

SURGICAL TREATMENT OF PRIMARY ESOPHAGEAL ADENOCARCINOMA

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Abstract

Objective: To study the biocharacteristics of primary esophageal adenocarcinoma (PEAC) and factors influencing patients' prognosis and to find rational surgical indications and combined therapy. **Methods:** To analyze the clinical material of 106 patients with PEAC and compared with that of patients with esophageal squamous-cell carcinoma (ESCC). **Results:** The overall resectability, morbidity and 30-day mortality rates of PEAC were 92.5%, 23.5% and 2.8% respectively, similar to those of ESCC. The TNM staging, lymph node metastasis, extraesophageal invasion and the nature of operation were major determinants influencing long-term prognosis. The 5-year survival rate of PEAC was 21.0%, which was lower than that of ESCC ($P < 0.01$). Metastasis or recurrence remained to be the cause of death in 82.4% of patients who lived longer than 5 years, which was higher than that of ESCC ($P < 0.01$). Adjuvant radiation did not influence survival of the patients with lymph node metastasis, but appeared helpful to the patients with no lymph node metastasis. **Conclusion:** compared with ESCC, PEAC is a malignant disease with poor prognosis. Surgical resection is the first and chief choice of treatment. Surgical indications include patients in stage 0, I, II and some in stage III and even in stage IV of PEAC. Early detection, early diagnosis and early treatment as well as radical operation could improve prognosis. Adjuvant radiotherapy appears helpful only to the patients without lymph node metastasis.

Key words: Esophageal neoplasm, Adenocarcinoma surgery, Carcinoma, squamous cell, Combined therapy, Prognosis.

Primary esophageal adenocarcinoma (PEAC) is a rare malignant disease of esophagus. Because of its lower incidence, the knowledge about it is limited and there are some problems requiring further study. During recent 30 years, 106 patients with PEAC had been treated surgically in our department. In order to understand characteristics of PEAC, the results of treatment were analyzed and compared with those of 3603 patients with esophageal squamous-cell carcinoma (ESCC) treated in our department within same period.^[1]

CLINICAL MATERIALS

General Clinical Data

During recent 30 years, 106 patients with PEAC had been treated with operation in our department: including 87 men and 19 women, in a ratio of 4.6:1, with an average age of 54.4 years. They accounted for 2.8 percent (106/3781) of the patients with esophageal malignant disease operated in our department. The pathological diagnoses of the 106 patients consisted of adenosquamous carcinoma (adenoacanthoma) 66 cases, adenocarcinoma, type ordinaries 33 cases, adenoid cystic carcinoma 5 cases and mucoepidermoid carcinoma 2 cases. The clinical symptoms, manifestations of barium esophagogram and FOE (fibropticoscopy of esophagus) findings as well as clinicopathological types of PEAC were similar to those of ESCC. According to the segments of esophagus as defined by 1987 UICC classification, the distribution of tumor sites located at cervical,

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thoracic higher, middle and lower segments were 1.9% (2/106), 9.4% (10/106), 54.7% (58/106) and 34.0% (36/106) respectively. The percentage of PEAC located at the lower thoracic segment was higher than that of ESCC ($P<0.01$).

The Approach of Operation, TNM Staging, and Resectability Rates

All the 106 patients were treated with operation. The overall resectability and radical resectability were 92.5% (98/106) and 71.7% (76/106) respectively, equal to those of ESCC. The 30-day mortality and morbidity rate were 2.8% and 23.5% respectively, similar to those of ESCC. The approach of operation depended upon the location of tumor, possible difficulty encountered during operation and the patient's general condition, like those of ESCC. The percentage of various approaches of operation and the ratio using stomach or colon as esophageal substitutes were similar to those of ESCC. According to the guidelines of TNM classification published by the UICC in 1987, the clinicopathological TNM staging

and resectability rates of each stage of 106 patients with PEAC were showed in Table 1. The resectability rates of each stage of PEAC were similar to those of ESCC, but the percentage of patients of stage IIb of PEAC was higher than that of ESCC ($P<0.01$).

Prognostic Factors

The postresectional 5-year survival rates of 92 patients showed that chief factors influencing the patients' prognosis with PEAC were TNM staging, lymph node metastasis, tumor infiltration and the nature of operation. The length and differentiation of tumor did not influence the patient's prognosis (Table 2). The lymph node metastasis rate of 96 patients was 50.0%. The situation of lymph node metastasis was shown in Table 3. The 5-year survival rates of patients with adenosquamous carcinoma, adenocarcinoma, adenoid cystic carcinoma and mucoepidermoid carcinoma were 22.0% (13/59), 25.9% (7/27), 25.0% (1/4) and 0.0% (0/2) respectively. No significant statistical difference could be detected among them ($P>0.05$).

