Int J Clin Exp Med 2016;9(1):379-384
www.ijcem.com /ISSN:1940-5901/IJCEM0014869

Case Report

Synchronous primary esophagus and stomach cancer: report of 18 patients in single institution from China

Jian-Peng Li[1], Qiang Ma[1], Chuan-Min Chen[1], Su-Fang Li[2]

[1]*Department of Oncology, People's Hospital of Xintai City, Affiliated to Taishan Medical University, Xintai 271200, Shandong Province, China;* [2]*Department of Neurology, The Third Affiliated Hospital, Xinxiang Medical University, Xinxiang 453003, Henan Province, China*

Received August 21, 2015; Accepted November 23, 2015; Epub January 15, 2016; Published January 30, 2016

Abstract: Objective: Synchronous primary esophagus and stomach cancer (SPES) is a rare disease with aggressive behavior and poor prognosis. Because of the rarity of this disease, standard therapy has not yet been established. We reviewed our experience in the management of patients with it. Methods: We analyzed the 3120 patients who were diagnosed malignant tumor between June 2011 and January 2014 in our hospital, and 18 patients with SPES were enrolled. We retrospectively collected presenting symptoms, staging, tumor characteristics, treatment, response, outcome, and survival. Results: The incidence of SPES was 0.58% in our hospital, and the gender ratio was 5:1 (male/female). 88.89% of the patients had some bad habits. The response for all sites was complete response (CR) in nine patients, partial response (PR) in five patients, stable disease (SD) in two patients, and progressive disease (PD) in two patients; the objective response rate (ORR) was 77.78%. For the 18 patients, the mean follow-up time was 15 months, and the median overall survival time (MST) was 10.6 months (range: 3.1-28.7 months). The 1-year and 2-years overall survival rates were 45% and 20% respectively. The MST for cases who received surgical resection was 24.6 months, and 10.6 months for non-surgical approaches (P=0.004). Conclusions: SPES is a rare and highly malignant tumor with dismal prognosis. Early diagnosis and detection, active and comprehensive treatment can prolong the survival span and improve the prognosis, and surgery is playing an important role in the treatment.

Keywords: Synchronous primary esophagus and stomach cancer (SPES), esophageal cancer, gastric cancer, comprehensive treatment, prognosis

Introduction

Esophageal or gastric cancer is one of the most common human malignant tumors worldwide. A national survey of malignant tumor mortality conducted between 2003 and 2006 showed that the esophageal cancer is the fourth deadly cancer in China, following gastric, liver, and lung cancers [1]. The incidence of synchronous multiple primary cancers (SMPCs) in esophagus and stomach is increasing very fast. According to the criterion of Warren and Gates [2], the SMPCs are defined as two or over two different cancerous lesions developed in the same or different organs within 6 months. There are few reports described the prevalence and clinicopathological features of SMPCs, especially from China-high-risk region for both esophageal and stomach cancers [3, 4]. In the same time, the standard treatment for Synchronous primary esophagus and stomach cancer (SPES) has not yet been established [5]. Herein, we retrospectively reviewed the clinical data of patients diagnosed as SPES in our hospital from June 2011 and January 2014, including clinical manifestations, treatment, surviving, and optimal treatment.

Materials and methods

Patients

Between June 2011 and January 2014, a total of 3120 Chinese patients with malignant neoplasm were diagnosed in the Hospital of Xintai city. All patients received detailed history taking, physical examination, and laboratory tests including complete blood count, blood biochemical panel, barium swallow examination, upper gastrointestinal endoscopic ultrasonog-

