

Simultaneous treatment of Multiple Primary Cancers of the Oral Cavity and Other Sites

Yoshihide OTA, Takayuki AOKI, Kazunari KARAKIDA, Hiroshi YAMAZAKI, Hiroyasu MAKUUCHI*, Osamu CHINO* and Muneo MIYASAKA**

*Departments of Oral Surgery, * Surgery and ** Plastic Surgery,
Tokai University School of Medicine*

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Multiple primary cancers are not uncommon in the head and neck region. Since the time for treatment will be prolonged if each lesion is treated separately, simultaneous treatment of the cancers is preferred to ensure complete remission of lesions and increased survival of patients. In this paper, the efficacy of combined treatment was evaluated in 9 patients with oral cancers and concurrent cancers in other sites. The mean age of the patients was 54 years (range 44 to 66). The tongue (8) and mandible (1) were the sites of involvement. Concurrent cancers were found most often in the esophagus, followed by stomach and lung. Histologically, 7 lesions were diagnosed as squamous cell carcinomas. All oral cancers were treated by surgery. Neck dissection and simultaneous reconstruction were performed in 5 patients. In addition, concurrent cancers were treated simultaneously by endoscopic mucosal resection in 2 patients and radical resection followed by immediate reconstruction in 6 other patients. However, simultaneous surgical treatment of all lesions could not be performed in an individual with 3 cancers. The time of surgery ranged from 23 minutes to 17 hours and 30 minutes. With the exception of 2 patients who died of postoperative complications and had needed treatment for dysphasia, all patients were discharged after 1 to 2 months. Four of the patients are still alive 2 years and 6 months after surgery. These results indicate that simultaneous treatment is effective in selected cases of multiple cancers.

Key words : Multiple primary cancers, Simultaneous surgery, Endoscopic esophageal mucosal resection, Oral cancer, Esophageal cancer

INTRODUCTION

Recently, reports of cases of multiple primary cancers in the head and neck area have been increasing. However, when a cancer of the oral cavity was assigned as the index cancer, concurrent cancers developing in distant areas were sometimes detected. In particular, multiple cancers in the head, neck, and upper gastrointestinal tract are frequently found concurrently [1, 2]. In the present study, multiple primary cancers in the oral cavity and in distant sites were found in 9 of 139 cases (6.5%), an incidence equal to previously published results [3-5]. All patients with cancers in the head and neck area that visited the departments of Oral Surgery and ENT Surgery in our hospital had undergone endoscopy of the upper gastrointestinal tract. Moreover, since all of the head and neck

cancers had received iodine staining, esophageal mucosal cancers difficult to find by routine endoscopy were detected, possibly inflating the incidence.

The prognosis for multiple cancers is poorer than that for a single cancer [6]. In the treatment of multiple cancers, when each cancer is treated separately, the therapeutic period is extended and the other cancers may grow during the lengthened period of treatment. Therefore, the shortest time possible for treatment is preferred towards securing longer survival and complete remission. Tachimori *et al.* [7] recommended that for concurrent head, neck, and esophageal tumors, surgery for each tumor is desirable. However, they did not state whether resection of all the tumors should be done simultaneously. Miyahara *et al.* [8] surgically treated 5 of 8 patients who had concurrent can-

cers in the head, neck, and stomach ; in each case, surgery of the head and neck tumors was performed first, followed by gastrectomy at a later date for the stomach cancer.

Tanaka [2] considered the prognosis for concurrent multiple cancers is better than for recurrent single cancers because the opportunity for a radical cure is higher in the former cases. Consequently, treating concurrent multiple cancers, surgery is performed under less physical and mental stress than surgery performed at periodic intervals. Therefore, we treated simultaneously when possible. In the present study, a retrospective evaluation of the treatment of multiple cancers was carried out. Our policy, for treating concurrent multiple cancers, is discussed.

MATERIALS AND METHODS

During the 4 years from January 1993 through December 1996, 139 patients with primary squamous cell carcinoma of the oral cavity were treated in our department. Nine of the patients (6.5%) were found to have had concurrent cancers by whole body examination and therefore were selected for the present study. The following parameters were examined; CT, MRI, ultrasonography of the head, neck, and abdomen, ⁹⁹Tc scanning, ⁶⁷Ga scanning, and endoscopy of the upper gastrointestinal tract. The age of the subjects ranged from 44–66 years (54.4 years average), and consisted of 8 males and 1 female.

