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Postoperative Adjuvant Therapy Plays Different Roles for Esophageal Squamous Cell Carcinoma with Different Pathological Staging

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Authors Contribution:

Yang J, Feng Y, Zhou Z, Ma Z, Wang J, Yang Y and all these authors contributed equally to this work.

1. Abstract

1.1. Background: Esophageal Squamous Cell Carcinoma (ESCC) causes a great disease burden in China and its prognosis remains poor. The role of adjuvant therapy in ESCC is controversial. The exploration of adjuvant therapy may benefit the maturation of the treatment strategy of ESCC.

1.2. Methods: Patients with ESCC who received surgery between 2007 to 2018 were enrolled. The primary endpoint was Overall Survival (OS). The effectiveness of adjuvant therapy was evaluated.

1.3. Results: 624 patients were enrolled. 374 patients received adjuvant therapy and 250 patients didn't. For patients staged pN0, adjuvant therapy didn't lead to better survival if neoadjuvant therapy wasn't given (p=0.002) but showed a tendency that may help to improve OS for those who received neoadjuvant therapy-(p=0.133). For pN1 patients, adjuvant therapy doesn't improve the long-term OS (p=0.368), but more patients in adjuvant group were staged pT3 or higher should be considered. Adjuvant therapy further improved survival for patients with pN2+3 (p=0.034).

1.4. Conclusions: Our study suggests adjuvant therapy doesn't benefit pN0 patients of ESCC who didn't receive neoadjuvant therapy. While for pN0 patients who received neoadjuvant therapy before and pN1 patients, adjuvant therapy may help to improve OS. For patients with more than two lymph nodes metastasis (pN2+3), adjuvant improves OS.

2. Introduction

Esophageal cancer causes a great disease burden worldwide especially in Eastern Asia [1]. In China, its incidence and mortality ranked sixth and fourth among all malignant tumors, respectively [2]. Comparing to western countries which adenocarcinoma accounts for the majority of esophageal cancer, m5ore than 90% of esophageal cancer is squamous cell carcinoma in China [3]. The past twenty years witnessed the exploration of the treatment model on ESCC. According to the most recent NCCN guidelines, the standard treatment for locally advanced esophageal squamous cell cancer is surgery following neoadjuvant chemo radiotherapy [4]. Although researchers and physicians paid great effort to the treatment of ESCC, the prognosis remains poor with 5-year postesophagectomy survival rates of about 15-40% [5].

Whether postoperative adjuvant therapy benefits patients with ESCC has long been controversial. The publication of CROSS [6] and NEOCRTEC5010 [7] finally confirmed the role of neoadjuvant chemo radiation on ESCC, however, no such well-designed large randomized clinical trials have been implemented on the efficiency of postoperative adjuvant therapy. Early researches led to inconsistent results [8-10]. Recently more and more patients receiving paclitaxel and cisplatin, instead of 5-FU and cisplatin in the early years. Based on the change of adjuvant chemotherapy regimen, the conclusion of early clinical trials needs to be reconsidered.

We thus designed this retrospective research to investigate the role of adjuvant therapy in the treatment of ESCC. We hope the results of this research would provide evidence for the designation of further clinical trials.

3. Materials and Methods

3.1. Patients

We identified 767 patients who received surgery of ESCC between January 2007 to December 2018 at the Department of Thoracic surgery II, Peking University Cancer Hospital. All patients were operated on by the same surgical team. Exclusion criteria included postoperative pathological subtypes other than squamous cell carcinoma, exploratory surgery implemented, death perioperatively or within postoperative 90 days, and loss of follow-up. Clinical and therapeutic data were collected from the medical record system. The Ethics Committee of Peking University Cancer Hospital waived the informed consent requirements of this study.

3.2. Staging and Follow Up

All patients conducted tumor staging examination before the operation, which include esophagoscopy and biopsy, upper gastrointestinal contrast, chest and abdomen computed tomography with contrast. Positron Emission Tomography/Computed Tomography (PET-CT) is widely used after 2010. A Multi-disciplinary team discussion would be held if the case is complicated. Generally, the therapeutic strategy was made by the Multidiscipline Team (MDT), with the consideration of clinical staging, cardiopulmonary function and patient's wills. The pathological stage was reviewed according to the 8th TNM classification system (Union for International Cancer Control and American Joint Committee on Cancer).

