Original Article

Equivalent prognosis with no lymph node metastasis to pathological complete remission in patients with localized advanced esophageal cancer after neoadjuvant triplet chemotherapy with docetaxel, cisplatin, and 5-fluorouracil followed by curative surgery: a single-center retrospective cohort study

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Background: Adjuvant nivolumab therapy has become the standard therapy for patients with localized advanced esophageal cancer with non-pathological complete response after neoadjuvant chemoradiotherapy followed by curative surgery. However, the necessity of this therapy for patients after neoadjuvant chemotherapy (NAC) with docetaxel, cisplatin, and 5-fluorouracil (DCF) regimen followed by surgery is unclear, and the prognosis of grouping based on the presence or absence of pathological tumor and lymph node findings has not been analyzed. Therefore, our study aimed to address these questions.

Methods: This retrospective cohort study included patients with cT1N1–3M0 and cT2–3N0–3M0 esophageal cancer according to the Japanese Classification of Esophageal Cancer, 11th edition, who received NAC with DCF followed by curative surgery between 2008 and 2020 at Jichi Medical University Hospital. We divided patients with ypT0–3N0–3M0 into four histological groups, namely ypT0N0, ypT+N0, ypT0N+, and ypT+N+, and we evaluated overall survival as the primary outcome and the prognostic relationship of lymph node metastasis as the secondary outcome.

Results: A total of 101 patients were included in this study. Kaplan-Meier analysis showed that the curves of the ypT0N0 and ypT+N0 groups were almost identical, while they differed from the other two groups. The hazard ratio of ypN+ was 4.44 (95% confidence interval: 2.03–9.71; P<0.001).

Conclusions: The prognosis of the ypT+N0 group after NAC with DCF followed by surgery was similar to that of pathological complete remission. Grouping patients according to pathological lymph node status is a reasonable predictor of prognosis.

Keywords: Chemotherapy; adjuvant; esophagus neoplasms; lymphatic metastasis; neoadjuvant therapy

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Introduction

Background

Esophageal cancer is a clinically challenging disease that requires multidisciplinary treatment strategies owing to its poor prognosis (1). It has a 5-year survival rate ranging from 10% to 30% worldwide (2). For localized advanced esophageal cancer, preoperative neoadjuvant chemotherapy (NAC) and neoadjuvant chemoradiotherapy (CRT) to complement surgery have been shown to be more effective than postoperative adjuvant chemotherapy (3-6). In addition to neoadjuvant CRT followed by surgery, adjuvant nivolumab has become the standard therapy for patients with non-pathological complete responses based on tumor-node-metastasis (TNM) classification (7,8).

Two types of preoperative treatments for esophageal cancer are performed worldwide: NAC and neoadjuvant CRT. Although several previous studies reported no difference between the two treatments (9-11), the JCOG1109 clinical trial has reported that neoadjuvant triplet chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (DCF) was more effective than neoadjuvant doublet chemotherapy with 5-fluorouracil plus cisplatin, with or without radiotherapy, for esophageal squamous cell carcinoma (12).

Highlight box

Key findings

- The prognosis of patients with squamous cell carcinoma of the thoracic esophagus in the ypT+N0 group who underwent esophageal surgery after neoadjuvant chemotherapy (NAC) with docetaxel, cisplatin, and 5-fluorouracil (DCF) followed by esophageal surgery closely resembled that of those who achieved pathological complete remission.

What is known and what is new?

- Adjuvant nivolumab therapy has emerged as the standard treatment for patients with localized advanced esophageal cancer who do not achieve a pathological complete response following neoadjuvant chemoradiotherapy and subsequent curative surgery.
- After undergoing NAC with DCF followed by esophageal surgery, prognosis is comparable to cases that achieve a complete response in ypT+N0 cases of squamous cell carcinoma in the thoracic esophagus.

What is the implication, and what should change now?

