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Characteristics and prognostic factors of synchronous multiple primary esophageal carcinoma: A report of 52 cases

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Keywords

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Abstract

Background: To retrospectively analyze the clinical characteristics and prognostic factors of 52 cases of synchronous multiple primary esophageal carcinoma (SMPEC), in order to provide a reference for treatment strategy.

Methods: Clinical and survival data of 52 patients with SMPEC were analyzed retrospectively. The rates of overall survival (OS), depending on the different factors, were calculated using Kaplan-Meier analysis. A log-rank test was used for univariate survival analysis and Cox's proportional hazards regression model was used for multivariate survival analysis.

Results: Clinical and survival data of 52 patients with SMPEC, hospitalized from 1 January 2003 to 31 October 2011, were analyzed. Twelve patients underwent surgical resection, five received adjuvant radiotherapy and one received adjuvant radiochemotherapy. Thirty-seven of the 40 non-operative patients received external beam radiation therapy and 20 of them received platinum-based chemotherapy. Another three non-operative patients were given platinum-based chemotherapy alone. The one, three, and five-year OS and the median survival time (MST) were 65.4%, 17.3%, 7.7%, respectively, and 15.0 months for the whole cohort. Tumor length and M stage were independent prognostic factors for the whole cohort by multivariate survival analysis ($P = 0.010$ and 0.047 , respectively). For the radiotherapy subgroup, multivariate analysis of prognostic factors identified that shorter tumor length, M0 stage, and chemotherapy were the predominant independent predictors of long-term survival ($P = 0.039$, 0.022 and 0.010 , respectively).

Conclusions: SMPEC is a relatively rare and aggressive tumor. Combined radiotherapy with chemotherapy seemed to bring a survival benefit and may be a better management choice for unresectable and non-operative SMPEC.

Introduction

Multiple primary esophageal carcinoma (MPEC) is a relatively rare and aggressive tumor, defined as two or more carcinomas occurring simultaneously or successively in different parts of the esophagus. MPEC may be synchronous or metachronous depending on the interval between their diagnosis. Synchronous multiple primary esophageal carcinomas (SMPEC) were diagnosed simultaneously or within an interval of less than six months, and metachronous multiple primary esophageal carcinomas (MMPEC) were secondary

cancers that developed more than six months after diagnosis of the primary. At present, multiple primary carcinomas (MPC) are usually diagnosed according to the principle of Warren and Gates: (i) each lesion is histopathologically malignant; (ii) each lesion is separated by the normal mucosa; and (iii) each lesion is not the result of local extension or metastasis of another lesion.¹ Xiao *et al.* proposed X-ray imaging diagnostic criteria of MPEC: (i) X-ray imaging displays two or more typical tumor signs; (ii) each lesion is separated by the normal mucosa, with a distance of 4 cm or more; and (iii) one lesion located in the hypopharynx or cardiac is excluded.²

The aim of our study was to retrospectively analyze the clinical characteristics and prognostic factors of 52 SMPEC cases, in order to provide a treatment reference.

Methods

Patient selection

The institutional review board of our hospital approved this study. There were 56 SMPEC patients, accounting for about 1% of the total 5276 esophageal carcinoma patents hospitalized in the Tumor Hospital of Shantou University Medical College from 1 January 2003 to 31 July 2011. Fifty-two cases had complete clinical, pathologic, and follow-up data. All of the lesions had been histopathologically diagnosed as esophageal squamous cell carcinoma, except for seven cases with esophagostenosis. For these cases, at least one lesion case had been histopathologically diagnosed as esophageal squamous cell carcinoma and X-ray imaging diagnostic criteria by Xiao² was used complementally for the remaining lesions. Exclusion criteria: (i) one patient of the radiotherapy alone subgroup received a total dose of less than 40Gy; (ii) one patient of the chemotherapy alone subgroup received less than one cycle of chemotherapy; and (iii) two cases did not receive any anti-tumor therapy.

Upper endoscopy, upper gastrointestinal barium X-ray examinations, chest and abdominal enhanced-computed tomography (CT) scans were carried out for all of the enrolled patients prior to treatment.

