whether the gender difference in prognosis is due to differences in the aggressiveness of the cancer itself or other factors is not well known.

In the current study, the clinical results of more than 1,000 patients undergoing esophagectomy were compared between the sexes. The characteristics of patients with esophageal cancer are discussed below, paying special attention to gender differences in prognosis, as well as mortality and morbidity.

Methods

Patients

The subjects evaluated in this study consisted of 1,131 Japanese patients with esophageal cancer who underwent esophagectomy for esophageal cancer between 1966 and 2010 at the Department of Surgery and Science (Department of Surgery II), Kyushu University Hospital in Japan. The primary location of the tumor was the cervical, thoracic and abdominal esophagus in 66, 989 and 76 patients, respectively. Histologically, the primary lesion was diagnosed as squamous cell carcinoma in 1,081 patients, adenocarcinoma in 30 patients and other histological types in 20 patients. The survival data were updated in May 2012. The follow-up ranged from 2 days to 32 years after the primary operation (median follow-up period of censored patients, 3.7 years), and data were available for all patients.

Among the 1,131 patients, 975 were male and 156 were female. The male to female ratio was, therefore, 6.25 to 1. The gender differences were examined, paying special attention to the patients' prognoses, as well as clinical backgrounds and surgical outcomes.

The clinicopathological factors were evaluated according to the guidelines for clinical and pathological studies on carcinoma of the esophagus [23]. The depth of invasion and presence of lymph node metastasis were defined according to the histological examination of surgically resected specimens. The postoperative histological T (pT) and N (pN) factors were adopted in all cases.

Since the medical charts were preserved and the details of the patients' clinical backgrounds could, therefore, be examined in all patients who underwent esophagectomy after 1998, we examined the incidence of comorbidities as well as smoking and drinking habits in 370 patients who underwent esophagectomy between 1998 and 2010. The criteria for comorbidities were defined as previously described [5]: patients with a history of cardiovascular disease (ischemic heart disease, heart failure, cardiomyopathy or aortic aneurysms), abnormal ECG findings, a left ventricular ejection fraction <55 % or a past history of either brain infarction or bleeding were considered to have cardiac and/or cerebrovascular risk factors. Pulmonary dysfunction was defined as a history of chronic pulmonary disease or an abnormal pulmonary function [vital capacity <80 %, forced expiratory volume at 1 s (FEV1) <70 %]. Liver dysfunction was defined as either the apparent findings of liver cirrhosis visualized on abdominal CT or US or an ICG retention rate >20 % at 15 min. An HbA1c value >6.5 mg/dl was regarded as indicative of the presence of diabetes. In addition to these risk factors, the presence of collagen vascular diseases or gastric cancer and a history of prior definitive chemoradiotherapy were regarded as comorbidities.

Regarding smoking and drinking habits, we used the same criteria as those described previously [24]: In terms of the accumulated smoking history, ''pack-years'' was defined as the number of cigarettes per day/20 multiplied by the number of years of smoking. With respect to drinking habits, we examined the quantity of alcoholic beverages currently consumed per week. Taking into account the different alcohol concentrations, one drink corresponded to 180 ml of sake (the most popular local alcoholic beverage in Japan), 120 ml of white liquor (the so-called "shochu''), 70 ml of whisky or 720 ml of beer.

The surgical methods have been described previously [4]. Briefly, in patients with thoracic esophageal cancer, we performed either subtotal esophagectomy with anterolateral right thoracotomy and cervical anastomosis or distal esophagectomy with posterolateral right thoracotomy, laparotomy and intrathoracic anastomosis (the modified Ivor Lewis procedure). For tumors located primarily in the abdominal esophagus with invasion of the lower thoracic esophagus, we performed distal esophagectomy either via a left thoracoabdominal approach or via an abdominal approach only. When performing thoracotomy was impossible due to a poor pulmonary function or the presence of pulmonary disease, such as old tuberculosis, we occasionally performed transhiatal esophagectomy via cervical and abdominal approaches. In patients with cervical esophageal cancer, we performed cervical esophagectomy with laryngectomy, which continues to be the standard procedure. Alternatively, transhiatal esophagectomy with laryngectomy was sometimes performed.

We evaluated the postoperative complications that developed within 30 days after esophagectomy and required medication or surgical intervention. The pulmonary complications included pneumonia (defined as a positive bacterial culture of sputum), atelectasis and hypoxia requiring reintubation.

Statistical analysis

The differences in the distribution frequencies among the groups were evaluated using Fisher's exact test or the

unpaired t test. The survival curves were plotted according to the Kaplan–Meier method, and any differences between two curves were analyzed using the log-rank test. We also tested for trends in survival across ordered groups using the trend log-rank test. A multivariate analysis with the Cox proportional hazard model was adopted to clarify the independent prognostic factors. Differences were considered to be significant for values of $P < 0.05$. The data were analyzed using the StatView software package (Abacus Concepts, Inc., Berkeley, CA, USA).

Results

Clinical characteristics

Table 1 summarizes the clinicopathological characteristics of the male and female patients with esophageal cancer. Cervical esophageal cancer was diagnosed in 23 (14.7 %) of the 156 female patients; this incidence was significantly higher than that observed in the male patients (4.4 %, $P < 0.01$). The male to female ratio of cervical esophageal cancer was, therefore, 1.87, while that of thoracic esophageal cancer was 7.38. There were no significant gender differences in the other background factors, including age, histological type, depth of invasion, lymph node metastasis, distant metastasis and pathological stage.

Table 2 summarizes the preoperative comorbidities and smoking and drinking habits of the 370 patients. Among the female patients, the incidence of preoperative comorbidities was 17.4 %, which was significantly lower than that observed in the male patients (32.4 %). With respect to liver dysfunction, most of which was due to alcoholic liver dysfunction, the incidence was 8 % in the male patients, while none of the female patients were considered to have this comorbidity. The incidences of both ever-smoking and habitual drinking were lower in the females than in the males (39.1 versus 82.4 % and 37.0 versus 82.4 %, respectively). Furthermore, the rates of both tobacco and alcohol abuse were significantly lower in the females than in the males.

Table 3 summarizes the therapeutic methods used in the male and female patients with esophageal cancer. The use of preoperative radiation was similar between the genders. Cervical esophagectomy and jejunal reconstruction were more frequently performed in females due to the higher incidence of cervical esophageal cancer in this population.

Gender differences in the clinical results observed after esophagectomy

Table 4 summarizes the postoperative complications and causes of death. Both the mortality and total morbidity were lower in the females than in the males; however, there were no statistically significant gender-related differences. The morbidity rates were 40.4 and 34.0 %, while the mortality (in-hospital death) rates were 5.7 and 3.8 % in the male and female patients, respectively. Approximately, half of the patients died due to either recurrence or regrowth of esophageal cancer. The incidence of death due to other causes than esophageal cancer was 12.2 and 10.5 % in males and females, respectively. Among the patients who died, a total 17 patients (15 males and two females) died due to cancers other than esophageal cancer. Head and neck cancer was the most common cause of

Table 1 Clinicopathological backgrounds of the male and female patients with esophageal cancer

Clinicopathological backgrounds	Male $n = 975$	Female $n = 156$
Age		
Mean ± SD	63.0 ± 9.1	62.6 ± 9.8
Location of the tumor		
Cervical esophagus	43 (4.4)	23 (14.7)*
Thoracic upper esophagus	117 (12.0)	14 (8.8)
Thoracic mid-esophagus	535 (54.9)	70 (44.9)
Thoracic lower esophagus	219 (22.5)	34 (21.8)
Abdominal esophagus	61 (6.3)	15 (9.6)
Histological type		
Squamous cell carcinoma	931 (95.5)	150 (96.2)
Adenocarcinoma	27 (2.8)	3 (1.9)
Others	17 (1.7)	3 (1.9)
Depth of invasion		
pT1a	70 (7.1)	5 (3.2)
pT1b	176 (18.1)	14 (9.0)
pT2	136 (13.9)	36 (23.1)
pT3	408 (41.8)	67 (42.9)
pT4	185 (19.0)	34 (21.8)
Pathological node metastasis		
Negative	499 (51.2)	87 (55.8)
Positive	476 (48.8)	69 (44.2)
Distant metastasis		
Negative	956 (98.1)	155 (99.4)
Positive	19 (1.9)	1 (0.6)
Pathological stage		
pStage 0	68 (7.0)	5 (3.2)
pStage I	128 (13.1)	12 (7.7)
pStage II	282 (28.9)	59 (37.8)
pStage III	328 (33.6)	52 (33.3)
pStage IVa	151 (15.5)	27 (17.3)
pStage IVb	18 (1.8)	1 (0.6)

The numbers in parentheses are percentages

* $P < 0.01$ in comparison to the male patients according to Fisher's exact test

Table 2 Preoperative comorbidities and the smoking and drinking habits in 370 patients who underwent esophagectomy between 1998 and 2010

	Male		Female		*P* values
	n = 324		*n* = 46		
Preoperative comorbidities					
Cardiac and/or cerebrovascular disorder	28 (8.6)		3 (6.5)		0.781
Pulmonary dysfunction	39 (12.0)		4 (8.7)		0.629
Liver dysfunction	26 (8.0)		0		0.058
Diabetes or collagen diseases	25 (7.7)		2 (4.3)		0.554
After gastrectomy	28 (8.6)		2 (4.3)		0.561
Prior definitive chemoradiotherapy (salvage surgery)	21 (6.4)		3 (6.5)		>0.999
Any comorbidities	105 (32.4)		8 (17.4)		0.040
Smoking habit (pack-years)					
0	57 (17.6)		28 (60.9)		<0.001
<0, <25	44 (13.6)	267	7 (15.2)	18	
≥25, <50	124 (38.3)	(82.4)	7 (15.2)	(39.1)	
≥50	99 (30.5)		4 (8.7)		
Drinking habit (drinks/week)					
0	57 (17.6)		29 (63.0)		<0.001
<0, <10	62 (19.1)	267	5 (10.9)	17	
≥10, <20	62 (19.1)	(82.4)	2 (4.3)	(37.0)	
≥20	143 (44.1)		10 (21.7)		

death (which developed in four males and one female), followed by lung cancer (three males) and pancreatic cancer (two males and one female).

Figure 1 shows the overall survival and disease-specific survival after esophagectomy in the male and female patients. The overall survival was significantly more favorable in the females than in the males ($P = 0.039$). The 2-, 5- and 10-year overall survival rates were 49.2, 32.6 and 20.5 % in the male patients and 52.3, 39.5 and 32.5 % in the female patients, respectively. A multivariate analysis using the Cox proportional hazard model revealed gender to be an independent prognostic factor after esophagectomy, along with age, the depth of invasion, node metastasis, the development of postoperative complications and the period of surgery (the year in which it was performed). The hazard ratio of the female to male gender was 0.767 (95 % confidence interval: 0.620–0.949) (Table 5). However, there were no statistically significant differences in the disease-specific survival between the males and females ($P = 0.246$).

