Research Letter

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Clinical outcomes and short-term survival of neoadjuvant immunochemotherapy for resectable esophageal cancer: a multicenter retrospective cohort study

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Objective: The present retrospective cohort study aims to evaluate the efficacy and safety of neoadjuvant immunochemotherapy for resectable esophageal cancer and report the preliminary short-term survival.

Methods: A multicenter, retrospective study was conducted concerning patients who received neoadjuvant PD-1 agents plus platinum-based chemotherapy between January 2019 and January 2022. The primary endpoint was the tumor pathologic complete response (pCR) rate.

Results: Two hundred and thirteen patients with initial stage cI-IVA esophageal cancer who received neoadjuvant immunochemotherapy were identified. The complete tumor resection(R0) rate was 99.1%. The pCR rate was 31.9%, and the overall major pathological response rate was 49.8%. The 2-year DFS rate was 78.9% (95% CI: 72.9–85.4%) and the 2-years OS rate was 80.9% (95% CI: 75.3–86.9%). The incidence of TRAEs and surgical complications rate were 68.5 and 35.2%, respectively.

Conclusion: The PD-1 agents combined with chemotherapy in the neoadjuvant treatment for resectable stage I–IVA esophageal cancer had a high pCR rate as well as good short-term survival benefits and tolerable toxicity.

Keywords: efficacy, esophageal cancer, neoadjuvant immunotherapy, retrospective cohort study, safety

Introduction

In recent years, immune checkpoint inhibitors (ICIs) have redefined the treatment paradigm of various types of advanced cancers. However, the safety and efficacy of immunotherapy for the treatment of locally advanced, surgically resectable esophageal cancer remains unknown. At present, a series of clinical trials for esophageal cancer neoadjuvant immunotherapy have been published, such as JCOG1804E[1] and TD-NICE[2]. Neoadjuvant immunotherapy is expected to require clinical practice support from a real-world analysis of consecutive neoadjuvant immunochemotherapy results. This real-world study, based on two high-volume institutional clinical patients, aims to demonstrate the efficacy and safety of neoadjuvant immunotherapy for resectable esophageal cancer, to provide further treatment options for resectable esophageal cancer in the future.

Materials and methods

Patient characteristics

This work has been reported in line with the strengthening the reporting of cohort, cross-sectional, and case–control studies in

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surgery (STROCSS) (Supplemental Digital Content 1, http://links.lww.com/JS9/D253) criteria[3]. Two hundred and thirteen esophageal cancer patients with stage I to IVA who were treated with ICIs plus chemotherapy as neoadjuvant immunochemotherapy in *** and *** Hospital was conducted. Clinical staging was evaluated referencing to the 8th edition of the AJCC/UICC staging system[4]. All patients received neoadjuvant chemotherapy, and the recommended regimens included nab-paclitaxel plus cisplatin, fluorouracil plus cisplatin, etc. Four PD-1 blockades that contained pembrolizumab, tislelizumab, camrelizumab, sintilimab (200 mg, i.v, q3w), were applied to neoadjuvant immunotherapy. Preoperative neoadjuvant therapy was given for 2–4 cycles. Surgery was performed within 4–6 weeks after the last treatment cycle.

Study endpoints

Pathological response was assessed by local pathologists, who measured the percentage of residual viable tumor in primary tumors using reported methods[5].

The primary endpoint of this study was pathological complete response (pCR), defined as the complete absence of all tumor cells from the primary site and lymph nodes. Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0[6]. Postoperative 30-days mortality and morbidity were assessed by Clavien–Dindo complications classification[7]. Efficacy: (1) Major pathological response (MPR), remaining tumor cells accounted for less than 10% or primary lesion disappearance with lymph node metastasis; (2) R0 resection rate; and (3) Disease-free survival (DFS) or overall survival (OS).

Result

Patient characteristics

From 2019 to January 2022, 213 patients administered ICIs and chemotherapy were treated with radical resection of esophageal cancer (Supplemental Item, Supplemental Digital Content 2, http://links.lww.com/JS9/D254). One hundred and sixty-two (76.1%) were male, the mean age was 62.3 years, and most tumors were esophageal squamous cell carcinoma (93.9%). Eighty-two (38.5%) patients had stage II, and 69 (32.4%) patients had stage III.

Efficacy and safety outcomes

Efficacy

The pCR was 31.9%. Waterfall Plot (Supplemental Item, Supplemental Digital Content 2, http://links.lww.com/JS9/D254) shows the pathological response in esophageal tumor after neoadjuvant immunochemotherapy. The overall MPR was 49.8%.

