

SURGICAL TREATMENT OF PRIMARY ESOPHAGEAL SMALL-CELL CARCINOMA

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ABSTRACT

Objective: To study the clinical biocharacteristics of primary esophageal small-cell carcinoma (PESC) and factors influencing prognosis and to find rational indications for combination therapy. **Methods:** To analyze the clinical materials of 47 patients who had undergone an operation with PESC and to compare it with those patients with esophageal squamous-cell carcinoma (ESCC) or primary esophageal adenocarcinoma (PEAC). **Results:** The overall resectability, morbidity and 30-day mortality rates of PESC were 93.6%, 17.0% and 2.1% respectively, similar to those of ESCC or PEAC. TNM staging and lymph node metastasis were the major determinants influencing long-term survival. Tumor length, depth of tumor invasion and type of operation had little influence on long-term prognosis. The 5-year survival rate of PESC was 7.5%, which was much lower than that of ESCC and PEAC ($P < 0.01$). Among the 42 deceased patients, one died of anastomotic leakage and the others died of remote metastasis and recurrence. Adjuvant chemotherapy did not help improve the patients' long-term survival. **Conclusions:** Compared with ESCC and PEAC, PESC is the most malignant type with early lymphatic and hematogenous metastases and poor prognosis. Lymph node metastasis is the major factor influencing the prognosis. Patients in stage 0, I and II a of PESC are indicated for surgical resection, while those in stage II b, III or IV should be managed with non-surgical combined therapy.

Key words: Esophageal carcinoma, Small-cell carcinoma, Squamous-cell carcinoma, Adenocarcinoma, Prognosis

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Primary esophageal small-cell carcinoma (PESC) is a rare malignant disease of esophagus. Because of its high malignancy and ability of invasion and early lymphatic and hematogenous metastases, the prognosis is poor. From 1974 to 1996, 47 patients with PESC had been treated surgically in our department. In order to understand the characteristics of PESC, the results of their treatment were analyzed and compared with those of the patients with esophageal squamous-cell carcinoma (ESCC)^[1] or with primary esophageal adenocarcinoma (PEAC)^[2] treated in our department.

CLINICAL MATERIALS

General Clinical Data

From 1974 to 1996, 47 patients with PESC had been treated surgically in our department, including 38 men and 9 women, with a ratio of 4.2:1, with an average age of 56.2 years (45-68 years). They accounted for 1.4% (47/3405) of the patients with esophageal malignant disease operated in our department. The clinical symptoms, manifestations of barium esophagogram were similar to those of ESCC. According to the classification of the segments of esophagus as defined by UICC in 1987, the distribution of tumor sites located at cervical, thoracic higher, middle and lower segments were 2.1% (1/47), 10.6% (5/47), 55.3% (26/47) and 31.9% (15/47) respectively. 23 patients were taken endoscopic biopsy and 13 were taken cytological examination of esophageal balloon. The correct diagnosis rates of both of them were 34.8% (8/23) and 38.5% (5/13) separately.

The Approach of Operation, Resectability Rates, Clinicopathological Types and TNM Staging

All 47 patients underwent an operation and the

stomach was used as the substitute for the esophagus. 6 of them had an esophagectomy with cervical anastomosis by left thoracic and cervical incisions. 31 had esophagectomy with supraaortic anastomosis and 6 with infraaortic anastomosis by left thoracotomy. One had esophagectomy with cervical anastomosis by inversion extraction and 3 had exploration alone. The overall resectability and radical resectability rates were 93.6% (44/47) and 83.0% (39/47) respectively. The morbidity and 30-day mortality rates were 17.0% (8/47) and 2.1% (1/47) separately.

Pathological examination was done on all the postoperative specimens and the diagnosis was conformed to the pathological diagnostic criteria of small-cell carcinoma defined by WHO. Immunohistological staining was done for 7 patients. The positive results were EMA 7 cases, kratin 1 case and NSE 3 cases. Of the 44 patients with tumor resection, the clinicopathological types were medullary 19 cases, fungating 14 cases, intraluminal 8 cases, ulcerating 1 case and early stage 2 cases. Of the 47 patients with PESC, the clinicopathological staging was stage I, 4 cases; stage IIa, 6 cases; stage IIb, 7 cases; stage III, 28 cases; stage IV, 2 cases. The percentage of the patients of stage IIa of PESC was 12.8% (6/47), which was lower than those of ESCC and PEAC. The percentage of the patients of stage IIb was 14.9% (7/47), which was higher than that of ESCC ($P < 0.01$).