Discussion

In the current study, gender differences were noted in tumor location: the females had a higher incidence of

Table 3 Therapeutic methods used in the male and female patients with esophageal cancer

Therapeutic method	Male $n = 975$	Female $n = 156$
Time of the operation		
The 1st period (1964–1989)	162 (16.6)	35 (22.4)
The 2nd period (1990–1999)	372 (38.2)	60 (38.5)
The 3rd period (2000–2010)	441 (45.2)	61 (39.1)
Preoperative radiation		
Performed	394 (40.4)	53 (34.0)
None	581 (59.6)	103 (66.0)
Method of esophagectomy		
Total or subtotal esophagectomy	659 (67.6)	97 (62.2)
Distal esophagectomy	266 (27.3)	34 (21.8)
Cervical esophagectomy	19 (2.0)	16 (10.6)*
Transhiatal esophagectomy	31 (3.2)	9 (5.8)
Organ used for reconstruction		
Gastric tube	841 (86.3)	124 (79.5)
Colon	71 (7.3)	7 (4.5)
Jejunum	45 (4.6)	23 (14.7)*
Others	18 (1.8)	2 (1.3)
Route of reconstruction		
Subcutaneous	427 (43.8)	76 (48.7)
Retro-sternal	177 (18.2)	23 (14.7)
Intra-thoracic/posterior mediastinum	327 (33.5)	41 (26.3)
Others	44 (4.5)	16 (10.2)

The numbers in parentheses are percentages

* $P < 0.01$ in comparison to the male patients according to Fisher's exact test

cervical esophageal cancer than thoracic esophageal cancer. We epidemiologically examined the risk factors for cervical and thoracic esophageal cancer specifically in males and found that heavy smoking and drinking, as well as a family history of upper aerodigestive tract cancer, were important factors for the development of these cancers in males [24, 25]. Both cigarette smoking and alcohol consumption have been previously reported to be significant risk factors for esophageal cancer in females [26]. However, Japanese studies have revealed that there is a lower incidence of smoking and alcohol consumption among female patients compared to male patients with esophageal cancer [19, 20]. The current study indicated similar results. Postcricoid carcinoma associated with Plummer–Vinson syndrome characterized by iron-deficiency anemia and esophageal webs is well known to be predominant in females (85 %) [27]. The relatively high incidence of cervical esophageal cancer in females suggests that some other factor(s) different from those associated with male thoracic esophageal cancer are related to the development of female cervical esophageal cancer.

Regarding the gender difference in the prognosis after esophagectomy, many authors have reported more favorable prognoses among females [4, 12–19]. A previous retrospective study that examined 2,400 patients in Europe revealed the 5-year survival rates of males and females to be 19 and 26 %, respectively [12]. Another European study examining en bloc resection revealed these rates to be 40 and 52 %, respectively [17]. Similar results have been reported in Asia [4, 14–16, 18]. Furthermore, several studies that have performed multivariate analyses have revealed a female gender to be a favorable prognostic factor, with a hazard ratio ranging from 0.49 to 0.76 [4, 14, 16, 19]. Koide et al. [20] recently examined gender differences in clinical outcomes after esophagectomy between 22 female and 114 male Japanese patients. In their study, the prognosis after esophagectomy was also found to be more favorable in the females; however, the gender difference was not an independent factor. A recent multivariate analysis from the US also demonstrated prognostic superiority among female patients compared to male patients with esophageal cancer. That study was based on the public use database of the clinical results observed after various types of treatments [28]. In the current study, which examined more than 1,000 patients undergoing esophagectomy at a single institute, the overall survival was found to be better in females, and the multivariate analysis revealed a female gender to be an independent favorable prognostic factor. The biologically favorable characteristics of female patients with esophageal cancer have been reported to be related to the sex hormone estrogen, based on an in vitro experiment [21] and clinical findings [22].

Although the current study revealed that the disease-specific survival was slightly better in the females, the difference was not statistically significant. These findings suggest that the prognosis after esophagectomy is better in female patients than in male patients; however, our present results also indicate that this difference may be due to gender differences in multiple clinical factors, rather than only the biological aggressiveness of the cancer itself. For example, life spans are, in general, longer in females than in males. The average life expectancies of Japanese males and females were 69.3 and 74.5 years in 1970 and 79.5 and 86.3 years in 2010, respectively [29]. The overall survival is affected by the patient's life span. Most instances of recurrence of esophageal cancer after esophagectomy occur within 5 years after esophagectomy [30]. The results of the current study suggesting that the gender difference in the overall survival rate is remarkable from 5 to 10 years after esophagectomy suggest that the difference in death rates, due to causes other than cancer recurrence, are related to the gender differences in the overall survival rates. The current study also revealed the incidence of

Table 4 The clinical results after esophagectomy, including the postoperative complications and causes of death

	Male		Female	
	$n = 975$		$n = 156$	
Postoperative complications				
All complications	394 (40.4)		53 (34.0)	
Pulmonary complications	175 (17.9)		25 (16.0)	
Cause of death				
In-hospital death	56 (5.7)		6 (3.8)	
Esophageal cancer	504 (51.7)		77 (49.4)	
Other cancers than esophageal cancer	15 (1.5)		2 (1.3)	
Pulmonary diseases	51 (5.2)	119 (12.2)	7 (4.4)	17 (10.5)
Cardiac and/or cerebrovascular disorder	21 (4.3)		6 (3.8)	
Others	27 (2.8)		2 (1.3)	
Unknown	27 (2.8)		6 (3.8)	
Alive	269 (27.6)		50 (32.0)	

The numbers in parentheses are percentages

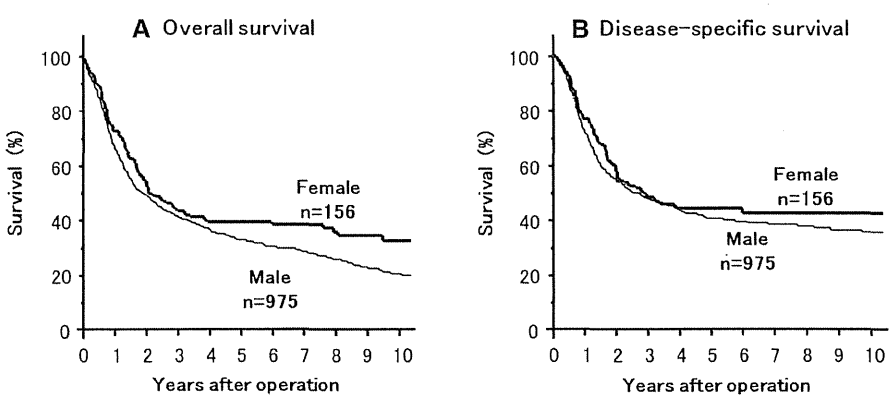

Fig. 1 **a** The overall survival curves after esophagectomy in the male and female patients with esophageal cancer. There was a statistically significant difference between the genders ($P = 0.039$). **b** The disease-specific survival curves after esophagectomy in the male and female patients with esophageal cancer. There were no statistically significant differences between the male and female patients ($P = 0.246$)

causes of death other than esophageal cancer to be slightly higher in males than in females. Among the causes of death observed in this study, the incidence of other cancers was relatively low; however, five of the 17 patients died due to head and neck cancer. Providing careful follow-up for the development of secondary cancers in the head and neck region is essential after esophagectomy, as we have previously described [24, 25]. The higher incidences of

Table 5 Independent prognostic factors according to the Cox proportional hazard model

Factor	Object	Control	Hazard ratio	95 % CI	*P* value
Age (years old)	Every 1 year old		1.011	1.003–1.019	<0.0001
Gender	Female	Male	0.767	0.620–0.949	0.0150
Location of the tumor	Cervical esophagus	Thoracic esophagus	1.014	0.726–1.416	0.9363
	Abdominal esophagus	Thoracic esophagus	0.801	0.605–1.060	0.1210
Depth of invasion	T3/T4	T1/T2	1.880	1.594–2.212	<0.0001
Lymph node metastasis	Positive	Negative	1.923	1.690–2.232	<0.0001
Postoperative complications	Present	None	1.431	1.239-1.652	<0.0001
Period of surgery	The 2nd period	The 1st period	0.604	0.513–0.711	<0.0001
	The 3rd period	The 1st period	0.344	0.344–0.277	<0.0001

cigarette smoking and alcohol consumption, as well as preoperative comorbidities, observed in the male esophageal cancer patients also likely affected the gender-related differences in prognosis after esophagectomy. The same possibility has been reported in other Japanese studies [19, 20]. Moreover, a cohort study of smoking-related mortality in Japan demonstrated that the age-adjusted hazard ratio is higher in males than in females with esophageal cancer [31]. Furthermore, the higher incidence of in-hospital deaths observed in males may also have an effect on the difference in overall survival, although this difference was not statistically significant in the present study.

Animal experiments have revealed that female animals exhibit enhanced immune responses following surgical damage, whereas male animals display decreased responsiveness, which suggests that females have an immunological advantage over males during the perioperative period [8, 10]. Furthermore, clinical studies have also revealed a female advantage in recovery from trauma [11]. In the current study, the incidence of postoperative complications and in-hospital death tended to be lower in females; however, this difference was not statistically significant. These results are consistent with the findings of other studies [19, 20]. Although not statistically significant, the difference in mortality did have an impact on the gender difference in overall survival.

In conclusion, the prognosis of female esophageal cancer patients is better than that of male patients after esophagectomy. The results of this study did not provide any significant evidence to suggest that esophageal cancer in females is biologically less aggressive than that observed in males. Instead, multiple clinical factors, such as a more favorable lifestyle, a lower incidence of preoperative comorbidities, a longer lifespan and lower mortality, are likely responsible for the more favorable prognosis observed in female patients.

