

Prognostic factors in patients with thoracic esophageal carcinoma staged pT_{1-4a}N₀M₀ undergone esophagectomy with three-field lymphadenectomy

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Background: To analyze prognostic factors in patients with thoracic esophageal carcinoma staged pT_{1-4a}N₀M₀ and undergone esophagectomy with 3-field lymphadenectomy and to evaluate the effect of postoperative radiotherapy.

Methods: From January 1993 to March 2007, 770 patients with stage pT_{1-4a}N₀M₀ underwent 3-field lymphadenectomy at Fujian Province Cancer Hospital, China were enrolled for analysis. The study consisted of 770 patients with stage pT_{1-4a}N₀M₀ who underwent 3-field lymphadenectomy at Fujian Province Cancer Hospital, China. A total of 687 had received surgery only, and 83 patients had undergone surgery followed by postoperative radiotherapy. Radiation dose was 50 Gy in 25 fractions.

Results: The overall survival rates at 1, 3, 5, and 10 years were 92.9%, 80.8%, 71.7% and 57.4%, respectively. Univariate analysis showed that age and T staging were two independent factors on prognoses. Five-year survival in cases younger and older than 60 were 76.5% vs. 63.3% (P=0.001), while those of pT₁, pT₂, pT₃, and pT_{4a} were 83.8%, 78.8%, 67.8% and 54.1%, respectively (P=0.000). Five-year survival in group of simple surgery was 71.3%, compared with 74.5% in group of surgery plus postoperative radiotherapy (P=0.763), while stratified analysis indicated that postoperative radiotherapy was able to boost the survival of patients in pT_{4a} which were 72.4% vs. 33.8% (P=0.036) and to lower relapse rate of tumor bed in patients with pT_{4a} (P=0.005). Multivariate analysis showed that age and T staging were two independent factors on prognoses.

Conclusions: Patients with high T staging and at an age more than 60 turned out bad prognoses, neither could postoperative radiotherapy improve their survival.

Keywords: Esophageal squamous cell carcinoma; 3-field lymphadenectomy; prognosis; adjuvant radiotherapy

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Introduction

Esophageal cancer is one of the most common malignancies in china, accounting for around 50% of incidence worldwide (1). Surgery is still one of the principal treatment methods for patients with esophageal cancer. Patients with

thoracic esophageal cancer were found to have relatively high cervical lymph node metastasis rate, ranging from 17.2% to 49.5% (2-4). The number of metastatic lymph nodes is a principal prognostic factor predicting the outcome of surgery (5,6). While report based on mass

cases had never been found on prognostic factors in patients neither with lymph node metastasis nor distant metastasis ($pT_{1-4a}N_0M_0$). Compared with traditional 2-field lymphadenectomy, esophagectomy plus lower cervical, mediastinal and upper abdominal lymph node resection, i.e., 3-field lymphadenectomy exhibits better surgical exposure, and is also considered to play a pivotal role in understanding the nodal metastatic pattern, and determining postoperative staging as well (2-4).

Materials and methods

Patient population

Seven hundred and seventy patients, diagnosed of thoracic esophageal squamous cell carcinomas only, had undergone subtotal esophagectomy plus 3-field lymphadenectomy, and pathologically staged of $pT_{1-4a}N_0M_0$ were entered into the study to find out the possible prognostic factors and the value of prophylactic postoperative radiotherapy. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Fujian Provincial Cancer Hospital. All patients provided written consent for storage of their information in the hospital database and for use of this information in our research.

Patients were involved in this study if they: (I) had received radical esophagectomy and 3-field nodal dissection in the first treatment; (II) had no evidence of distal hematogenous metastasis found in preoperative chest CT scanning, abdominal CT scanning and systematic ECT bone scanning; (III) with a strictly pathological diagnosis of squamous cell carcinoma only and no evidence of nodal metastasis; (IV) had not received radiotherapy or chemotherapy before surgery or chemotherapy after surgery; and (V) had untaken more than 15 lymph nodes removed in surgery. From January 1993 to March 2007, 2,665 patients with thoracic esophageal squamous cell carcinoma were treated with surgery at Fujian Province Cancer Hospital, Fuzhou, Fujian, China. A total of 1,090 cases of pathological diagnosis of lymph node metastasis, only 770 cases met with our criteria, 320 were excluded from this analysis for having received preoperative chemotherapy or radiation (156 cases), postoperative chemotherapy or postoperative concurrent chemoradiation (30 cases), surgical procedures other than an extended esophagectomy with 3-field lymphadenectomy that included removal of at least 15 nodes (126 cases), having had other malignancies before the diagnosis of esophageal cancer, or

having had disease of mixed histology (4 cases), R2 resection (4 cases). Of those 770 patients, 687 had received surgery only (aged 28-84 years, median 57 years), and 83 patients had undergone surgery followed by postoperative radiation therapy (aged 32-78 years, median 53 years). Altogether, 18,893 nodes had been removed, with a mean of 24.5 nodes per patient (range, 15-68).

