Comparison of the incidence of osteoradionecrosis with conventional radiotherapy and intensity-modulated radiotherapy

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ABSTRACT: *Background.* Modern techniques of radiotherapy are supposed to decrease the incidence of osteoradionecrosis of the mandible (ORNM). The purpose of this study was to compare the incidence of ORNM after intensity-modulated radiotherapy (IMRT) in comparison to conventional 3D conformal radiotherapy techniques (conventional RT).

Methods. We conducted a retrospective study of consecutive unselected patients treated in a single institution between 2002 and 2012. To minimize confounding effects, only patients with oropharyngeal carcinoma without surgery of the primary site were included.

Results. The cohorts included 145 patients in the conventional RT group and 89 patients in the IMRT group. Total incidence rate of ORNM was similar for both groups with rates of 11% versus 10% ($n = 16$ for conventional RT and $n = 9$ for IMRT; $p = 1.0$). Subanalysis revealed more ORNM in T4 classified lesions with IMRT ($p = .007$). Analysis of different risk factors showed no statistically significant difference between ORNM and no-ORNM patients.

Conclusion. We found no reduction in ORNM with IMRT. © 2016 Wiley Periodicals, Inc. *Head Neck* **38:** 1695–1702, 2016

KEY WORDS: oropharynx, head and neck, cancer, radiotherapy, intensity-modulated radiotherapy (IMRT), osteoradionecrosis

INTRODUCTION

Osteoradionecrosis of the mandible (ORNM) is one of the most devastating delayed complications of radiotherapy (RT). One pathogenesis theory[1] involves hypovascularity, hypocellularity, and hypoxia of the bone, leading to a deficient bony remodeling and fibrosis.[2] Radiation-induced endarteritis is a known side effect of irradiation and radiation-induced bone hypoxia has been clearly demonstrated.[3] Because the blood supply of the posterior horizontal branch of the mandible depends solely on the inferior alveolar artery,[4] this zone has the highest incidence of osteoradionecrosis (ORN) of any human bone.[2] The fibro-atrophic pathogenesis theory is complementary and emphasizes cellular and metabolic mechanisms: increased bone resorption by osteoclasts and decreased bone formation by osteocytes[5,6] leading to a decrease in mineral bone volume and hypocellularity.[6,7] This deficient bone remodeling leads to bone replacement with fibrosis that is mechanically and metabolically suboptimal.[2]

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Etiologic factors discussed in the relation to ORNM can be seen as related to the tumor, the patient, and/or the radiation.[8] Tumor-related factors have an impact on the mandible by influencing the radiation dose (proximity of the tumor to the mandible, tumor size) or by directly impairing the integrity of the bone (mandibular invasion by the tumor or mandibular resection). Patient-related factors also influence mandibular integrity because of the presence of dental disease, poor oral hygiene, and through comorbidities with impact on the vascular supply (eg, diabetes) or bone structure (eg, osteoporosis). These patient-related factors often lead to dental extractions which, if performed shortly before (within 2 weeks) or at any time after radiation, have been viewed as a major predisposing event for ORNM.[9] Finally, radiation-related factors deal mainly with the radiation dose, especially when greater than 65 Gy, and radiation field's size.[10,11] Although most of these factors remain beyond the control of the cancer treating physician, the biological mechanisms involved seem to be related mainly to the radiation dose administered and to the injury of the blood supply.

The incidence of ORNM seems to be progressively declining from about 20% in the 1940s[12] to 3% in the 2000s,[10] probably because of a better recognition of the causative factors and prevention. The advent of intensity-modulated radiotherapy (IMRT) raised the possibility of better sparing noninvaded tissues, including the mandible,

while delivering similar or higher doses to the tumor. Indeed, initial studies have shown absent or very low rates of ORNM, below 1%.[13–16]

The primary purpose of our study was to compare the incidence of ORNM after IMRT and after conventional RT. To minimize confounding factors introduced by preradiation surgery, only oropharyngeal carcinoma without surgery of the primary tumor were included. Secondary purposes were to identify potential risk factors and to compare overall survival and local recurrence in both groups.

MATERIALS AND METHODS

Study population

We retrospectively analyzed all consecutive patients who were treated for oropharyngeal carcinoma with radiotherapy with a curative intent, with or without concomitant chemotherapy, between the years 2002 and 2012. Consecutive, nonselected patients were identified through the head and neck multidisciplinary tumor board database. Exclusion criteria included palliative treatment, surgery at the primary site besides tonsillectomy, nonconventional radiation protocols, such as brachytherapy, and patients lost to follow-up.