- Further large-scale prospective multicenter studies are needed to validate whether adjuvant nivolumab is necessary for patients in the T+N0 groups after receiving NAC with DCF followed by esophageal surgery.

Rationale and knowledge gap

In Japan, esophageal cancer often presents as squamous cell carcinoma and most neoadjuvant therapies are chemotherapy, not CRT, and NAC with DCF has been the standard therapy based on the results of JCOG1109 (13). Although a study has shown the necessity of adjuvant nivolumab for patients with esophageal cancer with a non-pathological complete response after neoadjuvant CRT plus surgery (7), because the non-pathological complete response following chemoradiation therapy has a poor prognosis (14), the necessity of nivolumab in patients with esophageal cancer after NAC with DCF is unclear. In addition, after neoadjuvant CRT, prognoses differed with regard to the pathological responses of the tumor and lymph node (15,16). Specifically, a better prognosis was observed in the ypT+N0 group than in the ypT0N+ and ypT+N+ groups with regard to non-pathological complete remission (17). Additionally, the CheckMate 577 trial subgroup analysis did not show a statistically significant benefit of adjuvant nivolumab for the ypN0 group (18). However, to the best of our knowledge, no analysis for estimating its prognosis after NAC with DCF followed by curative surgery has been done on the four pathological types of esophageal cancer, ypT0N0, ypT+N0, ypT0N+, and ypT+N+.

Objective

This study aimed to examine the prognosis of squamous cell carcinoma of the thoracic esophagus in ypT0N0, ypT+N0, ypT0N+, and ypT+N+ groups after NAC with DCF followed by curative surgery. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1484/rc).

Methods

Study design and data sources

We performed a retrospective cohort study using data from a database of admission records at the Division of Gastroenterological, General, and Transplant Surgery, Department of Surgery, Jichi Medical University. From this database, the patients' ID, age, sex, operative findings, and the first day of administration for preoperative chemotherapy were obtained. We then collected data on

their clinical stage at the initial diagnosis based on computed tomography scan findings, especially for preoperative lymph node metastasis, determined by the reporting of fluorine-18-fluorodeoxyglucose-positron emission tomography or computed tomography by radiologists, pathological findings following NAC plus surgery, and the date of death or the last day of their survival, as indicated by the electronic medical records at Jichi Medical University Hospital. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of Jichi Medical University (No. RinA21–064), and individual consent for this retrospective analysis was waived. All eligible patients were included in the analysis, and any missing data were excluded.

Study population

The inclusion criteria were as follows: (I) patients with esophageal cancer on admission, pathological findings of squamous cell carcinoma of the esophagus, NAC with DCF or 5-fluorouracil plus cisplatin, first NAC between November 2008 and October 2020 and curative surgery; and (II) had cT1N1–3M0 and cT2–3N0–3M0 esophageal cancer according to the Japanese Classification of Esophageal Cancer, 11th edition. In this classification, the TM category aligns closely with the Union for International Cancer Control TNM classification, 8th edition, while the N category is classified by regional lymph nodes rather than the number of lymph node metastases (19,20). The choice of administering DCF or 5-fluorouracil plus cisplatin as NAC was made by the physician, with a preference for NAC with DCF, based on the preliminary results of our patients who participated in the CROC trial (21). NAC with 5-fluorouracil plus cisplatin was included in this section while excluded it in the next as it presented the standard of care at the time. This indicates a degree of selection bias.

Patients were considered ineligible based on the criteria outlined in the JCOG1109 study (22) based on the following criteria: (I) not aged 20–75 years, (II) location of cancer in the cervical or abdominal esophagus, (III) NAC other than two or three cycles of DCF regimens were administered, (IV) combined resection for double cancers whose stages were higher than esophageal cancer, (V) complete resection (R0) could not be performed and pathological findings after NAC with DCF plus surgery were ypT4a–b, and (VI) pathological findings were ypN4 according to the Japanese Classification of Esophageal Cancer, 11th edition (19), indicating involvement beyond regional lymph nodes and resulting in ypM1 according to the Union for International Cancer Control TNM classification, 8th edition (20).