Surgical procedure

The surgery included a subtotal esophagectomy, together with cervico-thoraco-celiac (3-field) lymphadenectomy. It started with a right posterolateral thoracotomy through the 5th intercostal space. When the thoracic maneuver was completed, the patient was repositioned for median laparotomy and cervical lymph node resection by means of a collar incision. Lymph node stations dissected in the superior mediastinum included the right and left pararecurrent laryngeal nerve nodes, the paratracheal nodes, and the paraesophageal nodes, in the mid-mediastinum included the subcarinal nodes and the paraesophageal nodes, and in the inferior mediastinum included the paraesophageal nodes and the diaphragm nodes. Lymph node stations dissected in the abdomen included the paracardiac nodes, the lesser curvature nodes, and the left gastric artery nodes. Lymph node stations dissected in the neck included the right and left supraclavicular nodes and cervical paraesophageal nodes (the deep cervical nodes) (2).

Radiotherapy methods

Radiotherapy was started 3-4 weeks postoperatively. The median radiation dose to the tumor bed was 50 Gy in 25 fractions at 2 Gy per fraction, 5 days a week.

Statistical analysis

The various clinical features of patients with esophageal cancer were input into the computer. Overall survival was calculated from the day of surgery to day of death or day of loss of follow-up or final day of follow-up. Follow-up and Survival condition Statistical analysis was performed using SPSS 15.0 (SPSS, Inc., Chicago, IL). Kaplan-Meier analysis was performed to estimate the survival rate, and the log-rank test was performed to calculate significance. Cox proportional hazards analysis was performed to calculate the hazard ratio (HR) and CI. The χ^2 test was used to compare the reasons of treatment failure between two groups.

Table 1 Univariate analysis of prognostic factors

Variable	No. of patients (%)	3-year survival rate (%)	5-year survival rate (%)	10-year survival rate (%)	HR (95% CI)	P value
Sex						0.141
Male	515 (66.9)	79.5	70.2	52.7	1.000 (ref)	
Female	255 (33.1)	83.8	75.1	65.5	0.795 (0.586-1.079)	
Age						0.001
<60	481 (62.5)	84.6	76.5	60.6	1.000 (ref)	
≥60	289 (37.5)	74.4	63.3	52.0	1.616 (1.229-2.125)	
Tumor location						
Upper thorax	128 (16.6)	87.3	75.5	59.4	1.000 (ref)	–
Mid thorax	569 (73.9)	79.3	71.2	56.4	1.206 (0.816-1.783)	0.347
Lower thorax	73 (9.5)	81.3	68.6	55.7	1.164 (0.661-2.050)	0.599
Tumor length of X-ray						0.231
≤5 cm	494 (64.2)	82.8	72.7	56.7	1.000 (ref)	
>5 cm	276 (35.8)	76.9	69.7	56.7	1.187 (0.897-1.571)	
Tumor grade						
Low	88 (11.4)	79.5	70.2	67.4	1.000 (ref)	–
Moderate	453 (58.8)	81.5	71.4	53.2	1.206 (0.760-1.915)	0.427
High	229 (29.7)	80.0	72.6	59.3	1.091 (0.665-1.790)	0.731
pT category						0.000
T ₁	100 (13.0)	92.4	83.8	71.9	1.000 (ref)	–
T ₂	181 (23.5)	85.3	78.8	67.4	1.561 (0.831-2.931)	0.166
T ₃	451 (58.6)	78.2	67.8	51.1	2.431 (1.376-4.293)	0.002
T _{4a}	38 (4.9)	58.3	54.1	38.5	4.024 (1.953-8.291)	0.000
Lymphovascular invasion						0.096
Negative	714 (92.7)	81.3	72.7	57.3	1.000 (ref)	
Positive	56 (7.3)	75.4	59.4	52.8	1.494 (0.931-2.397)	
Postoperative radiation						0.763
No	687 (89.2)	80.6	71.3	57.0	1.000 (ref)	–
Yes	83 (10.8)	82.8	74.5	55.8	0.938 (0.619-1.421)	0.763

HR, hazard ratio.

