SPANDIDOS PUBLICATIONS

Pre- and post-therapy nodal status equally affects survival of patients with oesophageal squamous cell carcinoma receiving preoperative chemoradiation

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Abstract. Patients with deeply invading (T3-T4) oesophageal cancers usually receive chemoradiotherapy with or without surgery. However, the prognostic significance of pre-therapy and post-therapy lymph node (LN) status remains unclear. We studied 195 patients who received chemoradiotherapy for deeply invading oesophageal cancers (T3-4, N0-1, M0). Of these, 105 patients underwent surgery while 90 were treated by chemoradiotherapy alone. Of the 105 surgically treated patients, overall survival was significantly better in cN0 patients than in cN1 (3-year survival rate, 65.3 vs. 25.8%, P=0.0014). This difference was similarly observed in 90 patients who received chemoradiotherapy alone. Patient survival differed significantly among patients with no positive LN, 1 positive LN and 2-4 positive LN (3-year survival rate, 57.1 vs. 40.5 vs. 17.6%, P<0.0001). However, there was no significant difference in survival between patients with 2-4 positive LN and ≥5 positive LN. Multivariate analysis identified pre-therapy LN status and the number of involved LNs as the most important independent prognostic factors prior to histopathological tumour regression. In conclusion, pre-therapy LN status and the number of post-therapy involved LNs equally affect survival of patients who receive neoadjuvant chemoradiotherapy. Control of systemic metastasis is required, based on pre- and post-therapy LN status.

Introduction

Oesophageal cancer is one of the most intractable gastrointestinal cancers. Locoregional and systemic recurrences remain common even after surgical curative resection, and the 5-year survival rate ranges from 15 to 39% (1-4). To improve the prognosis for these patients, multimodal therapy comprising preoperative or postoperative chemotherapy and/or radiotherapy has been developed. Neoadjuvant chemoradiotherapy followed by surgery is widely accepted as one of the most promising strategies for locally advanced oesophageal cancers. The main aim of this strategy is local tumour control, to facilitate complete resection of the primary tumour and decrease locoregional recurrence. Indeed, in several trials, neoadjuvant chemoradiotherapy prior to surgery increased complete resection rates and improved prognosis, compared with surgery alone (5-7). Moreover, two meta-analyses of randomized controlled trials revealed that neoadjuvant chemoradiotherapy followed by surgery improved patient prognosis and reduced locoregional recurrence, compared with surgery alone (8,9).

It is commonly accepted that patients who achieve a pathological complete response after neoadjuvant chemoradiotherapy for locally advanced oesophageal cancers have an improved prognosis (10-13). Moreover, several studies found the extent of residual tumour after neoadjuvant chemoradiotherapy to be an important prognostic factor (13-16). Thus, survival in these patients is closely affected by the response of the primary tumour to such therapy.

It should also be considered that more than half of patients with advanced oesophageal cancers have lymph node (LN) metastasis. The status of this metastasis is an independent and significant prognostic factor in patients who undergo surgical resection without neoadjuvant therapy. In particular, the actual number of involved LN is one of the most important prognostic factors for patients who undergo surgery alone (17-19). However, the prognostic significance of the number of metastasized LN after neoadjuvant therapy has not been fully elucidated. In addition, it remains unclear how pre-therapy clinical LN status affects survival of patients who undergo chemoradiotherapy followed by surgery. The present study investigated the prognostic significance of both pre- and post-therapy clinical LN status in patients with deeply invading oesophageal squamous cell carcinoma who either underwent chemoradiotherapy followed by surgery or chemoradiotherapy alone.

Materials and methods

Patients. From April 1994 to December 2006, 195 patients who received chemoradiotherapy as the primary treatment

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for deeply invading thoracic oesophageal carcinoma without distant metastasis [clinical (c T3)-cT4, N0-1, M0] at the Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, were included in this study. During the same period, 531 patients with thoracic oesophageal carcinomas underwent surgery with or without preoperative therapy in our institute. All patients had histologically confirmed squamous cell carcinoma of the thoracic oesophagus and received no prior treatment. Patients with distant organ metastasis (stage IVB) were excluded, although patients with cervical LN metastasis were deemed eligible. No patients were over 80 years of age, and all had adequate cardiac, hepatic, renal and bone marrow reserve to tolerate both the planned chemoradiotherapy and the surgical procedures. The study protocol was approved by the Human Ethics Review Committee of Osaka University School of Medicine.

