ANTICANCER RESEARCH *41*: 6259-6266 (2021)
doi:10.21873/anticanres.15446

Efficacy and Safety of Induction Chemotherapy and/or External Beam Radiotherapy Followed by Brachytherapy in Patients With Tongue Cancer

RYO-ICHI YOSHIMURA[1], KAZUMA TODA[1], HIROSHI WATANABE[2], ATSUSHI KAIDA[3], HIROYUKI HARADA[4], TAKAHIRO ASAKAGE[5] and MASAHIKO MIURA[3]

[1]*Department of Radiation Therapeutics and Oncology, Tokyo Medical and Dental University, Tokyo, Japan;*
[2]*Department of Oral Radiology, Tokyo Medical and Dental University, Tokyo, Japan;*
[3]*Department of Oral Radiation Oncology, Tokyo Medical and Dental University, Tokyo, Japan;*
[4]*Department of Oral and Maxillofacial Surgery, Tokyo Medical and Dental University, Tokyo, Japan;*
[5]*Department of Head and Neck Surgery, Tokyo Medical and Dental University, Tokyo, Japan*

Abstract. *Background/Aim: To evaluate the outcomes of induction chemotherapy and/or external beam radiotherapy (EBRT) followed by brachytherapy (BT) in patients with tongue cancer who had a waiting period for BT or a large tumor that was not suitable for BT. Patients and Methods: As an induction therapy, chemotherapy with tegafur/gimeracil/oteracil (S-1), EBRT or both S-1 chemotherapy and EBRT was prescribed. BT was performed using Au-198 grains or Ir-192 pins. Local control (LC), lymph node metastasis-free survival (LNMFS), overall survival (OS), and complication rates were calculated. Results: Forty-nine patients were enrolled in this study. The 3-year LC, LNMFS, and OS rates for cT1-2 patients were 84%, 45%, and 69%, respectively. The 3-year LC, LNMFS, and OS rates for cT3 patients were 77%, 58%, and 79%, respectively. The incidence of Grade 3 or 4 complications was 6%. Conclusion: Induction therapy contributed to the efficacy of the subsequent BT in LC rate.*

Brachytherapy (BT) is well-known to be effective in patients with localized cancer of the prostate (1), uterine cervix (2), and oral cavity (3). BT can deliver a high radiation dose to a limited volume, even if the tumor moves along with the motions of the organ, while sparing the surrounding normal tissues. BT yields a local control (LC) rate equivalent to surgery in patients with early T stage cancer, and the complications are usually localized and transient, enabling patient's quality of life to be maintained (1-4).

While low-dose-rate (LDR) sources such as iridium (Ir) -192 hairpins and single pins, and Au-198 grains have been used for BT against tongue cancer, they have not been manufactured domestically since the nuclear power plant accident in Fukushima during the Great Tsunami in 2011, and their supply in Japan is unstable. Therefore, there may be a waiting time before patients with early tongue cancer receive BT. Moreover, the proportion of patients with not early (T1-2), but advanced (T3) tongue cancer visiting our department is increasing, and these patients often desire to receive non-surgical therapy because they are elderly, they are not suitable surgical candidates, or they do not wish to undergo surgery. To prevent further tumor growth during the waiting period before BT can administered or to reduce the tumor size prior to BT, induction therapy might be necessary.

Combined external beam radiotherapy (EBRT) with BT has been reported as an alternative treatment modality for patients with late T2 or T3 tongue cancer (3, 5, 6). Although EBRT yields good primary control, it requires daily visits to the hospital and causes mucositis throughout the oral cavity. Although several studies have assessed the role of induction chemotherapy followed by EBRT for the non-surgical management of patients with locally advanced head and neck cancers, the percentage of oral cavity cancer patients included in these studies was small, and there have been no reports of combined chemotherapy plus BT (7). Scoffski (8) reported high response rates of unresectable solid tumors to tegafur/gimeracil/oteracil (S-1), an orally administered anticancer drug, and Harada *et al.* (9) reported that S-1 improved the outcomes of patients with oral cancer, while exerting little toxicity. Therefore, either S-1 chemotherapy and/or low-dose of EBRT have been used as induction therapy

Correspondence to: Ryo-ichi Yoshimura, MD, Ph.D., Department of Radiation Therapeutics and Oncology, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo, 1138519, Japan. Tel: +81 358035311, Fax: +81 358030147, e-mail: ysmrmrad@tmd.ac.jp

Key Words: Tongue cancer, induction therapy, external beam radiotherapy, S-1, local control, lymph node metastasis-free survival.

prior to BT in patients with tongue cancer. If the combination of induction therapy and BT is effective and safe, the indication for curative treatment other than surgery will expand, which is desirable for the upcoming aging society.

In the present study, we evaluated the efficacy and safety of induction therapy followed by BT in patients with tongue cancer.

