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Original Article

# Can Patients with Stage IVA Esophageal Squamous Cell Carcinoma Benefit from CROSS-based Neoadjuvant Therapy? A Single-center Retrospective Comparison with Stage II/III Disease

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## Abstract

**Background:** Neoadjuvant concurrent chemoradiotherapy (CCRT) followed by surgery is the standard of care for locally advanced esophageal cancer based on the CROSS trial. However, patients with clinical stage IVA disease were excluded from the CROSS trial, and no standard of care in this subgroup has been established. The benefit of neoadjuvant CCRT in this clinical setting remains uncertain. In this study, we explored the prognosis of patients with stage IVA disease who underwent neoadjuvant CCRT followed by esophagectomy, which is the standard of care for stage II/III disease. The study aimed were to investigate whether the same treatment modality administered to patients with more advanced stages would have comparable outcomes, and the influence of pathological response on prognosis in this setting. **Materials and Methods:** We retrospectively analyzed patients with clinical stage II–IVA (according to the AJCC 8th edition definition) esophageal squamous cell carcinoma (ESCC) treated with neoadjuvant CCRT followed by esophagectomy at MacKay Memorial Hospital between 2010 and 2023. Baseline characteristics, treatment patterns, and outcomes were compared between stage II/III and stage IVA patients. Kaplan–Meier survival analysis of overall survival (OS) and progression-free survival (PFS) was performed, stratified by pathological complete response (pCR). **Results:** A total of 215 patients were included (168 stage II/III; 47 stage IVA). The baseline characteristics were well balanced between the two groups. The median OS was significantly longer in the stage II/III patients compared to the stage IVA patients (31.18 vs. 19.00 months; hazard ratio [HR] 0.55, 95% confidence interval [CI] 0.35–0.86, $P = 0.0098$). The median PFS was 19.47 versus 9.93 months (HR 0.54, 95% CI 0.36–0.85, $P = 0.0065$). In subgroup analysis stratified by pCR status, OS and PFS were similar among the patients without pCR regardless of the staging (stage II/III vs. stage IVA patients: median OS, 18.82 vs. 19.82 months; median PFS, 11.75 vs. 9.65 months). The stage IVA patients who achieved pCR had better outcomes compared to the stage II/III patients without pCR (median OS, 35.24 vs. 18.82 months; median PFS, 18.75 vs. 11.75 months). **Conclusion:** Neoadjuvant CCRT followed by surgery may offer meaningful survival benefits in select patients with stage IVA ESCC, particularly those who achieve pCR. Stage IVA was associated with a poorer prognosis overall compared to stage II/III, based on the same treatment strategy. However, pCR status appeared to be another important prognostic factor.

**Keywords:** Chemoradiation, esophageal squamous cell carcinoma, neoadjuvant, stage IVA, treatment outcome

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## Introduction

Esophageal cancer is one of the most common cancers and a major global health issue. Esophageal squamous cell carcinoma (ESCC) and adenocarcinoma account for approximately 90% of esophageal cancers worldwide.[1] The incidence of ESCC is particularly high in East Asia, including China, Taiwan, and Japan, where dietary habits, tobacco use, alcohol consumption, and genetic predisposition contribute significantly to disease prevalence.[2-4] Over 250,000 new cases are diagnosed annually in China, where ESCC remains one of the leading causes of cancer-related death.[4] Despite improvements in early detection and treatment, the overall 5-year survival rate for ESCC remains low, ranging from 15% to 25%, largely due to late-stage diagnosis and high recurrence rates.[5]

In East Asian populations, ESCC has distinct epidemiological and molecular characteristics compared to adenocarcinoma-dominant regions in the West. Patients often present with more advanced-stage disease, and the burden of cervical and upper thoracic tumors is relatively higher.[6] Moreover, cultural and regional practices such as the consumption of hot beverages and nitrosamine-rich preserved foods may further increase the risk of ESCC.[7]

For patients with locally advanced resectable disease, the standard of care is neoadjuvant concurrent chemoradiotherapy (CCRT) followed by surgery, primarily based on the results of the CROSS trial, which demonstrated a survival benefit with this approach over surgery alone.[8] However, the CROSS trial excluded patients with clinical stage IVA disease, and thus, the efficacy of this approach in these patients remains uncertain.