Exposures and outcomes

This study aimed to compare the prognosis of four histological groups of esophageal cancer: ypT0N0, ypT+N0, ypT0N+, and ypT+N+, treated with two or three cycles of NAC with DCF followed by curative surgery. This NAC was a DCF regimen, which consisted of intravenous docetaxel 70 mg/m^2 and cisplatin 70 mg/m^2 on day 1, and continuous intravenous infusion of 5-fluorouracil 750 mg/m^2 on days 1–5 every 3 weeks. Dose reductions were made as appropriate for the physician's choice, and whether or not to administer a third round of DCF was determined by the effectiveness of the two doses on the stable disease or better and by the patients' tolerance to side effects. Pathological findings following NAC with DCF plus surgery were obtained from the pathology reports at Jichi Medical University Hospital, which included ypT, ypN, curativity, and pathological primary tumor regression according to the criteria of the Japanese Classification of Esophageal Cancer, 11th edition (19). The frequency and proportion of how each initial clinical evaluation of cT and cN resulted in the pathological findings of ypT and ypN were calculated.

The primary outcome measure of this study was the overall survival between the four pathological groups, while the secondary outcome was the prognostic impact of the pathological findings of ypT and ypN. Overall survival was calculated from the date of the beginning of the first DCF regimen to the last day of confirmed their survival, as indicated by the electronic medical records at Jichi Medical University Hospital.

Statistical analysis

All descriptive statistics are reported as frequencies and proportions for categorical variables, except for follow-up times, which are reported as medians and interquartile ranges, and as means and standard deviations for continuous variables. For the entire cohort, the median follow-up time and proportion of censored cases were counted, and the median overall survival and 5-year survival rates were estimated using the Kaplan-Meier method. The differences among the four groups were analyzed using Fisher's exact test and the Kruskal-Wallis test for categorical and