Safety

The overall TRAEs rate was 68.5%. No treatment-related surgical delay or death was observed (Table 1). Immune-related adverse event (irAE) was also reported, and the most common irAEs were rash or pruritus, immune-related pneumonia, and hypothyroidism. The incidence of surgical complications was 35.2%. One hundred and thirty-three (62.4%) patients completed Mckeown esophagectomy, 47 (22.1%) completed Ivor-Lewis esophagectomy. The surgical outcomes are summarized in Table 2. The incidence of surgical complications rate was 35.2%. Sankey diagram (Supplemental Item, Supplemental Digital Content 2, http://links.lww.com/JS9/D254) displayed the relationship of clinical and pathological response distinctly.

HIGHLIGHTS

- This study described immunochemotherapy in patients with resectable esophageal cancer.
- The treatments were associated with few side effects and induced a pCR in 31.9%.
- The short-term survival benefit requires further validation and long-term follow-up.

Table 1

Treatment-related adverse events and postoperative complications in patients underwent surgery.

Postoperative complications	Grade 1–2	≥ Grade3	Total
Pneumonia	11 (5.2)	6 (2.8)	17 (8.0)
Recurrent nerve paralysis	15 (7.0)	1 (0.5)	16 (7.5)
Heart failure	1 (0.5)	0 (0.0)	1 (0.5)
Subcutaneous emphysema	1 (0.5)	0 (0.0)	1 (0.5)
Pneumothorax	4 (1.9)	1 (0.5)	5 (2.3)
Incision infection	0 (0.0)	2 (1.0)	2 (1.0)
Incision dehiscence	0 (0.0)	1 (0.5)	1 (0.5)
Anastomotic leakage	5 (2.3)	12 (5.6)	17 (7.9)
Gastrointestinal bleeding	1 (0.5)	0 (0.0)	1 (0.5)
Myocardial infarction	1 (0.5)	0 (0.0)	1 (0.5)
Pleural effusion	10 (4.7)	2 (1.0)	12 (5.6)
Pulmonary atelectasis	1 (0.5)	0 (0.0)	1 (0.5)
Total	50 (23.5)	25 (11.7)	75 (35.2)
TRAE			
Leukopenia	41 (19.2)	14 (6.6)	55 (25.8)
Neutropenia	16 (7.5)	6 (2.8)	22 (10.3)
Anemia	34 (16.0)	5 (2.3)	39 (18.3)
Thrombocytopenia	22 (10.3)	6 (2.8)	28 (13.1)
Hypernatremia	1 (0.5)	0 (0.0)	1 (0.5)
Hyponatremia	1 (0.5)	0 (0.0)	1 (0.5)
Hypocalcemia	1 (0.5)	0 (0.0)	1 (0.5)
Hyperglycemi	4 (1.9)	1 (0.5)	5 (2.4)
Elevated serum lactate dehydrogenase	4 (1.9)	0 (0.0)	4 (1.9)
Elevated alanine aminotransferase	3 (1.4)	0 (0.0)	3 (0.4)
Pruritus	10 (4.7)	0 (0.0)	10 (4.7)
Nausea	7 (3.3)	0 (0.0)	7 (3.3)
Vomiting	3 (1.4)	0 (0.0)	3 (1.4)
Alopecia	7 (3.3)	0 (0.0)	7 (3.3)
Anorexia	3 (1.4)	0 (0.0)	3 (1.4)
Diarrhoea	1 (0.5)	0 (0.0)	1 (0.5)
Hiccup	1 (0.5)	0 (0.0)	1 (0.5)
Rash	9 (4.2)	0 (0.0)	9 (4.2)
Pneumonia	1 (0.5)	0 (0.0)	1 (0.5)
Febrile	3 (1.4)	0 (0.0)	3 (1.4)
Hyperthyroidism	3 (1.4)	0 (0.0)	3 (1.4)
Depression	1 (0.5)	0 (0.0)	1 (0.5)
Any	114 (53.5)	32 (15.0)	146 (68.5)

TRAE, Treatment-related adverse events.

Table 2

Baseline demographic and clinical characteristics.

