ORAL MEDICINE

Risk factors for osteoradionecrosis after head and neck radiation: a systematic review

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Objective. This systematic review aimed to answer the clinical question, "What is the current risk of developing osteoradionecrosis of the jaws among irradiated head and neck cancer patients?"
Study Design. A systematic review of published English-language randomized controlled trials on the outcome of radiation therapy was performed via Medline and Embase databases. Data on osteoradionecrosis/bone toxicity were collected and analyzed.
Results. Twenty-two articles reporting on a total of 5,742 patients were selected for final review based on strict eligibility criteria. An estimated 2% of the head and neck–irradiated patients are at risk of developing osteoradionecrosis. Patients receiving adjunctive radiotherapy, accelerated fractionation without dose reduction, and chemoradiotherapy show no increase in osteoradionecrosis risk. Accelerated fractionation with dose reduction is associated with a reduced risk, whereas hyperfractionation shows elevated risk of developing osteoradionecrosis.
Conclusions. The risk of developing osteoradionecrosis among the irradiated head and neck cancer patient has significantly declined in recent years. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:54-69)

Radiotherapy (RT) alone or in combination with surgery is an established form of therapy for the treatment or palliation of cancer patients. This treatment modality, however, has significant limitations in the form of acute and late toxicity. Acute side effects, such as moist desquamation, skin erythema, loss of taste, and especially mucositis, are often debilitating but resolve with time.[1] Late toxicity, such as radiation caries, trismus, xerostomia, myelitis, skin fibrosis, and osteoradionecrosis (ORN), however, can be more problematic, because they may be a lifelong problem for cancer survivors.[1-3] Along with tumor recurrence or development of a second malignancy, ORN of the jaws is a most dreaded complication among survivors of head and neck cancer.

In recent years, new advances in RT have been made, and there is increasing interest in combining chemotherapeutic (CT) agents with irradiation in an effort to achieve better locoregional disease control and higher survival rates.[4,5] The delivery of RT has also changed with the advent of new technologies, such as 3D conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT), with the purpose of reducing the radiation exposure of normal regional tissues.[6-9] The rate and total dose delivery have also been extensively tested to assess the effectiveness of different fractionation regimes and length of treatment in controlling disease and their effect on acute and late toxicity.[10,11]

Historically, the incidence of ORN in the head and neck–irradiated population was estimated to be 4.74%-37.5% (Table I).[12-20] With the current advances in radiation technologies and the introduction of dental care protocols for head and neck cancer patients, the current risk of developing ORN is assumed to have declined but is in fact unknown. Moreover, the differences in the incidence of ORN associated with different radiation regimens, different fractionations, and different delivery methods are unclear. The effect of combining CT with radiotherapy on ORN risk also is not known. The present systematic review aims to clarify the effects of different radiation protocols on the risk of developing ORN of the jaws in the irradiated head and neck cancer population.

MATERIALS AND METHODS

Objective

With the aim of answering the clinical question, "What is the current risk of developing ORN of the jaws among irradiated head and neck cancer patients?," a systematic literature search was performed to provide the best and most valid answer.

Study identification

An electronic search was performed through Medline and Embase using the combination of "head and neck cancer," "radiotherapy," "radiotherapy late toxicity,"

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Table I. Previously reported osteoradionecrosis (ORN) incidence

Author	Year	Period	No. of patients	No. of ORN	Percentage
Watson and Scarborough[12]	1938	1930-1937	1,819	235	12.9%
MacCombe[13]	1962	1952-1959	251	93	37.1%
Grant and Fletcher[14]	1966	1954-1962	176	66	37.5%
Bedwinek et al.[15]	1976	1966-1971	381	54	14.2%
Daly et al.[16]	1972	1966-1971	304	66	21.7%
Murray et al.[17]	1980	1966-1975	653	138	21.1%
Morrish et al.[18]	1981	1971-1977	100	22	22.0%
Withers et al.[19]	1995	1976-1985	676	32	4.7%
Reuther et al.[20]	2003	1969-1999	830	68	8.2%

and "osteoradionecrosis" as key words to identify relevant articles (Figure 1).

Study selection

The title and abstract of all articles retrieved by the electronic search were screened. For articles reporting the outcome of RT treatment for head and neck cancer or for those with insufficient data in the title and abstract to make a clear decision about, the full text of the articles were obtained. These articles were then evaluated, and articles meeting the inclusion criteria described in Table II were accepted for further assessment. Articles meeting the inclusion criteria were then assessed further using predefined eligibility criteria for their inclusion in the final review. Studies rejected at the eligibility assessment stage were recorded and the reasons for exclusion noted.

Type of study

Only randomized controlled trials (RCTs) involving RT on head and neck cancer patients with a minimum sample size of 20 patients per arm were considered. A minimum of 20 patients is needed to give at least 1 case of ORN based on the 4.74% ORN incidence rate reported by Withers et al.[19] (Table I). A smaller sample size could result in no ORN occurrence, which would make it impossible to compare the difference in the risk of developing ORN between different treatment arms. Articles also had to have reported late bone toxicity/ORN. Other restrictions were English language only, publication date after 1995, and study on humans.

Participants. Consecutive groups of adult patients who had radiation to the head and neck region excluding lymphoma, esophageal, thyroid, and tracheal tumors were eligible. Subjects who were reirradiated were excluded. Palliative radiation was excluded, owing to the expectation of a limited follow-up period relative to poor prognosis.

Intervention. Any RT regimes performed as a curative or adjunctive therapy with surgery in the management of head and neck cancer were included.

Outcome measures. The primary outcome measure was the occurrence of ORN after irradiation to the head and neck region. ORN can be reported as present (yes/no) or as the presence of bone toxicity according to the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema (RTOG/EORTC),[1] Late Effects of Normal Tissue/Somatic Objective Management Analytic (LENT/SOMA),[3] or the National Cancer Institute Common Toxicity Criteria (NCI-CTC).[2] In articles reporting bone toxicity, RTOG/EORTC and LENT/SOMA grade/score 3 or 4 bone toxicity and grade $\geq$1 for osteonecrosis in NTC-CTC were considered to be ORN for the purpose of this review. Other outcomes examined were ORN risk in different tumor locations, the use of chemoradiotherapy (CRT), adjunctive or curative therapy, RT delivery techniques, altered fractionation, ORN location within the jaws, and the reporting of dental evaluations.

