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Case report

Are intraoral customized stents still necessary in the era of Highly Conformal Radiotherapy for Head & Neck cancer? Case series and literature review

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ABSTRACT

Aim: To evaluate the dose sparing efficacy of intraoral customized stents in combination with IGRT/VMAT in Head & Neck cancer patients.
Background: Despite advances in high-dose conformal radiotherapy (RT) techniques, adverse effects (such as oral mucositis) during and after RT often require temporary suspension of treatment and affect the quality of life in survivors. Intraoral customized stents can decrease radiation doses in healthy tissues and minimize damage from radiations. At the best of our knowledge the clinical impact of such devices in combination with VMAT (volumetric modulated arc therapy) is not reported in the literature.
Cases description: Three Head & Neck cancer patients were submitted to image guided (IG) RT/VMAT in their treatment protocol. Dose distribution with and without the use of an intraoral stent was compared in each patient. Mean radiation doses proved to be lower in all patients, especially in the subsite: oral cavity.
Conclusions: There are several reports on the efficacy of IS during RT for Head & Neck cancer. Despite technological advances, the combination between high conformal RT and intraoral stents could still play a role in the management of this kind of patients. This strengthens the usefulness of the individualization of treatments and multidisciplinary approach.

1. Background

The global incidence of Head & Neck (HN) cancers is 550,000.[1] In Europe, 250,000 people were affected by HN cancers in 2012.[2] However, there are several geographic and demographic epidemiological differences in the prevalence of different types and primary location of HN cancers.[3,4] Nowadays, radiation therapy (RT) is the gold standard treatment for HN cancers together with surgery and chemotherapy.[5] Incidence of treatment related complications and side effects is still relevant: these adverse events continue to be detrimental for the patient's health and quality of life.[6,7] Oral mucositis,

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pain, xerostomia, taste changes, deafness, dysphagia, hoarse voice, aspiration, and trismus often occur during and after RT. Extensive surgery may involve multiple tooth extractions and prosthetic rehabilitation by dental implants placement could be difficult after RT because of the undefined risk of osteoradionecrosis.[8–10] Intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) have been introduced to decrease irradiation toxicity in order to allow the use of high and homogenous radiation doses to a localized target volume with minimal effects on the surrounding non-involved tissues.[11,12]

However, anatomical changes and positional variability can lead to significant dosimetric differences between planned and delivered dose distribution during IMRT.[13] Image guided (IGRT) and adaptive radiation therapies (ART) are useful to limit these anatomical and dosimetric uncertainties. Moreover, the IGRT technique is able to decrease the risk of a geographical miss and reduce anatomical margins.

Despite the advancements of RT techniques, commensurate dose delivering (especially for subsites in the oral cavity) and adequate protection of normal critical tissues remain challenging tasks because of the anatomical complexity of the HN region. The use of intraoral customized stents (IS) in combination with high-dose conformal RT techniques can decrease radiation doses in healthy structures and minimize the adverse effects of radiation.[14] There is little evidence about IS use in HN cancer patients treated with RT.[14–30] To the best of our knowledge, only a recent case report investigated the dosimetric analysis in the same patient treated with IMRT with or without device with a doubled Computed Tomography (CT) scan to determine its effectiveness in reducing dose radiation.[14] No clinical reports regarding combination of IGRT/VMAT in combination with IS are available in the literature.

2. Aim

We compared the VMAT dose distribution plans in a case series with an adjacent site of cancer with and without a custom made IS in order to further reduce radiation doses in healthy tissues.

2.1. *Case descriptions*

Between September 2015 and February 2017, three patients affected by locally advanced H&N cancer were treated in Radiotherapy, Dentistry & Oral Surgery and Otolaryngology departments. Patients were evaluated by a multidisciplinary team before starting the treatment protocol. The indication for using an IS in adjunction to IGRT–VMAT was defined considering the cancer site and position. Informed consent before beginning of oncologic treatments was obtained from each patient or from his family according to the Declaration of Helsinki.