Characteristics	Total ($n=213$)
Age, years	62.3 ± 7.0
Sex	
Male	162 (76.1)
Female	51 (23.9)
Smoking history	
Current or ever	110 (51.6)
Never	103 (48.4)
CCI	3 (2–3)
ECOG	
0	159 (74.6)
1	54 (25.4)
BMI (kg/m^2)	22.6 (4.3)
Clinical stage	
I	7 (3.3)
II	82 (38.5)
III	69 (32.4)
IVA	48 (22.5)
NA	7 (3.3)
cT	
1	8 (3.8)
2	37 (17.4)
3	128 (60.1)
4	34 16.0)
x	6 (2.3)
cN	
0	98 (46.0)
1	66 (31.0)
2	27 (12.7)
3	15 (7.0)
x	7 (3.3)
Histology	
Squamous cell carcinoma	200 (93.9)
Adenocarcinoma	12 (5.6)
Else	1 (0.5)
Type of tumor	
Esophageal cancer	210 (98.6)
Gastroesophageal junction carcinoma	3 (1.4)
ICIs type	
Camrelizumab	44 (20.7)
Pembrolizumab	60 (28.2)
Tislelizumab	78 (36.6)
Sintilimab	31 (14.6)
Treatment cycles	
1	12 (5.6)
2	70 (32.9)
3	110 (51.6)
4	21 (9.9)
Interval time (d)	34 (27–41)
Type of procedure	
Ivor-Lewis	47 (22.1)
Mckeown	133 (62.4)
Left-sided esophagectomy	33 (15.5)
Type of operation	
Traditional open approach	52 (24.4)
Minimally invasive approach	161 (75.6)
Operation time (min)	270 (69.7)
Blood loss (ml)	200 (100–300)
Lymph nodes removed	19 (12–25)
Length of stay (d)	14 (10-17)
R0	211 (99.1)
Clinical response	
PR	111 (52.1)
CR	30 (14.1)
SD	68 (31.9)
PD	4 (1.9)
MPR	106 (49.8)
pCR	68 (31.9)
Postoperative complications	
Any	75 (35.2)
None	124 (58.2)
Mortality (30-days)	2 (0.9)

Data are expressed as *n* (%) or median (interquartile range). NA, not available.

Survival analysis

With a median follow-up of 28.0 months (range 0.7–53.0), the median DFS and median OS had not reached, moreover, the 2-year DFS rate was 78.9% (95% CI: 72.9–85.4%) and 2-years OS rate was 80.9% (95% CI: 75.3–86.9%). There was not any significant correlation between the ICI type and the survival outcomes (Fig. 1).

Discussion

We administrated the neoadjuvant treatment regimen of camrelizumab, pembrolizumab, tislelizumab, and sintilimab combined with platinum-based chemotherapy to patients with potentially resectable esophageal cancer. No scheduled procedures were delayed, and 31.9% of tumors achieved pCR.

Several studies[8,9] investigated many emerging research and real-world clinical study which contains many cancers for neoadjuvant immunotherapies. This study also gone through with patients administered ICIs and chemotherapy which not performing radical resection of esophageal cancer. Real-world patients, include many elder patients with numerous comorbidities, are more representative of the actual scenario of clinical practice under an economic unbalanced society.

The incidence of grade 3–4 TRAEs was 11.7% in this study, which is similar with another meta-analysis of neoadjuvant immunochemotherapy for esophageal cancer, the pooled incidence of grade 3–4 TRAEs was 19.4%[10]. Nonetheless, the administering of neoadjuvant immunotherapy could lead to a dense and hard surgical field and may impede the feasibility of surgery and increase the difficulty of complete resection. However, neoadjuvant therapy did not cause more major postoperative complications, even in complex surgeries.

To our knowledge, this multicenter, retrospective real-world study has provided the larger quantity and variety of analysis of immunochemotherapy in patients with resectable esophageal cancer.

Conclusions

Neoadjuvant PD-1 blockade plus chemotherapy was associated with few side effects, did not delay surgery, and induced a pCR in 31.9% of resected tumors. The effectiveness should be confirmed in more multicenter studies with large samples and long-term follow-up.