The included cohort was divided in 2 groups: in one group were patients irradiated by conventional RT[17] mainly in the period between 2002 and 2007, whereas the second group included patients treated with IMRT, which was introduced in 2007 at our institution.

All patients underwent panendoscopy, had biopsy-proven squamous cell carcinoma, and underwent radiological evaluation, either by CT scan or MRI. The seventh Union for International Cancer Control classification was used for staging. According to our treatment policies, some patients underwent upfront neck dissection for bulky neck metastasis before radiotherapy.[18]

Dental evaluation and follow-up

Every patient received a dental evaluation within a week of the tumor board decision by the same oncology-trained dentist team. Dental guidelines did not change during the study period: conservational dental treatment was preferred in restorable teeth outside of the radiation fields, whereas nonrestorable teeth were extracted at least 2 weeks before the beginning of radiation. Patients were instructed about the side effects of radiation on the buccal mucosa, saliva, and teeth. The risks of ORN were explained, the importance of oral hygiene highlighted, and fluoride treatment with custom-made dental trays used in all patients.

Radiation treatment

CT-based treatment planning was used for all patients. Conventional radiation technique protocols used were previously described as a progressively accelerated concomitant boost schedule[17]: a total dose of about 69.9 Gy was delivered in 41 fractions over a period of 38 days. The first volume (generally the primary tumor area and both sides of the neck down to the clavicles) received a dose of 50.4 Gy in 28 fractions over 38 days given in daily fractions of 1.8 Gy, 5 times a week. The boost to the initially involved sites was delivered in 13 fractions of 1.5 Gy (total of 19.5 Gy) given as a second daily fraction in the last 17 days of treatment. The minimum interval between the 2 daily fractions was 6 hours. The majority of the patients were treated with 2 opposed lateral fields and 1 anterior field, using 6 MV photon beams.

For IMRT, the beam fluency was modulated by computer optimization to produce the best conformal plan, using 5 to 7 beam ports, with 6 MV energy photons. The prescribed dose was 69.96 Gy to the primary tumor and positive nodal volumes, and 52.8 Gy to the prophylactic neck regions, using a simultaneous integrated boost technique, delivering, in 33 fractions, 2.12 Gy and 1.6 Gy, respectively, once a day, 5 times a week, over 45 days.

Follow-up

After completion of treatment, patients were followed at the head and neck and radiation oncology clinics monthly during the first year; the interval was increased by 1 month each year until the fifth year, and then annually. In addition, regular biannual follow-up with a dental hygienist were scheduled. Minimal oncologic follow-up was 3 years.

Patients with exposed bone and with radiological suspicion of ORNM were referred to the maxillofacial clinic for further evaluation and treatment. The outcome of the treatment of ORNM is not part of this study.

Osteoradionecrosis

Presence of ORN was searched for by reviewing every medical record of follow-up consultations at the radiotherapy and head and neck clinics, as well as by reviewing every procedure, pathology, and radiology report since the end of treatment in the hospital digital records.

ORNM was diagnosed on clinical findings. Asymptomatic patients with the radiological diagnosis of ORNM were not included. ORNM was defined according to the description of Marx as any area >1 cm of exposed bone in a field of irradiation that failed to heal for at least 3 months and that is not caused by tumor recurrence.[1] Some cases presented without exposed bone but with prolonged mandibular pain and the diagnosis was confirmed radiologically.

ORNM severity was classified according to Schwartz and Kagan[19] in 3 stages: stage I consists of soft tissue ulceration with exposed cortical necrotic bone; stage II corresponds to medullary bone necrosis; and stage III is a diffuse mandibular involvement with full thickness necrosis down to the lower border of the mandible.

Radiation doses to the mandible and parotid glands

In patients with ORNM, detailed radiotherapy plans were searched for and the doses to the mandible and parotid gland were retrieved. Regarding the mandible, the following parameters were included: the maximal point dose (Dmax), the mean dose (Dmean), the dose received by 2% of the mandibular volume (D2), as well as V50, V60, and V70 (mandibular volume receiving 50, 60, and 70 Gy, respectively). For the parotid gland, we report the Dmean delivered to the ipsilateral (parotid on the same

TABLE 1. Patient characteristics in the conventional radiotherapy techniques and the intensity modulated radiation therapy groups.

