

Surgical outcomes in cases of postoperative recurrence of primary oral cancer that required reconstruction

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[Purpose] In order to clarify prognostic factors of recurrent oral cancer,

[Patients and Methods] In 17 oral cancer patients with their age ranging from 28 to 86 years old, who underwent extensive resection accompanied by reconstruction for recurrence of a primary oral cancer, correlations between survival rate after salvage surgery and subsite, T classification and N classification of their initial and recurrent tumors, and time of recurrence were analyzed by using Kaplan-Meier method and kai-square analysis.

[Results] Tongue cancer (10 patients) was found to have the poorest prognosis among all the subsites, and especially those who had recurrence within 3 months after previous surgery had extremely poor prognoses; 30% (3/10) of them died without being discharged from the hospital after salvage surgery, and in 40% of them QOL was remarkably impaired losing their voice and chance of peroral food intake, etc. While T classification and N classification of initial and recurrent tumors were found to have no correlations with the prognosis.

[Conclusion] More appropriate and realistic information should be provided to those patients to assist them to make a fully informed decision prior to surgery.

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Introduction

The oral cavity is involved in multiple bodily functions, such as swallowing and breathing, which are essential for maintaining life; articulation, which is an important human-specific function; and taste functions, which are closely related to quality of life (QOL). Therefore, treatment of oral cancer requires a high consistency of concurrent curative intervention and functional preservation.

Surgical resection is the primary treatment approach for oral cancer, including cases of recurrence.¹ However, after each subsequent primary tumor resection, the oral cavity

functions are impaired, while the difficulty of salvage surgery and postoperative complications increase. Moreover, the prognosis following oral cancer recurrence is one of the poorest among recurrent head and neck cancers.² Therefore, the question whether curative extensive resection, which causes impairment of patients' QOL, should be used for advanced cases of postoperative recurrence remains controversial. If there were appropriate factors predicting the prognosis of salvage surgery in patients with recurrent oral cancer, it would be useful for the decision making of the treatment of those patients including the indication of salvage surgery.

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To obtain a clue to answer to this question, we retrospectively analyzed the prognosis and functional ability in 17 patients who underwent extensive resection accompanied by reconstructive procedures to treat the postoperative recurrence of primary oral cancer at the Department of Otolaryngology-Head and Neck Surgery, Nagasaki University Hospital.

Patients and Methods

The study included 17 patients with oral cancer who underwent extensive resection accompanied by reconstruction for recurrence of a primary oral cancer that had been resected. All procedures were performed at the Department of Otolaryngology-Head and Neck Surgery at Nagasaki University Hospital between September 2003 and September 2011. There were 11 males and 6 females with a mean age of 58 years (range, 28–86 years). The patient observation period was from September 2003 to November 2013, with the day of salvage surgery counted as day 1. All patients were followed-up for at least 2 years (median follow-up, 3 years and 1 month).

Table 1 shows the tumor, nodes, and metastasis (TNM) classification at the time of the initial treatment and the treatment approach used for each patient. The initial treatment was surgery in 15 patients, intra-arterial chemoradiation (CRT) in 1 patient, and oral tegafur gimeracil oteracil potassium (TS-1, 120 mg/day) in 1 patient. T4 was most common at initial treatment (7 patients, 41.2%), and the tongue was the most frequent occurrence site of their primary tumor (10 patients, 58.8%). Before salvage surgery, rT4 was most common, accounting for 10 of 17 patients (58.8%), and 15 of 17 patients (88.2%) were in the stage IV. The second recurrence of the primary tumor occurred in five patients (29.4%), including a patients on whom the recurrence occurred after treatment with oral TS-1, and subtotal glossectomy was performed (case #1 in Table 1), a patient on whom partial glossectomy was performed twice (case #6), a patient on whom recurrence occurred after intra-arterial CRT and subtotal glossectomy was performed (case #9), a patient on whom partial maxillectomy was performed twice (case #11), and a patient on whom buccal mucosectomy was performed twice (case #16). Thus, salvage surgery was performed twice for these five patients, and two of them had undergone reconstruction at the initial salvage surgery, as well. In addition, among the 17 total patients evaluated, 7 patients received reconstruction with a free tissue flap, and 6 patients had a history of irradiation of the head and neck area. The pathological diagnosis was

squamous cell carcinoma for all but one patient, in whom there was a diagnosis of carcinoma ex pleomorphic adenoma. Oropharyngeal reconstruction was concomitantly performed during salvage surgery by using a free flap (12 patients), being more common than those using the pedicle flap (5 patients).