Results

Follow-up and survival condition

All patients took clinic visit every 3-6 months for 1-2 years, every 6-12 months for 3-5 years. They regularly received chest CT scanning, abdominal CT scanning and systematic ECT bone scanning every 3-6 months and had esophagogastrosocopy every year. Until the final day of follow-up on March 1, 2009, the number of cases of 1, 3, 5, 10 years follow-up was 633, 444, 258 and 75, respectively. Lymph node metastasis, local recurrence and hematogenous metastasis were judged

according to clinical signs and various kinds of imaging examinations. For the entire study patients, the overall survival rates at 1, 3, 5, and 10 years were 92.9%, 80.8%, 71.7%, and 57.4%.

Prognostic analysis

Age and pT staging were found closely correlated to prognosis by means of univariate analysis (*Table 1*). Five-year survival in cases younger and older than 60 were 76.5% *vs.* 63.3% ($P=0.001$, *Figure 1*), while those of pT₁, pT₂, pT₃, and

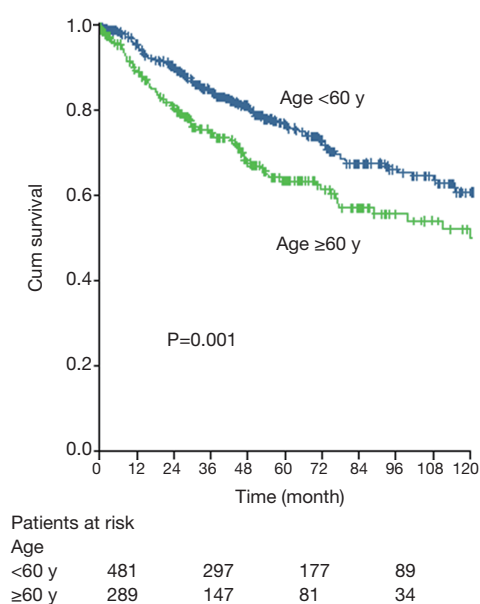


Figure 1 Overall survival rates of patients aged less than 60 years and patients aged 60 and older.

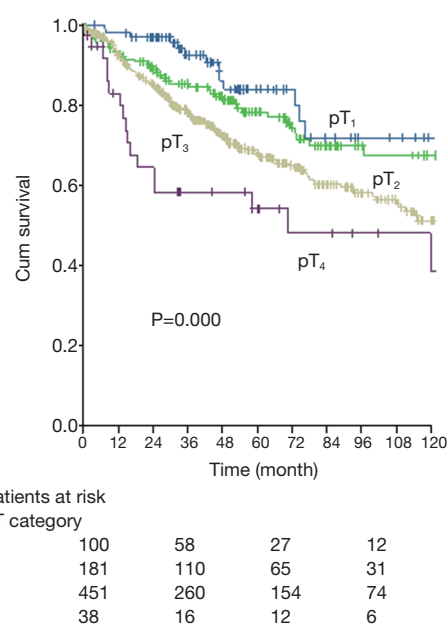


Figure 2 Overall survival rates of patients with different pT staging.

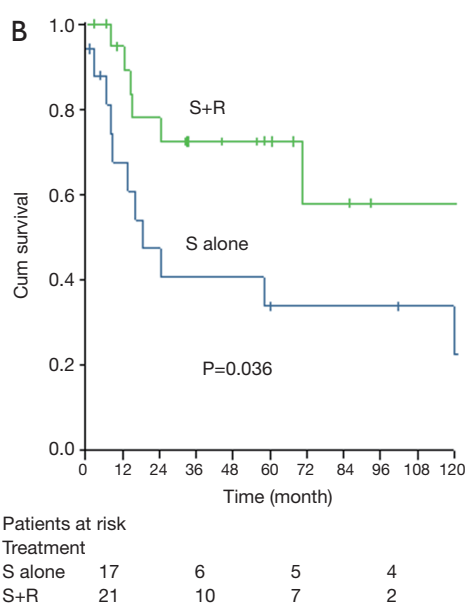
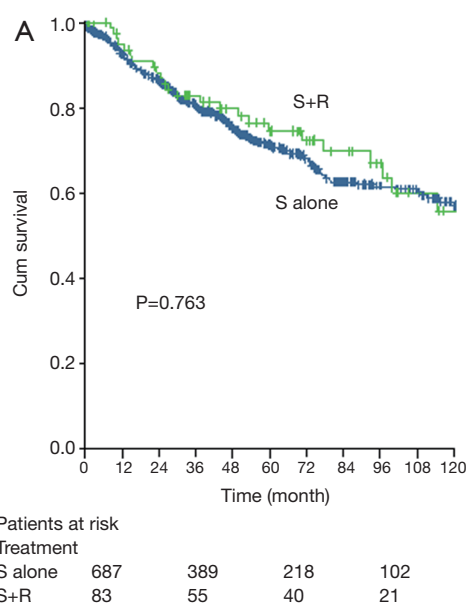


