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ORIGINAL ARTICLE

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Efficacy of programmed cell death protein 1 inhibitor in resection transformation treatment of esophageal cancer

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Abstract

Background: Surgery is an important component in the treatment of esophageal cancer. For patients not eligible for R0 resection, defined as locally advanced unresectable esophageal cancer, a new approach is to transform the cancer into a resectable state by preoperative treatment. However, preoperative chemo/radiation is unsatisfactory. Therefore, the aim of this study was to assess the safety and efficacy of chemo/radiotherapy combined with a programmed cell death protein 1 (PD-1) inhibitor in the preoperative transformation of unresectable esophageal cancer.

Methods: Patients were evaluated as having unresectable, locally advanced esophageal cancer at baseline and were re-evaluated as possible R0 resection candidates after PD-1 inhibitor treatment. Patient data were derived from the prospective database of Peking University Cancer Hospital Thoracic Surgery I. Preoperative chemotherapy plus PD-1 inhibitor treatment was defined as "transformation treatment." The objective response rate, operation rate (proportion of patients who underwent surgery), R0 rate, and treatment safety were analyzed retrospectively.

Results: A total of 36 patients were enrolled into the study, and 94.4% (34/36) completed the planned transformation treatment. The objective response rate was 71.4% (25/35), and 75% (27/36) of the patients who completed transformation treatment underwent surgery. For these surgical patients, 81.5% (22/27) obtained R0 resection, and 22.2% (6/22) had pathological complete response (pCR). During transformation treatment, 22.2% (8/36) patients had ≥ grade 3 complications. There were no reoperations or perioperative deaths. After surgery, 29.6% (8/27) had ≥ grade 3 complications.

Conclusions: Esophagectomy after immunotherapy is safe with acceptable complications. Compared with chemotherapy alone, chemotherapy combined with immunotherapy had a more favorable transformation effect for patients with unresectable esophageal cancer.

KEYWORDS
immunotherapy, PD-1 inhibitor treatment, unresectable esophageal cancer

INTRODUCTION

The staging of esophageal cancer determines the formulation of treatment strategy. Endoscopic treatment is generally accepted as the best treatment for patients with intramucosal cancer (T1aN0).[1–4] Endoscopic treatment can eradicate the disease while protecting the organ. For locally advanced esophageal cancer (T>2 or N+), the basic treatment principle is preoperative neoadjuvant treatment followed by surgery (based on current evidence), with the goal of improving long-term survival.[1–4] However, in clinical practice, some patients who are evaluated as unresectable (non-R0 resection) before treatment also undergo esophagectomy after preoperative treatment. In these patients, the preoperative treatment should be regarded as transformation treatment that increases the R0 resection rate, the aim of which is to transform unresectable cancer to

resectable status (R0). Unfortunately, the transformation rate of traditional preoperative treatment is relatively low.[5–7]

There are some positive data for the effect of programmed cell death protein 1 (PD-1) inhibitor treatment in advanced esophageal cancer and postoperative adjuvant treatment for locally advanced esophageal cancer.[8–16] It is still uncertain whether a PD-1 inhibitor could change the paradigm of esophageal cancer treatment, in particular whether it could finally improve long-term survival. Because many clinicians are investigating preoperative immunotherapy,[17–20] there is an urgent need to evaluate the safety of surgery after PD-1 inhibitor treatment. With good communication between clinicians and patients, and strict ethical supervision, it is reasonable to include immunotherapy in the preoperative setting and to perform surgery for unresectable locally advanced esophageal cancer as evaluated at baseline examination.

METHODS

Patient selection

We included patients who were treated between January 2018 and March 2021; patients were identified from the prospective database of Peking University Cancer Hospital Thoracic Surgery I. Inclusion criteria were as follows: (i) treatment of naïve patients who were pathologically confirmed as having esophageal cancer, (ii) cancers evaluated as unresectable (cT4 and/or cN3), and (iii) patients who received immunotherapy (PD-1 inhibitor). Exclusion criteria were as follows: (i) patients who were still receiving transformation treatment. The Ethics Committee of Peking University Cancer Hospital agreed exemption of informed consent for this study.

