Clinical Report

The Influence of Radiation Therapy and Hyperbaric Oxygen Therapy on Osteoradionecrosis of the Jaw

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(Acceted for publication, November 19, 2012)

Abstract: The object of this study was to estimate the influence of radiation therapy (RT) and hyperbaric oxygen therapy (HBO) on osteoradionecrosis of the jaw (ORNJ). This retrospective study included patients who were diagnosed with ORNJ from 1998 to 2012 (15 years) and who recieved a total dose of RT (Gy) for the duration of the study. The duration of ORNJ development and the healing period of ORNJ were examined. The mean dose of RT was 64.0 Gy. The mean healing period of ORNJ was 30.3 months in the continuous RT group, and 20.8 months in the pre- and post-operative irradiation group. The healing term for ORNJ with HBO was approximately the same as that without HBO. We concluded continuous RT may induce more severe ORNJ than pre- and post-operative RT, and that the effectiveness of HBO on ORNJ is suspicious.

Key words: Osteoradionecrosis of the jaw (ORNJ), Hyperbaric oxygen therapy (HBO), Radiation therapy

Introduction

Radiation therapy (RT) is one of the most frequent options available to treat patients with malignant tumors that arise in the head and neck regions. Sometimes RT is used as an adjuvant treatment before and/or after surgical treatment (ST) and as a concurrent chemoradiation therapy (CCRT) or a palliative strategy for an inoperative case. However, the onset of osteoradionecrosis of the jaw (ORNJ) after irradiation can induce subsequent problems¹⁾. The complications induced by ORNJ, such as exposure of the bone, sequestrum formation and subsequent pain and swelling, and osteomyelitis due to spread of inflammation from exposed bone or periodontal diseases, afflict the patient greatly²⁻⁴⁾. Moreover, the larger lesions may necessitate unilateral resection or segmental resection of the jawbone, which may significantly degrade the postoperative quality of life (QOL) for patients^{2,5)}.

Hyperbaric oxygen therapy (HBO) is one of the familiar treatments for patients afflicted with osteoradionecrosis (ORN). Marx reported⁶⁾ that the pathophysiological feature of ORN was

represented by hypoxia, hypovascularization and hypocellularity (3-H concept). HBO is believed to improve these poor biological conditions by inducing angiogenesis^{7,8)} and stem cell mobilization⁹⁾, thus resulting in enhanced wound healing⁹⁻¹¹⁾. Since Henk's first application of HBO to ORNJ in the 1960s¹²⁾, there has been numerous reports of the effectiveness of HBO on ORNJ^{10,11)}. ORNJ was recognized as an indication for HBO in "delayed radiation injury (soft tissue and bony necrosis) in the 2003 Undersea Hyperbaric Medical Society Committee Report (UHMS)¹³⁾. In addition, in 2004 the European Committee for Hyperbaric Medicine (ECHM) strongly recommended HBO for the treatment of patients with radionecrosis of the mandible¹⁴⁾. However, while the effectiveness of HBO on ORNJ has been reported, there have been reports which questioned that effect^{15,16)}. As a result, the effectiveness of HBO on ORNJ thus remains controversial¹⁷⁾. We herein evaluated the effectiveness of HBO on ORNJ according to the results of our study and published reports.

Materials and Methods

Patients

Patients who received RT for the treatment of head and neck cancer, and who were subsequently diagnosed with ORNJ and

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Table 1. General information regarding the patients.

Case	Gender	Age	Site	ST	CT	pre-RT (Gy)	post-RT (Gy)	Total (Gy)
1	M	61	Tongue	+	+(STA)	39.6	20	59.6
2	M	59	Pharynx	NA	+(STA)	NA	NA	67.6
3	M	54	Pharynx	+	+(STA)	39.6	56	95.6
4	M	63	Palate	+	+(STA)	50	NA	50
5	M	73	Pharynx	NA	+(STA)	NA	NA	69
6	F	39	Tongue	+	-	40	30	70
7	M	52	Pharynx	+	+(STA)	30.6	20.4	51
8	M	60	Tongue	+	+(STA)	24	30	54
9	M	54	Tongue	+	+	NA	60	60
10	F	17	Tongue	+	+(STA)	36	24	60
11	M	60	Pharynx	+(delay)	+	66	NA	66
12	M	72	Maxilla	NA	+(STA)	NA	N	65.6

CT; chemotherapy, NA; not applicable, post-RT; post-operative radiation therapy, pre-RT; pre-operative radiation therapy, Site; the site of the primary lesion, ST; surgical treatment, STA; tubing into the superficial temporal artery for concurrent chemoradiation therapy

Table 2. The osteoradionecrosis data.