Acknowledgments We thank Professor Brian Quinn for assisting with the preparation of this manuscript. This work was supported in part by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

1. Earlam R, Cunha-Melo JR. Oesophogeal squamous cell carcinoms: II. A critical view of radiotherapy. Br J Surg. 1980; 67(7):457–61.
2. Muller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. Br J Surg. 1990; 77(8):845–57.
3. Akutsu Y, Matsubara H. The significance of lymph node status as a prognostic factor for esophageal cancer. Surg Today. 2011;41(9):1190–5.
4. Morita M, Yoshida R, Ikeda K, Egashira A, Oki E, Sadanaga N, Kakeji Y, Yamanaka T, Maehara Y. Advances in esophageal cancer surgery in Japan: an analysis of 1000 consecutive patients treated at a single institute. Surgery. 2008;143(4):499–508.
5. Morita M, Nakanoko T, Fujinaka Y, Kubo N, Yamashita N, Yoshinaga K, Saeki H, Emi Y, Kakeji Y, Shirabe K, Maehara Y. In-hospital mortality after a surgical resection for esophageal cancer: analyses of the associated factors and historical changes. Ann Surg Oncol. 2011;18(6):1757–65.
6. Chandanos E, Lagergren J. The mystery of male dominance in oesophageal cancer and the potential protective role of oestrogen. Eur J Cancer. 2009;45(18):3149–55.
7. Ozawa S, Tachimori Y, Baba H, Fujishiro M, Matsubara H, Numasaki H, Oyama T, Shinoda M, Takeuchi H, Teshima T, Udagawa H, Uno T, Barron JT. Comprehensive registry of esophageal cancer in Japan, 2004. Esophagus. 2012;9(2):75–98.
8. Wichmann MW, Zellweger R, DeMaso CM, Ayala A, Chaudry IH. Enhanced immune responses in females, as opposed to decreased responses in males following haemorrhagic shock and resuscitation. Cytokine. 1996;8(11):853–63.
9. Angele MK, Schwacha MG, Ayala A, Chaudry IH. Effect of gender and sex hormones on immune responses following shock. Shock. 2000;14(2):81–90.
10. Matsuda A, Matsutani T, Sasajima K, Furukawa K, Tajiri T, Tamura K, Kogo H. Preoperative plasma adiponectin level is a risk factor for postoperative infection following colorectal cancer surgery. J Surg Res. 2009;157(2):227–34.
11. Majetschak M, Christensen B, Obertacke U, Waydhas C, Schindler AE, Nast-Kolb D, Schade FU. Sex differences in posttraumatic cytokine release of endotoxin-stimulated whole blood: relationship to the development of severe sepsis. J Trauma. 2000;48(5):832–9 (discussion 839–840).

12. Giuli R, Gignoux M. Treatment of carcinoma of the esophagus. Retrospective study of 2,400 patients. Ann Surg. 1980;192(1): 44–52.
13. Sugimachi K, Matsuoka H, Matsufuji H, Maekawa S, Kai H, Okudaira Y. Survival rates of women with carcinoma of the esophagus exceed those of men. Surg Gynecol Obstet. 1987; 164(6):541–4.
14. Ando N, Ozawa S, Kitagawa Y, Shinozawa Y, Kitajima M. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. Ann Surg. 2000;232(2):225–32.
15. Tsurumaru M, Kajiyama Y, Udagawa H, Akiyama H. Outcomes of extended lymph node dissection for squamous cell carcinoma of the thoracic esophagus. Ann Thorac Cardiovasc Surg. 2001; 7(6):325–9.
16. Law S, Kwong DL, Kwok KF, Wong KH, Chu KM, Sham JS, Wong J. Improvement in treatment results and long-term survival of patients with esophageal cancer: impact of chemoradiation and change in treatment strategy. Ann Surg. 2003;238(3):339–47 (discussion 347–338).
17. Mariette C, Taillier G, Van Seuningen I, Triboulet JP. Factors affecting postoperative course and survival after en bloc resection for esophageal carcinoma. Ann Thorac Surg. 2004;78(4): 1177–83.
18. Shimada H, Matsubara H, Okazumi S, Isono K, Ochiai T. Improved surgical results in thoracic esophageal squamous cell carcinoma: a 40-year analysis of 792 patients. J Gastrointest Surg. 2008;12(3):518–26.
19. Hidaka H, Hotokezaka M, Nakashima S, Uchiyama S, Maehara N, Chijiiwa K. Sex difference in survival of patients treated by surgical resection for esophageal cancer. World J Surg. 2007;31 (10):1982–7.
20. Koide N, Kitazawa M, Komatsu D, Suzuki A, Miyagawa S. Gender differences in clinicopathologic features and outcomes of esophageal cancer patients treated surgically. Esophagus. 2011;8(2):107–12.
21. Ueo H, Matsuoka H, Sugimachi K, Kuwano H, Mori M, Akiyoshi T. Inhibitory effects of estrogen on the growth of a human esophageal carcinoma cell line. Cancer Res. 1990;50(22):7212–5.
22. Badwe RA, Patil PK, Bhansali MS, Mistry RC, Juvekar RR, Desai PB. Impact of age and sex on survival after curative resection for carcinoma of the esophagus. Cancer. 1994;74(9): 2425–9.
23. Kuwano H, Nismura N, Ohtsu A, Kato H, Kitagawa Y, Tamai S, Toh Y, Matsubara H. Guidelines for diagnosis and treatment of carcinoma of the esophagus, April 2007 edition: part II, Edited by the Japan Esophageal Society. Esophagus. 2008;5(3):117–32.
24. Morita M, Kuwano H, Ohno S, Sugimachi K, Seo Y, Tomoda H, Furusawa M, Nakashima T. Multiple occurrence of carcinoma in the upper aerodigestive tract associated with esophageal cancer: reference to smoking, drinking and family history. Int J Cancer. 1994;58(2):207–10.
25. Morita M, Kuwano H, Nakashima T, Taketomi A, Baba H, Saito T, Tomoda H, Egashira A, Kawaguchi H, Kitamura K, Sugimachi K. Family aggregation of carcinoma of the hypopharynx and cervical esophagus: special reference to multiplicity of cancer in upper aerodigestive tract. Int J Cancer. 1998;76(4):468–71.
26. Engel LS, Chow WH, Vaughan TL, Gammon MD, Risch HA, Stanford JL, Schoenberg JB, Mayne ST, Dubrow R, Rotterdam H, West AB, Blaser M, Blot WJ, Gail MH, Fraumeni JF Jr. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst. 2003;95(18):1404–13.
27. Anderson SR, Sinacori JT. Plummer-Vinson syndrome heralded by postcricoid carcinoma. Am J Otolaryngol. 2007;28(1):22–4.
28. Bohanes P, Yang D, Chhibar RS, Labonte MJ, Winder T, Ning Y, Gerger A, Benhaim L, Paez D, Wakatsuki T, Loupakis F, El-Khoueiry R, Zhang W, Lenz HJ. Influence of sex on the survival of patients with esophageal cancer. J Clin Oncol. 2012;30(18):2265–72.
29. Ministry of Health, Labour and Welfare, Japan: Life Tables. http://www.mhlw.go.jp/english/database/db-hw/vs02.html.
30. Sugiyama M, Morita M, Yoshida R, Ando K, Egashira A, Takefumi O, Saeki H, Oki E, Kakeji Y, Sakaguchi Y, Maehara Y. Patterns and time of recurrence after complete resection of esophageal cancer. Surg Today. 2012;42(8):752–8.
31. Katanoda K, Marugame T, Saika K, Satoh H, Tajima K, Suzuki T, Tamakoshi A, Tsugane S, Sobue T. Population attributable fraction of mortality associated with tobacco smoking in Japan: a pooled analysis of three large-scale cohort studies. J Epidemiol. 2008;18(6):251–64.

Asian Journal of Endoscopic Surgery
Official Journal of ISES, ELSA, and AETF

Asian J Endosc Surg ISSN 1758-5902

ORIGINAL ARTICLE

Pure laparoscopic right-sided hepatectomy in the semi-prone position for synchronous colorectal cancer with liver metastases

Satoshi Ida,[1,2] Eiji Oki,[1] Koji Ando,[1] Yasue Kimura,[1] Yo-ichi Yamashita,[1] Hiroshi Saeki,[1] Toru Ikegami,[1] Tomoharu Yoshizumi,[1] Masayuki Watanabe,[2] Masaru Morita,[1] Ken Shirabe,[1] Tetsuya Kusumoto,[1] Tetsuo Ikeda,[1] Hideo Baba[2] & Yoshihiko Maehara[1]

1 Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
2 Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

Keywords
Colorectal cancer; laparoscopy; liver metastasis

Correspondence
Eiji Oki, Department of Surgery and Science, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan.
Tel: +81 92 642 5466
Fax: +81 92 642 5482
Email: okieiji@surg2.med.kyushu-u.ac.jp

Received: 17 August 2013; revised 22 December 2013; accepted 13 January 2014

DOI:10.1111/ases.12098

Abstract

Introduction: Simultaneous resection for colorectal cancer and synchronous colorectal liver metastases (SCRLM) has been found to be safe and effective. However, pure laparoscopic simultaneous resection (PULSAR) for primary colorectal cancer and SCRLM is usually difficult, especially in the right lobe of the liver. The purpose of this study was to assess the feasibility of PULSAR for patients with primary colorectal cancer and SCRLM.
Methods: From January 2008 to December 2012, a total of 10 patients (9 men and 1woman; mean age, 64 years) underwent PULSAR for a primary tumor and SCRLM.
Results: Seven patients (70%) with lesions in the right lobe (segments 6, 7, and 8) successfully underwent resection with a pure laparoscopic procedure while in the left semi-prone position. No patient was converted to conventional open surgery. The mean operative duration, volume of bleeding, and postoperative hospital stay were 606 ± 46 min, 585 ± 145 mL, and 18 ± 3.5 days, respectively. Although a liver abscess developed in one patient, no colonic complications or perioperative death occurred.
Conclusion: PULSAR for primary colorectal cancer and SCRLM is a feasible multidisciplinary treatment. Moreover, PULSAR can be safely and effectively performed with the patient in the semi-prone position, even when SCRLM exists in the right lobe of the liver.

Introduction

Among patients newly diagnosed with colorectal cancer (CRC), approximately 25% are found to have synchronous liver metastases (1). Surgery remains the only treatment that can achieve a potential cure, and the 5-year survival rate of patients who undergo curative liver resection is now approximately 40%–50% (2,3).

The optimal timing for surgical resection of synchronous metastasis has been debated and continues to evolve. The recommended surgical management for synchronous colorectal metastasis is a staged approach, with initial resection of the primary lesion followed by hepatic resection (4,5). Several recent reports have demonstrated that simultaneous resection does not increase mortality or morbidity rates and reduces hospital stays. Thus, it is an acceptable option in patients with resectable synchronous colorectal liver metastasis (SCRLM) (6,7). However, the safety of simultaneous resection of primary CRC and SCRLM, especially in the right lobe, has not been established.

A laparoscopic approach for CRC surgery was recently developed, and this approach is being increasingly applied following demonstrations of its oncological safety in randomized prospective trials (8,9). It has been reported that laparoscopic surgery can be performed safely, even for liver resection. Laparoscopic liver surgery has seen a remarkable surge in popularity worldwide (10).

Furthermore, successful major laparoscopic resections have been recently reported (10–12). We recently reported pure laparoscopic right hepatectomy, which involves complete intracorporeal laparoscopic hepatectomy without hand assistance. In addition, it can be performed with the patient in the semi-prone position (13,14). However, the application of pure laparoscopic surgery has not yet been fully accepted for right lobe hepatectomy.