Staging methods and follow-up

The work-up of the patients in the prospective database included the following tests: (i) gastroscopy and biopsy, (ii) chest enhanced computed tomography (CT) and esophageal enhanced magnetic resonance imaging (MRI), (iii) positron-emission tomography (PET)-CT, and (iv) upper gastrointestinal radiography. After each cycle of transformation treatment, chest enhanced CT was performed, and, after two or four cycles of transformation treatment, gastroscopy, esophageal enhanced MRI, and PET-CT were included to evaluate the efficacy of transformation treatment. The clinical and restaging after treatment were determined twice each week at the data evaluation meeting in the Peking University Cancer Hospital Thoracic Surgery I. Patient stage was established according to the eighth TNM staging system of Union for International Cancer Control and the American Joint Committee on Cancer staging system.[21]

Transformation treatment

The chemotherapy regimen included paclitaxel-albumin (260 mg/m^2 D1) and cisplatin (75 mg/m^2 D1) with a 21-day cycle. The immunotherapy regimen was a PD-1 inhibitor administered in at least two cycles. After transformation treatment, RECIST 1.1 standard was adopted for imaging evaluation. Adverse effects were evaluated according to CTCAE 4.0.

Surgical indications

After transformation treatment, the patients with initially unresectable esophageal cancer who obtained nonenlarged stable disease, partial, or complete response were re-evaluated as potential local (primary site and regional lymph nodes) R0 resection candidates. These candidates underwent surgery after full negotiation with the patients and their families.

Observation indices

Major indices: overall response rate (ORR); minor indices: surgical rate after transformation treatment, R0 resection rate, and perioperative complications. The definition and classification of perioperative complications were according to the Society of Thoracic Surgeons and the General Thoracic Surgery Database. The modified Clavien complication grading system was adopted for complication grading. Clavien 1–2 complications were defined as mild, and Clavien 3–5 were defined as severe.

Statistical analysis

This investigation was a nonrandomized retrospective study. SPSS 24.0 software was used for data analysis, and $p < 0.05$ was defined as statistically significant.

RESULTS

General characteristics of patients

Our department treated 628 esophageal cancer patients from January 2018 to March 2021. According to the inclusion and exclusion criteria, 36 patients were eventually enrolled into the study (Figure 1). Thirty-two patients (88.9%) were men, and four patients (11.1%) were women (male-to-female ratio of 8:1). The median age was 62 years (range 43–81). Table 1 shows the general characteristics of the patients and specific clinical stages. Six patients (16.7%) had cM1, five had supraclavicular lymph node metastasis, and one patient had vertebral metastasis.

Transformation treatment and outcome

All patients received preoperative immunotherapy, including one patient (2.8%) with immunotherapy alone,

