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ELECTIVE NECK IRRADIATION ON IPSILATERAL SIDE IN PATIENTS WITH EARLY TONGUE CANCER FOR HIGH-RISK GROUP WITH LATE CERVICAL LYMPH NODE METASTASIS

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ABSTRACT

A prospective study was performed to assess the efficacy of elective neck irradiation (ENI) on the ipsilateral side in patients with early tongue cancer among a high-risk group with late cervical lymph node metastasis. Patients in the high-risk group had T2-tumors, excluding superficials or T1-tumors ≧19 mm in maximal diameter with invasion or ulcer. Between February 1989 and October 1997, 70 patients with tongue cancer of Stages I and II were enrolled in the present study (ENI group: 31, non-ENI group: 39). In a combination therapy of external beam irradiation and brachytherapy, the standard dose of interstitial brachytherapy for primary tumors was approximately 60 Gy. Irradiation was initiated with a 9-MeV electron beam at a dose of 50 Gy on the ipsilateral side of the neck only when the day of brachytherapy approached. Three patients (9.7%) in the ENI group had neck lymph node metastasis as did 5 (12.8%) in the non-ENI group (p= 0.684). In patients with ulceration, the incidence of subsequent lymph node metastasis was significantly higher (p=0.029). Neck lymph node metastasis occurred in 2 (16.7%) of 12 patients with ulcers in the ENI group and in 2 (66.7%) of 3 with ulcers in the non-ENI group. Although we could not demonstrate the significant efficacy of ENI in the high-risk group in this study, ENI decreased the neck lymph node metastasis. In addition, our results suggested that ENI particularly inhibits cervical lymph node metastasis in tongue tumor patients with ulcers.

Key Words: Tongue cancer, Elective neck irradiation, Brachytherapy, Cervical lymph node metastasis

INTRODUCTION

In the treatment of early tongue cancer, the primary tumor can be effectively controlled by either radiotherapy or surgery. Brachytherapy is regarded as a particularly good modality for early lesions and yields a better functional result than surgery.[1-5)]

However, after the primary lesion has been treated, subsequent neck failure occurs in approximately 20% to 30%[3-6)] of patients with clinically negative lymph node metastasis (N0), even when good local control is achieved. Subsequent neck lymph node metastasis is the most

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important factor influencing the prognosis of oral cancer with the N0 neck.

Neck lymph node dissection is generally performed in many institutions when lymph node metastasis has clinically developed, without much consideration given to other options such as elective dissection or elective irradiation of the neck. This therapeutic strategy (a watch-and-wait policy) was previously employed in Aichi Cancer Center Hospital. However, upon developing subsequent neck failure, some patients showed a rapid swelling of metastatic lymph nodes, multiple lymph node metastases, or extracapsular extension. The prognosis of such patients was poor.[3,7-10] The proper management of the N0 neck in oral cancer remains controversial.[11,12]

It was suggested that a large-sized, thick, or invasive type of primary tumor[4,5,13-17] is associated with a higher incidence of occult neck metastasis. To further improve the treatment response of early tongue cancers, establishing some aggressive methods for cervical lymph node metastasis is clinically important. Therefore, since February 1989 we have performed elective neck irradiation (ENI) with additional electron beam irradiation on the ipsilateral side mainly in patients with T2N0 tongue cancer, which has been associated with a higher incidence of lymph node metastasis. In our institution, a Radiolucent Spacer[18] (protector), 8 mm in thickness, has been used since 1983 to reduce the dose to the gingiva and mandible, and no incidence of osteoradionecrosis of the mandible has been observed since then. In the present study, we report the results of a prospective study of ENI for tongue cancer patients and radiation-related late damage.

PATIENTS AND METHODS

1. Patient population

Eighty-six patients with early tongue cancer (Stages I and II, according to UICC, 1997) were treated by radiotherapy in the Aichi Cancer Center Hospital between February 1989 and October 1997. To examine the efficacy of ENI on the ipsilateral side, we established various exclusion criteria in addition to the following inclusion criteria:

1) Stage T2 patients in whom the tumor site is the lingual lateral
   middle third (excluding the central middle third (=dorsal surface), or
   anterior third (=tip or ventral surface) of the tongue).
2) Patients with an exophytic or invasive T2-tumor, but excluding superficial tumors (3 mm or less in thickness).
3) Stage T2 patients with ulcers.
4) Stage T1 patients with an invasive tumor or ulcer formation with a maximal diameter of 19 mm or greater.

