Esophagus (2019) 16:395–401
https://doi.org/10.1007/s10388-019-00679-8

ORIGINAL ARTICLE

Prognostic significance of pathological tumor response and residual nodal metastasis in patients with esophageal squamous cell carcinoma after neoadjuvant chemotherapy followed by surgery

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Received: 31 March 2019 / Accepted: 28 May 2019 / Published online: 12 June 2019

Abstract

Background The present study investigated prognostic factors in patients with resectable locally advanced esophageal squamous cell carcinoma (ESCC) among various clinicopathological features related to neoadjuvant chemotherapy (NAC) and surgery, and the indications for additional treatment after surgery were considered.

Methods A total of 113 patients with clinical stage II or III ESCC, who had undergone NAC followed by a thoracic esophagectomy with a three-field lymphadenectomy were retrospectively reviewed. NAC consisted of either two courses of cisplatin and 5-fluorouracil or three courses of docetaxel, cisplatin and 5-fluorouracil, with a new course beginning every 3 weeks.

Results The overall survival (OS) rate was poorer in the pN-positive group than in the pN-negative group ($P < 0.001$). In terms of the histological therapeutic effect, the OS rate was poorer in the worse pathological responder group than in the better pathological responder group ($P = 0.001$). A multivariate analysis examining overall survival suggested that only pN (HR 3.204, $P = 0.007$) and worse pathological responder (HR 2.347, $P = 0.041$) were independent prognostic factors. The OS rate was compared among four groups classified according to the different combinations of pN and pathological response. A group of patients with pN-positive and worse pathological response had a significantly poorer outcome than the other groups.

Conclusions The present study suggested that patients with resectable advanced ESCC undergoing NAC followed by surgery, who have both pN and worse pathological response, have a poor prognosis.

Keywords Esophageal squamous cell carcinoma · Neoadjuvant chemotherapy · Prognostic factor · Lymph node metastasis · Histological therapeutic effect

Introduction

The long-term outcomes of patients with locally advanced esophageal squamous cell carcinoma (ESCC) remain poor, and neoadjuvant therapy followed by surgery is now widely accepted as a standard treatment. In Japan, neoadjuvant chemotherapy (NAC) is recommended as a standard treatment based on the results of clinical trials [1, 2]. However, these trials suggested that the long-term outcomes of patients with stage III ESCC remain poor; therefore, a new therapeutic strategy should be established for high-risk patients. The histopathological findings of surgical specimens have not provided any evidence supporting additional treatment after surgery. Actually, whether additional treatment is indicated is determined on a case-by-case basis according to the experience of the doctors, the patient characteristics, and so on. To address this problem, patients with locally advanced ESCC who had undergone NAC followed by surgery at our institute were retrospectively evaluated.

The aim of the present study was to clarify whether any prognostic factors exist among clinicopathological features related to NAC and surgery, and to consider the indications for additional treatment after surgery.

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Patients and methods

Patients

A total of 113 patients with clinical stages II and III (the Japanese Classification of Esophageal Cancer, 11th edition) ESCC, who had undergone NAC followed by thoracic esophagectomy with a three-field lymphadenectomy at Tokai University Hospital between January 2009 and December 2015, was retrospectively reviewed. Surgery was performed 4–8 weeks after the completion of NAC. All patients had performed complete resection without pathological residual tumor (R0 resection). Additional treatment after surgery was not performed until recurrence. After surgery, all the patients underwent follow-up examinations (computed tomography and laboratory examinations) every 3 months for the first 2 years and every sixth months thereafter. Pertinent clinicopathological information was collected from the medical records of each patient.

Neoadjuvant chemotherapy

NAC consisted of either two courses of cisplatin (80 mg/m^2; day 1) and 5-fluorouracil (800 mg/m^2; days 1–5) (CF) or three courses of docetaxel (70 mg/m^2; day 1), cisplatin (70 mg/m^2; day 1) and 5-fluorouracil (700 mg/m^2; days 1–5) (DCF), with each course beginning every 3 weeks. A clinical trial in which these regimens are being compared is now ongoing; therefore, no evidence yet exists as to whether CF or DCF is superior for NAC [3]. CF therapy, which is presently the standard regimen, was usually selected; however, DCF therapy was selected for patients who were registered in the clinical trial and were assigned to the DCF group. CT examinations were performed after each course of NAC to evaluate the therapeutic effect, and patients whose tumors were deemed to be resectable underwent surgery after the planned NAC was completed. Response evaluation was performed according to the Response Criteria in Solid Tumors (RESIST) version 1.1.

