

# Osteoradionecrosis of the Jaws: A Retrospective Study of the Background Factors and Treatment in 104 Cases

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**Purpose:** This study analyzed potential risk factors in patients who received radiation therapy and then developed osteoradionecrosis (ORN).

**Patients and Methods:** A group of 104 patients who developed osteoradionecrosis of the jaws were reviewed treated between 1972 and 1992.

**Results:** The most common affected site was the mandible (99 cases, 95.2%), followed by the maxilla (5 cases, 4.8%). Among all cases, 93 (89.4%) were induced-trauma ORN, and 11 (10.6%) were spontaneous ORN. The following risk factors were considered as predisposing factors for the appearance of ORN: Anatomic location of the tumor, tumor surgery, total radiation dose, dose rate/day, mode of radiation delivery, time from radiation therapy until the onset of ORN, and dental status. ORN developed more frequently with oral cancer than other head and neck cancers. The size of the tumor seemed not to influence the incidence of ORN except when the tumor invade the adjacent bone. Type of radiation delivery total bone dose, and modes of radiation appeared to influence the risk of ORN occurrence. After conservative treatment, 44 (42.3%) cases had complete healing and resolution 34 (32.6%) cases had a stable, chronic ORN process, and 26 (25.1%) cases had acute and progressive ORN.

**Conclusion:** An understanding of the risk factors is important in preventing ORN after radiation therapy.

Radiation therapy in combination with surgery has been a very common oncologic treatment of head and neck cancers. This form of treatment has provided high cure rates, but has also called increasing attention to its side effects. Osteoradionecrosis (ORN) is one of the most severe and serious complications of head and neck cancer treatment.<sup>1-7</sup>

The term *osteoradionecrosis* has been used to describe the loss of the covering oral mucosa and exposure of necrotic bone for a period longer than 3 months.<sup>8</sup> This process is usually associated with such

signs and symptoms as cutaneous fistulas, trismus, pain, and masticatory difficulties. The incidence of ORN varies depending on the institution, and reports in the literature range from 1% to over 30% of cases.<sup>2,3,4,8-11</sup>

The pathogenesis of ORN is defined by a sequence of radiation, hypovascular-hypocellular-hypoxic tissue formation, and trauma-induced or spontaneous mucosa breakdown leading to a nonhealing wound.<sup>9</sup> Endarteritis, hyperemia, hyalinization, cellular loss, hypovascularization, thrombosis, and fibrosis are the most common histologic findings in ORN.<sup>12-14</sup> A wide variety of factors have been correlated with ORN, some of them originating in the oral cavity.<sup>6,10,11,15-18</sup>

Many modes of radiation have been used to treat head and neck cancer. External radiation sources alone or in association with internal radiation sources are the basic therapies. Other types of external radiation sources available are supervoltage and megavoltage (Cobalt 60 and linear accelerator, respectively). Radium needles and cesium and iridium wires are good

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examples of low-dose brachytherapy. The mode of radiation delivery, total radiation dose, dose rate/day, and radiation fields have been correlated with development of ORN.

On radiographic investigation, ORN frequently shows an undefined radiolucency without sclerotic demarcation surrounding the necrotic zone, but radiopaque areas can be identified when bone sequestra is formed. Computed tomography and bone scintigraphy have been used to evaluate the extension and behavior of ORN.<sup>16</sup>

The objective of this study was to review retrospectively 104 patients with ORN of the jaws who were treated at our institution. A detailed description of factors contributing to the onset of ORN, the treatment given, and its results are reported. The possible correlation between the preradiation oral care and the risk factors for osteoradionecrosis was also evaluated.

### Patients and Methods

The medical records of 104 patients with ORN of the jaws who were treated at the Oral Surgery Department, A. C. Camargo Hospital, São Paulo, Brazil, between 1972 and 1992, were reviewed. All of the cases had a history of ORN of at least 3 months duration and a follow-up of at least 1 year. Imaging techniques were used to evaluate the extension of ORN and the results of its treatment. Intraoral radiography, panoramic radiography, computed tomography, and technetium 99 scintigraphy were routinely used in this investigation.