Table 1. TNM staging and resectability rates of each stage of the 106 patients with PEAC

Staging	No. of Pts	%	Resection	
			No. of Pts	%
I	5	4.7	5	100.0
IIa	38	35.9	38	100.0
IIb	11	10.4	11	100.0
III	47	44.3	40	85.1
IV	5	4.7	4	80.0

Radiotherapy

Among 106 patients with PEAC, 10 patients accepted preoperative irradiation (40Gy). The 5-year survival rate was 50.0%. Although there were 7 cases of stage I and stage IIa among them, their 5-year survival rate of 57.1% was significantly higher than that of patients having corresponding stages but without preoperative radiotherapy. Nine patients accepted postoperative radiotherapy (60Gy). Only one of them with stage IIa survived longer than 5 years.

The Follow up

102 patients were followed up after operation. The follow up rate was 96.2% (102/106). The overall 1-yr, 3-yr, 5-yr, and 10-yr survival rates of patients with PEAC after operation were 69.8% (74/106), 33.3% (34/102), 21.0% (21/100) and 16.9% (11/65) respectively, much lower than those of ESCC. The mean postoperative survival time of

8 patients without tumor resection was 3 months. The mean postoperative survival time of 4 patients with remote metastasis (M_1) whose tumor was resected was 16.5 months. The majority of the patients with PEAC died of tumor metastasis or/and recurrence. The rate of the patients died of metastasis or/and recurrence 5 years after operation was 82.4% (14/17), significantly higher than the 60.9% of ESCC ($P<0.01$).

DISCUSSION

Incidence

The incidence of PEAC is much lower than that of ESCC. According to the literatures, the patients with PEAC were 0.4% to 18.0% of all the patients with esophageal malignant disease, and the incidence has a tendency to increase.^[2,3] In our material, the 106 patients with PEAC accounted for 2.8% of all the patients with esophageal malignant

disease treated in our department at the same period. It was much lower than the 95.3% of ESCC. The ratio of men to women was 4.6:1.0, higher

than the 3.6:1.0 of ESCC. The average age of patients with PEAC was 54.4 years, like the 55.4 years of ESCC.

Table 2. Factors influencing the patients' prognosis of PEAC

Factors	No. of Pts	5-year survival		P
		No. of Pts	%	
Staging				
I	3	2	66.7	
IIa	36	13	36.1	
IIb	10	2	20.0	<0.01
III	40	4	10.0	
IV	3	0	0.0	
Lymph node metastasis				
No	43	15	34.9	
Yes	49	6	12.3	<0.05
Extraesophageal invasion				
No	70	20	28.6	
Yes	22	1	4.6	<0.05
Nature of operation				
Curative	70	20	28.6	
Palliative	22	1	4.6	<0.05

Table 3. Incidence of lymph node metastasis in 96 PEAC patients treated with surgery

Site of tumor	Positive nodes by site (%)		
	Cervical	Mediastinal	Abdominal
Upper third	0	20.0 (2/10)	10.0 (1/10)
Middle third	0	47.2 (25/53)	30.2 (16/53)
Lower third	0	57.6 (19/33)	54.6 (18/33)

Histological Origins

The histological origins of PEAC have been a controversial topic for a long time. On general, there are three proposals of PEAC, namely: glands of esophagus itself, aberrant mucosa of stomach and the columnar epithelium of the lower segment of esophagus (Barrett's esophagus). Most western authors maintained that Barrett's esophagus was the major origin of PEAC. Some authors of our own country argued that Barrett's esophagus had little to do with PEAC, because the distributions of tumor sites of their material were different with those of western authors.^[4] In our material, the distribution of the tumor sites of PEAC was not only outwardly different from those of reports of western authors', but also different from that of ESCC treated in our department at corresponding period. The percentage that PEAC located in the lower segment of esophagus was higher than that of ESCC. This revealed that Barrett's esophagus is an important origin of PEAC, even though it is not the major ones. In our material, only 3

cases were reported with reflux esophagitis by postoperative pathological diagnosis. This maybe due to the diagnostic difficulty of Barrett's esophagus after the malignant change of the columnar epithelium of lower segment of esophagus.

