Original Article

Neoadjuvant sintilimab plus chemotherapy for locally advanced esophageal squamous cell carcinoma: a single-arm, single-center, phase 2 trial (ESONICT-1)

Zhenyang Zhang[1,2#], Zhi-Nuan Hong[1,3#^], Shuhan Xie[1,3#], Wenwei Lin[1], Yukang Lin[3], Jiafu Zhu[1], Xiaojie Yang[1], Zhiwei Lin[1], Jiangbo Lin[1,2*], Mingqiang Kang[1,2*]

[1]Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou, China; [2]Key Laboratory of Cardio-Thoracic Surgery (Fujian Medical University), Fujian Province University, Fuzhou, China; [3]Fujian Medical University, Fuzhou, China

Contributions: (I) Conception and design: J Lin, M Kang; (II) Administrative support: M Kang; (III) Provision of study materials or patients: Z Zhang, ZN Hong, S Xie; (IV) Collection and assembly of data: ZN Hong; (V) Data analysis and interpretation: ZN Hong, Z Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work and should be considered as co-first authors.

[*]These authors contributed equally to this work and should be considered as co-corresponding authors.

Correspondence to: Mingqiang Kang, MD; Jiangbo Lin, MD. Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou 350001, China. Email: kangmingqiang0799@163.com; jiangbolin8009@sina.com.

Background: To investigate the safety and feasibility of combining neoadjuvant sintilimab (Innovent Biologics, Suzhou, China) and chemotherapy for locally advanced esophageal squamous cell carcinoma (ESCC).

Methods: The study was an investigator-initiated, open-label, non-randomized, single-arm, single-center phase 2 trial. Patients aged between 18 to 75 years with locally advanced ESCC were eligible for neoadjuvant immunochemotherapy (nICT). The nICT included cisplatin (60 mg/m^2) on day 1, albumin-bound paclitaxel (125 mg/m^2) on days 1 and 8, and sintilimab (200 mg) on day 1 of each 21-day cycle. Clinical evaluation was conducted after 2 cycles of nICT. Within 4–6 weeks after nICT, patients underwent esophagectomy. The primary end points were pathological complete response (pCR) and adverse events (AEs). Secondary endpoints included major pathological response (MPR), R0 resection rate, interval to surgery, and 30-day complications. This trial was registered at chictr.org.cn, ChiCTR2100045659.

Results: From July 2020 to June 2021, 30 patients were enrolled. All patients successfully completed 2 cycles of nICT. AEs were common during nICT, and the most common AE was anorexia (20/30, 67%). However, only one patient with grade 3 ESCC had increased transaminase. According to radiologic evaluations, the objective response rate (ORR) was 67% (20/30) and the disease control rate 97% (29/30). Twenty-three patients underwent McKeown minimally invasive esophagectomy (MIE). The pCR rate of the primary tumor was 21.7%, and the MPR rate of the primary tumor was 52.2%. The median interval to surgery was 40 days, and no patients delayed surgery due to AEs. Pneumonia was the most common major 30-day postoperative complication (9/23, 39%). Anastomotic leakage (AL) occurred in two patients during the hospital stay, and one patient was readmitted due to AL. There was no treatment- or surgery-related deaths.

Conclusions: Neoadjuvant sintilimab plus chemotherapy for locally advanced ESCC appears to be safe and feasible with limited AEs, high R0 resection rate, promising pCR rate, and manageable postoperative complications. Long-term follow-up is required. A multicenter, randomized, phase III clinical trial assessing the efficacy and safety of sintilimab versus placebo in combination with chemotherapy in locally advanced ESCC is warranted to confirm these results.

^ ORCID: 0000-0002-1800-6158.

Keywords: Esophageal squamous cell carcinoma (ESCC); clinical trial; phase II; neoadjuvant immunochemotherapy (nICT)

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Introduction

With about 572,000 newly diagnosed cases and 509,000 deaths annually, esophageal cancer ranks as the seventh most commonly diagnosed cancer and the sixth most common cause of cancer-related mortality worldwide (1). Latest data from the National Cancer Center of China shows that the incidence of esophageal cancer ranked sixth, and mortality ranked fourth (2). Over 90% esophageal cancers are esophageal squamous cell carcinomas (ESCC). Currently, neoadjuvant chemoradiotherapy (nCRT) plus esophagectomy is the first choice for locally advanced, operable ESCC (3,4). Based on the JCOG9907 trial results, neoadjuvant chemotherapy (nCT) plus esophagectomy have been advocated as another standard care approach in Asia (5). However, the long-term survival of nCT or nCRT plus esophagectomy for ESCC is still not promising (6). Thus, the establishment of new and effective treatment strategies is crucial to further improve the long-term survival rate for people with ESCC.

