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*Original Article*

# Therapeutic efficacy of different adjuvant modalities in thoracic esophageal squamous cell carcinoma

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**Abstract:** Esophageal squamous cell carcinoma (ESCC) seriously threatens the people's health. This study evaluated the therapeutic efficacy of different postoperative adjuvant therapies in thoracic ESCC. 836 patients with thoracic ESCC were enrolled. Prognostic factors and effect of different postoperative adjuvant therapies on prognosis were analyzed. The survival was calculated using Kaplan-Meier method and compared using Log-rank test. Cox model analysis of prognostic factors was conducted and 1:1 propensity score matching was applied as well. Results showed that, the 1-, 3-, and 5-year overall survival (OS) and disease-free survival (DFS) of all patients were 89.7%, 62.1%, 51.7% and 76.8%, 52.1%, 44.2%, respectively, with median values of 67 months and 42 months respectively. There were significances among postoperative chemoradiotherapy (POCRT), postoperative radiotherapy (POCT) and postoperative chemotherapy (PORT) group (P=0.009, 0.001). Intraoperative esophageal lesions and the degree of adhesion between lesions and the surrounding tissues and organs, pathological TNM stage and number of positive lymph nodes were independent prognostic factors for OS and DFS of patients. In addition, independence prognostic factors for OS included gender and number of negative lymph nodes; independent prognostic factors for DFS involved past history of drinking, positive esophageal stump and treatment methods. The constituent ratio of general clinical data in three groups showed differences. The univariate analysis still showed significant difference in 1-, 3-, and 5-year OS and DFS in POCRT, POCT and PORT group (All P=0.000). Conclusion: Adjuvant POCRT has a better therapeutic effect on thoracic ESCC, compared with POCT and PORT.

**Keywords:** Esophageal squamous cell carcinoma, surgery, radiotherapy, chemotherapy, efficacy

## Introduction

Esophageal cancer (EC), one of malignancies of digestive tract, is a significant health problem worldwide, which is particularly prevalent in China. According to Epidemiological Statistics of Cancer in the World released by the American Cancer Society in 2015, an estimated 455,800 new cases of esophageal cancer and 400,200 cases of deaths were reported [1]. Based on registration data in China in 2010, there were approximately 287,632 new cases of EC and 208,473 deaths, ranking No. 5 and 4 in terms of morbidity and mortality in malignant tumors, respectively [2]. Similar to biological behavior of most malignant tumors, major failure in EC patients is attributed to local-regional recurrence and distant metastases. Currently, surgical resection remains the mainstay of treatment for EC, however, radical surgery also contributed to the recurrence rate as 40%-60% [3-5], seriously affecting the therapeutic efficacy and quality of life. EC is known to be a systemic disease, and as for limited-stage EC in clinical setting, the autopsy confirmed the presence of extensive lymph node metastasis in 70% or more cases, and distant metastasis in more than 50%. Thus, surgery alone leads to poor therapeutic efficacy. Surgery-based multidisciplinary management of EC involves neoadjuvant and adjuvant approaches in western countries and China respectively. Nonetheless, no optimal treatment has been confirmed. The information from the US SEER database only provides some preliminary insights. Given the retrospective nature of the current study and a small sample size, the findings should be further validated by prospective studies [6]. Given no strong evidence to suggest EC should be treated with neoadjuvant or adjuvant therapy, we still need to understand the optimal adjuvant strategies and technical parameters after

surgical resection of EC, thereby guiding clinical work. Currently, very few studies have compared the therapeutic efficacy of POCRT, POCT and PORT on EC patients after surgery. Therefore, 863 patients with thoracic esophageal squamous cell carcinoma (ESCC) were enrolled in the study, in an attempt to clarify the potential role of different postoperative adjuvant therapies in ESCC patients after surgery, thus finding the optimal treatment method and identifying the appropriate subgroups.

## Patients and methods

### *Patient recruitment*

Eight hundred and sixty-three patients with thoracic ESCC admitted in Fourth Hospital of Hebei Medical University from January 2007 to December 2010 were enrolled, including 107 cases in POCRT group, 635 in POCT group and 121 in PORT group. There were 628 males and 235 females with a median age of 59 years (range 37-79); The number of patients with upper, middle and lower thoracic EC were 84, 601 and 178, respectively; 55 cases had weight loss of ≥ 5 kg prior to surgery. The inclusion criteria were as follows: patients with thoracic ESCC undergoing radical esophagectomy (R0); postoperative pathological diagnosis of squamous cell carcinoma (SCC); periodic check-ups in our hospital; Patients with recurrence and/or metastasis diagnosed in our hospital; no chemotherapy or radiotherapy prior to surgery; Complete surgical and pathological data records; no metastasis and recurrence prior to adjuvant radiotherapy; interval between the first day of surgery and radiotherapy ≤3 months; three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) technology used following surgery. According to the sixth edition (2002) of UICC on Cancer TNM staging system, the number of patients with stage T1, T2, T3 and T4 EC was 96, 162, 562 and 43, respectively; 468 and 395 cases with stage N0 and N1 EC respectively; 71, 376, 78, 306, 7 and 25 patients with pathologically stage I, IIa, IIb, II, IV1a and IV1b EC, respectively. In addition, 173 cases received 3D-CRT, and another 45 underwent IMRT. The study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University, and all patients provided written informed consent.