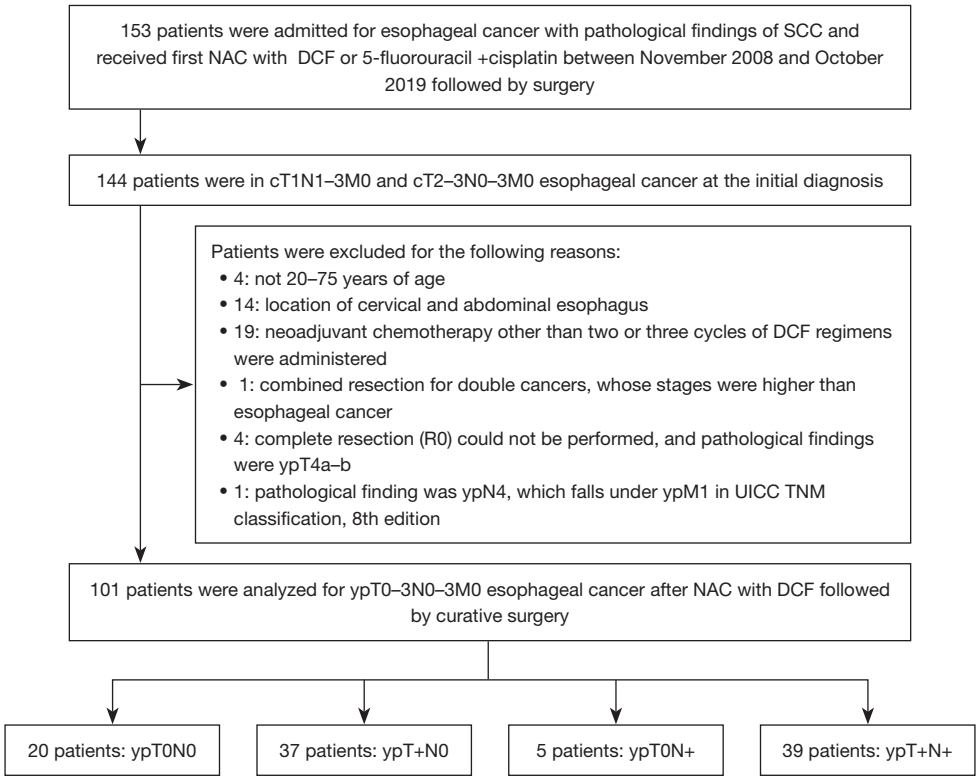

Figure 1 Flow diagram of this study selection process. The stage classifications was based on the criteria of the Japanese Classification of Esophageal Cancer, 11th edition. SCC, squamous cell carcinoma; NAC, neoadjuvant chemotherapy; DCF, docetaxel, cisplatin, and 5-fluorouracil; UICC TNM classification, Union for International Cancer Control tumor-node-metastasis classification.

continuous variables.

Overall survival among the four pathological groups, namely, ypT0N0, ypT+N0, ypT0N+, and ypT+N+, was estimated based on the Kaplan-Meier method, and the median survival times and the 5-year survival rates were calculated. Survival curves were compared using the log-rank tests.

Regarding the secondary outcomes, to determine the prognostic impact of the pathological findings of ypT and ypN on overall survival, overall survival was estimated and regrouped with ypT and ypN, respectively, and hazard ratios and 95% confidence intervals were calculated using a Cox proportional hazards model to ypT+ and ypN+. To avoid overfitting due to the small number of events, only two expiatory variables were selected.

Chemotherapy was administered following two or three cycles of NAC with DCF was considered palliative chemotherapy; the number of patients was counted in the four groups, including the history of nivolumab use for considering the potential impact of post-treatment on survival.

All statistical analyses were performed using the R version 4.3.1 software (the R Foundation, Vienna, Austria). P values of <0.05 were considered statistically significant.

Results

In total, 101 patients received two or three cycles of NAC with DCF and complete resection for esophageal cancer at the ypT0–3N0–3M0 stage, all of which were included in the study (*Figure 1*). No patients were excluded due to missing data. A total of 17 patients who received NAC with 5-fluorouracil plus cisplatin were excluded, and two patients who received 5-fluorouracil plus cisplatin after completing the DCF regimen as NAC were also excluded. No patients received CRT with 5-fluorouracil plus cisplatin. The primary location of the tumor was the upper thoracic esophagus in 10.9%, middle thoracic esophagus in 42.6%, and lower thoracic esophagus in 46.5% of cases.

For the entire cohort, the median follow-up time was 4.7 years (interquartile range, 2.5–6.2 years). The proportion of censored cases was 67.3%. The median

