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TREATMENT RESULTS IN ORAL SQUAMOUS CELL CACRCINOMA WITH HYPERFRACTIONATED RADIOTHERAPY -PRELIMINARY REPORT-

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Abstract Between December 1990 and November 1993, 21 cases of squamous cell carcinoam of the oral region were treated with twice-a-day irradiation(1.2 Gy/fraction, 4-hour interfraction interval). Ten of the patients had T4 tumors. Seventeen patients received irradiation alone to the primary site. The total dose administered was 70.8-74.4 Gy in the majority of cases. In all cases except one, the treatment was completed without a rest interval. Local control results at two years and the time of assessment were 1/2 and 1/2 for T1 tumors, 4/6 and 5/8 for T2 tumors, 0/1 and 0/1 for T3 tumors and 1/7 and 2/10 for T4 tumors. T stage was a significant prognostic factor for local control(p=0.007). The local control rate did not correlate well with the total dose(P=0.103). Only one pathologic fracture of the mandible was observed as a complication. It was considered that this treatment regimen was preferable for T1 and T2 tumors in respect of local control but was not sufficient for T3 and T4 tumors.

Key words: Hyperfractionation, Twice-a-day irradiation, Oral cancer

INTRODUCTION

Radiotherapy schemes using multiple fractions per day were introduced in the 1970s[1-5]. Among them, hyperfractionated radiotherapy is a method of delivering multiple fractions in a day without increasing the overall treatment time[2, 4]. Redistribution of surviving tumor cells into a more sensitive phase of the cell cycle takes place between fractions and the portion of the tumor most sensitive to irradiation will be killed with following fractions[2, 6]. That is, this fractionation scheme has the advantage of sparing tissues responsible for late effects (e.g. spinal cord and fibrovascular tissue) relative to the tumor cell population. Another advantage is that the total tumor dose is delivered in a shorter period of time and it may result in local tumor control in advanced cancers[1, 4, 7-9]. During these years, increase of the total dose up to 80 to 82 Gy has been found possible without any increase in acute or late effects[10-12]. Local control using hyperfractionation has been reported to be the same or slightly better compared with the conventional 2 Gy once-a-day fractionation[1, 4, 7-9]. A significantly better result was obtained in the treatment of oropharyngeal squamous cell carcinoma[11, 12]. Although there are many reports of hyperfractionated radiotherapy in head and neck cancers, few present treatment results for oral cancers alone[1-5, 7-9, 12, 13]. The purpose of this report is to present our preliminary treatment results, especially as regards local control, in squamous cell carcinomas in the oral region using hyperfractionated radiotherapy.

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MATERIALS AND METHODS

Between December 1990 and November 1993, 21 previously untreated oral cancer patients received radiotherapy with curative intent using twice-a-day irradiation at the Hiroshima University Hospital. Among these 21 patients, 5 were operation-refusal cases, and one was inoperable because of impaired renal function. Surgery on the primary lesion was reserved for irradiation failure by mutual consent. Thirteen patients were male and 8 female. The patients' age range was 47 to 90 years(mean 69.8 years; median 70 years). The patient distribution according to the TNM staging system(UICC 1987) and performance status is shown in Table 1. In 9 of 10 T4 cases, destruction of the mandible was observed, and 8 of them showed marked bone destruction and a large tumor volume, more than 4 cm in the greatest dimension. The histopathological type was squamous cell carcinoma in all cases.

A dose of 1.2 Gy was administered to the primary site at each treatment session. The interval between fractions was 4 hours. Treatment was delivered 5 days a week by continuous course irradiation. All of the patients were treated with 4 MV X rays. Radiotherapy was performed using immobilisation shells. Five patients who had upper gingival carcinoma received radiotherapy to the primary tumor only. In the remainder of the patients the field was planned to encompass the tumor and regional lymph nodes, using a shrinking field technique to include the primary tumor and involved nodes. The supraclavicular area was not treated because nodal stages were limited. Although the posterior cervical region was not routinely treated with the electron beam, an electron boost at a dose of 2 Gy was administered once a day to an involved solitary lymph node in 2 cases.

