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Intensity modulated radiation therapy and oral mucosa sparing in Head and neck cancer patients: A systematic review on behalf of Italian Association of Radiation Oncology – Head and neck working group

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ABSTRACT

Oral mucositis is a common dose-limiting toxicity during radiotherapy with or without chemotherapy in head and neck cancer patients. This potentially severe complication globally worsens quality of life and negatively impacts local control and survival's outcomes.

Several studies have been published on feasibility and/or clinical benefit of intensity modulated radiotherapy (IMRT) mucosa-sparing technique. In 2017, the Italian Association of Radiation Oncology Head and Neck Cancer Working Group organized a study group to perform a systematic review. The aim was to verify if practical indications, including dose-constraints and demonstrated clinical benefit, could be proposed for oral mucosa (OM)-sparing IMRT in order to reduce the incidence of severe acute mucositis. Although dose to OM should be reduced as much as possible without compromising target volumes coverage, it is still tricky to firmly state that OM-sparing procedure should be considered the standard of care, especially due to high subjective variability in OM contour.

1. Introduction

In head and neck cancer (HNC) patients, oral mucositis is a common dose-limiting and potentially severe complication encountered during radiation therapy (RT) with or without concomitant chemotherapy. Generally, oral mucositis causes significant pain, interferes with chewing and swallowing, and substantially worsens patients' quality of life (Lalla et al., 2014; De Sanctis et al., 2016).

Almost all HNC patients, especially those who undergo concomitant chemoradiotherapy (CRT), may develop oral mucositis during treatment, but the real risk of severe painful oral mucositis interfering with oral intake is still unpredictable (Cinausero et al., 2017; Bossi et al., 2017). Onset and severity of oral mucositis can be affected not only by primary tumor parameters (localization, tumor stage), but also by treatment-related variables (total dose, field size, type of energy, fractionation, concomitant systemic therapy, schedule) and patient-related factors (individual sensibility, general health, old age, poor hygiene and dental status, voluptuary habits). Concomitant systemic therapy mainly includes platinum-based drugs – alkylating agents that inhibit DNA replication – and a monoclonal antibody – that competively binds the epidermal growth factor receptor, providing primarily cell-cycle arrest and inhibition of angiogenesis – (De Sanctis et al., 2016). Systemic therapy tends to produce mucositis due to a direct damage interfering on mucosal cell-cycle and as a result of changes in microbial flora and

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Table 1
Research questions according to PICO criteria.

#Query	Population	Intervention	Comparison	Outcomes
#1	Head and neck cancer patients	OM-sparing IMRT with or without concomitant chemotherapy	IMRT treatment without OM-sparing, with or without concomitant chemotherapy	dosimetric correlations between acute severe OM and OM dose

myelosuppression (De Sanctis et al., 2016). The evidence of patient-related factors increases the risk of a more severe manifestation, imposing an adequate assessment, support and surveillance, especially in term of habits, comorbidities and oral hygiene (De Sanctis et al., 2016). Currently, in HNC RT treatment, either in definitive or postoperative setting, intensity modulated RT (IMRT) is the recommended technique due to its ability to assure high target coverage while minimizing dose exposure to surrounding organs at risk (OAR).

Although the use of IMRT can reduce the dose to oral mucosa (OM) from target coverage, on the other hand multibeam circumferential IMRT dose arrangement tipically spreads intermediate-low dose to non-target OM tissue. So that, despite IMRT could potentially decrease severe oral mucositis onset and its associated short- and long-term morbidity, the incidence of severe oral mucositis with IMRT without OM-sparing strategy, ranges between 20% and 100% (Kouloulias et al., 2013).

This paper aims to verify if practical indications, including dose-constraints and demonstrated clinical benefit could be made for OM-sparing IMRT in order to reduce the incidence of severe acute mucositis

2. Methods and material

The participants (VDS, AM, FDF, MT, IDO, LL, MM, RF, FB, AB, FP) were chosen on a voluntary basis among the Head and Neck Cancer Working Group (HNCWG) of the Italian Association of Radiation Oncology (AIRO) members. The group was coordinated by an expert head and neck radiation oncologist (VDS). A specific topic has been assigned to each member. The first draft (March 2018) was reviewed by all the HNCWG members in order to discuss critical issues and to homogenize the manuscript structure. The revised draft was again reviewed by 3 radiation oncologists with particular expertise in head and neck IMRT (AB, FP and AM).