Eligibility assessment

Articles meeting all of the following criteria were accepted for the final review:

1. Actual number of cases of bone toxicity/bone necrosis/ORN reported.
2. Treatment regimen uniform within each arm.
3. Original data (no secondary analysis).
4. Reported follow-up of >5 years or median/mean follow-up of surviving patients >3 years.
5. Patient recruitment beginning from 1985 onward.

Data collection

The data were collected in Microsoft Excel table form by the first reviewer. The second reviewer reevaluated the completed table to ensure that there were no irregularities or missing data during the data extraction process.

RESULTS

The electronic database search was last updated in June 2010. After title and/or abstract screening, 201 articles appeared to be relevant for this review. Full text evaluation of these 201 articles concluded that 53 articles met all of the inclusion criteria. After eligibility assessment, 31 articles did not meet $\geq$1 of the validity crite-

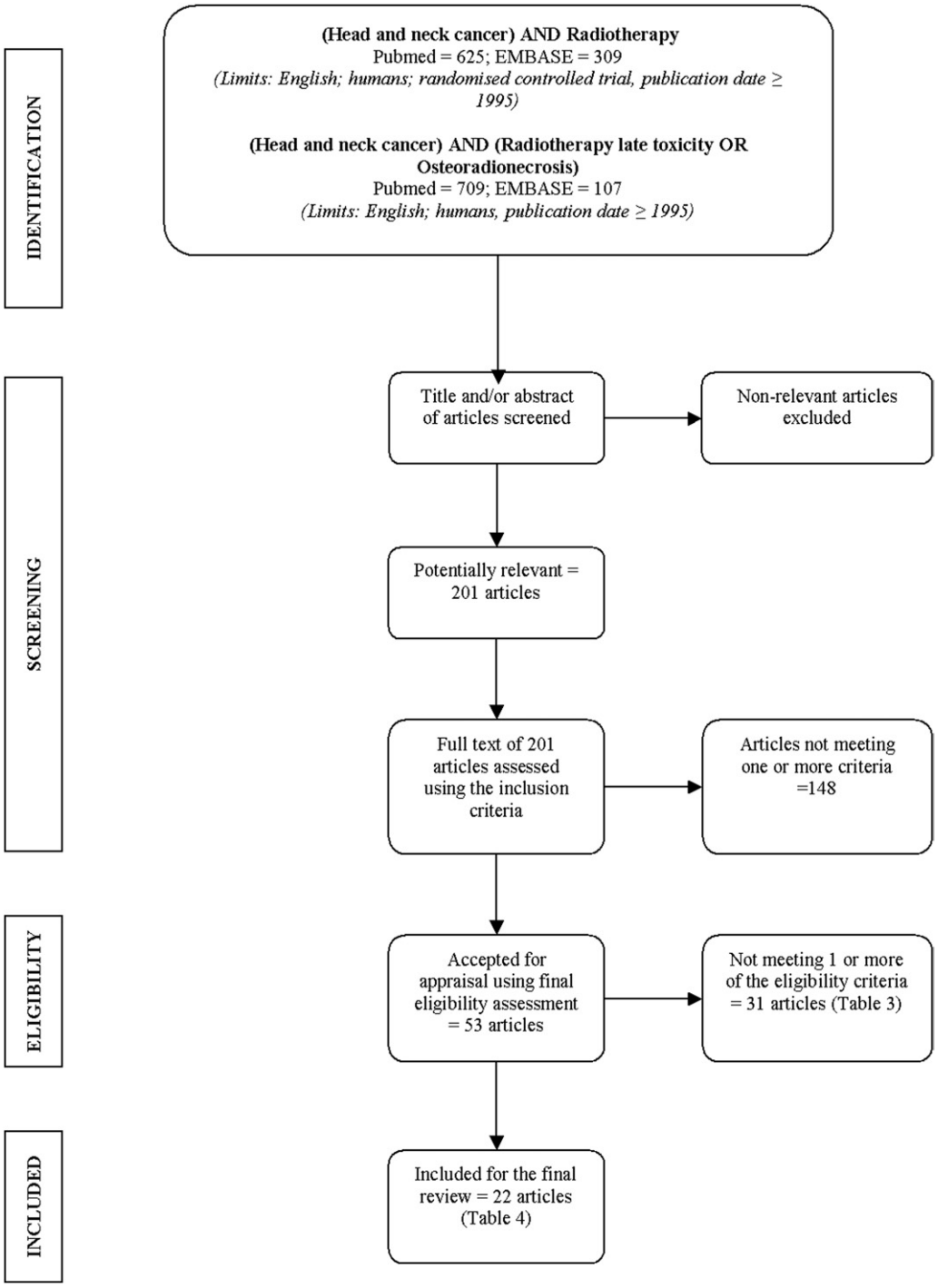

Figure 1. Flow diagram for study selection (as adapted from the PRISMA statement[132]).

ria. Reasons for exclusion are presented in Table III. A total of 22 articles were accepted for data extraction and analysis.[10,21-41] The flow chart of the systematic article selection and evaluation is illustrated in Figure 1.

Primary outcome

Based on 22 RCTs, a total of 117 cases of ORN from among 5,742 irradiated head and neck cancer patients were recorded, giving an incidence rate of 2% in the period between 1985 and 2010 (Table IV).

Risk of ORN for different tumor locations

Among the 22 selected articles, 18 articles reported the outcome of RT treatment within the region of the "head and neck cancer" (larynx, oral cavity, oropharynx, hypopharynx) without subdividing to a more specific tu-

Table II. Criteria for inclusion of articles in the final eligibility assessment phase

Randomized controlled trial comparing outcome of different radiotherapy treatment regimes
Patients who had undergone radiotherapy in head and neck region (excluding lymphoma, esophageal, thyroid, and tracheal tumors)
Reporting the late bone toxicity/bone necrosis/osteoradionecrosis
Sample size >20 in each arm
Excluding reirradiation
Excluding palliative treatment
Human subjects
Adult subjects

mor location. One article reported the outcome of RT in "nasopharyngeal carcinoma," and the remaining 3 reported on a subset of "head and neck cancer" (2 oropharynx and 1 tongue carcinoma). No selected articles reported the outcome of RT treatment in the sinonasal region (Table V). Among the 18 articles reporting outcome of treatment on "head and neck cancer" patients, none reported the relation of ORN/bone toxicity with the subset location (larynx, oral cavity, oropharynx, hypopharynx).