Characteristics	Conventional RT	IMRT	*p* value
No. of patients	145	89	
M/F ratio	0.79	0.74	.43
Age, y	60.5 ± 9.6	61.1 ± 9.8	.63
Median follow-up	4.9 ± 4.0	3.2 ± 1.8	< .001†
Subsite			.48
Tongue base	47 (32%)	28 (30%)	
Tonsil	67 (46%)	46 (50%)	
Posterior wall	10 (7%)	8 (8%)	
Soft palate	21 (15%)	11 (12%)	
T classification			.38
1	21 (15%)	13 (15%)	
2	54 (37%)	40 (45%)	
3	28 (19%)	18 (20%)	
4	42 (29%)	18 (20%)	
N classification			.69
0	24 (17%)	18 (20%)	
1	24 (17%)	18 (20%)	
2a	9 (6%)	5 (6%)	
2b	51 (35%)	22 (25%)	
2c	33 (23%)	21 (24%)	
3	4 (3%)	5 (6%)	
Active smoking	55 (38%)	37 (42%)	.57
Diabetes mellitus	8 (5.5%)	4 (4.4%)	1.0
Neck dissection	43 (30%)	32 (36%)	.32
Chemotherapy	112 (77%)	81 (91%)	.008†
Good dental health†	20 (24%)	16 (19%)	.40
Edentulous	20/85 (23%)	20/86 (23%)	1.0
Dental extraction pre-RT†	40/81 (49%)	46/85 (54%)	.59

Abbreviations: RT, radiotherapy; IMRT, intensity-modulated radiotherapy.
†$p < 0.05$.

side as the primary tumor) as well as the contralateral one.

For comparison of radiation doses, a subset of patients without ORN was selected: 18 treated by IMRT and 12 by conventional RT.

Variables and statistical analysis

The following initial characteristics were tabulated: age, sex, tumor subsite, T and N classification, overall stage, neck dissection, chemotherapy, active smoking, comorbidities, such as diabetes mellitus, dental status, and pretreatment dental extractions. After treatment, potential triggers for ORNM, such as dental extractions or any dental pathology, were identified. The delay of ORNM was calculated.

Data were analyzed with IBM SPSS Statistics version 22. Numeric and categorical variables were compared for significant differences with a bilateral *t* test and the Fischer exact test, respectively. Analysis in terms of local control and overall survival was performed according to the Kaplan–Meier product limit method and univariate statistical differences assessed using the log-rank test. Differences of radiation doses to the mandible and parotid glands were assessed with the Mann–Whitney *U* test. A *p* value of .05 was used to determine significant differences for all statistical tests.

For retrospective chart analysis studies, patient's consent and approval was waived by the Hospital Ethics Committee.

RESULTS

Osteoradionecrosis of the mandible incidence in conventional radiotherapy and intensity-modulated radiotherapy

Median follow-up was 4.9 ± 4.0 and 3.2 ± 1.8 years for the conventional RT and IMRT groups, respectively, which is significantly different ($p = .001$). Concomitant chemotherapy was used more frequently in the IMRT group (77% vs 91%; $p = .008$). All other patient characteristics at the start of treatment were similar for both groups (Table 1). No difference was found in 5-year overall survival ($p = .73$) and locoregional recurrence ($p = .44$) between the 2 groups (see Figure 1).

There was no difference in the rate of ORNM at the end of follow-up between both groups ($p = 1.0$): 16 of the 145 patients (11%) had mandible ORN in the conventional RT group and 9 of 89 patients (10.2%) in the IMRT group. A cumulative incidence risk was calculated at 3 years because there was a difference in follow-up duration: 4.8% for conventional RT and 8.9% for IMRT ($p = .03$).

Analysis of the time delay to ORNM appearance revealed 2 peaks in the conventional RT group: a first before the end of the first year after treatment and a second peak starting more than 5 years after the end of radiation. In contrast, the IMRT group showed a more homogeneous time distribution of ORNM (see Figure 2).