Patients were followed up at the outpatient clinic, and there is a surveillance team kept in touch with patients for updating.

3.3. Surgery

Surgical procedures were performed by a single surgical team. The most common procedures, by frequency, were modified Ivor-Lewis, modified McKeown, and modified Sweet. All procedures involved two-filed or three-field lymph node dissection. The stomach was the most often used substitution for the esophagus, and the anastomosis included mechanical (most frequently) and manual anastomosis.

3.4. Neoadjuvant and Adjuvant Therapy

Some patients were recommended to receive neoadjuvant therapy because their tumors are expected to be locally advanced. After surgery, the MDT usually recommend adjuvant chemotherapy if the patient was confirmed with lymph node meatstasis (pathological N positive), or adjuvant radiotherapy if the patient was confirmed with pT3 or pT4, or adjuvant chemoradiotherapy when both pT3/pT4 and N positive were confirmed. The patients and their family finally made decision on receiving neoadjuvant and/or adjuvant therapy or not after been well informed. In our institution, perioperative chemotherapies for esophageal cancer are mostly platinum-based doublet chemotherapy. Paclitaxel (175 mg/m2) and cisplatin (75 mg/m2) were the most often administered chemotherapy regimen. Usually, there were 2 cycles of chemotherapy before operation if needed. Postoperative chemotherapy routinely began within 60 days after the operation, or after the patient recovered from the complications. The cycles of adjuvant chemotherapy were variable as long as the combination of perioperative chemotherapy was a total 4 cycles. Adjuvant radiotherapies were administered by radiotherapy teams or in other institutions if needed.

3.5. Statistical Analysis

Kaplan-Meier graphs were used to demonstrate survival. Survival comparisons between groups of patients were completed using the Mantel-Cox log-rank test. All p values less than 0.05 were considered to be statistically significant. Data analysis was performed using SPSS (SPSS 21.0 for Windows).

4. Results

Between January 1st, 2007 and December 31st, 2018, 767 patients received surgery for esophageal cancer at thoracic surgery II. Among them, 143 patients did not meet inclusion criteria and were excluded, of whom 6 were due to loss of follow-up and 69 were because of lack of detailed adjuvant therapy data. Finally, 624 patients were enrolled in this research, of which 506 were males and 118 were females (Figure 1). The follow-up ended on January 1st, 2021, with a median follow-up of 45.3 (range, 3.8-145.9) months. The 1, 3, 5-year survival rates were 91.8%, 67.5%, 59.5% respectively for the entire cohort. According to received adjuvant therapy or not, the patients were divided into two groups: The Adjuvant Group (AD group) and the Observation Group (OB group). The characteristics of the eligible patients were shown in (Table 1). AD group presented a younger age comparing to OB group (median age 59.13±8.02 verses 61.78±7.75, p=0.000), which may indicate that older patients were more reluctanct to receive postoperative therapy.

Subgroup distribution and the regimen of neoadjuvant or adjuvant therapy were shown in Supplementary material.

The pT status of patients in each group are shown in (Table 2). For pN0 and pN1 patients, more patients with pT3 or higher received adjuvant therapy (p=0.000 and 0.014, respectively). For pN2+3 patients, no statistical differences were found on the pT status between OB and AD group (p=0.578)

(Figure 2a) shows the overall survival of patients without lymph node metastasis (confirmed by pathological test, pN0). As more patients were confirmed later pT stage in AD group (Table 2), the expected overall survival is lower than that of OB group. The addition of adjuvant therapy after surgery did not chage this tendancy (Figure 2a, p=0.002). On the other hand, if the patients received neoadjuvant therapy and been proved pN0, no statistical difference of overall survival between the OB and the AD groups was found

(Figure 2B, p=0.133). The small p-value and the separated curves may show a tendency that adjuvant therapy probably helps to improve the long-term overall survival, especially condering the later pT stage of AD group.

For patients with one to two lymph nodes metastasis (pN1), adjuvant therapy does not improve the long-term overall survival (p=0.368), although the survival rate of the AD group seems higher within 3 years postoperatively (Figure 2C). As more patients in AD group were staged pT3 or higher, the addition of adjuvant therapy may potentially contributed to the tendancy of improved OS.

For patients with more than two lymph nodes metastasis (pN2 and pN3, pN2+3), adjuvant treatment helps to improve the overall survival (Figure 2D, p=0.034).