Table 1. Patient characteristics

Age	47-90
mean	69.8
median	70
Sex	
male	13
female	8
T stage	
1	2
2	8
3	1
4	10
N stage	
0	13
1	7
2	1
Disease stage	
I	2
II	6
III	2
IV	11
Karnofsky performance status	
100	11
90	4
80	1
60	5

All of the patients except 4 received irradiation alone. These 4 patients received concurrent chemotherapy with carboplatin 30 mg/day, 5 days a week(3 cases) or 150 mg once a week(1 case). The total doses of carboplatin were 300 mg - 540 mg.

In seventeen patients, radiotherapy was performed with hyperfractionation alone. The other 4 patients were treated by combination with other fractionation or an electron boost. The usual primary tumor dose in cases treated by hyperfractionated radiotherapy alone was 70.8-74.4 Gy/59-62 fractions/30-33 treatment days/6-6.5 weeks(Table 2). Ten patients received this planned dose. Four patients received lower doses(45.6-70 Gy) because of a good response to the treatment. Three patients received larger doses, 81.2, 76.8 and 75.6 Gy, because their primary lesions remained and they showed good normal tissue tolerance at the time of reaching the planned dose. In 3 out of 4 patients treated by combination with other fractionation or an electron boost, radiotherapy was started with a 2 Gy once-a-day fractionation. Their doses were 10, 18 and 30 Gy. After that, the twice-a-day fractionation was used, and 62.4, 52 and 40.8 Gy were delivered. Their

Table 2. Distribution of total tumor dose

76.8 Gy <	2
75.6-76.8 Gy	2
70.8-74.4 Gy	12
< 70.8 Gy	5

total doses were 72.4, 70 and 70.8 Gy. The fourth of these patients received an electron boost of 10 Gy with the intraoral cone technique after 70.8 Gy of twice-a-day irradiation. Reductions in treatment volume were made whenever possible so as to limit the volume of tissues receiving the full tumor dose. The assessment of treatment results was performed in June 1994.

The follow-up period ranged from 7 to 37 months (mean 27.9 months, median 30 months). Sixteen patients were followed for 2 years or more. Only one patient had a follow-up time of less than one year, 7 months. All of the patients were included in this study.

RESULTS

Acute reactions

Most patients developed patchy mucositis 2 to 3 weeks after the start of the course of treatment. One patient showed severe mucositis at a lower dose, 45.6 Gy. At this time, the tumor was in complete response. The treatment of this patient was stopped and she was followed up carefully. No other patients except this one required a rest interval due to an acute reaction even if they had concurrent chemotherpy. Nasogastric feeding tubes were not used in any case. In most patients, mucositis was completely healed within 2-4 weeks after radiotherapy.

Local control

Although there were 4 patients who had concurrent chemotherapy, all of them were included for calculation of local control because they could not achieve local control. Six persistent tumors and 5 local recurrences were detected at the end of treatment or in the follow-up period. Four out of 5 recurrences were found within 7 months after irradiation. The other recurrence was found 16 months after treatment. In this case the treatment had been interrupted at 45.6 Gy because of severe mucositis. One patient died 19 months after treatment due to simultaneous esophageal carcinoma. He was also included in this evaluation because his primary lesion was under good control until he died. Local control results at 2 years and the time of assessment following radical irradiation according to T stage were 1/2 and 1/2 for T1 tumors, 4/6 and 5/8 for T2 tumors, 0/1 and 0/1 for T3 tumors and 1/7 and 2/10 for T4 tumors(Figure 1).

Eight out of 9 T1 and T2 lesions that recieved >61 Gy were controlled. In T4 cases, however, local control was not achieved even if they had received more than 70.8 Gy. Local control results at the time of assessment according to anatomical site are shown in Table 3. Two locally controlled patients who had died before the time of assessment were included. One had a T1 tumor in the retromolar area and the other a T2 tumor in the cheek. It was obvious that T1 and T2 lesions were controlled better regardless of anatomical site. Salvage operations following local failures were performed in 7 patients and 5 of them were well controlled. Of the remaining two, one died of persistent disease and the other died of distant metastasis. Salvage radiotherapy with interstitial brachytherapy was performed in 2 cases; one was an operation-refusal case and the other inoperable. They could not be controlled. Salvage treatment was not undertaken in one case, because she refused any

