Original Article

# Pattern of tumor regression after neoadjuvant chemoimmunotherapy for esophageal squamous cell carcinoma

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**Background:** Immune checkpoint inhibitors have been increasingly applied for esophageal cancer. The aims of this study were to evaluate the pattern of tumor regression after neoadjuvant chemoimmunotherapy.

**Methods:** From January 2020 to December 2021, 138 patients with esophageal squamous cell carcinoma who had esophagectomy after neoadjuvant chemoimmunotherapy were reviewed. Surgical and pathological results were analyzed, and tumor regression pattern was evaluated.

**Results:** Of the 138 patients, 65 (47.1%) patients had chemotherapy combined with camrelizumab, 48 (34.8%) with pembrolizumab, 13 (9.4%) with tislelizumab, and 12 (8.7%) with sintilimab. Sixty-four patients (46.4%) underwent McKewon procedure, and 74 (53.6%) Ivor-Lewis procedure, respectively. There were 131/138 patients (94.9%) who had R0 resections, and the median number of resected lymph nodes was 28. Pneumonia was the most common complication after surgery (14.5%). Pathological complete regression occurred in 28 patients (20.3%). Regarding to residual tumor, there were 50 patients (36.2%) with residual tumor in the mucosa, 81 (58.7%) in the submucosa, 85 (61.6%) in the muscularis propria, 47 (34.1%) in the adventitia and 71 (51.4%) in the lymph nodes. There were 88 patients with no residual tumor in the mucosa, of whom 60 (68.2%) had residual tumors in other layers or in the lymph nodes.

**Conclusions:** In this retrospective study, esophagectomy after neoadjuvant chemoimmunotherapy is safe with acceptable surgical risk. Preferential clearing of tumor cells in mucosa layer is common after immunotherapy, while the rate of complete pathological response is relatively low, indicating surgery is still necessary.

**Keywords:** Esophagectomy; chemoimmunotherapy; safety; tumor regression

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## Introduction

Esophageal cancer is one of the most common malignancies in the world. For locally advanced esophageal cancer, multidisciplinary treatment, involving surgery, chemotherapy, and radiotherapy, is required. However, long-term survival remains poor, with 5-year overall survival ranging from 47% to 55% (1,2).

Recent studies have shown the superiority of immune checkpoint inhibitors in improving survival among patients with esophageal cancer (3-5), justifying their use as neoadjuvant regimen. Published studies using immune checkpoint inhibitors as neoadjuvant regimen showed promising tumor response with objective response rate ranging from 22.2% to 55.6% (6-8). However, these studies were limited by small study numbers, and the type of tumor regression was unclear. The aim of the study was to assess the pattern of tumor regression after neoadjuvant chemoimmunotherapy. The safety of esophagectomy after neoadjuvant chemoimmunotherapy was also evaluated in this study. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-882/rc).

## Methods

### *Patients*

Between January 1st, 2020 and December 30th, 2021, 1,829 patients underwent esophagectomy due to cancer at Fudan University Shanghai Cancer Center, of which 251 patients received preoperative therapy before esophagectomy due to advanced tumor stage. The institutional review board of Fudan University Shanghai Cancer Center approved the use of database for this study (No. 1612167-18). Informed consent was taken from all the patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

The records of all patients were reviewed, and the inclusion criteria for this analysis were as follows: (I) esophageal squamous cell carcinoma by pathological confirmation; (II) neoadjuvant chemotherapy combined with immunotherapy; and (III) no radiotherapy prior to surgery. Ultimately, 138 patients were included in this retrospective analysis.

As there is still no consensus on the optimal neoadjuvant regimen, different types of immune checkpoint inhibitors were used based on surgeons' experience and preference in China. In Shanghai Cancer Center, chemoimmunotherapy was always applied to those with tumors of clinical stage T1–4aN2 or T3–4aN1 and no clinical evidence of metastatic spread (M0). Immunotherapy combined with chemoradiotherapy was not widely performed. Of the 138 patients in this study, there were 86 patients (62.3%) had immunotherapy in Shanghai Cancer Center, and 52 (37.7%) in their local hospitals.

### *Treatment*

Preoperative workup assessing patient operability included a complete history, physical examination, endoscopy of the entire upper gastrointestinal tract, histologic confirmation of the carcinoma, ultrasonography of the neck, computed tomography (CT) of the chest and abdomen. Pulmonary function testing and electrocardiography were also performed to assess fitness. Positron emission tomography and endoscopic ultrasonography were not performed routinely.