Surgery

Surgery was performed via a right thoracic approach using thoracoscopy or a thoracotomy and via an abdominal approach using laparoscopy or a laparotomy. Reconstruction was performed using the gastric tube or jejunum. A three-field lymphadenectomy was routinely performed. Postoperative complications were classified according to Clavien–Dindo (CD) classification. The surgical specimens were pathologically diagnosed by two independent investigators in our hospital according to the Japanese Classification of Esophageal Cancer, 11th edition. Pathological criteria for the effect of neoadjuvant chemotherapy are defined in the Japanese Classification of Esophageal Cancer as following; grade 0: no recognizable cytological or histological therapeutic effect, grade 1a: viable cancer cells accounting for 2/3 or more tumor tissue, grade 1b: viable cancer cells accounting for 1/3 or more but less than 2/3 of tumor tissue, grade 2: viable cancer cells accounting for less than 1/3 of tumor tissue, and grade 3: no variable cancer cells are evident [4].

Statistical analysis

The statistical analysis was performed using SPSS ver. 24 software (SPSS Inc., Chicago, IL, USA). Cox's proportional hazard regression model was used to analyze independent prognostic factors using univariate and multivariate analyses. Factors with a P value > 0.05 in a univariate analysis using the Cox proportional hazard model were considered to be potential risk factors and were further analyzed in a multivariate Cox model. In the survival analysis, the mean value was set as the cut-off for each factor. The survival rates were calculated using the Kaplan–Meier method, and the rates of the two groups were compared using a log-rank test. Statistical differences were considered significant at $P < 0.05$.

Results

Patients' characteristics

The clinicopathological factors of the 113 patients in our cohort are shown in Table 1. The mean age was 65.5 years (42–78 years); 95 patients (84.0%) were men, and 18 patients were women (16.0%). Ninety patients (79.6%) underwent NAC using the CF regimen, and the remaining 23 patients (20.4%) underwent NAC using the DCF regimen prior to surgery. Two NAC courses or more were usually performed. However, only one course followed by surgery was performed for 15 patients (13.3%) for the following reasons: severe NAC toxicity (7 patients), severe stenosis (4 patients), progressive disease after one course (2 patients), progressive anemia (1 patient) and the patient's wishes (1 patient). Seventy-nine patients (69.9%) had pathological lymph node metastasis (pN). The histological therapeutic effect (HTE) on the primary tumor was routinely diagnosed according to the Japanese Classification of Esophageal Cancer [4]; 9 patients (8.0%) had grade 0, 75 patients (66.4%) had grade 1a, 12 patients (10.6%) had grade 1b, 11 patients (9.7%) had grade 2, and 6 patients (5.3%) had grade 3.

Table 1 Clinicopathological characteristics of patients in present study

Characteristics	No. of patients ($n=113$) (%)
Age (mean; range)	65.5 (42–78)
Gender	
Male	95 (84.0)
Female	18 (16.0)
Location of tumor	
Upper	14 (12.4)
Middle	73 (64.6)
Lower	26 (23.0)
cT	
1	7 (6.2)
2	36 (31.9)
3	70 (61.9)
cN	
0	19 (16.8)
1	22 (19.5)
2	57 (50.4)
3	15 (13.3)
Stage	
II	29 (25.7)
III	84 (74.3)
Neoadjuvant chemotherapy	
CF	90 (79.6)
DCF	23 (20.4)
Clinical response of primary tumor	
CR	5 (4.4)
PR	49 (43.4)
SD	49 (43.4)
PD	10 (8.8)
Operation time (min: median; range)	525 (312–1295)
Blood loss (mL: median; range)	482 (145–4710)
Complication after surgery (≥CD grade II)	64 (56.6)
pT	
0	6 (5.3)
1	21 (18.6)
2	13 (11.5)
3	71 (62.8)
4	2 (1.8)
pN	
0	34 (30.1)
1	21 (18.6)
2	36 (31.9)
3	16 (14.1)
4	6 (5.3)
Histological therapeutic effect	
0	9 (8.0)
1a	75 (66.4)
1b	12 (10.6)
2	11 (9.7)
3	6 (5.3)

CR complete response, *PR* partial response, *SD* stable disease, *PD*: progressive disease

Overall survival analysis

The median follow-up period was 24.0 months (2–86 months). The overall survival (OS) rate, which was calculated using the Kaplan–Meier method, was poorer in the pN-positive group ($n=79$) than in the pN-negative group ($n=34$) when examined using a log-rank test ($P<0.001$). In terms of HTE, the OS rate was poorer in the grades 0–1a group ($n=84$) than that in the grades 1b–3 group ($n=29$) ($P=0.001$) (Fig. 1).