### *Surgery*

All patients underwent esophagectomy + modern two-field (complete mediastinal + abdominal) lymph node dissection. In terms of patients with thoracic EC, surgical procedure consisted of limited thoracotomy on the right side, left neck and upper abdomen, partial esophagogastrectomy, the left common carotid esophagogastrostomy and modern two-field lymphadenectomy. As for patients with middle and lower esophageal EC, surgical approach consisted of thoracotomy on the right side, upper abdominal incision, partial esophagogastrectomy, esophagogastrostomy on top of the right chest and modern two-field lymphadenectomy. All patients underwent lymph node dissection by the surgeon and the specimen was collected for counting and grouping. In all, 395 had pathologically confirmed positive lymph nodes, with a metastasis rate of 45.8%. A total of 12,868 surgically removed lymph nodes were documented, including 1,454 positive lymph nodes, with a metastasis rate of 11.3%. The number of lymph node dissected were 5 to 36, with a median number of 15. According to stratification criteria of intrathoracic lymph nodes by American Thoracic Society, location of lymph node metastasis was divided into three areas: supraclavicular and upper mediastinum (including lymph nodes in zone 2 and 4), middle and lower mediastinum (including lymph nodes in zone 5, 7, 8, 10 and 15) and abdominal (including lymph nodes in zone 16 to 20). In this group of patients, we recorded 210 patients with 1 metastasis area, 100 with 2 metastasis areas and 60 with 3 as well as 66 cases of positive esophageal stump and 32 cases of vascular invasion.

### *Postoperative chemotherapy (PORT)*

(1) Radiotherapy: A thermoplastic model was used to fix position of the patients. After CT scan simulation, digitized image were transmitted into the planning system for 3D reconstruction; (2) Extent of irradiation field. CTV was determined based on different tumor sites, including primary site + the lymphatic drainage area. The corresponding lymph nodes draining area was delineated according to lymph node grouping criteria of American Thoracic Society. As for those with upper thoracic EC, drainage areas encompassed bilateral supraclavicular fossa, paraesophageal area, zone 2, 4, 5 and 7, and

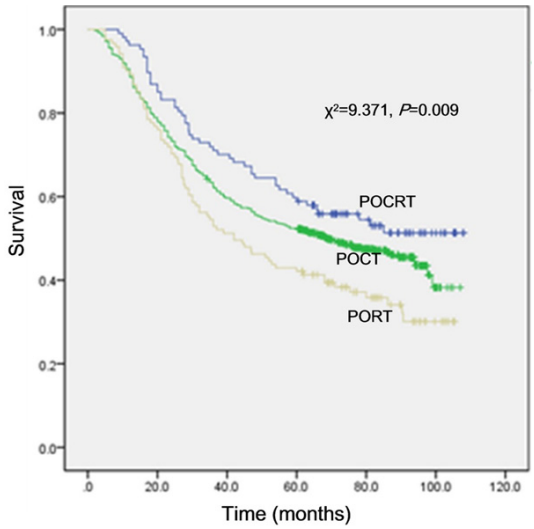


**Figure 1.** Kaplan-Meier estimates for OS of patients receiving POCRT compared with POCT and PORT.

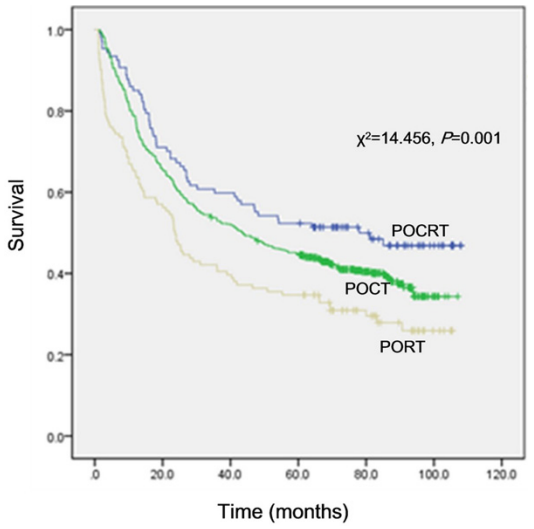


**Figure 2.** Kaplan-Meier estimates for DFS of patients receiving POCRT compared with POCT and PORT.

3.0 to 4.0 cm of subcarinal area; for those with middle thoracic EC, drainage areas included paraesophageal area, zone 2, 4, 5, 7, 8 and 9, and paracardial area; as for those with lower thoracic EC, drainage areas encompassed the paraesophageal area, zone 4, 5, 7, 8 and 9, pacardial area, left gastric area and paraceliac trunk. PTV was obtained by a 0.5-0.8 cm margin 3-D expansion from the CTV; (3) the prescribed dose, 95% PTV receiving a dose of 50-60 Gy, with 1.8-2.0 Gy/day and 5 times/week; (4) organs at risk (OAR) and its limits: The maximum dose to spinal cord was limited to ≤45 Gy; the volume of both lungs receiving V5 was ≤60%, that receiving V20 was ≤28-30%, and that receiving V30 was ≤18-20%; the volume of the heart receiving V30 was ≤40%, and that receiving V40 was ≤30%; (5) time of radiotherapy: time inteval between the first day of surgery and postoperative radiotherapy 26-90 days, with a median interval of 38 days.

*Postoperative radiotherapy (POCT)*

In 863 patients, 742 cases received POCT, including 635 cases of chemotherapy alone and 107 cases of concurrent radiotherapy, with chemotherapy course of 1-8 cycles and a median of 4 cycles. Chemotherapy was performed on the basis of "cisplatin", including "LFP (leucovorin 200 mg/day for five consecutive days; tegafur 1 g/day for five consecutive days; cisplatin 20 mg/day for five consecutive days)" and "TP (paclitaxel 240 mg/day on day 1; cisplatin 20 mg/day for five consecutive days)"; which was supplemented with other supportive treatments during chemotherapy, including antiemetics as well as immunity-enhancing and righting treatment.

*Follow-up*

All patients were followed up until December 31, 2015, including regular outpatient visits and telephone follow-up. The patients were followed up on a monthly basis until the date of death or for more than five years, whichever occurred first. The number of patients followed up for 1, 3 and 5 years was 787, 544 and 446, respectively, and 463 cases died at the end of the follow-up.

