

Osteonecrosis in Patients Irradiated for Head and Neck Carcinoma

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One hundred patients irradiated for cancers of the oral cavity, oropharynx, and nasopharynx were evaluated for the occurrence of osteonecrosis and associated predisposing factors. Selection was based on availability of complete dental records, a minimum of six months follow-up, and treatment fields, which included maxilla and/or mandible. Bone doses were calculated by using radiotherapy treatment records, port films, and isodose distributions. Osteonecrosis developed in 19 of 78 dentulous patients and in 3 of 22 edentulous patients. The time of development of osteonecrosis varied; in 15 cases osteonecrosis occurred more than one year after treatment. The most important risk factor for the development of osteonecrosis was the radiation dose to bone, particularly in the less vascular mandible. Osteonecrosis developed in 85% of the dentulous patients and in 50% of the edentulous patients who received more than 7500 rads to the bone. None of the patients who received less than 6500 rads developed osteonecrosis. The risk was significantly greater when teeth were removed after therapy compared with those individuals with extractions before radiation or no extractions at all.

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OSTEORADIONECROSIS IS ONE of the more serious complications in head and neck irradiation for cancer. Bone cells and vascularity may be irreversibly injured. Fortunately, in many cases, devitalized bone fragments will sequester, and lesions spontaneously heal. However, when radiation osteonecrosis is progressive, it can lead to intolerable pain, fracture, and necessitate jaw resection. The therapeutic roles and efficacy of antibiotics and hyperbaric oxygen remain unpredictable and often ineffective.

The incidence of osteoradionecrosis varies de-

pending upon the reporting institution, aggressiveness of radiotherapy and follow-up time (Table 1). The risk for developing a spontaneous osteoradionecrosis is somewhat unpredictable and related to the dose of radiation delivered. The risk of osteonecrosis is increased if teeth within the treatment field are removed either before or after therapy.

The objectives of this study are to review retrospectively the occurrence of osteoradionecrosis in a selected group of patients irradiated for head and neck cancer at the University of California Medical Center since 1971 and to assess critically the contributory risk factors in the development of osteoradionecrosis.

Materials and Methods

For this study, osteoradionecrosis was defined as a pathologic process that developed following irradiation of osseous tissue and was characterized by a benign chronic mucosal ulceration with exposure of the jawbone of more than three months' duration. It was usually painful, and suppuration was not evident in many patients. Histologic non-vital (necrotic) bone was found in all patients who had eventual sequestration or resection. Most exposed bone areas radiographically demonstrated some degree of decalcification.

The study population consisted of 100 patients treated at the University of California, San Francisco, for cancers involving the oral cavity, oropharynx, and nasopharynx from January 1971 to July 1977. The

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TABLE 1. Incidence of Osteonecrosis in Patients Irradiated for Head and Neck Cancer* Reported in the Literature

	Hospital	Patient no.	Years	Dosage (rads)	Osteonecrosis
Bedwinek (1976)	M. D. Anderson, Texas	381	1966-71	6000-7500	54 (14%)
Dodson (1962)	Geisenberger, Virginia	108	1948-60	5000-9500	10 (9%)
Wildermuth (1953)	Swedish, Washington	104	1939-51	4000-8500	6 (6%)
Meyer (1958)	Westfield, Massachusetts	491	1940-57	4000-18,000	26 (5%)
Beumer (1972)	Univ. California, San Francisco	278	1961-69	5000-7000	10 (4%)
Carl (1973)	Roswell Park, New York	47	1968-72	3600-12900	2 (4%)

* Oral cavity, nasopharynx, oropharynx.

selection of these 100 patients from 534 who were treated during this period was based upon evaluation requirements of complete dental records and a minimum of six months follow-up. All patients received megavoltage external beam radiotherapy and/or interstitial radium or iridium implants. The maxilla and/or mandible were within the treatment fields. The group comprised 60 men and 40 women with an average age of 65 years. At the time of diagnosis, 78 were dentulous, and 22 were edentulous.

Records from the Departments of Oral Medicine and Radiation Oncology were reviewed for the following data: radiation dose and treatment modality, initial dental status, dental care including time of extractions, and the development and site of osteonecrosis.

Special care was taken to calculate the bone dose (energy absorbed by bone mineral in the primary treatment field) compared with the tumor dose based on the radiotherapy treatment records, port films, and isodose distributions. The dose of external beam radiotherapy was usually in the range of 5000-7500 rads delivered at 180 rads per fraction, five daily fractions per week. The total radiation dose included the dose from external beam and interstitial implant.