Table 1. Patients' information and tumor characteristics

Patient	Gender/ Age	Alcohol or tobacco	Esophagus cancer			Gastric cancer			Response of all sites	OS (month)	Present status
			Primary site	TNM stage	Treatment course	Primary site	TNM stage	Treatment course			
1	M/64	yes	Mt	T3N2M0	NC+R	Antrum	T3N0M0	NC+S	CR	18.3	DOD
2	M/73	yes	Lt	T3N2M0	C+R	Antrum	T2N1M0	C	PR	10.6	DOD
3	M/50	yes	Ut	T4N2M0	C+R	Antrum	T4N2M0	C+R	PR	9.3	DOD
4	M/58	yes	Lt	T3N2M0	C+R	Antrum	T3N2M0	C+R	PR	10.4	DOD
5	F/54	no	CE	T2N1M0	C+R	Cardia	T2N1M0	S+C+R	CR	15.8	Alive
6	M/63	yes	Mt	T2N1M0	S+AC	Body	T2N1M0	S+AC	CR	24.6	DOD
7	M/75	yes	Lt	T3N1M0	C	Antrum	T3N2M1	C	SD	7.6	DOD
8	M/59	yes	Mt	T3N1M0	C+R	Body	T3N1M0	C+R	CR	12.3	DOD
9	M/65	yes	CE	T2N2M0	C+R	Antrum	T4N1M0	NC+S	CR	17.9	DOD
10	M/40	no	Lt	T3N1M0	S+AC	Body	T2N1M0	S+AC	CR	15.4	DOD
11	F/73	yes	Lt	T2N2M0	C+R	Antrum	T3N0M0	C	PR	10.8	DOD
12	M/75	yes	Mt	T3N1M0	C	Antrum	T3N2M0	C	SD	8.9	DOD
13	M/68	yes	Lt	T2N2M0	NC+S+R	Body	T3N1M0	NC+S+R	CR	26.3	Alive
14	M/74	yes	Lt	T3N1M0	C	Antrum	T4N1M1	C	PD	5.8	DOD
15	M/76	yes	Lt	T4N1M0	C+R	Body	T2N1M0	C	PR	9.7	DOD
16	M/68	yes	Lt	T2N2M0	Bsc	Antrum	T2N2M0	Bsc	PD	3.1	DOD
17	M/63	yes	Lt	T3N1M0	C+R	Antrum	T2N1M0	C+R	CR	19.8	DOD
18	F/70	yes	Mt	T3N1M0	S+C+R	Antrum	T2N0M0	S+C	CR	28.7	Alive

Abbreviations: Ut = upper thoracic esophagus; Mt = middle thoracic esophagus; Lt = lower thoracic; CE = cervical esophagus; M = male; F= female; Bsc = best supportive care; S = Resection; C = Chemotherapy; R = Radiotherapy; DOD = Death of disease; CCR: Concurrent chemoradiotherapy; NC: Neoadjuvant Chemotherapy; AC: Adjuvant Chemotherapy; OS: overall survival.

raphy, and computed tomography scan of neck, chest, and upper abdomen. Patients with advanced stage disease received magnetic resonance imaging of brain, emission computed tomography bone scan and all patients were diagnosed histologically before treatment. Among these patients, 18 cases were diagnosed as SPES. Informed consent had been obtained from each patient upon approval of the study by the ethics committee of the Hospital of Xintai city. The principles of the World Medical Association Declaration of Helsinki and Good Clinical Practice Guidelines were also strictly followed. All patients were staged according to the TNM staging system of the American Joint Committee on Cancer (7th edition) [6]. The characteristics of the patients were shown in **Table 1**.

Treatments

The treatment options of the patients were listed in **Table 1**. A total of 14 patients underwent the comprehensive treatment, including surgery, radiotherapy or chemotherapy. 3 cases were treated only by chemotherapy, and one underwent best supportive care.

Surgery

7 patients were underwent surgical resection and all R0 resection. Surgical method consisted of subtotal gastrectomy in 3 patients, and esophagogastrectomy in 4 patients.

Radiotherapy

RT was performed using 6, or 8 MV photon beams and delivered at a daily dose of 1.8-2 Gy, five times per week. An intensity-modulated radiation therapy technique was only used in 4 cases. 7 cases received three-dimensional conformal radiotherapy. The doses to the spinal cord and gastric was set to 45 Gy. Additionally, we checked lung dose as the percentage of total lung volume receiving less than or equal to 20 Gy (V20) < 20% using dose volume histogram. The total dose ranged from 45 to 70 Gy (median 54.8 Gy).

Chemotherapy

A total of 17 patients received chemotherapy. Regimens include cisplatin, oxalipltin, fluorouracil, paclitaxel and docetaxel. Paclitaxel-platinum-fluorouracil (TCF) was the most common regimen, accounting for 47.06% (8/17). 6 patients received oxalipltin combined with fluorouracil (FOLFOX), and 3 patients adopted docetaxel and oxalipltin. Concurrent chemoradiotherapy adopted the plan of continuous pumping with fluorouracil (2500 mg/m^2) for 120 hours.