Despite limited evidence, neoadjuvant CCRT is commonly administered to stage IVA patients in clinical practice, particularly in East Asia, due to the higher incidence of ESCC.[2] Whether these patients derive similar survival benefits remains an unanswered but clinically relevant question. Furthermore, a pathological complete response (pCR) after CCRT is associated with improved prognosis in ESCC.[9,10] However, its role as a predictive biomarker in stage IVA patients is not well established.

Recent studies have demonstrated the heterogeneity in treatment response and emphasized the importance of response-based prognostication. Emerging data suggest that tumor biology may play a more critical role than anatomical staging alone in determining outcomes after neoadjuvant treatment.[5,6] Given this background, we aimed to compare clinical outcomes between stage II/III and IVA ESCC patients treated with neoadjuvant CCRT followed by surgery, and to explore the prognostic significance of pCR in both groups.

## Materials and Methods

This retrospective study analyzed clinical data from patients with clinical stage II to IVA ESCC who underwent neoadjuvant CCRT followed by surgery at MacKay Memorial Hospital between January 2010 and December 2023. Staging was determined according to the AJCC 8$^{th}$ edition based on endoscopic ultrasound, computed tomography, positron emission tomography, and clinical records.

All patients received platinum-based chemotherapy (cisplatin or carboplatin) concurrently with radiation therapy (range: 41.4–50.4 Gy). Surgery was performed 4–8 weeks after completing CCRT. R0 resection was defined as no residual tumor cells at the surgical margin in microscopy. R1 and R2 resection indicated that residual tumor was found microscopically or macroscopically, respectively. Postoperative pathological response was classified as either pCR or non-pCR based on whether or not there were residual viable tumor cells.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of MacKay Memorial Hospital (Approval Number: 21MMHIS178e, Approval Date: June 8, 2023). All of the included patients provided informed consent for publication of the case.

Patient clinical characteristics, treatment details, and outcomes, including progression-free survival (PFS) and overall survival (OS), were collected. Descriptive statistics were used to summarize patient characteristics and treatment outcomes. Categorical variables were compared using the Chi–square test or Fisher's exact test, while continuous variables were compared using the Mann–Whitney *U*-test for nonparametric data. OS was defined as the time from diagnosis to death from any cause or the last known follow-up date. PFS was defined as the time from CCRT to disease progression, death, or the last known follow-up date. Kaplan-Meier survival curves were generated for both OS and PFS, and group differences were assessed using the log–rank test. Hazard ratios (HRs) for OS and PFS were calculated using the Mantel–Haenszel method and log–rank test. All figures and statistical analyses were performed using Prism version (10.1.1 [270], November 21, 2023) (GraphPad Software, San Diego, CA) and R Studio. Statistical significance was defined as a $P < 0.05$ in two-sided tests.

## Results

A total of 215 patients were included in the analysis: 168 with stage II/III and 47 with stage IVA disease [Table 1]. The baseline characteristics of the patients, including age, sex, ECOG performance status, and tumor location, were generally well balanced between the two groups. Other variables, including clinical T and N stage distributions, were comparable between the two groups. However, the stage II/III group had more comorbidities (49.4% vs. 23.4%, $P = 0.0015$).

In terms of treatment details, the chemotherapy regimen and radiation dose were not significantly different between the two groups [Table 2]. The R0 resection rate was similarly high in both groups (93.6% in stage II/III vs. 91.1% in stage IVA).

**Table 1: Baseline characteristics of esophageal squamous cell carcinoma patients with Stage II/III or Stage IVA disease**

