

Treatment of Early Tongue Carcinoma with Brachytherapy: Results over a 25-Year Period

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Abstract. *Background:* Brachytherapy for patients with early tongue cancer is an accepted method of treatment. *Patients and Methods:* The records of 409 patients with T1/2N0M0 tongue cancer treated with brachytherapy between 1978 and 2004 were reviewed. *Results:* The overall and disease-free 5-year survival rates were 82.3% and 64.6% for patients with T1 disease, and 72.2% and 56.0% for patients with T2 disease, respectively. The 5-year nodal metastasis-free survival rates for patients treated between 1978 and 1986, 1987 and 1996, and 1997 and 2004 were 64.8%, 74.8% and 81.3% for patients with T1 disease ($p=0.22$), and 47.4%, 70.4% and 76.4% for patients with T2 disease ($p=0.0011$), respectively. The 5-year local recurrence-free survival rates for patients treated between 1978 and 1986, 1987 and 1996, and 1997 and 2004 were 91.0%, 84.0% and 96.9% for patients with T1 disease ($p=0.31$), and 87.6%, 83.3% and 85.8% for patients with T2 disease ($p=0.90$), respectively. *Conclusion:* The incidence rate of nodal metastasis in patients with early tongue cancer improved over the 25-year period studied, while the local recurrence-free survival rates remained stable.

Brachytherapy for patients with early tongue cancer has been the accepted method of treatment because of the high local control rate and preservation of the shape and the function of the oral tongue (1, 2). However, even if local control is achieved by brachytherapy, cervical lymph node metastases

develop in a certain number of patients. The prognosis of early tongue cancer is strongly related to regional rather than local control (3, 4). Although the incidence rate of lymph node metastasis after brachytherapy has been reported to be 20-50% (1, 3-7), improvements in diagnosis and treatment may affect the incidence of nodal recurrence and mortality of patients with early tongue cancer.

In the present study, we retrospectively reviewed patients with T1/2N0M0 mobile tongue cancer treated with low-dose rate (LDR) brachytherapy during the past 25-year period in an attempt to investigate the changing trend in treatment results of early tongue cancer by LDR brachytherapy at our institution.

Patients and Methods

Patient characteristics. In July 1978, LDR brachytherapy commenced at our institution, and between 1978 and 2004 was used to treat 409 patients with early-stage mobile tongue cancer. Early stage was defined as Stage I (T1N0M0) or II (T2N0M0) according to the 2002 criteria of the International Union Against Cancer (UICC 2002) (8). Patient and treatment characteristics are presented in Table I. The patients in this study were divided into three groups according to the treatment period: 1978-1986: 149 patients; 1987-1996: 197 patients; 1997-2004: 63 patients. The 234 men and 175 women in the study group ranged in age from 21 to 89 years (median 57 years). The histopathological variants of the tumor were 399 squamous cell carcinomas, 5 mucoepidermoid carcinomas, and 5 of other types. At the initial workup, 190 patients were identified with Stage I cancer and 219 patients were classified as having Stage II cancer.

All patients were irradiated with radical intent. Interstitial brachytherapy was performed with Ra-226 needles in a total of 317 patients, Cs-137 needles in 60 patients, Ir-192 pins in 19 patients, and Au-198 seeds in 13 patients. All implantations were performed under local anesthesia. Radiation doses were delivered with the Paterson-Parker system using a reference point 5 mm distant from the implant plane. The total brachytherapeutic dose was 50-70 Gy

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Key Words: Brachytherapy, tongue cancer, local recurrence, lymph node metastasis.

Table I. Patient and treatment characteristics.

	Period		
	1978-1986	1987-1996	1997-2004
Total (No. of patients)	149	197	63
Gender			
Male	86	113	35
Female	63	84	28
Age (years)(median)	21-88(54)	22-89(58)	22-68(58)
Histology			
Squamous cell	146	190	63
Mucoepidermoid	1	4	0
Other	2	3	0
Stage			
I	74	84	32
II	75	113	31
Treatment source			
Ra-226	149	168	0
Cs-136	0	11	49
Ir-192	0	18	1
Au-198	0	0	13
External radiotherapy			
Yes	18	35	21
No	131	162	42
Chemotherapy			
Yes	12	94	17
No	137	103	46

(median 70 Gy). Spacers, which increase the distance between the mandible and the implanted radioactive sources during the implantation, have been used since 1979. Among the 409 patients, 335 were treated with brachytherapy alone. To make the dose to the primary site more uniform, 74 were treated with external radiotherapy with a median dose of 20 Gy (6-40 Gy) prior to receiving an interstitial implant. As a general rule, the total brachytherapeutic dose was not reduced even if the lesion had already been treated with external radiotherapy. Although the radiation field of the primary site might include the upper jugular lymph nodes, none of the patients received external radiotherapy as prophylactic neck irradiation. Combined brachytherapy and chemotherapy was administered to 123 patients, with or without external radiotherapy. Oral administration of 5-fluorouracil (5FU) or uracil-tegafur (UFT) was administered in 93 patients, and intramuscular administration of bleomycin or pepleomycin was performed in 22 patients. Systemic chemotherapy with a platinum-based regimen was given to 8 patients. Combined therapy was usually indicated for T2 lesions or infiltrative types of tumors according to the physician's preference, although the definite indications had not yet been established at that time.