Table I lists the patient characteristics. The median age of patients in this study was 62.3 years (range, 36-80), with 173 men and 22 women. All patients were staged before therapy and postoperatively according to the criteria of the International Union Against Cancer (UICC). Pre-therapy clinical staging was based on oesophagography, endoscopy and computed tomography (CT) of the neck, chest, and upper abdomen using continuous 5-mm-thick slices. Bronchoscopy was performed when tracheobronchial involvement was suspected. From March 2000, positron emission tomography (PET) was also used in our facility for clinical staging where possible. Endoscopic ultrasound (EUS) was not routinely used for staging of locally advanced oesophageal cancers, although it was used in staging superficial oesophageal cancers. Spherical LNs >1.0 cm in maximum transverse diameter were diagnosed as metastasis-positive on CT scans (13,20,21). LNs that were visible but <1.0 cm on the long axis by CT scan were regarded as metastasis-positive if focal prominent 18-FDG uptake was significant on the PET scan, compared with normal mediastinal activity (22-24).

Treatment regimen. The preoperative chemoradiotherapy regimen in our hospital consisted of simultaneous radiation with administration of 5-fluorouracil (5-FU) and cisplatin as described previously (25-27). 5-FU was administered by continuous intravenous infusion at a dose of 400 mg/m^2 in combination with cisplatin at 10 mg/m^2 administered by drip infusion for 5 days per week. The planning target volume for radiation therapy was defined as the macroscopic tumour volume plus a 5-cm cephalo-caudal margin and a 2-cm radial margin, including enlarged regional LNs. When the primary tumour was located at the upper third of the thoracic oesophagus, the supraclavicular fossa was included in the radiation field. External-beam radiation therapy was administered by a 10-Mv X-ray linear accelerator with 2 Grays (Gy) per fraction per day and 5 fractions per week for 4-6 weeks, for a total dose of 40-60 Gy. The radiation was generated using parallel-opposed fields in an anterior and posterior portal arrangement for 20 fractions followed by oblique or multiple fields for the remaining fractions to spare the spinal cord. In principle, surgery was performed 4-6 weeks after completion of the treatment, when downstaging was achieved by chemoradiotherapy and complete tumour resection was regarded possible.

Table I. Characteristics of 195 patients who received chemoradiotherapy as initial treatment.

	n (%)	
Age	62.3 (36-80)	
Gender		
Male	173	(89)
Female	22	(11)
Tumour location		
Upper third	74	(38)
Middle third	93	(48)
Lower third	28	(14)
Tumour depth		
cT3	67	(34)
cT4	128	(68)
Lymph node status		
cN0	63	(22)
cN1	132	(68)
Clinical response		
Complete response	32	(16)
Partial response	104	(54)
No change	57	(30)
Surgery		
Yes	105	(54)
No	90	(46)

When tumours were not downstaged or when patients selected chemoradiotherapy alone, surgical resection was not performed. A total of 105 patients received surgical resection: 25 patients underwent transthoracic esophagectomy with two-field lymphadenectomy, 57 underwent transthoracic esophagectomy with three-field lymphadenectomy and 23 patients underwent esophagectomy using the trans-hiatal approach.

Clinical response evaluation. Two weeks after completion of the chemoradiotherapy course, all patients were restaged by endoscopy, CT scan and, in recent cases, PET to evaluate the clinical response to chemoradiotherapy. The response was categorized based on World Health Organization response criteria for measurable disease and the criteria of the Japanese Society for Oesophageal Diseases (28). Complete response (CR) was defined as complete regression of disease. A CR of the primary tumours was determined when tumours disappeared on CT scan and/or PET scan and on endoscopy. If remaining ulceration and/or presence of cancer cells in biopsy samples were confirmed on endoscopy, the case was excluded from the CR category (29). Partial response (PR) was defined by >50% reduction in the size of the primary tumour and LN metastasis, as confirmed by CT and endoscopy. Progressive disease (PD) was defined by >25% increase

e of the primary tumour or the appearance of new ases that did not meet the criteria of PR or PD were defined as no change (NC) (28,29).