Prognostic factors in multivariate analysis

To extract prognostic factors from amongst the clinicopathological features, a survival analysis was performed using the Cox proportional hazard model for all the patients. A univariate analysis showed relationships between pT (HR 3.727, $P=0.005$), pN (HR 4.609, $P<0.001$), HTE grades 0–1a (HR 3.709, $P=0.003$) and OS. A multivariate analysis suggested that only pN (HR 3.204, $P=0.007$) and HTE grades 0–1a (HR 2.347, $P=0.041$) were independent prognostic factors (Table 2).

Prognostic impact of combination of pathological lymph node metastasis and tumor regression grade

Four groups were classified according to combinations of pN and HTE: group A ($n=15$), patients with pN-negative and HTE grades 1b–3; group B ($n=19$), patients with pN-negative and HTE grades 0–1a; group C ($n=14$), patients with pN-positive and HTE grades 1b–3; and group D ($n=65$), patients with pN-positive and HTE grades 0–1a. The OS rate was compared amongst these four groups, and group D had a significantly poorer outcome than the other groups (Fig. 2; vs. group B: $P=0.011$; vs. group C: $P=0.044$).

Recurrent pattern in each patient with pathological lymph node metastasis and low HTE

Fifty-seven patients (57/113, 50.4%) with recurrences after surgery were observed during the study period. To evaluate the relationship between prognostic factors and the pattern of recurrence, the number of patients with each recurrence pattern (lymph node or distant) for each of the groups described above was determined. For both recurrence patterns, the number of patients in group D was much larger than that in any other group. In particular, 92.9% of the patients with distant recurrence were in group D. On the other hand, all three patients in group B (pN-negative and

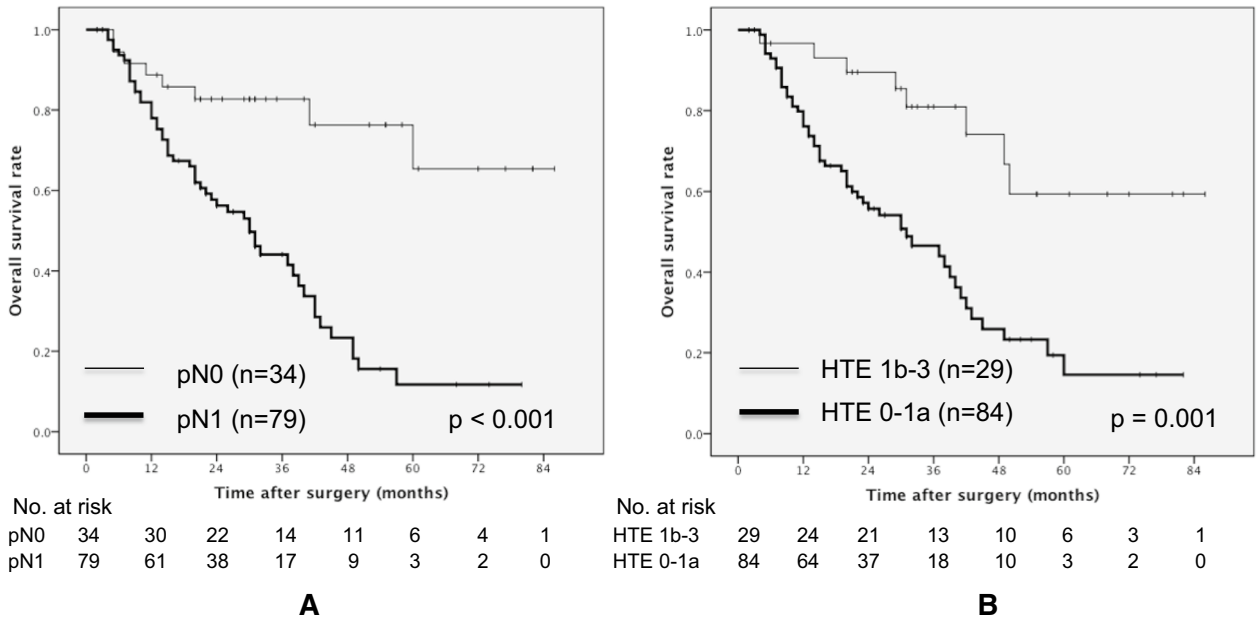

Fig. 1 Comparison of the overall survival curves for the two groups. The curves were calculated using the Kaplan–Meier method. Differences between the groups were evaluated using a log-rank test. **a** Comparison between pN1 patients and pN0 patients. **b** Comparison between patients with HTE grades 0–1a and patients with HTE grades 1b–3. *HTE* histological therapeutic effect

HTE grades 0–1a) had lymph node recurrence but did not have distant recurrences (Table 3).

