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Postoperative SBRT in the treatment of early-stage oropharyngeal and oral cavity cancers with high-risk margins: A dosimetric comparison of volumetric modulated arc therapy with or without non-coplanar arcs and acute toxicity outcomes from the STEREOPOSTOP GORTEC 2017–03 phase 2 trial

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ABSTRACT

Background and purpose: The STEREO POSTOP GORTEC 2017–03 phase 2 trial (NCT03401840) evaluates postoperative stereotactic body radiotherapy (SBRT) in case of high-risk margins for pT1-T2/N0 oropharyngeal and oral cavity tumors. The present ancillary study aimed to compare the dosimetric impact of adding non-coplanar arcs to the volumetric modulated arc therapy (VMAT) technique and to evaluate acute toxicities on the first patients included in this trial.

Materials and methods: Ten patients were included. Patients were treated with Novalis TX®. The total dose was 36 Gy (100 % isodose line) in 6 fractions, treated every other day. Two treatment plans were created for each patient: one plan using 2 coplanar arcs only (VMATc) and one plan using coplanar and 3 non-coplanar arcs (VMATc + nc). Acute toxicity was evaluated according to NCI CTCAE criteria V4.03.

Results: Median age was 62 years. Localization of tumor was the mobile tongue for 6 patients, floor of mouth for 2, cheek for 1, and gingiva for 1. Six patients had pT2N0 tumors (AJCC 7th edition) and 4 had pT1N0. Mean CTV and PTV volumes were 36.4 and 56.1 cc respectively. Mean PTV coverage by the 36 Gy isodose was 98.2 % for both techniques ($p = ns$), with comparable conformity indexes (1.1 for VMATc vs 1.07 for VMATc + nc; $p = 0.23$). VMATc + nc had a significantly better gradient index (3.45 vs 2.97; $p = 0.01$), resulting in a significantly better sparing of most organs at risk. For example, mean Dmean to the oral cavity, lips, and homolateral parotid were respectively of 16.8 Gy, 11.1 Gy, and 10.4 Gy for VMATc vs 14.8 Gy ($p = 0.005$), 8.1 Gy ($p = 0.001$), 6.5 Gy ($p = 0.04$) for VMATc + nc. No grade ≥ 4 or higher acute toxicity was reported. The most common acute toxicity was grade ≥ 2 mucositis.

Conclusion: VMATc + nc had better dosimetric outcomes than VMATc and has become the standard technique for patients treated in the STEREO POSTOP GORTEC 2017–03 trial (NCT03401840) in our institution. Acute toxicity appears acceptable.

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Background

Early-stage oropharyngeal and oral cavity cancers are mainly squamous cell carcinomas. Their incidence is rising [1]. Multidisciplinary management is usually needed. Primary surgery is one of the mainstay treatments [2]. Negative tumor margins are recommended (>5mm) [3,4]. If feasible, a re-resection of any positive margin is preferred. Otherwise, postoperative radiotherapy is indicated [5–8]. Limited adjuvant postoperative radiotherapy to the primary site for patients with pT1-T2 tumors and negative neck dissection, is a therapeutic option [8,9]. Both fractionated external beam radiotherapy and brachytherapy can have a role in this setting. Brachytherapy is a highly conformal radiotherapy technique that allows high-dose delivery to small volumes within a short overall treatment time [10–12]. However, implantation is not always technically possible and brachytherapy necessitates a highly experienced team and appropriate infrastructures. Post-operative external beam radiotherapy can also be used but the overall treatment time is longer (6–7 weeks) [13–17]. Another possible alternative could be postoperative hypofractionated Stereotactic Body Radiotherapy (SBRT), which is investigated in the STEREO POSTOP GORTEC 2017–03 multicentric phase 2 trial (NCT03401840) [18]. It is an attractive option because it delivers a highly conformal dose of radiation in a limited number of fractions, with steep dose gradients resulting in reduced normal tissue irradiation [19]. To our knowledge, STEREO POSTOP GORTEC 2017–03 (NCT03401840) is the first-in-human trial to deliver postoperative SBRT in this specific indication.

This manuscript presents the outcomes of an ancillary study issued from the STEREO POSTOP GORTEC 2017–03 trial (NCT03401840). The purpose of this ancillary study was to compare the dosimetric impact of adding non-coplanar arcs to the volumetric modulated arc therapy (VMAT) technique on a Novalis-type accelerator and to report the acute toxicity profile of the first ten patients from the STEREO POSTOP GORTEC 2017–03 trial (NCT03401840) [18].