Location of the primary cancer site was defined according to the American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) Classification of Carcinoma of the Esophagus (6th Ed, 2002). Lymph nodes were staged according to the AJCC TNM staging system for Carcinoma of the Esophagus (6th Ed, 2002) for patients with radical surgery. For patients without surgery, N stage was evaluated based on chest enhanced-CT image, abdominal enhanced-CT image or color Doppler ultrasonography.

The median length of involved lesions was judged by the pretreatment upper endoscopy. For the cases with esophagostenosis, chest enhanced-CT image or upper gastrointestinal barium X-ray imaging was used.

Treatment

All patients had signed informed consent forms before any treatment. Of the 12 patients who had undergone surgical resection, five pT3-4N1M0 patients received adjuvant radiotherapy and one had adjuvant radiochemotherapy, with a total dose of 40-60Gy/20-30 fractions and two cycles of platinum-based chemotherapy. The remaining 40 patients were medically unfit or refused surgery. Thirty-seven of the non-surgical patients received external beam radiation

therapy, with the median irradiation dose of 60Gy (range: 50-70Gy/25-35 fractions), and 20 of them received two to four cycles of platinum-based chemotherapy. The patients received a conventional-fraction schedule: 2Gy per fraction and five fractions per week with a 6-MV linear accelerator. Another three non-surgical patients were given platinum-based chemotherapy alone for advanced disease.

Follow-up

Overall survival (OS) time (from diagnosis to the point of death or the last follow-up) was calculated by month. Patient follow-up studies continued until 31 October 2012, mainly through outpatient review, phone calls, and letters.

Statistical analysis

Statistical analyses were performed using the SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). The rates of OS, depending on the different factors, were calculated using Kaplan-Meier analysis. A log-rank test was used for univariate survival analysis and Cox's proportional hazards regression model was used for multivariate survival analysis. A *P*-value of < 0.05 was considered statistically significant.

Results

Patient characteristics

Of the 52 SMPEC patients aged 40-78 years (median: 60 years), 41 were male and 11 were female, with a gender ratio of 3.7:1. Forty cases (76.9%) had a history of smoking.

Of the 108 lesions, there were 16 located at the cervical, 33 at the upper thoracic, 39 at the mid thoracic and 20 at the lower-thoracic segment of the esophagus. Of the 49 patients with double primary lesions, four were synchronous cervical associated with upper thoracic segment, 10 were synchronous cervical associated with mid thoracic segment, 17 were synchronous upper thoracic associated with mid thoracic segment, nine were synchronous upper thoracic associated with lower thoracic segment, and nine were synchronous mid thoracic associated with lower thoracic segment. Of the two patients with triple primary carcinomas, one was synchronous cervical associated with upper thoracic and mid thoracic segments and one was synchronous upper thoracic with mid thoracic and lower thoracic segments. There was one case of four primary carcinomas, located in the cervical, upper thoracic, mid thoracic, and lower thoracic segments.

Regional lymph node metastases (N1 stage) were found in 38 patients (73.1%), while the cervical (excluding cervical esophageal carcinoma patients with cervical lymph nodes) and/or celiac lymph nodes metastases (M1a stage) were found in eight patients (15.4%).

Figure 1 Survival curve for the 52 synchronous multiple primary esophageal carcinoma (SMPEC) patients.

The median length of all involved lesions was 9.5 cm (range: 3.8–17.5 cm). Of the 52 cases, eight were ≤ 5 cm, 23 were 6–10 cm, and 21 were >10 cm.

Overall survival

By 31 October 2012, after a median follow up of 15 months (two to 90 months), 44 patients had died, eight patients were still alive, and none were lost to follow-up. In the group which had expired, one (2.3%) died of infection of the upper respiratory tract, seven (15.9%) died of failure of local control and recurrence, five (11.4%) died of regional lymph node metastases, and 19 (43.2%) died of distant metastases (Fig. 1). In the remaining 12 cases, a reason for treatment failure (27.3%) could not be definitively ascertained because the follow-up feedback was not detailed enough. Table 1 shows the one, three, and five-year OS and the median survival time (MST) of the whole cohort and the subgroups.