Neck dissection was performed on patients with concurrent recurrence in the cervical lymph node. The criteria for performing additional postoperative irradiation included no history of irradiation, and also one of the followings: 1) pathological findings of positive margins after surgery; 2) extranodal invasion; and/or 3) metastases in three or more lymph nodes.

There were no deaths for other causes among these 17 patients. Correlation analyses between survival rate after salvage surgery and subsite, T classification and N classification of initial and recurrent tumors, and time of recurrence after initial surgery were performed. Postoperative oral functions were also analyzed. Survival rates were calculated using the Kaplan–Meier method, and statistical significance was determined by the χ^2 test.

Results

The survival curve after salvage surgery with reconstruction is presented in Figure 1. The 1-, 2-, and 3-year survival rates were 71% (12 patients), 53% (9 patients), and 41% (7 patients), respectively, with no deaths occurring more than 3 years after surgery. No significant correlation was noted between survival and tumor stage at first visit ($\chi^2 = 1.3243$, $p = 0.2498$), the presence/absence of lymph node metastasis at first visit ($\chi^2 = 0.8926$, $p = 0.3448$), or the presence/absence of lymph node metastasis at the time of recurrence ($\chi^2 = 1.4622$, $p = 0.2266$). The 1- and 2-year recurrence-free survival rates were 41% (7 patients) and 35% (6 patients), respectively, with no recurrences occurring more than 2 years after the initial surgery (Figure 2). Recurrence after the final salvage surgery was seen in 8 of 10 patients (80%) of tongue cancer, indicating a significantly poorer prognosis than the remaining 7 patients with other oral cancer, among which there were only two recurrences (29%, Figure 3). Furthermore, among patients with tongue cancer, the mean survival times was 174 days in those with less than 3 months of recurrence-free period before the present salvage surgery (4 patients), while it was 885 days in those with 3 months or longer (6 patients, Figure 5). This difference clearly demonstrates the significantly poorer prognosis for the patients with rapid recurrence ($\chi^2 = 7.4462$, $p = 0.0064$).

Table 1

Patient no.	Sex	Age	Site	Primary/ Recurrent T status	Primary/ Recurrent N status	Primary/ Recurrent stage	Previous ND/ Salvage ND	Previous RT/ Salvage RT	Previous CT/Salvage CT	Surgery Type	Reconstruction	Histologic Diagnosis	Time between last treatment and recurrence (month)	Feeding form	Tracheal cannula	Survival time after salvage surgery (month)	Outcome
1	F	70	Tongue	4/4	2c/0	IV / IV	+/+	+/+	-/-	SML	Plate	SCC	1	Tube feeding	+	1	DOD
2	M	52	Tongue	4/4	2b/0	IV / IV	+/-	+/-	+/-	SML	Plate, PM	SCC	3	Tube feeding	+	4	DOD
3	F	56	Tongue	2/3	0/2c	II / IV	-/+	+/-	+/-	TGL, SML	Plate, PM	SCC	3	Tube feeding	-	5	DOD
4	M	51	Tongue	2/4	2b/2b	IV / IV	+/+	-/+	-/+	Subtotal glossectomy, SML	Fibula	SCC	7	Tube feeding	+	12	DOD
5	M	54	Tongue	unknown /4	0/2c	unknown / IV	-/+	-/+	-/+	Subtotal glossectomy, PML, half Oropharyngectomy	PM	SCC	3	Blender food	-	13	DOD
6	M	53	Tongue	1/2	0/2c	I / IV	-/+	-/+	-/+	Subtotal glossectomy	Radial forearm	SCC	51	Blender food	-	14	DOD
7	M	62	Tongue	3/2	0/0	III / II	+/-	-/+	-/+	TGL	PM	SCC	7	Blender food	-	19	DOD
8	M	28	Tongue	2/2	0/2b	II / IV	+/+	-/+	-/+	Hemiglossectomy	ALT	SCC	13	Blender food	-	31	DOD
9	F	38	Tongue	4/4	2b/0	IV / IV	+/+	+/-	+/-	TGL, LO	ALT	SCC	8	Blender food	-	46	NED
10	F	62	Tongue	2/2	0/2b	II / IV	+/+	-/+	-/+	Subtotal glossectomy	ALT	SCC	34	Blender food	-	101	NED
11	M	50	Upper gingiva	4/4	2b/0	IV / IV	+/-	+/+	-/+	Total maxillectomy	PM	SCC	4	Normal food	-	7	DOD
12	F	78	Upper gingiva	4/2	2b/2b	IV / IV	+/+	+/+	-/+	Buccal mucosa resection	ALT	SCC	9	Blender food	-	54	NED
13	F	68	Lower gingiva	4/4	0/2c	IV / IV	-/+	-/+	+/-	SML	Fibula	SCC	2	Blender food	-	25	DOD
14	M	50	Lower gingiva	4/2	2b/1	IV / III	+/+	-/+	-/+	SML	Plate, PM	SCC	4	Blender food	-	117	NED
15	M	74	Buccal mucosa	1/4	0/1	I / IV	-/+	-/+	-/+	SML	Fibula	SCC	26	Normal food	-	27	NED
16	M	86	Buccal mucosa	2/4	0/0	II / IV	-/+	-/+	-/+	SML	Plate, PM	SCC	12	Normal food	-	32	NED
17	M	58	Oral floor	2/4	0/1	II / IV	+/+	-/+	-/+	SML	Fibula	Car ex pleo	56	Soft food	-	71	AWD