In this report, we review the clinical results of pure laparoscopic simultaneous resection (PULSAR) for primary CRC and SCRLM.

Materials and Methods

From January 2008 to December 2012, 22 patients with a primary CRC tumor and SCRLM underwent simultaneous resection by laparoscopy or conventional laparotomy at the Department of Surgery and Science (Department of Surgery II) of Kyushu University Hospital in Fukuoka, Japan. Among them, 10 patients underwent PULSAR for the primary tumor and SCRLM; this group included nine men and one woman and had a mean age of 64 years (range, 42–83 years).

The staging of the tumor was based on the UICC-TNM classification (15). The diagnostic assessments included endoscopy, barium enema, CT, ^{18}F-fluorodeoxyglucose PET-CT, and MRI. SCRLM were identified at the time of diagnosis of the primary CRC.

In this study, we reviewed 10 patients with SCRLM treated by PULSAR and analyzed their surgical data to evaluate the feasibility, safety, and effectiveness of this procedure. Postoperative complications were defined as grade II or higher according to the Clavien-Dindo classification (16) Data were available for all patients and are expressed as mean ± standard error. The study and patients' informed consent statements were approved by the Institutional Review Board of the Kyushu University Hospital.

Treatment strategy

Our criteria for laparoscopic simultaneous resection of SCRLM were as follows: (i) the primary lesion and liver tumors were resectable with curative intent; (ii) there was no extrahepatic metastatic disease; (iii) the patient had normal liver function and no high-risk background; and (iv) the procedure did not exceed segmentectomy of the liver. When the patients met these criteria, hepatic resection and primary resection were performed simultaneously. Initially, patients with SCRLM who did not receive induction chemotherapy were selected to undergo the operation; otherwise, induction chemotherapy was administered to patients for initially unresectable liver metastasis. Oxaliplatin-based chemotherapy was administered using either cetuximab combined with S-1 plus oxaliplatin or bevacizumab combined with oxaliplatin plus 5-fluorouracil and leucovorin. If an initially unresectable liver metastasis responded to chemotherapy and became resectable with curative intent at any time during the imaging evaluation, surgical resection was performed as soon as possible after prompt completion of the induction chemotherapy. All patients who underwent simultaneous resection received adjuvant chemotherapy as induction chemotherapy.

Surgical techniques

We performed the hepatectomy first followed by the colorectal resection. Details of our pure laparoscopic hepatectomy procedures were previously described (13,14). In brief, metastatic tumors in the right side lobe (S6, S7, and S8) were resected with the patient in the left semi-prone position (Figure 1). Four 12-mm trocars were placed in the right upper abdomen and in the navel. One 5-mm trocar was placed between the navel and rib. The locations of the metastases were identified with ultrasonography. The Glisson sheath was taped, and a Pringle maneuver using a Nelaton tube was performed. Resection of the metastatic tumor was then performed laparoscopically using an EnSeal (Ethicon Endo-Surgery, Cincinnati, USA). After completion of the hepatectomy, laparoscopic colorectal resection was performed. The patient was then changed to the lithotomy position. Colorectal resection with radical lymph node dissection

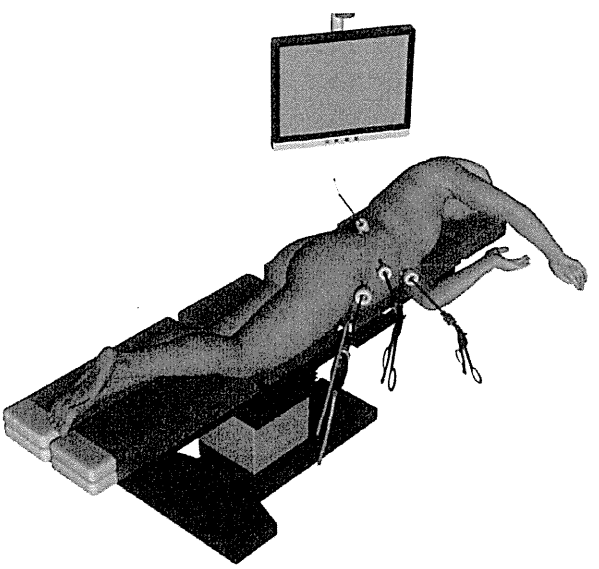

Figure 1 Illustration of patient position and trocar placement.

Asian J Endosc Surg 7 (2014) 133–137

Table 1 Patient characteristics and perioperative data

Case	Age (years)/Sex	Location of CRC	Location of CRCLM	Induction chemotherapy	Operative method		Complication
					Liver	Colon	
1	76/M	Cecum	S4, S8	–	Partial resection	Ileo-cecal resection	Liver abscess
2	61/M	Rectum	S2	–	Subsegmentectomy	Miles'	–
3	79/M	Sigmoid	S7	–	Partial resection	HAR	–
4	52/M	Ascending	S3	–	Subsegmentectomy	Right hemicolectomy	–
5	83/F	Rectum	S6	–	Partial resection	LAR	–
6	55/M	Sigmoid	S6	Cet+SOX	Subsegmentectomy	Sigmoidectomy	–
7	81/M	Sigmoid	S8	–	Subsegmentectomy	Sigmoidectomy	–
8	58/M	Rectum	S6	Bev+ mFOLFOX6	Partial resection	LAR	–
9	42/M	Sigmoid	S4	–	Partial resection	Sigmoidectomy	–
10	48/M	Rectum	S6, S8	–	Partial resection	LAR	–

Bev+mFOLFOX6, bevacizumab combined with oxaliplatin plus 5-fluorouracil and leucovorin; Cet+SOX, cetuximab combined with S-1 plus oxaliplatin; CRC, colorectal cancer; CRCLM, colorectal cancer liver metastases; F, female; HAR, high anterior resection; LAR, low anterior resection; M, male.

(D3) based on a no-touch isolation technique was performed. The incision on the navel was extended to 4 cm, and the liver and colorectal specimens were extracted from the peritoneal cavity. We designated this procedure as pure laparoscopic surgery because the large incision was only created to remove the specimen and not to perform the operation.

Results

Table 1 shows the clinical characteristics and treatment for the SCRLM. Primary CRC was located within the right colon ($n = 2$), left colon ($n = 4$), or rectum ($n = 4$). According to the TNM classification, these primary CRC were staged as T3 and T4a lesions in six and four patients, respectively. Lymph node metastasis in N0, N1, N2, and N3 disease were detected in one, four, three, and two patients, respectively. All patients underwent a radical resection for the primary cancer (colectomy, $n = 5$; anterior resection, $n = 4$; Miles' operation, $n = 1$) followed by anastomosis using a linear or circular stapler. CRC and liver metastases were located in the following places: S2 ($n = 1$), S3 ($n = 1$), S4 ($n = 2$), S6 ($n = 4$), S7 ($n = 1$), and S8 ($n = 3$); two patients had two metastatic lesions (patients 1 and 10). Two patients (patients 6 and 8) were initially treated with chemotherapy. Hepatectomy included partial resection ($n = 6$) and subsegmentectomy ($n = 4$). No patient was converted to conventional open surgery.

The mean operative duration and bleeding volume were 606 ± 46 min (median, 550 min; range, 416–804 min) and 585 ± 145 mL (median, 400 mL; range, 16–1179 mL), respectively. A liver abscess developed in one patient. However, no colonic complications (pelvic abscesses or anastomotic leakage) occurred. The mean postoperative hospital stay was 18 ± 3.5 days (median, 13.5 days; range, 10–45 days). In addition, the 30-day mortality rate was 0% (Table 2).

Table 2 Operative results

Variables	PULSAR ($n = 10$)
Median operative time, min (range)	550 (416–804)
Median blood loss, mL (range)	400 (16–1179)
Postoperative complications (n)	
Any	1
Liver abscess	1
Surgical-site infection	0
Ileus	0
Liver failure	0
Anastomotic leakage	0
Mortality (n)	0
Median postoperative hospital stay, days (range)	13.5 (10–45)

PULSAR, pure laparoscopic simultaneous resection.

Comparison of the intraoperative and postoperative outcomes of patients who underwent right lobe (S6–S8) or left lobe (S2–S4) hepatectomy showed no significant differences in the median operative time (554 vs 540 min, respectively), blood loss (400 vs 665 mL, respectively), or hospital stay (15 vs 12 days, respectively). Overall, the operative outcomes were good (Figure 2).

Discussion

In this study, we showed that PULSAR is safe and feasible for patients with SCRLM. Furthermore, in patients who underwent resection for SCRLM located in the right lobe, changing to a lithotomy position from the semi-prone position allowed for successful completion of PULSAR.

Compared with conventional laparotomy, the laparoscopic approach has several advantages. Many previous series have demonstrated the safety and feasibility of

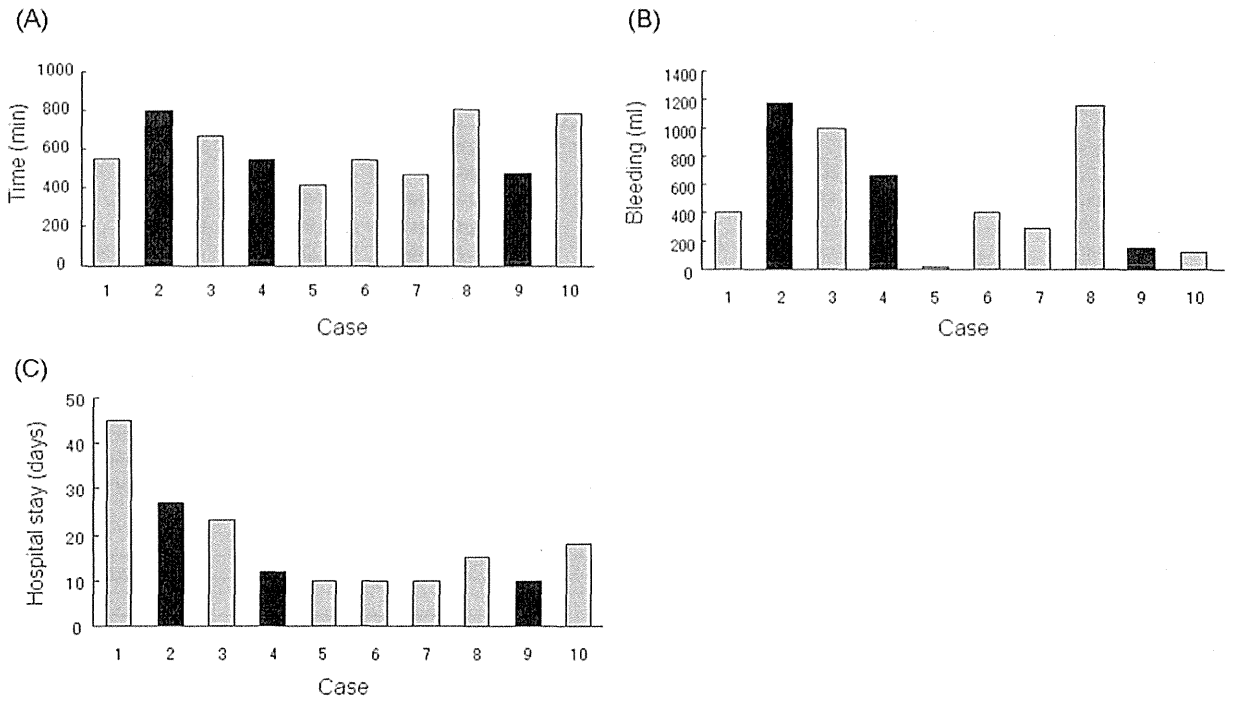

Figure 2 Intraoperative and postoperative outcomes. (a) Operative time, (b) intraoperative blood loss, and (c) postoperative hospital stay. Gray bar indicates a left-lobe (S2–4) hepatectomy; black bar indicates a right-lobe (S5–8) hepatectomy.