| | Stage IVA *n*=47 | Stage II/III *n*=168 | *P** |
|---|---|---|---|
| Age (years) | | | |
| Median | 57 | 58 | ns |
| Range | 41–69 | 34–81 | |
| Male sex, *n* (%) | 43 (91.5) | 151 (89.9) | ns |
| ECOG, *n* (%) | | | |
| 0 | 8 (17.0) | 51 (30.4) | ns |
| 1 | 38 (80.9) | 114 (67.9) | ns |
| 2 | 1 (2.1) | 3 (1.8) | ns |
| ≥1 comorbidities**, *n* (%) | 11 (23.4) | 83 (49.4) | 0.0015 |
| Tumor location, *n* (%) | | | |
| Cervical | 4 (8.5) | 10 (6.0) | ns |
| Proximal | 10 (21.3) | 32 (19.0) | ns |
| Middle | 20 (42.6) | 74 (44.0) | ns |
| Distal | 13 (27.7) | 49 (29.2) | ns |
| Unknown | 0 | 3 (1.8) | ns |
| Clinical T stage, *n* (%) | | | |
| cT1 | 1 (2.1) | 4 (2.4) | ns |
| cT2 | 11 (23.4) | 51 (30.4) | ns |
| cT3 | 22 (46.8) | 113 (67.3) | 0.0103 |
| cT4 | 13 (27.7) | 0 | <0.001 |
| Clinical N stage, *n* (%) | | | |
| cN0 | 2 (4.3) | 12 (7.1) | ns |
| cN1 | 2 (4.3) | 68 (40.5) | <0.001 |
| cN2 | 5 (10.6) | 88 (52.4) | <0.001 |
| cN3 | 38 (80.9) | 0 | <0.001 |

*For the comparison of continuous variables, Mann–Whitney *U*-test was used. For the percentage comparison, the Chi-square test or Fisher's exact test was used. Statistical significance was defined as a $P<0.05$ in two-sided tests. **Comorbidities included heart failure, chronic obstructive pulmonary disease, liver disease, second malignancy, diabetes, peptic ulcer disease, alcoholism. ns: No significant, ECOG: Eastern Cooperative Oncology Group

**Table 2: Treatment details and outcomes of esophageal squamous cell carcinoma patients with Stage II/III or Stage IVA disease**

| | Stage IVA | Stage II/III | *P** |
|---|---|---|---|
| Chemotherapy, *n* (%) | | | |
| Cis/carboplatin + paclitaxel | 21 (44.7) | 78 (46.4) | ns |
| weekly cis/carboplatin | 22 (46.8) | 85 (50.6) | ns |
| Others** | 4 (8.5) | 5 (3.0) | ns |
| Radiation dose (Gy) | | | |
| Median | 48 | 48 | ns |
| Range | 41.4–50.4 | 24.0–54.0 | |
| Types of resection | | | |
| R0 resection | 44 (93.6) | 153 (91.1) | ns |
| R1/2 resection | 2 (4.3) | 15 (8.9) | ns |
| Pathological stage, *n* (%) | | | |
| Complete response | 8 (17.0) | 59 (35.1) | 0.0179 |
| I/II | 11 (23.4) | 60 (35.7) | ns |
| III/IVA | 27 (57.4) | 49 (29.2) | <0.001 |
| Operation complications | | | |
| Any complications | 4 (8.5) | 15 (8.9) | ns |
| Anastomosis leakage | 2 (4.3) | 1 (0.6) | ns |
| Chylothorax | 1 (2.1) | 4 (2.4) | ns |
| Infection*** | 0 (0.0) | 5 (3.0) | ns |
| Death | 1 (2.1) | 3 (1.8) | ns |
| Others**** | 0 (0.0) | 2 (1.2) | ns |
| Adjuvant therapy | | | |
| Any therapy | 24 (51.1) | 64 (38.1) | ns |
| Radiation | 10 (21.3) | 16 (9.5) | 0.0289 |
| Chemotherapy | 22 (46.8) | 55 (32.7) | ns |
| Immunotherapy | 1 (2.1) | 4 (2.4) | 0.9189 |
| Type of recurrence | | | |
| Local | 2 (4.3) | 9 (5.4) | ns |
| Distant | 32 (68.1) | 34 (20.2) | <0.001 |

*For the comparison of continuous variables, Mann–Whitney *U*-test was used. For the percentage comparison, the Chi-square test or Fisher's exact test was used. Statistical significance was defined as a $P<0.05$ in two-sided tests. **Other regimen included cisplatin/fluorouracil, cisplatin/tegafur + uracil, ***Infection includes pneumonia, intra-abdominal infection, wound infection. ****Other complications included fistula formation, postoperative pyloric spastic paresis. ns: No significant

The incidence of postoperative complications did not differ significantly between the two groups. However, a statistically significant difference was observed in the pCR rate between the stage II/III and stage IVA groups (35.1% vs. 17.0%, $P=0.00179$). Significantly more patients with stage IVA disease underwent adjuvant radiation therapy (stage IVA: 21.3% vs. stage II/III: 9.5%, $P=0.0289$), and numerically more patients with stage IVA disease underwent chemotherapy (46.8% vs. 32.7%, $P=0.108$). Only a few patients underwent adjuvant immunotherapy in both groups (2.1% in stage IVA vs. 2.4% in stage II/III).