Risk of developing ORN when CT agents were used

Overall, 10 articles compared the outcome of RT alone to that of CRT. Five articles reported higher incidence of ORN when CRT was used,[26,28,30,31,37] 3 when RT alone was used,[22,29,38] whereas 2 articles reported no difference (Table VI).[25,32]

Risk of developing ORN in curative RT or adjunctive RT with surgery

One article reporting the outcome of RT in nasopharyngeal carcinoma was excluded from the present analysis to ensure homogeneity.[33] When curative-intent RT treatment was compared with adjunctive RT treatment after surgery, similar risk of developing ORN was seen (Table V).

Incidence with different delivery techniques

There were no RCTs selected for this review that compared different radiation delivery techniques, such as conventional external-beam radiotherapy (EBRT), IMRT, 3D-CRT, or brachytherapy. One article compared high dose rate (HDR) with low dose rate (LDR) brachytherapy and reported higher incidence with HDR.[35] Sixteen articles reported a comparison of different treatment regimen with the use EBRT in both arms. Six articles failed to report clearly the delivery technique used[22,26,27,30,34,40] and none of the articles selected used IMRT or 3D-CRT. Results are shown in Table V.

Difference in risk with different dose rates and treatment time (conventional, accelerated, hyperfractionated)

Altered fractionation was compared with conventional fractionation in 7 articles and the results are shown in Table VII. Further subdivision to different categories was performed according to an earlier meta-analysis.[11] When hyperfractionation was compared with conventional fractionation, both trials showed higher risk in the intervention group.[23,36] Two out of 5 articles comparing accelerated fractionation without dose reduction to conventional fractionation showed an increased risk for the intervention group,[21,24] 2 others showed a reduced risk,[34,36] and 1 showed no difference.[25] When the radiation dose was reduced and accelerated, the risk of developing ORN was reduced.[10]

Risk for the mandible and maxilla

The location of ORN was reported in only 7 of the 22 articles (Table V). Among those 7 articles, none reported the occurrence of ORN in the maxilla.

Reporting of dental evaluation

Of the 22 articles selected, dental evaluation before RT was reported in 7 articles. Differences in the risk of developing ORN are shown in Table V.

DISCUSSION

Osteoradionecrosis of the jaws is a well known complication of head and neck radiotherapy. It is a unique type of radiation late toxicity in the sense that its risk of occurrence is dependent not only on the extent of radiation damage to bone but also on the dental health of the patient. It is known that the risk of developing ORN is increased in patients with poor oral health because more traumatic dental events are to be expected.[17,42-44] This is further supported by the findings that edentulous patients are at a lower risk of developing ORN.[17] The association of radiation damage and oral health can also be explained by the observation of spontaneously occurring ORN and trauma-induced ORN.[45-47] Spontaneously occurring ORN is postulated to be dependent on the extent of radiation exposure, whereas trauma-induced ORN is more dependent on traumatic dental events.[45-48] Patients receiving higher radiation doses would therefore be more likely to develop spontaneously occurring ORN, whereas patients receiving lower doses would need trauma to the radiated tissue to initiate the development of ORN.[45] Marx and Johnson observed that most spontaneous presentations of ORN occurred between 6 months and 2 years after RT, whereas the risk of developing trauma-induced ORN lasts indefinitely.[46] This observation explains the occurrence of ORN even 10 years after

Table III. Articles excluded after final eligibility assessment (n = 31)

Author	Year	Total follow-up	ORN/total patients	%	Criteria of diagnosing ORN	Reason for exclusion
Sunders et al.[101]	2010	10 y	—/918*	—	Y/N	Duplicate data; exact no. of ORN cases not reported (only estimated)
Rischin et al.[102]	2010	27 mo	21/853	2.5	RTOG/EORTC	Insufficient follow-up
Pointreau et al.[103]	2009	36 mo	0/213	0	RTOG/EORTC	Treatment regimen not uniform within each arm
Zakotnik et al.[104]	2007	76 mo	—/114*	—	NCI-CTC	Duplicate data; exact no. of ORN cases not reported
Bourhis et al.[105]	2006	>6 y	—/266*	—	RTOG/EORTC	Exact no. of ORN cases not reported
Le et al.[106]	2006	61 mo	7/62	11.3	Y/N	Treatment regimen not uniform within each arm
Bonner et al.[107]	2006	54 mo	—/424*	—	RTOG/EORTC	Exact no. of ORN cases not reported
Bensadoun et al.[108]	2006	2 y	0/163	0	RTOG/EORTC	Insufficient follow-up
Zhang et al.[109]	2005	24 mo	0/115	0	Y/N	Insufficient follow-up
Rischin et al.[110]	2005	2.6 y	4/121	3.3	RTOG/EORTC	Insufficient follow-up
Homma et al.[111]	2004	63 mo	1/119	0.8	Y/N	Treatment regimen not uniform within each arm
Garden et al.[112]	2004	2.6-2.9 y	6/231	2.6	RTOG/EORTC	Insufficient follow-up
Bernier et al.[113]	2004	60 mo	—/323*	—	RTOG/EORTC	Exact no. of ORN cases not reported
Denis et al.[114]	2004	5.5 y	1/220	0.5	NCI-CTC	Duplicate data
Smid et al.[115]	2003	32.2 mo	3/114	2.6	NCI-CTC	Insufficient follow-up
Bartelink et al.[116]	2002	—	5/49	10.2	Y/N	Follow-up not reported
Gupta et al.[117]	2001	>15 y	12/313	3.8	Y/N	Accrual period before 1985
Staar et al.[118]	2001	22.3 mo	14/240	5.8	Y/N	Insufficient follow-up; duplicate data
Aref et al.[119]	2000	—	11/385	2.9	RTOG/EORTC	Secondary analysis
Skladowski et al.[120]	2000	>3 y	2/100	2.0	Y/N	Duplicate data
Calais et al.[121]	1999	35 mo	0/220	0	Y/N	Insufficient follow-up; duplicate data
Wendt et al.[122]	1998	—	7/270	2.6	Y/N	Follow-up not reported
Horiot et al.[123]	1997	4 y 9 mo	—/500*	—	RTOG/EORTC	Exact no. of ORN cases not reported
Jeremic et al.[124]	1997	—	3/154	2.0	RTOG/EORTC	Follow-up not reported
Inoue et al.[125]	1996	22 mo/24 mo	1/29	3.5	Y/N	Insufficient follow-up; duplicate data
Maciejewski et al.[126]	1996	<12 mo	2/44	4.5	Y/N	Insufficient follow-up; duplicate data
Bachaud et al.[127]	1996	>5 y	1/83	1.2	Y/N	Accrual period before 1985
Flores et al.[128]	1996	1 y	—/119*	—	Y/N	Insufficient follow-up; exact no. of ORN cases not reported
Fu et al.[129]	1995	2 y	3/70	4.3	RTOG/EORTC	Insufficient follow-up
Fu et al.[130]	1995	6.1 y	9/399	2.3	RTOG/EORTC	Accrual period before 1985
van den Bogaert et al.[131]	1995	—	10/498	2.0	Y/N	Follow-up not reported; accrual period before 1985
Total			123/5065	2.43		