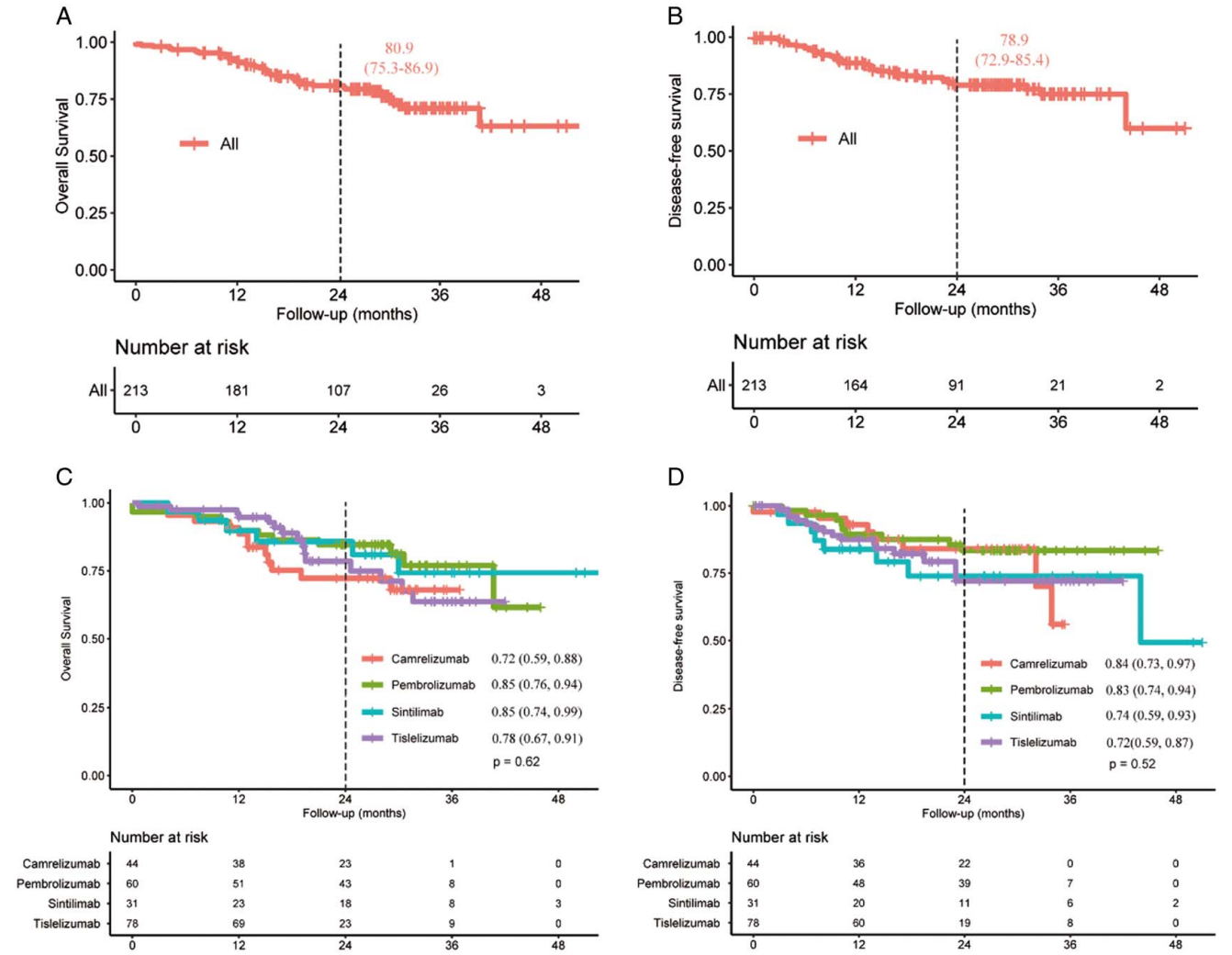

Figure 1. Kaplan–Meier survival curves of overall- (A) and disease-free survival (B) in all patients and of overall- (C) and disease-free survival (D) in different ICI type subgroup.

Ethical approval

Ethical approval for this study (Approved No. of the ethic committee: TDLL-202312-01) was provided by the Institutional Review Board of Tangdu Hospital, Air Force Military Medical University, Xi'an, Shaanxi, China on 14 December 2023.

Consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

K.L., X.Y., Z.G., L.H., Y.N., T.J., and J.Z.: conceptualization; K.L., J.L., X.G., Y.Z., X.W., H.L., F.T., Q.L., Z.G., J.S., E.Y., D.Z., T.W., J.W., Y.N., and J.Z.: data curation; K.L., J.L., F.T., Q.L., Z.G., J.S., L.H., J.W., X.L., Y.N., T.J., and J.Z.: formal analysis; K.L.: funding acquisition; K.L., J.L., X.G., Y.Z., X.W., H.L., F.T., Q.L., Z.G., J.S., E.Y., D.Z., T.W., L.H., J.W., Y.N., and J.Z.: investigation; K.L., J.L., F.T., Z.G., J.S., E.Y., D.Z., T.W., J.W., X.L., Y.N., and J.Z.: methodology; T.J. and J.Z.: project administration; X.Y., X.G., Y.Z., X.W., H.L., F.T., Q.L., Z.G., J.S., E.Y., D.Z., L.H., Y.N., T.J., and J.Z.: resources; H.L., J.S., E.Y., T.W.,

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Conflicts of interest disclosure

All other authors declare that they have no conflicts of interest. No potential conflict of interest relevant to this article could be reported.

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Guarantor

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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