Prognostic analysis for the whole cohort

Univariate survival analysis for the whole cohort

Patient gender, age, tumor length, smoking history, N stage, M stage, surgery, radiotherapy, and chemotherapy were put into univariate analysis. The MST of 47.0 months for cases with a tumor length of ≤ 5 cm was superior to that of 16.0 months for cases with a tumor length of 6–10 cm, and that of 10.0 months for cases with a tumor length of >10 cm ($P = 0.001$). Furthermore, the MST was superior for M0 stage cases (16.0 months) compared with M1a stage cases (7.0 months, $P = 0.008$), and for patients who underwent surgery (17.0 months) compared to non-surgical cases (14.0 months, $P = 0.045$). Other clinical features, such as gender, age, smoking history, N stage, radiotherapy, and chemotherapy did not show a statistically significant correlation with the prognosis ($P > 0.05$, Table 2).

Multivariate survival analysis for the whole cohort

Tumor length, M stage and surgery were put into multivariate analysis. As shown in Table 3, tumor length and M stage were independent prognostic factors for the whole cohort.

Prognostic analysis for the radiotherapy subgroup

Univariate survival analysis for radiotherapy subgroup

Of the 40 non-surgical patients, 37 received external beam radiation therapy and 20 of these patients also received platinum-based chemotherapy. The MST of 17.0 months for cases with a tumor length of ≤ 5 cm was superior to that of 15.0 months for cases with a tumor length of 6–10 cm, and that of 10.0 months for cases with a tumor length of >10 cm ($P = 0.029$). Furthermore, the MST was superior for M0 stage cases (16.0 months) compared to M1a stage cases (7.0 months, $P = 0.019$), and cases with chemotherapy (18.0 months) compared to cases without chemotherapy

Table 1 The overall survival (OS) one, three, and five-year survival rate of the whole cohort and treatment subgroups

Treatment	Number of patients	MST (months)		Survival rate (%)		
		Median	Range	1-year	3-year	5-year
Total number	52	15.0	2–90	65.4	17.3	7.7
Surgery	12	19.5	5–90	75.0	33.3	16.7
Non-surgery	40	14.5	2–73	62.5	10.0	5.0
Chemoradiotherapy	20	16.5	2–73	70.0	20.0	10.0
Radiotherapy alone	17	13.0	4–32	52.9	0.0	0.0
Chemotherapy alone	3	15.0	9–16	66.7	0.0	0.0

MST, median survival time.

Table 2 Prognostic factors by log-rank test and univariate survival analysis for the whole cohort

Factors	Group	Number of patients	MST (months, 95%CI)	X ² value	P value
Gender	Male	41	15.0 (11.863–18.137)	0.007	0.935
	Female	11	15.0 (7.032–22.968)		
Age	<60 years	25	14.0 (10.083–17.917)	0.502	0.479
	≥60 years	27	15.0 (12.045–17.955)		
Smoking history	Yes	40	15.0 (11.281–18.719)	0.044	0.834
	No	12	15.0 (11.653–18.347)		
Tumor length	≤5 cm	7	47.0 (0–118.855)	13.737	0.001
	6–10 cm	24	16.0 (14.258–17.742)		
	>10 cm	21	10.0 (7.037–12.963)		
N stage	N0	14	19.0 (10.473–27.527)	1.724	0.189
	N1	38	13.0 (10.584–15.416)		
M stage	M0	44	16.0 (13.288–18.712)	6.948	0.008
	M1a	8	7.0 (0.532–13.468)		
Surgery	Yes	12	17.0 (6.816–27.184)	2.632	0.045
	No	40	14.0 (11.344–16.656)		
Radiotherapy	Yes	44	14.0 (11.217–16.783)	1.844	0.174
	No	8	16.0 (14.152–17.848)		
Chemotherapy	Yes	24	16.0 (9.176–22.824)	0.901	0.343
	No	28	14.0 (11.407–16.593)		

MST, median survival time.

(13.0 months, $P = 0.047$). The other clinical features, such as gender, age, smoking history, and N stage did not show a statistically significant correlation with the prognosis ($P > 0.05$, Table 4).

Multivariate survival analysis for the radiotherapy subgroup

Tumor length, M stage, and chemotherapy were put into multivariate analysis. As shown in Table 5, they were all independent prognostic factors for the radiotherapy subgroup.