*Statistical analysis*

Statistical analysis was performed using SPSSI9.0 software. Overall survival (OS) and disease-free survival (DFS) were calculated by Kaplan-Meier method. Univariate analysis of the prognostic factors was made by Log-rank method and multivariate analysis was performed by Cox regression model; in OS calculation, death served as censored value, and survival as censored value; as for DFS, recurrence or distant metastasis was censored value, whereas no recurrence or distant metastasis and non cancer causes of death were censored values. Variables in multivariate analysis ($P<0.05$) between surgery alone group and surgery +

PORT group were matched using propensity score matching (PSM) method. P<0.05 was considered statistically significant.

## Results

*Survival in all patients*

The 1-, 3-, and 5-year OS of 863 patients were 89.7%, 62.1%, 51.7%, respectively, with a median OS of 67 months (95% CI: 54.5-79.5); the 1-, 3- and 5-year DFS were 76.8%, 52.1%, 44.2%, respectively, with a median of 42 months (95% CI: 33.3-50.7). The 1-, 3-, and 5-year OS of patients in POCRT, POCT and PORT group were 96.3%, 71.0%, 58.9%, 88.7, 62.4%, 52.3% and 89.3%, 54.5%, 42.1%, respectively; the 1-, 3- and 5-year DFS were 85.0%, 59.8%, 52.3%, 77.8%, 52.9%, 44.7% and 64.5%, 41.3%, 34.7%, respectively. Concerning overall comparison among the three groups, differences in OS and DFS were statistically significant ($X^2$=9.371, 14.456, P=0.009, 0.001) (**Figures 1** and **2**). Between-group comparison showed that, compared with patients in POCT group, DFS and OS of patients in POCRT group showed no significant difference ($X^2$=2.862, 3.551, P=0.091, 0.060), whereas those were significantly higher in POCRT group than in PORT group, and the differences were statistically significant ($X^2$=9.551, 12.274, P=0.002, 0.000). In addition, OS and DFS were also significantly higher in POCT group than in PORT group, and the differences were also significant ($X^2$=4.842, 8.806, P=0.028, 0.003).

*Univariate analysis of role of general clinicopathological factors in survival*

Analysis showed significant influencing factors for OS and DFS, including gender, history of smoking, intraoperative measurement of esophageal lesions in length, thickness and width, intraoperative adhesions between lesions and surrounding tissues and organs, postoperative pathological TNM stage, vascular invasion, positive esophageal stump, the number of positive lymph nodes based on postoperative pathology analysis, the number of surgically removed negative lymph nodes, different regions of positive lymph node metastasis and different treatment methods (all P<0.05). In addition, age and previous history of alcohol consumption were significant influencing factors for OS of the patients (P<0.05), whereas the incision site was the significantly influencing factor for DFS (P<0.05) (**Table 1**).

*Multivariate analysis*

Multivariate analysis of clinicopathological factors potentially affecting OS and DFS showed that, independent prognostic factors for OS and DFS included intraoperative adhesion of esophageal lesions and surrounding tissue and organs, pathological TNM stage, and the number of positive lymph nodes. Independent prognostic factors for OS also included gender and number of negative lymph nodes; independent prognostic factors for DFS included past history of drinking, positive stump and treatment option (**Tables 2** and **3**).

*General clinicopathological analysis of different treatment modalities*

Constituent ratio of general clinicopathological indicators in the three groups showed that gender, age, smoking history, drinking history, pathological stage M and constituent ratio of total number of removed lymph nodes and negative lymph nodes were not significant in the three groups; in PORT group, higher proportion was found in patients with upper thoracic EC, lesion >3 cm, moderate intraoperative adhesions in lesions, positive esophageal stump, pathologic stage T3, N1 and III EC. Nevertheless, in S + CT group, higher proportion was found in patients with stage T1 and T2 disease, mild intraoperative adhesions of lesions, stage N0 and IIa EC and the region without positive lymph node metastasis (**Table 4**).

*PSM analysis*

PSM method was used to analyze independent factors (gender, drinking history, the severity of intraoperative adhesion, pathological stage of TNM, postoperative stump, and number of positive and negative lymph nodes) that affected OS and DFS of all patients in COX multivariate analysis. After matching among the POCRT, POCT and PORT group, 87 well-balanced patients in each group were identified for comparison. After PSM, no statistically significant differences were observed in general clinicopathological features in the three treatment groups, as shown in **Table 6**. The 1-, 3-, and 5-year DFS and OS in patients in POCRT, POCT

**Table 1.** Univariate analysis of the effects of different adjuvant therapies on 863 patients with esophageal cancer after esophagecotomy