A preventive clinical oral examination was performed in the Dentistry & Oral Surgery Department before the start of VMAT. The oral health of each patient was assessed with a pre-RT dental care and oral hygiene instructions. Preventive and palliative measures were also recommended in order to prevent RT complications.

Intraoral stents were designed, adapted and delivered in the same department. IS were entirely made of acrylic resin and manufactured in cooperation with a dental technician. Alginate impressions of the patient's lower and upper jaws were taken. The shape of the IS relied on the anatomic configuration of the oral cavity of each patient. IS were fitted over occlusal surfaces of dentate regions or over unaffected alveolar ridges in order to assure a reliable position. The appropriate mouth opening was planned according to the radiotherapist advice and the maximum mouth opening possible for each patient. This recording was made during a second appointment by fixing the upper and lower acrylic plates with the use of base wax sheets for bite registration. In the definitive IS the plates were linked by an acrylic wedge in the anterolateral regions with a hole in the front to permit mouth breathing. The tongue depressor was positioned as part of the lower plate (Fig. 1). All IS were then adjusted before the beginning of RT in order to avoid possible discomfort and sore spots during treatment. Patients were carefully instructed how to wear the IS and clean it after use.

All patients then underwent a CT-plan simulation with and without the customized IS. Set up error and morphological changes in patient's anatomy, like tumor and normal tissue variations as a result of RT, location and shape of target volumes were daily estimated with IGRT with KV Cone Beam CT to improve the precision of radiation delivery. Patients were immobilized on a flat table in a supine position with head and shoulders thermoplastic masks. GTV was defined using both the radiological and clinical findings. Clinical and Planning Target Volume were defined in accordance with technical guidelines for Head & Neck cancer of the Italian Association of Radiation Oncology.[31] PTV coverage criteria were set according to the International Committee of Radiation Units and Measurement 50 (Table 1). Organs at risk were delineated with DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines.[32] Additional 3- and 5-mm margins were added to create a Planning Risk Volume (PRV) for the brainstem and spinal cord. Dose Volume Histograms (DVH) were calculated in order to evaluate the feasibility of the treatment plan according to the dose constraints. Three rotational VMAT plans were generated using one dual arc technique from 100° to −160°, from 180° to −179° and from 170° to −150°, respectively. The collimator angle was set at 5° and 10° using 6 MV photon beams commissioned for a Elekta Synergy with Agility linear accelerator equipped with a 160-leaves multi-leaf collimator (MLC) and kV Cone Beam CT (Elekta, Atlanta, GA, USA). Dose calculation was performed with the Optimization Module of RayStation V.7, Raysearch Laboratories, Stockholm, Sweden. VMAT schedule are shown in Table 2. The VMAT dose distribution plans were normalized such that 95% of the PTV was covered by 95% of the prescription dose with 2% of PTV that did not receive more than 107%. Set up error, volumetric localization of target volumes and organs at risk (OARs) and anatomical changes were evaluated daily with IGRT-CBCT in all patients. On-line correction was performed prior to each treatment to align target volumes relative to treatment beams using simple couch shifts. VMAT dose distribution for different OARs:

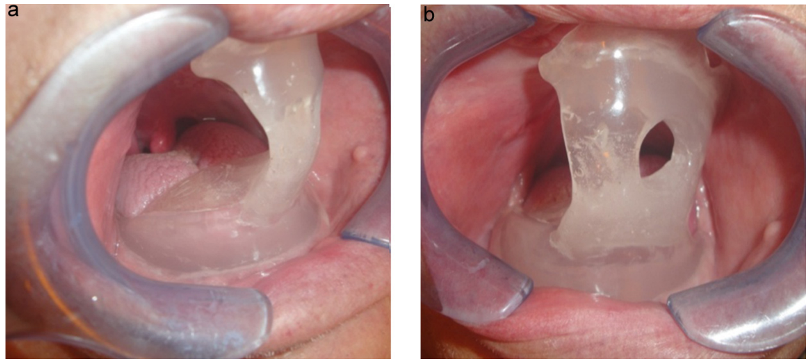

Fig. 1 – Intraoral stent. Clinical appearance of an IS in a patient with adenocarcinoma of minor salivary gland and hard palate following partial maxillectomy (right side). Lateral (a) and frontal (b) view. Main features of an intraoral device can be observed: acrylic plates fitting over alveolar ridges for support, the anterior acrylic wedge for displacement of jaws with a centered hole to permit breathing and the tongue depressor as part of the lower plate.