laparoscopy for minor resections of the liver edge and lateral segmentectomy (17,18). In addition, Nguyen *et al.* reported that laparoscopic right hepatectomy was performed in about 10% of international cases and was safe even when major hepatectomy was performed (10). However, hepatectomy of the right lobe, especially in S6–S8, is difficult with a pure laparoscopic method because of the technical difficulty associated with parenchymal transection, hemostasis at the transaction plane, risk of CO_2 embolism, and limitations in exploring the deeper regions of the liver (19–22). Therefore, we proposed the method of left semi-prone positional hepatectomy combined with laparoscopic colorectal surgery (13,14). The semi-prone position allows for a maximal amount of space within the subphrenic region, thus providing an expanded field of view of the back side of the liver produced by the weight of the liver's right lobe.

Recent studies comparing simultaneous and staged resections have confirmed that the simultaneous approach has significantly shorter operative times, reduced blood loss, reduced hospital stays, and reduced morbidity (6,23). Some reports have described simultaneous resection of colon cancer and liver metastases under laparoscopic surgery. Liver resection is often carried out using hybrid techniques such as hand-assisted or laparoscopically assisted methods (11,24). Some groups have described the safety and efficacy of pure laparoscopic procedures for simultaneous resection (24,25). In these studies, laparoscopic hepatic resection was performed in 20 cases, nine of which were right lobe resection in the lithotomy or left semi-decubitus position. The median operative time of these cases was 449 min (range, 230–540 min). In the current study, as in previous studies, seven patients (70%) with lesions in the right lobe successfully underwent simultaneous resection with a pure laparoscopic procedure. The median operative time was longer than in previous studies, but this increase likely occurred because of the time necessary to shift patients from the semi-prone position to the lithotomy position and to complete the colorectal procedures involved (i.e. anterior resection, Miles' operation). Spampinato *et al.* concluded that a laparoscopic approach involving simultaneous resection of primary CRC and liver metastasis is reasonable for selected patients (25). Obviously, patient selection is mandatory to achieve a good outcome. Reddy *et al.* indicatedfound that particular attention should be paid to elderly patients who undergo synchronous major hepatectomy (5). Furthermore, in a systematic review, Lupinacci *et al.* demonstrated that simultaneous resection is a very good option for non-rectal primaries and peripheral lesions requiring limited hepatectomy or left lateral sectionectomy (26). We share

Asian J Endosc Surg **7** (2014) 133–137

this belief, and at present, major hepatectomy is an exception to the indications for PULSAR. However, we safely performed laparoscopic major hepatectomy with patients in the semi-prone position (13,14). Therefore, major hepatectomy can also be performed for PULSAR cases in the near future.

In conclusion, PULSAR for primary CRC and SCRLM is a feasible multidisciplinary treatment. Our procedures for laparoscopic right-sided hepatectomy in the semi-prone position will allow patients to undergo cancer treatment more efficiently but without increased risks.

Acknowledgment

The authors have no conflicts of interest to disclose and received no financial support for this study.

References

1. Garden OJ, Rees M, Poston GJ *et al.* Guidelines for resection of colorectal cancer liver metastases. *Gut* 2006; **55**: Suppl 3: iii1–iii8.
2. Fong Y, Fortner J, Sun RL *et al.* Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases. *Ann Surg* 1999; **230**: 309–318. discussion 18-21.
3. Kokudo N, Imamura H, Sugawara Y *et al.* Surgery for multiple hepatic colorectal metastases. *J Hepatobiliary Pancreat Surg* 2004; **11**: 84–91.
4. Capussotti L, Ferrero A, Vigano L *et al.* Major liver resections synchronous with colorectal surgery. *Ann Surg Oncol* 2007; **14**: 195–201.
5. Reddy SK, Pawlik TM, Zorzi D *et al.* Simultaneous resections of colorectal cancer and synchronous liver metastases: A multi-institutional analysis. *Ann Surg Oncol* 2007; **14**: 3481–3491.
6. Martin RC, 2nd, Augenstein V, Reuter NP *et al.* Simultaneous versus staged resection for synchronous colorectal cancer liver metastases. *J Am Coll Surg* 2009; **208**: 842–850.discussion 50-2.
7. Vigano L. Treatment strategy for colorectal cancer with resectable synchronous liver metastases: Is any evidence-based strategy possible? *World J Hepatol* 2012; **4**: 237–241.
8. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 2004; **350**: 2050–2059.
9. Bai HL, Chen B, Zhou Y *et al.* Five-year long-term outcomes of laparoscopic surgery for colon cancer. *World J Gastroenterol* 2010; **16**: 4992–4997.
10. Nguyen KT, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. *Ann Surg* 2009; **250**: 831–841.
11. Kim SH, Lim SB, Ha YH *et al.* Laparoscopic-assisted combined colon and liver resection for primary colorectal cancer with synchronous liver metastases: Initial experience. *World J Surg* 2008; **32**: 2701–2706.
12. Tranchart H, Diop PS, Lainas P *et al.* Laparoscopic major hepatectomy can be safely performed with colorectal surgery for synchronous colorectal liver metastasis. *HPB (Oxford)* 2011; **13**: 46–50.
13. Ikeda T, Yonemura Y, Ueda N *et al.* Pure laparoscopic right hepatectomy in the semi-prone position using the intrahepatic Glissonian approach and a modified hanging maneuver to minimize intraoperative bleeding. *Surg Today* 2011; **41**: 1592–1598.
14. Ikeda T, Mano Y, Morita K *et al.* Pure laparoscopic hepatectomy in semiprone position for right hepatic major resection. *J Hepatobiliary Pancreat Sci* 2013; **20**: 145–150.
15. UICC International Union Against Cancer. *TNM classification of malignant tumors*, 7th edn. Hoboken, NJ: Wiley-Blackwell, 2009.
16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–213.
17. Chang S, Laurent A, Tayar C *et al.* Laparoscopy as a routine approach for left lateral sectionectomy. *Br J Surg* 2007; **94**: 58–63.
18. Vigano L, Tayar C, Laurent A *et al.* Laparoscopic liver resection: A systematic review. *J Hepatobiliary Pancreat Surg* 2009; **16**: 410–421.
19. Cho JY, Han HS, Yoon YS *et al.* Outcomes of laparoscopic liver resection for lesions located in the right side of the liver. *Arch Surg* 2009; **144**: 25–29.
20. Dagher I, Di Giuro G, Dubrez J *et al.* Laparoscopic versus open right hepatectomy: A comparative study. *Am J Surg* 2009; **198**: 173–177.
21. Han HS, Yoon YS, Cho JY *et al.* Laparoscopic right hemihepatectomy for hepatocellular carcinoma. *Ann Surg Oncol* 2010; **17**: 2090–2091.
22. Jayaraman S, Khakhar A, Yang H *et al.* The association between central venous pressure, pneumoperitoneum, and venous carbon dioxide embolism in laparoscopic hepatectomy. *Surg Endosc* 2009; **23**: 2369–2373.
23. Chen J, Li Q, Wang C *et al.* Simultaneous vs. staged resection for synchronous colorectal liver metastases: A metaanalysis. *Int J Colorectal Dis* 2011; **26**: 191–199.
24. Hayashi M, Komeda K, Inoue Y *et al.* Simultaneous laparoscopic resection of colorectal cancer and synchronous metastatic liver tumor. *Int Surg* 2011; **96**: 74–81.
25. Spampinato MG, Mandala L, Quarta G *et al.* One-stage, totally laparoscopic major hepatectomy and colectomy for colorectal neoplasm with synchronous liver metastasis: Safety, feasibility and short-term outcome. *Surgery* 2013; **153**: 861–865.
26. Lupinacci RM, Andraus W, De Paiva Haddad LB *et al.* Simultaneous laparoscopic resection of primary colorectal cancer and associated liver metastases: A systematic review. *Tech Coloproctol* 2014; **18**: 129–135.

Ann Surg Oncol (2014) 21:1175–1181
DOI 10.1245/s10434-013-3454-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Surgical Resection of Hypopharynx and Cervical Esophageal Cancer with a History of Esophagectomy for Thoracic Esophageal Cancer

Satoshi Ida, MD, PhD[1,3], Masaru Morita, MD, PhD, FACS[1], Yukiharu Hiyoshi, MD, PhD[1,3], Keisuke Ikeda, MD[1], Koji Ando, MD, PhD[1], Yasue Kimura, MD, PhD[1], Hiroshi Saeki, MD, PhD[1], Eiji Oki, MD, PhD[1], Tetsuya Kusumoto, MD, PhD[1], Sei Yoshida, MD, PhD[2], Torahiko Nakashima, MD, PhD[2], Masayuki Watanabe, MD, PhD, FACS[3], Hideo Baba, MD, PhD, FACS[3], and Yoshihiko Maehara, MD, PhD, FACS[1]

[1]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [2]Department of Otorhinolaryngology and Head and Neck Surgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [3]Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

ABSTRACT

Background. Cancer of the hypopharynx and cervical esophagus (PhCe cancer) frequently develops synchronously or metachronously with esophageal cancer. The surgical approach is usually difficult, especially in metachronous PhCe cancer after esophagectomy. The purpose of this study was to clarify the treatment outcomes of patients with metachronous PhCe cancer with a history of esophagectomy.

Methods. The subjects evaluated in this study were 14 patients with metachronous PhCe cancer who underwent pharyngo-laryngo-esophagectomy after subtotal esophagectomy and gastric tube pull-up for primary esophageal cancer.