Material and methods

Patients

This ancillary study included the ten first patients included in the STEREO POSTOP GORTEC 2017–03 (NCT03401840) phase 2 trial in our institution. The first patient was included in January 2018. A total of 90 patients was included. The entire detailed protocol has been published previously [18]. Main inclusion criteria included: squamous cell carcinoma of the oral cavity (except lips) or oropharynx; pT1 or pT2 (AJCC 7th edition) with an indication of postoperative tumoral bed irradiation (positive margin R1, close margin <5 mm or margin estimated at risk); N0 after surgical treatment (neck dissection or sentinel lymph node biopsy), or pN1 without extracapsular extension; and no prior radiotherapy. Main exclusion criteria included: pT3 or pT4 (AJCC 7th edition); pT2 >3 cm and R1 with concurrent chemoradiotherapy decided in multidisciplinary tumor board; lymphovascular invasion; distant metastasis; and lack of at least one of the following elements: preoperative medical imaging, endoscopy report, surgery report, and pathological report. The primary endpoint of the STEREO POSTOP GORTEC 2017–03 (NCT03401840) phase 2 trial was 2-year late toxicity.

All patients in this ancillary study were treated with Novalis TX® (Varian Medical Systems, Palo Alto, CA, USA and Brainlab, Munich, Germany). This ancillary study was foreseen in the study protocol [18].

Treatment preparation

All patients had a dental examination, including clinical and radiological examination. When indicated, extraction of dental elements was carried out. Adequate dental care (including daily fluorine application if necessary) was realized, at least during follow-up.

A planning CT of 1.25-mm thickness was acquired in supine position, including the whole skull to the lower border of the clavicle. Patients were immobilized using a noninvasive stereotactic thermoplastic mask. In the protocol [18], the use of devices for the immobilization of the tongue was left to the discretion of the investigators. In the present ancillary study, no specific device was used for the immobilization of the oral tongue for the 10 patients.

According to the study protocol [18], the CTV was defined as the initial tumor bed including the positive or close margins with a margin of 5 to 10 mm according to the anatomical barriers and extension pathways. In the case of flap reconstruction, CTV also included the junction normal tissue/flap +5 mm proximity flap. A 2-mm set-up margin was implemented around the CTV to create the PTV. Delineation of the organs at risk (OARs) was realized according to Brouwer et al. [20]. When necessary, a 2-mm margin was applied to the OARs to create the planning OARs volumes (PRVs).

According to the study protocol [18], the total dose was 36 Gy in 6 fractions, treated every other day; corresponding to biological effective dose (BED) BED_{10} of 64.2 Gy for the tumor (equivalent to BED_{10} of 60 Gy in 30 fractions), a BED_{10} of 54.4 Gy for early effects (equivalent to BED_{10} of 74 Gy in 37 fractions), and a BED_3 of 108 Gy for late effects (equivalent to BED_3 of 66 Gy in 33 fractions) [21,22].

Patients were treated with a volumetric modulated arc therapy (VMAT) technique with arcs of 6-MV photons. Treatment specifications were as follows: the prescription isodose line was 100 % of the prescribed dose (36 Gy), to encompass at least 95 % of the PTV, with no>5 % of the PTV receiving > 110 % of the prescribed dose i.e. 39.6 Gy. The prescription isodose line was chosen as 100 % due to the postoperative situation. Final calculations were performed using the AAA algorithm on Eclipse® TPS version 15.6 (Varian Medical Systems). The arc optimization algorithm, the *Photon Optimizer* used in Rapidarc®, optimized leaf position, dose rate, and gantry speed. Optimization parameters with *Normal Tissue Objectives* (NTO) were used to spare healthy tissues. The maximum dose rate was set at 600 MU/min.

For the treatment, daily pre-positioning was performed using an ExacTrac® stereoscopic X-ray system (Brainlab, Munich, Germany) and a robotic couch with six of freedom, and final positioning was performed using cone-beam CT.

Dosimetric comparison

Two treatment plans were created for each patient: one plan using coplanar arcs only (VMATc) and one plan using coplanar and non-coplanar arcs (VMATc + nc). The ten patients were ultimately treated with VMATc + nc.