Antibodies against the immune inhibitory pathway of programmed death 1 (PD-1) protein or PD-1 ligand 1 (PD-L1) checkpoint inhibitors is a relatively modern innovation in the treatment of malignancies. About 18.3% to 43.9% of ESCC patients have PD-L1 overexpression, and this overexpression is associated with poor prognosis (7,8). The PD-1-positive rate was ranged 33.5% to 50% in patients with ESCC (7,8). Pembrolizumab (targeting PD-1) plus chemotherapy have demonstrated antitumor effects and have already been recommended as first-line therapy for advanced esophageal cancer (9). Sintilimab (Innovent Biologics, Suzhou, China) is another monoclonal antibody against PD-1, which has been approved by China of National Medical Products Administration and the US Food and Drug Administration. Sintilimab binds to PD-1 and blocks the interaction between PD-1 and its ligand, helping to restore the anti-tumor response of T cells (10). *Previous vitro study indicated that* the binding affinity of sintilimab was high with a low dissociation constant. Thus, compared with pembrolizumab and nivolumab, sintilimab has shown anti-tumor effects and safety similar to those of pembrolizumab and nivolumab in advanced non-small cell lung cancer (NSCLC), Hodgkin's lymphoma, and natural killer/T cell lymphoma (10,11). Results of IBI308 confirmed a dose of 200 mg per 3 weeks (q3w) in further studies (12). In the ORIENT-2 trial, 190 patients with advanced ESCC refractory to first-line chemotherapy were randomly assigned to receive sintilimab (200 mg, q3w) or chemotherapy (albumin-bound paclitaxel, 175 mg/m^2, q3w; or irinotecan, 180 mg/m^2, per 2 weeks). The median overall survival (OS) was 7.2 and 6.2 months, respectively, and the objective response rates (ORRs) were 12.6% and 6.3%, respectively (13). Although immunotherapy has showed promising results in advanced ESCC, however, the efficacy and safety of combination of PD-1 or PD-L1 with chemotherapy for locally ESCC. Recently, a retrospective analysis showed that neoadjuvant immunochemotherapy (nICT) for locally advanced ESCC has promising outcomes including: a high pathological complete response (pCR) rate (9/27, 33.3%), high microscopically margin-negative (R0) resection rate (26/27, 96.3%), and a low-toxicity profile (2/28, 7.1%, ≥ grade 3) (14). Based on the above compelling rationale, the role of PD-1 or PD-L1 inhibitors combined with chemotherapy in neoadjuvant treatment for locally advanced ESCC has gained much attention (e.g., NCT04654403, NCT04506138, NCT03946969, NCT04177797, NCT04280822).

To our knowledge, there is still no report on nICT for locally advanced ESCC. It is reasonable to conduct this single-arm trial to investigate the safety and feasibility of neoadjuvant sintilimab plus chemotherapy as first-line therapy for locally advanced ESCC. We present the following article in accordance with the TREND reporting checklist (available at https://dx.doi.org/10.21037/atm-21-5381).

Methods

Study design and inclusion criteria

The study was an investigator-initiated, open-label, non-

randomized, single-arm, single-center phase 2 trial. This study was approved by the Ethics Committee of the Fujian Medical University Union Hospital (No. 2020YF021-02), China, and followed the principles of the Helsinki Declaration (as revised in 2013). Patients were recruited by the investigator, and the sample size was set as 30. In addition, patients' written informed consent was obtained. The trial registration number is ChiCTR2100045659.