Table 1 Baseline characteristics of the four groups

Characteristic	ypT0N0 (n=20)	ypT+N0 (n=37)	ypT0N+ (n=5)	ypT+N+ (n=39)	P value
Age (years), mean (SD)	61.7 (6.51)	64.7 (8.40)	65.0 (6.60)	65.7 (5.99)	0.23
Female, n (%)	3 (15.0)	6 (16.2)	0 (0.0)	4 (10.3)	0.70
cT, n (%)					0.55
cT0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
cT1	0 (0.0)	2 (5.4)	1 (20.0)	1 (2.6)	
cT2	4 (20.0)	7 (18.9)	1 (20.0)	6 (15.4)	
cT3	16 (80.0)	28 (75.7)	3 (60.0)	32 (82.1)	
cN, n (%)					0.11
cN0	7 (35.0)	14 (37.8)	1 (20.0)	6 (15.4)	
cN1	2 (10.0)	10 (27.0)	0 (0.0)	10 (25.6)	
cN2	9 (45.0)	6 (16.2)	3 (60.0)	18 (46.2)	
cN3	2 (10.0)	7 (18.9)	1 (20.0)	5 (12.8)	
Number of DCF cycles, mean (SD)	2.90 (0.31)	2.81 (0.40)	2.80 (0.45)	2.85 (0.37)	0.85
Number of lymph nodes resected, median (IQR)	42.5 (27.8–55.5)	42.0 (35.0–51.0)	39.0 (28.0–39.0)	42.0 (35.5–49.0)	0.74
Number of lymph nodes metastases, median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.0 (1.0–1.0)	2.0 (1.0–4.0)	<0.001
ypT, n (%)					<0.001
ypT0	20 (100.0)	0 (0.0)	5 (100.0)	0 (0.0)	
ypT1	0 (0.0)	15 (40.5)	0 (0.0)	7 (17.9)	
ypT2	0 (0.0)	9 (24.3)	0 (0.0)	3 (7.7)	
ypT3	0 (0.0)	13 (35.1)	0 (0.0)	29 (74.4)	
Pathological primary tumor regression, n (%)					<0.001
Grade 0 (ineffective)	0 (0.0)	2 (5.4)	0 (0.0)	0 (0.0)	
Grade 1 (slightly effective)	0 (0.0)	11 (29.7)	0 (0.0)	31 (79.5)	
Grade 2 (moderately effective)	0 (0.0)	24 (64.9)	0 (0.0)	7 (17.9)	
Grade 3 (markedly effective)	20 (100.0)	0 (0.0)	5 (100.0)	1 (2.6)	
ypN, n (%)					<0.001
ypN0	20 (100.0)	37 (100.0)	0 (0.0)	0 (0.0)	
ypN1	0 (0.0)	0 (0.0)	3 (60.0)	16 (41.0)	
ypN2	0 (0.0)	0 (0.0)	2 (40.0)	17 (43.6)	
ypN3	0 (0.0)	0 (0.0)	0 (0.0)	6 (15.4)	
Censored, n (%)	16 (80.0)	30 (81.1)	3 (60.0)	19 (48.7)	0.001
Observation times (years), median (IQR)	5.1 (4.2–6.0)	5.3 (3.7–7.1)	1.8 (1.6–2.6)	2.8 (1.6–5.3)	0.001

SD, standard deviation; IQR, interquartile range; DCF, docetaxel, cisplatin, and 5-fluorouracil.

overall survival was not reached, and the 5-year survival rate was 68.2% before grouping.

Table 1 shows the baseline characteristics of the four groups. The cycles of DCF and the number of lymph nodes resected were comparable in all groups. *Table 2* shows there were no patient with the cT0 stage and *Table 3* shows that all cN groups included some patients with the ypN0 stage after NAC with DCF.

Table 2 Frequency and proportion of which each initial clinical evaluation of cT that resulted in what pathological findings of ypT

Types of ypT	cT0	cT1	cT2	cT3
Total	0	4	18	79
ypT0, n (%)	0 (0.0)	1 (25.0)	5 (27.8)	19 (24.1)
ypT1, n (%)	0 (0.0)	2 (50.0)	9 (50.0)	11 (13.9)
ypT2, n (%)	0 (0.0)	0 (0.0)	2 (11.1)	10 (12.7)
ypT3, n (%)	0 (0.0)	1 (25.0)	2 (11.1)	39 (49.4)

Table 3 Frequency and proportion of which each initial clinical evaluation of cN that resulted in what pathological findings of ypN

Types of ypN	cN0	cN1	cN2	cN3
Total	28	22	36	15
ypN0, n (%)	21 (75.0)	12 (54.5)	15 (41.7)	9 (60.0)
ypN1, n (%)	4 (14.3)	6 (27.3)	8 (22.2)	1 (6.7)
ypN2, n (%)	2 (7.1)	1 (4.5)	11 (30.6)	5 (33.3)
ypN3, n (%)	1 (3.6)	3 (13.6)	2 (5.6)	0 (0.0)

The Kaplan-Meier curves between the four pathological groups: ypT0N0, ypT+N0, ypT0N+, and ypT+N+, are shown in *Figure 2*. The median overall survivals and the 5-year survival rates were similar in the ypT0N0 and ypT+N0 groups, but different from the other two.