2.1. Search strategy

The key issue was formulated according to the PICO (population, intervention, control, outcomes) criteria (see Table 1). Medline, Embase, Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Register were searched for relevant citations published from January 2006 to December 2016. Literature data were also included using handsearching (meeting proceedings of European Society for Radiotherapy & Oncology and American Society of Radiation Oncology). Two independent authors (VDS and AM) selected studies based on title and abstract. Reference lists of identified studies were also explored.

Search strategy is shown in Table 2.

2.2. Selection criteria for full-text article review

Studies were eligible if: 1) they were written in English language and published as full paper in peer-reviewed journals; 2) they had accrued HNC patients treated with IMRT; 3) their results recorded acute grade 3 mucositis rate and/or treatment interruption. Both interventional and observational study design types were included. Case reports, commentaries and letters were not included. Search results are shown in Table 3. Finally, a total of 10 articles met the inclusion criteria.

2.3. Data collection

Two independent investigators (VDS and AM) extracted data. Data from each study were tabulated and included authors, years of publication, simple size, treatment details and incidence of oral mucositis.

2.4. Data analysis

All authors performed data analysis. We assigned the retrieved studies to three categories reporting respectively: i) dosimetric and radiobiological parameters; ii) OM definition and contouring; iii) mucositis in IMRT treatment plan with or without OM-sparing.

Results are summarized in Table 4.

Statistical analysis was not feasible due to high heterogeneity of the studies. Risk of bias assessment was only reported for the randomized trial (Table 5).

3. Results

3.1. Dosimetric and radiobiological parameters

Statement: Although several studies have shown a trend of biologically effective dose (BED) to OM and severe oral mucositis incidence, a clear dose-toxicity relationship can not be unequivocally determined.

In the last few years, there has been a growing interest in HNC radiobiological modeling, in order to identify dosimetric parameters able to accurately predict both tumor and toxicity outcomes. Dose-volume information on target volumes and normal OM seems to be a crucial point to predict OM toxicity, in particular when concomitant chemotherapy is given (Hartley et al., 2011, 2010; Bhide et al., 2010).

Rosenthal et al showed a > 33.5 Gy dose correlation to anterior or lateral mandible and anterior oral mucositis onset (Rosenthal et al., 2008). In a retrospective analysis, oral and pharyngeal mucosal dose-volume histograms (DVHs) were generated for 253 HNC patients in order to identify dosimetric parameters that predict severe oral mucositis risk (Otter et al., 2015). Patients received IMRT alone or CRT (following induction chemotherapy in 84% cases). Several dose-volume constraints were obtained from entire individual patients DVHs, but only mean dose to OM resulted a significant predictor of G3 oral mucositis.

Similarly, in a retrospective analysis of 88 HNC patients, Werbrouck et al. described a positive correlation between the risk of confluent mucositis and the mean dose to the oral cavity (Werbrouck et al., 2009).

Shogan et al. showed a statistically significant correlation between

Table 2
Search strategy: identification of citation to submit for inclusion criteria.

Database	Date searched	#	Search terms	Citations
Embase + Medline	2006- 2016	1	'head and neck cancer'/exp OR 'ent cancer' OR 'orl cancer' OR 'cancer, head and neck' OR 'cervicofacial cancer' OR 'ear nose throat cancer' OR 'head and neck cancer' OR 'head neck cancer' OR 'otorhinolaryngeal cancer' OR 'otorhinolaryngologic cancer' OR 'otorhinolaryngological cancer'	15643
		2	'mucositis' OR 'IMRT' OR 'intensity-modulated radiotherapy' OR 'mucosa' OR 'mucosa-sparing'	1105
		#1 AND #2		186
		4	#3 AND (2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016)	129
Cochrane Library/ Cochrane Central Register of Controlled Trials	2006- 2016	#1	'head neck cancer'	3970
		#2	#1 and 'mucositis' OR 'IMRT' OR 'intensity-modulated radiotherapy' OR 'mucosa' OR 'mucosa-sparing'	36
Manual search				5
Total number of unduplicated citation				**144**

acute mucositis grade and percentage of volume of oral cavity receiving 15, 30, 40, and 45 Gy (Shogan et al., 2005). In a retrospective analysis on 351 patients Dean et al. found that the volume of OM receiving more than 2.2 Gy per daily fraction was strongly associated with severe mucositis (Dean et al., 2016). Moreover, Narayan et al showed that the cumulative dose to the oral cavity greater than 39 Gy were related to severe mucositis and longer duration (Narayan et al., 2008). Yahya et al., instead, failed to show a relationship between dosimetric parameters derived from OM contours and the duration of G3 oral mucositis or opiate use in a retrospective analysis on 66 patients treated with IMRT for oropharyngeal cancer (Yahya et al., 2016).