Patients and Methods

Between July 2014 and December 2018, 161 patients with squamous cell carcinoma of the tongue received BT at our hospital. Among these 161 patients, 52 patients received S-1 chemotherapy (n=31), EBRT (n=16), or both S-1 chemotherapy and EBRT (n=5) prior to BT as induction therapy to prevent tumor growth during the waiting period for BT, or to reduce the tumor size in cases of large tumors, making the tumor amenable to BT. The data of these 52 patients were retrospectively analyzed after obtaining the approval of our institutional review board (Approval No. M2019-089). All the tumors were restaged according to the UICC TNM classification, 8th edition. None of the patients had lymph node metastasis or distant metastasis at the start of the induction therapy, although 4 patients developed tumor recurrence after a partial glossectomy.

Treatment. Induction chemotherapy with S-1 was administered to patients with creatinine clearance (Ccr) values of >60 ml/min. Patients with a body surface area of less than 1.25 m^2, 1.25 m^2 to 1.5 m^2, and ≥1.5 m^2 received S-1 at a daily dose of 80 mg, 100 mg, and 120 mg, respectively. Patients received S-1 for 2 weeks followed by 1 week of no chemotherapy, or they received the drug every other day.

Induction EBRT was selected for patients who were comprehensively judged as being unsuitable to receive S-1 chemotherapy because of visceral dysfunction, including kidney dysfunction, other complications, or the wishes of the patients. Induction EBRT was administered to the affected area of the tongue using the conventional method and a 4- or 6-MV X-ray beam. Although the radiation dose was set at 30 Gy (divided into 15 fractions) as the standard dose, the doses varied because of the existence of a relation between the length of time until the start of BT and the tumor response. Both S-1 chemotherapy and EBRT were administered to patients for whom S-1 chemotherapy alone was considered inadequate.

BT was administered using LDR sources: either Au-198 grains or Ir-192 hairpins and single pins. The sources were implanted in a single plane or two planes, and a standard dose of 70 Gy to the tumor edge was prescribed for the entire period in cases receiving BT with Ir-192 pins, while a standard dose of 80-90 Gy was prescribed for permanent implantation in cases receiving BT with Au-198 grains. Because Au-198 grains are small and can be easily applied without causing severe pain or discomfort during the insertion and treatment, they are usually prescribed for elderly patients or patients with a poor performance status (PS), who are unable to tolerate BT using Ir-192 pins (10).

Follow-up and analysis. Patients were followed up periodically by physical examination, computed tomography (CT), and magnetic resonance imaging (MRI) or fluoro deoxy glucose-positron emission tomography (FDG-PET)/CT, as clinically indicated. The follow-up visits were scheduled every 2 weeks after hospital discharge for the first 2 or 3 months, then every month for one year, and then every 2 or 3 months thereafter.

The LC, lymph node metastasis-free survival (LNMFS), and overall survival (OS) rates were calculated using the Kaplan-Meier method, and their relations with the treatment procedure were evaluated using a univariate analysis with the log-rank test. A *p*-value of <0.05 was considered as denoting a statistically significant difference. All statistical analyses were performed using the Statistical Package for Social Sciences, version 23.0 (IBM, Chicago, IL, USA). Complications were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Results

Of the 52 patients, three were excluded from this study because their follow-up durations were less than one year without local recurrence or lymph node metastasis. The patient and tumor characteristics of the remaining 49 patients with tongue cancer enrolled in this study are shown in Table I. The percentages of patients with an advanced age, a high ACE-27 score, and a high PS in the EBRT group tended to be higher than those in the S-1 chemotherapy group. Although the overall follow-up duration ranged from 1 to 77 months (median, 43 months), the follow-up duration for the surviving patients without local recurrence or lymph-node metastasis ranged from 19 to 77 months (median, 47 months).

cT1-2 tongue cancer patients. For patients with cT1-2 tongue cancer, induction therapy was performed to prevent tumor growth during the waiting period for BT.

The interval between the start of induction therapy and the start of BT in 23 patients with cT1-2 tongue cancer ranged from 12 to 108 days, with a median of 20 days. S-1 chemotherapy was administered to 70% (n=16) of the 23 patients, and the total drug dose ranged from 560 to 3,960 mg (median, 1,440 mg) delivered over 12 to 66 days (median, 20 days). EBRT was performed in 17% (n=4) of the patients, and the total radiation dose ranged from 18 to 40 Gy (median, 24 Gy) delivered over 14 to 49 days (median, 26 days). Thirteen percent (n=3) of the patients received both S-1 chemotherapy (range=1,600-2,280 mg; median, 1,680 mg) and EBRT (range=20-36 Gy; median, 20 Gy) delivered over 54 to 108 days (median, 59 days).

Reassessments of tumor size following induction therapy showed a decrease in 57% (n=13), no change in 39% (n=9), and an increase in 4% (n=1). According to the T stage, down-staging was observed in 13% (n=3) of patients, no change was observed in 87% (n=20), and up-staging was observed in 0%. No significant relation between the kind of induction therapy and change in tumor size (p=0.9) or T stage (p=0.6) was observed.