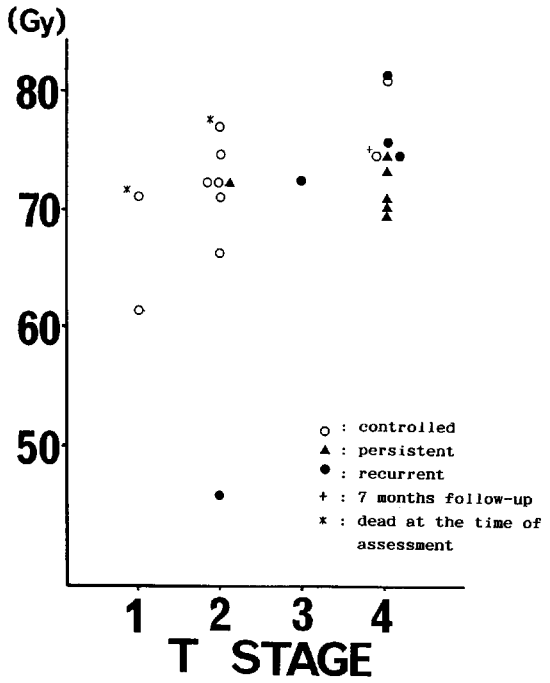

Figure 1: Local control according to T stage and tumor dose

Table 3. Local control rate after hyperfractionated radiotherapy according to T stage and primary site (controlled cases / treated cases)

	T1	T2	T3	T4
Upper gingiva	1/1	2/3		0/1
Lower gingiva		1/1		0/4
Cheek		*1/1	0/1	+1/1
Retromolar areas	*1/1	1/2		1/3
Tongue		1/1		
Floor of mouth				

(+: The follow-up period is 7 months.)
(*: dead at the time of assessment)

Two locally controlled patients(*) who had died before the time of assessment were included. One had a T1 tumor in the retromolar area, and the other a T2 tumor in the cheek.

additional treatment. The other case is now being treated palliatively with external irradiation.

Regional control

Regional control results are shown in Figure 2. All of the patients whose regional lymph nodes were irradiated were treated by hyperfractionation. The total dose to lymph nodes was the same as that which primary lesions received. In the patient whose treatment was stopped due to severe mucositis at the dose of 45.6 Gy, 22 Gy boost irradiation was performed with a 12 MeV electron beam. Five patients who had upper gingival carcinoma did not receive irradiation to the neck because their N stages were zero. Neck failures occurred in only 2 out of 8 patients with neck disease. One had persistent disease and the other developed recurrence. Both of them refused surgical salvage. There was no neck failure in N0 patients.

Survival

Crude survival rates at 2 years and the time of assessment according to T stage were 1/2 and 1/2 for T1 tumors, 5/6 and 7/8 for T2 tumors, 0/1 and 0/1 for T3 tumors and 4/7 and 6/10 for T4 tumors. The crude survival rates at 2 years and the time of assessment according to stage were 1/2 and 1/2 for stage Ⅰ, 5/5 and 6/6 for stage Ⅱ, 0/1 and 1/2 for stage Ⅲ and 4/8 and 6/11 for stage IV.