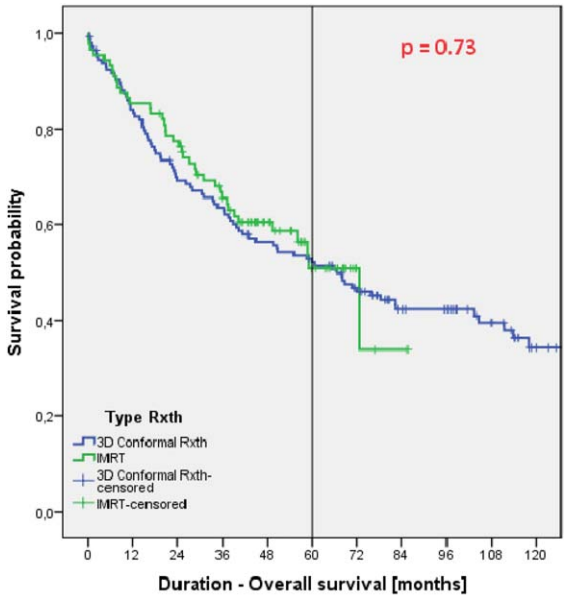
Significantly more ORNM were observed in T4 classified tumors in the IMRT group ($p < .01$) with 0/13 T1, 2/40 T2, 1/18 T3, and 6/18 T4 patients developing ORNM. No such T classification-related difference was observed in conventional RT.

A nonsignificant trend was found for ORNM location and severity distribution. ORNM was more often ipsilateral to the primary tumor in IMRT (8/9; the ninth being bilateral) than in conventional RT (9/16; $p = .16$). There was also a trend for more ORNM located in the premolar region with IMRT with 4 of 9 versus 3 of 16 in conventional RT ($p = .20$). No events were noted in the anterior mandibular region for both groups. ORNM was more severely graded in the IMRT group (1 stage I, 5 stage II, and 3 stage III) than in the conventional RT group in which the distribution was more homogenous (6 stage I, 5 stage II, and 5 stage III; $p = .26$).

Osteoradionecrosis of the mandible risk factors

When considering the entire cohort, the different risk factors for ORNM development were not different between patients with ORNM and patients without ORNM (Table 2).

Dental health status before radiotherapy was available in 171 patients. No significant difference was found between both groups ($p = .40$). An equal amount of patients were edentulous in both groups (20/85 for conventional RT and 19/86 for IMRT). Edentulous state at



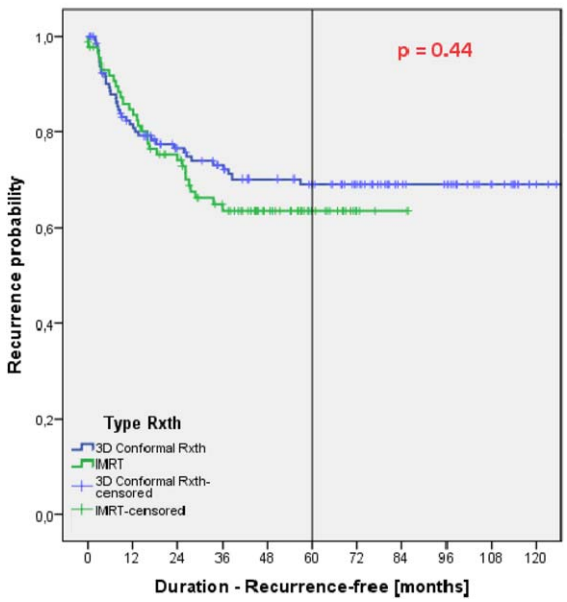


FIGURE 1. Overall and duration-free survival in the conventional radiotherapy (Rxth) and the intensity-modulated radiotherapy (IMRT) groups. [Color figure can be viewed at wileyonlinelibrary.com]

the dental pretreatment workup proved to be a significant protective factor with only 1 of the 40 edentulous patients developing ORNM in contrast to 24 of 134 patients with residual dentition developing ORNM ($p = .01$). No protective measure of pretreatment dental extraction could be demonstrated ($p = .2$).

Dental extraction after radiation was the most frequent trigger factor for ORN, present in about 50% of patients: 8 of 16 in the conventional RT group and 4 of 9 in the IMRT group. The delay after treatment for tooth extraction was 77 months (range, 12–103 months) and 25 months (range, 8–54 months) for conventional RT and IMRT, respectively.