| Variable | n | OS (%) | | | $X^2$ | *P* | DFS (%) | | | $X^2$ | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 Y | 3 Y | 5 Y | | | 1 Y | 3 Y | 5 Y | | |
| Gender | | | | | 7.987 | 0.005 | | | | 5.204 | 0.023 |
| Male | 628 | 89.0 | 59.9 | 48.5 | | | 76.1 | 49.8 | 41.8 | | |
| Female | 235 | 91.5 | 68.1 | 60.0 | | | 78.7 | 58.3 | 50.6 | | |
| Age (year) | | | | | 5.255 | 0.022 | | | | 1.347 | 0.246 |
| ≤60 | 814 | 89.3 | 62.4 | 52.7 | | | 76.3 | 52.7 | 44.8 | | |
| >60 | 49 | 95.9 | 57.1 | 34.7 | | | 85.7 | 42.9 | 34.7 | | |
| History of smoking | | | | | 4.442 | 0.035 | | | | 2.970 | 0.085 |
| No | 424 | 92.2 | 64.9 | 54.5 | | | 78.5 | 54.5 | 46.5 | | |
| Yes | 439 | 87.2 | 59.4 | 48.9 | | | 75.2 | 49.9 | 42.1 | | |
| History of drinking | | | | | 7.703 | 0.008 | | | | 9.326 | 0.002 |
| No | 595 | 91.1 | 64.0 | 54.3 | | | 79.3 | 55.6 | 46.7 | | |
| Yes | 268 | 86.6 | 57.8 | 45.8 | | | 75.2 | 49.9 | 42.1 | | |
| Weight loss (≥5 Kg) | | | | | 3.572 | 0.059 | | | | 0.819 | 0.365 |
| No | 808 | 90.0 | 62.6 | 52.3 | | | 77.2 | 52.2 | 44.3 | | |
| Yes | 55 | 85.5 | 54.5 | 41.8 | | | 70.9 | 50.9 | 43.6 | | |
| Lesion area | | | | | 0.078 | 0.962 | | | | 0.299 | 0.861 |
| Upper thoracic segment | 84 | 92.9 | 63.1 | 56.0 | | | 73.8 | 50.0 | 46.4 | | |
| Middle thoracic segment | 601 | 90.3 | 61.4 | 50.6 | | | 77.9 | 51.6 | 44.7 | | |
| Lower thoracic segment | 178 | 86.0 | 64.0 | 53.3 | | | 74.7 | 55.0 | 42.0 | | |
| Intraoperative tumor length (cm) | | | | | 23.219 | 0.000 | | | | 17.980 | 0.000 |
| ≤3.0 | 161 | 95.7 | 72.0 | 65.2 | | | 88.2 | 63.4 | 55.9 | | |
| 3.1-5.0 | 356 | 92.9 | 64.6 | 53.8 | | | 80.2 | 53.0 | 45.0 | | |
| 5.1-7.0 | 229 | 86.8 | 55.5 | 43.6 | | | 70.5 | 44.9 | 37.9 | | |
| ≥7.0 | 117 | 76.7 | 53.4 | 41.4 | | | 62.9 | 47.4 | 37.1 | | |
| Intraoperative tumor width (cm) | | | | | 15.650 | 0.000 | | | | 16.586 | 0.000 |
| ≤2.0 | 171 | 96.2 | 72.4 | 63.5 | | | 85.9 | 66.0 | 57.1 | | |
| 2.1-4.0 | 473 | 91.1 | 62.3 | 52.7 | | | 77.8 | 50.1 | 41.6 | | |
| ≥4.1 | 219 | 80.0 | 52.7 | 42.9 | | | 65.9 | 43.9 | 37.6 | | |
| Intraoperative tumor thickness (cm) | | | | | 21.863 | 0.000 | | | | 20.564 | 0.000 |
| ≤2.0 | 186 | 95.3 | 72.5 | 63.2 | | | 84.8 | 62.0 | 54.4 | | |
| 2.1-3.0 | 486 | 89.6 | 62.0 | 50.7 | | | 77.3 | 51.6 | 43.1 | | |
| ≥3.1 | 191 | 82.3 | 50.3 | 40.5 | | | 65.1 | 40.6 | 33.6 | | |
| Intraoperative adhesion between tumor and surrounding tissue | | | | | 29.279 | 0.000 | | | | 31.956 | 0.000 |
| No | 83 | 98.8 | 81.9 | 73.5 | | | 92.8 | 72.3 | 65.1 | | |
| Mild | 441 | 90.7 | 66.0 | 54.6 | | | 78.9 | 56.2 | 46.9 | | |
| Moderate to severe | 339 | 86.7 | 52.2 | 42.5 | | | 70.2 | 41.9 | 35.7 | | |
| pT-category | | | | | 57.525 | 0.000 | | | | 38.184 | 0.000 |
| T1 | 96 | 92.7 | 76.0 | 69.8 | | | 87.5 | 68.8 | 61.5 | | |
| T2 | 162 | 95.1 | 74.7 | 63.0 | | | 85.8 | 64.2 | 55.6 | | |
| T3 | 562 | 88.4 | 57.5 | 46.6 | | | 73.7 | 46.8 | 39.1 | | |
| T4 | 43 | 79.1 | 44.2 | 34.9 | | | 60.5 | 39.5 | 30.2 | | |
| pN-category | | | | | 119.231 | 0.000 | | | | 133.365 | 0.000 |
| N0 | 468 | 95.5 | 78.0 | 67.7 | | | 87.8 | 68.6 | 60.6 | | |
| N1 | 395 | 82.8 | 43.3 | 32.7 | | | 63.8 | 32.7 | 24.8 | | |
| pM-category | | | | | 35.547 | 0.000 | | | | 27.344 | 0.000 |
| M0 | 829 | 90.7 | 63.3 | 53.1 | | | 78.4 | 53.4 | 45.4 | | |
| M1a + 1b | 34 | 64.7 | 26.5 | 17.6 | | | 38.2 | 20.6 | 14.7 | | |
| pTNM-category | | | | | 161.902 | 0.000 | | | | 167.598 | 0.000 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| I | 71 | 93.0 | 81.7 | 74.6 | | | 88.7 | 76.1 | 67.6 | |
| IIa | 376 | 96.0 | 78.2 | 67.5 | | | 88.3 | 67.8 | 60.3 | |
| IIb | 78 | 92.3 | 61.5 | 50.0 | | | 29.5 | 48.7 | 39.7 | |
| III | 306 | 83.3 | 41.5 | 30.7 | | | 63.1 | 31.4 | 23.2 | |
| IVa | 7 | 85.7 | 42.9 | 42.9 | | | 57.1 | 42.9 | 42.9 | |
| IVb | 25 | 56.0 | 24.0 | 12.0 | | | 36.0 | 16.0 | 8.0 | |
| Vascular invasion | | | | | 16.684 | 0.000 | | | | 14.467 | 0.000 |
| No | 831 | 90.0 | 63.3 | 52.8 | | | 77.6 | 53.1 | 45.3 | |
| Yes | 32 | 81.3 | 31.3 | 21.9 | | | 56.3 | 28.1 | 15.6 | |
| Osophageal stump | | | | | 9.391 | 0.002 | | | | 11.610 | 0.001 |
| Negative | 797 | 90.2 | 63.0 | 53.1 | | | 77.8 | 53.6 | 45.6 | |
| Positive | 66 | 83.3 | 51.5 | 34.8 | | | 65.2 | 34.8 | 27.3 | |
| Number of surgically removed lymph nodes | | | | | 0.070 | 0.792 | | | | 0.069 | 0.792 |
| ≥10 | 459 | 89.5 | 61.9 | 52.5 | | | 77.1 | 51.6 | 45.1 | |
| <10 | 404 | 89.9 | 62.4 | 50.7 | | | 76.5 | 52.7 | 43.2 | |
| Number of positive lymph nodes | | | | | 156.083 | 0.000 | | | | 165.939 | 0.000 |
| 0 | 468 | 95.5 | 78.0 | 67.7 | | | 87.8 | 68.6 | 60.6 | |
| 1-2 | 261 | 85.4 | 49.8 | 39.5 | | | 69.3 | 39.1 | 31.0 | |
| ≥3 | 134 | 77.6 | 30.6 | 19.4 | | | 53.0 | 20.1 | 12.7 | |
| Number of negative lymph nodes | | | | | 7.603 | 0.006 | | | | 6.710 | 0.010 |
| ≥10 | 324 | 93.5 | 67.6 | 56.1 | | | 80.6 | 57.1 | 48.7 | |
| <10 | 539 | 87.4 | 58.8 | 49.0 | | | 74.6 | 49.2 | 41.6 | |
| Number of metastasis area | | | | | 153.356 | 0.000 | | | | 157.621 | 0.000 |
| 0 | 468 | 97.4 | 78.0 | 67.7 | | | 87.8 | 686 | 60.6 | |
| 1 | 231 | 83.5 | 48.9 | 39.0 | | | 66.2 | 37.7 | 30.7 | |
| 2 | 104 | 85.6 | 41.3 | 28.8 | | | 63.5 | 29.8 | 22.1 | |
| 3 | 60 | 75.0 | 25.0 | 15.0 | | | 55.0 | 18.3 | 6.7 | |
| Treatment methods | | | | | 9.371 | 0.009 | | | | 14.456 | 0.001 |
| POCRT | 107 | 96.3 | 71.0 | 58.9 | | | 85.0 | 59.8 | 52.3 | |
| PORT | 121 | 89.3 | 54.5 | 42.1 | | | 64.5 | 41.3 | 34.7 | |
| POCT | 635 | 88.7 | 62.4 | 52.3 | | | 77.8 | 52.9 | 44.7 | |