Table 1 – PTV coverage criteria set according to International Committee of Radiation Units and Measurement 50.

Patient (no.)	Plan dose	PTV[b] volume (cm^3)	Dose (Gy)[c]						
			D99	D98	D95	Average	D50	D2	D1
1	With IS[a]	155.14	61.88	62.83	64.08	66.25	66.35	68.66	69.22
	Without IS	129.77	62.26	63.36	64.59	66.45	66.50	69.09	69.93
2	With IS	106.80	57.30	57.94	58.69	60.00	60.12	61.03	61.16
	Without IS	102.30	57.46	58.00	58.92	60.16	60.24	61.39	62.16
3	With IS uncorrect	95.45	65.04	65.86	66.90	69.96	70.32	72.03	72.17
	Without IS	94.63	63.70	65.22	66.97	70.41	70.66	73.23	73.80
	With IS correct	94.36	59.84	61.99	65.33	69.91	70.57	72.50	72.73

[a] IS: intraoral stent.
[b] PTV T: Planning Target Volume.
[c] Gy: Gray radiation dose absorbed by human tissue (dose).

Table 2 – Oncologic and treatment features of three HN cancer patients.

Patient	Gender[a]	Age (y)	Risk factors	Primary site of H&N cancer	Hystology	TNM stage[b]	Margins	VMAT[c] schedule	
								PTV T[d]	PTV N[e]
1[g]	M	72	Smoker	Minory salivary gland/hard palate	Adenocarcinoma	pT4/pN0	R1	66 Gy[f]/33 fr	/
2[g]	M	82	Smoker	Nasal fossa	Adenocarcinoma	cT4b/cN0	/	64 Gy/32 fr	/
3[g]	M	63	Smoker/ alcohol consump- tion	Soft palate	Squamous cell carcinoma	cT1c/cN0?	/	69.96 Gy/ 33 fr	56.1 Gy/33 fr (SIB[g])

[a] M: male.
[b] TNM: tumor-node-metastasis (TNM) staging system.
[c] VMAT: Volumetric modulated arc therapy.
[d] PTV T: Planning Target Volume (tumor).
[e] PTV N: Planning Target Volume (lymph nodes).
[f] Gy: Gray, radiation dose absorbed by human tissue.
[g] SIB: simultaneous integrated boost.

oral cavity (tongue), mandible and parotid glands, were evaluated with and without IS in each patient according to the same optimal PTV coverage. DVH detail analyses of PTV and OAR (D99%, D98%, D95%, mean dose, D50%, D2% and D1%) were compared to choose the most appropriate dose delivery strategies.

All patients were affected by tumors located at the level or above the hard palate in an anterior position in the middle third of the face. The oncologic and treatment features of them are summarized in Table 2.

Patient #1: C.G. was diagnosed of adenocarcinoma of minor salivary glands and hard palate in September 2015, the patient was a smoker and was also affected by hypertension, obstructive sleep apnea syndrome and depressive disorder; he was treated with sertraline, amlodipine and losartan. He underwent a partial maxillectomy with selective lymphadenectomy (I–II–III), temporalis musculofascial flap for reconstruction of maxillary defect and post-operative VMAT in late 2015. The patient was edentulous, no dental treatments were necessary before RT.

Patient #2: R.S. was diagnosed of adenocarcinoma of left nasal fossa in September 2015, was a smoker and was in antihypertensive therapy (angiotensin-converting enzyme inhibitors and amlodipine) and used acetylsalicylic acid following biologic aortic valve substitution. Following preventive dental assessment, three teeth were extracted in both jaws (1.4, 1.8, 4.6) due to extensive caries. Fluoride trays were employed in this patient to prevent radiation induced caries.