Case	P-1 (M)	P-2 (M)	HBO (T)	Se (T)	Ext (T)	ID (T)	Re (T)
1	12	38	60	4			
2	14	12	20	2	1		
3	3	8	0	1			
4	13	37	0	1			1
5	29	15	10	1			1
6	76	UT (95)	17	2		3	
7	11	7	5	2			1
8	36	39	40	2			
9	48	7	15	2			
10	3	UT (13)	30		1	3	
11	17	UT (69)	28	1	1		
12	14	UT (16)	0	2			

Ext; extraction of tooth which may cause the infection, HBO; hyperbaric oxygen therapy, ID; incision drainage, M; months, P-1; the period between the last radiation therapy (RT) and diagnosis of an osteoradionecrosis of the jaw (ORNJ), P-2; the period to achieve the healing of ORNJ, Re; reconstruction by bone transplantation or distraction osteogenesis, Se; sequestrectomy, T; times, UT; under treatment

Table 3. First symptoms when the patient was diagnosed as having osteoradionecrosis.

Symptom	swelling	bone exposed	fistula	pain	paresthesia of IAN	fever	redness	mobility of tooth	fracture	epistaxis
Number of cases	4	4	4	3	3	1	1	1	1	1

IAN: inferior alveolar nerve

received treatment for it from April 1998 to March 2012, were included in this study. This study received ethical approval from the institution.

Assessment

The general contents of the therapy for the primary diseases and ORNJ are shown in Tables 1 and 2, respectively. Table 3 also shows the initial symptoms at the time the patients were diagnosed with

Table 4. The influence of the total dose of RT on the incidence of ORNJ.

P-1 (M)	Number of cases	Dose (Gy)
- 12	3	68.9
12 – 24	4	65.6
24 -	4	63.3

M; months, P-1; the period between the last RT and diagnosis

Table 6. The influence of RT on the healing of ORNJ. The cases under treatment were excluded from this table.

Radiation therapy	Number of cases	Dose (Gy)	P-2 (M)
continuous irradiation	3	59.7	30.3
pre-and post-operative irradiation	5	65.6	20.8

M; months, P-2; the period to achieve the healing of ORNJ

Table 8. The effectiveness of the number of HBO on the healing of ORNJ. The cases under treatment were excluded from this table.

HBO (T)	Number of cases	Dose (Gy)	P-2 (M)
1 - 20	4	61.9	10.3
21 -	2	56.8	38.5

M; months, P-2; the period to achieve the healing of ORNJ, T; times

ORNJ. In order to examine the effect of RT on the incidence of ORNJ, the period before the onset of ORNJ following RT (period 1; P-1) was divided into three groups (less than 12 months, 12 to 24 months, and more than 24 months) and the average total irradiation dose (gray; Gy) in each group was calculated (Table 4). The healing period of ORNJ (period 2; P-2) was also divided into three groups similar to what was done for P-1, i.e., less than 12 months, 12 to 24 months, and more than 24 months, and the average total irradiation dose was calculated in each group (Table 5). RT was performed continuously until the total dose (RT-1) or it was done twice, before and after surgery (RT-2). To assess the difference between these two irradiation strategies, P-2 was compared between these two groups (Table 6). The effectiveness of HBO on ORNJ was estimated in the following two ways: 1) whether HBO was applied or not (Table 7); and 2) the relationship between P-2 and the number of HBO (Table 8).