OS, overall survival; DFS, disease free survival; POCRT, postoperative chemoradiotherapy; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy; Y, year (s).

**Table 2.** Multivariate analysis results of factors affecting OS

| Variable | B | SE | Wald | Sig. | Exp (β) | 95% CI | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Gender | -0.244 | 0.113 | 4.635 | 0.031 | 0.784 | 0.628 | 0.978 |
| Intraoperative adhesion between tumor and surrounding tissue | 0.322 | 0.080 | 16.101 | 0.000 | 1.380 | 1.179 | 1.616 |
| pTNM staging | 0.252 | 0.060 | 17.473 | 0.000 | 1.287 | 1.143 | 1.448 |
| Number of positive lymph nodes | 0.403 | 0.090 | 20.135 | 0.000 | 1.497 | 1.255 | 1.785 |
| Total number of surgically removed lymph nodes | -0.252 | 0.1.1 | 6.149 | 0.013 | 0.778 | 0.637 | 0.949 |

OS, overall survival; B, regression coefficient; SE: standard error; Wald: corresponding to $X^2$ value; Sig., *p* value; Exp (β): relative risk; CI: confidence interval.

and PORT group showed significant differences after PSM ($X^2$=25.330, 27.365, all P=0.000) (**Figures 3**, **4**; **Table 5**). Between-group comparison revealed that, significant difference was noted in the 1-, 3-, and 5-year OS and DFS in both POCRT and PORT group ($X^2$=8.630, 10.263, P=0.003, 0.001); in POCRT and POCT group, significant differences were found in 1, 3, and 5-year OS and DFS ($X^2$=23.836, 28.575, all P=0.000). The 1, 3 and 5-year DFS and OS in PORT and POCT group were also statistically significant ($X^2$=5.311, 4.026, P=0.021, 0.045 (**Table 6**).

## Discussion

Surgical resection is currently the standard of care for the management of EC. Despite signifi-

**Table 3.** Multivariate analysis results of factors affecting DFS

| Variable | B | SE | Wald | Sig. | Exp (β) | 95% CI | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| History of drinking | 0.204 | 0.095 | 4.659 | 0.031 | 1.227 | 1.019 | 1.477 |
| Intraoperative adhesion between tumor and surrounding tissue | 0.310 | 0.076 | 16.732 | 0.000 | 1.364 | 1.175 | 1.583 |
| pTNM staging | 0.221 | 0.058 | 14.445 | 0.000 | 1.247 | 1.113 | 1.397 |
| Postoperative stump | 0.316 | 0.150 | 4.461 | 0.035 | 1.372 | 1.023 | 1.840 |
| No. of positive lymph nodes | 0.449 | 0.088 | 26.267 | 0.000 | 1.567 | 1.320 | 1.861 |
| Adjuvant therapies | 0.208 | 0.483 | 6.374 | 0.012 | 1.232 | 1.048 | 1.448 |

DFS, disease free survival; B, regression coefficient; SE: standard error; Wald: corresponding to $X^2$ value; Sig., *p* value; Exp (β): relative risk; CI: confidence interval.