Patient #3: S.V. was diagnosed of squamous cell carcinoma of soft palate in November 2016, he had a history of smoking and alcohol consumption and used acetylsalicylic acid for hypertension primary prevention and dyslipidemia. Three mandibular teeth (33.6, 3.4, 3.3) were extracted due to mucosal trauma on the opposite edentulous jaw.

Patients #2 and #3 underwent exclusive curative VMAT. All patients completed VMAT course as planned during multidisciplinary meeting with no interruptions.

The radiation doses received by three OARs (oral cavity, mandible and parotid glands) in each patient with and without IS are reported in Table 3. The mean mouth opening obtained with our IS in our series was 20 mm. The mean radiation doses proved to be lower in all patients. The reduction was more relevant for the subsite: oral cavity (tongue) where the calculated mean radiation doses with/without IS were (Gy): 7.13/25.94 (patient #1) (Figs. 1 and 2), 1.73/5.02 (patient #2) and 27.81/29.25 (patient #3) (Fig. 3). Mean dose reduction regarding parotid glands and mandible subsites was effectively less evident but always respectful of dose constraints for the parotid glands and mandible, except for patient #3. For this case, the IS was employed as well because of better protection of the oral cavity and mandible subsites (Table 3). It was generally easy for each patient to wear IS appropriately before every fraction, except for patient #3 who accidentally wore his device in a wrong position at the beginning of treatment. This patient was edentulous and had a mouth opening capability of more than 5 cm, he accidentally wore the IS by putting the maxillary edentulous alveolar ridge on the edge of the buccal flange of the IS instead of the maxillary base and furthermore moved the tongue above instead of under the tongue depressor. A VMAT plan was generated in order to evaluate the dosimetric impact of incorrect positioning. In this patient, the mean dose to the oral cavity was 35.77 Gy with IS misplaced, 29.25 Gy without IS and 27.81 with IS correctly positioned (Table 3 and Fig. 3). The patient was carefully assisted in properly wearing the IS and completed treatment without other complications or misfits. No specific IS-related side effects during RT were reported. In particular no decubitus was observed during RT. Patients were followed up during and after VMAT once a week and at fixed times (1–3–6 months) after the end of treatment. Acute toxicity, according to the RTOG classification[33] was mainly represented by grade 2 (G2) mucositis during RT (all patients), one patient showed skin erythema G1 (#1) and another one complained about skin erythema and patchy moist desquamation (G2) (#3); dysgeusia was reported just in one patient (#3). Xerostomia was observed to be mild (G1) in two cases (patient #2–3) during RT and remained stable or ameliorated during follow up. In one patient (#1) xerostomia became moderate (G2) at the end of RT; however, it slightly decreased (G1) within 14 days of the end of treatment. Late toxicity was represented by xerostomia and dysgeusia in one patient (#1). Oral mucositis was alleviated by the use of mucosal topic agents and rinses of sodium bicarbonate solution in all patients. Mucosal coating and lubricant agents as well as compounds of amino acids and sodium hyaluronate were employed in two patients within 7–15 days since the beginning of RT (#2–3). Oropharyngeal candidiasis affected one patient 15 days after the beginning of RT (#2). This patient was treated with systemic fluconazole (200 mg/die for 5 days, then 100 mg/die for 10 days) with complete resolution of symptoms and no relapse during continuation of RT. No radiation induced caries was detected in patient #2 during the follow up period. No signs or symptoms of osteoradionecrosis were detected during follow up in two patients. A millimetric bone exposure in the premolar region of maxillary alveolar ridge was observed 6 months after the end of RT in patient #3. A traumatic etiology during eating was hypothesized since the patient did not wear dentures. The exposure was surgically removed under local anesthesia and antibiotic therapy (875 mg amoxicillin + 125 mg clavulanic acid orally twice a day from the day before surgical intervention until day 6 after surgery) with piezoelectric surgical osteoplasty followed by primary wound closure with resorbable sutures. No recurrence of bone exposure was observed during follow up lasting for 8 months after surgical intervention.