Patients with histologically confirmed ESCC were eligible for inclusion in the study. Patients diagnosed with adenocarcinoma or large-cell undifferentiated carcinoma were excluded. Patients who had esophagogastric junction tumors or proximal gastric tumors with minimal invasion of the esophagus were excluded. Only patients with cT3-T4aN0-3M0 or cT1-2N1-3M0 were enrolled. Tumor, nodes, and metastases (TNM) or clinical stage was determined according to the 8th edition American Joint Committee on Cancer/Union for International Cancer Control staging system (AJCC 8th). Eligible patients were aged between 18 to 75 years with Eastern Cooperative Oncology Group (ECOG) status below 2 (with 0 indicating fully active, 1 unable to carry out heavy physical work, and 2 unable to carry out any work activities). Patients with heart, lung, or liver dysfunction, or acute infection were excluded. Patients with a history of other cancers or previous therapy (including radiotherapy, chemotherapy, and submucosal resection) were also excluded.

Therapy protocol

Pretreatment staging

Pretreatment staging includes taking a history; physical examination; routine hematology and biochemical tests; upper gastrointestinal endoscopy combined with tissue biopsy; computed tomography scans of the neck, chest, and upper abdomen; lung function tests; and cervical ultrasonography.

Neoadjuvant therapy

Cisplatin (60 mg/m^2) on day 1, albumin-bound paclitaxel (125 mg/m^2) on days 1 and 8, and sintilimab (200 mg) on day 1 were administered intravenously during each cycle (of 21-day duration). Patients regularly received intravenous administration of methylprednisolone, omeprazole, and glutathione, and oral administration of loratadine. The neoadjuvant therapy cycle was cycle 2. Clinical evaluation was conducted after 2 therapy cycles. For patients with tumor shrinkage, a multidisciplinary discussion took place to determine whether to continue with nICT or carry out surgery.

Surgery

Esophagectomy was performed within 4–6 weeks after completion of nICT. In our institution, McKeown minimally invasive esophagectomy (MIE) with two-field lymphadenectomy and gastric reconstruction is regularly conducted. For patients with cervical lymph node involvement or a tumor located in the proximal third of the esophagus, McKeown MIE with three-field lymphadenectomy was performed. All operations were conducted by M Kang and J Lin at the Fujian Medical University Union Hospital. Both surgeons perform more than 100 esophagectomy per year. Follow-up were conducted every 3 months during the first year after the end of treatment, and every 6 months during the second year, and then at the end of each year until 5 years after treatment.

Outcome assessment

Toxic effects were closely monitored using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (CTC AE5.0) up to 90-day after the last cycle of nICT. The key secondary and exploratory end points were pathological. Changes in tumor size were evaluated following response evaluation criteria in solid tumors (RECIST) version 1.1 (15) and categorized into progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR).

The depth of invasion, lymph node metastasis, and resection margin were evaluated and staged based on the AJCC 8th (16). Major pathological response (MPR) was defined as less than 10% of residual tumor cells, and pCR was defined as no evidence of residual tumor cells. Microscopically positive (R1 resection) was defined as a vital tumor is present at 1 mm or less from the proximal, distal, or circumferential resection margin (17).

Interval to surgery was defined as the end of last cycle to date of surgery. Operation time was defined as time from the incision to wound closure. Postoperative complications within 30-day after operation were coded using the Clavien-Dindo classification. Major complications were defined as Clavien-Dindo classification grade ≥3.

Statistical analysis

Normally distributed continuous variables were described

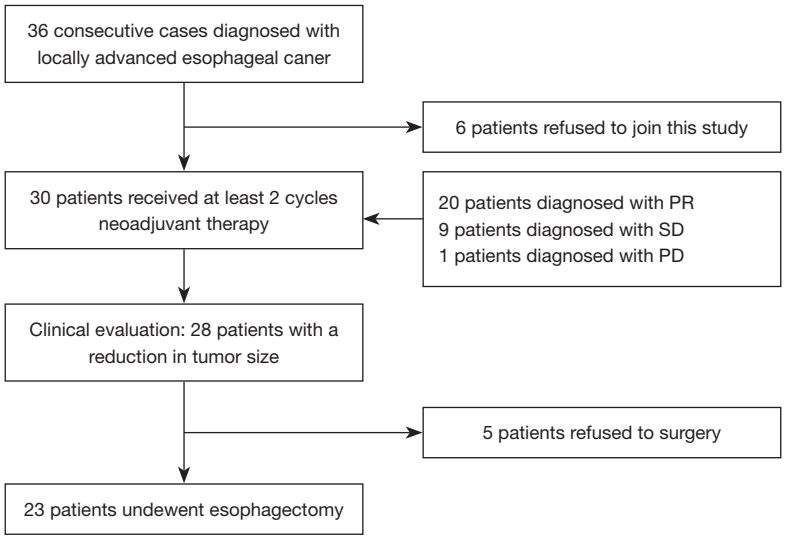

Figure 1 Patient selection flowchart. PR, partial response; SD, stable disease; PD, progressive disease.