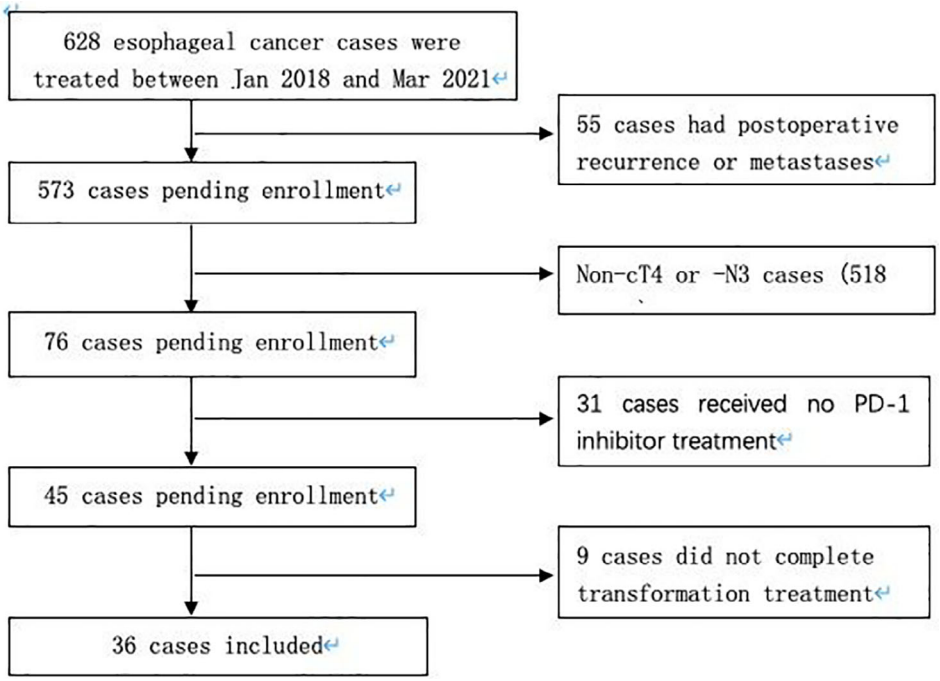

FIGURE 1 Study enrollment

TABLE 1 General information and patient clinicopathological characteristics

Characteristics		No. (%)
Age, year	Median	62
	Range	43–81
Sex	Male	32 (88.9%)
	Female	4 (11.1%)
ECOG performance status	0	26 ((72.2%)
	1	10 (27.8%)
Tumor length, cm	Median	5
	Range	2–10
Tumor location	Cervical	1 (2.8%)
	Proximal third	6 (16.7%)
	Middle third	13 (36.1%)
	Distal third	16 (44.4%)
Clinical T stage	cT1	1 (2.8%)
	cT2	4 (11.1%)
	cT3	13 (36.1%)
	cT4	18 (50.0%)
Clinical N stage	cN1	10 (27.8%)
	cN2	10 (27.8%)
	cN3	16 (44.4%)
Clinical M stage	cM0	30 (83.3%)
	cM1	6 (16.7%)
Clinical stage	cIVa	30 (83.3%)
	cIVb	6 (16.7%)

34 patients (94.4%) with immunotherapy combined with chemotherapy, and one patient (2.8%) with immunotherapy combined with chemoradiotherapy. The patients received 1–7 cycles of preoperative treatment, 83.3% received 2–4 cycles of preoperative treatment, and the chemo-regimen was predominantly paclitaxel and cisplatin (94.1%). A total of 35 patients (97.2%) had restaging examinations after immunotherapy; one patient did not have a restaging examination due to severe pulmonary infection. The ORR was 71.4% (25/35), including nine clinically complete response (cCR) patients (25.7%) and 16 pCR patients (45.7%). Twenty-three patients (65.7%) had tumor downstage after treatment.

Surgical treatment

A total of 27 patients (75%) underwent surgery after immunotherapy, nine patients did not undergo surgery, including five with cSD/PD, three with cCR, and one patient with a grade 3 adverse effect due to immunotherapy.

Table 2 and Figure 2 summarize the general information of the 27 patients who underwent surgery. Twenty-two of the patients (81.5%) had R0 resection, one (3.7%) had R1 resection, and four patients (14.8%) had R2 resection, one of which was found to have liver metastases intraoperatively. Six patients (22.2%) had salvage surgery. The median operative time of the group was 221 min, and average blood loss was 104 ml. Fifteen patients (55.6%) had abnormal esophageal mesentery. Six patients (22.2%) had pCR as confirmed by postoperative pathological report. Twenty-three patients had endoscopic esophagectomy, two had transhiatal esophagectomy, and two patients had Sweet esophagectomy. There was no conversion to thoracotomy.

TABLE 2 Staging and surgical information of patients that underwent surgery (N = 27)