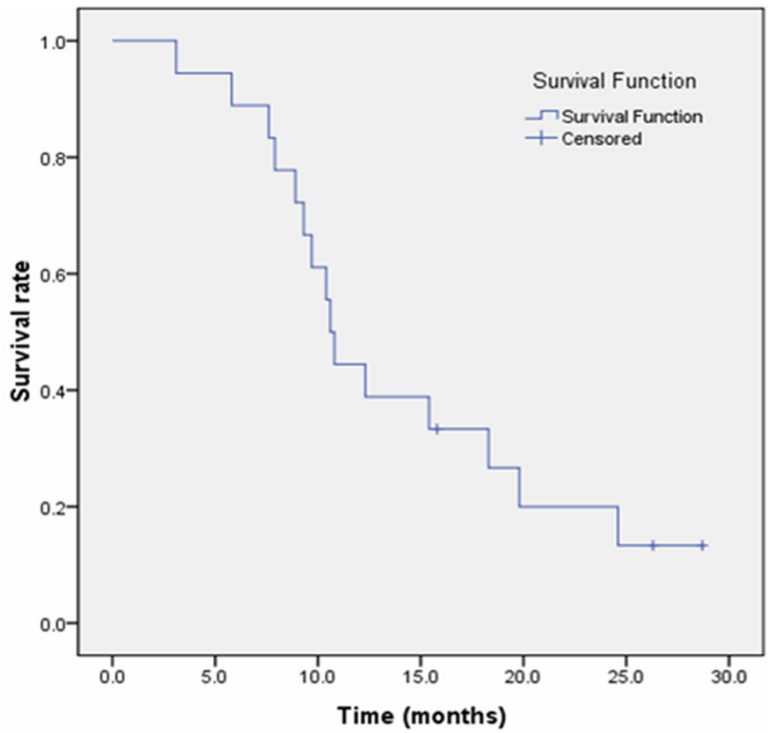

Figure 1. Kaplan-Meier curve of overall survival for 18 patients with SPES.

Response evaluation

For measurable disease, responses were evaluated according to the World Health Organization (WHO) criteria [7]. Response for all sites was as follows: complete response (CR) was assigned by disappearance of all visible tumors including distant metastasis which were determined by two observations not less than four weeks apart. Partial response (PR) was assigned by the volume of all visible tumors reduced at least 50%, and not less than four weeks. Progressive disease (PD) was assigned by an increase in the tumor area by 25% or developing distant metastasis. But no change (NC) was assigned between PR and PD.

Follow-up of patients

In general, a follow-up examination was performed every 3 months for the first year, every 4 months for the next year. The routine examination during follow-up included a physical examination, blood chemistry, measurement of serum tumour markers, upper gastrointestinal endoscopic ultrasonography, computed tomography scan of chest, and upper abdomen. If the patient had specific symptoms, the examination was performed as soon as possible for a more careful assessment.

Statistical analysis

The survival time was calculated from the date of treatment initiation to that of death from any causes or to the last date of confirmation of survival. The χ^2 test was used to compare frequencies, and significance was defined as a value of $P < 0.05$. We estimated survival curves using the Kaplan-Meier method.

Results

Tumor characteristics and response

The number of patients with SPES accounted for 0.58% (18/3120) of all tumor cases diagnosed in our hospital and the gender ratio was 5:1 (male/female). Among the 18 patients with SPES, 16 of them had smoking or drinking habits. The response for all sites was CR in 9 patients, PR in 5 patients, SD in 2 patients, and PD in 2 patients. ORR for all sites was 77.78%. The summary of treatment results was listed in **Table 1**.

Survival

The median follow-up time was 15 months, by March 2015, 3 patients were still alive; 14 patients died of cancer; one died of accident; the overall median survival time (MST) was 10.6 months. The one-year and two-years overall survival rates were 45% and 20% respectively (**Figure 1**). The MST of patients with or without surgery had significant difference in the comprehensive treatment group (χ^2=8.175, P=0.004; **Figure 2**). The MST for patients who received surgical resection was 24.6 months, and for those taking non-surgical approaches was 10.6 months.

Discussion

Esophagus cancer and stomach cancer are common malignant tumors with high-incidence