Results

Osteoradionecrosis developed in 22 of these 100 patients (Table 2). A higher percentage of dentulous patients developed osteonecrosis (24.4%) compared with those who were edentulous (13.6%); all but one necrosis developed in the mandible. There was no correlation between tumor size and the incidence of osteonecrosis (Table 3).

Thirty-nine of the 100 patients received a higher radiation dose to the bone compared with the tumor. The data were insufficient to properly evaluate osteonecrosis in relation to irradiated bone volume.⁶ The incidence of osteonecrosis appears to be directly related to the radiation dose to the bone (Table 4). Osteonecrosis developed in 85% of the dentulous patients and in 50% of the edentulous patients who received more than 7500 rads to the bone. None of the

patients who received less than 6500 rads developed osteoradionecrosis.

All patients were followed for at least six months. The time at which osteonecrosis developed was variable. In 15 of the 22 cases, it occurred more than one year after treatment was completed. In the edentulous patients, it appeared from 1 to 18 months (average ten months) after treatment; in the dentulous group, it appeared from 6 to 72 months after treatment (average 22 months). Follow-up observations of those who did

TABLE 2. Incidence of Osteonecrosis in 100 Selected Patients Irradiated for Head and Neck Cancer at U.C.S.F. (followup 6 to 76 months)

	Radiation dose to bone range in rads (av)	Number of patients with osteoradionecrosis
Edentulous	6480-9755 (7688)	3/22 (13.6%)*
Dentulous	4950-9700 (6192)	19/78 (24.4%)†
TOTAL	4950-9755 (6521)	22/100 (22.0%)

* All three occurred in mandible.

† 18 occurred in mandible; 1 in maxilla.

TABLE 3. Occurrence of Osteoradionecrosis Compared with Tumor Size

	Number of patients	Osteonecrosis
T1	16	5 (31%)
T2	52	8 (15%)
T3	28	8 (29%)
T4	4	1 (25%)
TOTAL	100	22 (22%)

TABLE 4. Incidence of Radionecrosis according to the Radiation Dose to the Bone

	Incidence of osteonecrosis	
	Dentulous patients	Edentulous patients
<6500 rads	0/36 (0%)	0/3 (0%)
6500-7500 rads	8/29 (27.6%)	1/15 (6.6%)
>7500 rads	11/13 (84.6%)	2/4 (50%)
TOTAL	19/78 (24.4%)	3/22 (13.6%)

TABLE 5. Association of Dental Extractions and Osteonecrosis in 78 Irradiated Dentulous Patients

	Occurrence of osteonecrosis	Radiation dose in rads—range (Average)	Average time of onset of osteonecrosis after treatment in months
No extractions	5/41 (12.2%)	6940–9280 (7871)	29
Before radiotherapy	3/19 (15.8%)	7580–9610 (8500)	41
After radiotherapy	11/18 (61.1%)	6700–8100 (7346)	20
TOTAL	19/78 (24.4%)	6700–9610 (7666)*	22

* Radiation in dentulous patients without osteonecrosis ranged between 4950–9700 rads (average 6450 rads).

not develop osteonecrosis ranged from 6 to 76 months (average 24 months).

Table 5 shows the incidence of osteonecrosis in relation to dental status and extractions. The risk was significantly greater for patients whose teeth were extracted after radiation therapy than for those with extractions before radiation or no extractions at all. Of the 14 dentulous patients who had osteonecrosis and who had extractions, the necrosis was associated with dental extraction sites in only nine and was apparently spontaneous in the remaining five. All nine cases of necrosis associated with dental extractions occurred with extractions after radiation.

Sixteen patients who had osteonecrosis were treated conservatively with supportive care. Four of these individuals were healed within 3 to 24 months, with an average of 12 months (Table 6). Ten of these 16 patients had persistent osteonecrosis that was clinically non-progressive, and two others with progressive necrosis refused suggested surgical intervention. The other six patients were managed surgically 11 to 36 months after appearance of the osteonecrosis; three had recurrences after surgery. Six patients with persistent osteonecrosis died from various causes 10 to 35 months after the exposed jawbone was first observed.