Discussion

In the present study, the prognostic factors for patients with locally advanced ESCC who received NAC followed by surgery were analyzed, and pN-positivity and HTE grades 0–1a were identified as independent prognostic factors. Moreover, patients with both of these factors had a significantly worse outcome than patients with either of these factors.

Recently, neoadjuvant therapy for patients with locally advanced ESCC has been widely accepted, and reports on prognostic factors have been gradually increasing in number. Some reports have suggested that pN-positivity and HTE are prognostic factors for patients with ESCC who receive neoadjuvant chemoradiotherapy [5, 6]. However, very few reports have evaluated prognostic factors for patients with ESCC who have received NAC. One report suggested that the preoperative cT stage, serum albumin and postoperative pN, and pathological curability were independent prognostic factors for patients undergoing NAC followed by surgery [7]. On the other hand, another report suggested that venous invasion and the tumor HTE of the primary tumor, but not lymph node metastasis, were prognostic factors [8]; yet another report suggested that the HTE of metastatic lymph nodes was a prognostic factor [9]. Thus, the evaluation of prognostic factors for patients with ESCC undergoing NAC followed by surgery remains controversial.

Several reports have suggested that lymph node metastasis is the most important prognostic factor, even after neoadjuvant therapy [10, 11]. There is no doubt that pN is a prognostic factor regardless of the use of neoadjuvant therapy, since lymph node metastasis is a very strong prognosis regulative factor. A previous report suggested that the therapeutic effect on metastatic lymph nodes was a prognostic factor [9]; however, the present study did not evaluate the histological therapeutic response of metastatic lymph nodes. The prognostic impact of pN in patients undergoing NAC followed by surgery should be investigated in further detail.

There have been almost no reports comparing the pathological tumor depth with HTE as a more impact prognostic factor for the primary tumor. The former factor depends on the deepest portion of the residual tumor, while the latter factor depends on the volume of the residual tumor. HTE was classified according to the proportion of residual tumor based on the tumor volume before treatment; therefore, it was closely related to the depth of invasion before treatment. Although estimated depth of tumor invasion prior to treatment in patients with pT0 should be also considered, there was almost no sign of previous tumor involvement in the pathologic specimens of all six patients with pT0 in our cohort. In the present study, both the pN and a lower HTE were independent prognostic factors. NAC might be effective against not only visible lesions, but also circulating tumor cells in chemotherapy responders. Such efficacy might

Table 2 Univariate and multivariate analyses of overall survival for patients in present study by Cox's proportional hazard model

Characteristics	No. of patients	Univariate analysis			Multivariate analysis		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years)							
≥ 66	68	1.015	0.714–1.658	0.914			
≤ 65	52						
Gender							
Male	95	1.407	0.655–3.022	0.381			
Female	18						
Location of tumor							
Upper	14	0.359	0.166–1.154	0.086			
Middle and lower	99						
Neoadjuvant chemotherapy							
CF	90	0.599	0.281–1.279	0.186			
DCF	23						
cT							
≥ 2	106	2.689	0.314–18.227	0.332			
1	7						
cN							
≥ 1	94	1.376	1.002–1.891	0.050			
0	19						
Stage							
III	84	1.623	0.822–2.945	0.128			
II	29						
Operation time							
> 526	54	0.645	0.442–1.155	0.155			
≤ 526	59						
Blood loss							
> 484	57	0.746	0.448–1.315	0.269			
≤ 484	56						
Complication after surgery							
+	64	1.335	0.765–3.044	0.259			
–	49						
pT							
2–4	86	3.727	1.475–9.413	0.005	1.793	0.636–5.059	0.269
0–1	27						
pN							
≥ 1	79	4.609	2.045–10.390	< 0.001	3.204	1.355–7.576	0.007
0	34						
Histological therapeutic effect							
0–1a	84	3.709	1.567–8.780	0.003	2.347	1.066–5.102	0.041
1b–3	29						

affect long-term outcomes [12]. Some patients had a slight amount of residual tumor at the deepest tumor site. These patients had a discrepancy between the pathological T and the volume of the residual tumor; therefore, the pathological depth of invasion might not be a prognostic factor.