Esophagectomy via the right thoracic approach with radical two-field lymphadenectomy was widely used after the trial compared to esophagectomy via the left thoracic approach with limited two-field lymphadenectomy at the Shanghai Cancer Center (9). The McKeown procedure with cervical anastomosis and Ivor-Lewis procedure with thoracic anastomosis, via open or minimally invasive approach, were performed depending on the surgeon's preference.

**Highlight box**

**Key findings**

- Preferential clearing of tumor cells in the mucosa layer is common after chemoimmunotherapy. However, the rate of complete pathological response is relatively low in a real-world setting.

**What is known and what is new?**

- The use of immune checkpoint inhibitors as neoadjuvant regimen showed promising tumor response rate.
- Absent residual tumors in the mucosa layers were observed in approximately 28–29% of patients with residual tumors after chemoradiotherapy. Whereas in this study, higher rates of absent residual tumors in the mucosa were observed, accounting for 55% (60/110) of patients with residual tumors after chemoimmunotherapy.

**What is the implication, and what should change now?**

- Negative endoscopic biopsies should be carefully evaluated in patients after chemoimmunotherapy, and esophagectomy is still warranted.

Extended radial two-field lymphadenectomy is routinely performed. When lymph node metastasis in the neck was indicated on CT or ultrasonography, cervical lymph nodes dissection was performed. Patients were staged according to the tumor-node-metastasis classification of the eighth edition of the American Joint Committee for Cancer Staging Manual (10).

At the end of surgery, patients were extubated if physiologically stable and then admitted to a general surgical ward. On postoperative day 1, the patients were encouraged to move out of bed, and enteral nutrition was initiated via the feeding tube. Oral intake began on postoperative day 6 without evidence of anastomotic leakage, and the patients were discharged on postoperative day 7 or 8.

Morbidity and mortality were examined within 90 days of surgery. Postoperative complications were recorded, including anastomotic leakage, pulmonary infection, cardiovascular complications, chylothorax, and other complications (intestinal obstruction, wound infection, and vocal cord paralysis). The severity of complications was assessed based on the Clavien-Dindo classification (11).

### *Histopathological assessment*

Esophageal resection specimens were histopathologically evaluated by experienced pathologists specializing in esophageal cancer. During the original pathological examination, the tumor type, differentiation grade, depth of invasion, number of involved lymph nodes, and presence of lymphovascular invasion were recorded. Sample margins, including the circumferential resection margin, were also recorded. Radical resection (R0) was defined as the absence of tumor cells at all resection margins; R1 resection involved microscopic residual tumors, and R2 resection involved macroscopic residual tumors.

For primary tumors, tumor regression grade (TRG) was evaluated using the modified Mandard scoring system. TRG 1 was defined as no residual tumor cells [pathological complete response (pCR)], TRG 2 as 1–10% residual tumor cells, TRG 3, as 11–50% residual tumor cells, and TRG 4 as more than 50% residual tumor cells (12).

All specimens were reviewed by a pathologist (Wang Y) who was blinded to the previous pathological records. Residual tumors in each layer of the esophageal wall were re-reviewed.

### *Statistical analysis*

Data were presented as numbers and percentages, means and standard errors, or medians and interquartile ranges. Fisher's exact test was used to compare the frequencies of pathological complete regression among different immune checkpoint inhibitors. All statistical analyses were performed using SPSS statistical software (SPSS 22.0, Chicago, IL, USA).

## Results

Of the 138 patients, the mean age was 62±7 years. There were 126 male patients (91.3%) and 66 patients (47.8%) had the tumors located in the middle thoracic esophagus (*Table 1*).

All patients received platinum-based chemotherapy, of which 120 (87.0%) combined with paclitaxel and 18 (13.0%) combined with docetaxel. There were 48 patients (34.8%) who received chemotherapy combined with pembrolizumab, 65 (47.1%) combined with camrelizumab, 13 (9.4%) combined with tislelizumab, and 12 (8.7%) combined with sintilimab. There were 10 patients (7.2%) having only one cycle, 102 (73.9%) having two cycles, and 26 (18.8%) having three cycles or more. There were 86 patients who had immunotherapy in Shanghai Cancer Center, of which 31 (36.0%) had treatment-related adverse events, and 14 leukocytopenia (16.3%) and 5 increased transaminase (5.8%), being the most common treatment-related adverse events.

Majority of patients had clinical T2 (59, 42.8%) or N1 (59, 42.8%) disease before surgery. Surgical outcomes are shown in *Table 2*. There were 64 patients (46.4%) who underwent McKewon procedure and 74 (53.6%) underwent Ivor-Lewis procedure. Majority of the surgeries were completed using open thoracic approach (130, 94.2%). A total of 131 patients (94.9%) underwent R0 resections, 4 (2.9%) R1 resections, and 3 (2.2%) R2 resections.