Discussion

Before 1971, osteoradionecrosis developed in less than 4% of our patients irradiated for cancer of the oral cavity, oropharynx, and nasopharynx. During this study, an attempt to improve the cure rate in patients with head and neck cancer with more aggressive radiation therapy may have led to an increase in complications. Osteonecrosis now seems to be a significant

problem apparently involving more than one in every five of this group of 100 selected patients. However, the scope of this retrospective analysis of osteoradionecrosis was limited by the fact that complete dental records were not available for all patients treated during the study period and that follow-up times varied. Therefore, the 22% osteonecrosis rate may not reflect the true incidence for all patients irradiated with malignancies of similar sites. Yet, certain facts emerged from our study:

1. Patients who were edentulous at the time of diagnosis of cancer had a relatively low risk for osteonecrosis.
2. Patients who were dentulous had a greater risk.
3. The increased risk in dentulous patients appeared to be associated with those who had tooth extractions following radiation therapy.
4. Dentulous patients with pretreatment extractions or no extractions appeared to have risks similar to the edentulous patients.
5. The most important risk factor for the development of osteonecrosis appeared to be the radiation dose to the bone, particularly in the less vascular mandible.

In our experience, the risk of osteonecrosis is negligible when the bone dose was less than 6500 rads but great when the dose exceeded 7500 rads. The occurrence of oral mucosal radiation complications had been estimated by Rubin⁷ to vary from 5–50% in patients who received 6500 to 7500 rads. Our data suggest that radiation tolerance of the mandible may parallel that of the oral mucosa. Fortunately for the patient's function and esthetics, the risk for osteonecrosis does not appear to be related to denture wearing.³

TABLE 6. Epicrises of 22 Patients with Osteoradionecrosis

	No. of patients	Associated cause	Management		Healed	
			Supportive	Resection	Yes	No
Edentulous	3	Spontaneous	2	1	1	2
Dentulous	10	Spontaneous	7	3	3	7
Dentulous	9	Extractions	7	2	3	6

Radiation dose to the bone was also an important consideration in the management of patients with osteonecrosis. From previous experience when the dose to the bone was relatively low,² most necroses could be managed conservatively, and spontaneous sequestration eventually occurred. However, in our current selected group of patients who received higher doses, necroses appeared to be associated with increased severity of pain and compromised function, and fewer resolved spontaneously. The question that eventually needs to be addressed is the balance between tumor cure rate and morbidity associated with more aggressive radiation therapy.

In view of the risk that accompanies high dose irradiation, special attention to pretreatment dental planning appears critical. Factors important in the dental management of these patients include the following: 1) anticipated bone dose¹; 2) pretreatment dental status, dental hygiene, and retention of teeth that will be exposed because of high dose irradiation^{4,5}; 3) extraction techniques; and 4) allowance of adequate healing time for teeth extracted before radiotherapy.⁸ We are now designing a prospective study to help de-

fine these parameters and to clarify risk factors, which should assist in establishing standards of dental care before radiation treatment of the head and neck cancer patient.

REFERENCES

1. Bedwinek J, Shukovsky LJ, Fletcher GH, Daley TE. Osteonecrosis in patients treated with definitive radiotherapy for squamous cell carcinomas of the oral cavity and naso- and oropharynx. *Radiology* 1976; 119:665-667.
2. Beumer J, Silverman S Jr, Benak S. Hard and soft tissue necroses following radiation therapy for oral cancer. *J Pros Dent* 1972; 27:640-644.
3. Beumer J, Curtis T, Morrish R. Radiation complications in edentulous patients. *J Pros Dent* 1976; 36:193-203.
4. Beumer J, Curtis T, Harrison RE. Radiation therapy of the oral cavity. I. Sequelae and management. *Head Neck Surg* 1979; 1:301-312.
5. Beumer J, Curtis T, Harrison RE. Radiation therapy of the oral cavity. II. Sequelae and management. *Head Neck Surg* 1979; 1:392-408.
6. Fu K, Chan E, Ray JW, Phillips T. Time, dose and volume factors in interstitial radium implants of carcinoma of the oral tongue. *Radiology* 1976; 119:209-213.
7. Rubin P, Casarett G. A direction for clinical radiation pathology. The tolerance dose. *Front Radiat Ther Oncol* 1972; 6:1-16.
8. Starcke EN, Shannon IL. How critical is the interval between extractions and irradiation in patients with head and neck malignancy? *Oral Surg* 1977; 43:333-337.