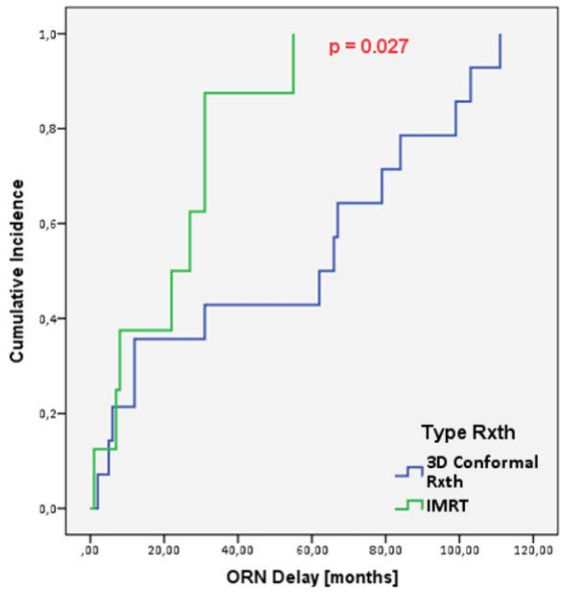


FIGURE 2. Delay in the development of osteoradionecrosis (ORN) in the conventional radiotherapy (Rxth) and the intensity-modulated radiotherapy (IMRT) groups. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2. Patient characteristics and risk factors for osteoradionecrosis of the mandible.

Characteristics	With ORNM	Without ORNM	*p* value
No. of patients	25	209	
M/F ratio	0.76	0.80	.21
Age, y	56.9 ± 10.3	61.1 ± 9.5	.06†
Median follow-up	5.4 ± 3.8	4.1 ± 3.4	.94
Subsite			1.0
Tongue base	8 (32%)	76 (36%)	
Tonsil	12 (48%)	97 (46%)	
Posterior wall	2 (8%)	11 (5%)	
Soft palate	3 (12%)	25 (12%)	
T classification			.37
1	1 (4%)	25 (12%)	
2	9 (36%)	86 (41%)	
3	4 (16%)	42 (20%)	
4	11 (44%)	56 (27%)	
N classification			.94
0	4 (16%)	36 (17%)	
1	5 (20%)	37 (18%)	
2a	2 (8%)	10 (5%)	
2b	7 (28%)	66 (32%)	
2c	7 (28%)	51 (24%)	
3	0	9 (4%)	
Active smoking	13 (52%)	78 (37%)	.10
Diabetes mellitus	1 (4%)	11 (5%)	1.00
Neck dissection	7 (28%)	67 (32%)	.82
Chemotherapy	22 (88%)	171 (82%)	.58
Good dental health†	3/20 (15%)	33/146 (23%)	.57
Edentulous	1/25 (4%)	39/146 (27%)	.01†
Dental extraction pre-RT†	9/20 (45%)	80/146 (55%)	.47

Abbreviation: ORNM, osteoradionecrosis of the mandible.
†$p < 0.05$

TABLE 3. Radiation doses to the mandible and parotid glands in patients treated with intensity-modulated radiotherapy and conventional radiotherapy.

