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Safety and benefit of curative surgical resection for esophageal squamous cell cancer associated with multiple primary cancers

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Abstract

Background: Enhancements in surgical techniques have led to improved outcomes for esophageal cancer. Recent findings have showed that esophageal cancer is frequently associated with multiple primary cancers, and surgical resection is usually complicated in such cases. The aim of this study was to clarify the clinical significance of surgery for patients with esophageal squamous cell cancer associated with multiple primary cancers.

Methods: The clinical outcomes of surgical resection for esophageal cancer were compared among 79 patients with antecedent and/or synchronous cancers (Multiple cancer group) and 194 patients without antecedent and/or synchronous cancers (Single cancer group).

Results: The most common site of multiple primary cancers was the pharynx (36 patients; 29.7%), followed by the stomach (24 patients; 19.8%). The reconstruction method was more complicated in the Multiple cancer group as a result of the prolonged surgery time and increased blood loss. However, postoperative morbidity and overall survival (OS) did not differ between the two groups. After esophagectomy, metachronous cancers were observed in 26 patients, with 30 regions in total, and 93.1% were found to be curable. Sex was the only independent risk factors for developing metachronous cancer after esophagectomy.

Conclusions: The presence of antecedent and synchronous cancers complicates the surgical resection of esophageal cancer; however, no differences were found in the OS and postoperative morbidity between the two groups. Therefore, surgical intervention should be selected as a first-line treatment. Because second primary cancers are often observed in esophageal cancer, we recommend a close follow-up using esophagogastroduodenoscopy and contrast-enhanced computed tomography.

Keywords: Esophageal cancer; Squamous cell carcinoma; Multiple primary cancer; Esophagectomy

Introduction

Advances in surgical techniques and treatment modalities have led to the improvement of the 5-year overall survival (OS) rate of patients undergoing esophagectomy from 14.4% to 46.3% over the last few decades.[1] However, the surgery is still invasive and is associated with high mortality and morbidity rates.[2] Alcohol is carcinogenic to humans, and many malignant tumors are related to alcohol consumption.[3] We have previously reported that 36.2% of esophageal cancers present with multiple primary cancers,[4] and several factors need to be taken into consideration when treating these patients. All cancers should be treated with curative intent, and multiple primary cancers often require extremely complex and more invasive surgical procedures to resect all affected regions curatively. In addition,

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there is a limit to the scope of reconstruction in some organs. Combined chemoradiotherapy (CRT) leads to less invasiveness; however, there are limitations in the cumulative dose of chemotherapy[5] and the dose per fraction.

Surgical resections have been performed in patients with esophageal cancer associated with multiple primary cancers by applying treatment modalities. Here we retrospectively review the clinical results after esophagectomy in patients with multiple primary cancers.

Patients and methods

From April 2006 to December 2013, 294 patients who were diagnosed with esophageal cancer and underwent surgery at Kobe University Hospital were assessed. Since the majority of histological type of esophageal cancer observed in Japan is squamous cell carcinoma (SCC),[6] we only included 273 patients with SCC. All patients were examined by an esophageal surgeon and then consulted with a head and neck surgeon to check for head and neck cancers. The treatment was determined during a meeting with the surgical team. Clinical follow-up data were obtained by retrospectively studying patients' clinical charts. All study participants provided informed consent, and the study design was approved by the ethics review board at Kobe University Hospital and conforms to the provisions of the 1995 Declaration of Helsinki.

Two hundred seventy-three patients were divided into two groups, with antecedent and/or synchronous cancers (Multiple cancer group) and without initial and/or synchronous cancers (Single cancer group). Antecedent cancers in the multiple cancer group were checked to not have any recurrence and under control before esophagectomy. The tumor node metastasis (TNM) criteria from the 6th edition of the Unio Internationalis Contra Cancrum (UICC) classification were applied to stage the esophageal cancer.[7]

OS was calculated from the date of the surgery to the occurrence of the event or to the last known date of the follow-up. Actual survival was calculated by the Kaplan–Meier method and analyzed using the log-rank test. Comparisons between the multiple cancer group and the single cancer group were made using the chi-square test, Fisher's exact test, and Student's *t* test. The risk factors for developing second primary cancers were analyzed by using multiple logistic regression analysis. For all analyses, a P value of <0.05 was accepted as statistically significant. Descriptive statistics were obtained using the JMP statistical software package (JMP® 10; SAS Institute Inc., Cary, NC, USA).

Results

Among the 273 patients, 98 patients (35.9%) had another primary cancer (Supplemental Table 1). The regions of the synchronous and metachronous multiple primary cancers are listed in Table 1. The most common region was the pharynx (29.7%), followed by the stomach (19.8%). The most common region for synchronous cancers was the pharynx (47.0%), followed by the stomach (29.4%), and the most common region for metachronous cancers was the colon/rectum (18.4%) in the Multiple cancer group and pharynx and stomach (19.0%) in the single cancer group. Among the patients with metachronous cancers, 32 patients had antecedent malignancies and 26 patients had subsequent malignancies. In four patients, multiple primary cancers were found both before and after esophagectomy.

Table 1
The region of the multiple primary cancers with esophageal cancer.

	Multiple cancer group		Single cancer group	Total (%)
	Synchronous (%)	Metachronous (%)	Metachronous (%)	
Pharynx	24 (47.0%)	8 (16.3%)	4 (19.0%)	36 (29.7%)
Stomach	15 (29.4%)	5 (10.3%)	4 (19.0%)	24 (19.8%)
Colon/Rectum	2 (3.9%)	9 (18.4%)	0 (0%)	11 (9.1%)
Oral cavity/Gingiva/Tongue	4 (7.8%)	4 (8.2%)	1 (4.8%)	9 (7.4%)
Esophagus	1 (2.0%)	4 (8.2%)	2 (9.5%)	7 (5.8%)
Lung	2 (3.9%)	4 (8.2%)	0 (0%)	6 (5.0%)
Prostate	1 (2.0%)	3 (6.1%)	2 (9.5%)	6 (5.0%)
Bladder	0 (0%)	2 (4.1%)	2 (9.5%)	4 (3.3%)
Larynx	0 (0%)	4 (8.2%)	0 (0%)	4 (3.3%)
Breast	0 (0%)	1 (2.0%)	2 (9.5%)	3 (2.5%)
Kidney	1 (2.0%)	1 (2.0%)	1 (4.8%)	3 (2.5%)
Blood cancer	0 (0%)	1 (2.0%)	1 (4.8%)	2 (1.7%)
Urinary tract	0 (0%)	1 (2.0%)	1 (4.8%)	2 (1.7%)
Bile duct	0 (0%)	1 (2.0%)	0 (0%)	1 (0.8%)
Gall bladder	1 (2.0%)	0 (0%)	0 (0%)	1 (0.8%)
pancreas	0 (0%)	0 (0%)	1 (4.8%)	1 (0.8%)
Uterus	0 (0%)	1 (2.0%)	0 (0%)	1 (0.8%)
Total	51	49	21	121