The Followed-up

All the patients were followed up after their operations, but 2 were lost in the course of the followed-up. The follow up rate was 95.8% (45/47). The overall 1-yr, 3-yr, 5-yr and 10-yr survival rates of patients with PESC after their operations were 40.4% (19/47), 13.3% (6/45), 9.1% (4/44) and 7.5% (3/40). Among the 42 deceased patients, one died of anastomotic leakage and others died of remote metastasis and recurrence.

Prognostic Factors

The postoperative 5-yr survival rate of 40 patients showed that the chief factors influencing the prognosis with PESC were TNM staging and lymph node metastasis (Table 1). The 5-yr survival rate of the patients with stage I or stage IIa (3/9) was higher than that of the patients with stage IIb, stage III or stage IV (0/3 1, $P < 0.01$). The 5-yr survival rate of the patients without lymph node metastasis (3/10) was higher than that of those with lymph node metastasis (0/30, $P < 0.02$). Extraesophageal invasion, the nature of operation and tumor length had little influence on long-term prognosis. The lymph node metastasis rate of 44 patients with tumor resection was 65.9% (29/44). The situation of lymph node metastases of

43 patients with thoracic segments of PESC is shown in Table 2.

Adjuvant Therapy

Among 47 patients with PESC, 24 patients accepted postoperative chemotherapy (COMVp, CAP or CE regimen). The mean postoperative survival time of them was 17.1 months, which was similar to the 16.5 months of the 19 patients with only an operation alone. 3 patients accepted preoperative irradiation (40 Gy) and one patient accepted postoperative radiotherapy (60 Gy).

DISCUSSION

Incidence

The incidence of PESC is much lower than that of ESCC. According to literatures, patients with PESC were 0.05%–5.5% of all patients with esophageal malignant diseases.^[3, 4] In our study, the 47 patients with PESC accounted for 1.4% of all patients with esophageal malignant diseases treated in our department at the same period, which was lower than the 2.8% of PEAC. The ratio of men to women was 4.2:1 and the average age was 56.2 years, like those of ESCC and PEAC.

Histological Origin

The histological origin of PESC has been a controversial topic for a long time. Ibrahim et al.^[5] considered that like the small-cell carcinoma of the lungs, PESC came from the neuroendocrine system, namely the so called APUD cell. On the other hand, APUD cell was also found histologically in esophageal mucosa. Ho et al.^[6] argued that PESC, ESCC and PEAC all originated from the multipotential primitive stem cells of esophageal mucosa and were the results of different differentiations of multipotential primitive stem cells after carcinogenesis. During recent years, some authors have held that the APUD cell of the alimentary tract was not from neural crest but from endoderm, like the origin of epithelium of alimentary glands, namely the multipotential primitive stem cells.^[7] In a word, the histological origin of PESC needs further study.

Clinical Manifestations and Biocharacteristics

The symptoms, manifestations of barium esophagogram and FOE (fibro-optic esophagoscopy) findings of PESC are similar to those of ESCC and PEAC. The incidence of clinicopathological types of PESC is different from those of ESCC. In our material, the

percentage of the patients with fungating type or intraluminal type was 50.0%, similar to the 45% in

literature reports^[8] but higher than the 18.5% of ESCC treated in our department.