as means ± standard errors of the mean, nonnormally distributed continuous variables were described as medians (interquartile ranges), and categorical variables were described as frequencies (percentages). A two-sided P value <0.05 was considered as indicating statistical significance. The statistical analysis was conducted using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline demographic and clinical characteristics

From July 2020 to June 2021, a total 36 patients were eligible for inclusion, and six patients declined to participate in this study. In total, 30 patients were enrolled and treated with at least two cycles of nICT (*Figure 1*). Most patients were male (26/30, 87%), and only four patients were female. Mean age was 58.3±7.1, and mean body mass index (BMI) was 21.5±2.5. Due to the high proportion of males, smoking history (18/30, 60%) and drinking history (14/30, 47%) were high. There were three patients diagnosed with diabetes (3/30, 10%), and three patients diagnosed with hypertension (3/30, 10%). Eighteen tumors were located in the middle third of esophagus (18/30, 60%). Only two tumors were located in the upper third of esophagus (2/30, 7%). Stage III ESCC accounted for 90% of included patients (27/30), whereas three patients (3/30, 10%) were diagnosed with stage IVA. Baseline demographic and clinical characteristics are summarized in *Table 1*.

Safety and feasibility

The therapy-related AEs are summarized in *Table 2*. During the nICT period, 28 patients developed treatment-related AEs of any grade. The most common AEs were anorexia (20/30, 67%), anemia (15/30, 50%), increased transaminase (9/30, 30%), decreased neutrophil count (8/30, 27%), and leucopenia (8/30, 27%). Most treatment-related AEs were grade 1 or grade 2. Only one patient suffered grade 3 increased transaminase and recovered after drug treatment (1/30, 3%). No patient had pneumonitis or esophageal hemorrhage.

All patients received two cycles of treatment, 23 (23/30, 77%) patients underwent McKeown MIE. Reasons for not undergoing surgery were: one patient with PD after completing two therapy cycles, and in six patients refusal to undergo surgery due to high risk of surgery or low quality of life after surgery. Patients who refused surgery continued to receive sintilimab combined chemotherapy. The interval to surgery was 40.0 days ((interquartile range, 31.5–48.5 days). No surgery was delayed due to treatment-related events. Among the 23 patients who underwent esophagectomy (one robotic-assisted MIE and 22 video-assisted MIE), no patient was converted to open surgery. The median harvest number of lymph nodes were 13.0 (interquartile range, 12.5–14.0). Postoperative complications are summarized in *Table 3*. Pneumonia was the most common postoperative complication (15/23, 65%) and major postoperative complication (9/23, 39%).

Table 1 Baseline demographic and clinical characteristics

Characteristics	Value
Male, n [%]	26 [87]
Age (years), mean ± SEM	58.3±7.1
Body mass index (kg/m^2), mean ± SEM	21.5±2.5
Eastern Cooperative Oncology Group performance status, n [%]	
0	5 [17]
1	25 [83]
Smoking history, n [%]	18 [60]
Drinking history, n [%]	14 [47]
Diabetes, n [%]	3 [10]
Hypertension, n [%]	3 [10]
Tumor location, n [%]	
Upper	2 [7]
Middle	18 [60]
Lower	10 [33]
Clinical tumor (T) stage, n [%]	
cT3	27 [90]
cT4a	3 [10]
Clinical node (N) stage, n [%]	
cN0	0 [0]
cN1	12 [40]
cN2	18 [60]
Clinical stage, n [%]	
III	27 [90]
IVA	3 [10]
Neoadjuvant therapy cycle (N=23), n [%]	
2	18 [78]
>2	5 [22]
Interval to surgery (days), mean (IQR) (N=23)	40.0 (31.5, 48.5)

IQR, interquartile range; SEM, standard error of the mean.