ORN, Osteoradionecrosis; *Y/N,* yes or no; *RTOG/EORTC,* Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema; *LENT/SOMA,* Late Effects of Normal Tissue/Somatic Objective Management Analytic; *NCI-CTC,* National Cancer Institute Common Toxicity Criteria.
*Not included in calculation.

RT.[45,49] Because the risk of developing ORN lasts for many years after RT, it is essential when estimating or comparing data that a sufficient follow-up period is given in published reports to provide enough time for valid results.

For this reason, we set the criteria for acceptance of studies into the present review to be >5 years of follow-up or a median/mean follow-up of >3 years. This period of follow-up provides validity by ensuring sufficient time after RT for most ORN to have occurred. Longer follow-up might be desirable but may not be entirely possible, owing to the limitation imposed by the survival rate of head and neck cancer patients. This minimum follow-up period was also set to conform with the findings in the literature where it is reported that 90% or more of ORN cases occur within the first 3 years after RT.[14,15,50,51] Others have found that 70%-80% ORN developed within the first 3 years.[45,52-54] Shorter mean and median times to onset of ORN after RT of <6 months and 13 months, respectively, also have been reported.[20,55]

ORN is defined as an area of exposed devitalized irradiated bone that fails to heal over a period of 3-6 months in the absence of local neoplastic disease.[48,54,56-58] In reporting late radiation toxicity, however, several scoring systems are used to describe the

Table IV. Articles selected for final analysis

No.	Author	Year	Follow-up	Total patients	ORN cases	Criteria of diagnosing ORN	Cancer location	Curative vs. adjunctive
1	Suwinski et al.[21]	2008	48 mo	274	4	RTOG/EORTC	Head and neck	Adjunctive
2	Racadot et al.[22]	2008	106 mo	103	2	RTOG/EORTC	Head and neck	Adjunctive
3	Cummings et al.[23]	2007	6. 9 y	331	3	RTOG/EORTC	Head and neck	Curative
4	Skladowski et al.[24]	2006	96 mo	90	2	RTOG/EORTC	Head and neck	Curative
5	Fallai et al.[25]	2006	8.35 y	112	0	Y/N	Oropharynx	Curative
6	Semrau et al.[26]	2006	57.3 mo	240	17	Y/N	Head and neck	Curative
7	Mendenhall et al.[27]	2005	38 mo	101	4	Y/N	Head and neck	Curative
8	Budach et al.[28]	2005	5 y	322	18	RTOG/EORTC	Head and neck	Curative
9	Huguenin et al.[29]	2004	39.5 mo	211	7	RTOG/EORTC	Head and neck	Curative
10	Cooper et al.[30]	2004	45.9 mo	409	8	RTOG/EORTC	Head and neck	Adjunctive
11	Denis et al.[31]	2003	5.5 y	44	1	NCI-CTC and LENT/SOMA	Oropharynx	Curative
12	Corvo et al.[32]	2001	60 mo	32	0	Y/N	Head and neck	Curative
13	El-Weshi et al.[33]	2001	55 mo	34	0	RTOG/EORTC	NPC	Curative
14	Ang et al.[34]	2001	59 mo	182	3	RTOG/EORTC	Head and neck	Adjunctive
15	Inoue et al.[35]	2001	78/85 mo	51	2	Y/N	Tongue	Curative
16	Fu et al.[36]	2000	41.2 mo	1,029	17	RTOG/EORTC	Head and neck	Curative
17	Jeremic et al.[37]	2000	79 mo	130	7	RTOG/EORTC	Head and neck	Curative
18	Brizel et al.[38]	1998	41 mo	116	2	Y/N	Head and neck	Curative
19	Eschwege et al.[39]	1997	5 y	374	0	RTOG/EORTC	Head and neck	Curative
20	Dische et al.[10]	1997	6 y	918	8	Y/N	Head and neck	Curative
21	Maor et al.[40]	1995	3.5 y	135	4	RTOG/EORTC	Head and neck	Curative
22	Lee et al.[41]	1995	3.38 y	504	8	RTOG/EORTC	Head and neck	Curative
Total				5,742	117	2.04%		

NPC, Nasopharyngeal carcinoma; other abbreviations as in Table III.