After the completion of induction therapy followed by BT, the 3-year LC, LNMFS, and OS rates were 84%, 45%, and 69%, respectively (Figure 1). The relations between the outcomes and the treatment processes are shown in Table II. The LC was not associated with differences in any processes in this study. However, the LNMFS of the patients with

Table I. *Patients and tumor characteristics*.

	Total	Induction therapy			
	n	EBRT	S-1	Both	*p*-Value
Total	49	13	31	5	
Age (years)					0.09
Median (range)	72 (33-97)	78 (59-85)	71 (33-97)	75 (65-80)	
<75	29	5	22	2	
≥75	20	8	9	3	
Gender					0.8
Female	13	3	8	2	
Male	36	10	23	3	
ACE-27 score					0.009
0	12	0	10	2	
1	14	3	11	0	
2	8	1	6	1	
3	15	9	4	2	
Performance status score					0.04
0	23	2	19	2	
1	10	2	7	1	
2	9	6	2	1	
3	7	3	3	1	
Category of tumor					0.8
Primary	45	12	29	5	
Recurrence	4	1	3	0	
T stage at diagnosis					0.6
1	2	0	2	0	
2	21	4	14	3	
3	26	9	15	2	
Duration of induction therapy (days)					0.009
Median (range)	35 (12-108)	33 (14-59)	31 (12-69)	54 (32-108)	
≤50	42	12	28	2	
>50	7	1	3	3	
Brachytherapy					0.1
Au grains [median, range (Gy)]	22 (84, 60-93)	9	11	2	
Ir pins [median, range (Gy)]	27 (70, 60-70)	4	20	3	

EBRT: External beam radiotherapy; S-1: tegafur/gimeracil/oteracil; ACE-27: adult comorbidity evaluation-27.

induction S-1 chemotherapy was significantly better than that of the patients with induction EBRT or both S-1 chemotherapy and EBRT ($p<0.001$), and the LNMFS of the patients with a duration of induction therapy of >50 days tended to be lower than that of patients with a duration of ≤50 days, although the difference was not statistically significant ($p=0.06$). The OS of patients with BT using Ir-192 pins was significantly better than that of the patients with BT using Au-198 grains ($p=0.001$). Lymph-node metastasis was observed in 57% (n=8) of the 14 patients who received BT using Au-198 grains, and 5 of these patients could not undergo a neck dissection because of an advanced age, comorbidity, or a poor PS. Moreover, 14% (n=2) of the patients who received BT using Au-198 grains died from other diseases.

cT3 tongue cancer patients. For patients with cT3 tongue cancer, induction therapy was performed to reduce the tumor size so as to make the tumor amenable to BT. The interval between the start of induction therapy and the start of BT in the 26 patients with cT3 tongue cancer ranged from 13 to 69 days, with a median of 35 days. S-1 chemotherapy was administered to 58% (n=15) of the 26 patients, and the total drug dose ranged from 560 to 5,460 mg (median, 1,680 mg) delivered over 13 to 69 days (median, 37 days). EBRT was performed in 35% (n=9) of the patients, and the total radiation dose ranged from 27 to 50 Gy (median, 30 Gy) delivered over 14 to 59 days (median, 33 days). Eight percent (n=2) of the patients received both S-1 chemotherapy (480 mg and 2,700 mg, respectively) and EBRT (both 30 Gy) delivered over 32 and 35 days, respectively.

Reassessments of tumor size following induction therapy showed a decrease in 88% (n=23), no change in 4% (n=1), and an increase in 8% (n=2). According to the T stage, down-staging was observed in 65% (n=17), no change was observed

