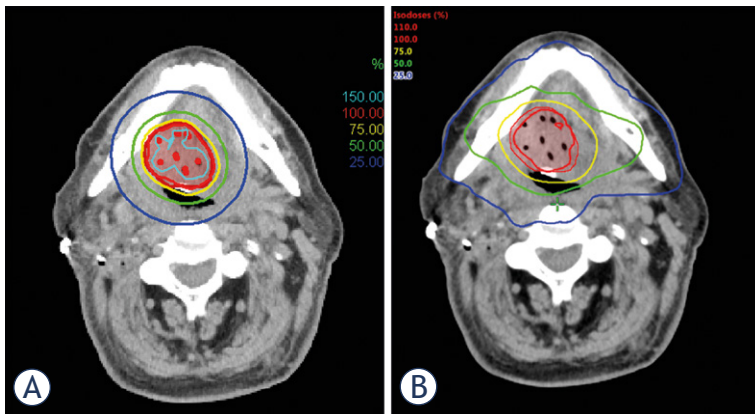


FIGURE 1. Representative dose distribution of (A) image guided high-dose-rate brachytherapy (IGBT) and (B) volumetric modulated arc therapy (VMAT).

TABLE 4. Dosimetry of submandibular gland

Parameters	IGBT		VMAT		p-value
	mean	S.D.	mean	S.D.	
ipsilateral side					
Dmean (%), n=20*	16.4	10.7	21.9	19.9	>0.05
D0.1cm ³ (%), n=20*	27.4	15.6	39.9	23.3	>0.05
D1cm ³ (%), n=18**	19.4	11.2	27.2	17.6	>0.05
D2cm ³ (%), n=17**	16.1	9.4	20.8	14.7	>0.05
D10 (%), n=20*	22.6	13.9	33.2	23.0	>0.05
D30 (%), n=20*	18.3	11.7	25.8	21.9	>0.05
D50 (%), n=20*	15.7	10.4	21.0	20.9	>0.05
V10 (%), n=20*	61.3	38.6	63.9	33.6	>0.05
V30 (%), n=20*	14.5	28.0	30.1	38.7	>0.05
V50 (%), n=20*	1.4	3.7	14.1	27.4	>0.05
contralateral side					
Dmean (%), n=34***	8.2	4.8	16.9	10.8	<0.05
D0.1cm ³ (%), n=34***	13.4	5.3	29.7	12.0	<0.05
D1cm ³ (%), n=32****	9.4	3.2	21.7	8.6	<0.05
D2cm ³ (%), n=32****	8.1	2.9	18.3	8.3	<0.05
D10 (%), n=34***	11.1	5.6	25.3	12.2	<0.05
D30 (%), n=34***	9.2	5.1	20.4	11.4	<0.05
D50 (%), n=34***	8.0	4.7	16.7	11.4	<0.05
V10 (%), n=34***	26.0	30.2	69.9	27.5	<0.05
V30 (%), n=34***	1.2	7.0	14.1	25.1	<0.05
V50 (%), n=34***	0.0	0.0	2.7	12.1	N.A.

Dmean = minimum relative dose of the planning dose delivered to the organs; DX = minimum relative dose of the planning dose delivered to X% of the PTV; DXcm³ = minimum relative dose of the planning dose delivered to most exposed X cm³ of the organs; IGBT = image guided high-dose-rate brachytherapy; n = number of patients for analysis; N.A. = not available; S.D. = standard deviation; VMAT = volumetric modulated arc therapy; VX = relative volume of the PTV receiving at least X% of the planning dose

* in fifteen patients the submandibular glands were resected by operation and three patients were not evaluated because of central implantation.

** two and three patients, respectively, were additionally excluded from the analysis of D1cm³ and D2cm³ because the volume was too small.

*** in one patient the submandibular gland was resected by operation and three patients were not evaluated because of central implantation.

**** two and two patients, respectively, were additionally excluded from the analysis of D1cm³ and D2cm³ because the volume was too small.

techniques, and the data were compared using the non-parametric Mann-Whitney U test with GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego, CA). The level of statistical significance was set at $p \leq 0.05$.