Of the 138 patients, 99 (71.7%) had no postoperative complications. Majority of postoperative complications (46.2%, 18/39) were classified as grade II complications. Two patients (1.4%) died during hospitalization, one due to severe pneumonia following an anastomotic leak on postoperative day 23 and one due to tracheoesophageal fistula on postoperative day 41.

Pathological outcomes are shown in *Table 3*. Pathological complete regression was observed in 28 patients (20.3%),

**Table 1** Patient characteristics of 138 patients

| Characteristics | Values |
|---|---|
| Age (years) | 62±7 |
| Gender | |
| Male | 126 (91.3) |
| Female | 12 (8.7) |
| BMI (kg/m$^2$) | 23±3 |
| Hypertension | 41 (29.7) |
| Diabetes | 11 (8.0) |
| Smokers[†] | 94 (68.1) |
| Drinkers[‡] | 78 (56.5) |
| Tumor locations | |
| Upper | 49 (35.5) |
| Middle | 66 (47.8) |
| Lower | 23 (16.7) |
| ASA fitness grade | |
| 1 | 9 (6.5) |
| 2 | 122 (88.4) |
| 3 | 7 (5.1) |
| Immune checkpoint inhibitors | |
| Camrelizumab | 65 (47.1) |
| Pembrolizumab | 48 (34.8) |
| Tislelizumab | 13 (9.4) |
| Sintilimab | 12 (8.7) |
| Clinical T-stage[§] | |
| 1 | 34 (24.6) |
| 2 | 59 (42.8) |
| 3 | 44 (31.9) |
| 4 | 1 (0.7) |
| Clinical N-stage[§] | |
| 0 | 48 (34.8) |
| 1 | 59 (42.8) |
| 2 | 23 (16.7) |
| 3 | 8 (5.8) |

Data are shown as mean ± standard error or n (%). [†], at least ten cigarettes per week for more than 6 months, including former and current smoker; [‡], any alcoholic beverage containing at least 20 g ethanol per week for more than 6 months, including former and current drinkers; [§], clinical stage after chemoimmunotherapy. BMI, body mass index; ASA, American Society of Anaesthesiologist.

**Table 2** Surgical outcomes of 138 patients

| Surgical outcomes | Values |
|---|---|
| Surgery procedure | |
| McKewon | 64 (46.4) |
| Ivor-Lewis | 74 (53.6) |
| Surgical approach | |
| Minimally invasive | 8 (5.8) |
| Open | 130 (94.2) |
| Extent of lymphadenectomy | |
| Three-field | 11 (8.0) |
| Two-field | 127 (92.0) |
| Operative time (min) | 200 [180–234] |
| Postoperative complications | |
| Anastomotic leak | 8 (5.8) |
| Pneumonia | 20 (14.5) |
| Arrhythmia | 8 (5.8) |
| Vocal cord paralysis | 15 (10.9) |
| Chylothorax | 5 (3.6) |
| Reintubation | 5 (3.6) |
| Uroschesis | 1 (0.7) |
| Wound infection | 2 (1.4) |
| Intestinal obstruction | 1 (0.7) |
| Re-operation | 1 (0.7) |
| 90-day mortality | 2 (1.4) |
| Hospital stay (days) | 13 [10–18] |
| Clavien-Dindo classification | |
| I | 9 (6.5) |
| II | 18 (13.0) |
| III | 4 (2.9) |
| IV | 6 (4.3) |
| V | 2 (1.4) |

Data are shown as median [interquartile range] or n (%).

whereas 110 patients (79.7%) had residual tumors. Pathological complete regression was observed in 9 patients (18.8%) using pembrolizumab, 14 (21.5%) using camrelizumab, 2 (15.4%) using tislelizumab, and 3 (25.0%) using sintilimab, P=0.919.