Results. Definitive chemoradiotherapy (CRT; radiation dose >50 Gy) was performed for primary laryngeal ($n = 1$), pharyngeal ($n = 2$), esophageal ($n = 1$), and recurrent esophageal cancer ($n = 2$). For seven patients with metachronous PhCe cancer, induction CRT (radiation dose <40 Gy) was performed. In all 14 patients, pharyngo-laryngo-esophagectomy was followed by free jejunal graft interposition with reconstruction of the jejunal vessels. Although postoperative complications developed in four patients, no perioperative death or necrosis of the reconstructed free jejunum occurred. The 2- and 5-year overall survival rates were 84 and 50 %, respectively.

Conclusions. Pharyngo-laryngo-esophagectomy with free jejunal transfer is considered to be safe for metachronous PhCe cancer, even in patients with a history of CRT and esophagectomy.

It is well known that patients with upper aerodigestive tract cancer are at an increased risk of developing squamous cell carcinoma (SCC) in an adjacent region, such as the esophagus, pharynx, or larynx. With improvement in surveillance and long-term follow-up, the prevalence of patients with esophageal cancer who are subsequently found to have head and neck (H&N) cancer is reportedly 1.5–5.1 %.[1–6]

Cancer of the hypopharynx and cervical esophagus (PhCe cancer) frequently develops synchronously or metachronously with thoracic esophageal cancer. Complete surgical removal of the primary cancer and regional lymph nodes is considered to be the most effective treatment for PhCe cancer. However, the surgical approach for PhCe cancer frequently results in disturbances of vocal and swallowing functions. Therefore, surgical treatment for PhCe cancer, either synchronously or metachronously associated with esophageal cancer, is extremely difficult. SCC of the upper aerodigestive tract is relatively sensitive to radiation and anticancer drugs such as 5-fluorouracil (5-FU) and cisplatin. Indeed, definitive chemoradiotherapy (CRT) has been considered to be one of the most favorable

First Received: 16 June 2013;
Published Online: 1 January 2014

M. Morita, MD, PhD, FACS
e-mail: masarum@surg2.med.kyushu-u.ac.jp

treatment modalities for unresectable PhCe cancer or resectable locally advanced lesions, especially for the purpose of organ preservation.[7,8] However, locoregional disease persists or recurs in 40–60 % of patients who undergo CRT for PhCe cancer.[8,9] Long-term survival can be expected if complete (R0) resection is performed for such residual or recurrent lesions after definitive CRT.[10] Thus, salvage pharyngo-laryngo-esophagectomy could be the only treatment choice that provides a chance of a cure for PhCe cancer. However, the surgical risk of this procedure is still considered to be extremely high, with high mortality and morbidity rates.[11–14]

Treatment strategies for metachronous PhCe cancer following esophagectomy and/or definitive CRT are extremely problematic. Although recent developments in plastic and reconstructive surgery for H&N cancer are extending the indications for surgical treatment, treatment of metachronous PhCe cancer is difficult, especially post-esophagectomy. We recently reported the results of esophagectomy for thoracic esophageal cancer associated with H&N cancer.[15] However, few reports have described the details of surgical resection and its outcomes in regard to metachronous PhCe cancer after esophagectomy and/or definitive CRT. We herein review the clinical results after salvage pharyngo-laryngo-esophagectomy for metachronous PhCe cancer in patients with a history of esophagectomy.

PATIENTS AND METHODS

Patients

Fourteen patients with a history of esophagectomy for thoracic esophageal cancer underwent pharyngo-laryngo-esophagectomy for PhCe cancer. All patients developed metachronous advanced PhCe cancer following subtotal esophagectomy for the esophageal cancer. All resections for PhCe cancer were performed in our hospital between 1994 and 2012. However, two patients underwent previous esophagectomy in our hospital, and the remaining 12 underwent previous esophagectomy in another hospital. There were 12 male and two female patients with a mean age of 63 years (range 41–72 years). The main lesion was histologically diagnosed as SCC in all patients.

Metachronous cancers were defined as second neoplasms diagnosed 6 months after identification of the primary lesion. Tumor staging was based on the tumor, node, metastasis system (TNM) classification defined by the Union for International Cancer Control.[16] The pre-treatment diagnostic evaluations comprised a barium swallow, endoscopy, cervical ultrasound, and computed tomography (CT).

Treatment

Details of the operative procedures were previously described for thoracic esophageal cancer[17] and involved either subtotal esophagectomy with cervical anastomosis or distal esophagectomy with intrathoracic anastomosis (modified Ivor-Lewis procedure). For early-stage cancer located mainly in the lower thoracic and occasionally in the mid-thoracic esophagus, we performed distal esophagectomy via a right thoracotomy and laparotomy with intrathoracic anastomosis. A gastric tube was used for esophageal reconstruction unless the patient had undergone previous gastrectomy or had gastric cancer. In the past, we routinely performed reconstruction via a subcutaneous route; however, we now perform either a cervical anastomosis via a posterior mediastinal route or an intrathoracic anastomosis if no adventitial invasion has occurred. A retrosternal route was often used for patients with very advanced cancer, and a subcutaneous route was used for patients with a high risk of anastomotic leakage. For mucosal esophageal cancer, endoscopic submucosal dissection was performed.

The treatment strategy for metachronous PhCe cancer was determined by the managing surgeon and otolaryngologist. In our institution, CRT is principally aimed at radical cure and preservation of the vocal and swallowing functions. The treatment was finally determined after informed consent had been obtained from patients. Chemotherapy mainly comprised 5-FU/cisplatin or monotherapy of 5-FU or oral S-1. When simultaneous CRT was indicated, PhCe cancer was initially irradiated to approximately 40 Gy. The response to CRT was then evaluated by endoscopic examination and CT. Those with a poor response underwent the planned operation. Those with a good response received definitive CRT to approximately 70 Gy with chemotherapy for curative intent and preservation of the larynx. The radiotherapy area routinely included the bilateral neck. Pharyngo-laryngo-esophagectomy was performed at our department and the Department of Otolaryngology and Head and Neck Surgery. Free jejunal graft interposition was used for reconstruction, and microscopic vessel anastomosis was performed in all cases.

Screening and Follow-Up

Screening and follow-up were performed as previously described.[18] In brief, because recurrence frequently develops within 2 years postoperatively, both office visits and tumor marker measurements were performed every month during this period. Endoscopy was performed annually to detect anastomotic recurrence and the development of second primary cancers, particularly H&N

cancer. Laryngoscopy was performed by an otolaryngologist for high-risk patients. CT was performed at least twice yearly within this period. Positron emission tomography–CT was also performed 1-year postoperatively for high-risk patients.

In this study, we focused on the surgical management and outcome of all patients. Follow-up evaluations ranged from 10 to 108 months after pharyngo-laryngo-esophagectomy (median follow-up period of censored patients 35.2 months), and data were available for all patients.

Postoperative complications were defined as grade II or higher according to the Clavien–Dindo classification.[19] Data are expressed as mean ± standard error. The survival curves were plotted according to the Kaplan–Meier method. The study protocol and patients' informed consent statements were approved by the Institutional Review Board of Kyushu University Hospital.

RESULTS

The primary esophageal cancers are summarized as follows: three patients had stage I cancer and 11 patients had stage II–IV cancer. Subtotal esophagectomy followed by reconstruction with a gastric tube was performed in 13 patients. The remaining one patient (case number 10) was treated with endoscopic submucosal dissection for primary esophageal cancer followed by 50.4 Gy of radiation for cervical lymph node metastases. Furthermore, this patient developed recurrence 2 years later and underwent distal esophagectomy with intrathoracic anastomosis using a gastric tube. Reconstruction using a gastric tube via the retrosternal route, intrathoracic route, and subcutaneous route was performed in nine, four, and one patient, respectively. Cervical anastomosis was performed in ten patients; four patients who underwent reconstruction via the intrathoracic route were excluded. R0 resection was performed in all patients.

Table 1 shows the clinical characteristics and treatments for the metachronous PhCe cancers. The average interval from the first operation for esophageal cancer was approximately 52 months (range 8 months–10 years). All patients consulted with the hospital for evaluation of either sore throat or dysphagia, and endoscopy was performed. The main location of the metachronous PhCe cancer was in the hypopharynx in 13 patients and the residual cervical esophagus in one patient. Figure 1 shows a flow chart of the treatment strategies. Nine of the metachronous PhCe cancers were initially treated with CRT to approximately 40 Gy. Among these patients, two (22 %) demonstrated good responses to definitive CRT to approximately 65.4 Gy, and a complete response (CR) was finally achieved. However, these patients who achieved a CR developed local recurrence of their hypopharyngeal cancer 2 or 4 months after definitive CRT, following which pharyngo-laryngo-esophagectomy was performed. The other seven patients demonstrated poor responses to irradiation of less than 40 Gy, and CRT was discontinued. In five of 14 patients, the pharyngo-laryngo-esophagectomy was performed with no preoperative CRT for metachronous PhCe cancer. In four patients, definitive radiotherapy had been previously performed; one was for local recurrence of the esophageal cancer, two were for metastasis or recurrence of the cervical lymph node of the esophageal cancer, and one was for laryngeal cancer. All were evaluated during CR status. The remaining patient refused CRT. In terms of the chemotherapy regimen, cisplatin/5-FU, 5-FU alone, S-1 alone, and carboplatin alone was administered in six, three, three, and one patient, respectively.

For all 14 patients, pharyngo-laryngo-esophagectomy was performed and reconstruction was completed by a free jejunal graft. The pharyngojejunal anastomosis (proximal anastomosis) was performed in an end-to-end or side-to-end fashion (11 and 3 patients, respectively). For the anastomosis of the distal side, seven patients underwent reconstruction by jejunum-gastric tube anastomosis, and the other seven underwent reconstruction by jejunum-cervical esophagus anastomosis using a hand-sewing technique (Fig. 2). In 12 patients, the anastomosis site was raised from the sternum, and in two patients it was placed in the mediastinum (case numbers 2 and 7). We also reconstructed the jejunal arteries and veins in all cases. The superior thyroid artery, transverse cervical artery, common carotid artery, and external carotid artery were used for recipient arteries in seven, three, two, and two patients, respectively. For recipient veins, the external jugular vein, internal jugular vein, common facial vein, and facial vein were used in six, three, three, and two patients, respectively. No vascular complications were seen. The mean operative duration and bleeding volume were 682.5 ± 35.7 min (median 657 min; range 562–1,015 min) and 726.8 ± 104.3 ml (median 656 ml; range 200–1,500 ml), respectively. Postoperative complications developed in five events involving four patients (28.6 %). Postoperative bleeding, anastomotic leakage, ileus, and subcutaneous abscess developed in two, one, one, and one patient, respectively. The two cases of postoperative bleeding were resolved after hemostasis; however, both a perioperative death and necrosis of the reconstructed free jejunum occurred in this study. The mean interval until achievement of oral intake and the mean postoperative hospital stay were 12.4 ± 1.2 days (median 14; range 7–22) and 36.6 ± 4.1 days (median 29; range 21–77), respectively (Table 2). The 2- and 5-year overall survival rates after pharyngo-laryngo-esophagectomy were 84 and 50 %, respectively.