Patients who met the above inclusion criteria were morphologically assigned to a high-risk group for subsequent cervical lymph node metastasis from early tongue cancer. In the ENI group, ENI was performed under these inclusion criteria. However, in many Stage T2 patients in whom the tumor site is the central middle third and anterior third, the primary tumor does not metastasize to the neck lymph node on the ipsilateral side even though they are morphologically assigned to a high-risk group.[19,20] Such patients were excluded from this study. We also excluded those who had previously undergone cervical lymph node dissection for cancer of the head and neck or esophageal cancer. ENI was not performed for untreated patients who did not meet the above criteria during the same period. As a result, 70 patients were enrolled in this study during this period (ENI group: 31, non-ENI group: 39). Patient characteristics are shown in Table 1. In the present study, tumor thickness was determined not with ultrasound devices, but by palpation, following a consensus among several physicians. The histological type of tumor was confirmed as squamous cell carcinoma in all patients. Informed consent was obtained from

Table 1 Patient characteristics

	ENI (+)	ENI (–)	p-value
Age (yrs)	38–84	25–83	0.1538
median	53	59	
Sex			0.4164
Male	22	24	
Female	9	15	
T stage			<0.0001
T1	5	32	
T2	26	7	
Length of tumor (mm)	12–40	5–38	<0.0001
median	25	15	
Thickness (mm)	3–28	1–10	<0.0001
median	7	3	
Morphology			<0.0001
superficial	0	22	
exophytic	10	14	
invasive	21	3	
Ulcer			
yes	12	3	0.0018
no	19	36	
Site of tumor			
lateral third	31	32	0.0137
dorsal	0	1	
ventral	0	5	
tip	0	1	

Abbreviation: ENI = elective neck irradiation

Table 2 Treatment method

	ENI (+)	ENI (–)	p-value
Radiotherapy			
External irradiation (Gy)	40–54.4	0–33.3	<0.0001
median	50	0	
Brachytherapy (Gy)	50–70.2	40–80	0.7245
median	60	60	
Au	5	19	0.0064
Cs	14	13	
Ra	11	5	
Chemotherapy			0.0148
yes	8	2	
no	23	37	

Abbreviations: Au = Au 198 grain; Cs = Cesium 137 needle; Ra = Radium 226 needle

all study subjects.

2. Treatment

As shown in Table 2, the primary tumor was treated with brachytherapy using ^{198}Au grain, [37] a Cesium needle, or ^{226} Radium needle.

In general, when the tumor was thin, radiotherapy was mainly performed by a permanent

insertion of ^{198}Au seeds. When a Cesium needle or a Radium needle was used, a single-plane implant was employed in most patients. Intraoral cone irradiation was performed with electron beams only in patients whose tumor was very short and thin. However, in 1 patient with invasive T2-cancer in whom combination therapy[21] with arterial infusion chemotherapy and external irradiation resulted in disappearance of the tumor, as described below, additional treatment for the primary tumor was performed using electron beams alone without brachytherapy. In most patients, the primary tumor and neck were externally irradiated prior to interstitial brachytherapy. However, in the non-ENI group, since the tumor volume was small in many patients, 21 of 39 received brachytherapy alone without external irradiation. In a combination therapy of external beam irradiation and brachytherapy, the standard dose for interstitial brachytherapy was approximately 60 Gy. However, in patients who did not undergo external irradiation, the target dose was 65 to 70 Gy even when the tumor was small.

For ENI, as a rule, a spacer was prepared to prevent mandibular osteoradionecrosis before treatment. Simultaneously, external beam irradiation was performed with anterior and lateral fields for the primary lingual tumor and the neck on the ipsilateral side using 6 MV or ^{60} Co at 2 Gy/fr/day. The dose ranged from 20 to 30 Gy. Irradiation was initiated on the ipsilateral side of the neck with a 9-MeV electron beam (6 to 12 MeV, selected by measuring the depth of the neck-deep lymphatics from the skin surface on computed tomography (CT)) only when the day of brachytherapy approached. After brachytherapy, electron beams were delivered to the ipsilateral side of the neck at a total dose of 50 Gy. When the anterior and lateral fields were employed, the irradiation field involved the lower neck region of the ipsilateral side. When additional irradiation with electron beams was performed in the neck region alone, the neck on the ipsilateral side was sufficiently extended, and the irradiation field involved the lower neck region, regarding the inferior margin of the mandible as the superior margin.