Results

General information about the patients is presented in Table 1. Twelve patients (10 men; 2 women) were diagnosed with ORNJ from April 1998 to March 2012. One maxilla (case 12) and 11 mandibles suffered from ORNJ. The patients' age ranged from 17 to 73 years (mean 54.1 years) at the time their primary diseases were diagnosed as head and neck cancers. Primary cancer occurred

Table 5. The influence of the total dose of RT on the healing of ORNJ.

P-2 (M)	Number of cases	Dose (Gy)
- 12	3	68.9
12 – 24	2	68.3
24 -	3	54.5
UT (48.3)	4	65.4

M; months, P-2; the period to achieve the healing of ORNJ, UT; under treatment cases

Table 7. The effectiveness of HBO on the healing of ORNJ. The cases under treatment were excluded from this table.

HBO	Number of cases	Dose (Gy)	P-2 (M)
No	2	72.8	27.5
Yes	6	60.2	23.6

M; months, P-2; the period to achieve the healing of ORNJ

in the tongue (5 cases), pharynx (5 cases), palate (1 case) and maxilla (1 case). The average dose in 12 cases was 64.0 Gy (range 50-95.6 Gy). RT was performed continuously (RT-1) in 6 cases and RT pre- and post-operatively (RT-2) in the other cases. The combination of chemotherapy (CT) and RT with or without ST was performed in 11 cases (except for case 6). Concurrent chemoradiation therapy (CCRT) with tubing in the superficial temporal artery was performed in 9 of 11 cases. Case 11 was originally scheduled to receive the combination treatment with CT and RT; however, tumor recurrence was found 23 months after the original treatment and subsequently ST was performed.

The mean age of patients who were first diagnosed with ORNJ was 57.8 years (range: 18-5 years) (Table 2). P-1 ranged from 3 to 76 months (mean: 23.2 months). Healed ORNJ was observed in 8 cases and P-2 ranged from 3 to 39 months (mean: 20.4 months) in 8 healed cases. HBO therapy was applied in 9 cases. ST was performed in all cases. Sequestrectomy was selected in 11 cases, teeth extraction in 3 cases, and incisional drainage in 2 cases. Reconstruction of the mandible was performed in 3 cases after healing the ORNJ. There were multiple sequestrectomies or incisional drainage in some cases (Table 2). The initial symptoms of ORNJ are shown in Table 3. Swelling, bone exposure and fistula were observed in 4 cases, and pain and paresthesia of the mental region were detected in 3 cases. Fever, redness, tooth mobility, mandibular fracture and epistaxis were observed in one case (Table 3).

The influence of total radiation dose on ORNJ is shown in Tables 4 and 5. P-1 was less than 12 months in 3 cases (average radiation dose: 68.9 Gy), 12-24 months in 5 cases (65.6 Gy) and more than 24 months in 4 cases (63.3 Gy) (Table 4). Among 8 cases in which healing of ORNJ was observed, P-2 was less than 12 months in 3 cases (average radiation dose: 68.9 Gy), 12-24 months in 2 cases

Figure 1: Intraoral finding of case 8. An exposed bone (arrowheads) was found on the left side of the mandible.

Figure 2: Orthopantomography of case 8. A sequestrum (arrowheads) was separated from the left side of the mandible.

Figure 3: Computed tomography (axial image) of case 8. The sequestrum (arrowheads) was separated from the mandible similar to the OPG finding.

Figure 4: Histopathological findings of the extirpated specimen of case 8. The specimen included the sequestrum with empty lacunae (arrows). The bar represents 200 μ m.

(68.3 Gy) and more than 24 months in 3 cases (54.5 Gy). P-2 was 13-95 months in 4 cases receiving treatment; these 4 cases received more than 60 Gy (Table 5). ORNJ was healed in 3 of 5 cases; P-2 for these cases was 30.3 months (average radiation dose: 59.7 Gy) in the RT-1 group (Table 6). On the other hand, ORNJ was healed in 5 of 7 cases; P-2 was 20.8 months (65.6 Gy) in the RT-2 group.

HBO was applied to 9 of 12 cases and ORNJ was healed in 6 cases (P-2: 23.6 months). On the other hand, ORNJ was healed in 2 of 3 cases without HBO and P-2 was 27.5 months (Table 7). P-2 was 10.3 months (average radiation dose: 61.9 Gy) in cases who received HBO less than 20 times and 38.5 months (56.8 Gy) in cases who had HBO more than 21 times (Table 8).