Table V. Osteoradionecrosis (ORN) incidence in relation to tumor site, treatment aims, radiation delivery mode, jaw involved, and dental evaluation

Variable	Articles	Total patients	ORN cases	%
Tumor sites				
Head and neck	10, 21-32, 34-41	5,708	117	2.04%
Nasopharynx	33	34	0	0%
Sinonasal	—	0	0	—
Treatment				
Adjunctive	21, 22, 30, 34	968	17	1.76%
Curative	10, 23-29, 31-33, 35-41	4,740	100	2.11%
Delivery				
EBRT	10, 21, 23-25, 28, 29, 31-33, 36-39, 41	4,521	77	1.70%
Brachytherapy	35	51	2	3.92%
IMRT/3D-CRT	—	—	—	—
Not clear	22, 26, 27, 30, 34, 40	1,170	38	3.25%
Mandible/maxilla				
Mandible	21, 22, 24, 25, 27, 31, 35	775	15	1.94%
Maxilla	—	—	—	—
Not reported	10, 23, 26, 28-30, 32-34, 36-41	4,967	102	2.05%
Dental evaluation				
Reported	22, 23, 26, 30, 31, 34, 36	2,338	51	2.18%
Not reported	10, 21, 24, 25, 27-29, 32, 33, 35, 37-41	3,404	66	1.94%

"event" of ORN. None of these scoring systems conforms perfectly to the definition. The most common scoring system used is the RTOG/EORTC Late Radiation Morbidity Scoring Scheme, which was introduced in 1984.[1] This scoring system is stratified to different grades based on signs and symptoms of bone toxicity (Table VIII). Grade 4 of this scoring system includes bone necrosis and spontaneous fracture, which fit the symptoms and description of advanced ORN. Grade 3 of the RTOG/EORTC classification, however, is less definitive. While severe bone pain is a symptom of ORN, no mention is made of bone exposure or sequestrum in grade 3. This lack of specificity is likely due to this classification not being designed specifically for ORN of the jaws but rather to report the radiation bone toxicity for the whole skeletal system. In this review,

Table VI. The use of chemoradiotherapy (CRT) and osteoradionecrosis (ORN) incidence

		ORN with CRT		*ORN with RT only*	
		n	%	*n*	%
Curative					
Fallai et al.[25]	2006	0/39	0%	0/73	0%
Semrau et al.[26]	2006	10/113	8.9%	7/127	5.5%
Budach et al.[28]	2005	10/164	6.1%	8/158	5.1%
Huguenin et al.[29]	2004	3/105	2.9%	4/106	3.8%
Denis et al.[31]	2003	1/27	3.7%	0/17	0%
Corvo et al.[32]	2001	0/20	0%	0/12	0%
Jeremic et al.[37]	2000	4/65	6.2%	3/65	4.6%
Brizel et al.[38]	1998	0/56	0%	2/60	3.3%
Subtotal		28/589	4.75%	24/618	3.88%
Adjuntive					
Racadot et al.[22]	2008	0/52	0%	2/51	3.9%
Cooper et al.[30]	2004	6/201	3.0%	2/208	1.0%
Subtotal		6/253	2.37%	4/259	1.54%
Total		34/842	4.04%	29/877	3.19%

Table VII. Use of altered fractionation and osteoradionecrosis (ORN) incidence

		ORN with altered fractionated RT		*ORN with control*	
		n	%	*n*	%
Hyperfractionation					
Cummings et al.[23]	2007	2/169	1.2%	1/162	0.6%
Fu et al.[36]	2000	7/253	2.8%	4/254	1.6%
Subtotal		9/422	2.13%	5/416	1.20%
Accelerated fractionation without total dose reduction (curative)					
Fallai et al.[25]	2006	0/37	0%	0/36	0%
Skladowski et al.[24]	2006	2/50	4.0%	0/40	0%
Fu et al.[36]	2000	6/522	1.2%	4/254	1.6%
Subtotal		8/609	1.31%	4/330	1.21%
Accelerated fractionation without total dose reduction (adjunctive)					
Suwinski et al.[21]	2008	4/137	2.9%	0/137	0%
Ang et al.[34]	2001	1/76	1.3%	2/75	2.7%
Subtotal		5/213	2.35%	2/212	0.94%
Accelerated fractionation with total dose reduction					
Dische et al.10	1997	2/552	0.36%	6/366	1.64%
Subtotal		2/552	0.36%	6/366	1.64%
Total		24/1796	1.34%	17/1,324	1.28%

Table VIII. Late radiation bone toxicity according to the Radiation Therapy Oncology Group scoring criteria

Grade	*Bone morbidity*
0	None
1	Asymptomatic; no growth retardation; reduced bone density
2	Moderate pain or tenderness; growth retardation; irregular bone sclerosis
3	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis
4	Necrosis; spontaneous fracture
5	Death directly related to radiation late effects

we accepted grades 3 and 4 of RTOG/EORTC as ORN, because their descriptions best fit the signs and symptoms of ORN. The LENT/SOMA scoring system, which was introduced to replace the RTOG/EORTC scoring system, is more specific in its description, which is based on subjective and objective signs and symptoms, management, and radiographic findings (Table IX).[3] It also specifies the mandible as one of its categories of late toxicity. The clearly described symptoms, clinical signs, and radiographic features allow interpretation of the severity of bone toxicity. A score of 3 or 4 using the LENT/SOMA scale was considered to be ORN for the purpose of this review. The LENT/SOMA scale, however, is not widely used, as is evident in the present review, with only 1 article using it (Table IV).[31] One further comment regarding the LENT/SOMA scale is that it specifies the mandible but omits the maxilla, so ORN in the maxilla would not be reported or would be reported as mandibular ORN, which would cause underreporting of ORN in the max-

Table IX. Late radiation mandibular morbidity according to the Late Effects of Normal Tissue/Somatic Objective Management Analytic scale*

	Grade 1	*Grade 2*	*Grade 3*	*Grade 4*
Subjective				
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Mastication		Difficulty with solids	Difficulty with soft foods	
Denture use		Loose denture	Inability to use dentures	
Trismus	Noted but unmeasurable	Preventing normal eating	Difficulty eating	Inadequate oral intake
Objective				
Exposed bone		≤2 cm	>2 cm or limited sequestration	Fracture
Trismus		1-2 cm opening	0.5-1 cm opening	<0.5 cm opening
Management				
Pain	Occasional nonnarcotic	Regular nonnarcotic	Regular narcotic	Surgical intervention or resection
Exposed bone		Antibiotics	Debridement, HBO2	Resection
Trismus and mastication		Soft diet	Liquid diet, antibiotics, muscle relaxant meds.	NG tube, gastrostomy
Analytic				
Mandibular radiograph	Questionable changes or none	Osteoporosis (radioluscent) osteosclerosis (radiodense)	Sequestra	Fracture
Panograph x-ray/CT		Assessment of necrosis progression		

*Instruction: Score the 9 SOM parameters with 1-4 (score = 0 if there are no toxicities); total the score and divide by 9.

illa and overreporting of ORN in the mandible. Another scale that has been used in reporting late bone toxicity is the NCI-CTC scoring system (Table X). The newest version 4.0 of this scoring system specifies osteonecrosis of the jaws as a separate category, thus making it specific but broad enough to include the maxilla.[2] Only 1 article used the NCI-CTC scoring system in reporting late toxicity, and grade ≥1 in this system was accepted as ORN for the purpose of this review (Table IV). There are also a few articles that reported ORN as present or not without a scoring system (Table IV). Though deficient in measuring the severity of ORN, this is nevertheless a simple and flexible way of reporting ORN. The lack of uniform scoring, however, can cause differences in interpretation of ORN among different investigators, thus affecting the reporting rates.