After ENI was started, the 3rd patient developed lymph node metastasis in the accessory nerve area (outer field of ENI). Later, the ENI treatment included this area. Therefore, all Level II and III lesions in the classification published by the Memorial Sloan-Kettering Cancer Center[11] were included. More than half of Level I, IV, and V lesions were included.

Chemotherapy was concurrently administered to 8 patients in the ENI group and to 2 patients in the non-ENI group with different regimens. In 4 patients, CDDP (75 mg, twice) and 5-FU (1,000 mg) were continuously administered for 5 days of neoadjuvant chemotherapy prior to radiotherapy. In 1 patient, a low dose of CDDP (6 mg/day) was administered concomitantly with external irradiation, and in 3 others, arterial infusion therapy (20-30 mg/day of carboplatin) in which a catheter was inserted through the superficial temporal artery was carried out concurrently with external irradiation. Pepleomycin sulfate was intramuscularly injected into 1 patient and 5-FU was orally administered to another.

3. Evaluation of cervical lymph node metastasis

Before treatment, the detection of neck lymph node metastasis was clinically evaluated by radiological oncologists and head and neck surgeons on palpation, followed by examinations with CT and/or magnetic resonance imaging (MRI). The clinically negative (N0) neck was comprehensively evaluated based on the results of these examinations.

4. Statistics

Values were compared between the ENI and non-ENI groups. Significance in the two groups was determined using the Mann-Whitney U test, and differences among the subgroups were evaluated by Fisher's test.

The survival rate was calculated using the Kaplan-Meier method, and significance was tested

using the log-rank test. These analyses were calculated using a personal computer (Stat View Version 4.5J, and Survival Tools version 1.1, Abacus Concepts, Berkeley, USA).

RESULTS

1. Relapse of the primary site

Two patients (6.4%) in the ENI group showed recurrence of the primary site, one in the 25th month and the other in the 51st month. One patient (2.3%) in the non-ENI group also showed recurrence in the 15th month. All were salvaged by surgery.

2. Cervical lymph node metastasis and prognosis in patients with relapse

The 5-year cumulative incidence rate in the ENI group was 9.7% and 13.1% in the non-ENI group, with no significant difference observed between the two groups ($p < 0.646$). Three patients (9.7%) in the ENI group had cervical lymph node metastasis as did 5 (12.8%) in the non-ENI group. In the ENI group, the metastatic sites were the ipsilateral neck region (within the irradiation field) in 1 patient, the outer field on the ipsilateral neck region in 1 and the contralateral neck region in 1. Therefore, lymph node metastasis in the field of elective neck irradiation occurred in only 1 patient (3.2%). The relapse time ranged from 7 to 14 months (median: 9 months) in the ENI group and from 6 to 15 months (median: 7 months) in the non-ENI group. Four of the relapsed patients underwent radical neck dissection and none developed further relapse. Three patients who underwent radical neck dissection on the ipsilateral side and postoperative irradiation died of distant metastasis, as did another who received radical neck dissection for cervical lymph node metastasis on the contralateral side and postoperative irradiation. Therefore, only 4 of the 8 patients with subsequent cervical lymph node metastasis survived.

Among the 8 patients with cervical lymph node metastasis during follow-up, the 5-year survival rate was 46.9%. Of the 62 patients without lymph node metastasis, the 5-year survival rate was 93.0%, revealing a significant difference between the two groups ($p < 0.0001$).

3. Survival

The median follow-up period was 61.8 months (17.4–113.5 months) in the ENI group and 55.8 months (11.4–104.8 months) in the non-ENI group. Concerning patient status, 27 survived and 4 died in the ENI group, while 35 survived and 4 died in the non-ENI group. The cause of primary disease-related death was distant metastasis resulting from poor control of cervical lymph node metastasis. The causes of other disease-related deaths were lung cancer in 1 patient and esophageal cancer in another in the ENI group, and gingival cancer in 1 and myelodysplastic syndrome in another in the non-ENI group. In the ENI group, the 5-year and 7-year cumulative survival rates were 84.2% and 84.2%, and 90.8% and 81.7%, in the non-ENI group, respectively. There were no significant differences. In the ENI group, the 5-year and 7-year cause-specific survival rates were 93.1% and 93.1%, and 94.0% and 94.0%, in the non-ENI group, respectively. There were no significant differences between the two groups.