With a median follow up of (15 months), two patients (#1 and #2) died. In particular, patient #1 died for distant spread while in patient 2# a recurrence in the right posterior ethmoid cells and medial orbital wall with endo-orbital invasion was diagnosed 14 months after the end of RT. Patient #3 is alive without evidence of recurrent disease.

3. Discussion

Despite advanced planning and delivery radiotherapy techniques, treatment of HN cancer remains a challenge because of elevated incidence of loco-regional recurrence and its serious side effects. Previous studies report that the use of intraoral stents, determining a physical spacer in the intraoral space, reduce the doses to normal tissues in order to decrease radio-induced toxicity.[14,23,25,29,30] The protection of normal tissue can be obtained by enhancing its displacement or by shielding it.[17,18,22,24–26] However, usefulness of IS in shielding normal tissues is a matter of debate because it does not protect from back scattered radiation due to the metal alloy used for their fabrication.[18,34] Furthermore it also introduces a major challenge in determining a correct dose distribution because of considerable artifacts in CT images.[35] In spite of these considerations, together with a few available data in

Table 3 – Radiation doses received by the oral cavity, mandible and parotid glands in three H&N cancer patients.

Patient (no.)	Plan dose	OAR[b]	ROI[c] volume (cm^3)	Dose (Gy[d])						
				D99	D98	D95	Average	D50	D2	D1
1	With IS[a]	Oral cavity	42.31	1.75	1.83	1.93	7.13	2.97	44.35	46.44
	Without IS	Oral cavity	73.66	2.21	2.3	2.48	25.94	14.37	75.1	76.49
	With IS	Mandible	53.53	0.44	0.46	0.51	6.54	1.32	38.57	43.81
	Without IS	Mandible	50.78	0.77	0.81	0.87	6.7	1.93	38.81	41.79
	With IS	Parotid gland left	31.74	0.72	0.76	0.85	3.47	2.28	12.04	12.84
	Without IS	Parotid gland left	30.49	0.7	0.73	0.81	2.98	2.04	9.45	10.02
	with IS	parotid gland right	36.63	0.76	0.83	0.95	4.35	2.46	14.08	15.3
	Without IS	Parotid gland right	34.75	0.84	0.89	1.01	4.46	2.65	14.07	15.21
2	With IS	Oral cavity	70.9	0.58	0.59	0.61	1.73	1.25	8.54	11.2
	Without IS	Oral cavity	100.92	0.47	0.49	0.54	5.02	1.46	41.13	49.77
	With IS	Mandible	75.82	0.19	0.21	0.27	2.46	0.8	17.04	18.41
	Without IS	Mandible	75.18	0.27	0.29	0.35	2.56	0.96	17.01	18.31
	With IS	Parotid gland left	23.28	0.4	0.41	0.45	2.33	1.09	10.54	11.93
	Without IS	Parotid gland left	22.43	0.4	0.42	0.46	2.2	1.09	10.22	11.31
	With IS	Parotid gland right	30.76	0.38	0.4	0.44	2.29	1	10.88	11.6
	Without IS	Parotid gland right	30.23	0.38	0.4	0.44	2.24	1	10.62	11.37
3	With IS no correct	Oral cavity	74.86	7.12	7.25	7.95	35.77	28.52	70.12	70.43
	Without IS	Oral cavity	70.17	7.26	7.42	8.12	29.25	21.91	70.01	70.36
	With IS correct	Oral cavity	75.12	7.09	7.25	7.89	27.81	19.4	69.76	70.01
	With IS no correct	Mandible	49.82	5.52	5.77	6.52	27.76	22.6	65.69	67.27
	Without IS	Mandible	45.06	5.6	5.91	7.3	30.62	27.32	65.92	67.23
	With IS correct	Mandible	49.68	5.54	5.83	6.6	27	21.17	64.63	66.72
	With IS no correct	Parotid gland left	15.44	8.22	8.42	8.94	23.76	18.38	55.35	56.36
	Without IS	Parotid gland left	15.49	8.02	8.3	8.87	25.76	19.85	57.84	59.17
	With IS correct	Parotid gland left	13.08	8.26	8.42	8.95	26.81	20.79	57.39	58.38
	With IS no correct	Parotid gland right	14.71	6.22	6.4	6.92	24.71	18.87	55.01	55.72
	Without IS	Parotid gland right	14.76	6.16	6.36	6.83	25.6	21.26	56.53	57.85
	With IS correct	Parotid gland right	11	6.63	6.85	7.47	28.16	23.95	58.03	58.99