The present systematic review attempted to provide conclusive data on the current risk of developing ORN in the irradiated head and neck population. The selection of only RCTs assures prospectively collected data and well planned assessment of bone toxicity. This provides a well known advantage over retrospective data, which are exposed to bias, inconsistent follow-up, and inorganized late toxicity assessment. Systematic review of RCTs also allows valid comparison between different RT modalities. The adoption of systematic reviews ensures a multicentered data collection which would allow generalization of the result. We limited this review to articles published from 1995 onward and recruitment of subjects after 1985 to get the current risk of developing ORN with sufficient follow-up period. Among 5,742 irradiated head and neck cancer patients since 1985, ORN occurred in only 117 of them. This puts 2 out of 100 irradiated head and neck cancer patients at risk of developing ORN and shows a declining trend compared with older studies (Table I) but is in agreement with more recent data.[59] The declining trend was also highlighted by Clayman, where he grossly compared ORN incidence reported in the literature before and after 1968 and noticed a reduction of incidence from 11.8% in the earlier period to 5.4% in the later period.[60] He selected 1968 as the comparison point because the use of megavoltage and supervoltage had by then replaced most orthovoltage machines in oncologic units.[60] Coincidentally, the implementation of a systematic dental program for patients undergoing head and neck irradiation also started during that period.[16,61,62] This combination of advances in RT technologies, better understanding of biologic tissue reac-

Table X. Bone toxicity according to the National Cancer Institute Common Toxicity Criteria

Grade	*Osteonecrosis of jaw*
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated
2	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL
3	Severe symptoms; limiting self-care ADL; elective operative intervention indicated
4	Life-threatening consequences; urgent intervention indicated
5	Death

ADL, Activities of daily living.

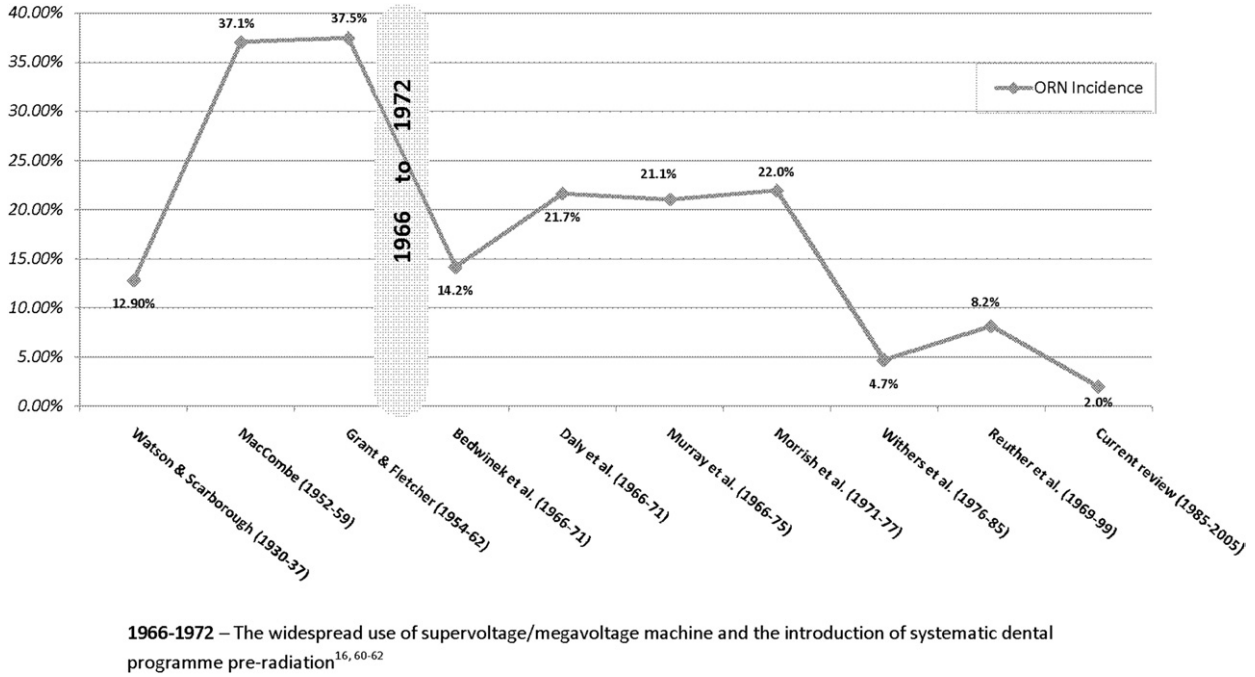

Figure 2. Osteoradionecrosis incidence rate trend.

tion to radiation and better oral health care among the irradiated population are the likely contributing factors to the sharp decline in ORN incidence seen in recent years (Figure 2).[55,63] Another possible explanation for the low incidence of ORN seen in the present review is the inclusion of all head and neck cancer sites. Earlier studies tended to show a higher incidence of ORN when they reported on high-risk cancer locations, such as the oral cavity.[12,13,17] The exclusion of reirradiation subjects in this review could also be a factor explaining the low rate of ORN. Further evidence supporting the diminished ORN risk may also be observed in postirradiation extraction ORN, where the incidence after 1990 was also much lower.[64]

Several factors are associated with increased risk of developing ORN. Some that have been suggested include gender,[20] tobacco and alcohol,[20,43] tumor site or stage,[20,43,45,47,53] invasion or proximity of tumor to bone,[17,20,43,47,53,54] dental health status,[17,43] treatment type (EBRT, brachytherapy, neutron beam),[17,46,48,54] chemoradiotherapy,[20,43,46] radiation dose,[20,45-47,50,54,55,65,66] trauma to the bone (extraction, denture-related, cancer surgery),[20,43,45,46,48,66] and dose rate/fractionation.[46,53,54] In the present systematic review of articles reporting outcome of radiation therapy, we aimed to investigate the radiation-related risk factors, including the location of tumor, radiation delivery methods, curative or adjunctive therapy, different fractionation schedules, and the use of CRT. The reporting of dental evaluation before RT and location of ORN were also investigated.