4. Late damage induced by irradiation

None of the patients in the two groups developed mandibular osteoradionecrosis (Table 3). Late damage to the tongue was detected in 8 patients (25.8%) in the ENI group and in 4 patients (10.2%) in the non-ENI group, which included transient ulcers, refractory ulcers requiring surgery, and an ulcer difficult to differentiate from relapse that also required surgery. There was a significant difference in the incidence, but in the patients' condition both groups improved

Table 3 Treatment results

	ENI (+)	ENI (–)	p-value
Lymph node metastasis	3	5	0.6836
Ipsilateral	2	5	
inner field	1	–	
outer field	1	–	
Contralateral	1	0	
Local recurrence	2	1	0.4284
Actual survival rate			0.9555
5-yrs	84.2%	90.8%	
7-yrs	84.2%	81.7%	
Cause-specific survival rate		0.9348	
5-yrs	93.1%	94.0%	
7-yrs	93.1%	94.0%	
Late effect			
Bone necrosis	0	0	>0.9999
Tongue ulcer	8	4	0.00887
conservative	6	3	
operation	2	1	

Table 4 Incidence of neck lymph node metastasis from tongue cancer with or without ulcer

	ENI (+)	ENI (–)	
Ulcer			
yes	2 (16.7%)	2 (66.7%)	*p=0.154
no	1 (5.3%)	3 (8.3%)	

*Fisher's exact test

by conservative treatment in 75% of the above patients. Two patients (6.4%) in the ENI group and 1 (2.6%) in the non-ENI group underwent surgery due to difficulty in differentiating their ulcers from relapse (Table 3).

Furthermore, in the neck region on the ipsilateral side where elective irradiation was performed, slight fibrosis and muscular atrophy were observed, but no symptoms developed. Follow-up neck examinations revealed no abnormalities.

5. Survival rates for primary disease with respect to Stages T1 and T2

Calculations from the 70 patients enrolled in this study revealed that 5-year survival rates of Stage T1 and T2 patients were 91.0% and 96.3%, respectively. Although there was no significant difference, long-term results were somewhat better in Stage T2 patients. The lower survival rate in Stage T1 patients was associated with poor control after subsequent cervical lymph node metastasis.

6. Relationship between ulceration in the primary tumor and cervical lymph node metastasis

We examined the relationship between ulceration in the primary tumor and cervical lymph node metastasis. The latter occurred in 2 (16.7%) of the 12 patients with ulcers in the ENI group and in 2 (66.7%) of the 3 with ulcers in the non-ENI group. When patients with and without ulcers were compared, lymph node metastasis occurred in 1 (5.3%) of the 19 patients

without ulcers in the ENI group and in 3 (8.3%) of the 36 without ulcers in the non-ENI group (Table 4). Statistical comparisons between the two groups were calculated with Fisher's exact test (p=0.154).

With respect to the presence or absence of ulceration (Table 1), cervical lymph node metastasis was developed in 4 (26.7%) of the 15 patients with ulcers and in 4 (7.2%) of the 55 without ulcers. The 5-year incidence rate of cervical lymph node metastasis was 26.5% in the patients with ulcers and 7.5% in those without ulcers. In patients with ulceration, the incidence of subsequent lymph node metastasis was significantly higher (p=0.0287).

DISCUSSION

Primary control of early tongue cancer with radiation proved favorable. The rate of primary control with interstitial brachytherapy was particularly high. Although primary relapse occurred in 4 (5.7%) of the 70 patients, the control rate was high (94.3%). However, based on many previous studies or findings, even when the stage was clinically evaluated as N0 neck before treatment, subsequent lymph node metastasis developed in approximately 20% to 30% of patients.[3-6] This was reported to be an important factor in reducing the survival of early tongue cancer after treatment.[3,7-10] Therefore, management of the N0 neck in oral cancer is an especially important issue. Previous studies have reported that both morphologically larger, thicker tumors and highly infiltrated tumors show a higher incidence of cervical lymph node metastasis.