Following initial treatment, the tongue and neck nodes were closely followed up for signs of recurrence or metastasis once a month during the first year, then every 2-4 months for the next 2 years and every 6-12 months thereafter. To evaluate the tongue, careful inspection and palpation were performed. Biopsy was also performed if necessary. Since 1987, ultrasonographic examination has been used to evaluate neck nodes at least once every 2 months after brachytherapy for the first 2 years of follow-up, and

Table II. Distribution of initial treatment failures.

	Stage I (n=190)	Stage II (n=219)	Total (n=409)
Failure			
Local	20 (10.5%)	15 (6.8%)	35 (8.6%)
Nodal	46 (24.2%)	63 (28.8%)	109 (26.7%)
Local + nodal	7 (3.7%)	18 (8.2%)	25 (6.1%)
Distant	0	2 (0.9%)	2 (0.5%)
Total	73 (38.4%)	98 (44.7%)	171 (41.8%)

computed tomography (CT) if necessary. Ultrasonographic examination with the power Doppler mode has also been used since 1997 (9). The follow-up periods ranged from 3 to 271 months (median 84 months).

The survival and the locoregional control rates were calculated using the Kaplan-Meier method. The statistical significance of differences between the survival curves was assessed with the log-rank test. A *p*-value less than 0.05 was considered to indicate a statistically significant difference.

Results

Control of disease and patterns of failure. By the last follow-up, 171 patients (41.8%) had developed recurrence (Table II). Lymph nodal metastasis was seen in 134 patients (32.7%) from 0.4 months to 178 months (median 5.2 months). Within 2 years after brachytherapy, lymph nodal metastasis was observed in 94.0% (126/134) of patients. Local recurrence occurred in 60 patients (14.7%) from 1 month to 176 months (median 15.5 months). Seventeen (28.3%) of them occurred more than 3 years after brachytherapy. Local failure with lymph node metastasis was seen in 25 patients (6.1%). Distant metastasis occurred in 2 patients (0.5%). Although most patients with recurrent disease underwent glossectomy and/or neck dissection (7), 57 patients (13.9%) died of the disease, while 66 patients (16.1%) died of other causes.

Survival. The overall, disease-specific, and disease-free 5-year survival rates according to the T-category were 82.3%, 88.5% and 64.6% for patients with T1 disease, and 72.2%, 83.2% and 56.0% for patients with T2 disease, respectively (Figure 1). The 5-year disease-specific survival rates for patients treated between 1978 and 1986, 1987 and 1996, and 1997 and 2004 were 84.7%, 88.8% and 96.9% for patients with T1 disease (*p*=0.19), and 80.5%, 82.6% and 92.3% for patients with T2 disease (*p*=0.30), respectively. Although there was no statistical significance, the disease-specific survival rates tended to improve with a more recent treatment period.

The nodal metastasis-free survival rate and local recurrence-free survival rate according to the treatment

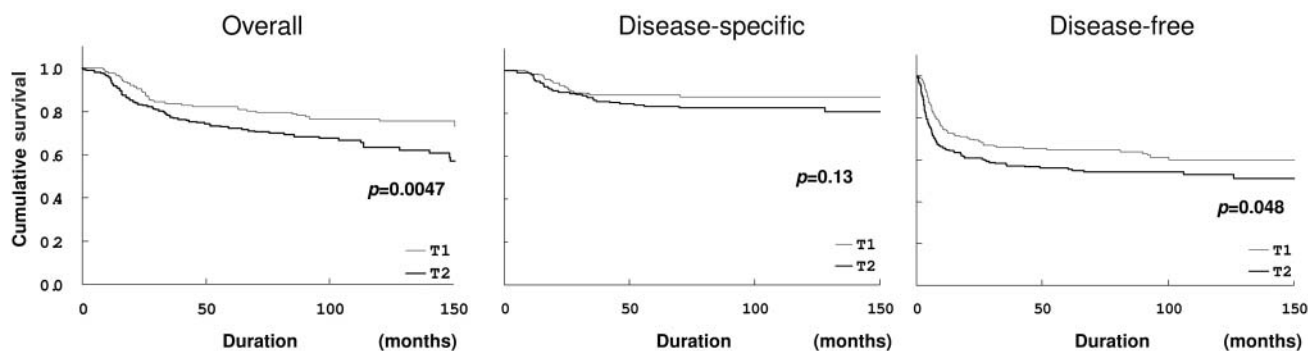


Figure 1. Overall, disease-specific and disease-free survival rates for 409 patients with early-stage tongue cancer.