Tongue cancers were found in 8 of the 9 patients; by disease staging, Stage 1 (3), Stage 3 (1) and Stage 4 (4) were diagnosed. The remaining patient had a Stage 4 gingival cancer of the mandible. Concurrently, esophageal cancers were found in 7 of the 9 patients and were diagnosed as squamous cell carcinoma. Five of these 7 patients were early cancers; the other 2 were advanced cases. One case was a progressive gastric cancer Borrmann type II (adenocarcinoma), and the other was a tongue cancer found concurrently with an early gastric cancer IIc + III (adenocarcinoma), and a Stage IIIb pulmonary squamous cell carcinoma (Table 1).

According to the definitions published by Warren and Gates [9], Gluckmann *et al.* [6] and Panosetti *et al.* [10], multiple cancers are defined as those diagnosed simultaneously with the index (chief complaint) cancer.

RESULTS

< Therapeutic procedures >

Surgery was performed on the 9 patients with oral and multiple cancers. For the oral cancers, the surgical procedures were: partial glossectomy (3), partial glossectomy and functional neck dissection (1), subtotal glossectomy, bilateral functional neck dissection and reconstruction with rectus abdominis myocutaneous free flap (4), and subtotal mandibulectomy, bilateral functional neck dissection and reconstruction with titanium plate and rectus abdominis free flap (1). For concurrent cancers, endoscopic esophageal mucosal resection (EEMR) was performed in 2 patients with esophageal mucosal cancer. The other 7 patients underwent radical operations; esophagectomy with thoracotomy (3), transhiatal esophagectomy (blunt resection) (1), distal gastrectomy (1), and a total pharyngo - laryngo - esophagectomy (TPLE) associated with subtotal glossectomy (1). All surgical procedures were conducted simultaneously with the resection of the oral cancer. In patient No. 9, an individual with 3 cancers, a right pneumonectomy was first performed for the most advanced lung cancer, followed by surgery for the oral and gastric cancers 1 month later (Table 2).

< Surgical time and estimated blood loss >

The time of surgery for partial glossectomy or partial glossectomy and total esophagectomy ranged from 23 minutes to 8 hours, and blood loss was approximately 730 ml. In resections of tongue cancers with reconstruction and radical esophagectomy, the time for surgery averaged 16 hours, and estimated blood loss at about 1500 ml. In resections of tongue cancer with reconstruction and subtotal gastrectomy, the time for surgery was about 10 hours, and estimated blood loss at 1600 ml (Table 2).

< Hospital stay and complications >

One patient died 18 days after surgery from airway obstruction due to mucous plugging. Another patient was hospitalized for 70 days for postoperative wound infection, and a third patient, who had dysphagia and was fed by gastrogavage, was hospitalized for 172 days. The time in-hospital for the remaining 5 cases was from 24 to 39

Table 1 Characteristics of patients with multiple primary cancers (1)

Case No.	Age/Sex	PS*	Oral Cancers			Concurrent Cancers				
			site	histological type	TNM	stage	site	histological type	depth of invasion	stage/TMN
1	56/M	1	tongue	S.C.C.*	T ₁ N ₀ M ₀	I	esophagus	S.C.C.*	m2	O-II b
2	66/M	1	tongue	S.C.C.*	T ₂ N ₁ M ₀	III	esophagus	S.C.C.*	m1	O-II c
3	58/M	1	tongue	S.C.C.(CSF*)	T ₁ N ₀ M ₀	I	esophagus	S.C.C.*	m2, sm3	O-II b, III c
4	62/M	1	tongue	S.C.C.*	T ₁ N ₀ M ₀	I	esophagus	S.C.C.*	m2	O-II b, II c
5	53/M	1	tongue	S.C.C.*	T ₄ N ₀ M ₀	IV	esophagus	S.C.C.*	m1	advanced type I
6	44/F	2	tongue	S.C.C.*	T ₄ N ₀ M ₀	IV	esophagus	S.C.C.*	m1	O-II b
7	53/M	3	mandible	S.C.C.*	T ₄ N _{3c} M ₀	IV	esophagus	S.C.C.*	pm, m2	advanced type II
8	44/M	1	tongue	S.C.C.*	T ₃ N ₀ M ₀	IV	stomach	Adeno Ca*	ss	Borr. II
9	54/M	1	tongue	S.C.C.*	T ₃ N ₁ M ₀	IV	lung	S.C.C.*		T ₃ N ₃ M ₀
							stomach	Adeno Ca*	sm	II c, III

*PS: performance status, S.C.C.: squamous cell carcinoma, CSF: tumor producing colony-stimulating factor, Adeno Ca.: adenocarcinoma

Table 2 Characteristics of patients with multiple primary cancers (2)