**Table 4.** Constituent ratio of data on different treatment methods after esophagectomy

| Variable | N | Treatment method (n, %) | | | $X^2$ | *P* |
|---|---|---|---|---|---|---|
| | | S + POCRT (n=107) | S + POCT (n=635) | S + PORT (n=121) | | |
| Gender | | | | | 0.295 | 0.863 |
| Male | 628 | 79 (73.8%) | 459 (72.3%) | 90 (74.4%) | | |
| Female | 235 | 28 (26.2%) | 176 (27.7%) | 31 (25.6%) | | |
| Age (yr) | | | | | 1.124 | 0.570 |
| ≤60 | 814 | 100 (93.5%) | 602 (94.8%) | 112 (92.6%) | | |
| >60 | 49 | 7 (6.5%) | 33 (5.2%) | 9 (7.4%) | | |
| History of smoking | | | | | 1.719 | 0.432 |
| No | 424 | 58 (54.2%) | 304 (47.9%) | 62 (51.2%) | | |
| Yes | 439 | 49 (45.8%) | 331 (52.1%) | 59 (48.8%) | | |
| History of drinking | | | | | 1.450 | 0.484 |
| No | 595 | 74 (69.2%) | 432 (68.0%) | 89 (73.6%) | | |
| Yes | 268 | 33 (30.8%) | 203 (32.0%) | 32 (26.4%) | | |
| Lesion area | | | | | 1.538 | 0.021 |
| Upper thoracic segment | 84 | 9 (8.4%) | 57 (9.0%) | 18 (14.9%) | | |
| Middle thoracic segment | 601 | 82 (76.6%) | 432 (68.0%) | 87 (71.9%) | | |
| Lower thoracic segment | 178 | 16 (15.0%) | 146 (23.0%) | 16 (13.2%) | | |
| Intraoperative tumor length (cm) | | | | | 17.070 | 0.009 |
| ≤3.0 | 161 | 19 (17.8%) | 135 (21.3%) | 7 (5.8%) | | |
| 3.1-5.0 | 356 | 39 (36.4%) | 259 (40.8%) | 55 (45.5%) | | |
| 5.1-7.0 | 229 | 31 (29.0%) | 157 (24.7%) | 39 (32.2%) | | |
| ≥7.0 | 117 | 15 (14.0%) | 83 (13.1%) | 18 (24.9%) | | |
| Intraoperative adhesion between tumor and surrounding tissue | | | | | 17.354 | 0.002 |
| No | 83 | 15 (14.0%) | 62 (9.8%) | 6 (5.0%) | | |
| Mild | 441 | 43 (40.2%) | 345 (54.3%) | 53 (43.8%) | | |
| Moderate to severe | 339 | 49 (45.8%) | 228 (35.9%) | 62 (51.2%) | | |
| Postoperative stump | | | | | 7.977 | 0.019 |
| Positive | 66 | 8 (7.5%) | 41 (6.5%) | 17 (14.0%) | | |
| Negative | 797 | 99 (92.5%) | 584 (93.5%) | 104 (86.0%) | | |
| pT-category | | | | | 29.121 | 0.000 |
| T1 | 96 | 5 (4.7%) | 86 (13.5%) | 5 (4.1%) | | |
| T2 | 162 | 21 (19.6%) | 131 (20.6%) | 10 (8.3%) | | |
| T3 | 562 | 76 (71.0%) | 386 (60.8%) | 100 (82.6%) | | |
| T4 | 43 | 5 (4.7%) | 32 (5.0%) | 6 (5.0%) | | |
| pN-category | | | | | 28.186 | 0.000 |
| N0 | 468 | 46 (43.0%) | 378 (59.5%) | 44 (36.4%) | | |
| N1 | 395 | 61 (57.0%) | 257 (39.5%) | 77 (63.6%) | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| pM-category | | | | | 0.286 | 0.869 |
| M0 | 829 | 102 (95.3%) | 610 (96.1%) | 117 (96.7%) | | |
| M1a + 1b | 34 | 5 (4.7%) | 25 (3.9%) | 4 (3.3%) | | |
| pTNM-category | | | | | 50.388 | 0.000 |
| I | 71 | 1 (0.9%) | 68 (10.7%) | 2 (1.7%) | | |
| IIa | 376 | 41 (38.3%) | 296 (46.6%) | 38 (31.4%) | | |
| IIb | 78 | 15 (14.0%) | 55 (8.7%) | 8 (6.6%) | | |
| III | 306 | 45 (42.1%) | 196 (30.9%) | 69 (57.0%) | | |
| IVa | 7 | 2 (1.9%) | 4 (0.6%) | 1 (0.8%) | | |
| IVb | 25 | 2 (1.9%) | 20 (3.2%) | 3 (2.8%) | | |
| Number of surgically removed lymph nodes | | | | | 2.037 | 0.361 |
| ≥10 | 459 | 51 (47.9%) | 339 (53.4%) | 69 (57.0%) | | |
| <10 | 404 | 56 (52.1%) | 296 (46.6%) | 52 (43.0%) | | |
| Number of positive lymph nodes | | | | | 28.536 | 0.000 |
| 0 | 468 | 46 (43.0%) | 378 (13.5%) | 44 (4.1%) | | |
| 1-2 | 261 | 41 (38.3%) | 171 (26.9%) | 49 (7.7%) | | |
| ≥3 | 134 | 20 (18.7%) | 86 (71.2%) | 28 (23.1%) | | |
| No. of negative lymph nodes | | | | | 5.086 | 0.079 |
| ≥10 | 324 | 69 (64.5%) | 384 (60.5%) | 86 (71.2%) | | |
| <10 | 539 | 38 (35.5%) | 251 (39.5%) | 35 (28.8%) | | |
| Number of metastasis area | | | | | 28.883 | 0.000 |
| 0 | 468 | 46 (43.0%) | 378 (59.5%) | 44 (36.4%) | | |
| 1 | 231 | 38 (35.5%) | 148 (23.3%) | 45 (37.2%) | | |
| 2 | 104 | 14 (13.5%) | 69 (10.9%) | 21 (17.4%) | | |
| 3 | 60 | 9 (8.4%) | 40 (6.3%) | 11 (9.1%) | | |