VMATc plans were created with two full coplanar arcs (Fig. 1). The first arc was planned in a clockwise direction and the second in a counter-clockwise direction. For all the plans, the collimator was rotated to 30° for the first arc and to 330° for the second arc to reduce the tongue-and-groove effect.

VMATc + nc plans were created with one full coplanar arc and 3 partial non-coplanar arcs spaced by about 45° (Fig. 1). The maximum arc rotation amplitude was 160°. The rotation of the collimator was 10°, 350°, 350°, 350° and 10° for the first, second, third, and fourth arcs respectively.

Acute toxicity assessment

Acute toxicity was defined as any ≤ 3-month toxicity related to SBRT according to NCI CTCAE criteria V4.03. To evaluate early toxicity, 3 visits with a physical evaluation were planned during SBRT: at the first fraction (day1), the fourth (expected date: day8), and the last fraction (day11 to day13). After SBRT treatment, a visit was planned 1 week after the last fraction, at 1 month, and at 3 months. The 10 patients used for the dosimetric analysis were the same as the ones included in the acute toxicity assessment.

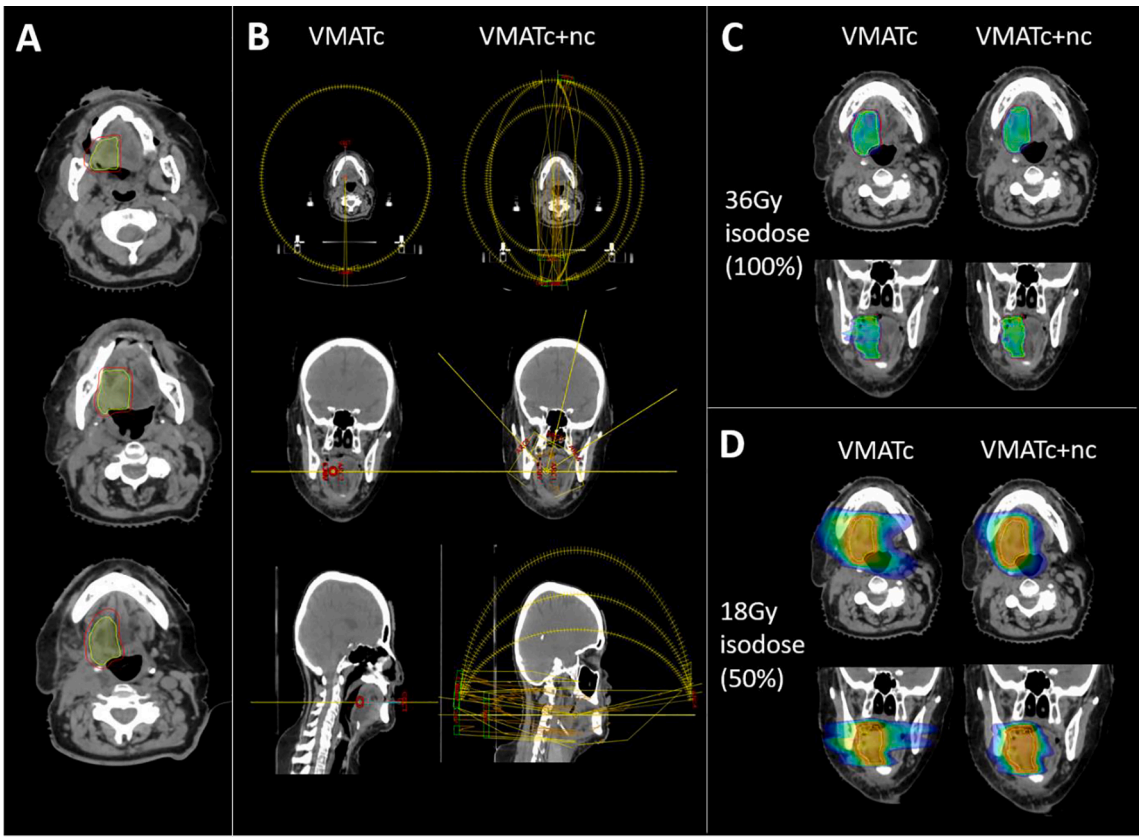

Fig. 1. Treatment planning of a patient with a pT1-R1 tumor of the posterior right mobile tongue. A/ Axial views of the planning CT with the CTV (yellow) and PTV (red). B/ Axial, coronal and sagittal views of VMAT technique with coplanar arcs only (VMATc), and of VMAT technique with coplanar and non-coplanar arcs (VMATc + nc). C/ Axial and coronal views representing the 36 Gy isodose (100 %) for VMATc and VMATc + nc. D/ Axial and coronal views representing the 18 Gy isodose (50 %) for VMATc and VMATc + nc. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Statistical analysis