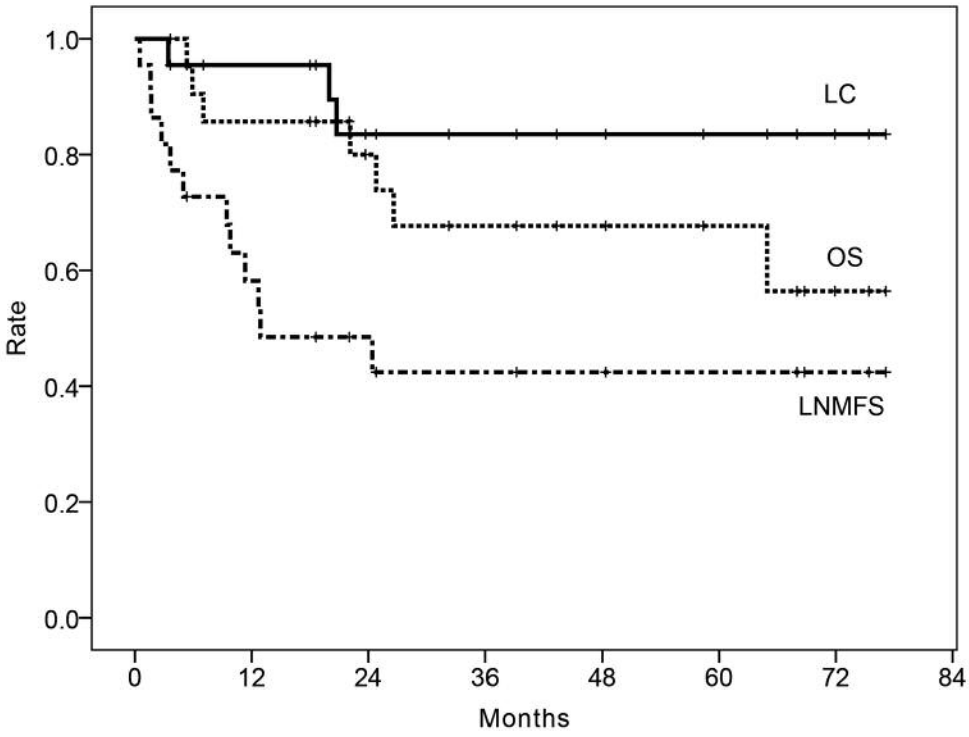

Figure 1. *LC, LNMFS, and OS curves of patients with cT1-2 tongue cancer. LC: Local control; LNMFS: lymph node metastasis-free survival; OS: overall survival.*

Table II. *LC, LNMFS, and OS of cT1-2 patients according to the treatment processes.*

			LC		LNMFS		OS	
		n	3-y rate	*p*-Value	3-y rate	*p*-Value	3-y rate	*p*-Value
Total		23	84%		45%		69%	
Induction therapy	EBRT	4	75%		0%		38%	
	S-1	16	85%		66%		78%	
	Both	3	100%	0.5	0%	0.000	67%	0.3
Duration of	≤50 days	19	88%		49%		68%	
induction therapy	>50 days	4	83%	0.4	25%	0.06	75%	0.8
Change of size following	Decrease	13	92%		51%		65%	
to induction therapy	No change	8	67%	0.3	33%	0.7	73%	0.4
	Increase	1	-		-		-	
BT sources	Au grains	14	72%		35%		46%	
	Ir pins	9	100%	0.1	56%	0.6	100%	0.01

LC: Local control; LNMFS; lymph node metastasis-free survival; OS: overall survival; BT: brachytherapy.

in 35% (n=9), and up-staging was observed in 0%. No significant relation between the kind of induction therapy and change in tumor size (p=0.1) or T stage (p=0.6) was observed.

After the completion of induction therapy followed by BT, the 3-year LC, LNMFS, and OS rates were 77%, 58%, and 79%, respectively (Figure 2). The relations between the outcomes and the treatment processes are shown in Table III. The LC of patients with down-staging as a result of induction therapy was significantly better than that of the patients with no change in stage (p=0.015). LNMFS was not associated with differences in any of the processes. However, a duration of induction therapy >50 days tended to reduce the rates of LC, LNMFS, and OS, compared with a duration of ≤50 days, and this difference was statistically significant for OS (p=0.004).

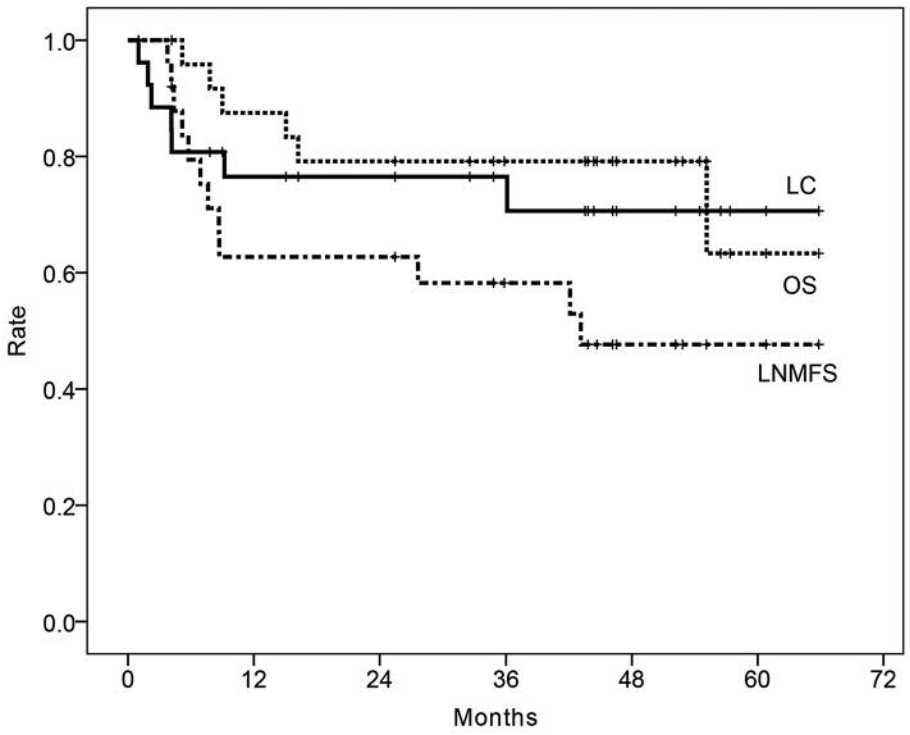

Figure 2. *LC, LNMFS, and OS curves of patients with cT3 tongue cancer. LC: Local control; LNMFS: lymph node metastasis-free survival; OS: overall survival.*