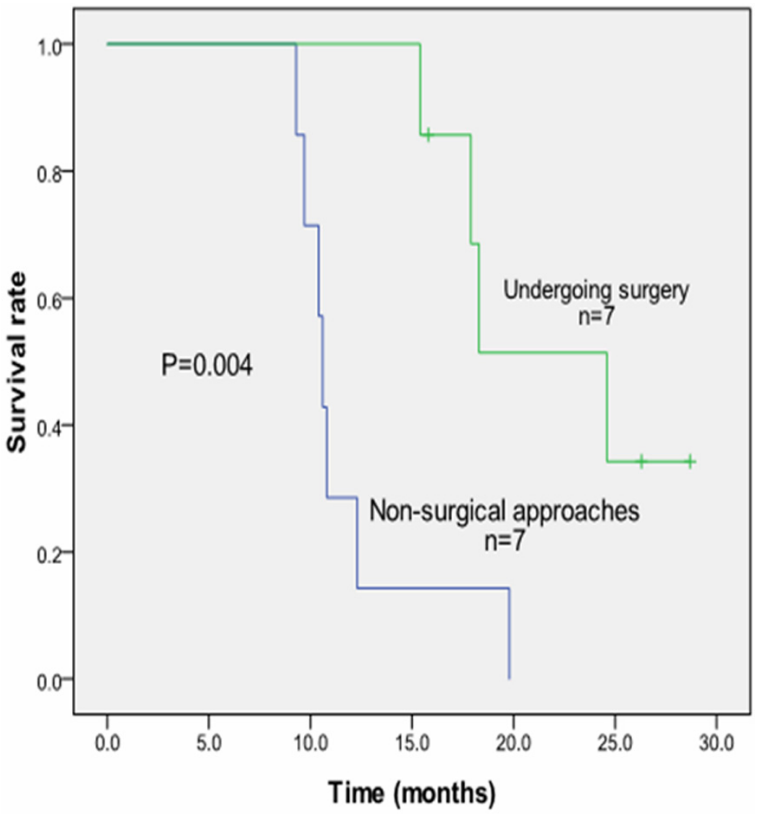

Figure 2. Kaplan-Meier curve of overall survival comparing patients with comprehensive treatments who underwent surgery versus non-surgical approaches (P=0.004).

especially in underdeveloped regions. However, few studies had been conducted on SPES. For the esophageal cancer, gastric cancer is the most common second primary cancer according to a series of reports [8], and the incidence of synchronous cancers was significantly higher in men than in women. It also increased with age. In this study, a total of 3120 Chinese patients with malignant neoplasm were enrolled in our hospital, and 18 cases were diagnosed as SPES, the incidence was 0.58%, and with a male-to-female ratio of 5. These data were a little higher than the other Chinese previous study [3]. He reported about 0.07% patients with SMPCs in esophagus and stomach (32/45032). The specific etiology of SMPCs is unknown. First of all, it is presumed that there is association with such genetic factors as microsatellite instability [9]. Cancer patients had genetic susceptibility and individual susceptibility towards carcinogenic factors, so the second primary tumors were easy to relapse after the treatment of the first primary cancer. Next, the esophageal and gastric cancers share the same risk factors. Reviews of epidemiological evidence lent strong support to the effects of smoking and alcohol consumption in the development of MPCs [10, 11]. 88.89% (16/18) of our patients had the bad habits of smoking or drinking. Moreover, with the aging of population and the constant improvement of early diagnosis technology and tumor treatment, double primary tumor became more possible to occur. In addition, for the decline of immunity level, and the damage to the systemic and partial immune function by chemotherapy drugs, tumor patients faced increasing risk of double primary tumor with the activating of potential virus and higher risk of inducing carcinoma.

Along with the progress of surgery and radiotherapy technology, and also the development of tumor chemotherapy drugs, the diagnosis and treatment level for esophageal and gastric cancer has improved significantly. Several retrospective studies had reported a CR rate of 22-24.3% to chemoradiotherapy for advanced esophageal cancer [12, 13]. In contrast, the rate of the CR to chemotherapy for advanced gastric cancer was only as low as 0-0.7% [14, 15], so the comprehensive treatment is given priority to treat the esophageal and gastric cancer at present. But owing to the paucity of cases, the optimal treatment for SPES is still not well established at this moment. At the moment, there was only individual case reported that chemotherapy or concurrent radio chemotherapy had been used to cure SPES [5, 16]. Because of poor prognosis of supportive care or chemotherapy, we tended to take the way of comprehensive treatment. In our study, the response for all sites was CR in 9 patients, PR in 5 patients, SD in 2 patients, and PD in 2 patients. ORR for all sites was 77.78%, and the 1- and 2-year overall survival rates were 45% and 20% respectively. These results indicated that comprehensive

treatment is very effective. During the process of comprehensive treatment, we found the significant difference between patients with or without surgical resection (MST 24.6 months vs 10.6 months P=0.004). So, the preferred treatment for patients with early stage SPES is surgery and the postoperative chemoradiotherapy according to the situation. For patients with advanced SPES, the proposed treatment is synchronous or sequential chemoradiotherapy first and then surgery. Furthermore, SPES is considered as a systemic disease with a high risk of distal metastasis, so the comprehensive treatment can be considered as the primary treatment. Due to the limitations of this study including the number of patients enrolled, its retrospective design, and the fact that not every patient received comprehensive treatment, the median overall survival is as low as 10.6 months.