The plan analyses were based on dose-volume histogram (DVH) data. For target volume coverage, V100% (36 Gy), and the maximum dose (Dmax) to the PTV were noted. We also calculated three indexes for the PTV: the inverse Paddick conformity index (CI), the gradient index (GI), and the homogeneity index (HI).

The inverse Paddick CI is defined as follows:

$$\mathrm{CI} = \frac{(Totalvolumereceiving \geq D\mathrm{coverage})}{(PTVvolumereceiving \geq D\mathrm{coverage})} * \frac{(PTVvolume)}{(PTVvolumereceiving \geq D\mathrm{coverage})}$$

A value of 1 is the ideal case. The larger the value, the less conformal the treatment.

The GI is defined as follows:

$$GI = \frac{(Totalvolumereceiving \geq 50\% D\mathrm{coverage})}{(Totalvolumereceiving \geq 100\% D\mathrm{coverage})}$$

The GI describes the steepness of the dose fall-off from the 36 Gy isodose (Dcoverage in our case) to the 18 Gy isodose (50 % of Dcoverage). The larger the value, the shallower the gradient.

The HI is defined as follows:

$$HI = \frac{D2\% - D98\%}{Dmean}$$

where D2 % was the dose delivered to 2 % of the PTV volume, D98 % was the dose delivered to 98 % of the PTV volume, and Dmean was the mean dose to the PTV. Small values of HI indicated more homogeneous irradiation of the PTV.

For organs at risk, Dmean and/or D2% were noted.

Statistical analyses were performed using R v2.15.1 (https://www.cran.r-project.org). To compare the dosimetric indices for the different modalities, non-parametric Wilcoxon tests for paired samples were used. If the associated p-value was less than the significance level ($\alpha = 0.05$), it was assumed that there was a statistically significant difference between the compared data sets. Due to the low number of patients, data concerning acute toxicities were only descriptive.

Results

Patient characteristics

All patients' characteristics are detailed in Table 1. The median age was 62 years (min–max: 36–81). Six of the 10 patients had mobile tongue tumors, 2 had floor of mouth tumors, 1 had a cheek tumor, and 1 had a gingiva tumor. Six of the 10 patients had T2 tumors (AJCC 7th edition) and 4 had T1 tumors. Five of the 10 patients had a flap reconstruction surgery. The indications of postoperative SBRT for the 10 patients were as follows: 1 positive R1 margin, 8 close margin <5 mm, and 1 extensive microscopic perineural invasion. Median follow-up was 12 months (min–max: 3 – 33).

The mean CTV volume was 36.4 cc (min–max: 22.3–65.9) and the mean PTV volume was 56.1 cc (min–max: 37.6–92.3).

Dosimetric comparison

Table 2 summarizes dosimetric parameters for both VMATc and VMATc + nc techniques. Mean PTV coverage (prescription isodose 36 Gy) was 98.2 % for both techniques (p = ns), with a comparable CI (mean CI of 1.1 for VMATc vs 1.07 for VMATc + nc; p = 0.23).

Table 1
Patients characteristics.

	Age	Localization	T stage	N stage	Indication	Flap	CTV (cc)	PTV (cc)
Patient 1	41	Floor of mouth	T2	N0	Close margin	Yes	49.5	75.0
Patient 2	36	Mobile tongue	T2	N0	Close margin	No	41.6	64.1
Patient 3	71	Gingiva	T2	N0	Close margin	No	28.2	44.9
Patient 4	68	Mobile tongue	T1	N0	Close margin	No	27.6	43.3
Patient 5	34	Mobile tongue	T1	N0	Perineural invasion	Yes	27.7	45.6
Patient 6	51	Cheek	T1	N0	Close margin	Yes	65.9	92.3
Patient 7	63	Mobile tongue	T2	N0	Close margin	Yes	35.4	54.2
Patient 8	80	Mobile tongue	T2	N0	Close margin	No	22.3	37.6
Patient 9	61	Mobile tongue	T1	N0	Close margin	No	29.0	46.7
Patient 10	69	Floor of mouth	T2	N0	R1 margin	Yes	36.9	56.8

Table 2
Summary of dosimetric results comparing volumetric modulated arc therapy with coplanar arcs only (VMATc) or with coplanar and non-coplanar arcs (VMATc + nc).