[a] IS: intraoral stent.
[b] OAR: organ at risk (contourned).
[c] ROI: region of interest (dimension).
[d] Gy: Gray radiation dose absorbed by human tissue (dose).

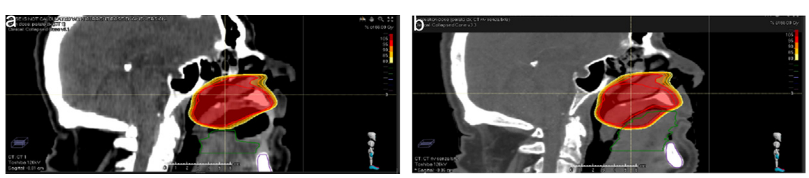

Fig. 2 – Dose distribution analysis. CT scan with dose distribution for IGRT–VMAT planning of the same patient as in Fig. 1 wearing (a) or not (b) an intraoral stent, respectively. The displacement of the contoured OAR: oral cavity (i.e. body of tongue green line) is evident when the stent is employed (a). The red colored area indicates the planned target volume. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

terms of efficacy,[17,18,22,24–26] some concerns remain about the use of shielding IS during RT for HN cancers, especially in association with conformational RT techniques (e.g. IMRT, VMAT). Another favorable feature of the combination of IS and conformational RT techniques is the stabilization of the patient's position during a multiple-sessions treatment. This combination seems significantly associated with reduced interfraction setup errors during IMRT.[16,27,28] In our series, we evaluated the DVHs in order to compare the dosimetric analysis in IGRT–VMAT planning with and without the employment of customized IS in the RT of H&N cancers. Since we were mainly interested in the adverse effects of radiation affecting the oral environment not involved by cancer, three specific OARs were contourned (oral cavity, mandible, parotid glands). In our case series the combination of IS plus IGRT/VMAT determined a reduction of radiation doses in healthy tissues: the extent of reduction depending on cancer site and correct stent position. As Najar reported, the dose reduction may not be observed in some clinical conditions, such as tumors involving structures near both jaws or large nodes and oropharyngeal cancers. In these situations, the jaw separation is less evident as it moves posteriorly so the biological benefit of IS is smaller.[16] Considering the mechanism of action of IS, we were not surprised by the fact that the reduction was more relevant in the subsite nearer tumor (i.e. oral cavity). However, a slight reduction in mean radiation doses was also achieved in the other two OARs