Table 1. Factors influencing the patients' prognosis of PESC

Factors	No. of patients	5-year survival		P
		No. of patients	%	
Staging				
I	3	1	1/3	<0.01
IIa	6	2	2/6	
IIb	5	0	0/5	
III	24	0	0.0	
IV	2	0	0/2	
Lymph node metastasis				
No	30	0	0.0	<0.02
Yes	10	3	30.0	
Extraesophageal invasion				
No	15	0	0.0	>0.05
Yes	25	3	12.0	
Methods of operation				
Curative	32	3	9.4	>0.05
Palliative/explorative	8	0	0/8	
Tumor length				
<3 cm	6	1	1/6	>0.05
3-5 cm	14	1	7.8	
>5 cm	20	1	5.0	

Table 2. Incidence of lymph node metastasis in 43 patients with PESC resected

Site of tumor	Positive nodes by site (%)		
	Cervical	Mediastinal	Abdominal
Upper third	0	40.0 (2/5)	20.0 (1/5)
Middle third	0	79.2 (19/24)	16.7 (4/24)
Lower third	0	57.1 (8/14)	57.1 (8/14)

PESC is a highly malignant disease with rapid progression and poor prognosis. In our study, the 1-yr, 3-yr and 5-yr survival rates of PESC were 40.4%, 9.1% and 7.5% respectively, which were lower than those of ESCC and PEAC ($P < 0.01$). The high malignancy of PESC displays itself mainly with early and extensive lymph node and hematogenous metastases. According to Mandard's autopsy results of 25 patients who died of PESC, the local lymph node metastasis rate and hematogenous metastasis rate were 91% and 87% separately. In our study that the lymph node metastasis rate was as high as 65.9% and the percentage of the patients with stage IIa disease was much lower than those of ESCC and PEAC. Also the percentage of the patients with stage IIb disease was much higher than that of ESCC

and it revealed that the lymph node metastasis of PESC was early and its rate was high. The lymph node metastasis pattern of PESC is different from that of PEAC. Especially in those patients with a tumor located in the middle thoracic segment of esophagus, the metastasis rate of abdominal lymph nodes of PESC was only 16.7%, which was lower than that of PEAC but similar to that of ESCC. This is seemingly discompartible with the features of high malignancy of PESC, so that we infer the metastasis rate of supraclavicular lymph nodes of PESC was higher than that of ESCC. Because of no patients with supraclavicular lymph node metastases in our study, who abstained from operation, this point remains to be confirmed. The high malignancy of PESC is also manifested by its early hemotogenous metastases. In our

study, most of the patients died of distant metastasis after their operation.

The extraesophageal invasion rate of PESC in our material was 36.2%, which was higher than those of ESCC and PEAC. But different from ESCC and PEAC, the depth of tumor invasion had little influence on the long-term survival of the patients with PESC. This was verified by the comparison of the mean postoperative survival times of the patients with stage IIb disease and with stage III disease. In our material, the mean postoperative survival time of the patients with stage IIb of PESC was 10.2 months, which was a little longer than the 9.5 months of the patients with stage III disease (There was only one patient with T₄N₀M₀ disease). Different from ESCC and PEAC, though the types of the operative procedures had some influence on the mean postoperative survival time of the patients with PESC, it had little effect on the long-term survival of the patients due to the rapid progression of PESC.

Surgical Treatment and Combination Therapy

There were different views about surgical treatment for PESC. Some authors hold that because PESC was prone to early metastasis and turned into systemic disease of the body, non-surgical treatment should be used. Mori et al.^[9] maintained that because of lacking of effective chemotherapy medicines and regimens, surgical resection should be done to the patients with a limited disease. In our material, most of the patients with PESC died within one year after operation and the patients who survived longer than two years usually were those with stage I or stage IIa disease. The mean postoperative survival time of the patients with stage IIb, stage III or stage IV was 9.2 months and only one of them survived longer than two years. From the above results, we consider that surgical indications should include only those patients with stage 0, stage I or stage IIa of PESC. In order to make precise preoperative TNM staging, trans-abdominal ultrasonography, thoracic and abdominal CT scanning and ultrasonic FOE test should be taken by the patients with PESC. This is very important for examining the surgical

indications. Non-surgical treatment should be used if lymph node metastasis is found.

Because of early lymphatic and hemogenous metastases, PESC easily turns into systemic disease of the body and make the local treatments such as surgical resection and irradiation ineffective. Even though the results of chemotherapy of PESC were not satisfying, combined therapy still should be emphasized. That the average postoperative survival time of the patients with chemotherapy in our material was not prolonged revealed that the medicines and regimens we used were ineffective. Therefore, to find effective medicine and regimen and to find rational combined therapy are the direction to take in out work in treating PESC.

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