Discussions

SMPEC is far rarer than single primary esophageal carcinoma, with the incidence rate reportedly 1–30%. Our data showed that 52 of 5276 esophageal carcinoma patients (incidence 1%) were found to have SMPEC. The patients with SMPEC were more often male, with a gender ratio of 3.7:1 (male/female). The involved sites of the esophagus were more often at upper thoracic and mid thoracic segments, with the

incidence 33.6% (33/108) and 36.1% (39/108) respectively. These results were consistent with the previous study by Morita *et al.*³ Male patients could be more likely to devour foods, have poor eating habits, and have a history of simultaneous exposure to tobacco smoking and alcohol drinking. Shibuya *et al.* reported that the most commonly involved sites were the upper and mid thoracic segments of the esophagus, for foods went through these two segments first, and mucosa impaired most often.⁴

The data of the primary tumor (T) stage of the 12 surgical patients were available, however, data for the other 40 non-operative patients were unavailable because endoscopic ultrasound (EUS) was not performed. The relationship between T stage and prognosis could, therefore, not be identified.

The regional lymph node (N) stage for surgical patients was judged by numbers according to the latest American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) staging system for Carcinoma of the Esophagus and Esophagogastric Junction (7th Ed, 2010). However, the 2002 version (6th Ed) was used for most of the enrolled patients

Table 3 Multivariate survival analysis for the whole cohort

Factors	B value	SE	Wald	P value	RR	95% CI for RR	
						Lower	Upper
Tumor length	0.125	0.048	6.721	0.010	1.134	1.031	1.247
M stage	−0.743	0.416	3.191	0.047	0.476	0.211	0.751
Surgery	0.093	0.422	0.049	0.825	1.098	0.480	2.509

B-value, Regression coefficient; CI, Confidence interval; RR, Relative risk; SE, Standard error.

Table 4 Prognostic factors by log-rank test and univariate survival analysis for the patients with radiotherapy

Factors	Group	Number	MST (months,95%CI)	X ² value	P value
Gender	Male	29	13.0 (9.484–16.516)	0.735	0.391
	Female	8	15.0 (9.060–20.940)		
Age	<60 years	18	13.0 (8.842–17.158)	0.515	0.473
	≥60 years	19	15.0 (9.727–20.273)		
Smoking history	Yes	28	13.0 (7.828–18.172)	0.568	0.451
	No	9	15.0 (12.078–17.922)		
Tumor length	≤5 cm	4	17.0 (10.140–23.860)	2.432	0.029
	6–10 cm	14	15.0 (11.526–18.474)		
	>10 cm	19	10.0 (7.188–12.812)		
N stage	N0	11	19.0 (13.233–24.767)	0.814	0.367
	N1	26	13.0 (9.297–16.703)		
M stage	M0	30	15.0 (11.113–18.887)	5.536	0.019
	M1a	7	7.0 (4.434–9.566)		
Chemotherapy	Yes	20	18.0 (5.930–30.070)	4.153	0.047
	No	17	13.0 (6.950–19.050)		

MST, median survival time.

(40/52, 76.9%) who did not undergo surgery and, therefore, the data on lymph node numbers was lacking.

In a study by Pesko *et al.*, the most deeply infiltrating tumor was identified as the main tumor and the remainder were called associated lesions.⁵ They found that the deeper the main tumor infiltrated, the greater the chances of second lesion and lymph node metastases. That is, the main tumor had existed for some time and infiltrated deeply when multiple lesions were identified, with a high incidence of regional and non-regional lymph nodes. In our study, the regional lymph node metastases (N1 stage) were found in 38 patients (73.1%), while the cervical and celiac lymph nodes metastases (M1a stage) were found in eight patients (15.4%). The high incidence and wide distribution of lymph node metastases were one of the reasons for a low resection rate.