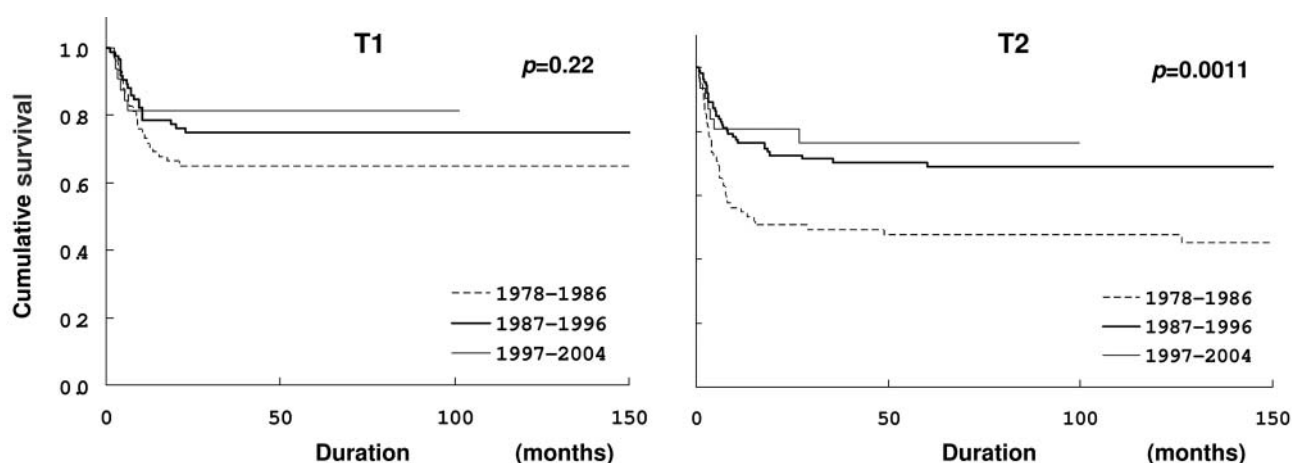


Figure 2. Nodal metastasis-free survival rates for patients with T1 or T2 disease as a function of the treatment period.

period are shown in Figures 2 and 3, respectively. The 5-year nodal metastasis-free survival rates for patients treated between 1978 and 1986, 1987 and 1996, and 1997 and 2004 were 64.8%, 74.8%, and 81.3% for patients with T1 disease, and 47.4%, 70.4% and 76.4% for patients with T2 disease, respectively. The 5-year local recurrence-free survival rates for patients treated between 1978 and 1986, 1987 and 1996, and 1997 and 2004 were 91.0%, 84.0%, and 96.9% for patients with T1 disease, and 87.6%, 83.3% and 85.8% for patients with T2 disease, respectively. The nodal metastasis-free survival rates tended to improve with a more recent treatment period, whereas the local recurrence-free survival rates remained stable during the 25-year period.

Complications. Prolonged complication of duration more than 6 months was seen in 108 patients (26.4%). Soft tissue necrosis/ulcer occurred in 81 patients (19.8%). Surgical resections were performed in two patients because local recurrence was suspected, however, there was no recurrence

pathologically. Bone exposure/osteonecrosis of the mandible occurred in 27 patients (6.6%). One patient required surgical interventions.

Discussion

Although brachytherapy provides a high rate of local control in the treatment of early tongue cancer, regional metastasis is frequently observed. The incidence of late regional metastasis of early-stage tongue cancer after brachytherapy ranged from 20 to 50% (1, 3-7). The results from the elective neck dissection for clinical N0 tongue cancer also showed similar incidence rates of occult neck metastasis (10, 11). In an earlier study, Vermund *et al.* reported that nodal metastases developed in 45% of patients with T1N0 tongue cancer and in 51% of patients with T2N0 tongue cancer who were treated between 1958 and 1972 (3). In 1986, Cunningham *et al.* also documented a high incidence of neck recurrence (42%) in patients with