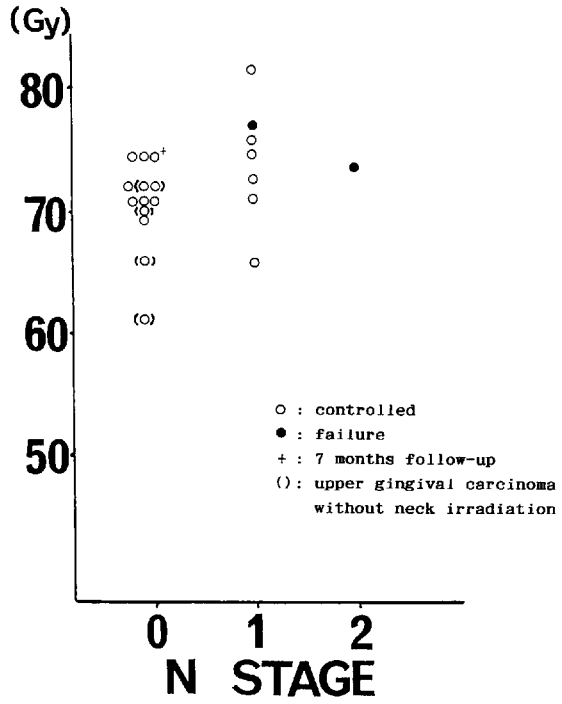

Figure 2: Regional control according to N stage and tumor dose

The overall survival rate at the time of assessment was 14/21. Four patients died of local failure. One patient died of failure of neck disease, and one of distant metastasis. The other patient with carcinoma of the retromolar area died of simultaneous esophageal cancer.

Prognostic factors

The following variables were investigated as prognostic factors for local control and survival: T stage, N stage, total dose, performance status, age and sex. The influence of these factors on local control was estimated by univariate analysis and the Chi-square test for comparison. All these factors have been further analysed with Logistic regression analysis[14] to determine a set of independently significant prognostic factors and to estimate the effect of treatment after adjustment for these factors.

Univariate analysis

T stage was correlated with the probability of local control at a significant level($P<0.01$). That

is, the failure rate increased according to T stage(T1 and T2 versus T3 and T4). Survival was found to be worse(P=0.07) in higher T stages(T1 and T2 versus T3 and T4).

Multivariate analysis

All these prognostic factors were investigated in a Logistic regression analysis to find a set of independently significant prognostic factors for local control and survival. For local control, the only independently significant prognostic factor was T stage. The probability was 0.007. Total dose correlated weakly with local control(p=0.103).

As to survival, there were no independent prognostic factors, but T stage and performance status showed probabilities of 0.115 and 0.151, respectively.

Complications

No complications were observed after the definitive radiotherapy except for one patient, who developed a pathologic fracture 31 months after radiotherapy of 70.8 Gy. No complications related to salvage operations with and without neck dissection were observed.

DISCUSSION

Clinical trials have shown benefits of hyperfractionated radiotherapy for treatment of head and neck cancers compared with conventional 2 Gy once-a-day fractionation[1, 4, 7, 9]. Among them, Horiot et al.[11] reported that significantly better local control was obtained with hyperfractionated radiotherapy in oropharyngeal squamous cell carcinoma. Oral cancers have been included and treated in those clinical trials[1, 2, 4, 7-9]. However, there are few reports showing treatment results focusing on oral cancers[1, 2, 4, 7-9]. We, therefore, examined the possibility of improving local control in oral cancer treatment by using hyperfractionated radiotherapy.

Acute mucosal reactions with 1.2 Gy/fraction, twice-a-day irradiation have been reported to develop 4-6 weeks after commencement of treatment and to be comparable to or more severe than those observed with 2 Gy/fraction[1, 2, 4, 5, 7, 10, 12]. In our study, however, the mucosal reaction became severe in the second and third weeks. We felt that the timing of mucositis was earlier than that with 2 Gy/fraction, and that the degree of mucositis was generally less severe. Therefore, almost all the patients did not need a rest interval and could complete the whole course of treatment.

The local control rate of all T stages was considered comparable to that with conventional 2 Gy fractionation to total doses of about 70 Gy[1]. In T1 and T2 tumors, good local control was obtained in 8 out of 10 cases, as shown in Table 3. One of the major reasons was considered to be a smaller tumor size as shown in the statistical analysis. The primary sites in most of those cases were the upper and lower gingiva and retromolar areas. Tumors in these areas have often been operated upon after preoperative radiotherapy in our institution. However, this result has encouraged us to choose definitive hyperfractionated radiotherapy for T1 and T2 lesions in respect of preservation of shape and function. Furthermore, we could reserve surgery as a salvage treatment. The low complication rate also favours the use of this radiotherapy regimen although the follow-up period is still short. At the moment, we consider that this treatment regimen is preferable for smaller tumors. On the other hand, only 2 out of 11 cases of T3 and T4 tumors were controlled. Eight patients with uncontrolled T4 tumors showed marked destruction of the mandible and a tumor volume more than 4 cm in the greatest dimension. It has been reported that the control rate decreased with advancing stage[9], but no description of bone destruction was found. Increase of the total dose is one possible strategy to improve the local control rate[9] and a total dose of 80 Gy or more has been recognised to be possible to use in this hyperfractionation scheme[10-12]. In most cases of this study, we did not administer an excessive dose over the planned dose, because we had the impression, from our observations of tumor regression during treatment, that an increased total dose might not provide better tumor control in cases in which tumors persist. We think that there may be a limit to the tumor controllability with hyperfractionated radiotherapy alone. Four patients were treated with concurrent chemotherapy using carboplatin in this study, but all of them could not be cured. However, one of the authors has reported on