The one, three, and five-year OS of the whole cohort were 65.4%, 17.3%, and 7.7%, respectively, and 75.0%, 33.3%, and 16.7%, respectively, for the surgical subgroup. The one, three, and five-year OS of the 20 radiochemotherapy patients were 70.0%, 20.0%, and 10.0%, respectively. Survival data for MPEC patients was rare and variable in previous reports. Li *et al.* stated that there was no obvious difference between MPEC and esophageal single carcinoma cases in the lesion invasion depth and lymph node metastases.⁶ The three, five, and 10-year survival rates of post-operative MPEC patients

were 82%, 60%, and 50%, respectively. The author did not clarify the TNM stage of the MPEC cases, and in some cases there were synchronous lesions in other organs. Gao *et al.* reported the one, three, and five year survival rates of 40 MPEC patients who had been treated by radiotherapy alone, 10% of whom had supraclavicular lymph node metastases, were 45.0%, 16.7%, and 6.7%, respectively.⁷ Our survival data was comparable to Gao's, owing to the similar constituent ratio of M1a patients. While the one, three, and five-year survival rates of the esophageal single carcinoma patients of the same period in our hospital were 71.0%, 33.1%, and 26.2%, respectively,⁸ SMPEC appears to have a poorer prognosis than esophageal single carcinoma.

In a study by Huang *et al.*, univariate analysis and multivariate analysis of prognostic factors identified that curative resection was one of the predominating independent predictors of long-term survival of synchronous gastric adenocarcinoma associated with squamous carcinoma of esophagus.⁹ In our univariate analysis, tumor length (≤5 cm/6–10 cm/>10 cm) ($P = 0.024$), M stage (M0/M1) ($P = 0.008$), and surgery (Yes/No) ($P = 0.045$) significantly influenced the OS of SMPEC patients. The median OS was superior for surgical patients (17.0 ± 5.196 months) compared to non-surgical patients (14.0 ± 1.355 months, $P = 0.045$). But multivariate survival analysis by Cox's proportional hazards regression

Table 5 Multivariate survival analysis for the radiotherapy subgroup

Factors	B value	SE	Wald	P value	RR	95% CI for RR	
						Lower	Upper
Tumor length	0.136	0.066	4.245	0.039	1.146	1.007	1.304
M stage	−1.122	0.490	5.248	0.022	0.326	0.125	0.850
Chemotherapy	1.065	0.414	6.620	0.010	2.901	1.289	6.531

B-value: Regression coefficient; CI, Confidence interval; RR, Relative risk; SE, Standard error.

model identified that only tumor length and M stage were independent prognostic factors for the whole cohort ($P = 0.010$, 0.047 , respectively). This may be a result of the small sample size and the confounding factors of a low resection rate (23.1%, 12/52), early stage without M1a in the surgical subgroup, and different post-operative adjuvant treatments. Further research is needed to determine the significance of surgery in SMPEC cases.

In meta-analysis by Rebecca *et al.*, concluding 769 patients of eight concomitant radiotherapy and chemotherapy (RTCT) studies, concomitant RTCT provided a significant overall reduction in mortality and recurrence rate at one and two years than radiotherapy alone.¹⁰ The RTOG 85-01 trial confirmed that, for locally advanced esophageal cancer patients, combined radiotherapy and chemotherapy could prolong five-year survival time, compared to radiotherapy alone (27% vs. 0%).¹¹ For the radiotherapy subgroup patients in this study, multivariate survival analysis by Cox's proportional hazards regression model identified that chemotherapy was an independent prognostic factor ($P = 0.010$). And as shown above, distant metastases accounted for the first of the treatment failure elements. For the SMPEC patients with unfavorable features, such as clinical T4 cancer and/or patients who were not expected to withstand surgery, combined chemotherapy to radiotherapy may improve radiation sensitivity and eliminate metastases and micro metastases, resulting in a survival benefit.

There were some obvious limitations of our study: (i) part lesions were not histopathologically diagnosed with esophagostenosis, but were diagnosed according to X-ray imaging diagnostic criteria by Xiao; (ii) we could not offer the accurate T stage data for the non-operative patients because of a lack of EUS; (iii) the significance of surgery for SMPEC cases is not yet clear; and (iv) the treatment recommendations of our retrospective study need to be confirmed by further prospective randomized clinical trials.

Conclusion

In summary, SMPEC is a relatively rare and aggressive tumor, with distinct clinical characteristics. Prognosis for SMPEC is worse than esophageal single carcinoma, with distant metastases accounting for the first of the treatment failure elements. No standard treatment has ever been established. Combined radiotherapy with chemotherapy seemed to

provide a survival benefit and should be considered for the management of unresectable and non-operative SMPEC.

Disclosure

No authors report any conflict of interest.

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