	Indices	VMATc	VMATc + nc	p-value
PTV	V36Gy (%)	98.2	98.2	ns
	CI	1.1	1.07	0.23
	HI	0.1	0.07	0.004
	GI	3.45	2.97	0.01
	Dmax (Gy)	35.7	33.8	0.005
Jaw	D2% (Gy)	30.3	27.8	0.01
	Dmean (Gy)	12.6	10.6	0.009
HL Cheek	D2% (Gy)	34.2	33.3	0.02
	Dmean (Gy)	19.2	15.2	0.007
CL Cheek	D2% (Gy)	16.0	11.4	0.006
	Dmean (Gy)	10.6	7.4	0.01
Lips	D2% (Gy)	26.7	23.1	0.003
	Dmean (Gy)	11.1	8.1	0.001
Spinal cord	D2% (Gy)	10.0	6.4	0.001
Brainstem	D2% (Gy)	5.0	4.8	0.78
HL Parotid	Dmean (Gy)	10.4	6.5	0.04
CL Parotid	Dmean (Gy)	6.2	3.07	0.02
Oral Cavity	D2% (Gy)	29.8	28.6	0.36
	Dmean (Gy)	16.8	14.8	0.005

Data are presented as mean doses of all patients ± standard deviation. VxGy = volume receiving at least xGy; and Dx% is the minimum dose received by x% of the structure volume.
CI = Conformity Index; HI = Homogeneity Index; GI = Gradient Index; Dmax = maximum dose; Dmean = mean dose; HL = homolateral; CL = contralateral; Gy = Gray.

Treatment plans were significantly more homogeneous with VMATc + nc (mean HI of 0.1 for VMATc vs 0.07 for VMATc + nc; p = 0.004) with a significantly better gradient index (mean GI of 3.45 for VMATc vs 2.97 for VMATc + nc; p = 0.01).

Most of the organs at risk were significantly better spared with VMATc + nc (Table 2). For example, the mean Dmean to the oral cavity was 16.8 Gy for VMATc vs 14.8 Gy for VMATc + nc (p = 0.005), mean Dmean to the lips was 11.1 Gy for VMATc vs 8.1 Gy for VMATc + nc (p = 0.001) and mean Dmean to the homolateral parotid was 10.4 Gy for VMATc vs 6.5 Gy for VMATc + nc (p = 0.04).

Acute toxicity

Patients' acute toxicities are summarized in Table 3. There was no grade ≥ 4 acute toxicity. The ten patients experienced grade ≥ 2 mucositis (3 grade 2 and 7 grade 3). For all patients, the maximum grade of mucositis was reached 1 week after the end of the treatment; and progressively decreased to disappear at 1 month for 40 % of patients, and at 3 months for 100 % of patients. Xerostomia was noticed for 5 of the 10 patients, all grade 1. There were no grade ≥ 3 dysphagia (4 grade 2 and 5 grade 1). At 3 months, dysphagia was improved in all the patients, with only 4 patients with persistent grade 1 dysphagia. Epidermitis was noticed in 3 of the 10 patients (2 grade 2 and 1 grade 1) and was also totally resolved at 1 month. Two of the 10 patients experienced pain (1 grade 2 and 1 grade 1). One patient experienced grade 2 tongue edema, one had grade 2 trismus, and one had grade 2 cheilitis.

Table 3
Acute toxicities related to SBRT treatment.

	Mucositis	Xerostomia	Dysphagia	Epidermitis	Others
Patient 1	Grade 2	None	Grade 2	Grade 2	Mycosis (Grade 2) Tongue edema (Grade 2)
Patient 2	Grade 3	Grade 1	Grade 1	None	Pain (Grade 2)
Patient 3	Grade 3	None	Grade 1	None	None
Patient 4	Grade 3	None	Grade 1	None	None
Patient 5	Grade 3	Grade 1	Grade 2	None	Mycosis (Grade 2) Pain (Grade 1)
Patient 6	Grade 3	Grade 1	None	Grade 2	Trismus (Grade 2)
Patient 7	Grade 3	Grade 1	Grade 2	None	Cheilitis (Grade 2)
Patient 8	Grade 2	None	Grade 1	None	None
Patient 9	Grade 2	Grade 1	Grade 1	Grade 1	Mycosis (Grade 2)
Patient 10	Grade 3	None	Grade 2	None	None