Histopathological examination. After fixation in 10% buffered formalin, the entire surgical specimen was cut into 5-mm slices parallel to the long axis. The tissue slices were embedded in paraffin and cut into at 4-μm sections. These thin sections of the primary tumours and LNs were stained with hematoxylin and eosin using routine methods for microscopic examination. Two observers independently examined all specimens. The histopathological findings were classified according to the UICC TNM classification. The degree of histopathological tumour regression in the surgical specimens was classified into five categories. The extent of viable residual carcinoma at the primary site was assessed semiquantitatively, based on the estimated percentage of viable residual carcinoma in relation to the macroscopically identifiable tumour bed that was evaluated histologically. Therapy-induced changes included reactive changes such as necrosis, fibrosis, foamy histiocytes, mucosal oedema, vascular changes in the tumour periphery, and giant cell reactions. Such characteristics were considered signs of neoplastic regression after neoadjuvant chemoradiotherapy (30,31). The percentage of viable residual tumour cells within the total cancerous tissue was assessed as follows: Grade 3, no viable residual tumour cells; Grade 2, <1/3 residual tumour cells; Grade 1b, 1/3-2/3 residual tumour cells; Grade 1a, >2/3 residual tumour cells; Grade 0, no significant response to chemoradiotherapy (25,28).

Statistical analysis. Overall survival was calculated from the date of preoperative chemoradiotherapy to the occurrence of the event or to the last known date of follow-up. Actual survival was calculated by the Kaplan-Meier method and statistically evaluated by the log-rank test. The Cox proportional hazards regression model was used to analyze the simultaneous influence of prognostic factors. P-values <0.05 were considered to indicate statistical significance. These analyses were carried out using the StatView J5.0 software package (Abacus Concepts, Berkeley, CA).

Results

Clinical response. In 195 patients who received chemoradiotherapy for deeply invading oesophageal squamous cell carcinoma, CR was achieved in 32 cases (16%) and PR was gained in 104 patients (54%), while the remaining 57 (30%) were considered NC. In 163 patients who did not achieve CR, surgical resection after chemoradiotherapy offered survival benefit for those patients (3-year survival rate, 33.1 vs. 0%; Fig. 1). On the other hand, prognosis of the 32 CR patients was not different in the 16 who underwent surgical resection and the remaining 16 who received chemoradiotherapy alone (3-year survival rate, 64.0 vs. 55.7%, P=0.655; Fig. 1).

Lymph node status before and after therapy. In 105 patients who underwent chemoradiotherapy followed by surgery, overall survival was significantly better in patients who had no LN metastasis before treatment (cN0) than in patients who had LN metastasis before treatment (cN1) (3-year survival rate, 65.3 vs. 25.8%; Fig. 2). Similarly, in 90 patients who received chemoradiotherapy alone, overall survival was significantly better in cN0 patients than in cN1 patients (3-year survival rate, 22.5 vs. 6.2%; Fig. 2). Thus, pre-therapy LN status significantly affected prognosis of patients, irrespective of receiving surgical resection after chemoradiotherapy.

Next, we investigated the prognostic significance of the number of involved LNs. In 105 patients who underwent surgical resection, the number of involved nodes correlated inversely with overall survival (Fig. 3). The 3-year survival rates were 57.1% in patients who had no positive LN metastasis, 40.5% in patients who had 1 positive LN, and 17.6% in those who had 2-4 positive LNs. However, there was no significant difference in overall survival between patients with 2-4 LN and >5 positive nodes.

Prognostic factors affecting survival. Univariate analysis of factors affecting survival of 105 patients who underwent

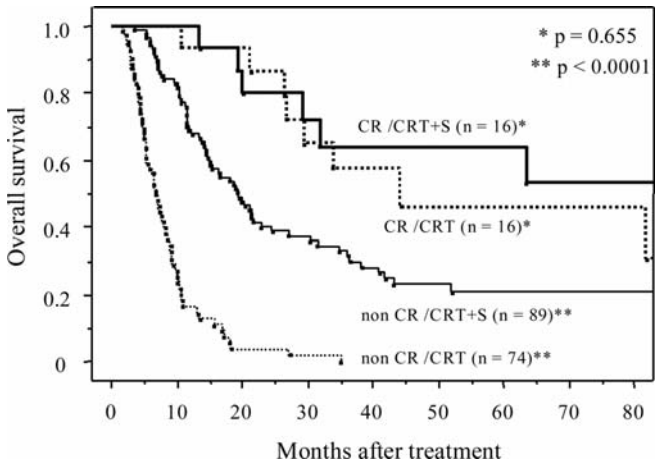

Figure 1. Overall survival of 195 patients, according to clinical response to chemoradiotherapy and surgical resection. CR, complete response; non-CR, partial response, no change and progressive disease. CRT, chemoradiotherapy; S, surgical resection.