Globally, although the vast majority of these studies showed a relationship between cumulative radiation dose delivered to the OM and the incidence of grade 3 oral mucositis, definitive conclusions cannot be drawn. Several factors should be considered: firstly, the non-homogeneous OM contouring method; secondly, the different radiobiological algorithms used to compute the dose to the OM; thirdly, the different grading scales for oral mucositis used. Moreover, a different radiobiological sensibility of different OM parts, such as buccal mucosa, mucosa of the ventral tongue, floor of the mouth and soft palate cannot be excluded (Narayan et al., 2008). Surely, in the near future, it would be desirable to establish a valid dosimetric relationship between the dose distribution to OM, contouring as OAR, and toxicity, to reduce the risk of severe oral mucositis.

3.2. Definition and contouring oral mucosa volume

Statement: Although OM-sparing IMRT seems to be a promising and attractive approach to decrease the severity of acute mucositis, there is currently no standard method for contouring OM volume.

The OM surface has a complex anatomical shape and it is poorly visualized on computed tomography (CT). Therefore, the definition of OM surface as OAR is very challenging. Several authors have proposed different methods for OM contouring. Sanguineti et al. defined OM as a single solid volume encompassing the oral cavity, including buccal mucosa, oropharynx, and hypopharynx (Sanguineti et al., 2006). Werbrouck et al. contoured the oral cavity volume in a similar way, including the buccal mucosa, but excluded the air within the cavity (Werbrouck et al., 2009). The surfaces of the inner lips, buccal mucosa, tongue, base of tongue, floor of mouth and palate composed a distinct organ, “oral cavity” (extending to include the surface of the base of tongue) in the paper of Eisbruch et al (Eisbruch et al., 2001). Finally, Van de Water et al. divided OM into smaller substructures to establish which substructures, if any, are most radiosensitive but only for xerostomia-related endpoints (van de Water et al., 2009). Recently practical CT-based guidelines for contouring OAR in the head and neck region were published. Authors provided recommendations for oral cavity, lips and buccal mucosa delineation (Charlotte and Brouwer, 2015). The mucosa of the oral cavity was delineated into a “virtual solid volume”, named extended oral cavity, occupying the entire oral cavity. The extended oral cavity was defined as a structure posterior to the internal arch of the mandible and maxilla without including the inner surface of the lips. It was comprehensive of hard palate mucosa, base of tongue, posterior borders of soft palate and uvula, inner surface of the mandible and maxilla. The delineation of buccal mucosa and lips was included to obtain a complete clinical scenario.

Dean et al. proposed a novel contouring method to delineate OM, based only on mucosal surfaces of the oral cavity (Dean et al., 2015). The mucosal surface was defined as a 3 mm thick wall of tissue of the following surfaces: buccal mucosa, buccal gingiva, proper gingiva, lingual gingiva, lingual frenulum, alveolar mucosa, labial mucosa, labial gingiva, labial frenulum, mucosal surface of the floor of mouth, mucosal surface of the anterior tongue up to the terminal sulcus, and the hard palate mucosal surface. The contouring was performed mainly on coronal and sagittal CT slices, initially as a single line and after expanded to a 3 mm annulus. The coronal and sagittal slices were

Table 3
Search results: abstracts screened for eligibility and inclusion of full papers.

Records after duplicates removal: n = 144	
Records screened on title/abstract: n = 26	Records excluded: n = 118
Full text articles assessed for eligibility: n = 12	Full text articles excluded n = 2 (wrong population = no IMRT)
Studies included in qualitative synthesis: n = 10	

preferred in presence of artifacts due to dental implants that may hinder mucosal contouring on axial slices. An atlas-based segmentation was used, so the delineation process was semi-automated. This method provided a more anatomically representative contour of the OM but it should be tested in a large cohort of patients with oral mucositis rate data.