Information about primary tumor site, clinical tumor stage (TNM), and oncologic treatment were obtained from the patient records. A new individual patient file was developed to record the risk factors for the appearance of ORN in each case. The following features were considered as possible factors contributing to the appearance of ORN: anatomic location of the tumor, tumor surgery, total dose of tumor radiation, dose rate/

**Table 1. Incidence of ORN According to Anatomic Site of the Tumor**

Anatomic Site	Patients
Lips	8
Tongue	17
Gingiva	7
Floor of the mouth	27
Palate	6
Retromolar region	25
Oropharynx	2
Rinopharynx	6
Hypopharynx	2
Larynx	1
Salivary gland	3
Total	104

**Table 2. Incidence of ORN According to Clinical Stage of the Tumor**

TNM	N0	N1	N2	N3	Total
T1	8	1	1	—	10
T2	9	6	3	1	19
T3	9	6	2	2	19
T4	9	9	10	5	33
Tx	6	2	7	8	23
Total	41	24	23	16	104

day, mode of radiation delivery, time from radiation therapy to the onset of ORN, dental trauma after radiation therapy, and dental status.

### Results

Ninety-six of the patients reviewed (92.3%) were men, and eight (7.7%) were women. The age distribution ranged between 10 and 78 years, and the mean age was 48.1 years. Eighty-two patients (78.8%) were white, 15 (14.4%) were black, and seven (6.8%) were Japanese. The most commonly affected site was the mandible (99 cases, 95.2%), followed by the maxilla (5 cases, 4.8%). The anatomic sites and clinical stage of the primary tumor (TNM) for each case are shown in Table 1 and 2, respectively.

Therapy consisted of external beam radiation in 94 (90.4%) patients and a combination of external and implant sources in 10 (9.6%) patients. The combined radiation therapy was performed in seven patients with tongue cancer and in three patients with palatal cancer. The implant sources used were cesium and iridium wires, and the total dose ranged from 1,000 to 4,000 cGy. Of the 94 cases irradiated with an external beam, 84 (89.3%) received megavoltage delivery (linear accelerator 4 MeV) and 10 (10.7%) supervoltage delivery (cobalt 60). The total radiation dose ranged from 3,000 to 7,400 cGy. The incidence of ORN according to the total radiation dose is shown in Table 3.

Of the 104 cases of ORN, 93 (89.4%) were related to induced mucosal trauma and 11 (10.6%) to spontaneous mucosal breakdown. The trauma-induced ORN developed on average 18 months after radiation therapy, with a range from 15 days to over 192 months. Two bimodal peaks of incidence of trauma-induced ORN were identified, the first at 12 months and the second at 24 to 60 months after radiation therapy (Table 4).

The method in which ORN was treated is shown in Table 5. Complete healing and resolution of signs and symptoms were observed in only 44 (42.3%) cases. ORN healing occurred in 27 cases during the first 24 months after radiation therapy. An acute and progressive ORN process was observed in 26 (25.1%) patients,

**Table 3. Incidence of ORN According to Total Radiation Dose**

Total Radiation Dose	No. of Osteoradionecrosis Cases
<5,000 cGy	5
5,000-6,000 cGy	24
6,000-7,000 cGy	33
>7,000 cGy	42

leading to pathologic mandibular fracture in 10 (9.6%). A stable and chronic ORN process occurred in 34 (32.6%) patients (Table 5).

At the end of the study, nine patients (6.9%) were lost to follow-up. Twenty patients (19.2%) were alive with ORN, and 33 (31.7%) were alive without ORN. Thirty-four (34.6%) died with active ORN, and eight (7.6%) died without ORN. None died because of ORN.

### Discussion

The incidence of ORN at our institution could not be determined in the current study because the total number of patients submitted to radiation therapy during this period was not available. However, according to the studies reported in the literature, ORN has been a very serious side effect of head and neck cancer treatment and has not decreased in the last decades, as indicated by the unchanged number of new cases reported per year.<sup>1-7</sup>

In this study, age and sex distribution were in accordance with the population profile of patients with head and neck cancer. ORN occurred more often in the mandible (99 cases 95.2%) than in the maxilla (5 cases, 4.8%). The higher susceptibility of the mandible has been reported to be attributable to its lower blood supply compared with the maxilla.<sup>2,4,14</sup> The compact bone structure of the mandibular bone has also been suggested as a reason for ORN susceptibility.<sup>2,4,14</sup>

It has been discussed whether the primary tumor site may influence the onset of ORN.<sup>3,4,6,8,14,19</sup> In our study, a positive correlation was identified between tumor site and ORN incidence. Oral cancers (82 cases, 78.8%)