No.	Age	Clinical stages	Stages after transformation therapy	Clinical efficacy evaluation	Surgical procedure	Curative extent	Pathological staging	Surgical time (min)	Blood loss (ml)	Normal esophageal mesentery
1	56	cT3N2M1	ycT2N1M1	PR	McKeown	R0	ypT0N1M1	489	110	No
2	81	cT4N2	ycT1N0	CR	THE	R0	ypT0N0	190	120	No
3	53	cT3N2M1	ycT2N1	PR	McKeown	R0	ypT2N0	208	90	Yes
4	64	cT4N2M1	ycT1N0	CR	McKeown	R0	ypT0N0	180	50	No
5	62	cT1bN3	ycT1N3	SD	McKeown	R0	ypT1bN1	170	55	No
6	62	cT4N1	ycT2N1	PR	McKeown	R0	ypT2N0	180	60	No
7	60	cT3N3	ycT3N1	PR	McKeown	R0	ypT3N0	208	55	Yes
8	67	cT4N2	ycT4N2	SD	McKeown	R0	ypT4aN2	250	90	No
9	59	cT4N3	ycT3N2	PR	Sweet	R0	ypT4aN1	180	150	No
10	43	cT4N2	ycT3N2	PR	McKeown	R1	ypT2N1	340	400	No
11	70	cT4N1	ycT3N1	PR	McKeown	R0	ypT3N0	180	55	No
12	68	cT3N3	ycT1N0	CR	McKeown	R0	ypT0N0	150	90	Yes
13	71	cT3N3	ycT1N0	CR	McKeown	R0	ypT0N0	160	100	Yes
14	53	cT4N1	ycT2N1	PR	THE	R0	ypT1bN1	190	135	Yes
15	54	cT3N3	ycT3N2	PR	McKeown	R0	ypT3N1	160	105	No
16	52	cT4N2	ycT4N1	SD	McKeown	R0	ypT4aN1	220	90	No
17	45	cT4N1	ycT4N1	PD	Sweet	R2	ypT4bN2	360	300	No
18	63	cT4N1	ycT3N0	PR	McKeown	R2	ypT4bN0	130	85	No
19	61	cT3N3	ycT3N2	PR	McKeown	R0	ypT0N1	170	50	Yes
20	54	cT3N3M1	ycT3N3M1	SD	McKeown	R2	ypT4aN3M1	240	110	No
21	62	cT3N3	ycT1N0	CR	McKeown	R0	ypT0N0	220	95	Yes
22	56	cT2N2M1	ycT2N1	PR	McKeown	R0	ypT2N0	213	60	Yes
23	65	cT2N3	ycT2N1	PR	McKeown	R0	ypT1bN1	235	45	Yes
24	59	cT3N3	ycT3N2	PR	McKeown	R0	ypT3N0	250	95	Yes
25	57	cT2N3	ycT1N1	PR	McKeown	R2	ypT1bN2M1	240	105	Yes
26	65	cT3N3	ycT1N0	CR	McKeown	R0	ypT0N0	245	50	Yes
27	49	cT4N1	ycT3N1	PR	McKeown	R0	ypT3N0	210	55	No

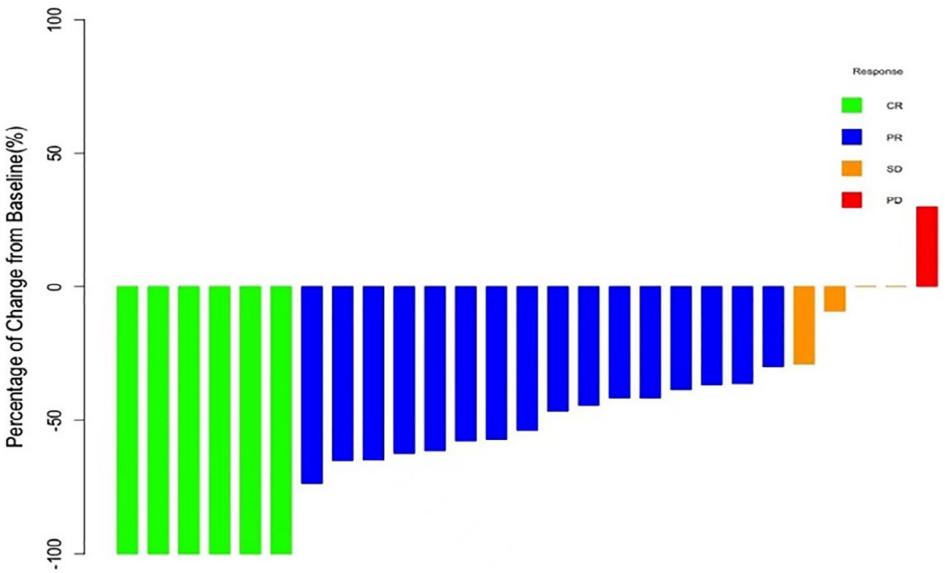

FIGURE 2 Waterfall chart of curative effect of transformation therapy for surgical patients