Table 2 Therapy-related adverse events

Events	Number [%]
Adverse events of any grade during neoadjuvant therapy (n=30)	
Leucopenia	8 [27]
Decreased neutrophil count	8 [27]
Lymphopenia	2 [7]
Anemia	15 [50]
Increased transaminase	9 [30]
Anorexia	20 [67]
Constipation	8 [27]
Diarrhea	5 [17]
Fatigue	11 [37]
Nausea	9 [30]
Vomiting	3 [10]
Dermatitis	0 [0]
Pneumonitis	0 [0]
Esophageal hemorrhage	0 [0]
Esophagitis	0 [0]
Adverse events of grade ≥3 during neoadjuvant therapy (n=30)	
Increased transaminase	1 [3]

Anastomotic leakage (AL) occurred in two patients during the hospital stay, and one patient was readmitted to hospital due to AL on the second day after discharge. Both AL cases were grade 2 and recovered through dressing. Only one patient was readmitted to the intensive care unit (ICU) due to pneumonia. No patients died within 30 days after the operation.

Efficacy

Based on radiological evaluation after neoadjuvant therapy, there were 28 patients with a reduction in tumor size. A total of 20 patients (20/30, 67%) had PR, and nine patients (9/30, 30%) had SD. Only one patient (1/30, 3%) had PD. The ORR was 67% (20/30), and the disease control rate (DCR) was 97% (29/30). For all 23 patients (23/23, 100%) who underwent surgery, R0 resection was achieved. Four patients (4/23, 17%) had pCR in primary tumors and lymph nodes. One patient (1/23, 4.3%) had pCR in the primary tumor, however, there were still residual cancer cells in lymph nodes. Twelve patients (12/23, 52%) had MPRs in primary tumors and lymph nodes. The median primary tumor pathologic regression rate was 90.0% (interquartile range, 40.0–99.5%) (*Figure 2*). With a median postoperative follow-up of 6 months (interquartile range, 1–11 months), patients who received R0 resection and refused to undergo

Table 3 30-day postoperative complications and major postoperative complications

Events	Number [%]
30-day postoperative complications	
Pneumonia	15 [65]
Pleural effusion	10 [43]
Chylothorax	1 [4]
Cardiac events	5 [22]
Anastomotic leakage	3 [13]
Palsy of recurrent laryngeal nerve	1 [4]
Bleeding	1 [4]
Major 30-day postoperative complications	
Pneumonia	9 [39]
Pleural effusion	2 [9]
Chylothorax	0 [0]
Cardiac events	0 [0]
Anastomotic leakage	0 [0]
Palsy of recurrent laryngeal nerve	0 [0]
Bleeding	0 [0]
Intensive care unit readmission	1 [4]
30-day readmission	1 [4]
30-day mortality	0 [0]

surgery were free of disease recurrence.

Discussion

We demonstrated that nICT (sintilimab at a dose of 200 mg, q3w) in patients with locally advanced ESCC led to limited therapy-related AEs, a perfect R0 resection rate (23/23, 100%), and a promising pCR rate (5/23, 22%) without delays in surgery. Further, nICT did not increase the degree of difficulty and risk associated with surgery, and the postoperative complications were relatively manageable.

Treatment-related AEs were common in this cohort. However, only one patient experienced grade 3 increased transaminase (1/30, 3%). No patient died due to treatment-related AEs (esophageal hemorrhage or pneumonitis). Compared to the results from studies of nCRT (CROSS, NEOCRTEC5010) or nCT (JCOG9907), nICT tended to have a lower incidence of grade 3 or above AEs. Recently, Wang *et al.* reported that the occurrence of grade 3 and grade 4 AEs was 15.3% and 6.9%in the nCRT and nCT group, respectively (18). Further, compared to PALACE-1 (combination of neoadjuvant immunotherapy and chemoradiotherapy), which reported that grade ≥3 leukopenia was 10% (2/20), decreased neutrophil count was 5% (1/20), lymphopenia was 60% (12/20), and esophageal hemorrhage was 5% (1/20), nICT also showed advantages in terms of grade ≥3 AEs incidence (19). A total of 23 patients underwent surgery within 4–6 weeks after completion of nICT, and no operation was postponed due to AEs. Although above results confirmed the manageable safety and feasibility of nICT, we should still pay attention to AEs especially immune-related adverse events (irAEs). irAEs can affect any organ system, and the implementation of early diagnosis and early intervention is critical to patient safety and is the key to the management of irAEs. Patients should report irAEs to their doctor as soon as possible, even if the symptoms aren't severe. irAEs is typically treated with suspension or continuation of immune treatment, elimination of infection, oral or intravenous steroids, and gradual dose reduction over a period of several weeks. If hormone therapy fails, mycophenolate or infliximab should be considered, and a specialist in the affected organ should be consulted if necessary.