			Mandible								
	Patient #	Technique	V50, %	V60, %	V70, %	D2%, Gy	Dmax, Gy	Dmean, Gy	Volume, cc	Ipsilateral parotid Dmean, Gy	Contralateral parotid Dmean, Gy
ORNM	1*	IMRT	43.4	32.2	15.3	77.2	82.6	47.8	74.5	38.8	28.6
	2	IMRT	25.6	18.5	0	67.9	70.4	41.8	74.3	49.2	27.6
	3*	IMRT	46.2	17.2	0	68.5	69.9	44.3	56.1	28.7	27
	4*	IMRT	39.7	2.3	0	60.4	70.5	42.4	64	33.1	32.6
	5	IMRT	27.8	14.2	2.7	70.6	75	40.3	58.8	33.2	28.4
	6*	IMRT	80	55.5	8.2	71.6	75.4	58.1	79	47.9	26.1
	7	IMRT	51.3	35.9	21.4	74.5	78.1	51.1	72.4	43.7	25.5
	8*	IMRT	58.4	27.9	1.6	69.9	74.6	50.6	69	29.6	29.3
	9	IMRT	16.7	6	0	64.8	69.9	28.9	54.4	45.8	16.2
	Mean		**43.23**	**23.30**	**5.47**	**69.49**	**74.04**	**45.03**	**66.94**	**38.89**	**26.81**
	SD		**19.11**	**16.50**	**7.91**	**4.98**	**4.37**	**8.27**	**8.95**	**8.02**	**4.48**
ORNM	10*	Conventional RT	30	23.6	0	67	67.7	36.6	35.6	47.9	22.6
	11	Conventional RT	53.3	46.7	17.6	72.8	73.7	41.6	54.8	47	26.9
	12*	Conventional RT	73.9	55.6	19.7	71	72	57	38.5	64	47.5
	13	Conventional RT	58.5	44.5	25.9	72.2	72.8	46	58	55.6	47.6
	14	Conventional RT	95.2	88	0	67.9	69.7	61.2	53.2	60.5	59.6
	15*	Conventional RT	95.6	84	0	69.3	70.2	63.9	73.8	50.3	60.9
	Mean		**67.75**	**57.07**	**10.53**	**70.03**	**71.02**	**51.05**	**52.32**	**54.22**	**44.18**
	SD		**25.64**	**24.78**	**11.86**	**2.35**	**2.22**	**11.20**	**13.94**	**6.99**	**16.15**
p value ORNM IMRT vs conventional RT			***0.078***	***0.019***	***0.385***	***0.781***	***0.102***	***0.290***	***0.053***	***0.002***	***0.046***
No ORN	18 patients	IMRT									
	Mean		**23.26**	**9.28**	**0.29**	**63.07**	**68.00**	**35.12**	**60.37**	**32.84**	**19.31**
	SD		**14.88**	**9.74**	**0.55**	**6.07**	**5.23**	**6.68**	**13.66**	**7.02**	**11.00**
p value IMRT ORNM vs no ORNM			***0.017***	***0.039***	***0.085***	***0.009***	***0.005***	***0.008***	***0.148***	***0.075***	***0.019***
No ORN	12 patients	Conventional RT									
	Mean		**58.45**	**49.44**	**16.49**	**70.89**	**72.07**	**46.27**	**59.36**	**55.13**	**45.41**
	SD		**21.27**	**18.41**	**17.58**	**1.64**	**1.72**	**15.07**	**12.83**	**9.97**	**9.12**
p value conventional RT ORNM vs no ORNM			***0.474***	***0.531***	***0.433***	***0.455***	***0.347***	***0.482***	***0.337***	***0.833***	***0.870***

Abbreviations: V50, V60, and V70 = mandibular volume receiving 50, 60, and 70 Gy, respectively. D2%, the dose received by 2% of the mandibular volume; Dmax, the maximal point dose to the mandible; Dmean, the mean dose to the mandible; ORNM, osteoradionecrosis of the mandible; IMRT, intensity-modulated radiotherapy; ORN, osteoradionecrosis; RT, radiotherapy.
For the parotid gland, we report the mean dose (Dmean) delivered to the parotid on the same side as the primary tumor as well as the contralateral one.
* Patients with tooth extraction post-RT.

Radiation doses to the mandible and parotid glands

Detailed radiation plans were available for the total 9 cases of ORNM treated with IMRT, and 6 patients with ORNM who received conventional RT (Table 3). The average Dmax of the mandible was 71.1 ± 2.2 Gy for conventional RT and 74.04 ± 4.37 for IMRT-treated patients ($p = .10$). The average Dmean of the mandible was 51.1 ± 11.2 Gy for conventional RT and 45.03 ± 8.27 for IMRT-treated patients ($p = .29$). The D2% doses were also similar, around 70 Gy in both groups.

All mandible volumes were higher with conventional RT, reaching statistical significance for V60 ($p = .02$). Similarly, the average Dmean for the ipsilateral and contralateral parotid were higher in the conventional RT group than for IMRT, with statistically significant differences.

When comparing IMRT patients with and without ORNM, significant differences were observed for all radiation volumes and doses, with higher values in IMRT patients with ORNM (Table 3). A similar comparison in conventional RT patients did not find significant differences in patients with and without ORNM.

In patients with ORNM treated by IMRT, the Dmean of the mandible was 48.6 ± 6.1 and 40.5 ± 9.1 in patients with and without teeth extraction, respectively ($p = .18$). In patients with ORNM treated by conventional RT, the Dmean of the mandible was 46.8 ± 14.4 and 53.2 ± 11.0 in patients with and without teeth extraction, respectively ($p = .65$).

DISCUSSION

We examined the impact of 2 different radiation techniques, conventional RT and IMRT, on ORNM development by comparing its incidence in 2 cohorts of similar patients, with similar tumor characteristics, and whose dental management was similar. A single primary site and the exclusion of patients undergoing surgery to the primary allowed controlling other confounding parameters. The hypothesis generated was that patients treated with IMRT will ultimately have a lower rate of ORNM.