ND : Neck dissection , RT : Radiation therapy , CT : Chemotherapy ,SML:Segmental mandibulectomy , PML: Partial mandibulectomy , PM : Pectoralis major myocutaneous flap ,ALT : Anterior lateral thigh flap , SCC : Squamous cell carcinoma , Car ex pleo : Carcinoma ex pleomorphic adenoma, DOD : Died of disease, NED : No evidence of disease , TGL : Total glossectomy , LO : Lateral oropharyngectomy

For postoperative swallowing function, 4 of 10 patients with tongue cancer required tubal feeding because of difficulty with oral ingestion, whereas 4 patients with gingiva cancer, 2 patients with buccal mucosa cancer, and one patient with oral floor cancer were capable of surviving with oral intake alone after surgery (Figure 4). Among the 4 patients requiring tubal feeding, the tracheal cannulae were difficult to be removed in 3 patients, and 3 patients died without being discharged. For these 3 patients who died without a postoperative in-home period, the periods between the previous surgery and the present salvage surgery were all less than 3 months.

Table 2

Patient no	initial surgery type
2	Subtotal glossectomy
3	Partial glossectomy
4	Subtotal glossectomy
5	Partial glossectomy
6	Partial glossectomy
7	Subtotal glossectomy
8	Partial glossectomy
10	Partial glossectomy
11	Partial maxillectomy
12	Partial maxillectomy, Total hard palate resection
13	Partial mandibulectomy
14	Segmental mandibulectomy
15	Buccal mucosa resection
16	Buccal mucosa resection
17	Partial glossectomy

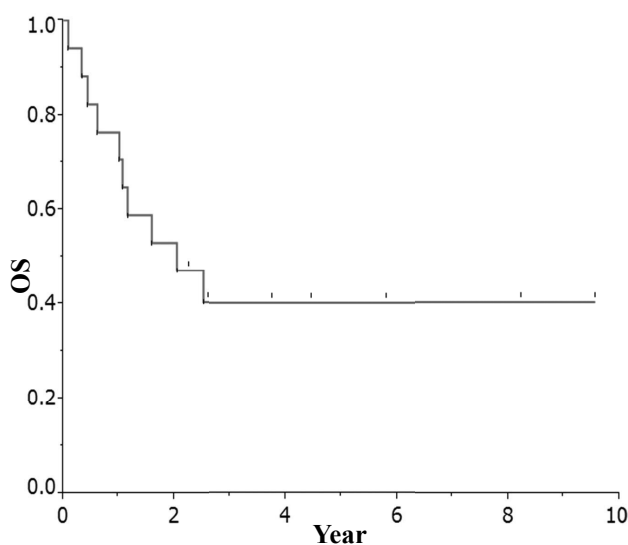


Figure 1. Overall survival (OS) rates for patients after salvage operation. (n=17)

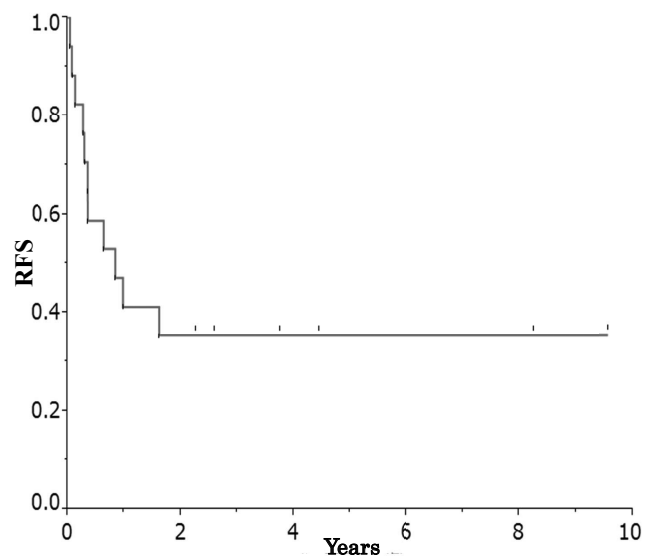


Figure 2. Recurrence-free survival (RFS) for patients after salvage operation. (n=17)