3.3. Incidence of acute mucositis after IMRT treatment with or without OM-sparing

Statement: Despite limits in OM definition and contouring, the OM-sparing IMRT approach seems to be correlated with a reduced risk of acute mucositis and percutaneous endoscopic gastrostomy (PEG) placement. Dose to OM should be limited to 30–32 Gy.

IMRT represents the standard RT technique in HNC, due to its ability to conform higher doses to target volumes minimizing dose to the surrounding OAR (Marta et al., 2014). Whilst selective sparing of parotid glands improves salivary flow rates and quality of life compared to 3D-conformal RT (Nutting et al., 2011; Scott-Brown et al., 2010), other head and neck regions may receive higher doses, resulting in additional toxicities that may limit IMRT therapeutic advantage (Rosenthal et al., 2008). In fact, because of seven to nine beams, several non target areas, as non-target oral mucosa, previously spared due to 3D-conformal two opposed lateral beam approach, are now exposed to low/intermediate doses. It may result in different pattern of oral mucositis that was uncommon in the 3D-conformal RT era (Rosenthal et al., 2008).

Due to the paucity of therapeutic options to prevent and/or treat acute oral mucositis, a OM dose-sparing could represent an optimal strategy to reduce its risk. Several studies investigated whether dose to non-target OM can be minimized when planning radiation treatment. Details are listed in Table 4. Independently of concomitant chemotherapy, OM-sparing seems to be associated with little effect on severe mucositis incidence, but no definitive conclusions can be drawn. In fact, the vast majority of studies were retrospective, therefore oral mucositis rates could be underestimated and results were hypothesis generating rather than confirmatory. Moreover, data were further limited by heterogeneous inclusion criteria, both patient- and treatment-related. Putting all different primary tumor subsite together represented the main bias.

Sanguineti et al. analyzed the potential OM-sparing effect if IMRT is adopted. Dosimetric data revealed a significant decrease in oral mucositis rate if normal oropharyngeal mucosal wall received doses lower than 30 Gy (Sanguineti et al., 2006). Moreover, an absolute dose of 9.5 Gy per week was associated with a higher need for feeding tube during IMRT treatment (Sanguineti et al., 2011, 2013). Whereas, reducing the percentage of OM volume (below 50-60 cm^3) exposed to doses greater than 9.5–10 Gy per week may result in a significantly decreased risk of PEG placement (Sanguineti et al., 2013). A dosimetric analysis of oropharyngeal cancer patients submitted to CRT with OM-sparing IMRT revealed a statistically significant correlation between mucositis risk and both radiation dose to OM and use of concomitant chemotherapy (Sanguineti et al., 2012). OM data were extracted as absolute cumulative DVH, corrected for the elapsed treatment days and reported as weekly. The occurrence of severe oral mucositis was related to the dosimetric value of 10.1 Gy per week (V10.1) and OM volume of 21 cc (D21). On multivariate analysis, D21 and concomitant chemotherapy were the only independent predictors of acute mucosal toxicity. Although this study included only oropharyngeal cancer cases, its dosimetric data should be considered in HNC IMRT treatment to reduce the incidence of severe acute mucositis. Moreover, it should be reminded the negative impact of concomitant chemotherapy on acute mucositis onset, despite of OM-sparing technique.

Recently, a prospective randomized trial has been conducted to compare the severity of acute mucositis in patients who received adjuvant IMRT with or without OM-sparing for oral tongue cancer (Wang et al., 2012). In 24/48 patients with oral tongue cancer who were treated with adjuvant IMRT, the mucosa including the bilateral cheeks, upper lip, and lower lip was defined as united site and received less than 32 Gy. Compared to OM-unsparing approach, OM-sparing resulted in significant lower incidence of G2-3 oral mucositis (0% and 25% versus 45.8% and 54.2%, respectively) and significant reduction in analgesics use without compromising local control.