**Table 4. Incidence of ORN According to the Time (mo) After the End of Radiation Therapy**

Time (mo)	No. of Osteoradionecrosis (%)
<12	60 (57.7)
12-24	11 (10.6)
24-60	22 (21.1)
>120	7 (6.7)
Ign	4 (3.9)
Total	104 (100)

**Table 5. Treatment of 104 Patients With Osteoradionecrosis**

Treatment	No. of Patients
Clinical (BCG, antibiotics, etc.)	83
Clinical + sequestrectomy	16
Clinical + resection	5

showed the highest incidence of ORN, especially those of the tongue, retromolar region, and floor of the mouth. In our opinion, possible reasons for the higher incidence of ORN at these oral sites are the direct involvement of the mandibular bone in the radiation fields and the aggressive and radical surgical approach necessary for tumor resection. These surgical procedures often consist of mandibular osteotomies or mandibulectomies that are traumatic to bone tissue. Other head and neck cancer sites did not need osteotomy or mandibulectomy for tumor resection, and therefore there was less trauma to bone tissue. In the current study, we observed that the aggressive surgery necessary for oral cancer resection frequently involved removal of arteries necessary for the maintenance of mandibular blood flow, possibly increasing the risk of ORN.<sup>20</sup> Other authors agree about a positive relation between ORN and tumor primary site.<sup>3,6</sup>

ORN has been correlated with more advanced tumors and with tumor invasion of adjacent bone.<sup>2-4,6,8</sup> The current study showed no difference in ORN incidence when tumor size increased from T1 to T3. However, when the tumor invaded the adjacent bone, the number of ORN cases increased abruptly. Thirty-three cases of T4-stage developed ORN in two cancer treatment conditions: patients with surgically unresectable tumors submitted to radiation therapy that resulted in ORN because of tumor necrosis, and patients submitted to surgical treatment followed by radiation therapy with insufficient time for wound healing. No difference was observed when the neck was N1, N2, or N3, but there was a significantly higher incidence of ORN when the neck was NO. In long-term head and neck cancer follow-up, patients with no cervical metastases have a better prognosis than patients with cervical involvement and therefore are at higher risk to develop ORN.

The modes of radiation, the total radiation dose, and the dose rate/day have been correlated with ORN.<sup>2-4,6,9,12,14,18-22</sup> In our study, 94 (90.4%) patients were radiated with an external beam source, and 10 (9.6%) patients were radiated with an external beam source plus an implant source. The external radiation dose to the tumor site ranged from 3,000 cGy (85 cGy/day, 35 fractions) to 7,400 cGy (210 cGy; 35 fractions), with an average dose of 5,950 cGy (170 cGy/day; 35 fractions). Few patients (5 cases, 4.8%) developed ORN

when the total dose and the dose rate were below 5,000 cGy (140 cGy/day; 35 fractions). These results agree with other studies showing a positive relation between increased risk of ORN and mode of irradiation, implant source and total dose.<sup>2-4,6,9,12</sup>

We identified 44 (42.3%) patients who received preradiation oral care and 60 (57.7%) who did not. The role of preradiation oral care was to prevent and reduce the risk of radiation caries and ORN. According to oral health conditions, patient wishes, socioeconomic status and prognosis of the cancer stage, a decision was made about the patient's dental management before starting radiation therapy. If significant dental caries was seen in the field of radiation on the occasion of the preradiation oral assessment, and a high risk of ORN development was foreseen, clinical and surgical approaches were adjusted accordingly.

Patients who maintained good dental health before radiation therapy were included in an intensive preventive program, which was then continued for years after the end of treatment. It consisted of regular dental prophylaxis, restoration of carious lesions of salvage teeth, endodontic therapy, and home care oral hygiene instructions. Fluoride gel (1%) was administered to the patients for daily home self-application using custom-made trays. Patients who required tooth extraction and a surgical approach before radiation therapy were submitted to a procedure involving minimal trauma that consisted of reflection of mucoperiosteal flaps, alveolectomy, and primary closure without tension. Our team believes that a healing time is necessary for the oral mucosa at the surgical site before oncologic treatment is started. Usually this on healing time ranges from 7 to 10 days.

Spontaneous or "idiopathic" ORN occurred in 11 (10.6%) cases, whereas trauma-induced ORN occurred in 93 (89.4%) cases. The average time for onset of trauma-induced ORN was 18 months after radiation therapy and ranged from 15 days to over 192 months. In agreement with Marx and Johnson's study,<sup>12</sup> we also found two peaks of trauma-induced ORN, the first peak within the initial 12 months and the second 24 to 60 months after the end of radiation therapy. In the first peak, no significant difference was observed between patients who received preradiation oral care and those who did not with respect to the risk factors of trauma-induced ORN. Tumor surgery and tumor necrosis were the main contributing factors to the appearance ORN in this initial phase. Only 16% of the cases could be correlated to factors originating from oral and dental infections during this period. (Table 6).