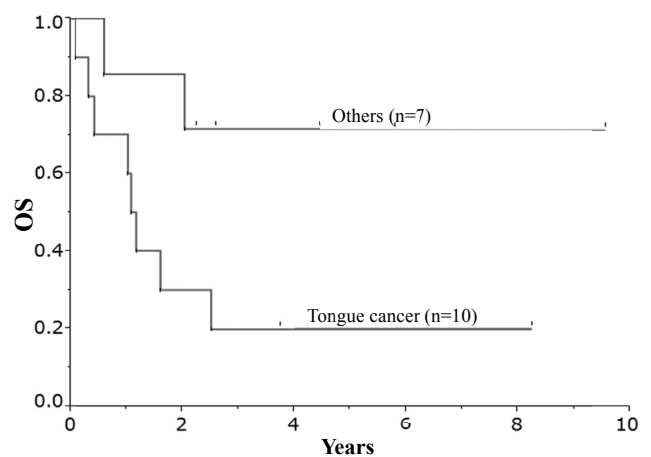


Figure 3. Overall survival (OS) rates for tongue cancer patients and others after salvage operation. (p=0.0450)

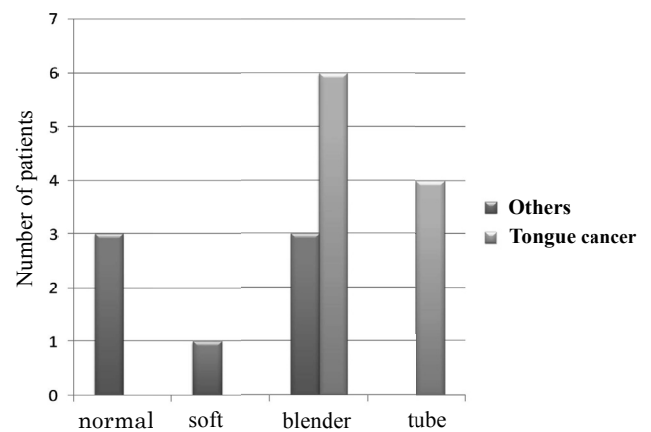


Figure 4. Feeding form after salvage surgery.

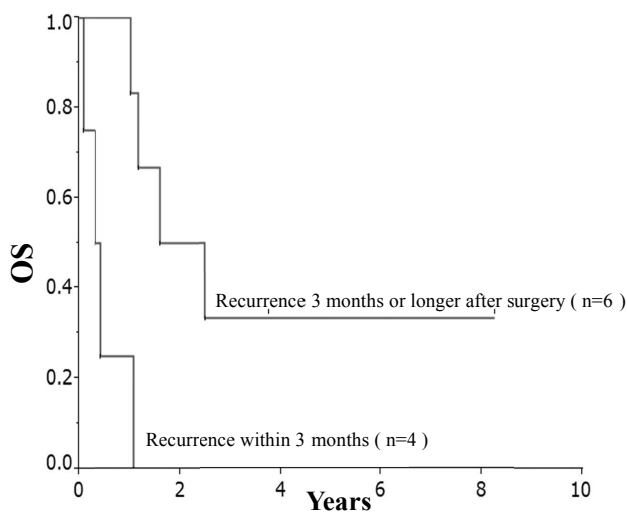


Figure 5. Overall survival (OS) rates for tongue cancer patients who developed recurrence within 3 months and longer after surgery.

Discussion

In a meta-analysis of 377 recurrent head and neck cancer cases by Wong LY et al.³, no cases were successfully salvaged by radiation therapy or chemotherapy alone, and 5-year disease-free survival was achieved only by patients who underwent salvage surgery. The median survival after salvage surgery for primary tumor recurrence was 33 months, whereas the median survival periods for patients who underwent radiation or chemotherapy as a non-surgical salvage attempt and for those who underwent best supportive care were 7 and 5 months, respectively, and treatment with radiation or chemotherapy was found to extend survival only by 2 months. Therefore, salvage surgery appears to be the only treatment option for head and neck cancer recurrence that can achieve a complete cure. Among the various types of head and neck cancer, oral cancer is particularly refractory to CRT,² and therefore, resection is the only curative approach available for oral cancer, including cases of recurrence. However, the following problems that are associated with salvage surgery are a dilemma for head and neck surgeons in readily deciding to perform a resection.