The median follow-up was 60.32 months. The stage II/III patients had significantly better survival outcomes than the stage IVA patients [median OS: 31.18 vs. 19.00 months, HR 0.55, 95% confidence interval (CI) 0.35 − 0.86, $P = 0.0098$; median PFS: 19.47 vs. 9.93 months, HR 0.54, 95% CI 0.36 − 0.85, $P = 0.0065$; Figure 1a and b ].

When stratified by pathological response, the patients who achieved pCR had a better prognosis compared to their non-pCR counterparts in both the stage II/III and stage IVA groups [Figure 2a and b]. Among the stage II/III patients, the median OS was 47.08 months for those with pCR versus 18.82 months for those without pCR. In the stage IVA group, the median OS was 35.24 months for those with pCR compared to 19.02 months for those without pCR. Notably, the stage IVA patients who achieved pCR following neoadjuvant CCRT had both longer OS and PFS than the stage II/III patients who failed to achieve pCR, underscoring the prognostic significance of pathological response across different stages and suggesting that tumor biology may outweigh anatomic stage in determining clinical outcomes.

## Discussion

Globally, treatment guidelines for clinical stage IVA ESCC vary significantly. Western guidelines, including those

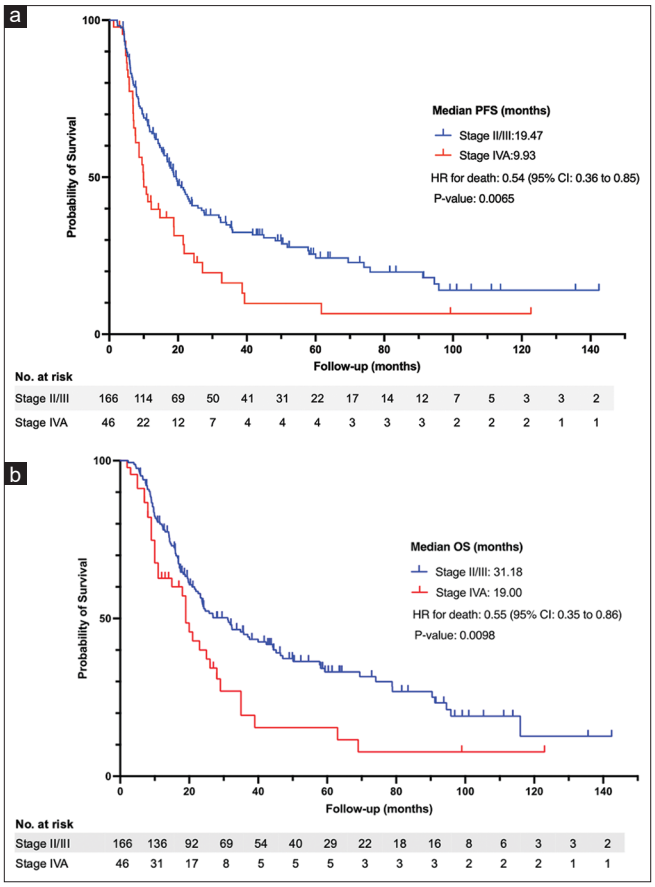


**Figure 1:** Progression-free survival (a) and overall survival (b) of stage II/III and IVA

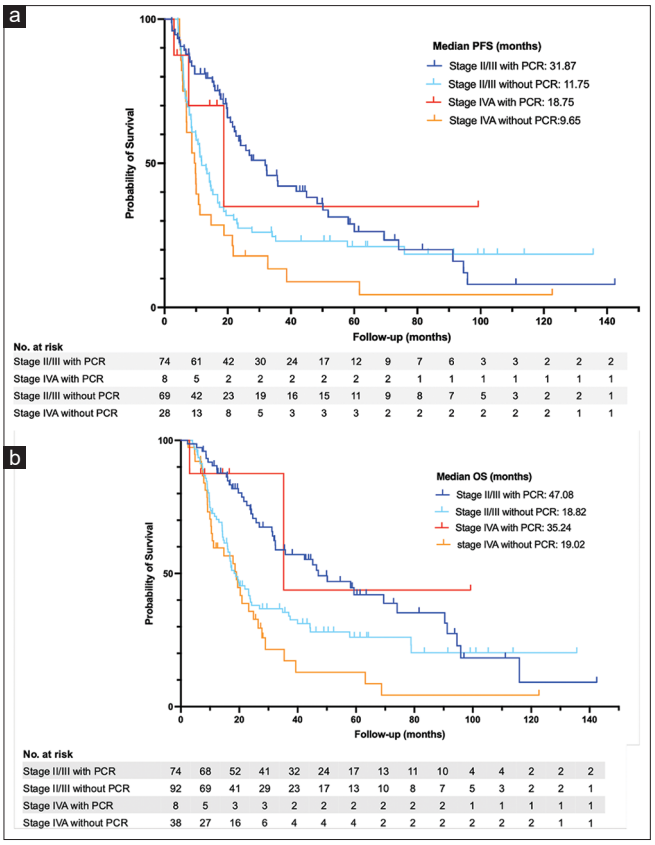


**Figure 2:** Progression-free survival (a) and overall survival (b) of stage II/III and IVA stratified by pathological complete response status

from the national comprehensive cancer network, typically recommend definitive chemoradiotherapy for unresectable T4 disease, with surgery reserved only for highly selected patients who show a good response.[11] In contrast, East Asian countries such as Japan and Korea frequently adopt a more aggressive, multimodality approach, favoring induction chemoradiotherapy or chemotherapy followed by surgery for patients with T4b or stage IVA disease.[12-15] According to the Japanese Esophageal Society guidelines and retrospective data from Yamaguchi *et al.*, Makino T *et al.*, and Teranishi R *et al.*, patients with initially unresectable T4b tumors may become eligible for curative surgery following a favorable response to induction therapy, with 3-year OS rates ranging from 30% to 35%.[12-14] These observations support the notion that neoadjuvant therapy followed by surgery may offer survival benefits even for select stage IVA ESCC patients, a view consistent with our findings.

