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\textsuperscript{®}. 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 were 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 edition); pT2 >3 cm and R1 with concurrent chemoradiotherapy (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) BED10 of 64.2 Gy for the tumor (equivalent to BED10 of 60 Gy in 30 fractions), a BED3 of 54.4 Gy for early effects (equivalent to BED10 of 74 Gy in 37 fractions), and a BED3 of 108 Gy for late effects (equivalent to BED10 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 in Eclipse® TPS version 15.6 (Varian Medical Systems). The arc optimization algorithm, the Photon Optimizer used in Rapidarc®, optimized lead 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.
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:
$$CI = \frac{\text{Total volume receiving } \geq \text{D coverage}}{\text{PTV volume receiving } \geq \text{D coverage}} \times \frac{\text{PTV volume}}{\text{Total volume receiving } \geq \text{D coverage}}$$
A value of 1 is the ideal case. The larger the value, the less conformal the treatment.

The GI is defined as follows:
$$GI = \frac{\text{Total volume receiving } \geq 50\%\text{D coverage}}{\text{Total volume receiving } \geq 100\%\text{D coverage}}$$

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:
$$HI = \frac{D2\% - D98\%}{\text{Dmean}}$$
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.r-project.org](https://www.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 (α = 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).
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.

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 acceleration 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 = 0.005), with a marginally better gradient index (mean GI of 3.45 for VMATc vs 3.47 for VMATc + nc; p = 0.01).

Most of the organs at risk were significantly better spared 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).

Data are presented as mean doses of all patients ± standard deviation. VsGy = volume receiving at least xGy; and Dc% is the minimum dose received by c% of the structure volume.

Cl = Conformity Index; HI = Homogeneity Index; GI = Gradient Index; Dmax = maximum dose; Dmean = mean dose; HL = homolateral; CL = contralateral; Gy = Gray.
describe that in their experience, they initially favored Cyberknife but Pittsburg Cancer Institute is probably the most important team that had 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 Pittsburgh 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 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 Pittsburgh 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. Gineau et al. [23] published a series of 112 patients treated with post-operative interstitial low dose rate (LDR) brachytherapy for mobile tongue squamous cell carcinoma. The main acute toxicity, present in all patients, was grade 2–3 mucositis. Ferenci 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 ≥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 2017–2013 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.

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