TABLE 1 Summary of treatment for PhCe cancer

Case nos.	Age (years)/sex	Main lesion of cancer	Total dose of radiation (Gy)	Route of reconstruction for esophagectomy	Operative method for PhCe cancer			
					Anastomosis of distal side	Recipient artery	Recipient vein	Complications
1	41/M	Hypopharynx	27	Intrathoracic	E	Common cartid	External jugular	None
2	65/M	Hypopharynx	30	Retrosternal	G	Common cartid	Internal jugular	Ileus
3	70/M	Hypopharynx	0	Subcutaneous	G	Transverse cervical	External jugular	None
4	52/M	Hypopharynx	30	Retrosternal	G	Superior thyroidal	Common facial	None
5	66/M	Hypopharynx	28.8	Intrathoracic	E	Superior thyroidal	Common facial	None
6	62/M	Hypopharynx	60	Intrathoracic	E	Superior thyroidal	Common facial	None
7	58/F	Hypopharynx	60	Retrosternal	G	External jugular	External jugular	None
8	72/M	Hypopharynx	60	Retrosternal	E	Superior thyroidal	Facial	None
9	59/F	Hypopharynx	60	Retrosternal	E	Transverse cervical	External jugular	None
10	69/M	Hypopharynx	50.4	Intrathoracic	G	Superior thyroidal	External jugular	None
11	65/M	Hypopharynx	65.4	Retrosternal	G	Superior thyroidal	External jugular	Anastomotic leakage
12	71/M	Hypopharynx	41.4	Retrosternal	E	External jugular	Internal jugular	Bleeding[a]
13	65/M	Cervical esophagus	40	Retrosternal	E	Superior thyroidal	Facial	Subcutaneous abscess, bleeding[a]
14	67/M	Hypopharynx	41.4	Retrosternal	G	Transverse cervical	Internal jugular	None

PhCe hypopharynx and cervical esophagus, *M* male, *F* female, *E* esophageal stump, *G* gastric tube

[a] Re-operation

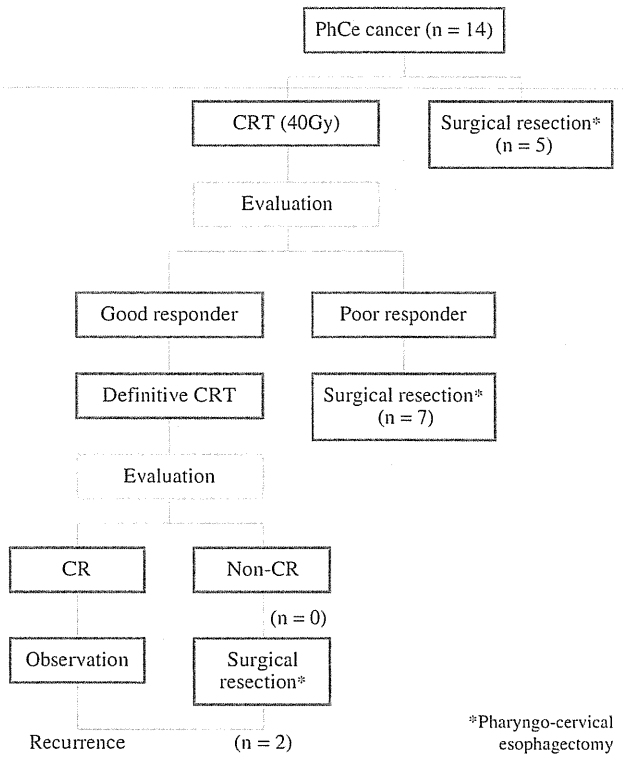

FIG. 1 Flowchart of the treatment strategies for PhCe cancer. *PhCe* hypopharynx and cervical esophagus, *CRT* chemoradiotherapy, *CR* complete response

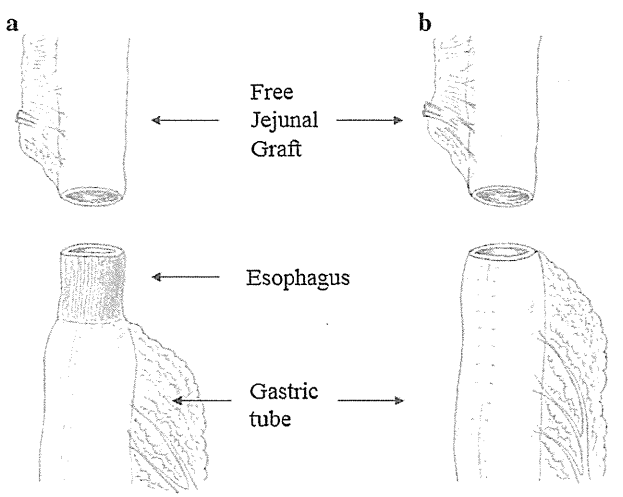

FIG. 2 Schema of the distal anastomosis. The distal jejunal stump is anastomosed to **a** the esophageal stump; and **b** the gastric tube

DISCUSSION

In this study, we showed that pharyngo-laryngo-esophagectomy reconstructing jejunal transfer was safe and effective for patients with metachronous PhCe cancer with a history of esophagectomy. A nationwide registry of 5,066 Japanese patients with esophageal cancer treated in 2004 showed that second cancers in another organ were present in 981 patients (19.4 %). Gastric cancer was the most common (353 lesions), followed by H&N cancer, including 162 pharyngeal cancers.[20] A multicenter study including cancer data from 13 population-based cancer registries in Europe, Australia, Canada, and Singapore clearly revealed the risk of first and second primary esophageal cancers according to the data from a large number of patients ($N = 52,589$). The risk (standardized incidence ratio) of second cancers of the H&N lesion significantly increased to 6.68 (95 % CI 5.33–8.26) after SCC of the esophagus compared with the expected number of cancers.[21] In our institute, esophagectomy was performed for 459 patients with SCC of the thoracic esophagus during this study period. Among these patients, 46 (10.0 %) had associated H&N cancer lesions (54 lesions among the 46 patients). Thirty of the 54 H&N cancers developed synchronously with the esophageal cancer. Another 24 lesions developed metachronously: 13 lesions were detected before the esophageal cancer, and 11 lesions were detected following the esophageal cancer. Furthermore, Tachimori et al. [2] reported that in 24 % of patients who developed metachronous H&N cancer, the 2- and 5-year survival rates after treatment of the H&N tumor were 56.3 and 23.1 %, respectively. In the present study, the 2- and 5-year survival rates were 73 and 49 %, respectively. Although the current study included a small number of patients, these results were satisfactory.

TABLE 2 Operative results

Variables	Number
Operative time [min; median (range)]	657 (562–1,015)
Blood loss [ml; median (range)]	656 (200–1,500)
Hospital death	0
Post operative complication	
Any	4
Bleeding	2
Anastomotic leakage	1
Ileus	1
Subcutaneous abscess	1
Oral intake [days; median (range)]	14 (7–22)
Hospital stay after operation [days; median (range)]	29 (21–77)

The survival rate from the first tumor is obviously related to the risk of developing a second primary tumor. With recent progress in diagnosis and treatment, more than half of the patients with esophageal cancer appeared to be cured after surgical resection at a high-volume center in Japan.[17] On the other hand, since the prognosis of esophageal cancer has improved, some patients with a history of

esophagectomy have developed metachronous cancers of the H&N.[2,3,23] A past history of treatment of the first primary cancer often affects the therapy of the second cancer. The surgical approach tends to be complicated and highly invasive. Larynx preservation can be achieved by preoperative CRT. Even when CR is not achieved with CRT, good local control and survival rates can reportedly be achieved.[24,25] Thus, we performed CRT to preserve vocal and swallowing functions following salvage surgery.

Pharyngo-laryngo-esophagectomy for patients with metachronous PhCe cancer is difficult because of the effect of previous surgery and/or irradiation of the neck region. Irradiation can disrupt wound healing and cause poor blood flow secondary to disruption of the microcirculation. As a result, anastomotic leakage develops more frequently after salvage esophagectomy following definitive CRT.[12,13,26] Furthermore, an increase in thrombus formation in the irradiated recipient beds was reported in an experimental study.[27] Preoperative CRT is also considered to suppress the immune function.[28] Suppression of the immune function is significantly associated with an increase in postoperative complications. However, we previously described the clinical results of 14 patients who underwent salvage pharyngo-laryngo-esophagectomy with free jejunal transfer after definitive CRT (>50 Gy).[10] Microvascular anastomosis was safely applied with no critical postoperative complications.[10,15,29,30]

Previous operations resulted in the formation of fibrous adhesion to the surrounding tissue, which makes subsequent surgery difficult. The gastric tube was pulled via either the retrosternal or posterior mediastinal route to the neck for reconstruction after esophagectomy. In the subsequent operation for the metachronous PhCe cancer, dissection of the adhesion surrounding the gastric tube may have had adverse results. In particular, ten patients who underwent cervical anastomosis for reconstruction after esophagectomy had extremely tight adhesions in the cervicothoracic region. Furthermore, it is difficult to anastomose the distal side of the reconstructed free jejunum to the gastric tube or cervical esophagus because the procedure must be carried out in a deep, narrow space. Because the anastomosis of two patients was placed in the mediastinum, the operation was difficult; however, no postoperative complications occurred.

Free jejunal transfer is considered to be safe and effective after salvage pharyngo-laryngectomy and pharyngo-laryngo-esophagectomy. Some previous reports have indicated that this procedure is highly successful, with few postoperative complications.[10,22,31] Suga et al.[22] reported that despite a history of esophagectomy and gastric pull-up, free jejunal transfer and microvascular anastomosis can be successfully performed. This technique can also be applied to salvage pharyngo-laryngo-esophagectomy in patients with a history of esophagectomy and gastric pull-up. Furthermore, these patients can ingest a normal diet without dysphagia.

CONCLUSIONS

Pharyngo-laryngo-esophagectomy with free jejunal transfer is considered to be safe, even in patients with a history of CRT and/or esophagectomy, and will extend the possibility of surgical treatment for metachronous PhCe cancer. Furthermore, close cooperation among medical staff members, including the esophageal surgeon, H&N surgeon, and plastic surgeon, is essential.

ACKNOWLEDGMENT This work was supported in part by a Grant-in-Aid from the Ministry of Education, Culture, Sport, Science and Technology of Japan.

DISCLOSURE The authors report no financial interests or potential conflicts of interest.