Results

The dosimetric parameters of PTV are presented in Table 2. Dose distribution of BT and VMAT are presented in Figure 1. The dose conformity was excellent with both techniques. V95 was significantly better with VMAT (98.4% vs. 92.1%, $p < 0.05$), but V100 was superior with IGBT (89.0% vs. 76.7%, $p < 0.05$). V98 was similar in both techniques (90.2% vs. 90.4% for IGBT and VMAT, $p > 0.05$, respectively). Relative dose coverage to PTV, D90 was statistically significantly better with IGBT (98.6% vs. 98.2%), probably without clinical consequences. However, D100 showed a reverse result (58.6% vs. 87.0%).

As for OARs, the mandible and the spinal cord were better protected by IGBT (Table 3). For doses to small volumes (D0.1cm³, D1cm³ and D2cm³) significantly lower values were obtained with IGBT (e.g. D0.1cm³ was 77.0% vs. 85.4% and 9.7% vs. 12.3% to the mandible and the spinal cord).

Doses to the salivary glands were generally lower with IGBT (Tables 4 and 5). Six parameters of ipsilateral PAGs (iPAGs) were significantly lower with IGBT than with VMAT (e.g. D0.1cm³ was 11.2% vs. 18.0%, D10 was 7.3% vs. 11.2% and V10 was 3.1% vs. 18.0%, respectively) (Table 4). Two parameters (Dmean and D30) were identical for the two techniques (4.6% and 5.5%). Parameters of contralateral PAGs (cPAGs) showed the same tendency as iPAGs (Table 4). Dosimetry of iSMGs indicated that doses with IGBT were smaller than with VMAT, but no significant differences were found between the two techniques (Table 5). All dose parameters of cSMGs were significantly smaller with IGBT than with VMAT (e.g. Dmean was 8.2% vs. 16.9%, D10 was 11.1% vs. 25.3% and V10 was 26.0% vs. 69.9%, respectively) (Table 5).

Discussion

The comparison of new technologies in the H&N region is a very interesting area of research.⁷ Sresty *et al.* compared plans of IGBT and IMRT for mobile tongue cancer directly, and found a very good dose conformity between the two techniques.¹⁴ Our study also revealed good target coverage with both

IGBT and VMAT. Our results confirmed that the volumes irradiated by 100% of the PD were larger and the dose gradient around PTV was higher with IGBT than with VMAT - because of the physical characteristics of BT. Moreover, IGBT yielded better values in D90, but worse in D100. The majority of locoregional treatment failures occur within the target volumes irradiated with high doses by IMRT.^{15,16} These regions are thought to represent areas of hypoxia and radiation resistant tumor cells, and may require higher doses to improve local control.¹⁷ These observations might support the theory that the PTV of the primary tumor or tumor bed - if it is technically feasible - can be treated with IGBT.

Owosho *et al.* analyzed oral and oropharyngeal cancer patients and 96% of the osteoradionecrosis (ORN) affected regions of the jaw received doses over 60 Gy, suggesting >60 Gy as a threshold for ORN risk.¹⁸ In the current research mean D0.1cm³ of the mandible was 85.4% with VMAT, so 0.1cm³ received at least 59.8 Gy (70 Gy × 0.854). The mandible was significantly better protected with IGBT than with VMAT, due to intensity modulation with stepping source technology avoiding high irradiation of the mandible.¹ IGBT provided safe and secure treatment for the mandible.

For tonsillar cancer patients Stielier *et al.* reported 41.6 Gy and 42.6 Gy as mean maximum dose to the spinal cord with IMRT (9 fields) and VMAT (single arc), respectively, including the neck region in the treatment fields.¹⁹ In the direct comparison of plans of IGBT and IMRT for mobile tongue cancer, Sresty *et al.* reported maximum doses to the spinal cord from 9% to 14% with IGBT, whereas from 15.6% to 24.6% with IMRT.¹⁴ Meanwhile our results of mean D0.1cm³, which represents the maximum dose to the spinal cord, showed 9.7% (4.4 Gy) with IGBT and 12.3% (8.6 Gy) with VMAT ($p < 0.05$). The results were similar and doses to the spinal cord were acceptable for both techniques in patients, in whom only the primary lesion was irradiated.