Complications during transformation treatment

A total of 34 patients (94.4%) completed preoperative treatment; two patients did not complete the treatment plan, either because of pneumonia or upper gastrointestinal bleeding. Eight patients (22.2%) had ≥ grade 3 complications during transformation treatment, including five patients with leukocytopenia (two patients also combined with granulocytopenia), one patient with pulmonary infection, one patient with upper gastrointestinal bleeding, and one patient with hair loss. There was no death caused by the transformation treatment, and no reoperations or perioperative deaths. The postoperative complication rate was 51.9% (14/27), and ≥ grade 3 complication rate was 29.6% (8/27). Six patients incurred respiratory complications (four with pleural effusion, one with pulmonary infection, and one with respiratory insufficiency), one patient had anastomotic leakage, and one patient had anastomotic stenosis (see Table 3).

TABLE 3 Complications during transformation therapy

Events	No. (%)
Postoperative events of grade ≥3 ($N = 27$)	
Pleural effusion	4 (14.8%)
Pneumonia	1 (3.7%)
Respiratory insufficiency	1 (3.7%)
Anastomotic leakage	1 (3.7%)
Anastomotic stenosis	1 (3.7%)
Events of any grade during neoadjuvant therapy ($N = 36$)	
Leukopenia	8 (22.2%)
Decreased neutrophil count	4 (11.1%)
Elevated transaminase	6 (16.7%)
Thyroid dysfunction	3 (8.3%)
Pneumonitis	1 (3.7%)
Esophageal hemorrhage	1 (3.7%)
Alopecia	1 (3.7%)
Events of grade ≥3 during neoadjuvant therapy ($N = 36$)	
Leukopenia	5 (13.9%)
Decreased neutrophil count	2 (5.6%)
Pneumonitis	1 (3.7%)
Esophageal hemorrhage	1 (3.7%)
Alopecia	1 (3.7%)

DISCUSSION

The patients assessed in this study were initially evaluated as having unresectable (non-R0) esophageal cancer, including cT4 or N3 with supraclavicular lymph nodes metastasis and staging IV esophageal cancer with M1. After preoperative treatment including a PD-1 inhibitor, the ORR was 71.4% (25/36), and 83.3% (30/36) of the patients were re-evaluated as having resectable cancers (R0). Three patients who obtained subjective clinical symptom disappearance and objective cCR refused surgical treatment. Therefore, the actual R0 resection rate was 81.5% (22/27) for patients who underwent surgery. After surgery, 22.2% (6/27) had pCR confirmed by postoperative pathology. The R0 resection rate in our study was higher than the 39.6% R0 resection rate in a study by Yokota et al. in which a DCF regimen was used.[22]

As to surgical safety, we suggest that it can be divided into two aspects. First, there was no perioperative death. During preoperative treatment, only one patient failed to undergo surgery due to severe pneumonia. Further, there was a complete absence of postoperative complications linked to immunotherapy. In addition, inclusion of a PD-1 inhibitor enhanced the treatment efficacy. We suggest that the addition of immunotherapy did not increase surgical difficulty or perioperative complications. However, we did observe that although intraoperative blood loss did not increase (104 ml in our group compared with 118 ml after chemotherapy alone), the surgery was more difficult. The dense fibrous scar tissue in the esophageal mesentery obscured the boundary between the "tumor" and surrounding organs and tissues during resection (55.6%), and the operation time was longer (221 min as compared with 214 min after chemotherapy alone). In addition, postoperative complications were greater than the complications of patients at earlier stages. The postoperative complication rate was 51.9% (14/27) in this study, and 29.6% (eight patients) had ≥grade 3 complications, whereas for the entire group, the postoperative complication rate and ≥grade 3 complication rate were 48.8% and 17.8%, respectively.[23] In contrast, in the study of Yokota et al., the postoperative complication rate and ≥grade 3 complication rate after chemotherapy alone were 76.2% (16/21) and 23.8% (5/21), respectively.[22] However, it remains to be determined whether the difficulty of surgery after transformation therapy was related to immunotherapy or related mainly to the tumor itself. Our study group initially had unresectable cancers, including cT4 and multistations of lymph nodes with extranodal invasion. In these patients, even if the tumor had shrunk after transformation treatment, there was still fibrous scarring in the esophageal mesentery. This kind of mesangial change was also common in patients with tumors of the same stage who received neoadjuvant chemo/radiotherapy.[24,25]

