

Successful treatment of quintuple primary cancer, including esophageal cancer: A case report

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Abstract. The present study reports the rare case of a patient with quintuple primary cancer that underwent systematic treatment, including surgical intervention. A 63-year-old male patient was initially diagnosed with primary esophageal cancer and hypopharyngeal cancer. The patient underwent total pharyngolaryngoesophagectomy using a thoracoscopic method and reconstruction using the free jejunal flap and gastric tube and was subsequently administered adjuvant chemotherapy (80 mg/m² intravenously on day 1, cisplatin; 800 mg/m² continuous intravenous administration on days 1-5, 5-fluorouracil). At 66 years old, the patient was diagnosed with left maxillary sinus cancer and underwent chemoradiotherapy (four 100 mg/m² arterial cisplatin injections; 70 Gy/35 f radiotherapy, 2 Gy per day over 35 days). At 68 years old, the patient was diagnosed with gastric tube cancer and underwent gastric tube resection followed by pedicled jejunum flap reconstruction. At 69 years old, the patient was diagnosed with tongue cancer and underwent resection and reconstruction of the tongue by pectoralis major myocutaneous flap. Six years subsequent to the primary surgery, the patient remains alive, without metastasis of the lesions. To the best of our knowledge, the present study is the first report of a patient that underwent a curative procedure for the treatment of five primary multiple cancers in five organs, including esophageal cancer.

Introduction

Alcohol is carcinogenic in humans, and the occurrence of malignant tumors of the oral cavity, pharynx, larynx, esophagus, liver, colorectum and female breast are causally associated with alcohol consumption (1). Approximately 17,000 cases of

esophageal cancer and 22,220 cases of gastric cancer are diagnosed every year in the USA (2). The incidence rate of head and neck cancers is 20 cases in every 100,000 persons (3). According to the National Cancer Institute, the number of second- or higher-order malignancies is increasing, accounting for ~16% of all cases registered in 2003 in the Surveillance Epidemiology and End Results database (4). However, patients with more than five primary cancers that have previously undergone esophagectomy are rarely encountered, since the five-year overall survival rate of esophageal cancer is 48.0%. This is particularly relevant for stage III lesions, as the five-year overall survival rate deteriorates to 32.0% (5). The standard treatment for stage II hypopharyngeal cancer is surgery with or without radiation treatment with a 5-year overall survival rate of 71% (6). The treatment for stage II oral cavity cancer is surgery either with or without radiation treatment with a 5-year overall survival rate of 54% (6). The treatment for stage II gastric cancer is surgery with a five-year overall survival rate of 65% (7). There are only a small number of studies that report more than five malignancies occurring in the same patient and in five different organs (8). In the present study, PubMed (National Center for Biotechnology Information, US National Library of Medicine, Bethesda, MD, USA) was used to perform a search with the keywords 'quintuple', 'cancer' and 'esophagus', however, no studies reporting esophageal cancer were identified. The present study reports the case of a patient with quintuple primary cancer in five different organs. Written informed consent was obtained from the patient.

Case report

In February 2007, a 63-year-old male presented to Kobe University Hospital (Kobe, Japan) due to mild dysphagia for one month. The patient had a history of smoking and heavy drinking, and demonstrated an alcohol flush reaction subsequent to consuming alcohol. Esophagogastroduodenoscopy (EGD) revealed one tumor in the hypopharynx and two tumors in the middle and lower thirds of the esophagus. All three tumors were revealed to be squamous cell carcinoma (SCC) by biopsy. As there was no distant metastasis, total pharyngolaryngoesophagectomy using a thoracoscopic method, permanent tracheostomy, and reconstruction using the free jejunal flap and gastric tube were performed. According to

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Table I. Number of multiple primary cancers observed subsequent to the occurrence of esophageal cancer.

Number of primary cancers	Cases, n (%)
Single	162 (63.8)
Double	75 (29.5)
Triple	12 (4.7)
Quadruple	3 (1.2)
Quintuple	2 (0.8)
Total	254 (100.0)

the tumor-node-metastasis (TNM) criteria stated in the 6th edition of the Union for International Cancer Control classification (9), esophageal cancer was diagnosed as T3N1M0, stage III, and the hypopharyngeal cancer was classified as T2N0M0, stage II. The patient underwent two three-weekly cycles of adjuvant chemotherapy using intravenous 5-fluorouracil (800 mg/m², days 1-5) and cisplatin (80 mg/m², day 1).

At 66 years old, the patient experienced epistaxis from the left nose. Detailed examination revealed a tumor in the left maxillary sinus and the biopsy identified the lesion as SCC. Since the tumor was localized, four 100 mg/m² arterial cisplatin injections (days 1, 8, 15 and 22) and radiation therapy (70 Gy/35 f; 2 Gy/day for 35 days) were administered and a complete response (10) was observed.

EGD was subsequently performed when the patient was 68 years old, as a routine examination, and revealed a tumor in the gastric tube. Biopsy revealed the lesion to be adenocarcinoma, and a fourth primary cancer was diagnosed. The patient underwent gastric tube resection using a right thoracotomy approach, followed by pedicled jejunum flap reconstruction.

The pathological TNM stage was classified as T2aN0M0, stage IB.