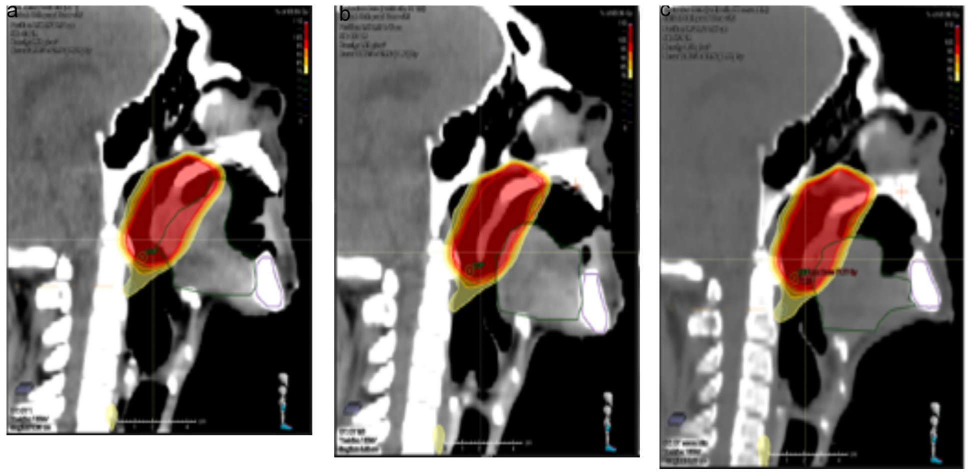

Fig. 3 – Dose distribution analysis. CT scan with dose distribution for IGRT–VMAT planning of the patient with squamous cell carcinoma of soft palate wearing incorrectly (a), correctly (b) or not wearing (c) an intraoral stent, respectively. The unfavorable displacement of the body of tongue when the device is wrongly worn can be seen. In this case the entire upper surface of the body of tongue was included in the planned target volume (red colored area) (a). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

considered. The correct position of such devices is important for the daily reproducibility of RT.[27] We found that an inappropriate positioning of these devices can lead to an increase in dose to OAR, too. This was possible thanks to the use of CBCT performed daily before each treatment session. A wrong placement of IS determined an increase in mean radiation dose to the oral cavity which outstood the mean radiation dose associated with the absence of IS in one patient. Our experience suggests that daily assessment of patient position and appropriate matching to treatment plan is crucial, especially when using IS.

Mucositis is one of the most common radio-induced toxicities: some authors reported taste alteration improvement and a decreased incidence and severity of mucositis and xerostomia with the use of IS, probably determined by the maxilla and the parotid glands exclusion from the radiation field.[20,21]

IS were found to be effective in reducing incidence or delaying the occurrence of severe mucositis[15,18,20–22] salivary alterations,[21,23–25] trismus,[16,24] dysgeusia,[20,24,25] dysphagia,[24,25] dental caries, pain[24] and in providing better scores in quality of life tests.[23] According to the existing data, in our patients, the acute radiation toxicity was mild or moderate; we did not observe any signs or symptoms of third grade toxicity. No interruptions of treatment occurred in our series.

Since this study took place in a national health service hospital, we were also interested in cost effectiveness of the implementation of advanced highly conformal RT techniques with IS. IS are custom made prosthetic devices; they can be obtained with easily and rapidly in office procedures. They are low cost devices as made entirely with acrylic material. So, they can be a suitable dose sparing aid in our setting. Nowadays, definitive indications regarding IS use are not defined yet, even if some authors pointed out that they could be useful in the irradiation of tongue or nasopharynx cancers.[14,20,21,23,27–30] The lower incidence of HN cancers located above the hard palate in the middle third of the face should be taken into account. Indeed, the global incidence of nasopharynx cancers is reported to be almost 3 times lower than cancers affecting the oral cavity and lip.[1]

4. Conclusions

To the best of our knowledge, there is little clinical experience regarding the efficacy of IS in combination with highly conformal RT techniques and, specially, IGRT/VMAT.[14–16,27,28] Dosimetric data with experimental oral phantoms revealed promising results regarding the protection from oral mucositis in combination with IMRT–VMAT and IS.[36] Since RT is a fundamental and frequent treatment modality in H&N cancer management,[5] great advances have been made in the development of highly conformal RT techniques, such as IMRT[11] and VMAT.[37,38] Nevertheless, several RT side effects continue to deteriorate the quality of life of HN cancer patients during and after treatment. We observed that the combination of IS and VMAT was able to further diminish radiation doses to OARs. This permitted a better tolerance to treatment with no need for suspension. However, our experience suggests that correct positioning of such devices is crucial in determining the desired dose sparing effect to normal critical tissues. A significant impairment of functions related to the oral cavity (e.g. chewing, swallowing, talking) is strongly associated with cancer therapy.[39] The combination of IS with highly conformal RT techniques could be of some help in reducing adverse effects of RT and spare oral hard and soft tissues that could be more safely manageable also in terms of subsequent prosthetic rehabilitation and dental implant placement. This results in enhanced masticatory function and better quality of life.[40] Further studies are needed to define the significance of the benefit of intraoral stents in sparing adjacent OARs by decreasing the related radiotherapy toxicity and to establish which HN cancers could better benefit from IS use.

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Conflict of interest

None declared.

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