In the present study, we assigned patients with a large tumor of maximal diameter, ulcerative lesions, or marked infiltration to a high risk group for subsequent neck lymph node metastasis, as described in the inclusion criteria. In this group, we performed ENI on the ipsilateral side. Since 1983, we have employed a spacer, 8 mm in thickness, between the tongue and mandible to relieve late mandibular damage caused by interstitial brachytherapy for tongue cancer. Since this spacer was introduced, no mandibular osteoradionecrosis has occurred. Previous studies have reported that a combination therapy of interstitial brachytherapy and external beam irradiation reduced the risk of subsequent lymph node metastasis.[22-24] However, in most cases, a high dose (40–50 Gy) was needed. A combination therapy of interstitial treatment and high-dose external irradiation causes a high incidence of late bone damage, markedly degrading the quality of life (QOL). This may be the major reason why ENI has not been aggressively used. We performed external beam irradiation (24–30 Gy) prior to interstitial treatment to reduce the tumor size, with a matched radiation source between the two methods, and decreased the dose for interstitial brachytherapy to approximately 60 Gy, which is relatively low compared with that used in other institutions. Using the electron beam instead of X-rays for external irradiation worked so well that none of the patients in the ENI group developed bone damage. Fibrosis at the neck irradiation site and muscular atrophy were both slight. Two factors, i.e., no late damage and no reduction in the QOL, suggest that this elective neck irradiation procedure is very simple and useful. Since most metastases were observed in the upper jugular (Level II) and submandibular (portion of Level I) regions on the ipsilateral side, at least 70% of metastases may be avoided if the irradiation field involves only these regions. The Level IV and V (more than half) regions were included in the irradiation field, allowing about 90% of the metastatic site to be covered. Patients in whom the tumor site was the anterior third or central middle third were excluded from this study, because the primary tumor was less likely to metastasize to the upper jugular (Level II) and submandibular (portion of Level I) regions on the ipsilateral side, while the incidence of metastases to other levels or the contralateral neck region was higher.[19,20] Therefore, we considered that the usefulness of ENI on the ipsilateral side could not be accurately evaluated

in tumors at those sites.

The results of this study showed that cervical lymph node metastasis developed in 3 patients (9.7%) in the ENI group, among whom relapse in the irradiation field was detected in only one (3.2%). In the non-ENI group, neck lymph node metastasis developed in 5 patients (12.8%). Since there was no significant difference between the two groups, the usefulness of ENI was not significant from the perspective of controlling lymph node metastases. However, on further examination, when results were compared between patients with and those without ulcers (Table 4), lymph node metastasis was detected in 2 (16.7%) of the 12 with ulcers in the ENI group, and 2 (66.7%) of 3 with ulcers in the non-ENI group. In the latter group, the incidence of neck lymph node metastasis was higher. Among patients without ulcers, both the ENI and non-ENI groups showed a similar incidence of lymph node metastasis. Considering the background factors in the 2 groups, ENI in patients with ulcers is suggested to inhibit the incidence of subsequent cervical lymph metastasis. This suggests that ENI for invasive tumors and tumors with ulcers is significant. ENI should be aggressively performed for patients with underlying diseases whose general condition is poor, elderly patients in whom radical neck dissection (RND) can not be performed upon the development of cervical lymph node metastasis, and patients in whom continued follow-up is presumably impossible.

Although primary tongue tumor thickness was measured on palpation in this study, the usefulness of an ultrasonic apparatus has recently been reported.[13] This issue should be considered in further studies. Furthermore, not only examinations of a morphologically evaluated high-risk group for cervical lymph node metastasis but also of such a group identified by recent immunohistochemical studies[25-27] should be considered.

We evaluated N0 by palpation and diagnostic imaging methods such as CT and/or MRI. However, a previous study detected a high incidence of lymph node metastasis during preventive dissection even when diagnostic imaging showed N0, and also suggested the limitations of diagnostic imaging methods in the detection of micrometastasis.[28,29] Therefore, as the accuracy of N0 evaluation could not be rapidly improved, ENI for early tongue cancer should be aggressively performed. A future issue is the selection of patients for whom ENI is suggested.

In conclusion, although we could not demonstrate a significant efficacy of ENI in our high-risk group, it was found to decrease the appearance of neck lymph node metastasis. In addition, our results suggested that ENI particularly inhibits neck lymph node metastasis in tongue tumor patients with ulcers.

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