Currently, the data are promising for immunotherapy in esophageal cancer, including the second-line treatment for advanced esophageal cancer in Keynote-181,[11,12] the first-line treatment for advanced esophageal cancer in Keynote-590,[13] the first-line treatment for east Asian advanced esophageal squamous cell carcinoma in ATTRACTION-03,[9] the adjuvant treatment for N+ patients in CheckMate-577,[14] and the induction treatment for locally advanced resectable esophageal squamous cell carcinoma in PALACE-1.[18] However, for this new mode of treatment, the safety of surgery is the first concern. With complete communication and strict supervision, it is a reasonable option to assess the safety of surgery after induction immunotherapy for patients with unresectable esophageal cancer.

In clinical practice, most esophageal cancer patients are locally advanced, and they receive treatment with dismal efficacy. For the treatment principle of locally advanced resectable esophageal cancer, the current data support surgery after preoperative neoadjuvant chemoradiotherapy. However, there are some problems with preoperative chemoradiotherapy. First, preoperative chemoradiotherapy requires a high demand of treatment facilities, particularly a high demand of radiation techniques. However, not all Chinese medical centers have a radiotherapy department. For some centers, even if they have a radiotherapy department, the staff, devices, and techniques are not uniform, making radiotherapy in China hard to standardize. In addition, because the perioperative complications after chemoradiotherapy are numerous, the requirements for a management team, anesthesia, and ICU are also high. However, in China, the management team, anesthesia, ICU, and postoperative management homogenization level for esophageal cancer are also not the same. Therefore, although the data is promising for preoperative chemoradiation for locally advanced esophageal cancer, the proportion of patients who receive chemoradiation is less than 10%. Conversely, neoadjuvant chemoradiation increased the pCR rate of locally advanced esophageal cancer (NEOCRTEC5010: 43.2%, CROSS: 29%); data from NEOCRTEC5010 and CROSS both showed that higher pCR did not mean better overall survival.[26–28]

For patients considered to have unresectable cancers at the time of initial diagnosis, the standard treatment was curative chemoradiotherapy. Although a small number of patients obtained long-term survival from this treatment strategy, 77.5% of patients had disease progression after treatment, and 44.4% died of tumor progression.[29] At the same time, esophageal fistula caused by curative chemoradiotherapy has been of great concern in clinical practice. Yokota et al.[22] conducted a phase II clinical trial of patients who had unresectable cancers at the time of initial diagnosis. The patients were treated with three cycles of transformation therapy with a DCF regimen, and were then selected for surgical resection or curative chemoradiotherapy according to the efficacy of chemotherapy. The response rate of DCF chemotherapy was 31.3%, and 37.5% (18/48) of the patients underwent the subsequent surgical treatment. One patient underwent surgical resection after chemoradiation, and the total R0 resection rate was 39.6%. There were no postoperative complications or surgery-related death.

With the introduction of immunotherapy, new theories and treatment methods should be investigated for esophageal cancer treatment strategies. These strategies should include scenarios such as preoperative treatment and postoperative treatment for patients with advanced or locally advanced resectable/unresectable disease.

Our study had some limitations. First, it was retrospective with a relatively small sample size. The aim of the study was not to measure improvement of long-term survival or R0 resection. Second, the patients had clinically unresectable cancers (cT4 or cN3), and it was not known whether the difficulty of surgery after transformation therapy was related to immunotherapy or to the tumor itself. Third, the study was an investigational observation analysis without data for long-term efficacy.

In conclusion, esophagectomy after immunotherapy is safe with acceptable complications for unresectable locally advanced esophageal cancer. Compared with chemotherapy alone, chemotherapy combined with immunotherapy might become the new treatment strategy for patients with unresectable esophageal cancer.

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CONFLICT OF INTEREST

The authors confirm that there are no conflicts of interest.

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