The clinical findings of a typical case (case 8) are shown in Figures 1-4. The intraoral finding of the first visiting showed an exposed bone in the left mandible (Fig. 1). Orthopantomography and computed tomography (axial) images clearly showed a separated sequestrum from the mandible (Figs. 2 and 3). The histopathological findings of the extirpated specimen are shown in Figure 4.

Discussion

The incidence of ORNJ has been reported to be 5-15%^{5, 18-20)} after irradiation and the risk of ORNJ occurrence increased by more

than 60 Gy of RT for head and neck cancer²⁰⁻²²⁾. While the average radiation dose was 64.0 Gy, there were 3 ORNJ cases which were induced by 50 to 55 Gy in our study (Table 1). This suggests that the risk of ORNJ can increase when the total radiation dose to head and neck region is more than 50 Gy. Of course it depends on the irradiation region. Table 2 shows the big range of the P-1, from 3 to 76 months and in all cases except for case 6 in which ORNJ occurred within 5 years after RT. Previous reports²³⁾ are consistent with our results. Bagan *et al.*⁴⁾ reported that 60% of ORNJ patients were smokers in their study. In our study, 9 of 12 ORNJ patients (75%) were smoker (data not shown). According to these results, smoking may also be one of the risk factors for ORNJ.

In our study, sequestrectomy was mainly selected, in addition to HBO, as a treatment strategy for ORNJ. Silverstre-Rangil and Silverstre²⁾ classified ORNJ into three stages according to the severity of ORNJ. Based on their classification, surgical management was not recommended for the first stage which did not have any uncomfortable feeling. At the second and third stages, they adopted minor or major surgery. Several reports advocated that minor surgical intervention, such as sequestrectomy and curettage, should be the first choice for the second stage of ORNJ²⁴⁾ and ablation and reconstruction for the third stage^{24, 25)} since more severe cases should be more refractory. There are 7 cases which underwent multiple sequestrectomies in this study (mean P-2: 20 months), thus suggesting that ORNJ progression is usually refractory.

Based on the data in Tables 4 and 5, the total radiation dose appears to influence neither P-1 nor P-2. Interestingly, P-2 in the RT-1 group was longer than that in the RT-2 group (Table 6). It is believed that bone can be affected by continuous irradiation, thus resulting in more severe ORNJ in comparison to that observed pre- and post-operative irradiation.

Although HBO was recommended to treat ORNJ in two global committees^{13, 14)}, the effectiveness of HBO on ORNJ remains controversial. In the reports recommending HBO for the treatment

of patients with ORNJ, HBO was performed until the mucosa was closed. They showed the shorter healing term of ORNJ with HBO compared with non-HBO. In the report that questioned the effectiveness of HBO on ORNJ, the cases which were healed by only HBO did not have severe ORNJ. Approximately 80% of the cases required surgical management ¹⁵⁾. Moreover, some reports agreed that HBO was effective on only minor ORNJ ¹⁶⁾. Our data also showed no obvious shortening of the healing term for ORNJ (Table 7). P-2, in the group which had a small number of HBO (less than 20), tended to be shorter than that in the group which had a large number of HBO (more than 20), although the total radiation dose was approximately the same (Table 8). This probably means small number of HBO was sufficient to heal the ORNJ since these ORNJ cases in our series were not severe. Only 2 of 9 cases which had HBO treatment were performed major surgeries with reconstructions and this suggests the others (7 cases) are minor, stage I. In spite of this, the healing period of ORNJ had a wide range, 7 to 39 months, moreover case 6 and 11 has been still under long-term treatment for 95 and 69 months, respectively. According to these results, the effectiveness of HBO on ORNJ is considered to be suspicious.

In conclusion, continuous irradiation appears to induce more severe ORNJ than pre- and post-operative irradiation when the total radiation dose was approximately the same. The obvious effectiveness of HBO on ORNJ was not observed. We conclude that HBO does not have a sufficient effectiveness on ORNJ.

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