All 23 patients successfully underwent McKeown MIE without conversion to open surgery. Previous studies suggested that surgery following immunotherapy may be a challenge for surgeons. Chaft *et al.* reported that dense fibrosis may develop in NSCLC patients as result of response to immunotherapy. Mediastinal and hilar dissection can be technically challenging for patients with dense fibrosis (20). Bott *et al.* reported the possibility of an unexpected transformation from thoracoscopic lobectomy to thoracotomy lobectomy following immunotherapy (21). However, we noticed that most ESCCs after nICT do not adhere closely to the surrounding tissues and are easily resected (*Figure 3*). This observation suggests that response to immunotherapy is different in different types of cancer. Preoperative imaging could help in locating dense fibrosis and developing a suitable operation plan. Wang *et al.* reported that the incidence of pneumonia in the nCT and nCRT groups were 13.0% and 14.9%, respectively. The incidence of pneumonia in this cohort seemed to be higher (15/23, 65%) than that in nCT or nCRT. This difference may be due to the high proportion of smokers and bias due to limited sample size. The incidence of ALs

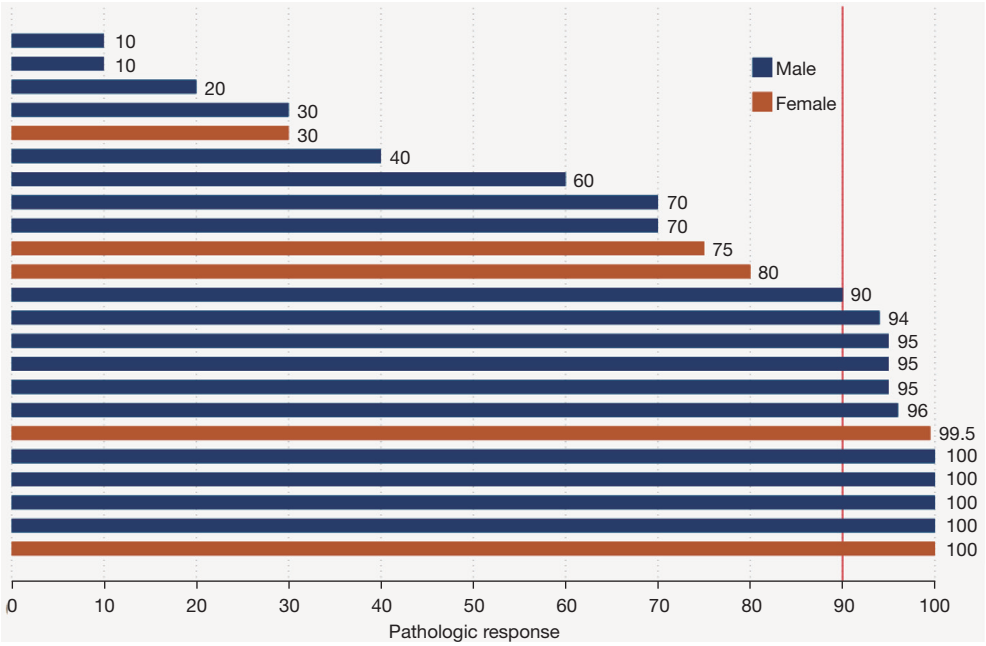

Figure 2 Pathological regression percentage in primary tumors after neoadjuvant treatment.