Table III. *LC, LNMFS, and OS of cT3 patients according to the treatment processes.*

			LC		LNMFS		OS	
		n	3-y rate	*p*-Value	3-y rate	*p*-Value	3-y rate	*p*-Value
Total		26	77%		58%		79%	
Induction therapy	EBRT	9	78%		63%		63%	
	S-1	15	80%		50%		86%	
	Both	2	50%	0.7	100%	0.4	100%	0.5
Duration of	≤50 days	23	83%		62%		86%	
induction therapy	>50 days	3	0%	0.069	33%	0.275	33%	0.004
Change of T stage following	Decrease	17	94%		46%		71%	
to induction therapy	No change	9	44%	0.015	86%	0.123	100%	0.107
	Increase	0	-		-		-	
BT sources	Au grains	8	75%		54%		71%	
	Ir pins	18	77%	0.9	59%	0.7	82%	0.6

LC: Local control; LNMFS; lymph node metastasis-free survival; OS: overall survival; EBRT: external beam radiotherapy; S-1: tegafur/gimeracil/oteracil; BT: brachytherapy.

Complications. During or after induction therapy, 22% (n=11) of all 49 patients suffered from Grade 2 or 3 complications (Table IV). The incidence of complications in patients receiving induction S-1 chemotherapy (35%) was less than that in patients receiving induction EBRT (77%) or both S-1 chemotherapy and EBRT (100%), and all the complications in patients receiving EBRT or both S-1 chemotherapy and EBRT were oral mucositis.

After BT, 33% (n=16) of all 49 patients suffered from Grade 2 complications, and 6% (n=3) suffered from Grade 3

Table IV. *Number of complications (%).*

		Induction therapy		
		EBRT	S-1	Both
Complications of induction therapy				
Grade 0	-	3 (23)	20 (65)	0 (0)
Grade 1	Oral mucositis	4 (31)	-	3 (60)
	Nausea	-	3 (10)	-
	Diarrhea	-	2 (6)	-
	Eye watering	-	1 (3)	-
	Hepatobiliary disorders	-	1 (3)	-
	Kidney injury	-	1 (3)	-
Grade 2	Oral mucositis	4 (31)	-	1 (20)
	Fatigue	-	1 (3)	-
Grade 3	Oral mucositis	2 (15)	-	1 (20)
	Anorexia	-	1 (3)	-
	Blood bilirubin increased	-	1 (3)	-
Complications after BT				
Grade 0-1	-	9 (69)	15 (58)	3 (60)
Grade 2	Oral mucositis (ulcer)	1 (8)	12 (39)	2 (40)
	Osteonecrosis of mandibular	-	1 (3)	-
Grade 3	Aspiration pneumonia	2 (15)	-	-
Grade 4	Aspiration pneumonia	1 (8)	-	-

EBRT: External beam radiotherapy; S-1: tegafur/gimeracil/oteracil.

Table V. *Relationship between complications after BT and treatment processes.*

	Number of complications after BT (%)			
	Grade 0-1	Grade 2	Grade3-4	*p*-Value
Induction therapy				
EBRT	9 (69)	1 (8)	3 (23)	
S-1	18 (58)	13 (42)	0 (0)	
Both	3 (60)	2 (40)	0 (0)	0.018
Duration of induction therapy				
≤50 days	25 (60)	14 (33)	3 (7)	
>50 days	5 (71)	2 (29)	9 (0)	0.7
Complications of induction therapy				
Grade 0-1	22 (58)	14 (37)	2 (5)	
Grade 2-3	8 (73)	2 (18)	1 (9)	0.5
BT sources				
Au grains	15 (68)	4 (18)	3 (14)	
Ir pins	15 (56)	12 (44)	0 (0)	0.038

BT: Brachytherapy; EBRT: external beam radiotherapy; S-1: tegafur/gimeracil/oteracil.

or 4 complications. Although Grade 3 or 4 complications were not observed in the patients who received induction S-1 chemotherapy or both S-1 chemotherapy and EBRT, aspiration pneumonia of Grade 3 was observed in 15% (n=2) and that of Grade 4 was observed in 8% (n=1) of the 13 patients with induction EBRT followed by BT using Au-198 grains. The ages of these 3 patients were relatively high (76, 80, and 81 years old, respectively), the ACE-27 scores were high (all 3), and the PS were also high (2, 2, and 3, respectively). The duration of induction therapy and the grade of complications arising from induction therapy were not related to the incidence of complications after BT (Table V).