Regarding the secondary outcomes, the Kaplan-Meier curves showed that regrouping with the ypN stage was a more reliable prognosis predictor than regrouping based on the ypT stage when dividing patients according to their grading (*Figure 3*). The hazard ratio was statistically significant for the ypN stage but not for the ypT stage, suggesting that the ypN stage may be a more accurate indicator of prognosis stage than ypT.

The number of patients who underwent palliative chemotherapy in the ypT+N0 group was two, whereas those in the ypT0N0, ypT+N0, and ypT+N+ groups were 1, 1, and 14, respectively. Palliative use of nivolumab was only administered to one patient in the ypT+N0 group and seven patients in the ypT+N+ group.

Discussion

Key findings

We found that the prognosis of patients with squamous cell carcinoma of the thoracic esophagus in the ypT+N0 group was similar to that of the ypT0N0 group, regardless of the grading of cN+ before NAC with DCF and different from that of ypT0N+ and ypT+N+.

Strengths and limitations

To the best of our knowledge, our study is the first to investigate the prognosis of locally advanced esophageal cancer after NAC with DCF and curative surgery when grouped according to the presence or absence of pathological tumors and lymph node findings. Nevertheless, our study has some limitations. First, these data were collected retrospectively from a single institution and were limited to patients who usually received NAC with DCF and were amenable to surgery. Second, the sample sizes among the four groups were disproportionately small and may not have been sufficient to detect differences between the groups. Third, other than pathological findings, differences in patient backgrounds may be a confounding factor. Lastly, although three-field lymphadenectomy has been widely performed for upper and middle thoracic esophageal cancer in Japan (23), its validity is debatable (23-25), and the external validity of this study is limited when considering that local effects cannot be excluded by surgical intervention.

Comparison with similar research

To explore the poor prognostic factors for esophageal

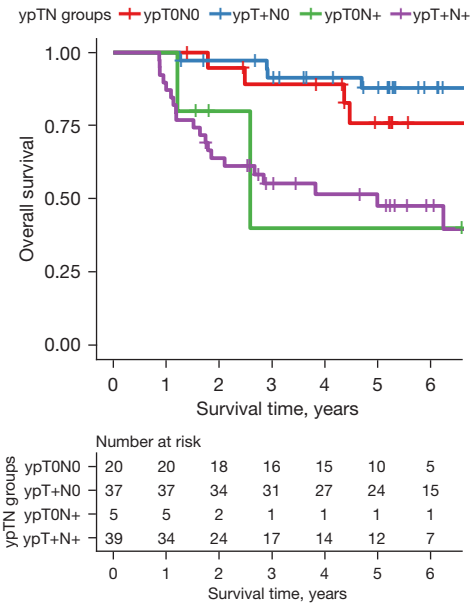

Figure 2 Kaplan-Meier survival curves for the four groups of ypT0N0, ypT+N0, ypT0N+, and ypT+N+ after NAC with DCF followed by surgery. These Kaplan-Meier curves showed the overall survival of patients with locally advanced esophageal cancer after NAC with DCF followed by surgery. The median overall survival in the four groups was not reached (95% CI: NA–NA years), not reached (95% CI: NA–NA years), 2.59 years (95% CI: 2.58–NA years), and 5.00 years (95% CI: 2.11–NA years), respectively. The 5-year survival rates for the four groups were 74.8%, 88.3%, 40.0%, and 47.6%, respectively. The log-rank test showed a P value <0.001. NAC, neoadjuvant chemotherapy; DCF, docetaxel, cisplatin, and 5-fluorouracil; CI, confidence interval; NA, not available.