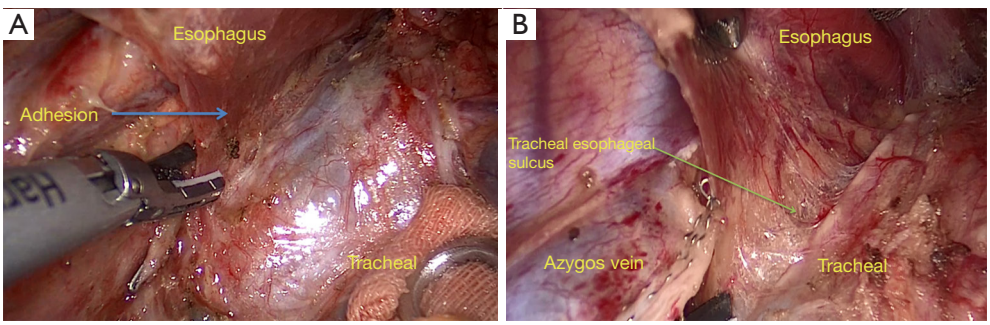

Figure 3 Separation of fibrosis. (A) Separation of fibrosis between esophagus and trachea; (B) separation of fibrosis in trachea esophageal sulcus.

(13%) was similar in nCT (11.1%) and nCRT (9.6%) (18). However, 30-day postoperative morbidity and mortality were acceptable, and we contributed this to early diagnosis and early intervention.

Compared with adjuvant therapy, neoadjuvant therapy can reduce the primary lesion, control lymph node metastasis and micro metastasis, improve R0 resection rate, and prolong long-term survival time. Surgically resected specimens can also be used to assess tumor response to drugs and guide later administration. However, in some patients who do not respond to neoadjuvant therapy, local treatment is delayed and metastasis may develop. The neoadjuvant therapy may lead to drug resistance (6). There still no long-term result of nICT in patients with ESCC, and which is the best medication regimen for locally advanced ESCC is still unclear. However, the anti-tumor effect of nICT was promising, with a pCR rate of 21.8% in the primary tumor and a MPR rate in the tumor of 52.2%. Pathological response to neoadjuvant therapy is significantly associated with long-term survival in patients with ESCC (22). The pCR rate of resected tumors was 55.6% in PALACE-1 (19), 43.2% in NEOCRTEC5010 (3), 49% with ESCC in CROSS (4), and 2.4% in JCOG9907 (6). Wang *et al.* reported that the pCR rate of resected tumors was 35.7%

in the nCRT group and 3.8% in the nCT group (18). Combined immunotherapy appears to increase the pCR rate compared to nCT only, and it seems that the pCR rate in this cohort was inferior to that in nCRT. However, all patients in this study had locally advanced ESCC. Considering the differences in TNM stages reported in previous reports and the promising MPR rate, whether nICT could achieve a similar or even better pathological response than nCRT requires further confirmation in a two-arm study. Due to the quality control of radiation therapy and the radiation induced toxicity, we recommend nICT as the first choice for neoadjuvant therapy for patients with locally advanced ESCC.

To date, this was the first report of nICT for locally advanced ESCC. Present study has several limitations. First, the sample was small, highly selected, and from a single center. All patients were diagnosed with ESCC, and only underwent McKeown MIE. Second, this was a single-arm study, and a control group is needed to explicitly assess the role of sintilimab in nICT. Thus, our conclusions may not generalize to patients treated with other operative approaches, other histology types, or those treated with other immune checkpoint inhibitors. Third, long-term follow up (investigating OS and disease-free survival) is necessary to evaluate the efficacy of nICT for locally advanced ESCC. Fourth, appropriate biomarkers need to be selected to accurately identify patients who respond to nICT.

Conclusions

Based on our preliminary experience, neoadjuvant sintilimab plus chemotherapy as first-line therapy for locally advanced ESCC appears to be safe and feasible with limited AEs, a high R0 resection rate, promising pCR rate, and manageable postoperative complications. A multicenter, randomized, phase III clinical trial assessing the efficacy and safety of sintilimab versus placebo in combination with chemotherapy in locally advanced ESCC is warranted to confirm these findings.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-5381

Data Sharing Statement: Available at https://dx.doi.org/10.21037/atm-21-5381

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-5381). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of the Fujian Medical University Union Hospital (No. 2020YF021-02), China, and followed the principles of the Helsinki Declaration (as revised in 2013). Patients' written informed consent was obtained.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. He F, Wang J, Liu L, et al. Esophageal cancer: trends in incidence and mortality in China from 2005 to 2015. Cancer Med 2021;10:1839-47.
3. Yang H, Liu H, Chen Y, et al. Neoadjuvant Chemoradiotherapy Followed by Surgery Versus Surgery Alone for Locally Advanced Squamous Cell Carcinoma