Risk of ORN for different tumor locations

Tumor site is an important factor in predicting ORN risk. Within the head and neck, oral cavity tumors, especially of the tongue, floor of mouth, alveolar ridge, or retromolar region, are sites with the highest risk of developing ORN after irradiation, owing to their proximity to the mandible.[12,20,47,52,67,68] Tumors originating in the sinonasal or nasopharyngeal areas present a higher risk for developing ORN in the maxilla.[69-71] The importance of tumor location as a risk factor can be explained by the inclusion of the jaws in the field of radiation. As observed by Glanzmann and Gratz, no cases of ORN were seen in their series when a head and neck tumor located outside the oral cavity, oropharynx, or nasopharynx regions was irradiated.[53] This is further supported by the findings of Thorn et al., who reported that all but 1 of 80 ORN cases in their series occurred inside the radiation field.[45] The differences in tumor site also determine if parts of the jaws are included in the radiation field.[72] An example of this is in nasopharyngeal tumors, where most of the radiation dose would include the posterior maxilla and mandible,[69,71-73] whereas in sinonasal tumors the whole maxilla would be included in the irradiation treatment volume.[70] The significance of the relationship of tumor locations and radiation field to the occurrence of ORN can be observed in earlier studies. Reuther et al., who reviewed a series of 830 patients of oral cavity, lip, and oropharyngeal tumors, noted that only 1 out of 68 ORN cases developed in the maxilla.[20] Madani et al. reviewed 84

cases of sinonasal tumor and observed only 1 case of maxillary ORN and none in the mandible, thus agreeing with findings by Homma et al. of 5 maxillary and 1 mandibular ORN observed in a series of 47 sinonasal tumor patients.[70,74] In their series of 1,758 cases of nasopharyngeal carcinoma, Cheng et al. reported 48 and 30 cases of ORN seen in the maxilla and mandible, respectively.[71] Based on these findings, it can be postulated that tumors of the oral cavity or oropharyngeal region would result in a higher incidence rate of ORN because of the inclusion of the mandible in the radiation field. Tumors of nasopharyngeal or sinonasal origin may present a lower risk of ORN owing to the maxilla being more resistant to radiation necrosis and the exclusion of most of the mandible from the radiation field. One of the aims of the present systematic review was to confirm these differences in tumor location effects on the risk of ORN. However, we could not achieve this aim, because most studies reported treatment outcome in the head and neck region without further subdividing data according to specific tumor sites.

Risk of developing ORN when CT agents were used

Chemoradiotherapy (CRT) offers better locoregional control and overall survival[5,75] and is also used to eradicate micrometastases.[5,76] It is divided into induction, concomitant, or adjuvant therapy based on the timing of CT in relation to the RT.[5,77] CRT has been shown to increase acute toxicity especially mucositis,[30,78] but its effect on late toxicity is less clear.[22,26,28-30] Others have found an increase in late toxicity with the use of CRT.[31,79] When they looked specifically at the ORN risk, Glanzmann and Gratz found no increased risk of ORN when CT was added to the RT regimen.[53] Reuther observed earlier occurrences of ORN when CT was used in combination with RT.[20] In the present review, 10 trials compared the use of CRT with RT alone. Five studies reported worse ORN outcome when CRT was used compared with 3 when RT alone was used. Two other studies reported no difference. This variable outcome indicates that the addition of CT agents to RT does not appear to increase the risk of developing ORN.

Risk of developing ORN in curative RT or adjunctive RT with surgery

It has been suggested that ablative surgery, including bone resection or osteotomy before radiation is associated with the development of ORN in the residual or healing bone.[17,20,43,45,46,80-82] Marx and Johnson found that among 536 ORN cases, 48 of them were considered to be directly caused by the ablative surgery before radiation, and Thorn et al. observed that 10% of ORN in their series were initiated by the tumor surgery.[45,46] Specific procedures, such as mandibulotomy and mandibulectomy have been considered to cause an increased risk of developing ORN after radiation.[80,81,83-85] Other observations suggested that when more radical surgery on the bone is performed, ORN will occur sooner.[20] In the present review, when subjects who received curative RT were compared with those receiving adjunctive RT, no important difference in the risk of developing ORN was seen. A possible explanation for this finding is that the higher ORN risk associated with surgical procedures is similar to that which is associated with the more aggressive therapy of curative intent.

Incidence with different delivery techniques

Different radiation delivery methods are said to present different levels of risk for developing ORN of the jaws.[17,46,48,52,54,86] Brachytherapy has been implicated in a higher risk of developing ORN.[17,54] It is postulated that because of the proximity of the implant source to the bone, an increased radiation dose is absorbed.[86] The increased incidence of ORN cases related to brachytherapy could also be related to the tumor site, because it is used frequently in tongue cancer. The use of a spacer has been reported to reduce the risk of developing ORN in such cases.[87,88] More recently, advances in the delivery of RT, such as 3D-CRT or IMRT, have raised optimism in the probability of reducing the risk of developing ORN.[63,89,90] With the use of these modalities, parts of the mandible can be spared, thereby reducing the risk of ORN.[63,89] Although IMRT has the potential to reduce the incidence of ORN by excluding the mandible from the high-dosage radiation field, IMRT has primarily been assessed in prospective trials only for its ability to exclude the parotid gland from the radiation field to reduce xerostomia.[7-9,91] This is exemplified in a multiinstitutional trial by Eisbruch et al., in which the primary objective of the trial was to assess the feasibility of parotid gland sparing with the use of IMRT.[92] With dose constraint to the mandible set to 70 Gy, 6% of patients developed ORN in that trial.[92]