Case No.	Treatment				Time for surgery			EBL* (mL)	Duration (days)		Status
	Oral cancer		concurrent cancers		oral cancer	concurrent cancer	total		from surgery to Hospital discharge	total	
	resection	reconstruction	resection	reconstruction							
1	partial glossectomy	-	EEMR*	-	23min	-	23min	a little	30	34	alive
2	partial glossectomy FND*	-	EEMR	-	4hr30mi	-	4hr30min	157	24	44	alive
3	partial glossectomy	-	esophagectomy with thoracotomy	organ: colon route: subcutaneous	19min	13h0min	13hr0min	730	38	65	died of tongue cancer
4	partial glossectomy	-	esophagectomy with thoracotomy	organ: stomach route: subcutaneous	25min	8hr5min	8hr5min	680	31	60	died of hypopharyngeal cancer
5	subtotal glossectomy, bilateral FND*	RAMC*	total pharyngo laryngoesophagectomy	jejunal free transfer	8hr49min	8hr9min	15hr0min	1598	70	96	alive
6	subtotal glossectomy, bilateral FND*	RAMC*	transhiatal esophagectomy (bluent resection)	organ: stomach route: subcutaneous	10hr55mi	14hr15m	15hr30m	1046	172	202	alive
7	subtotal mandibulotomy, subtotal glossectomy, bilateral FND*	RAMC* titanium plate	esophagectomy with thoracotomy	organ: stomach route: subcutaneous	9hr55min	7hr32min	17hr30min	1862	18	32	surgical complications death
8	subtotal glossectomy, bilateral FND*	RAMC*	distal pneumonectomy	B-I* anastomosis	9hr58min	2hr47min	9hr58min	2150	39	60	died of stomach cancer
9	subtotal glossectomy, bilateral FND*	RAMC*	right pneumonectomy distal gastrectomy	B-I* anastomosis	9hr30min	2hr12min 4hr30min	9hr30min 4hr30min	350 1060	30 28	84	died of lung cancer

*FND: functional neck dissection, RAMC: rectus abdominis myocutaneous free flap, EEMR: endoscopic esophageal mucosal resection, EBL: estimated blood loss, B-I: Billroth-I

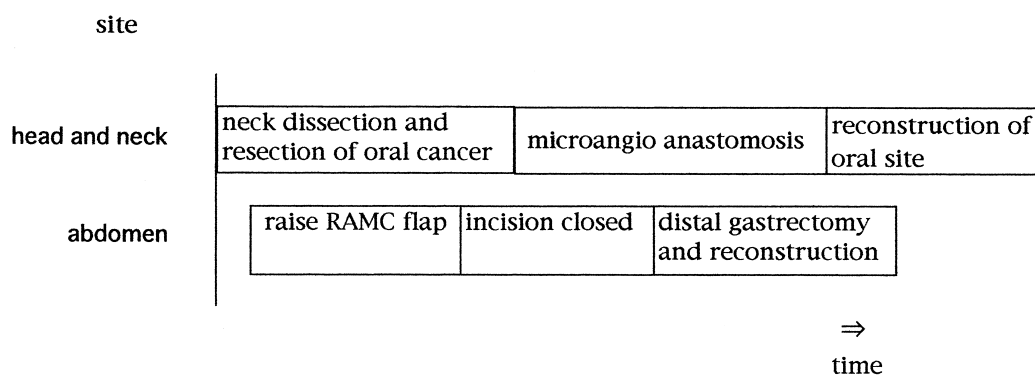


Fig. 1 Surgical procedure

days. The triple cancer patient underwent 2 operations and was discharged 67 days after the initial surgery (pneumonectomy) (Table 2).

< Long-term outcome >

During the postoperative period of observation of 2.5 years, 4 of the 9 patients are still surviving without recurrences or metastases. The cause of death of the 5 deceased patients was: direct operative death (1), death due to primary oral cancer or concurrent multiple cancer (3), and multiple cancers developing postoperatively (1) (Table. 2).

DISCUSSION

The frequent development of other types of cancer in an individual can be explained by the “field cancerization” theory originally proposed by Slaughter *et al.* [11]. It is now well documented that concurrent multiple primary cancers in the head and neck and in the upper gastrointestinal tract occur frequently [1, 2]. Rogers *et al.* [12] reported that nitrosation may be involved in field cancerization and Yokoyama *et al.* [13] suggested that acetaldehyde may also play a critical role.

Treatment of multiple cancers encompasses EEMR and the simultaneous resection of the oral and other cancers. In the present study, EEMR (endoscopic esophageal mucosal resection [14, 15]), was performed in 2 of 7 patients with concurrent esophageal cancer. When EEMR is feasible, it can be done regardless of the oral cancer resection. Therefore, this method of treating multiple cancers shows little difference in comparison with the treatment of single oral cancers,

regarding surgical time and stress to patient.