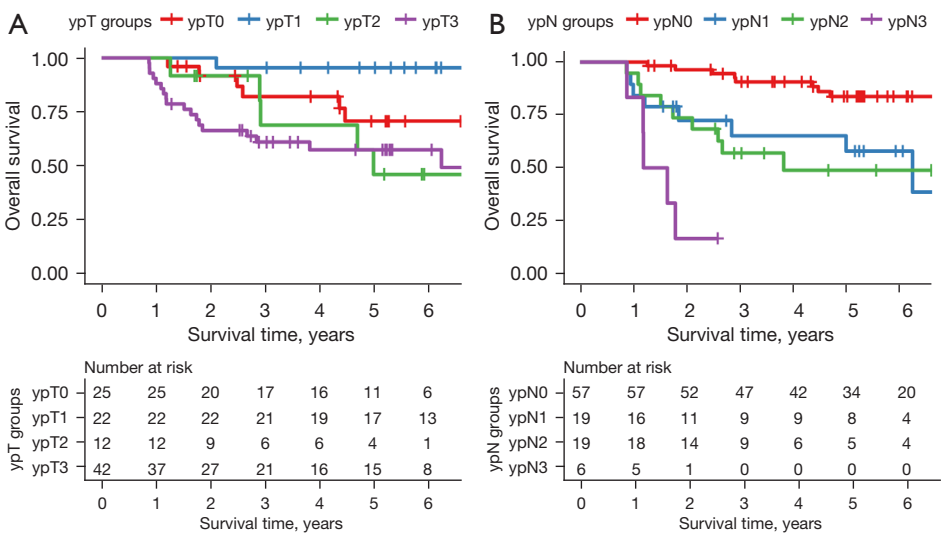

Figure 3 Comparison of the Kaplan-Meier survival curves regrouped with ypT and ypN after NAC with DCF followed by surgery. The hazard ratio of ypT stage and ypN stage was 0.93 (95% confidence interval: 0.37–2.36; P=0.88) and 4.44 (95% confidence interval: 2.03–9.71; P<0.001), respectively. NAC, neoadjuvant chemotherapy; DCF, docetaxel, cisplatin, and 5-fluorouracil.

squamous cell carcinoma, several previous studies have shown that post-neoadjuvant pathological lymph node status was most associated with its prognosis, but tumor status was not (26-30). This could be one of the theoretical considerations for grouping by ypN0 and ypN+ to predict the prognosis after NAC with DCF followed by surgery. In our study, some patients had a grade of cN+ before NAC with DCF, but finished in the ypN0 group after NAC with DCF, and several studies have published that pathological regression of lymph node metastasis predicts prognosis (31,32).

Explanations of findings

Although the number of people in each group was small, the Kaplan-Meier curves in *Figure 2* and these pairwise comparisons in *Table 2* showed significant differences between the ypT+N0 type and the two types of ypN+. In addition, the Kaplan-Meier curves in *Figure 3* indicated that the grouping by ypN+ rather than ypT+ reflected poor prognosis.

Implications and actions needed

Considering the similar prognosis of patients in the ypN0 groups in our study, it is possible that patients in the ypT+N0 group, who underwent NAC with DCF followed by curative surgery, may not require adjuvant nivolumab treatment if the patients in the ypT0N0 group do not require it. However, further large-scale prospective multicenter studies are warranted to determine whether the potential benefits of adjuvant nivolumab for patients in the ypT+N0 group outweigh the associated risk of immune-related adverse events.

Conclusions

The prognosis of the ypT+N0 patient group with squamous cell carcinoma of the thoracic esophagus after NAC with DCF followed by curative surgery was similar to that of pathological complete remission. The grouping of patients by pathological lymph node status after NAC with DCF followed by esophageal surgery, was reasonable for predicting prognosis.

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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-23-1484/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1484/dss

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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-23-1484/coif). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of Jichi Medical University (No. RinA21–064) and individual consent for this retrospective analysis was waived.

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