REFERENCES

1. Fogel TD, Harrison LB, Son YH. Subsequent upper aerodigestive malignancies following treatment of esophageal cancer. *Cancer.* 1985;55:1882–5.
2. Tachimori Y, Watanabe H, Kato H, Ebihara S, Ono I, Nakatsuka T, et al. Treatment for synchronous and metachronous carcinomas of the head and neck and esophagus. *J Surg Oncol.* 1990;45:43–5.
3. Shibuya H, Wakita T, Nakagawa T, Fukuda H, Yasumoto M. The relation between an esophageal cancer and associated cancers in adjacent organs. *Cancer.* 1995;76:101–5.
4. Morita M, Kumashiro R, Kubo N, Nakashima Y, Yoshida R, Yoshinaga K, et al. Alcohol drinking, cigarette smoking, and the development of squamous cell carcinoma of the esophagus: epidemiology, clinical findings, and prevention. *Int J Clin Oncol.* 2010;15:126–34.
5. Morita M, Kuwano H, Nakashima T, Taketomi A, Baba H, Saito T, et al. Family aggregation of carcinoma of the hypopharynx and cervical esophagus: special reference to multiplicity of cancer in upper aerodigestive tract. *Int J Cancer.* 1998;76:468–71.
6. Morita M, Kuwano H, Ohno S, Sugimachi K, Seo Y, Tomoda H, et al. Multiple occurrence of carcinoma in the upper aerodigestive tract associated with esophageal cancer: reference to smoking, drinking and family history. *Int J Cancer.* 1994;58:207–10.
7. Nishimura G, Tsukuda M, Horiuchi C, Satake K, Yoshida T, Nagao J, et al. Concurrent chemoradiotherapy for T4 patients with hypopharyngeal and laryngeal squamous cell carcinomas. *Auris Nasus Larynx.* 2007;34:499–504.
8. Nakahara R, Kodaira T, Furutani K, Tachibana H, Tomita N, Inokuchi H, et al. Treatment outcomes of definitive chemoradiotherapy for patients with hypopharyngeal cancer. *J Radiat Res.* 2012;53:906–15.
9. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA.* 1999;281:1623–7.
10. Kadota H, Fukushima J, Nakashima T, Kumamoto Y, Yoshida S, Yasumatsu R, et al. Comparison of salvage and planned pharyngolaryngectomy with jejunal transfer for hypopharyngeal carcinoma after chemoradiotherapy. *Laryngoscope.* 2010;120:1103–8.

11. Clark JR, de Almeida J, Gilbert R, Irish J, Brown D, Neligan P, et al. Primary and salvage (hypo)pharyngectomy: analysis and outcome. *Head Neck*. 2006;28:671–7.
12. Tachimori Y, Kanamori N, Uemura N, Hokamura N, Igaki H, Kato H. Salvage esophagectomy after high-dose chemoradiotherapy for esophageal squamous cell carcinoma. *J Thorac Cardiovasc Surg*. 2009;137:49–54.
13. Morita M, Kumashiro R, Hisamatsu Y, Nakanishi R, Egashira A, Saeki H, et al. Clinical significance of salvage esophagectomy for remnant or recurrent cancer following definitive chemoradiotherapy. *J Gastroenterol*. 2011;46:1284–91.
14. Yoshida R, Morita M, Ando K, Masuda T, Saeki H, Oki E, et al. Salvage esophagectomy after definitive chemoradiotherapy for synchronous double cancers of the esophagus and head-and-neck. *Dis Esophagus*. 2010;23:59–63.
15. Morita M, Kawano H, Otsu H, Kimura Y, Saeki H, Ando K, et al. Surgical resection for esophageal cancer synchronously or metachronously associated with head and neck cancer. *Ann Surg Oncol*. 2013;20:2434–9.
16. UICC International Union Against Cancer. TNM classification of malignant tumors. 6th ed. New York: Wiley; 2002.
17. Morita M, Yoshida R, Ikeda K, Egashira A, Oki E, Sadanaga N, et al. Advances in esophageal cancer surgery in Japan: an analysis of 1000 consecutive patients treated at a single institute. *Surgery*. 2008;143:499–508.
18. Morita M, Maehara Y. Esophagus carcinoma surveillance counterpoint: Japan. In: Johnson FE, Maehara Y, Browman GP, et al., eds. Patient surveillance after cancer treatment. New York: Springer; 2013: pp.101–5.
19. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–13.
20. Ozawa S. Comprehensive registry of esophageal cancer in Japan, 2004. In: Ozawa S, ed. Chiba: The Japan Esophageal Society; 2012: p.8.
21. Chuang SC, Hashibe M, Scelo G, Brewster DH, Pukkala E, Friis S, et al. Risk of second primary cancer among esophageal cancer patients: a pooled analysis of 13 cancer registries. *Cancer Epidemiol Biomarkers Prev*. 2008;17:1543–9.
22. Suga H, Okazaki M, Sarukawa S, Takushima A, Asato H. Free jejunal transfer for patients with a history of esophagectomy and gastric pull-up. *Ann Plast Surg*. 2007;58:182–5.
23. Thompson WM, Oddson TA, Kelvin F, Daffner R, Postlethwait RW, Rice RP. Synchronous and metachronous squamous cell carcinomas of the head, neck and esophagus. *Gastrointest Radiol*. 1978;3:123–7.
24. Morita M, Kuwano H, Ohno S, Furusawa M, Sugimachi K. Characteristics and sequence of the recurrent patterns after curative esophagectomy for squamous cell carcinoma. *Surgery*. 1994;116:1–7.
25. Sugiyama M, Morita M, Yoshida R, Ando K, Egashira A, Takefumi O, et al. Patterns and time of recurrence after complete resection of esophageal cancer. *Surg Today*. 2012;42:752–8.
26. Oki E, Morita M, Kakeji Y, Ikebe M, Sadanaga N, Egasira A, et al. Salvage esophagectomy after definitive chemoradiotherapy for esophageal cancer. *Dis Esophagus*. 2007;20:301–4.
27. Watson JS. Experimental microvascular anastomoses in radiated vessels: a study of the patency rate and the histopathology of healing. *Plast Reconstr Surg*. 1979;63:525–33.
28. Tsutsui S, Sonoda K, Sumiyoshi K, Kitamura K, Toh Y, Kitamura M, et al. Prognostic significance of immunological parameters in patients with esophageal cancer. *Hepatogastroenterology*. 1996;43:501–9.
29. Saeki H, Morita M, Harada N, Egashira A, Oki E, Uchiyama H, et al. Esophageal replacement by colon interposition with microvascular surgery for patients with thoracic esophageal cancer: the utility of superdrainage. *Dis Esophagus*. 2013;26:50–6.
30. Uchiyama H, Shirabe K, Morita M, Kakeji Y, Taketomi A, Soejima Y, et al. Expanding the applications of microvascular surgical techniques to digestive surgeries: a technical review. *Surg Today*. 2012;42:111–20.
31. Sarukawa S, Sakuraba M, Kimata Y, Yasumura T, Uchiyama K, Hishinuma S, et al. Standardization of free jejunum transfer after total pharyngolaryngoesophagectomy. *Laryngoscope*. 2006;116:976–81.

Analysis of Adverse Events of Bevacizumab-containing Systemic Chemotherapy for Metastatic Colorectal Cancer in Japan

TAICHI ISOBE[1], KEITA UCHINO[2], CHINATSU MAKIYAMA[1], HIROSHI ARIYAMA[1], SHUJI ARITA[1,6], SHINGO TAMURA[1], MASATO KOMODA[2], HITOSHI KUSABA[1], TSUYOSHI SHIRAKAWA[3], TAITO ESAKI[3], KENJI MITSUGI[4], SHIGEO TAKAISHI[5], KOICHI AKASHI[1] and EISHI BABA[6]

[1]*Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan;*
[2]*Department of Medical Oncology, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan;*
[3]*Department of Gastroenterology and Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan*
[4]*Department of Oncology, Hamanomachi Hospital, Fukuoka, Japan;*
[5]*Center for Advanced Medical Innovation, Kyushu University, Fukuoka, Japan;*
[6]*Department of Comprehensive Clinical Oncology, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan*

Abstract. *Background: Bevacizumab (BV) is widely used in chemotherapy for metastatic colorectal cancer (mCRC). Although specific adverse events have been observed, their risk factors have not been clarified. Patients and Methods: 178 mCRC patients who underwent chemotherapy were retrospectively examined and correlations between possible risk factors and adverse events were analyzed. Results: 87 out of 178 patients were treated with BV-containing chemotherapy. Possible risk factors for BV-related adverse events were: remaining primary tumor, current bleeding, history of arterial thromboembolism (ATE), hypertension, and proteinuria, and these were observed in 22%, 2%, 7%, 16%, and 8% of patients, respectively. Patients with hypertension prior to chemotherapy developed significantly worse hypertension (p=0.018). Gastrointestinal bleeding occurred in 3 out of 18 patients with residual primary tumor (16.7%) and 6 out of 63 patients with no primary tumor (8.7%) (p=0.385). Conclusion: Pre-existing hypertension appears to be a risk factor for BV-related deterioration of hypertension.*

Correspondence to: Eishi Baba, MD, Ph.D, Department of Comprehensive Clinical Oncology, Faculty of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582 Japan. Tel: +81 926426921, Fax: +81 926426922, e-mail: e-baba@c-oncology.med.kyushu-u.ac.jp

Kew Words: Colorectal cancer, chemotherapy, bevacizumab, adverse events.

Systemic chemotherapy has been developed as a standard therapy against metastatic colorectal cancer (mCRC), and therapeutic outcomes have since improved. In addition to cytotoxic agents, inhibition of vascular endothelial growth factor (VEGF) has been one of the key strategies for several types of solid tumors whose growth depends on neovascularization (1). VEGF is a glycoprotein physiologically-regulating vascular permeability and neovascularization. Moreover, tumor cells often produce large amounts of VEGF and depend on VEGF-induced neovascularization supplying oxygen and nutrition.

Bevacizumab (BV) is a recombinant, humanized, monoclonal antibody against human VEGF-A that inhibits the binding of VEGF-A to VEGFR and subsequent growth of endothelial cells. It has also been reported that normalization of abnormal tumor vasculature by BV contributes to maintaining interstitial pressure of tumor tissue and effectively delivering drugs to the tumor cells (2-4). BV has been well-investigated for its therapeutic effects on mCRC in clinical trials (5-8). In combination with fluorouracil-based regimens, BV has been reported to provide longer progression-free survival and overall survival in large-scale, randomized, clinical trials (5-7). Based on these results, BV was approved for the first-line and second-line treatment of mCRC in the United States in 2004 and in Japan in 2007.

Although BV shows remarkable clinical benefits, specific adverse events including not only frequently-observed proteinuria and hypertension, but also more serious conditions including gastrointestinal (GI) perforation, bleeding, and arterial thromboembolism (ATE), have been

0250-7005/2014 $2.00+.40