Discussion

This study is the first ancillary study from the STEREO POSTOP GORTEC 2017–03 trial (NCT03401840) [18]. This phase 2 trial evaluates postoperative SBRT in the treatment of early-stage oropharyngeal and oral cavity cancers with high risk margins. In this trial, SBRT is limited to the primary site for patients with pT1-T2 tumors and negative neck dissection [8,9]. Omitting neck irradiation for pN0 patients is a controversial topic. The main series reporting this strategy for localized tumors come from post-operative brachytherapy with favorable outcomes [23,24]. A total of 90 patients are planned to be included in the STEREO POSTOP GORTEC 2017–03 trial (NCT03401840). The primary endpoint of this trial is 2-year late toxicity. Here, we report the results of a dosimetric study of the 10 first patients treated with a Novalis-type accelerator as well as acute toxicity results. We compared the dosimetric impact of adding non-coplanar arcs using a VMAT irradiation technique. We found that both VMATc and VMATc + nc were highly conformal techniques (CI of 1.1 and 1.07 respectively, p = 0.23), but that VMATnc resulted in a steeper dose gradient (GI of 2.97 vs 3.45 for VMATc, p = 0.01). This steeper dose gradient resulted in better organs at risk sparing (Table 2). For example, the mean Dmean to the homolateral parotid gland was reduced by 3.9 Gy (10.4 Gy for VMATc vs 6.5 Gy for

VMATnc, p = 0.05), mean Dmean to the lips was reduced by 3 Gy (11.1 Gy for VMATc vs 8.1 Gy for VMATnc, p = 0.0004), and mean Dmean to the oral cavity was reduced by 2 Gy (16.8 Gy for VMATc vs 14.8 Gy for VMATnc, p = 0.005). We found that this dosimetric impact was sufficiently meaningful to use VMATc + nc as the reference technique for all the patients included in this trial in our institution. To date, SBRT in head and neck cancers has been mainly validated in the case of reirradiation. Recently, the International Stereotactic Body Radiotherapy Consortium (ISBRTC) has published a survey of current practices in SBRT for head and neck cancer reirradiation [25]. Of the 15 international institutions included in this survey, a majority of the institutions (11 out of the 15) used linear accelerators with cone-beam CT to treat patients, and 9 institutions used a VMAT technique. However, there were no precisions regarding whether non-coplanar arcs were used or not. The department of radiation oncology from the University of Pittsburg Cancer Institute is probably the most important team that had published in the field of head and neck cancers SBRT [26–31]. They describe that in their experience, they initially favored Cyberknife almost exclusively. However, with advances in treatment delivery and image guidance, they transitioned to almost exclusively linear accelerators with cone-beam CT (Trilogy and Truebeam). They use both static IMRT and VMAT plans and only coplanar beams or arcs are used (except for skull base lesions for which non-coplanar arcs are commonly incorporated) [27]. To date, this dosimetric study is the first published to demonstrate that non-coplanar arcs might be useful in head and neck SBRT (other than skull base).

The acute toxicity profile that we report here appears favorable. However, this report only concerned 10 patients. The most common acute toxicity that we report was grade 2 to 3 acute mucositis (Fig. 2). This toxicity profile seemed comparable with the one reported in the series of post-operative brachytherapy. Goineau *et al.* [23] published a series of 112 patients treated with post-operative interstitial low dose rate (LDR) ^{192}Ir brachytherapy for mobile tongue squamous cell carcinoma. The main acute toxicity, present in all patients, was grade $\geq$ 2 mucositis. Ferenczi *et al.* [24] published a series of 44 patients treated with high dose rate tumor bed brachytherapy for floor of mouth tumors. They reported 75 % of grade $\geq$ 2 acute mucositis. Even if the acute toxicity profile that we reported here seemed favorable, it is rather late toxicity that should be looked at closely in this situation. Indeed, the STEREO POSTOP GORTEC 2017–03 trial (NCT03401840) includes pT1/pT2 N0 oral cavity or oropharyngeal squamous cell carcinomas with high risk margins, which have a potential long survival. The reports of late toxicity and oncological long-term outcomes are expected for 2023.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009;45:309–16. https://doi.org/10.1016/j.oraloncology.2008.06.002.