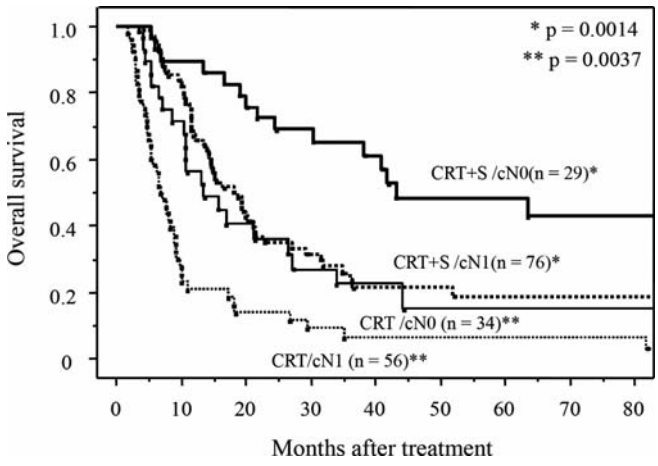

Figure 2. Overall survival of 195 patients according to pre-therapy clinical lymph node status and surgical resection. CRT, chemoradiotherapy; S, surgical resection.

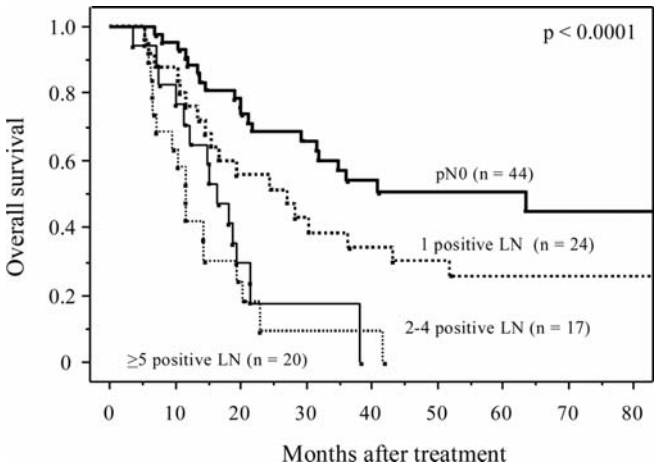

Figure 3. Influence of the number of involved lymph nodes on survival of 105 patients who underwent chemoradiotherapy followed by surgery. LN, lymph node.

chemoradiotherapy followed by surgery showed that the number of involved LN, histopathological tumour regression, clinical response, pre-therapy LN status, pathological T stage, and gender were significantly associated with patient prognosis (Table II). Multivariate analysis identified pre-therapy LN status and the number of involved LN as the most important independent prognostic factors prior to histopathological tumour regression (Table III). For further analysis, we separated survival curves according to the subclassification of each of these parameters (Fig. 4). Survival was therefore affected by pre-therapy LN status and the number of involved LN, as well as by pre-therapy LN status and histopathological tumour regression.

Discussion

The number of involved LN correlates closely with poor prognosis in patients who undergo surgery alone. This is

Table II. Univariate analysis of overall survival in 105 patients treated with chemoradiotherapy followed by surgery.

Variables	n	HR	95% CI	P-value
No. of involved LNs				
0-1	68			
≥2	37	3.636	2.188-6.024	<0.001
Histopathological tumour regression				
major R	66			
minor R	39	3.108	1.876-5.151	<0.001
Clinical response				
CR	16			
NC/PR	89	2.646	1.206-5.814	0.015
Pre-therapy LN status				
cN0	29			
cN1	76	2.506	1.403-4.484	0.002
Pathological T stage				
pT0-2	51			
pT3-4	54	2.481	1.524-4.049	0.001
Gender				
Female	93			
Male	12	1.531	1.049-6.536	0.039
Tumour location				
Middle/Lower	121			
Upper	74	1.481	0.923-.375	0.104
Age				
<70	93			
≥70	12	1.449	0.719-2.919	0.299
Clinical T stage				
cT3	36			
cT4	69	0.935	0.572-1.527	0.787

HR, hazard ratio; CI, confidence interval; CR, complete response; PR, partial response; NC, no change; LN, lymph node; major R, major regression (Grade 2 or 3); minor R, minor regression (Grade 0 or 1).