Dose to PAGs is important in terms of xerostomia, because they produce up to 70% of the total stimulated saliva.²⁰⁻²³ Owosho *et al.* analyzed the role of PAGs irradiation in the development of severe xerostomia defined as Grade 4 according to the LENT SOMA scales after IMRT, and reported that xerostomia occurred in a follow-up time of <6 months, when the Dmean to iPAG and cPAG was 43.8 Gy and 24.9 Gy, respectively.²³ They concluded that the incidence of xerostomia could be decreased by limiting the mean dose to both PAGs to values below 25 Gy. In our study the mean doses

to iPAG and cPAG were 4.6% (3.2 Gy) and 3.9% (2.7 Gy) with VMAT and 4.6% (2.1 Gy) and 3.0% (1.4 Gy) with IGBT, respectively. Dose delivery to PAGs by both techniques probably has a little impact on xerostomia in patients, whose PTV includes only the primary tumor or tumor bed, but in IGBT the dose to PAGs was somewhat lower. Maintenance of adequate SMG function is also important in the reduction of xerostomia because SMGs produce about 20% to 30% of salivary output, including up to 90% of unstimulated salivary output.²⁴⁻²⁷ Wang *et al.* reported SMG dosimetry using IMRT with or without cSMG sparing.²⁷ In their study the mean doses to iSMGs and cSMGs were 60.8 Gy and 20.4 Gy, in the cSMG-sparing group as opposed to the unsparing group, where these parameters were 60.9 Gy and 57.4 Gy, respectively. They observed that xerostomia grades at 2 and 6 months post-IMRT were significantly lower among patients in the cSMG-sparing group than in the unsparing group. In our study all parameters of cSMGs were smaller with IGBT than with VMAT ($p < 0.05$). Dmean of cSMGs with VMAT was 16.9% (11.8 Gy). Dmean of cSMGs with IGBT was 8.2% (3.7 Gy), about one third of the value with VMAT, so IGBT had a more significant effect on dose reduction to cSMGs.

A major source of concern with VMAT and IMRT is the higher low dose radiation to surrounding normal tissue, which potentially increases the risk of secondary malignancy.¹⁷ As for our results, V10 with VMAT was appreciably large especially for PAG. Immobilization for precise irradiation and the possibility of tumor repopulation during the long treatment time can also be a problem with VMAT. On the other hand, technique sensitivity is one of the drawbacks of IGBT. However, some measures have been introduced for easy implantation, such as the use of a vinyl template or ultrasound guided technique.⁵

One of the limitations of our study is that the Task Group (TG)-43 formalism, implemented in our planning system for dose calculation, has not taken into consideration tissue heterogeneities.²⁸ However, Peppia *et al.* revealed that the absolute differences in the parameters are too small to warrant clinical importance in terms of tumor control or complication probabilities.²⁹ The second drawback is that the catheters in the target have a small tissue inhomogeneity effect. However, according to our investigation the variations in density in small volumes cause less than a 0.5% change in dosimetry. We are aware of that in EBRT the PTV should be larger than in BT, but our aim was to make comparison between two largely different irradiation

techniques, and since the same PTVs were used in plans of both treatment modalities in our study the dosimetric results apply only to the differences between BT and VMAT.

Though this article deals with the dosimetric and not the therapeutic comparison of the above mentioned two techniques, we would like to emphasize that the fractionation schedule, which we used in our BT treatment, was based on the European and American recommendations, where the suggested boost dose is 21-30/3 Gy with HDR after 45-50 Gy EBRT and the definitive dose is 45-60/3 Gy.^{2,30} Using $\alpha/\beta = 10$ Gy and without taking into consideration the time factor, the calculated biological effective dose (BED) for BT alone (15 x 3 Gy) was 58.5 Gy, for EBRT (25 x 2 Gy) and BT boost (7 x 3 Gy) 87.3 Gy (60 Gy + 27.3 Gy), for EBRT alone (35 x 2 Gy) 84 Gy and for EBRT (25 x 2 Gy) and EBRT boost (10 x 2 Gy) 84 Gy (60 Gy + 24 Gy). We applied lower BT dose for BT alone because of the lack of long-term experiences with HDR BT.

Conclusions

This is the first study with direct dosimetric comparison between IGBT and VMAT for H&N cancer applying various parameters. Both techniques provided excellent target coverage, but IGBT was found superior in protecting OARs. Adverse events, such as xerostomia and osteoradionecrosis, derived from irradiation of OARs could be serious problems in the H&N cancer radiotherapy. Therefore, it is clinically important to keep the dose for OARs as low as possible. In this respect the results confirm the important role of interstitial RT in the era of new external beam RT techniques. To translate the results of these dosimetric findings into clinical practice, more patients and long term follow-up with prospective collection of toxicities are necessary.

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