S, surgery; POCRT, postoperative chemoradiotherapy; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy.

cantly improved surgical techniques and markedly decreased perioperative mortality in recent years, surgery alone reveals modest therapeutic efficacy. This might be attributed to local-regional recurrence or distant metastases. In order to improve surgical outcomes and to effectively reduce the failure rate, PORT, POCT and PORT combined with POCT have been widely applied in the adjuvant therapy of patients with EC. Preoperative neoadjuvant chemotherapy improves therapeutic efficacy mainly by improving the surgical resection rate, lowering preoperative staging of lesions and killing tumor cells. And its therapeutic efficacy has been widely recognized, particularly in the United States and Europe, in which preoperative neoadjuvant chemoradiation has gradually become a standard treatment for EC [7-10]. Currently, the role of postoperative adjuvant chemoradiation in EC remains controversial [11, 12], wherein the main issues involve whether PORT or cocurrent POCRT should be applied, patients benefiting from adjuvant therapy and extent of irradiation area in postoperative adjuvant therapy. In China, surgery followed by POCRT is currently the mainstay of the comprehensive treatment for EC. Of these, PORT has played a predominant role in the past decades. Although preoperative chemoradiation is accepted by most researchers, it is controversial whether its therapeutic efficacy is superior to POCRT. Chen et al. [13] analyzed EC patients who underwent surgery alone, preoperative chemoradiation and POCRT, respectively. They enrolled 78 patients in each group, and 3-year OS was 23.3%, 46.8% and 46.3%, respectively in the three groups. Survival rate was significantly higher in combined treatment group than in surgery alone group (P=0.005), whereas no significant difference was observed in both preoperative chemoradiation and POCRT groups (P=0.544). In terms of $T_{3/4}$ patients, the therapeutic efficacy was better in preoperative chemoradiotherapy group than in POCRT group, and 3-year OSR were 40.0% and 29.1% respectively (P=0.006). SEER-Medicare data in the United States indicated that OS and PFS in patients receiving preoperative chemoradiotherapy were not superior to those in patients undergoing POCRT (P>0.05) [6]. Lv et al. [14]

**Table 5.** Constituent ratio of data on three different adjuvant therapies after PSM

| Variable | N | Treatment method (n) | | | $X^2$ | *P* |
|---|---|---|---|---|---|---|
| | | S + POCRT (n=87) | S + POCT (n=87) | S + PORT (n=87) | | |
| Gender | | | | | 0.146 | 0.930 |
| Male | 195 | 65 (74.7%) | 64 (73.6%) | 66 (75.9%) | | |
| Female | 66 | 22 (25.3%) | 23 (26.4%) | 21 (24.1%) | | |
| History of drinking | | | | | | |
| Yes | 78 | 27 (31.0%) | 28 (32.2%) | 23 (26.4%) | 0.768 | 0.681 |
| No | 183 | 60 (69.0%) | 59 (67.8%) | 64 (73.6%) | | |
| Intraoperative adhesion between tumor and surrounding tissue | | | | | | |
| No | 14 | 4 (4.6%) | 6 (6.9%) | 4 (4.6%) | 1.128 | 0.890 |
| Mild | 126 | 41 (47.1%) | 44 (50.6%) | 41 (47.1%) | | |
| Moderate to severe | 121 | 42 (48.3%) | 37 (42.5%) | 42 (48.3%) | | |
| Postoperative stump | | | | | 0.151 | 0.927 |
| Positive | 14 | 4 (4.6%) | 5 (5.7%) | 5 (5.7%) | | |
| Negative | 247 | 83 (95.4%) | 82 (94.3%) | 82 (94.3%) | | |
| pTNM-category | | | | | 0.543 | 0.747 |
| II | 127 | 42 (48.3%) | 45 (51.7%) | 40 (46.0%) | | |
| III | 134 | 45 (51.7%) | 42 (48.3%) | 47 (54.0%) | | |
| Number of positive lymph nodes | | | | | 0.546 | 0.969 |
| 0 | 70 | 22 (25.3%) | 23 (26.4%) | 25 (28.7%) | | |
| 1-2 | 140 | 48 (55.2%) | 48 (55.2%) | 44 (50.6%) | | |
| ≥3 | 51 | 17 (19.5%) | 16 (18.4%) | 18 (20.7%) | | |
| Number of negative lymph nodes | | | | | 0.638 | 0.727 |
| ≥10 | 92 | 31(35.6%) | 33(37.9%) | 28(32.2%) | | |
| <10 | 169 | 56(64.4%) | 54(62.1%) | 59(67.8%) | | |

PSM, propensity score matching; S, surgery; POCRT, postoperative chemoradiotherapy; PORT, postoperative radiotherapy; POCT, postoperative chemotherapy.

**Table 6.** Survival analysis of three adjuvant therapies after PSM

| Treatment method | n | OS (%) | | | $X^2$ | P | DFS (%) | | | $X^2$ | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 Y | 3 Y | 5 Y | | | 1 Y | 3 Y | 5 Y | | |
| POCRT | 87 | 95.6 | 73.3 | 61.1 | 25.330 | 0.000 | 85.6 | 61.1 | 54.4 | 27.365 | 0.000 |
| POCT | 87 | 81.1 | 38.9 | 31.1 | | | 67.8 | 27.8 | 20.0 | | |
| PORT | 87 | 92.2 | 55.6 | 44.4 | | | 67.8 | 44.4 | 36.7 | | |

PSM, propensity score matching; OS, overall survival; DFS, disease free survival. Y, year (s).

also believe that both preoperative chemoradiotherapy and POCRT can significantly improve survival rate of the patients, but no significant difference was found.