Discussion

The use of induction therapy to prevent increases in tumor size while waiting for the start of curative treatment in patients with early tongue cancer has not been previously reported. Induction therapies with S-1 chemotherapy and/or EBRT reduced or prevented increases in tumor size in 96% of the patients with cT1-2 tongue cancer in this study, and the 3-year overall LC rate of these patients after induction therapy followed by BT was 84%. The previously reported LC rates at 2-6 years in patients with T1-2 tongue cancer treated with BT are 71%-88% (10-14). Because the findings of the present study were consistent with those of previous reports, induction therapy with S-1 chemotherapy or EBRT may have contributed to the maintenance of the treatment outcomes after BT despite the waiting time until the start of BT. However, the 3-year LNMFS rate and the OS rate were 45% and 69%, respectively, and these rates were much lower than those of previous reports, in which the LNMFS and OS rates were 65%-70% and 74%-88%, respectively (11, 12, 14). Lymph node metastasis was observed in all the patients who received induction EBRT or both S-1 chemotherapy and EBRT. The EBRT field did not include the lymph node area in this study, and the duration of induction therapy consisting of EBRT or both S-1 chemotherapy and EBRT was 14-108 days (median, 49 days); this was longer than the duration of induction S-1 chemotherapy, which was 12-66 days (median, 20 days). Although the depth of primary tumor invasion is a predictor of lymph node metastasis (15, 16), the length of the waiting time until the start of local treatment and the use of an induction therapy that helps to prevent lymph node metastasis during the waiting time might also be prognostic indicators. Moreover, the incidence of lymph node metastasis and its treatment likely affected the OS rate and might have been responsible for the low OS rate of patients with cT1-2 tongue cancer who received BT using Au-grains in our study.

Although BT is usually recommended for patients with T1-2N0 tongue cancer, the GEC-ESTRO has recommended treatment with EBRT at 40-45 Gy plus BT at 25-30 Gy as a boost for patients with late T2 tongue cancer and a tumor diameter of more than 3 cm (3). Ihara *et al*. (6) and Kakimoto *et al*. (5) treated T3 tongue cancer using a combination of EBRT at 30 Gy and definitive BT at 65-68 Gy in 74% and 88% of the patients in their series, and they reported 3-year LC rates of 67% and 68%, respectively. In our current study examining induction therapy followed by definitive BT, the 3-year LC rate in patients with cT3 was 77%, while that in patients whose tumors were downsized from cT3 to cT1-2 after induction

therapy was 94%. Although there have been no previous studies clarifying the effect of induction chemotherapy prior to BT, our study showed that S-1 chemotherapy as well as EBRT are effective as induction therapies prior to BT in patients with cT3 tongue cancer. Moreover, induction therapy may play a role in helping to select a curative treatment strategy, since the LC rate was much better in patients with tumor down-staging after induction therapy than in those whose T stage remained unchanging. If induction therapy proves to be effective, then subsequent BT could be recommended; but if induction therapy is not effective, then surgery could be recommended, although recommendation for surgery were difficult in the present study because many of the patients were not suitable candidates for surgery or refused surgery.

Several studies have assessed the role of induction chemotherapy for the non-surgical management of patients with locally advanced head and neck cancers using a combination of cisplatin and fluorouracil (CF), or a combination of paclitaxel, cisplatin, and fluorouracil (PCF), prior to EBRT with or without concurrent chemotherapy; these studies concluded that induction chemotherapy was associated with an improvement in the rate of distant metastases, but not in the survival or locoregional control rates (7). However, the percentage of oral cavity cancer patients that was included in these studies was relatively small. In some studies of patients with oral cavity cancer, induction chemotherapy was prescribed before surgery; a meta-analysis of such studies demonstrated that induction chemotherapy did not improve the clinical outcomes in terms of locoregional recurrence, disease-free survival, or the OS rate (7, 17). Although no trials have used S-1 as an induction therapy (18, 19), the present study used induction S-1 chemotherapy and/or EBRT followed by BT in patients with cT3 tongue cancer, and the OS was improved somewhat, compared with previous studies (5, 6). However, a long duration of induction therapy was significantly associated with a poor OS, probably because of a high incidence of lymph node metastasis.