In this study, we investigated the use of two treatment modalities based on the CROSS trial in patients with more locally advanced stage IVA disease. However, different staging systems were used in the CROSS trial and in our study. In the CROSS trial, the staging of patients was based on AJCC 6$^{th}$ edition, and any number of positive lymph nodes was considered as N1. However, we used the AJCC 8$^{th}$ edition, in which N1, N2, and N3 were introduced based on the number of positive lymph nodes. Therefore, some patients with N3 disease, which would be stage IVA according to the AJCC edition 8$^{th}$, may have been enrolled in the CROSS trial. Although, to the best of our knowledge, it has not been reported whether this group of patients were included in the CROSS trial, we believe that the number of this group of patients would have been small and unlikely to fulfill the inclusion criteria. In addition, nearly half of the patients in our study underwent platinum monotherapy for chemoradiation, which was not the standard regimen administered in the CROSS trial. The patients receiving the single platinum regimen included those who were older, had more comorbidities (i.e., cachexia, lung disease, cardiovascular disease), and synchronous or metachronous secondary malignancies such as head and neck cancers.

Recent evidence underscores the prognostic importance of pCR after neoadjuvant therapy. Lin *et al.* and Wu *et al.* identified pCR as an independent predictor of both OS and disease-free survival in patients with ESCC across clinical stages.[9,10] Our results are consistent with their findings, demonstrating that the patients with stage IVA disease who achieved pCR had comparable survival outcomes to stage II/III patients with pCR. Notably, pCR status appeared to outweigh the initial stage in determining long-term outcomes, reinforcing its clinical relevance.

Despite the promising outcomes associated with pCR, patients who failed to achieve pCR (non-pCR) remained at high risk

of recurrence and poor survival. One potential strategy to improve their outcomes is the addition of adjuvant therapy. The CheckMate 577 trial showed that adjuvant nivolumab significantly prolonged disease-free survival in patients with residual disease following neoadjuvant chemoradiotherapy and resection.[16] Although this trial excluded stage IVA patients, the rationale for adjuvant immunotherapy in non-pCR patients remains valid. In our cohort, however, only a minority of the non-pCR patients received adjuvant immunotherapy, likely due to delayed regulatory approval and the absence of national health insurance reimbursement in Taiwan during much of the study period. This therapeutic gap may have negatively impacted outcomes in the non-pCR subgroup.