At 69 years old, the patient experienced pain in the tongue. Positron emission tomography examination was performed and SCC of the tongue was diagnosed. Resection of the tongue and reconstruction using the free pectoral major myocutaneous flap was performed. The pathological TNM stage was classified as T2N0M0, stage II. Six years subsequent to the primary surgery, the patient remains alive without recurrence.

Discussion

Synchronous and metachronous multiple cancers are often observed in esophageal cancer due to the advances in surgical techniques and treatment modalities. In Japan, esophageal cancer is frequently identified as SCC, but the incidence of SCC is decreasing and the incidence of adenocarcinoma is increasing in Western countries (11). A previous study performed in Japan reported that the overall five-year survival rate of patients that undergo esophagectomy increased between 14.4 and 46.3% in the previous 30 years (12). A nationwide registry of Japanese patients with esophageal cancer treated in 2006 revealed that second primary cancers in a separate organ were present in 21.8% of patients (5). The rate of second cancers of the head and neck significantly increased to 6.68% (95% CI, 5.33-8.26) subsequent to the development of squamous cell carcinoma of the esophagus compared with the expected number of cancers (13).

The clinical follow-up data of the patients who underwent esophagectomy subsequent to diagnosis with esophageal cancer in Kobe University Hospital were retrospectively collected by studying the clinical charts of patients treated between April 2006 and December 2012, in order to identify the rate of primary multiple cancers. Table I summarizes the results of multiple primary cancer lesions observed in patients treated

Table II. The lesions of the multiple primary cancers that occurred with esophageal cancer treated in Kobe University Hospital.

Location	Synchronous, n (%)	Metachronous, n (%)	Total, n
Pharynx	23 (47.9)	9 (13.8)	32
Stomach	13 (27.1)	8 (12.3)	21
Oral cavity/gingiva/tongue	4 (8.3)	8 (12.3)	12
Colon/rectum	3 (6.3)	8 (12.3)	11
Lung	2 (4.2)	4 (6.2)	6
Esophagus	0 (0.0)	5 (7.8)	5
Prostate	2 (4.2)	3 (4.6)	5
Larynx	0 (0.0)	4 (6.2)	4
Bladder	0 (0.0)	3 (4.6)	3
Blood cancer	0 (0.0)	3 (4.6)	3
Breast	0 (0.0)	3 (4.6)	3
Kidney	1 (2.0)	2 (3.1)	3
Urinary tract	0 (0.0)	2 (3.1)	2
Bile duct	0 (0.0)	1 (1.5)	1
Pancreas	0 (0.0)	1 (1.5)	1
Uterus	0 (0.0)	1 (1.5)	1
Total	48 (100.0)	65 (100.0)	113

with esophageal cancer and Table II summarizes the numbers of primary multiple cancers observed. In total, 36.2% of all patients with esophageal cancer developed multiple primary cancers and predominantly possessed double cancer. Overall, head and neck cancer was the most frequently observed lesion and lesions of the pharynx were the most common synchronous lesion (data not shown). Gastric cancer was a commonly observed lesion, synchronously and metachronously.

Routine screening and close follow-up for the detection of secondary cancers, performed using laryngoscopy, bronchoscopy and EGD, have been recommended for patients with head and neck cancers (14). Gastrointestinal endoscopy with Lugol's staining and using narrow-band imaging is a powerful tool for not only detecting early cancer, but also for evaluating the intraepithelial spread of esophageal SCC (15,16).

Chemotherapy, radiotherapy and surgery, or a combination of these treatments, are widely used to treat esophageal and head and neck cancer. Morita *et al* reported that the mortality, morbidity and long-term prognosis were similar between synchronous or metachronous esophageal cancers and solitary esophageal cancer (17). This indicates that curative treatment should be performed despite the frequency of the multiple primary cancers.

The treatment strategy differs between the lesions of multiple primary cancers. When the multiple primary cancers are observed in distant organs, surgery and other treatments can be performed. However, when the multiple primary cancers are observed in adjacent organs, as in the present case, the treatment modalities are limited. The post-operative adhesions and the organs to use for reconstructions require consideration. Adhesion usually occurs following surgery, which makes the subsequent procedure challenging. This can be prevented by performing thoracoscopic or laparoscopic surgery. Each method yields a considerable benefit in the reduction of post-operative adhesions and leads to an easier procedure when surgery is subsequently performed (18). In the present case, gastric tube resection was performed using a right thoracotomy approach subsequent to esophagectomy, due to the decreased adhesions.

A dose limitation also occurs in chemotherapy and radiotherapy. The key drug for chemotherapy in esophageal cancer is cisplatin, which is also effective for the treatment of head and neck or gastric cancer. Since cisplatin induces neuropathy above a cumulative dose of 300 mg/m² (19), it is challenging to use frequently. Modern techniques for radiation, including three-dimensional conformal radiation therapy, intensity-modulated radiation therapy and image-guided RT aids in the reduction of the toxicity (20). However, limitations in the cumulative dose and dose per fraction remain. Since there is a limitation in the dose of chemotherapy and radiotherapy that may be administered, surgery is the only curative treatment that is not limited.

In conclusion, if the patient is able to tolerate the procedure, surgery should be performed using a minimally invasive method in patients with multiple primary cancers.

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