We found no difference in the incidence in ORNM between both groups (11% for conventional RT and 10.2% for IMRT). These rates are higher than those published recently. Several factors could be advanced as an explanation: (1) longer follow-up; (2) thorough follow-up evaluation; (3) proximity of the primary tumor to the mandible; and possibly (4) higher than tolerated radiation dose delivered to the mandible.

Although ORNM is probably a lifelong risk after radiation,[20] few long duration studies are available. Chronopoulos et al,[21] in a 10-year retrospective study of 142 patients with ORNM, found that 38% occurred in the first 3 years, 28% between 3 and 6 years, 15% between 6 and 9 years, and 18% after 9 years. A first-year incidence peak, when about half of the ORNM develop, has been found by others[22] and our data show 40% of ORNM occurring within 1.5 years after completion of radiotherapy (Figure 2). There is a plateau for conventional RT, whereas the IMRT rate seems stable, reaching a cumulative incidence of 8.9% at 3 years versus 4.8% for conventional RT. This time course difference has not been previously reported and it remains unclear if it is somehow related to the IMRT delivery schedule. Notwithstanding the exact time course, ORNM cumulative incidence will increase with time and in all publications with IMRT, the median follow-up has been shorter than 3 years.[13–16]

Our ORNM rates even in the conventional RT group seem larger than those of the literature. In the pre-IMRT era, reviews by Clayman[12] and Wahl[10] found an average incidence of ORNM of 12% in the 1940 to 1970 period, 4.4% from 1970 to 1995, and 3% from 1997 to 2004. Besides thorough follow-up and reporting, another explanation is that the entire study population received up to a dose of 70 Gy to the posterior mandible site because of its proximity to the oropharyngeal primaries. As discussed below, most series include diverse head and neck primaries in which the mandible might be receiving smaller doses. In addition, the severity of ORNM is not uniformly reported and stage I ORNM is sometimes not included in the reports.

Different incidences of ORNM according to the primary tumor localization have been published.[20,22] In the study by Chronopoulos et al,[21] of 142 patients with ORNM, 60% had oral primaries close to the mandible, 27% were oropharyngeal primaries, 10% were maxillary, and only 4% of cases were due to other (salivary gland, larynx, hypopharynx, and neck) primaries. Including all head and neck sites will certainly lower the incidence of ORNM, especially with "organ-sparing" radiation techniques, such as IMRT.

We did not find any risk factor predictive for the development of ORNM except for T4 classified tumors in the IMRT group. It is probable that for T4 oropharyngeal primaries, the angle region of the mandible is receiving the full tumor target dose of 70 Gy. This reinforces the hypothesis that dose-volume distribution at the mandible is the primary culprit of ORNM, irrespective of how radiation is delivered (conventional RT or IMRT).[14,23]

It is universally accepted that poor dental status is a major risk factor for ORNM, especially posttreatment extractions. In agreement with multiple studies, we found that about 50% of patients with ORNM had posttreatment dental extractions, irrespective of the radiation group, and therefore can be seen as a trigger for ORNM, regardless of the RT technique. As discussed, radiation changes of the bone lead to suboptimal equilibrium that can be tipped off toward ORNM by any additional stress, being extraction or other dental or periodontal diseases. In that context, we found edentulous state as the only protective factor against ORNM, as described by others.[20,22] As in other studies, we did not find pretreatment extractions to be a protective nor a risk factor, although the subject is more debatable.[10,24,25]

Three other studies have compared the incidence of ORNM in conventional RT and IMRT treated patients. Beadle et al[26] analyzed the Surveillance, Epidemiology, and End Results-Medicare database for "jaw complications" (ORNM, osteomyelitis, inflammatory conditions; alveolitis, periradicular pathology, …): in 1848 patients, similar outcome for IMRT (14%) and conventional RT (17%) was found. Tsai et al[23] examined ORNM in oropharyngeal carcinoma and found ORNM in

6% (21/335) with IMRT and 13% (9/68) with conventional RT, a nonsignificant difference. In addition, the study was limited to T1 to T2 patients, was unbalanced for edentulous state (21% in IMRT vs 7% in conventional RT), and the median follow-up was short (31 months). Quite interestingly, the ORNM rate was related to the volume of mandible receiving more than 50 and 60 Gy. Recently, Duarte et al[27] compared dental status and found ORNM in 0% (0/59) with IMRT and 10% (10/99) with conventional RT ($p = .014$); however, the primaries covered all head and neck sites and the follow-up was not specified.