Figure 3 (A) Overall survival rates of patients treated with surgery and those treated with surgery plus postoperative radiation; (B) overall survival rates of patients with pT_{4a} treated with surgery and those treated with surgery plus postoperative radiation.

pT_{4a} were 83.8%, 78.8%, 67.8% and 54.1% respectively ($P=0.000$, Figure 2). Five-year survival of groups of simple surgery and surgery plus postoperative radiotherapy were 71.3% and 74.5% respectively ($P=0.763$, Figure 3A), while further analysis indicated that postoperative radiotherapy was able to boost the survival of patient in pT_{4a} which were 72.4% vs. 33.8% ($P=0.036$, Figure 3B). Multivariate analyses

also proved that age and T staging were two independent factors on prognoses (Table 2).

Analyses of complications

The incidence of operative complication was 14.3% (98/687), including pneumonia 5.7% (39/687), trachyphonia

2.5% (17/687), anastomotic leakage 2.2% (15/687), severe cardiac complication (such as, acute heart attacks and serious heart rhythm disorders) 1.7% (12/687), incision infection 1.3% (9/687), hemorrhage of digestive tract 0.3% (2/687) and others 2.2% (15/687). Around 2% (14/687) died of operative complications, and 1.2% of them died within 30 postoperative days. Toxicities related to receipt of postoperative radiation, scored according to the RTOG/EORTC (1992) criteria (7,8). In our study, the incidence of acute complication was hematologic toxicity, neutropenia grade 2, 14.5% (12/83) and grade 3, 1.2% (1/83); grade 1-2 mucosal toxicity of esophagus 12.0% (10/83), grade 1-2 pulmonary toxicity 19.2% (16/83). And the incidence of late complication was: grade 5 pulmonary toxicity 1.2% (1/83), grade 5 cardiac toxicity (non-cancerous hydropericardium) 1.2% (1/83) and grade 5 upper digestive tract toxicity (thoracic stomach hemorrhage) 1.2% (1/83).

Analysis of the reasons for failure

Of the entire study patients, a total of 208 patients died: 180 in the surgery-only group and 28 in the postoperative radiation group. Among the surgery-only group, the cause of death in 49 cases was unknown, 106 died from cancer, and 25

died from other diseases. Among the postoperative radiation group, the cause of death in 9 cases was unknown, 16 died from cancer, and 3 died from other diseases. Five cases in the surgery-only group and three cases in the postoperative radiation group had a second primary tumor. The overall recurrence rate in our study was 19.1% (147/770). Among the cases with known cause of treatment failure, only one patient in the surgery-only group had lower mediastinal lymph node metastasis, and no lower mediastinal lymph node metastasis was found in the postoperative radiation group. Postoperative radiation did not affect local control rate or hematogenous metastasis rate. The specific failure reasons in the two groups are shown in Table 3. Further analysis showed that when compared to surgery alone, postoperative radiotherapy reduced the tumor bed recurrence rate of pT_{4a} patients; in the surgery-only group, eight patients exhibited recurrence at the tumor bed, while there was only one such case in the postoperative radiotherapy group (P=0.005, Fisher's exact test).

Discussion

It's indicated in our study that both age and pT staging were significant and independent factors influencing the prognosis of patients at a stage of pT_{1-4a}N₀M₀. Those with an advanced staging of pT and with an age more than 60 turned out with an unsatisfactory prognosis. Although it's reported that postoperative radiotherapy made no significance in the survival rate, some further studies concluded that it could not only reduce the incidence of relapse in tumor bed but also boost the survival of those with a lesion longer than 5 cm and at a stage of T_{4a}.