Recently, some authors hold that PEAC, ESCC as well as primary small-cell carcinoma of esophagus are all originated from the multipotential primitive stem cells of esophageal mucosa. This view makes the explaining of the origin of adenoacanthoma much easier. From this view, adenoacanthoma is the result of two different differentiating processes of the same multipotential stem cell.^[5]

Clinical Manifestations and Biocharacteristics

The symptoms, manifestations of barium esophagogram and FOE findings as well as gross pathological types of PEAC are similar to those of ESCC. According to most references, PEAC is a highly malignant disease with rapid progression and poor prognosis. In our material, the 5-yr and 10-yr

survival rates of PEAC were 21.0% and 16.9% respectively, much lower than those of ESCC ($P < 0.01$). The high malignancy of PEAC displays itself in three aspects: extensive tumor infiltration, more lymph node metastasis and farther site of metastasis. In our material, the 5-yr survival rates of the patients of stage IIa and the patients with extraesophageal invasion were much lower than those of the patients of stage I and the patients without extraesophageal invasion respectively. This indicates that depth of infiltration of PEAC is an important factor influencing patients' prognosis, and its influence is stronger than that of ESCC. As high as 50.0% of our patients had lymph node metastases and the higher percentage of the PEAC patients were stage IIb comparing with that of ESCC dictated that lymph node metastasis of PEAC occurred more earlier and frequent. The lymph node metastasis pattern of PEAC is also different from that of ESCC. Especially those patients with tumor located in the lower thoracic segment of esophagus, the metastasis rate of abdominal lymph nodes was 30.2%, which was higher than the 17.9% of ESCC ($P < 0.05$). The jumping metastasis rate of lymph nodes of PEAC was 6.1%. The high malignancy of PEAC is also manifested by the early hematogenous metastasis and the high percentage of postoperative recurrences and metastases. In our material, 82.4% of the patients who lived longer than 5 years postoperatively was died of recurrence or/and metastasis, higher than that of ESCC, and most of metastases were remote ones.

The pathological types of PEAC had little influence on the prognosis of PEAC, evidenced by the 5-yr survival rates with difference of no statistical significance.

Surgical Treatment

Surgical resection is the first choice of treatment of PEAC. As regard to the approach of operation, Bai et al.^[2] maintained that the PEAC tend to have extensive submucous infiltrating and the subtotal esophagectomy with cervical anastomosis should be performed. Simon et al.^[6] argued that the multifocus origins of PEAC and its submucous invasions were less than those of ESCC, and a resection margin greater than 2 cm was safe. In our series, the criteria of choosing operative approach of PEAC were the same as those of ESCC, and the rates of residual tumor at cut edges were similar.

According to our material, the main factors influencing the prognosis of PEAC were TNM staging, lymph node metastasis, extraesophageal invasion of tumor and the nature of operation. This was incompatible with Chen et al.^[7] report that lymph node metastasis did not influence the prognosis. In order to promote the long-term survival rates of PEAC, early finding, early diagnosis and early treatment should be

stressed and the extended lymph node dissection and the "cleanness" of resection of tumor should be underlined.

Because of the insensitiveness to irradiation and the lacking of effective chemotherapy drugs, the surgical treatment of PEAC should be much more emphasized than that of ESCC in our opinion. Surgical indications should include the patients with stage 0, I, II and some in stage III and even in stage IV of PEAC. Especially with those patients undergoing exploration, efforts should be made to resect tumor if it was possible even though the patient had distant metastasis (M_1). This not only could relieve the dysphagia, but also provide basis of implementing other therapeutic regime. That the postoperative mean survival time of 4 patients with distant metastasis (M_1) but with resection was much longer than that of 8 patients without tumor resection in our material is a good proof for this attitude.

Combined Therapy

The study about adjuvant treatment of PEAC is keeping on. Robert et al.^[8] reported that adjuvant chemotherapy had little effect on the patients' prognosis. Steven et al.^[9] reported that preoperative radiotherapy played a role in preventing tumor's local recurrence but had no effect on preventing remote metastasis. The patients with preoperative or postoperative radiotherapy in our material were few, but the results convinced us that irradiation might have some help to the patients with no lymph node metastasis but have no help to those with N_1 . Because of early lymph node metastasis and tendency of abdominal lymph node metastasis, the precise preoperative TNM staging of PEAC is difficult to make even with the help of routine thoracic and abdominal CT scan. On the other hand, PEAC is insensitive to chemotherapy and radiotherapy, and both of them have definite side effects. For these reasons, the using of adjuvant radiotherapy and chemotherapy should be considered carefully, and should be planed after operation. In order to find rational combined therapy of PEAC, we should try postoperative irradiation for the patients with N_0 and give tentative adjuvant chemotherapy to patients with extensive lymph node metastases or/and distant metastases.

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