[2] Eckel HE, Volling P, Pototschnig C, Zorowka P, Thumfart W. Transoral laser resection with staged discontinuous neck dissection for oral cavity and oropharynx squamous cell carcinoma. The Laryngoscope 1995;105:53–60. https://doi.org/10.1288/00005537-199501000-00013.

[3] Meier JD, Oliver DA, Varvares MA. Surgical margin determination in head and neck oncology: current clinical practice. The results of an International American Head and Neck Society Member Survey. Head Neck 2005;27:952–8. https://doi.org/10.1002/hed.20269.

[4] Bradley PJ, MacLennan K, Brakenhoff RH, Leemans CR. Status of primary tumour surgical margins in squamous head and neck cancer: prognostic implications. Curr Opin Otolaryngol Head Neck Surg 2007;15:74–81. https://doi.org/10.1097/MOO.0b013e328058670f.

[5] Gomez DR, Zhung JE, Gomez J, Chan K, Wu AJ, Wolden SL, et al. Intensity-modulated radiotherapy in postoperative treatment of oral cavity cancers. Int J Radiat Oncol Biol Phys 2009;73(4):1096–103.

[6] Hinerman RW, Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Villaret DB. Postoperative irradiation for squamous cell carcinoma of the oral cavity: 35-year experience. Head Neck 2004;26:984–94. https://doi.org/10.1002/hed.20091.

[7] Zelefsky MJ, Harrison LB, Fass DE, Armstrong JG, Shah JP, Strong EW. Postoperative radiation therapy for squamous cell carcinomas of the oral cavity and oropharynx: impact of therapy on patients with positive surgical margins. Int J Radiat Oncol Biol Phys 1993;25(1):17–21.

[8] Beitler JJ, Smith RV, Silver CE, Quish A, Deore SM, Mullokandov E, et al. Close or positive margins after surgical resection for the head and neck cancer patient: the addition of brachytherapy improves local control. Int J Radiat Oncol Biol Phys 1998;40(2):313–7.

[9] Jäckel MC, Ambrosch P, Christiansen H, Martin A, Steiner W. Value of postoperative radiotherapy in patients with pathologic N1 neck disease. Head Neck 2008;30:875–82. https://doi.org/10.1002/hed.20794.

[10] Lapeyre M, Coche-Dequéant B, Moreira J-F, Le Bourhis J, Peiffert D. Brachytherapy for head and neck cancers. Cancer Radiothérapie J Société Fr Radiothérapie Oncol 2013;17:130–5. https://doi.org/10.1016/j.canrad.2013.01.007.

[11] Mazeron J-J, Ardiet J-M, Haie-Méder C, Kovács G, Levendag P, Peiffert D, et al. GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas. Radiother Oncol J Eur Soc Ther Radiol Oncol 2009;91(2):150–6.

[12] Strnad V. Treatment of oral cavity and oropharyngeal cancer. Indications, technical aspects, and results of interstitial brachytherapyTherapie von Mundhöhlen- und Oropharynxkarzinomen. Indikationen, technische Aspekte und Ergebnisse der interstitiellen Brachytherapie. Strahlenther Onkol Organ Dtsch Röntgenges Al 2004;180(11):710–7.

[13] Chen P-Y, Chen HHW, Hsiao J-R, Yang M-W, Hsueh W-T, Tasi S-T, et al. Intensity-modulated radiotherapy improves outcomes in postoperative patients with squamous cell carcinoma of the oral cavity. Oral Oncol 2012;48(8):747–52.

[14] Chen AM, Farwell DG, Luu Q, Chen LM, Vijayakumar S, Purdy JA. Marginal misses after postoperative intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2011;80:1423–9. https://doi.org/10.1016/j.ijrobp.2010.04.011.

[15] Geretschläger A, Bojaxhiu B, Crowe S, Arnold A, Manser P, Hallermann W, et al. Outcome and patterns of failure after postoperative intensity modulated radiotherapy for locally advanced or high-risk oral cavity squamous cell carcinoma. Radiat Oncol Lond Engl 2012;7(1). https://doi.org/10.1186/1748-717X-7-175.

[16] Collan J, Lundberg M, Vaalavirta L, Bäck L, Kajanti M, Mäkitie A, et al. Patterns of relapse following surgery and postoperative intensity modulated radiotherapy for oral and oropharyngeal cancer. Acta Oncol Stockh Swed 2011;50(7):1119–25.