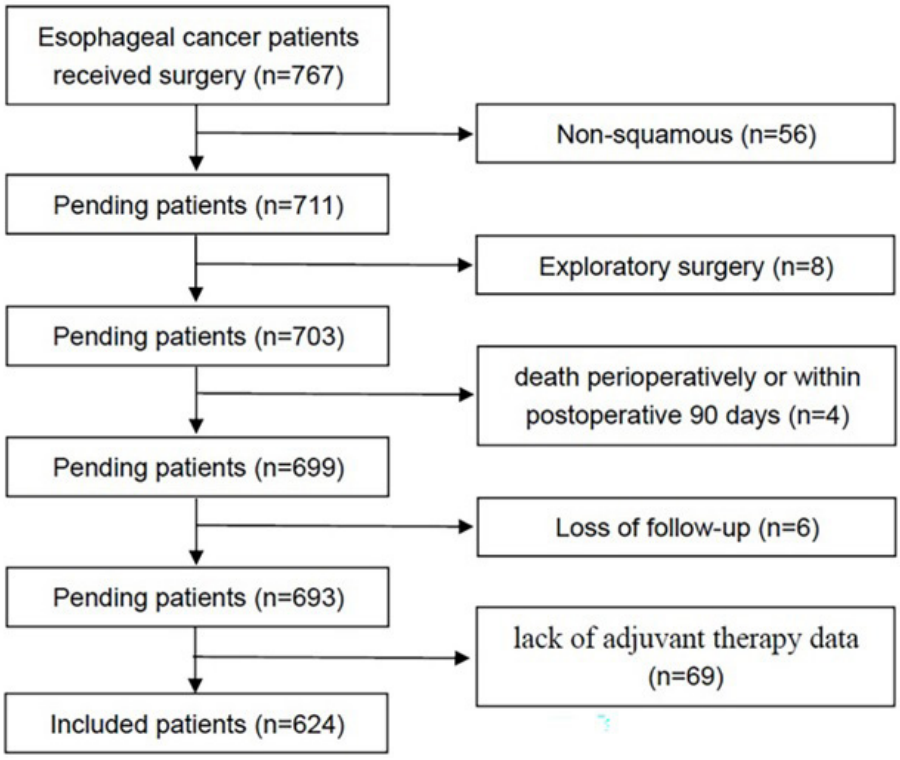

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) Diagram

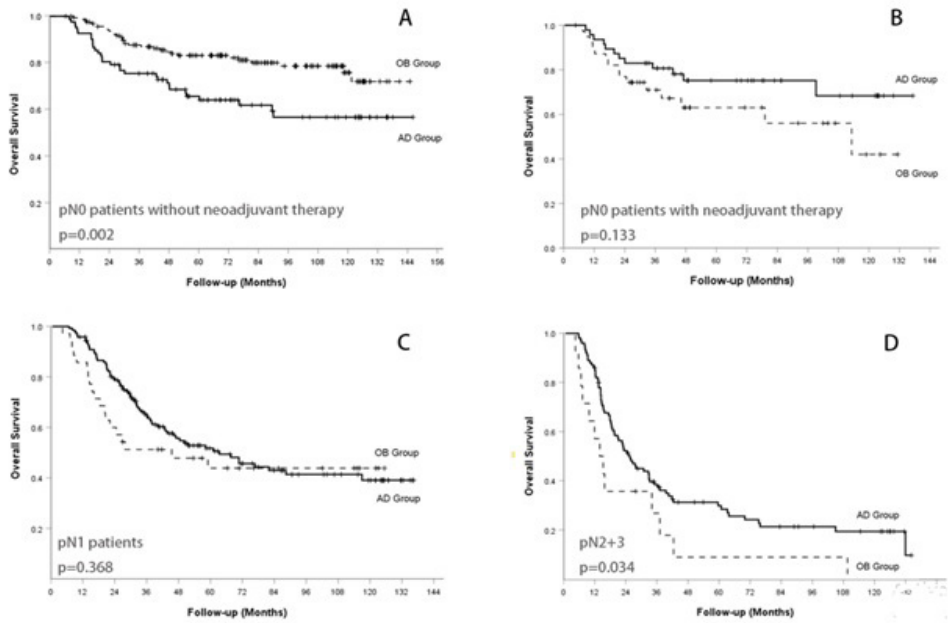

Figure 2: (A) For ESCC patients without neoadjuvant therapy, if pN0 was confirmed after surgery, patients received additional adjuvant therapy had worse survival outcome, which can be explained by the nature of later pT stage in this AD subgroup. (B) For ESCC patients who received neoadjuvant therapy and confirmed pN0 after surgery, adjuvant therapy does not benefit the overall survival (p=0.133). (C) For patients who confirmed pN1 after surgery, adjuvant therapy does not improve the long-term overall survival (p=0.368). (D)For patients with more than two lymph nodes metastasis (pN2+3), adjuvant therapy improved the overall survival (p=0.034).

Table 1: Characteristics of The Eligible Patients

	Total	OB group	AD group	P Value
Gender				0.069
Male	506	194	312	
Female	118	56	63	
Age	60.19±8.02	61.78±7.75	59.13±8.02	0.000
Location of tumor				0.031
Cervical	13	7	6	
Upper thoracic	126	62	64	
Middle/Lower thoracic	485	181	304	
Surgery				0.841
(Modified) Sweet	14	6	8	
(Modified) Ivor-Lewis	383	150	233	
(Modified) McKeown	227	94	133	
Grade				0.524
Well-differentiated	53	25	28	
Moderately differentiated	350	137	213	
Poorly differentiated	187	67	120	
Undifferentiated	3	0	3	
Unknown	31	21	10	

OB group: observation group; AD group: adjuvant group

Table 2: The pT status of different pN staging

		OB group (%)	AD group (%)	P value
pN0	pT0	10	3	0
	pT1	83	4	
	pT2	50	19	
	pT3	57	99	
	pT4	1	5	
pN1	pT0	2	1	0.014
	pT1	4	24	
	pT2	12	22	