Multivariate analysis of overall survival in 105 patients treated with chemoradiotherapy followed by surgery.

Variables	n	HR	95% CI	P-value
No. of involved LNs				
0-1	68			
≥2	37	2.463	1.418-4.274	0.001
Pre-therapy LN status				
cN0	29			
cN1	76	2.299	1.264-4.184	0.006
Histopathological tumour regression				
major R	66			
minor R	39	1.840	1.064-3.184	0.029
Clinical response				
CR	16			
NC/PR	89	1.842	0.800-4.237	0.151

HR, hazard ratio; CI, confidence interval; CR, complete response; PR, partial response; NC, no change; LN, lymph node; major R, major regression (Grade 2 or 3); minor R, minor regression (Grade 0 or 1).

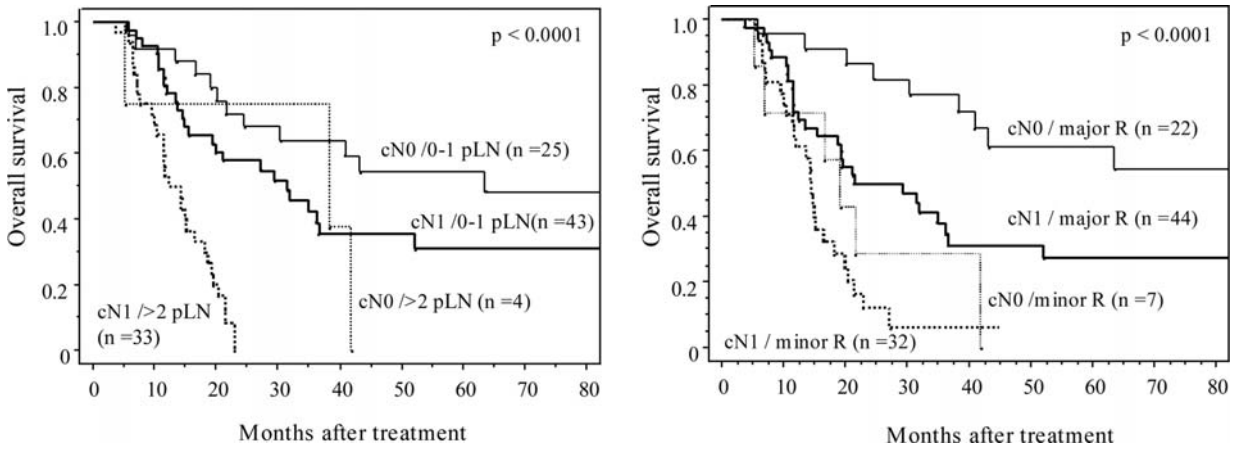

Figure 4. Overall survival of 105 patients who underwent chemoradiotherapy followed by surgery, according to (A) pre-therapy clinical lymph node status and the number of involved lymph nodes or (B) pre-therapy clinical lymph node status and histopathological tumour regression. LN, lymph node; major R, major regression (Grade 2 or 3); minor R, minor regression (Grade 0 or 1).

because the number of involved LN influences the incidence of systemic disease in patients with oesophageal cancer (32). However, the prognostic significance of the number of involved LN has not been fully elucidated in the setting of neoadjuvant chemoradiotherapy, with several studies identifying post-therapy pathological nodal status (pN0 or pN1) as a significant independent prognostic factor in such cases (13,15,33). Gu *et al* reported that overall survival of patients with one metastasis-positive LN was similar to that of patients with no nodal metastasis, but was significantly better than that of patients with ≥2 positive nodes (34). In contrast, Rizk *et al* demonstrated that the pathological major response of the primary tumour predicts the best survival in squamous cell carcinoma of the oesophagus unlike adenocarcinoma, in which residual nodal disease is the most significant survival predictor (35). In this study, patients were separated into 4 groups according to involved LN (0, 1, 2-4 and ≥5), and survival curves were clearly separated among 0, 1 and 2-4 patients. However, survival of patients with >5 involved LN was similar to that of patients with 2-4 involved LN. These findings suggested that patients with ≥2 involved LN after neoadjuvant chemoradiotherapy have systemic disease, and may require adjuvant chemotherapy after surgical resection to eradicate systemic micrometastasis.