4. Conclusion

Despite significant advances in radiation techniques, oral mucositis still represents a common and multifactorial side effect during IMRT treatment in HNC and it seems to be affected by both patient- and treatment-related parameters. Close attention should be paid to minimize dose exposure to OM and it may be possible with OM-sparing approach. However it is difficult to firmly state that OM-sparing procedure should become the standard, especially due to the high subjective variability in OM contour. The risk of severe oral mucositis significantly increases over 32 Gy. Therefore, dose to OM should be reduced as much as possible, without compromising target volumes coverage. Ideally, OM dose limit should be 30 Gy. New dose-volume constraints should be described to better define OM-sparing clinical benefit in IMRT treatment plan. Given their potential consequences in terms of treatment tolerance, prospective studies based on OM DVH analysis should be proposed. Study end-points should shift towards functional outcomes, including onset and duration of severe oral mucositis and incorporate patient-reported toxicity outcomes. At present, more precise dose-volume parameters, as well as OM anatomic boundaries definition should be paramount to reduce subsequent oral mucositis incidence in HNC. Undoubtedly, optimal primary tumor coverage remains a top priority over toxicity risk.

Table 4
Key characteristics and description of studies included.

Study	Type of study	N° of patients	subsite	treatment	Delineation method for OM	OM-sparing IMRT	Dose constraint for G3 OM	Statistical analysis	Incidence of G3OM
Rosenthal et al., 2008	retrospective	160	oropharynx	58% RT, 42% CRT	Anterior mucosa: lower lip; anterior, mid, and posterior segments of the maxilla and mandible	no			9% RT 22% CRT
Otter et al., 2015	retrospective	253	Oropharynx, nasopharynx, larynx, hypopharynx,	74% IC 86% CRT	Entire volume (as opposed to volume outside PTV) of each OAR. The superior border of this volume was the hard palate. The inferior border was the superior aspect of the vallecula.	no		MD to OM significant at MVA	46%
Werbrouck et al., 2009	retrospective	88	Larynx, oropharynx, oral cavity, CUP	50% postoperative RT ort CRT, 50% radical treatment (16% CRT)	The entire oral cavity was contoured	no		a statistically significantly higher Dmean to the oral cavity was found for the G3 + OM G0-2 group (p = 0.042).	31%
Shogan et al., 2005	retrospective	70	Not declared	CRT	Not declared	no	statistically significant correlation between acute G3 OM and the V15, 30,40,45		16%
Yahya et al., 2016	retrospective	66	oropharynx	CRT	4 different methods for each patient	no	No dosimetric parameters correlation for the duration of G3 OM or duration of opiate use		100%
Dean et al., 2016	retrospective	351	Various sites	29% RT, the others CRT	mucosal surface contours (3 mm thick wall of tissue of the surfaces of structures of oral cavity)	no	the volume of OM receiving more than 2.2 Gy per fraction had the strongest association with the incidence of severe mucositis.	The volumes of oral cavity receiving intermediate and high doses were associated with severe mucositis.	73%
Sanguineti et al., 2013	retrospective	164	oropharynx	57% CRT, 22% altered fractionation	mucosa of the oral cavity, oropharynx, and hypopharynx	yes	At multivariate analysis, cCHT (odds ratio [OR] = 4.118; 95% CI, 1.659–10.217; $p = 0.002$) and D21 (OR = 1.016; 95% CI, 1.009–1.023, $p < 0.001$) were the only independent predictors	the amount of OM exposed to 10.1 Gy/week as independent predictors of the development of G3OM. cCHT increases the risk of G3-OM 4 times over RT alone	78.7%
Sanguineti et al., 2011	retrospective	59	oropharynx	RT (42% hyperfractionation)	mucosa of the oral cavity, oropharynx, and hypopharynx	yes			81.3%
Wang et al., 2012	Randomized trial	48	Oral tongue	Postoperative IMRT	bilateral cheeks, upper lip, and lower lip was defined as the united site	24 randomized to OM-sparing IMRT			25% vs 52% (P < 0.05)

Abbreviations OM: oral mucositis; IMRTIntensity Modulate Radiation Therapy; RTRadiation Therapy; CRTChemoradiotherapy; PTVPlanning Target Volume; OAROrgan At Risk; ICinduction Chemotherapy; MDMedian Dose; MVAMultivariate analysis; D meanmean dose; V15, 30,40,45Volume of the considered organ/tissue that receive 15, 30, 40, 45 Gy; cCHTconcurrent Chemotherapy.

Table 5
Risk of bias assessment.

Study	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study free of other problems that could put it at a high risk of bias?	Summary assessement
Wang et al., 2012	Not clear	no	yes	yes	No (calculating the dose at a reference point instead using dose-volume characteristics of the oral mucosa may introduce some bias)	High risk of bias

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