The location of the tumor also plays a part in the possibility to exclude the mandible from the radiation field.[93] In tumors of the oral cavity, parts of the mandible would be within the target volume.[89] The exclusion of the jaws from the radiation field could be better achieved in tumor locations distant from the jaws, such as nasopharyngeal carcinoma.[72] So far, there have been no RCTs reporting the bone toxicity outcome of IMRT compared with other radiation delivery methods. Data supporting the benefit of IMRT in preventing ORN also have been weak, with only retrospective case series showing reduced incidence of ORN after IMRT.[63,89,93,94] Other studies show no reduced risk with the use of IMRT.[92,95] Without a control arm, it is difficult to assess the benefit of

IMRT in reducing the risk of ORN, owing to the heterogeneity of RT regimens and other confounding factors. Most RCTs on 3D-CRT or IMRT have reported only their efficacy in preventing xerostomia.[8,9,91,96] It should be pointed out that by preventing xerostomia, the risk of developing ORN could be indirectly reduced owing to the improvement of oral health following the preservation of saliva production in the mouth.

Difference in risk with different dose rates and treatment time

Although it is known that the associated risk of developing ORN increases with higher RT doses,[19,20,45,47,53,54,97] the effects of altered fractionation regimens to ORN risk is less clear. Conventional RT is usually described as 1.8-2.0 Gy once daily, 5 days a week, over 4-8 weeks.[77] Altered fractionation involves modification of this delivery schedule and is usually divided into hyperfractionation and accelerated fractionation. The use of altered fractionation schedules is associated with better locoregional control and survival rate.[11] In these altered fractionation schedules, beside the total dose, other factors, such as dose per fraction and interfraction interval, could also influence the outcome of late toxicity.[19,53,82] Hyperfractionation involves delivering an increased total dose and number of fractions with smaller dose per fraction to enable better tumor control while not increasing the late toxicity associated with increased doses.[77]

Data on the effects of hyperfractionation schedules on ORN risk have been conflicting. Struder et al.[98] reported reduced incidence of ORN with the use of hyperfractionation, agreeing with the conclusion of Glanzmann and Gratz.[53] In contrast, Niewald et al. observed an increased risk with its use, which was mainly attributed to reduced interfraction interval.[82] In the present review, 2 trials compared the use of hyperfractionation with conventional regimens. Both of those trials found a slight increase of ORN incidence in the hyperfractionated group, but because of the very minimal difference in incidence and the inclusion of only 2 trials, the effects of confounding factors on this finding cannot be excluded.

Accelerated fractionation is the shortening of treatment time in an attempt to prevent tumor repopulation.[77] There has been suggestion of possible reduced ORN risk with its use.[98] The present review concluded that there was no difference in the risk of developing ORN with the use of accelerated fractionation without dose reduction, based on 2 trials showing reduced incidence and 2 others showing an increased risk. When accelerated fractionation with total dose reduction is used, there is a reduction in ORN incidence compared with conventional fractionation, a finding that is expected owing to the total dose reduction.

Risk for the mandible and maxilla

This review further supports earlier reports that the mandible is at a higher risk of developing ORN.[18,20,43,45,47,54] The pattern of mandibular blood supply has been implicated as the primary reason for this predilection.[45,99] Others suggest that this observation can be attributed to the fact that the mandible is included in the radiation field more frequently than the maxilla.[45,55,100] In the present review, only 7 articles provided information on the location of ORN in relation to the mandible or maxilla. None of the articles reported the presence of ORN in the maxilla. Besides the vulnerability of the mandible, this finding is also in line with the lack of articles on the nasopharynx and sinonasal region in this review. The failure in most trials of reporting the location of bone toxicity can be attributed to the use of the RTOG/EORTC toxicity scale in most articles.

Reporting of dental evaluation

More than two-thirds of articles included in the present review failed to report dental assessment. The importance of dental evaluation and treatment before radiation cannot be overemphasized. Most reported ORN cases developed directly owing to a dental cause, such as tooth extraction due to dental caries or periodontal disease.[45,46,54] Reporting of dental evaluation is important to assess the effectiveness and the outcome of such protocols in preventing ORN. Detailed reporting of the dental protocol should be included in published studies so that effective protocols are identified and followed. Recent efforts by the RTOG to specify prophylactic dental care guidelines is a step in the right direction.[63,92] In the present review, we noted 7 articles that reported dental evaluation. None, however, reported it in detail or made reference or mention of the protocol adhered to. When the incidence of ORN in articles that reported dental evaluation before RT was compared with the remaining articles, there was no increase in ORN incidence in the nonreporting group.

Conclusion

Our results estimate that 2 out of 100 irradiated patients are at risk of developing ORN. This provides information on the risk of developing ORN in the largest collection of irradiated population with uniform selection criteria and prospectively collected data. The low incidence can possibly be explained by the increase in oral hygiene awareness, better radiation technologies, inclusion of low-risk and high-risk tumor sites, and the exclusion of reirradiation patients. This risk is a general

estimation for the whole of the head and neck cancer population undergoing irradiation. As with other risk estimation, an increased risk is expected in patients with known risk factors for ORN, such as poor oral health, gender, tobacco/alcohol consumption, etc. For example, when a patient undergoes radiotherapy for head and neck cancer, the general risk is 2%, but the risk would be higher (6.88%) among the subset of this population that undergoes postirradiation tooth extraction.[64]

It is also assumed that the risk could be higher in specific tumor sites, such as oral cavity tumors, information that this systematic review unfortunately failed to provide. Patients receiving adjunctive RT, accelerated fractionation, and CRT show no definitive increase in ORN risk. Accelerated fractionation with dose reduction shows that a lower radiation dose is associated with a lower risk for ORN. Hyperfractionation, in contrast, shows a possible increased risk. On the whole, the risk stratification for this unique late radiation toxicity risk appears to be dependent not entirely on radiation damage but also on the influence of external factors, such as gender, tobacco/alcohol use, dental health status, or trauma to the bone, highlighting ORN risk as being of multifactorial etiology. Future research is needed to confirm the differences in the risk of developing ORN related to tumor location and various radiation delivery techniques. The specific effect of preradiotherapy dental assessment on the risk of developing ORN also needs to be clarified.

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