The worst problem that surgeons face is a poor prognosis following surgery for recurrence. It has been reported that 30% of patients with local recurrence of oral cancer are eligible for salvage surgery but only approximately 10% can be successfully salvaged.^{3,4,5} Thus, in oral cancer salvage surgery, even after successfully completing a very difficult

surgery through careful preoperative preparations and postoperative management, it is not uncommon for the disease to recur soon after surgery. Our study showed marginal results for the duration of recurrence-free survival, which was 41% at 1 year and 35% at 2 years. Regarding the prognosis, some have reported that the disease stage at first visit affects prognosis, but restaging at the time of recurrence has no relevance.^{6,7} However, others have reported that the disease stage at the time of recurrence correlates most closely with prognosis.⁸ In this study, only patients with advanced recurrence requiring extensive resection and reconstruction were selected, and they were expected to have a poor prognosis. Moreover, there was no correlation between prognosis and disease stage at the initial visit or at the time of recurrence, presumably because stage IV cases accounted for approximately 88% of all the patients. In addition, prognosis is favorable for cases of late recurrence defined as no earlier than 6 months after completion of the primary treatment, with some investigators attributing this relationship to the fact that lesions of late recurrence tend to be less invasive and more localized.^{7,9} A similar result was obtained in the present study, with the difference in the survival rate increased with case stratification using a 3-month threshold (Figure 5) in those with tongue cancer. Four patients who had recurrence within 3 months died approximately within an year after surgery, with 3 deaths due to distant metastases and 1 due to parapharyngeal lymph node metastases. All 4 patients had recurrent tongue cancer, and when these patients were compared with those involving other oral sites, prognosis appeared to be quite difficult to predict on the basis of findings at the first visit or at the time of initial treatment. Therefore, when the time of recurrence from the initial surgery is 3 months or shorter, local control may be possible through extensive resection and reconstructive surgery, but even with good local control, distant metastases are likely to occur early and thus prognosis is expected to be poor.

Second problem surgeons facing is the reduced postoperative QOL. The functions of the oral cavity rapidly decrease as the extent of resection increases. In particular, extensive resection combined with reconstructive surgery for recurrent tongue cancer often causes a marked reduction in QOL, including difficulties with oral ingestion and conversation. It has been reported that QOL is immediately reduced after surgery and that it takes 1 year to recover the patient's preoperative QOL.¹⁰ Among the 10 tongue cancer patients in the present study, postoperative QOL after salvage surgery was quite poor in terms of feeding and articulation as described in the results, and 3 of them died within

6 months without ever regaining their oral ingestion/vocalization capabilities and without being discharged. Patient satisfaction was not assessed in this study, but admittedly these outcomes were severe and very difficult to accept as outcomes following highly invasive radical surgery.

Limited evidence is available on the surgical indications of the postoperative recurrence of oral cancer, and it is very difficult to differentiate between resectable and permanently curable cases. Final decisions on treatment methods are based on the preferences of patients and family members and the level of their physicians' experience. However, in the present study, even though salvage surgery was performed, all advanced cases of recurrence that occurred within 3 months after tongue cancer surgery resulted in a significantly reduced QOL which was difficult to improve and fairly rapid death. For similar advanced cases of early postoperative recurrence, an adequate length of time should be devoted to providing patients and family members with explanations regarding the reality that a favorable prognosis cannot be expected, that eating and vocalization capabilities are likely to be lost after surgery, and that they should arrange an environment that allows patients to make fully-informed decisions regarding their own treatment. Also this is a study in patients with limited 17 cases, further studies with more cases should be performed in the future in order to confirm the present results.

Conclusion

Despite retrospective analysis, this study of the outcomes following extensive resection combined with reconstructive surgery in patients with postoperative recurrence of oral cancer brought us precious facts. Tongue cancer had a poorer prognosis than those in the other oral subsites. In particular, patients with a recurrence-free period of less than 3 months were more likely to cause early recurrence, distant metastases, and a severe reduction in QOL; thus, more appropriate information should be provided to assist them to make a fully informed decision prior to surgery.

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