	pT3	17	91	
	pT4	0	6	
pN2+3	pT0	0	0	0.578
	pT1	0	8	
	pT2	2	8	
	pT3	12	82	
	pT4	0	2	
	total	250	374	

Supplementary table 1: Subgroup distribution

			OB group (%)	AD group (%)
pN0	Neoadjuvant therapy	Yes	39 (19.4)	48 (39.1)
		No	162 (80.6)	82 (63.1)
	total		201	130
pN1	Neoadjuvant therapy	Yes	12 (34.3)	52 (36.1)
		No	23 (65.7)	92 (63.9)
	total		35	144
pN2+3	Neoadjuvant therapy	Yes	3 (21.4)	30 (30.0)
		No	11 (78.6)	70 (70.0)
	total		14	100

Supplementary table 2:

Treatment	Cases
Neoadjuvant therapy*	
No	440
Yes	184
Chemotherapy	173
Radiotherapy	0
Chemo+Radio, concurrent	2
Chemo+Radio, sequential	9
Adjuvant therapy	
No	250
Yes	374
Chemotherapy	99
Radiotherapy	156
Chemo+Radio, concurrent	30
Chemo+Radio, sequential	89

Most frequently used chemotherapy regimen is paclitaxel + platinum (88.56%). Other regimen included platinum with 5-FU, irinotecan, gemcitabine, docetaxel, albumin bound paclitaxel or tegafur.

5. Discussion

For patients with resectable esophageal squamous cell carcinoma, the latest NCCN guidelines for esophageal cancer and gastroesophageal junction carcinoma recommend no further therapies for patients after esophagectomy as long as R0 resection is achieved [4]. However, although supported only by weak evidence, the guidelines from Japanese Esophageal Society still recommends postoperative chemotherapy for cStage II or III esophageal carcinoma patients with pathologically confirmed lymph node metastasis who have undergone surgery without preoperative chemotherapy [11]. The role of adjuvant therapy for esophageal squamous cell cancer is still controversial.