Moreover, patients with both pN and a lower HTE had a significantly worse prognosis than patients with either factor alone. Although almost the same combination of prognostic factors was analyzed in patients with esophagogastric junctional cancer in the MAGIC trial [13], there have not been any reports, to our knowledge, suggesting that the combination of these two factors was a strong prognostic factor for patients with advanced ESCC who underwent NAC followed by surgery. In the future, the need for additional treatment after surgery should be evaluated taking these factors into consideration.

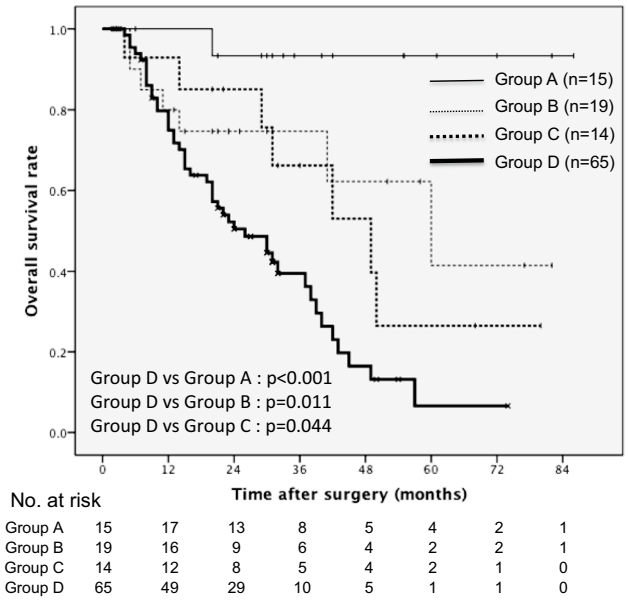

Fig. 2 Overall survival curves according to the combined classification of pN and THE in four groups: group A, patients with pN0 and HTE grades 1b–3; group B, patients with pN0 and HTE grades 0–1a; group C, patients with pN1 and HTE grades 1b–3; group D, patients with pN1 and HTE grades 0–1a. The curves were calculated using the Kaplan–Meier method. Differences between the groups were evaluated using a log-rank test. *Group A* patients with pN-negative and HTE grades 1b–3, *Group B* patients with pN-negative and HTE grades 0–1a, *Group C* patients with pN-positive and HTE grades 1b–3, *Group D* patients with pN-positive and HTE grades 0–1a

Table 3 Recurrence pattern in each patient with pathological lymph node metastasis and lower histological therapeutic effect

Group (pN1/low HTE)	Lymph node recurrence ($n=30$)	Distant recurrence ($n=28$)	Both ($n=1$)
Group A (−/−)	0	0	0
Group B (∓)	3 (10.0%)	0	0
Group C (±)	5 (16.7%)	2 (7.1%)	0
Group D (+/+)	22 (73.3%)	26 (92.9%)	1 (100%)

Group A: patients with pN-negative and HTE grades 1b–3, group B: patients with pN-negative and HTE grades 0–1a, group C: patients with pN-positive and HTE grades 1b–3, group D: patients with pN-positive and HTE grades 0–1a

HTE histological therapeutic effect

An evaluation of the recurrence patterns suggested that additional treatment for local control was only important for patients with a lower THE (group A), since they all had regional lymph node recurrence. On the other hand, systemic control should be considered for patients with a pN (group C) and patients with both a pN and a lower THE (group D), since these patients developed both lymph node and distant recurrences. Further study is needed to consider an appropriate modality for additional treatment based on the relationship between prognostic factors and the pattern of recurrence.

The limitations of this study included its single-center, retrospective design. Furthermore, the median follow-up period was 24 months, which was insufficient to evaluate the long-term outcome and recurrences after surgery. Different grading systems have been used to assess the degree of primary tumor response after neoadjuvant therapy, and a standardized grading system does not yet exist [5, 14, 15]. In the present study, the HTE of the primary tumor was diagnosed according to the Japanese Classification of Esophageal Cancer from the Japan Esophageal Society; however, the standardization of international criteria for HTE is needed in the future.

In conclusion, the present study suggested that patients with resectable advanced ESCC undergoing NAC followed by surgery, who have both pN and a lower HTE, may have a poor prognosis. Additional treatment including novel modalities for these ESCC patients should be investigated in the future to improve therapeutic outcomes for advanced ESCC patients.

Compliance with ethical standards

Ethical Statement The protocol for this retrospective study has been approved by the institutional review board of the Tokai University Hospital (Registration No.18R208). This work followed the guidelines set forth in the Helsinki Declaration of 1975, as revised in 2000, concerning Human and Animal Rights. This article does not contain human or animal subjects performed by any authors.

Conflict of interest Authors declare no conflict of interest for this article.

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