Regarding primary tumors, there were 36 patients

**Table 3** Pathological outcomes of 138 patients

| Pathological outcomes | Values |
|---|---|
| Tumor length (cm) | 2.0 [1.5–3.0] |
| T-stage | |
| T0 | 36 (26.1) |
| T1 | 25 (18.1) |
| T2 | 21 (15.2) |
| T3 | 51 (37.0) |
| T4 | 5 (3.6) |
| N-stage | |
| 0 | 67 (48.6) |
| 1 | 38 (27.5) |
| 2 | 19 (13.8) |
| 3 | 14 (10.1) |
| Number of lymph nodes resected | 28 [21–38] |
| Lymphovascular invasion | |
| Yes | 49 (35.5) |
| No | 89 (64.5) |
| Tumor differentiation | |
| Well | 3 (2.2) |
| Moderate | 56 (40.6) |
| Poor | 40 (29.0) |
| Unknown | 39 (28.3) |
| TNM classification | |
| YI | 50 (36.2) |
| YII | 15 (10.9) |
| YIIIa | 21 (15.2) |
| YIIIb | 34 (24.6) |
| YIVa | 17 (12.3) |
| YIVb | 1 (0.7) |
| TRG | |
| 1 | 36 (26.1) |
| 2 | 18 (13.0) |
| 3 | 31 (22.5) |
| 4 | 53 (38.4) |

Data are shown as median [interquartile range] or n (%). TNM, tumor, node, and metastasis; TRG, tumor regression grade.

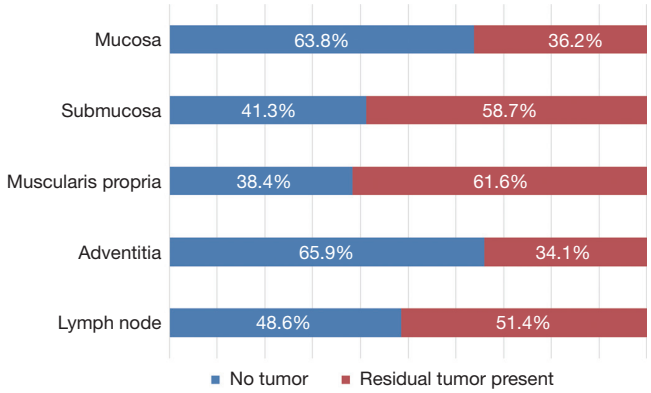


**Figure 1** Frequencies of residual tumor in each individual layer of the esophageal wall and all resected lymph nodes in 138 patients.

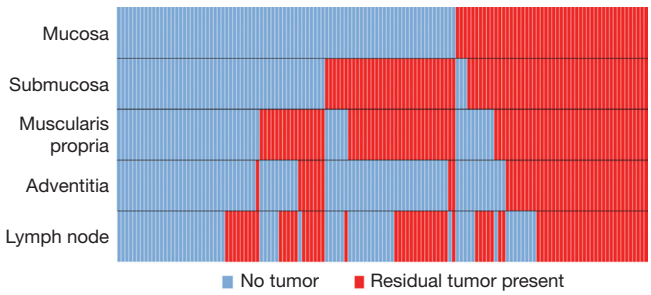


**Figure 2** Distribution of residual tumors in 138 patients.

(26.1%) who had TRG1 tumors, 18 (13.0%) with TRG2 tumors, 31 (22.5%) with TRG3 tumors, and 53 (38.4%) with TRG4 tumors. There were 50 patients (36.2%) with residual tumor in the mucosa, 81 (58.7%) in the submucosa, 85 (61.6%) in the muscularis propria, 47 (34.1%) in the adventitia, and 71 (51.4%) in the lymph nodes (*Figure 1*). There were 88 patients with no residual tumor in the mucosa, of whom 60 (68.2%) had residual tumors in other layers or in the lymph nodes. There were 54 patients with no residual tumor in the mucosa or submucosa, of which 26 (48.1%) had residual tumor in other layers or in the lymph nodes (*Figure 2*).

Regarding the possible regression pattern of primary tumors by Shapiro *et al.* [2013] (13). Of the 102 patients who had residual tumors in the esophageal wall (mucosa, submucosa, muscularis propria, and adventitia, as showed in *Figure 2*), 30 (29.4%) showed regression toward the lumen (more regression in the muscularis propria and the

adventitia), 8 (7.8%) had regression toward the invasive front (more regression in the mucosa and the submucosa), 27 (26.5%) had concentric regression (more regression in the mucosa and the adventitia), and 37 (36.3%) had random regression (comparable extent of regression in all layers).

## Discussion

In patients with esophageal squamous cell carcinoma, our results showed the safety of esophagectomy after neoadjuvant chemoimmunotherapy in a real-world scenario. Notably, preferential clearing of tumor cells in the mucosal layer is common after neoadjuvant chemoimmunotherapy.