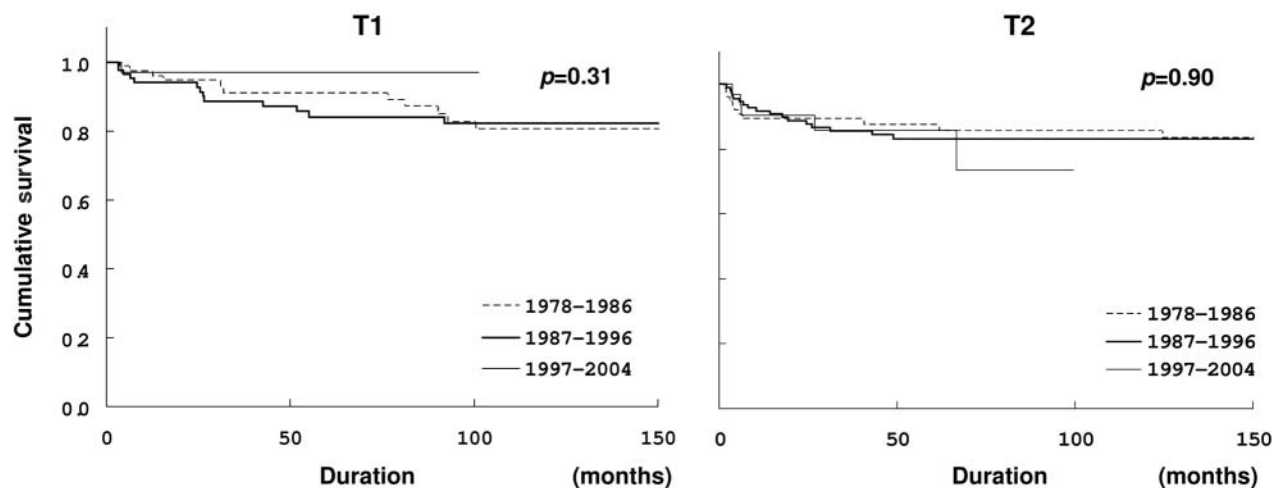


Figure 3. Local recurrence-free survival rates for patients with T1 or T2 disease as a function of the treatment period.

stage I-II carcinoma of the oral cavity treated by primary tumor excision alone (12). On the other hand, Keski-Santti *et al.* demonstrated in 2006 that the histopathological examination of the elective neck dissection specimens of 44 patients revealed metastatic lymph nodes in 34% of the patients with clinical N0 early tongue cancer (10). A report published in 2006 by Lim *et al.* showed that 28% of the patients with stage I-II tongue cancer treated with elective neck dissection had occult nodal metastasis (11). The regional disease-specific survival rates appear to improve with a more recent treatment period. Shibuya *et al.* reported that the incidence of late nodal metastasis in patients treated with brachytherapy without regional prophylactic irradiation between 1966 and 1988 was 21/67 (31%) in the T1 lesions and 73/170 (42.9%) in the T2 lesions (1). Another recent report from the same institution revealed that the incidence of nodal metastasis of patients treated from 1971 to 1998 was 25% and 41% for stage I and stage II tongue cancer, respectively (5). Ichimiya *et al.* demonstrated that the 5-year progression-free survival rates for stage I tongue cancer treated during 1996-1990 and 1991-2001 were 57.4% and 83.7%, respectively (6). In our institution, we also observed an improvement of nodal metastasis-free survival rates with more recent treatment. Although there was no clear evidence of this trend, this improvement may be in part due to the development of imaging modalities in the neck evaluation in tongue cancer patients. The CT scanner was installed in our institution in 1976, while the ultrasound scanner was installed in 1986. The ultrasonographic examination with the power Doppler mode has also been used for the follow-up study of patients with tongue cancer since 1997

(9). These imaging modalities, which are used as an adjunct to physical examination, may have improved the staging accuracy (13).

Although some investigators have recommended aggressive treatments including elective nodal dissection (10, 14, 15), we have adopted a wait-and-see policy for patients with N0 early-stage tongue cancer who undergo initial brachytherapy (7). In particular, patients who were treated between 1997 and 2004 showed excellent disease-specific survival rates of more than 90% in this study. If careful observation is realized with imaging of the neck including ultrasonography, a wait-and-see policy for patients with N0 early-stage tongue cancer seems to be one of the best approaches.

Another interesting finding from this study is that the rates of local control have largely remained stable in the past 25 years. Brachytherapy was historically performed with Ra-226 needles. We changed the radioactive source used in brachytherapy from Ra-226 to Cs-136, Ir-192, and Au-198. Although Au-198 tended to be prescribed for the superficial type of tongue cancer, treatment modalities did not affect the local control rates in this study. Because T-stage classification for early-stage tongue cancer is performed mainly by careful inspection and palpation, the possibility of T-stage migration over time may be low.

Severe complications requiring surgical intervention were seen in only one patient. Most patients with tongue cancer were able to maintain their daily activities without severe restrictions after brachytherapy (2). The introduction of a mandibular protective spacer can decrease the late complication rate (16). However, bringing about a further reduction in the number of complications is still a major challenge in the treatment of tongue cancer.

Acknowledgements

This study was supported in part by the Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Sciences (No. 18209040 and 18591383).

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Received May 14, 2007

Revised July 25, 2007

Accepted August 2, 2007