[17] Chan AK, Huang SH, Le LW, Yu E, Dawson LA, Kim JJ, et al. Postoperative intensity-modulated radiotherapy following surgery for oral cavity squamous cell carcinoma: patterns of failure. Oral Oncol 2013;49(3):255–60.

[18] Biau J, Thivat E, Millardet C, Saroul N, Pham-Dang N, Molnar I, et al. A multicenter prospective phase II study of postoperative hypofractionated stereotactic body radiotherapy (SBRT) in the treatment of early-stage oropharyngeal and oral cavity cancers with high risk margins: the STEREO POSTOP GORTEC 2017–03 trial. BMC Cancer 2020;20(1). https://doi.org/10.1186/s12885-020-07231-3.

[19] Lo SS, Fakiris AJ, Chang EL, Mayr NA, Wang JZ, Papiez L, et al. Stereotactic body radiation therapy: a novel treatment modality. Nat Rev Clin Oncol 2010;7(1):44–54.

[20] Brouwer CL, Steenbakkers RJHM, Bourhis J, Budach W, Grau C, Grégoire V, et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. Radiother Oncol J Eur Soc Ther Radiol Oncol 2015;117(1):83–90.

[21] Fowler JF. Is there an optimum overall time for head and neck radiotherapy? A review, with new modelling. Clin Oncol R Coll Radiol G B 2007;19(1):8–22.

[22] Fowler JF. Optimum overall times II: Extended modelling for head and neck radiotherapy. Clin Oncol R Coll Radiol G B 2008;20:113–26. https://doi.org/10.1016/j.clon.2007.11.003.

[23] Goineau A, Piot B, Malard O, Ferron C, Lisbona A, Cassagnau E, et al. Postoperative interstitial brachytherapy for resectable squamous cell carcinoma of the tongue. Brachytherapy 2015;14(1):71–6.

[24] Ferenczi Ö, Major T, Akiyama H, Fröhlich G, Oberna F, Révész M, et al. Results of postoperative interstitial brachytherapy of resectable floor of mouth tumors. Brachytherapy 2021;20(2):376–82.

[25] Karam I, Yao M, Heron DE, Poon I, Koyfman SA, Yom SS, et al. Survey of current practices from the International Stereotactic Body Radiotherapy Consortium (ISBRTC) for head and neck cancers. Future Oncol Lond Engl 2017;13(7):603–13.

[26] Heron DE, Ferris RL, Karamouzis M, Andrade RS, Deeb EL, Burton S, et al. Stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck: results of a phase I dose-escalation trial. Int J Radiat Oncol Biol Phys 2009;75(5):1493–500.

[27] Ling DC, Vargo JA, Ferris RL, Ohr J, Clump DA, Yau W-Y, et al. Risk of Severe Toxicity According to Site of Recurrence in Patients Treated With Stereotactic Body Radiation Therapy for Recurrent Head and Neck Cancer. Int. J Radiat Oncol 2016;95(3):973–80.

[28] Vargo JA, Ferris RL, Ohr J, Clump DA, Davis KS, Duvvuri U, et al. A prospective phase 2 trial of reirradiation with stereotactic body radiation therapy plus cetuximab in patients with previously irradiated recurrent squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2015;91(3):480–8.

[29] Vargo JA, Heron DE, Ferris RL, Rwigema J-C, Kalash R, Wegner RE, et al. Examining tumor control and toxicity after stereotactic body radiotherapy in

locally recurrent previously irradiated head and neck cancers: implications of treatment duration and tumor volume. Head Neck 2014:n/a–.

[30] Vargo JA, Kubicek GJ, Ferris RL, Duvvuri U, Johnson JT, Ohr J, et al. Adjuvant stereotactic body radiotherapy±cetuximab following salvage surgery in previously irradiated head and neck cancer. The Laryngoscope 2014;124:1579–84. https://doi.org/10.1002/lary.24441.

[31] Quan K, Xu KM, Zhang Y, Clump DA, Flickinger JC, Lalonde R, et al. Toxicities Following Stereotactic Ablative Radiotherapy Treatment of Locally-Recurrent and Previously Irradiated Head and Neck Squamous Cell Carcinoma. Semin Radiat Oncol 2016;26(2):112–9.