of the Esophagus (NEOCRTEC5010): A Phase III Multicenter, Randomized, Open-Label Clinical Trial. J Clin Oncol 2018;36:2796-803.
4. Kong M, Shen J, Zhou C, et al. Prognostic factors for survival in esophageal squamous cell carcinoma (ESCC) patients with a complete regression of the primary tumor (ypT0) after neoadjuvant chemoradiotherapy (NCRT) followed by surgery. Ann Transl Med 2020;8:1129.
5. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol 2012;19:68-74.
6. Pasquali S, Yim G, Vohra RS, et al. Survival After Neoadjuvant and Adjuvant Treatments Compared to Surgery Alone for Resectable Esophageal Carcinoma: A Network Meta-analysis. Ann Surg 2017;265:481-91.
7. Nomoto D, Baba Y, Okadome K, et al. Prognostic Impact of PD-1 on Tumor-Infiltrating Lymphocytes in 433 Resected Esophageal Cancers. Ann Thorac Surg 2021. [Epub ahead of print].
8. Hatogai K, Fujii S, Kitano S, et al. Relationship between the immune microenvironment of different locations in a primary tumour and clinical outcomes of oesophageal squamous cell carcinoma. Br J Cancer 2020;122:413-20.
9. Smyth EC, Gambardella V, Cervantes A, et al. Checkpoint inhibitors for gastroesophageal cancers: dissecting heterogeneity to better understand their role in first-line and adjuvant therapy. Ann Oncol 2021;32:590-9.
10. Jiang H, Zheng Y, Qian J, et al. Safety and efficacy of sintilimab combined with oxaliplatin/capecitabine as first-line treatment in patients with locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma in a phase Ib clinical trial. BMC Cancer 2020;20:760.
11. Zhang L, Mai W, Jiang W, et al. Sintilimab: A Promising Anti-Tumor PD-1 Antibody. Front Oncol 2020;10:594558.
12. Xu JM, Jia R, Wang Y, et al. A first-in-human phase 1a trial of sintilimab (IBI308), a monoclonal antibody targeting programmed death-1 (PD-1), in Chinese patients with advanced solid tumors. J Clin Oncol 2018;36:e15125.
13. Xu J, Li Y, Fan Q, et al. Sintilimab in patients with advanced esophageal squamous cell carcinoma refractory to previous chemotherapy: A randomized, open-label phase II trial (ORIENT-2). J Clin Oncol 2020;38:abstr 4511.
14. Shen D, Chen Q, Wu J, et al. The safety and efficacy of neoadjuvant PD-1 inhibitor with chemotherapy for locally advanced esophageal squamous cell carcinoma. J Gastrointest Oncol 2021;12:1-10.
15. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
16. Rice TW, Ishwaran H, Ferguson MK, et al. Cancer of the Esophagus and Esophagogastric Junction: An Eighth Edition Staging Primer. J Thorac Oncol 2017;12:36-42.
17. Chirieac LR, Swisher SG, Ajani JA, et al. Posttherapy pathologic stage predicts survival in patients with esophageal carcinoma receiving preoperative chemoradiation. Cancer 2005;103:1347-55.
18. Wang H, Tang H, Fang Y, et al. Morbidity and Mortality of Patients Who Underwent Minimally Invasive Esophagectomy After Neoadjuvant Chemoradiotherapy vs Neoadjuvant Chemotherapy for Locally Advanced Esophageal Squamous Cell Carcinoma: A Randomized Clinical Trial. JAMA Surg 2021;156:444-51.
19. Li C, Zhao S, Zheng Y, et al. Preoperative pembrolizumab combined with chemoradiotherapy for oesophageal squamous cell carcinoma (PALACE-1). Eur J Cancer 2021;144:232-41.
20. Chaft JE, Hellmann MD, Velez MJ, et al. Initial Experience With Lung Cancer Resection After Treatment With T-Cell Checkpoint Inhibitors. Ann Thorac Surg 2017;104:e217-8.
21. Bott MJ, Cools-Lartigue J, Tan KS, et al. Safety and Feasibility of Lung Resection After Immunotherapy for Metastatic or Unresectable Tumors. Ann Thorac Surg 2018;106:178-83.
22. Berger AC, Farma J, Scott WJ, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. J Clin Oncol 2005;23:4330-7.

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