For pT_{1-4a}N₀M₀ esophageal carcinoma patients after RO radical surgery, the number of negative lymph node was an import predictor. Bollschweiler *et al.* (9) reported that after RO radical surgery for esophageal carcinoma, the long-term survival rate in patients with >15 negative lymph

Table 2 Multivariate analysis of prognostic factors

Variable	HR (95% CI)	P value
Sex	0.913 (0.669-1.245)	0.564
Age	1.604 (1.213-2.121)	0.001
Tumor location	1.090 (0.833-1.428)	0.529
Tumor length of X-ray	0.985 (0.735-1.320)	0.919
Tumor grade	0.945 (0.760-1.174)	0.609
pT category	1.622 (1.305-2.016)	0.000
Lymphovascular invasion	1.441 (0.893-2.324)	0.134
Postoperative radiation	0.818 (0.528-1.269)	0.370

Table 3 Analysis of the failure reasons among the two groups

Variable	All [% (cases/overall cases)]	Surgery only [% (cases/overall cases)]	Postoperative radiation [% (cases/overall cases)]	χ^2 value	P value
Overall recurrence and metastasis	19.1 (147/770)	18.5 (127/687)	24.1 (20/83)	1.509	0.219
Neck lymph nodal metastasis	23.8 (35/147)	24.4 (31/127)	20.0 (4/20)	0.022	0.882
Mediastinum lymph nodal metastasis	30.6 (45/147)	30.7 (39/127)	30.0 (6/20)	0.004	0.949
Abdominal lymph nodal metastasis	8.2 (12/147)	7.9 (10/127)	10.0 (2/20)	0.000	1.000
Tumor bed recurrence	14.3 (21/147)	15.0 (19/127)	10.0 (2/20)	0.060	0.806
Hematogenous metastasis	49.7 (73/147)	48.8 (62/127)	55.0 (11/20)	0.264	0.607

nodes was significantly superior to that in patients with <15 negative lymph nodes ($P < 0.01$). Greenstein *et al.* (10) reported that in postoperative esophageal carcinoma patients with negative metastatic lymph nodes, the age, pT stage, and the number of negative lymph node are independent predictors, while sex and postoperative radiotherapy showed no apparent association to prognosis ($P > 0.05$). In this study, each patient has at least 15 negative lymph nodes (mean, 24.5; range, 15-68). Univariate and multivariate analysis showed that the age and pT staging are independent predictors. It's also reported that cancer embolus was one of the most important factors influencing the prognosis. Lymphovascular invasion often result in lymph node metastases and distant metastasis after surgery (11-13), so patients with positive lymphovascular invasion often turn out a poor prognosis. Data from the present study indicate that 5-year survival of patients with or without cancer emboli were 59.4% or 72.7%, respectively ($P = 0.096$). The statistical insignificance was considered due to the small number of samples.

The most important reason for postoperative failure with esophageal cancer is recurrence and metastasis. Patients with squamous cell carcinoma of the thoracic esophagus who had no lymph node metastasis and had undergone 3-field lymphadenectomy, the local-regional recurrence rate was 16.1-29% (11,12,14). Theoretically, prophylactic radiotherapy after resection of esophageal carcinoma could kill residual tumor cells, eradicate micro-metastases, decrease local recurrence, and increase survival. Several RCTs on the effect of postoperative radiotherapy on lymph node negative patients with esophageal cancer turned out with a negative result (15-17). And it's the same with our study. The overall recurrence rate of patients in this study was 19.1% (147/770), which was consistent with previous reports (11,12,14). The 5-year survival rates in the surgery-only group and in the postoperative radiation group were 71.3% and 74.5%, respectively ($P = 0.763$), suggesting that postoperative radiotherapy has no effect on survival rate. With further analysis showed that postoperative radiotherapy did somehow boost the survival of pT_{4a} cases, with a 5-year survival of 72.4% *vs.* that of simple surgery 33.8% ($P = 0.036$), Postoperative radiation also reduced the tumor bed recurrence of patients with pT_{4a} tumors. the reason was thought to be that, with an obvious limitation that surgery could not remove all the infiltrating malignancy in paraesophageal loose connective tissue postoperative radiotherapy might probably become an indispensable redeem for surgery, eliminating the residual tumor cells and

eradicating micro-metastases, so as to lower the incidence of local relapse and improve its postoperative survival. Fok *et al.* (18) reported that late complications of esophageal carcinoma in patients with postoperative radiation included radiation-induced pulmonary fibrosis, non-cancerous pericardial and pleural effusion and alimentary tract hemorrhage. While there were 3.6% (3/83) cases who died of late radiotherapeutic complications, which was considered as a result that the heart, lungs and thoracic-stomach all received some dosage of radiation. Due to small number size of samples and relevant statistical bias, the value of postoperative radiotherapy need to be further studied in other randomized clinical studies.

In conclusion, age and T staging were independent prognostic factors for patients with thoracic esophageal carcinoma staged pT_{1-4a}N₀M₀ undergone esophagectomy with 3-field lymphadenectomy. Patients with high T staging and at an age more than 60 turned out bad prognoses, neither could postoperative radiotherapy improve their survival.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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