In patients that underwent resections of oral and concurrent cancers, the time required for surgery was minimal because the surgery in the oral and other sites was performed at the same time (Fig. 1).

Radical resections of oral cancers and esophageal cancers could not be performed simultaneously because the 2 sites were too close to each other. Therefore, oral cancers were resected after esophagectomy, and more than 15 hours were needed to complete both procedures in 2 patients. However, the postoperative course did not differ greatly when compared with the postoperative course after resection of either an oral or esophageal cancer. The 2 patients, after only 1 day in the surgical intensive care unit, were discharged. This is probably due to the relatively small volumes of blood loss during surgery. For the esophageal cancer in the cervical region, TPLE associated with subtotal glossectomy was performed. Since both the tongue and esophagus required reconstruction, 15 hours were needed for surgery. For reconstruction of the cervical esophagus, a free jejunal transfer was performed. The segment of jejunum used was obtained via an abdominal incision. The postoperative course of the patient was favorable. For the simultaneous resection of multiple cancers, major surgery is required at two or more sites. By treating both the oral cavity and the abdomen simultaneously, the time spent in surgery is shortened, blood loss lessened, and surgical stress reduced [16, 17], contributing to a favorable recovery.

RAMC (rectus abdominis myocutaneous) free flaps were used to cover surgical defects

after resections of oral cancers, with the addition of a titanium plate to reconstruct the mandible. Surgery of thoracic esophageal and gastric cancers required a median laparotomy. When the RAMC flap was prepared first, the underlying wound was closed before the laparotomy incision was performed. When laparotomy was first, the RAMC flap was removed after completion of the abdominal surgery. Noteworthy problems did not occur with either method, and postoperative incisional hernias were not observed.

The course of recovery shortly after surgery was not too different between resection of esophageal cancer alone or when combined with resection of an oral cancer plus reconstruction. Chino *et al.* [18] reported 11 patients over 80 years of age that underwent surgery for esophageal cancer. One patient expired due to sepsis and DIC following aspiration pneumonia 3 weeks after surgery. On the basis of these results, simultaneous resections appeared possible if total blood loss was kept under 2000 ml, and respiratory function be continuously evaluated.

The interval from surgery to discharge from the hospital, for 6 of the 9 patients, was at most 39 days. The 3 exceptions were one patient who underwent gastrostomy due to dysphagia (hospital stay 172 days), another patient with a postoperative wound infection (hospital stay 70 days), and the third patient who died 32 days after surgery. The extension of hospitalization was not related to either tongue or esophageal surgery.

Kanata *et al.* [19] performed radical surgery on a patient with cancers of the hypopharynx, stomach and lung. Since the 3 cancers were resected sequentially, it took 9 months for resection of all the cancers. During the postoperative follow up, the patient died from renal failure 9 months later. Even for the patients dying during the postoperative period, their daily life was relatively good until the terminal stage. Therefore, the simultaneous surgical treatment was beneficial although the patients eventually died of recurrent or metastatic cancer. In addition, since the hospital stay for the multiple primary cancers was shortened by the simultaneous surgery, the time spent at home increased, and this was important in improving the quality of life. Tanaka

[2] reported that multiple cancer patients belong to a high risk group because of the possible development of additional cancers. It appears necessary to establish a more effective follow-up for this type of patient.

Preoperative irradiation was not performed because we considered the cancers in our 9 patients to be too advanced. Since a sufficient surgical margin was secured for the oral cavity, esophagus, and lungs, postoperative irradiation was not considered necessary. Chemotherapy also has an important role in the treatment of cancer. Because both oral and esophageal cancers are squamous cell carcinomas, the chemotherapy of both is similar [20–22]. However, a common regimen effective for oral, lung, and gastric cancers is not available at present. Previously, some investigators noted that chemotherapy for esophageal cancers was not effective [23] and their use extended the in-hospital stay of patients [24]. Since immunosuppression can contribute to the development of multiple cancers [25], immunosuppressive drug chemotherapy was not administered.

Problems related to the simultaneous surgery of multiple cancers are (1) surgical stress, (2) extension of surgical time and (3) postoperative intensive care. The approach to treating multiple cancers should take into consideration not only the cancer sites, stage of development, mutuality, and histological type, but also the possible cause of the cancers and even the patient's social background. In the present study, the simultaneous surgery of multiple cancers is possible (depending on the circumstances), and our procedure was shown to reduce the burden on patients.

SUMMARY

1. We treated 9 cases of multiple primary cancers, located in the oral cavity and other sites.

2. Our strategy for treating multiple primary cancers is as follows: radical treatment should be carried out in conjunction with EEMR for the esophageal mucosal cancers, and simultaneously resection of cancers in the oral cavity and in sites distant from the head and neck.

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