Regarding radiation dose delivered to the mandible with conventional RT, Glanzmann and Grätz[28] found no ORNM after target doses of 60 to 65 Gy, despite the Dmax to the mandible between 64 and 72 Gy. The incidence of ORNM increased to 13% with target doses of 66 to 72 Gy (Dmax to the mandible 66–80 Gy). The group with the highest target doses of 72 to 78 Gy (Dmax to the mandible 74.4–82.3 Gy) showed only a modest ORNM increase to 15% and mostly of lower grade ORNM. This somewhat paradoxical finding might be due to the use of hyperfractionation (2×1.2 Gy/day), as reported by others.[29] Our doses to the mandible in conventional RT cases with ORNM did not exceed the ones reported by Glanzmann and Grätz[28] and Jereczek–Fossa et al[29] and a hyperfractionation schedule was also used.

If a Dmax of 70 to 72 Gy is generally accepted as the highest dose constraint to the mandible to reduce the risk of ORNM at 5 years to <5%, this constraint will occasionally not be respected if it compromises the planning target volume coverage. In our patients with ORNM, the Dmax to the mandible was, on average, higher than recommended (74 Gy). Furthermore, a significant difference was observed in Dmax between patients with and without ORNM treated by IMRT. Besides tumor location close to the mandible, additional factors responsible include the unpredictable dose distribution heterogeneity of IMRT and Dmax shifts to higher values during treatment because of tumor volume reduction or patient weight loss. An effort to adapt the initial treatment plan when using IMRT is largely being assessed in contemporary literature.[30–32]

Beside the maximal radiation dose, the mandibular receiving the volume is of importance. In one publication, no ORNM was observed with mean V50, V60, and V70 of 62%, 35%, and 6.5%, respectively.[13] Our patients with ORNM treated with IMRT had comparable average mean V50, V60, and V70, being 61.7%, 33%, and 7.8%, respectively. However, these mandibular volume values might still be too high because the mandibular volumes were significantly smaller in IMRT-treated patients without ORNM.

In contrast to conventional RT, IMRT is a technique that allows improved normal tissue sparing, especially by reducing volumes of the contoured organs (such as the mandible and the parotid glands) at risk that are receiving high doses, thanks to rapid dose falloff. To achieve this, a specific plan optimization is required to conform the dose falloff as tightly as possible. With a 5 to 7-field IMRT plan, when using a parotid-sparing optimization as a priority, we can appreciate often that the dose distribution will increase anteriorly, where the mandible lies, in order to maintain target volume coverage. There has been no attempt to reduce mandibular volumes receiving a high dose, in other words, reduce the dose gradient across the bone thickness, as a maximal point dose was the only optimization constraint we used. This may help explain the lack of any improvement of the rate of ORNM with IMRT compared to conventional RT in our series.

Withers et al[33] contributed in the 1990s to the knowledge of radiobiological characteristics of bone. The authors concluded that not only total dose, but also dose per fraction was a significant factor for bone injury. The bone is a slowly responding normal tissue (α/β 0.85 Gy), with increased probability of damage when the dose per fraction increases. It can be argued that the high incidence of ORNM in our cohort of patients treated with IMRT could be related to a higher dose per fraction (2.12 Gy) and a somewhat similar incidence of ORNM (6%) was found in the Radiation Therapy Oncology Group 00-22 study, which also used a high dose per fraction (2.2 Gy).[34]

The prescribed 69.96 Gy to our cohort of patients treated with IMRT, is actually higher in terms of total biologically equivalent doses in 2 Gy fractions, translating in an even higher Dmax to the mandible than reported (with an $\alpha/\beta = 0.85$; equivalent doses in 2 Gy fractions = 80 Gy). Moreover, the addition of concomitant chemotherapy to such a dose/fractionation regimen may be responsible of excessive acute mucositis and thereafter of an increased risk of overlying bone exposure.

CONCLUSIONS

We found no reduction in ORN with IMRT compared to conventional RT in oropharyngeal carcinoma. A high-dose distribution to the mandible, especially a high-dose per fraction, rather than the modality per se seems to be the most contributing factor. ORN with IMRT occurs with shorter time intervals since the end of treatment than with conventional RT. Dental extraction after RT seems to be the main precipitating factor and edentulous state of a protective factor.

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