The second peak of trauma-induced ORN differed greatly from the first peak. Oral and dental factors were involved in 60% of cases of ORN. These basically consisted of exodontia performed by general practitioners who believed that tissue radiation injury de-

**Table 6. Relation Between Preradiation Oral Care and Contributing Factors to ORN Appearance**

Factors of ORN Onset	Patients With Oral Care (%)	Patients With No Oral Care (%)
Tumor surgery	14 (13.5)	30 (28.8)
Tumor necrosis	13 (12.6)	10 (9.6)
Exodontia	3 (2.9)	10 (9.6)
Dental abscess	—	5 (4.8)
Injury from prosthesis	6 (5.7)	—
Periodontal disease	2 (1.9)	—
Spontaneous breakdown	6 (5.7)	5 (4.8)
Total	44 (42.3)	60 (57.7)

creases months/years after the end of radiation therapy. In the current study, seven (6.7%) patients developed ORN after tooth extraction performed by general practitioners more than 120 months after the end of radiation therapy. None of these patients had been instructed about the risk of ORN if surgical dental procedures were done. Pretherapy oral care seems to play an important role in preventing trauma-induced ORN in this second peak. There is disagreement in the reviewed literature concerning the risk of onset of ORN within the years after the end of the radiation therapy.<sup>2,8,14 15,18</sup>

During the 20 years of this study, many different methods of treatment were used, although they basically consisted of conservative and radical approaches. In the conservative approach, patients were seen weekly by the physician, and local debridement of the wound was performed with antiseptic solutions such as chlorhexidine digluconate (0.12% aqueous solution) and a combination of sodium iodite (2%) and peroxide (10%). The patients were also instructed to rinse the mouth with the antiseptic solution every day at home. Decortication and fenestration with burs were done when necessary. Contributing factors to the maintenance of local infection, such as fixation plates and screws, were removed on exposure as the ORN wound increased in size. Sequestrectomy was only performed when a sequestrum was identified by radiologic techniques. Analgesics and antiinflammatory drugs were prescribed when the physicians judged it necessary (increasing signs and symptoms of pain, discomfort, etc.). When surgery was performed, antibiotic therapy consisted of 1 week of cephaloxitin 500 mg orally four times daily, starting 1 day before surgical treatment. Radical treatment was only performed when extension of ORN impaired the continuity of the mandible. The therapy consisted of mandibular resection without any attempt at mandibular reconstruction.

The conservative treatment used at our institution obtained high cure rates when compared with other studies reported in literature.<sup>6,15</sup> Complete ORN healing occurred in 44 cases (42.3%), stable/chronic ORN

in 34 cases (32.6%), and acute/progressive ORN in 26 cases (25.1%). Hyperbaric oxygen (HBO) therapy has been used to promote tissue revascularization after radiation therapy.<sup>12,14,20,23,24</sup> It has also been used after radiation therapy to prevent ORN development when surgical procedures are necessary. HBO treatment alone seems to be ineffective in controlling the ORN process, but it can be very helpful when associated with a surgical approach.<sup>11,19,20,22</sup>

Hyperbaric oxygen therapy was used in only one case because other patients had economic difficulties. HBO treatment was used because of an aggressive ORN process on both sides of the mandible that led to pathologic fracture on one side. After 35 sessions of HBO treatment (2.4 ATA 90 minutes/day) the patient underwent a sequesterectomy. The acute/progressive ORN process became a less painful, asymptomatic stable/chronic ORN process. Since 1993, 10 of our patients have been treated with HBO therapy.

Osteoradionecrosis is one of the most serious oral complications of head and neck cancer treatment. The aim of all professionals involved in this treatment should be its prevention. Rehabilitation of the patient with ORN already present is extremely difficult and unpredictable. In our study, primary tumor site and clinical stage appeared to influence development of ORN. External radiation sources in association with implant sources, high total doses, and super and megavoltage delivery are factors that increase the risk of ORN. Preradiation oral care can be effective in preventing late trauma-induced ORN. The treatment of osteoradionecrosis varies, depending on the institution. Promising results can be expected with HBO treatment in conjunction with necessary surgery.

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