In the present study, pre-therapy LN status had an equally significant impact on patient prognosis as post-therapy LN status. Chirieac *et al* reported that post-therapy pathological stage was a better survival predictor than pre-therapy clinical stage (14), while Reynolds *et al* showed that clinical nodal status did not affect prognosis, but that achieving a node-

negative status was the major determinant of outcome following neoadjuvant chemoradiotherapy (13). In contrast, Rice *et al* reported that cN1 patients who were downstaged to pN0 by preoperative chemoradiotherapy have a better prognosis than cN1 patients who were not downstaged, confirming the importance of clinical staging and downstaging (36). The current study revealed a significant difference in prognosis between cN1 patients and cN0 patients, despite both showing only 0-1 involved LN after chemoradiotherapy. Moreover, systemic recurrence was more frequent in cN1 patients compared to cN0 patients, albeit with no significant difference in the rate of local recurrence between these patient groups (data not shown). These results indicated that pre-therapy LN status might be associated with the extent of systemic disease after chemoradiotherapy irrespective of response to the therapy. From this, it could be recommended that neoadjuvant treatment is modified according to pre-therapy LN status to eradicate systemic LN micrometastasis. This might include adding induction chemotherapy prior to the chemoradiotherapy or introducing a more powerful chemotherapy regimen concurrently with radiotherapy.

The present study used CT and FDG-PET, but not endoscopic ultrasound (EUS), to evaluate pre-therapy LN status. EUS has been used widely as a powerful means of assessing clinical T and N status, with some studies reporting that EUS is superior to CT for evaluating regional LN metastasis and a diagnostic accuracy for LN involvement of approximately 80% (37-40). However, other studies found that EUS tended to overestimate LN involvement and that the EUS accuracy was operator-dependent due to the experience required to master the technique (21,41,42). In our institute, EUS is routinely performed for staging of superficial oesophageal cancers, but not for deeply invading (T3-T4) oesophageal cancers because the fiberscope often could not pass through the latter tumours due to stenosis. From March 2000, we have used FDG-PET for the clinical staging of locally advanced oesophageal cancers and for evaluating the patient response to neoadjuvant treatment (22-24). FDG-PET reportedly achieves higher specificity and comparable sensitivity for assessing regional and distant LN involvement, compared with CT and EUS (21,43,44). However, the ability of FDG-PET to determine the number of involved LN remains in question. Nodes less than 8 mm in diameter are difficult to detect by PET, as is the case with EUS (21,43,45). Future advances in diagnostic techniques are therefore needed to enable more accurate, sensitive, and reliable assessment of involved LN.

There was no survival benefit from surgical resection in the current study for patients who achieved a clinical CR to preoperative chemoradiotherapy, while surgical resection provided significant survival benefit to patients who did not achieve a clinical CR. The retrospective study was clearly a limitation by allowing selection bias, in that indication for surgical resection depends not only on resectability but also on patient selection. Despite this drawback, the current results should be considered in developing a treatment strategy for locally advanced oesophageal cancers. To date, few randomized controlled trials have compared neoadjuvant chemoradiotherapy followed by surgery with chemoradiotherapy alone for advanced oesophageal cancers (46,47). One such study that compared induction chemotherapy followed by chemoradiotherapy with and without surgery found that surgical resection improved local tumour control, although the survival benefit from surgical resection did not reach statistical significance (46). Another study, the EORTC trial (FFCD 9102), compared chemoradiotherapy with surgery to chemoradiotherapy alone for locally advanced resectable oesophageal cancers. It showed no survival benefit from surgical resection for the patients who achieved good response to induction chemoradiotherapy, similar to our result (47). Thus, further studies are required to resolve the question of which patients may truly benefit from surgical resection, and to devise treatments for patients with locally advanced oesophageal cancers based on their response to induction therapy.

In conclusion, the current study demonstrated that pre-therapy and post-therapy LN status equally influences survival of patients who receive chemoradiotherapy followed by surgery for deeply invading oesophageal squamous cell carcinoma. In addition, both pre-therapy LN status and the number of post-therapy involved LN may be good indicators of the extent of systemic LN micrometastasis. Thus, control of systemic LN according to pre-therapy and post-therapy LN status may be required, even in patients receiving chemoradiotherapy for deeply invading oesophageal squamous cell carcinoma.

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