Currently, very few comparative studies have been conducted on a large cohort of EC patients who underwent PORT, POCT and POCRT respectively. To clarify the optimal treatment modality and the appropiate patients, in the present study a retrospective analysis was performed in patients with EC undergoing adjuvant POCT or PORT in our hospital. The 1-, 3- and 5-year OS and DFS in 863 cases were 89.7%, 62.1%, 51.7% and 76.8%, 52.1%, 44.2%, respectively, which was similar to survival rate of patients who had received adjuvant therapy after esophagectomy [15-18]. To elucidate the effects of different treatment methods on the prognosis of patients, we conducted a stratified analysis, which showed OS and DFS were significantly better in POCRT group than in POCT and PORT groups. Currently, the literature reported that prophylactic irradiation after esophagectomy reduced local-regional recurrence rate, and improved long-term survival of patients with stage III disease and with number of lymph nodes ≥3 after the surgery [15, 19]. Clinical

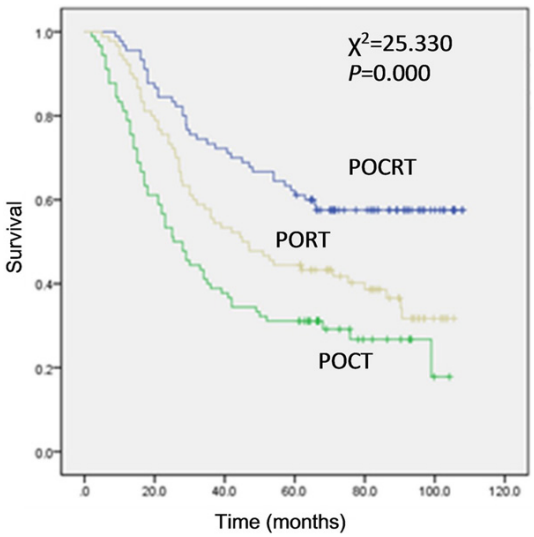


**Figure 3.** Kaplan-Meier estimates for OS of patients receiving POCRT compared with POCT and PORT after PSM.

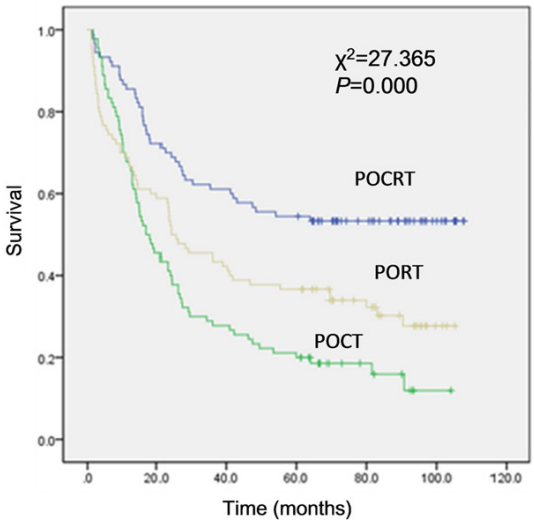


**Figure 4.** Kaplan-Meier estimates for DFS of patients receiving POCRT compared with POCT and PORT after PSM.

researches indicate that after radical resection of EC, POCT can help delay the recurrence and metastasis, and prolong DFS of patients, but it is controversial whether OS will be prolonged [20]. However, esophagectomy followed by POCRT can improve long-term survival of patients [21]. Based on our findings, the therapeutic efficacy of patients seems better in POCT group than in PORT group, but the general clinical and pathological data of the three groups showed no dominant clinicopathological features in PORT group. PSM analysis revealed the optimal therapeutic efficacy in POCRT group after esophagectomy, and the efficacy of PORT was significantly better compared to POCT. Rice et al. [21] studied patients receiving POCRT using PSM. The results demonstrated that median survival (28 months) and 4-year OS (44%) were significantly higher in the combined treatment group than in surgery alone group (15 months and 0%). Findings by Bedard et al [22] indicated a median survival of 47.5 months after adjuvant POCRT, which was significantly longer than that in surgery alone group (14.1 months). Thus, they believe that adjuvant POCRT provides survival benefits to patients.

Lymph node metastasis is one of the main prognostic factors in patients with EC after surgerical resection. Previous studies related to PORT have reported that the number of postoperative positive lymph node metastasis and metastasis area underlie PORT and that adjuvant PORT will bring survival benefit for these patients. However, previous studies focus more on surgery alone and adjuvant POCRT, and there are rare studies on combination therapy, such as adjuvant PORT, POCT and POCRT. The results of this study showed that three treatments all had a good therapeutic effect on patients with negative lymph nodes. There was no conclusive result about whether EC patients without lymph node metastasis should undergo adjuvant POCT and PORT, but previous studies have reported that despite a good survival rate in these patients, some patients still present with early local recurrence of tumor [23, 24]. Some scholars propose that early local-regional recurrence of EC in patients with stage pN0 disease after surgery may be associated with lumph node micrometastases that are missed out in routine pathological examination [25, 26]. Therefore, it is reasonable to assume that in the era of precise radiotherapy, the application of PORT and POCT in patients with stage pN0 disease should be further studied. Our study indicated POCRT was more effective than PORT and POCT, with significant difference, which was in accordance with previous findings [21, 22, 27].

In conclusion, we believe that adjuvant POCRT provides survival benefit to EC patients with positive lymph node metastasis after surgical resection. This may be related to greatly improved sensitivity of tumor cells to chemotherapy and radiotherapy owing to rapid entry

into proliferation phase of cells at quiescent phase left in the body after esophagectomy. PORT combine with POCT exerts a role in synergistic sensitization and kills tumor cells. Given the retrospective nature of the present study, the relevant findings should be confirmed by prospective studies.

## Disclosure of conflict of interest

None.

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