JCOG 9204 was a randomized controlled trial comparing the outcomes of surgery alone with those of surgery plus postoperative chemotherapy [8]. No significant difference was observed in the 5-year overall survival rate between the two groups (52% vs 61%, P=0.13), however, a significant prolongation of the 5-year disease-free survival rate was noted in the latter group (45% vs 55%, P=0.037). Risk reduction by postoperative chemotherapy was remarkable in the subgroup with lymph node metastasis (5-year disease-free survival rate 38% vs 52%, P=0.041). A recent retrospective study was published in January 2021, Yang and colleagues enrolled 5944 patients with ESCC in total and found that patients with pN1 tend to benefit from adjuvant therapy but not pN0 patients [12]. A meta-analysis published in 2018 enrolled 9 studies to show that postoperative chemotherapy could improve overall survial (HR 0.78, 95% CI 0.66-0.91; P = 0.002) and disease-free survival (DFS) (HR 0.72, 95% CI 0.6-0.86; P < 0.001) in overall population [9].

On the contrary, some researchers found adjuvant therapy may not be as beneficial as expected, although most of the studies were retrospective. Chen and colleagues in their retrospective study enrolled 426 ESCC patients, among whom 272 patients did surgery alone and 154 patients did surgery plus adjuvant therapy [10]. In subgroup analysis (based on pN status), longer DFS was only found for surgery alone patients in pN0 subgroup (P=0.013) while no significant difference was found for DFS or OS between other subgroups. Yan and colleagues conducted another retrospective study with a propensity score match [13]. The research concluded that in patients who received esophagectomy, comparing with neoadjuvant therapy plus surgery, additional adjuvant therapy does not improve disease-free or overall survival (5-year disease-free survival 52.4% vs 43.6%, p=0.372, overall survival 68.6% vs 62.4%, p=0.359).

In our research, we enrolled 624 patients with ESCC, among whom 374 conducted adjuvant therapy. We found that adjuvant therapy plays different roles (harmful or beneficial) in patients with different pN statuses.

For patients with pN0, adjuvant therapy did not provide survival benefit for those who did not receive neoadjuvant therapy (Figure 2A, p=0.002). AD group had more pT3 or pT4 patients comparing to OB group and they were expected to suffer lower survival rate. However, for patients received neoadjuvant therapy and then confirmed pN0 after surgery, AD group showed a better survival curves, although no significant difference existed (Figure 2B, p=0.133). Besides the result that supported by other published researches mentioned before [8, 9, 12], We believe that adjuvant therapy benefits certain pN0 patients especially for those who received neoadjuvant therapy before. We consider that for these patients, their pN0 status may come from the downstage of neoadjuvant therapy. They may not be at the “real” early stage. Therefore, adjuvant therapy is perhaps useful for them.

For pN1 patients, no significant difference was found in long-term overall survival between the subgroups (Figure 3, p=0.368). However, in Figure 3, we can find that within 36 months of follow-up, the AD group enjoys a higher survival rate. This may be a clue that adjuvant therapy may benefit 1- and 3-year survival. In addition, AD group contained more patients staged pT3 or pT4, which is another clue that adjuvant therapy benefits this subgroup of patients.

For patients with more lymph nodes metastasis (pN2 or pN3), our research found that adjuvant therapy improves overall survival (Figure 4, p=0.034). This result is consistent with another research conducted by Matsuura and colleagues that concluded adjuvant chemotherapy may offer a significant additional benefit to the prognosis of esophageal cancer patients who have many positive lymph nodes (≥7, recurrence-free survival 25.9% vs 7.1%, p=0.04) even after neoadjuvant chemotherapy [14].

Overall, our research finds a clue that adjuvant therapy may benefit selected ESCC patients. Surgeons and the whole multidiscipline team should take into full consideration of patient's preoperative treatment, pathological staging, and postoperative recovery, to provide the most potentially beneficial and individualized treatment plan. On the other hand, neoadjuvant therapy has been established as a standard treatment for patients with locally advanced ESCC while immune checkpoint inhibitors now are actively involving in the war against tumors. More well-designed prospective researches are eagerly needed for the exploration of the best treatment model for ESCC patients, including the role of adjuvant therapy, in the coming new times.

Our study is limited by its retrospective nature. The sample size is not big enough for the most satisfying subgroup analysis. Most importantly, selection bias existed when physicians made decisions on which patients should receive adjuvant therapy.

6. Conclusion

Our study suggests adjuvant therapy does not benefit pN0 patients of ESCC who did not receive neoadjuvant therapy. While for pN0

patients who received neoadjuvant therapy before and pN1 patients, adjuvant therapy may help to improve the overall survival. For patients with more than two lymph nodes metastasis (pN2+3), adjuvant improves the overall survival. Researches with larger case number are needed to confirm these results.

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