Taken together, our data and the existing literature support a treatment paradigm wherein selected stage IVA patients may benefit from neoadjuvant chemoradiotherapy followed by surgery, particularly if pCR is achieved. For non-pCR patients, future research should explore the integration of novel adjuvant strategies, including immune checkpoint blockade.

This study has several limitations. First, its retrospective and single-center nature may have introduced selection bias and limited the generalizability of our findings. Second, while our sample size represents one of the largest datasets for stage IVA ESCC in Taiwan, the number of patients in stratified subgroups (e.g., stage IVA with pCR) was limited. Third, data on important factors such as molecular subtype, immunological profile, and treatment compliance were not available and may have confounded interpretation. Fourth, selection bias existed because not all patients with stage IVA disease are eligible for neoadjuvant CCRT or esophagectomy, and whether this treatment strategy can be applied to all patients with stage IVA disease and whether similar treatment outcomes can be achieved remains unclear. Future prospective studies are warranted to validate our observations and explore biomarkers predictive of treatment response and long-term survival.

## Conclusion

Neoadjuvant CCRT followed by surgery may offer survival benefits in select stage IVA ESCC patients. Achieving pCR was associated with favorable outcomes regardless of clinical stage. Future prospective studies should explore biomarkers and imaging modalities to predict treatment response and guide therapy for locally advanced ESCC.

### Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

## References

1. Global Cancer Observatory. International Agency for Research on Cancer. World Health Organization. Available from: https://gco.iarc.fr/. [Last accessed on 2025 April 22].
2. Kitagawa Y, Ishihara R, Ishikawa H, Ito Y, Oyama T, Oyama T, *et al*. Esophageal cancer practice guidelines 2022 edited by the Japan esophageal society: Part 1. Esophagus 2023;20:343-72.
3. Lin Y, Totsuka Y, He Y, Kikuchi S, Qiao Y, Ueda J, *et al*. Epidemiology of esophageal cancer in Japan and China. J Epidemiol 2013;23:233-42.
4. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, *et al*. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115-32.
5. Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. Lancet 2013;381:400-12.
6. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med 2003;349:2241-52.
7. Islami F, Ren JS, Taylor PR, Kamangar F. Pickled vegetables and the risk of oesophageal cancer: A meta-analysis. Br J Cancer 2009;101:1641-7.
8. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, *et al*. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
9. Lin JW, Hsu CP, Yeh HL, Chuang CY, Lin CH. The impact of pathological complete response after neoadjuvant chemoradiotherapy in locally advanced squamous cell carcinoma of esophagus. J Chin Med Assoc 2018;81:18-24.
10. Wu YY, Dai L, Yang YB, Yan WP, Cheng H, Fan MY, *et al*. Long-Term Survival and Recurrence Patterns in Locally Advanced Esophageal Squamous Cell Carcinoma Patients with Pathologic Complete Response After Neoadjuvant Chemotherapy Followed by Surgery. Ann Surg Oncol 2024;31:5047-54.
11. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers. Version 1.2025. Available from: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. [Last accessed on 2025 April 22].
12. Yamaguchi S, Morita M, Yamamoto M, Egashira A, Kawano H, Kinjo N, *et al*. Long-Term Outcome of Definitive Chemoradiotherapy and Induction Chemoradiotherapy Followed by Surgery for T4 Esophageal Cancer With Tracheobronchial Invasion. Ann Surg Oncol 2018;25:3280-7.
13. Makino T, Yamasaki M, Tanaka K, Miyazaki Y, Takahashi T, Kurokawa Y, *et al*. Treatment and clinical outcome of clinical T4 esophageal cancer: A systematic review. Ann Gastroenterol Surg 2018;3:169-80.
14. Teranishi R, Makino T, Tanaka K, Yamashita K, Saito T, Yamamoto K, *et al*. Long-Term Survival and Prognostic Factors Associated With Curative Conversion Surgery for Ct4b Esophageal Squamous Cell Carcinoma: Analysis of 200 Consecutive Cases. Surgery 2023;174:558-66.
15. Shin A, Won YJ, Jung HK, Kong HJ, Jung KW, Oh CM, *et al*. Trends in incidence and survival of esophageal cancer in Korea: Analysis of the Korea Central Cancer Registry Database. J Gastroenterol Hepatol 2018;33:1961-8.
16. Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, *et al*. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med 2021;384:1191-203.