The study reveals that the incidence of synchronous Gastric cancer and esophageal cancer was very low, but it grows very fast. So, we suggest that elderly male patients who have a history of smoking or drinking and a family history of gastric or esophageal cancer should have physical examination every year. Based on our study results, we can see the effect of comprehensive treatment in improving OS of patients and the important role played by surgery in comprehensive treatment. Besides, a survival benefit from comprehensive treatment should not be ignored.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Su-Fang Li, Department of Neurology, The Third Affiliated Hospital, Xinxiang Medical University, Xinxiang 453003, Henan Province, China. Tel: 86-373-3029483; Fax: 86-373-3029483; E-mail: asd297108065@163.com; Dr. Chuan-Min Chen, Department of Oncology, People's Hospital of Xintai City, Affiliated to Taishan Medical University, Xintai 271200, Shandong Province, China. Tel: 86-538-7269262; Fax: 86-538-7260098; E-mail: chen20150718361@sina.com

References

[1] Zhang XY, Zhuang DF, Ma X, Dong J. Esophageal cancer spatial and correlation analyses: Water pollution, mortality rates, and safe buffer distances in China. J Geogr Sci 2014; 24: 46-58.

[2] Warren S, Gates O. Multiple primary malignant tumors. A survey of the literature and a statistical study. American Journal of Cancer 1932; 16: 1358-1414.

[3] Wang R, Wang MJ, Yang JL, Tang CW. Upper Gastrointestinal Endoscopy Detection of SynchronousMultiple Primary Cancers in Esophagus and Stomach: Single Center Experience from China. Gastroenterol Res Pract 2012; 2012: 432367.

[4] Koide N, Adachi W, Koike S, Watanabe H, Yazawa K, Amano J. Synchronous gastric tumors associated with esophageal cancer: a retrospective study of twenty-four patients. Am J Gastroenterol 1998; 93: 758-62.

[5] Yoshida N, Kochi M, Fujii M, Kanamori N, Kaiga T, Mihara Y, Funada T, Tamegai H, Watanabe M, Takayama T. Complete Response to Chemoradiotherapy in a Patient withSynchronous Double Gastric and Esophageal Cancer. Anticancer Res 2011; 31: 2339-42.

[6] In: Edge SB, Byrd DR, Carducci MA, Compton CC, Fritz AG, Greene FL et al, editors. AJCC cancer staging manual. 7th edition. New York, NY: Springer; 2010.

[7] Miller AB, Frcpc MB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207-214.

[8] Ikeda Y, Saku M, Kishihara F, Maehara Y. Effective follow-up for recurrence or a second primary cancer in patients with early gastric cancer. Br J Surg 2005; 92: 235-239.

[9] Pasławski M, Złomaniec J, Rucińska E, Kołtyś W. Synchronous primary esophageal and gastric cancers. Ann Univ Mariae Curie Sklodowska Med 2004; 59: 406-410.

[10] Ray G, Henson DE, Schwartz AM. Cigarette smoking as a cause of cancers other than lung cancer: an exploratory study using the Surveillance, Epidemiology, and End results Program. Chest 2010; 138: 491-499.

[11] Ono K, Takenaka M, Yokoyama E, Oka S, Baba T, So T, So T, Uramoto H, Takenoyama M, Hanagiri T, Yasumoto K. Clinical analysis of esophageal cancer associated with other primary cancers. Kyobu Geka 2011; 64: 93-98.

[12] Akutsu Y, Matsubara H, Shuto K, Uesato M, Mori M, Hoshino I, Shiratori T, Miyazawa Y, Ito H, Uno T. Clinical and pathologic evaluation of the effectiveness of neoadjuvant chemoradiation therapy in advanced esophageal cancer patients. World J Surg 2009; 33: 1002-1009.

[13] Donington JS, Miller DL, Allen MS, Deschamps C, Nichols F, Pairolero PC. Tumor response to induction chemoradiation: influence on surviv-

al after esophagectomy. Eur J Cardiothorac Surg 2003; 24: 631-636.

[14] Yoshikawa T, Omura K, Kobayashi O, Nashimoto A, Takabayashi A, Yamada T, Yamaue H, Fujii M, Yamaguchi T, Nakajima T. A phase II study of preoperative chemotherapy with S-1 plus cisplatin followed by D2/D3 gastrectomy for clinically serosa-positive gastric cancer (JACCRO GC-01 study). Eur J Surg Oncol 2010; 36: 546-551.

[15] Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008; 9: 215-221.

[16] Han JS, Choi SR, Jang JS, Roh MH, Kim DC, Ryu SH, Woo SM, Hsing CT. A Case of Synchronous Esophagus and Stomach Cancer Successfully Treated by CombinedChemotherapy. Korean J Gastroenterol 2012; 60: 113-118.