In our study, the incidence of complications grade ≥2 during or after induction therapy was 22%, while that after BT was 39%; these incidences were higher than those reported previously for BT in patients with tongue cancer. The incidence of ulcers in the oral cavity after BT alone in patients with tongue cancer was previously reported to be 3%-25% (11, 12, 14). Kakimoto *et al*. (5) adopted EBRT plus BT for the treatment of almost all of their patients with tongue cancer, and they reported that 16% of their patients developed bone exposure and/or osteomyelitis and 8% developed soft tissue ulcers. Ihara *et al*. (6) also used EBRT plus BT for the treatment of tongue cancer, and they reported that 10% of all their patients suffered from mandibular osteoradionecrosis necessitating surgery, and 9% suffered from local ulcers or fibrosis necessitating surgery. S-1 chemotherapy caused systemic and organ complications, although the incidence was low; after the subsequent BT, however, the incidence of ulcers in the oral cavity tended to be higher than that in patients who received induction EBRT followed by BT, although all the ulcers were localized and transient. Harada *et al*. (20) speculated that S-1 treatment combined with radiation therapy may suppress cancer cell division effectively and induce significant apoptosis, and this response of the tumor cells may extend to normal tissue cells through strong local irradiation as a result of BT. On the other hand, induction EBRT or both S-1 chemotherapy and EBRT caused oral mucositis, and after subsequent BT, severe aspiration pneumonia was observed in 23% of the patients. EBRT followed by BT should be avoided for patients with an advanced age, a high ACE-27 score, and a high PS. If treatment must be performed for these patients, then careful follow-up must also be required.

The limitations of this study include its retrospective nature, the performance of the study at a single institution, the small number of patients, and the short follow-up period. However, because oral function is very important for breathing, eating and conversations, if oral cancer patients lose these functions because of the need for surgery, they are likely to suffer from permanent dysfunction. To broaden the patient eligibility for BT or to increase the chances of patients receiving less invasive treatments, a prospective study of induction therapy may be warranted.

Conclusion

Induction therapy with S-1 chemotherapy and/or EBRT contributed to the efficacy of subsequent BT in terms of the LC rate in patients with cT1-2 tongue cancer who required the prevention of tumor growth during a waiting period prior to the start of BT and in patients with T3 tumors who required reductions in tumor size to make their tumors amenable to BT. However, a long duration of induction therapy was associated with an increase in the incidence of lymph node metastasis, resulting in reduced OS rate. Moreover, induction EBRT followed by BT for patients with an advanced age, a high ACE-27 score, and a high PS can cause severe complications, such as aspiration pneumonia.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Ryo-ichi Yoshimura: Study concept, study design, data collection, data analysis, and manuscript drafting. Kazuma Toda: Data collection and manuscript review and editing. Hiroshi Watanabe: Data collection and manuscript review and editing. Atsushi Kaida: Data collection and manuscript review and editing. Hiroyuki Harada: Manuscript review and editing. Takahiro Asakage: Manuscript review and editing. Masahiko Miura: Data collection and manuscript review and editing.

Acknowledgements

This work was supported by JSPS KAKENHI [Grant Number JP15K09990].

References

1 Stone NN, Potters L, Davis BJ, Ciezki JP, Zelefsky MJ, Roach M, Shinohara K, Fearn PA, Kattan MW and Stock RG: Multicenter analysis of effect of high biologic effective dose on biochemical failure and survival outcomes in patients with Gleason score 7-10 prostate cancer treated with permanent prostate brachytherapy. Int J Radiat Oncol Biol Phys *73(2)*: 341-346, 2009. PMID: 18597953. DOI: 10.1016/j.ijrobp.2008.04.038

2 Nag S, Erickson B, Thomadsen B, Orton C, Demanes JD and Petereit D: The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys *48(1)*: 201-211, 2000. PMID: 10924990. DOI: 10.1016/s0360-3016(00)00497-1

3 Mazeron JJ, Ardiet JM, Haie-Méder C, Kovács G, Levendag P, Peiffert D, Polo A, Rovirosa A and Strnad V: GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas. Radiother Oncol *91(2)*: 150-156, 2009. PMID: 19329209. DOI: 10.1016/j.radonc.2009.01.005

4 Yoshimura R, Shibuya H, Miura M, Watanabe H, Ayukawa F, Hayashi K and Toda K: Quality of life of oral cancer patients after low-dose-rate interstitial brachytherapy. Int J Radiat Oncol Biol Phys *73(3)*: 772-778, 2009. PMID: 18676096. DOI: 10.1016/j.ijrobp.2008.05.001

5 Kakimoto N, Inoue T, Inoue T, Murakami S, Furukawa S, Yoshida K, Yoshioka Y, Yamazaki H, Tanaka E and Shimizutani K: Results of low- and high-dose-rate interstitial brachytherapy for T3 mobile tongue cancer. Radiother Oncol *68(2)*: 123-128, 2003. PMID: 12972306. DOI: 10.1016/s0167-8140(03)00055-0

6 Ihara N, Shibuya H, Yoshimura R, Oota S, Miura M and Watanabe H: Interstitial brachytherapy and neck dissection for Stage III squamous cell carcinoma of the mobile tongue. Acta Oncol *44(7)*: 709-716, 2005. PMID: 16227161. DOI: 10.1080/02841860500267881