combined treatment with hyperfractionated radiotherapy and chemotherapy and shown good results although the follow-up period was only 3-4 years[15]. His findings seem to suggest that it may be better to combine hyperfractionated radiotherapy and anti-cancer drugs.

In a past report[9], "nodal clearance" was also shown to be better than conventional 2 Gy fractionation. Regional control in our study was better compared with past reports[1, 2, 9]. However, 13 cases were N0 before treatment and our results cannot be directly compared with those of previous studies.

Our main interest in this study was focused on local control of primary tumors, but the crude survival rate of all cases at the time of assessment was not bad(14/21). Half of them(7/14) were T1N0 and T2N0 lesions. Five cases(1 T2N0 and 4 T4N0 or N1) out of 7 local failures which were operable were salvaged by operation. From these figures, it was concluded that this study had been suitably conducted. The actuarial survival rate was not examined because of the short follow-up. The distribution of the cause of death was considered the same as in past reports[1, 8, 9, 12].

One pathologic fracture was found in a T2N0 tongue cancer case. His follow-up radiographs showed tooth extraction to be the cause. No differences in late sequelae between conventional fractionation and hyperfractionation have been reported[1, 5, 11]. However, the follow-up period in this study is still short and careful follow-up and proper maintenance is necessary for the patients treated by hyperfractionation.

CONCLUSION

In this study, 21 previously untreated squamous cell carcinomas in the oral region were treated using twice-a-day irradiation with 1.2 Gy/fraction. Although the number of cases was small, follow-up periods were short and various disease stages were involved, the following findings were noted.

(1) Twice-a-day irradiation with 1.2 Gy/fraction, 4 hour interval between fractions, was feasible without a rest interval for most oral cancer patients up to 70 to 80 Gy.
(2) Local control at 2 years and the time of assessment was 5/8 and 6/10 for T1 and T2 lesions and 1/8 and 2/11 for T3 and T4 lesions. Especially in cases with marked bone destruction, the local control rate was extremely poor. Most of the uncontrolled cases were found within 7 months after the commencement of treatment.
(3) The crude survival rate at 2 years and the time of assessment was 10/16 and 14/21.
(4) One pathologic fracture, probably due to tooth extraction, was found. There was no interference with the healing process in patients who underwent a salvage operation.

From these findings, it was concluded that this treatment regimen was preferable for T1 and T2 tumors in respect of local control but was not sufficient for T3 and T4 tumors.

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要旨：1990年12月から1993年11月までの間に21例の口腔領域扁平上皮癌に対して一日二回照射法（一回1.2 Gy，照射間隔4時間）による放射線治療が行なわれた．10例がT4症例であった．17例は放射線治療単独で原発巣の治療が行なわれた．総線量は大部分の症例で70.8－74.4 Gyであった．一例を除いて，治療は休止期間を置くことなく行なわれた．2年及び調査時での局所制御は，T1でそれぞれ1/2，1/2，T2で 4/6，5/8，T3で 0/1，0/1，T4で1/7，2/10であった．局所制御に対する重要な予後因子としてT病期が挙げられた．局所制御率と総線量とは相関しなかった．下顎骨の病的骨折一例が障害として観察された．今回の治療法は，T1及びT2病変には局所制御という点で適切と考えられたが，T3及びT4病変に対しては十分ではないと考えられた．