Current guidelines recommend esophagectomy after neoadjuvant chemoradiotherapy for advanced esophageal squamous cell carcinoma. However, in the 10-year survival report of the ChemoRadiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS), chemoradiotherapy reduced locoregional recurrence compared to surgery alone, whereas distant metastases were similar between the two groups (14). In a trial comparing esophagectomies via the left versus right thoracic approaches, extended radical lymphadenectomy via the right thoracic approach reduced locoregional recurrence compared with inadequate lymphadenectomy via the left thoracic approach, whereas distant metastases were still the reason for treatment failure (9). Therefore, it is important to reduce distant metastases to improve the survival of patients with resectable esophageal cancer.

Recent studies have justified the perioperative use of immune checkpoint inhibitors in resectable esophageal cancer (6-8). However, in Keynote 590 study on advanced esophageal cancer (3), treatment-related adverse events of grade 3 or higher occurred in 72% of patients in the pembrolizumab plus chemotherapy group. Thus, one important concern is that immunotherapy would potentially increase the surgical risk. In the current study, most treatment-related adverse events were minor and manageable before surgery. No immunotherapy-related deaths were observed in the current cohort after esophagectomy. Moreover, both the incidence of postoperative complications and length of hospital stay were consistent with our previous report in patients who underwent upfront esophagectomy (15). This is probably due to fewer treatment cycles before surgery, and esophagectomy was always performed after 2–3 cycles of therapy. Therefore, we presume that the preoperative use of immunotherapy is safe without increased surgical complications.

Pathological complete response, which is a prognostic factor for patient survival in the era of neoadjuvant chemoradiotherapy (16), was the primary outcome in most published phase II trials referring to neoadjuvant immunotherapy, ranging from 21.7% to 39.2% (7,17,18). In this retrospective setting, pathological complete response was only 20.2%. To date, long-term survival data for immune checkpoint inhibitors used as neoadjuvant regimens are still rare. However, in a trial comparing neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy followed by minimally invasive esophagectomy, there was a significant difference in the pathological complete responses (35.7% *vs.* 3.8%), but with no significant difference in the 1-year overall survival (87.1% *vs.* 82.6%) (19). Therefore, it is still unclear whether a higher pathological complete response is related to better patient survival, and future prospective randomized trials are needed to clarify the value of immunotherapy by comparing with other neoadjuvant regimens.

In the CROSS study, 150 of 184 (84%) patients in the chemoradiotherapy arm had esophageal cancer of clinical T3 staging before treatment, pathological complete response after chemoradiotherapy was 49% for esophageal squamous cell carcinoma, indicating wait-and-see strategy, and avoiding esophageal resection could be feasible in selected patients (1). Accurate detection of residual tumors is important to determine the appropriate management. Previous studies have reported absent residual tumors in the mucosa layers were observed in approximately 28–29% of patients with residual tumors after chemoradiotherapy (13,20). Whereas in this study, higher rates of absent residual tumors in the mucosa were observed, accounting for 55% (60/110) of patients with residual tumors after chemoimmunotherapy. Different results indicated different regression patterns after chemoimmunotherapy. Endoscopic bite-on-bite biopsies are recommended to improve the diagnostic accuracy. However, it might be challenging due to a preferential clearing of the tumor cells in the mucosa or the submucosa rather than in the muscle and adventitia layers, which were observed in approximately 48% of the patients in our study. Therefore, negative endoscopic biopsies should be carefully evaluated in patients after immunotherapy.

This study has some limitations. Firstly, the study was limited by its retrospective nature: only patients who underwent esophagectomy were included. The number of patients who did not undergo surgery due to tumor

progression or adverse event was not available, and the incidence of treatment-related adverse events was underestimated. Secondly, the expression of programmed death-ligand 1 was not evaluated before treatment. Thirdly, different types of immune checkpoint inhibitors were used in this study. Although frequencies of pathological complete regression were comparable among different inhibitors, it is unclear whether the regression patterns were similar due to small study numbers of the four inhibitors. However, this study revealed the value of esophagectomy after neoadjuvant chemoimmunotherapy, particularly a high incidence of complete pathological response in the mucosa showing different regression patterns compared with that after neoadjuvant chemoradiotherapy.

## Conclusions

In this retrospective study, esophagectomy after neoadjuvant chemoimmunotherapy can be safely performed. Preferential clearing of tumor cells in the mucosal layer is common after immunotherapy; however, the rate of complete pathological response is relatively low. Esophagectomy is still warranted after neoadjuvant chemoimmunotherapy.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-882/rc

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-882/coif). Haiquan Chen serves as an unpaid editorial board member of *Journal of Thoracic Disease* from October 2022 to September 2024. The other 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. The institutional review board of Fudan University Shanghai Cancer Center approved the esophageal carcinoma database used in the present study (No. 1612167-18). Informed consent was taken from all the patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).



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