7 Marta GN, William WN Jr, Feher O, Carvalho AL and Kowalski LP: Induction chemotherapy for oral cavity cancer patients: Current status and future perspectives. Oral Oncol *51(12)*: 1069-1075, 2015. PMID: 26522693. DOI: 10.1016/j.oraloncology.2015.10.009

8 Schöffski P: The modulated oral fluoropyrimidine prodrug S-1, and its use in gastrointestinal cancer and other solid tumors. Anticancer Drugs *15(2)*: 85-106, 2004. PMID: 15075664. DOI: 10.1097/00001813-200402000-00001

9 Harada K, Ferdous T and Ueyama Y: Therapeutic strategies with oral fluoropyrimidine anticancer agent, S-1 against oral cancer. Jpn Dent Sci Rev *53(3)*: 61-77, 2017. PMID: 28725297. DOI: 10.1016/j.jdsr.2016.11.001

10 Ryu Y, Shibuya H and Hayashi K: 198Au grain implantation for early tongue cancer in patients of advanced age or poor performance status. J Radiat Res *54(6)*: 1125-1130, 2013. PMID: 23685669. DOI: 10.1093/jrr/rrt060

11 Abdalmear MM, Tomita M and Shibuya H: Long-term results of brachytherapy in early mobile tongue cancer with 10-year minimal follow-up. Anticancer Res *33(1)*: 317-324, 2013. PMID: 23267163.

12 Potharaju M, E HR, Muthukumaran M, Venkataraman M, Ilangovan B and Kuppusamy S: Long-term outcome of high-dose-rate brachytherapy and perioperative brachytherapy in early mobile tongue cancer. J Contemp Brachytherapy *10(1)*: 64-72, 2018. PMID: 29619058. DOI: 10.5114/jcb.2018.74139

13 Oota S, Shibuya H, Yoshimura R, Watanabe H and Miura M: Brachytherapy of stage II mobile tongue carcinoma. Prediction of local control and QOL. Radiat Oncol *1*: 21, 2006. PMID: 16834784. DOI: 10.1186/1748-717X-1-21

14 Yamazaki H, Inoue T, Yoshida K, Yoshioka Y, Furukawa S, Kakimoto N, Shimizutani K and Inoue T: Brachytherapy for early oral tongue cancer: low dose rate to high dose rate. J Radiat Res *44(1)*: 37-40, 2003. PMID: 12841597. DOI: 10.1269/jrr.44.37

15 Yamazaki H, Inoue T, Yoshida K, Tanaka E, Yoshioka Y, Nakamura H, Furukawa S, Shimizutani K, Kakimoto N and Inoue T: Lymph node metastasis of early oral tongue cancer after interstitial radiotherapy. Int J Radiat Oncol Biol Phys *58(1)*: 139-146, 2004. PMID: 14697431. DOI: 10.1016/s0360-3016(03)01459-7

16 Shan J, Jiang R, Chen X, Zhong Y, Zhang W, Xie L, Cheng J and Jiang H: Machine learning predicts lymph node metastasis in early-stage oral tongue squamous cell carcinoma. J Oral Maxillofac Surg *78(12)*: 2208-2218, 2020. PMID: 32649894. DOI: 10.1016/j.joms.2020.06.015

17 Marta GN, Riera R, Bossi P, Zhong LP, Licitra L, Macedo CR, de Castro Junior G, Carvalho AL, William WN Jr and Kowalski LP: Induction chemotherapy prior to surgery with or without postoperative radiotherapy for oral cavity cancer patients: Systematic review and meta-analysis. Eur J Cancer *51(17)*: 2596-2603, 2015. PMID: 26318725. DOI: 10.1016/j.ejca.2015.08.007

18 Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K and ACTS-GC Group: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med *357(18)*: 1810-1820, 2007. PMID: 17978289. DOI: 10.1056/NEJMoa072252

19 Sano D, Tanabe T, Kubota A, Miyamoto S, Tanigaki Y, Okami K, Komatsu M, Ikoma R, Suzuki K, Akazawa Y, Kobayashi S, Yamada Y and Oridate N: Addition of S-1 to radiotherapy for treatment of T2N0 glottic cancer: Results of the multiple-center retrospective cohort study in Japan with a propensity score analysis. Oral Oncol *99*: 104454, 2019. PMID: 31675682. DOI: 10.1016/j.oraloncology.2019.104454

20 Harada K, Kawaguchi S, Supriatno, Onoue T, Yoshida H and Sato M: Combined effects of the oral fluoropyrimidine anticancer agent, S-1 and radiation on human oral cancer cells. Oral Oncol *40(7)*: 713-719, 2004. PMID: 15172641. DOI: 10.1016/j.oraloncology.2004.01.013

Received September 8, 2021
Revised September 26, 2021
Accepted September 27, 2021