Extracapsular Lymph Node Involvement Is a Negative Prognostic Factor After Neoadjuvant Chemoradiotherapy in Locally Advanced Esophageal Cancer

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Introduction: To assess prognosis depending on whether lymph node involvement (LNI) is intracapsular or with extracapsular breakthrough in patients with a locally advanced esophageal cancer treated with neoadjuvant chemoradiation and surgery.

Methods: Ninety-four consecutive patients with an esophageal cancer staged IIB ($n = 17$) and III ($n = 77$) received neoadjuvant chemoradiation followed by transthoracic esophagectomy with two-field lymphadenectomy. Histology was squamous cell carcinoma ($n = 46$) and adenocarcinoma ($n = 48$). Neoadjuvant therapy consisted of association of 5-fluorouracil/cisplatin concomitantly with a 45-Gy radiation therapy. Disease-free survival (DFS) excluding the in-hospital mortality was analyzed according to the nodal status and the invaded/resected lymph node ratio (LNR). Clinical factors affecting survival or predictors of extracapsular invasion were investigated by multivariate analysis.

Results: Five-year DFS rates were 46, 36, and 11% in N0 patients ($n = 56$), intracapsular LNI patients ($n = 18$), and extracapsular LNI patients ($n = 10$), respectively ($p = 0.002$). Intracapsular LNI patients with an LNR <0.1 ($n = 12$) had a 5-year DFS rate similar to N0 patients (44 versus 46%, $p = 0.95$). Intracapsular LNI patients with an LNR ≥ 0.1 ($n = 6$) had a DFS rate similar to extracapsular LNI patients (18 versus 11%, $p = 0.69$). Multivariate analysis revealed that the sole independent factor affecting DFS was the extracapsular LNI (HR = 3.9, $p = 0.026$). The number of invaded LN seemed to be the sole significant predictive factor for the development of ECLNI (HR = 2.39, $p = 0.008$).

Conclusion: After neoadjuvant chemoradiotherapy, there was a significant difference on DFS depending on whether LNI was intracapsular or extracapsular. Extracapsular invasion seems to be an independent negative prognostic factor affecting survival, and its presence is related to the number of invaded LN.

Key Words: Esophagectomy, Esophageal cancer, Chemoradiotherapy, Neoadjuvant treatment, Lymph node ratio, Extracapsular lymph node involvement.

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Lymph node involvement (LNI) is a well-recognized negative factor affecting survival in patients with cancer of the esophagus and/or gastroesophageal junction (GEJ).[1–4] Different characteristics of the lymph node (LN) dissemination (location, number, lymph node ratio [LNR]) might affect survival. More specifically, extension of tumor cells through the nodal capsule into the fatty tissue—extracapsular LNI—has been suggested to have a prognostic value on survival for adenocarcinoma[5,6] and for squamous cell carcinoma.[7] This pathologic behavior of the tumor cells extension is related to a reduced survival and a negative effect on local control of the tumor.[5–7]

Because of poor outcomes with surgery alone, an increasing number of patients with locally advanced esophageal cancer are currently treated with preoperative chemoradiation therapy (CRT). The largest and most complete meta-analysis of randomized neoadjuvant treatment trials provides evidence supporting surgery after induction CRT as the standard of treatment for fit patients with locally advanced esophageal cancer, especially in cases of adenocarcinoma.[8]

After neoadjuvant CRT, a limited number of studies have explored the prognostic factors of survival for advanced esophageal cancer. The posttherapeutic stage (ypTNM),[9,10] the number of positive LNs[11,12], and the LNR[13] are considered as negative prognostic factors for adenocarcinoma. However, little attention has been paid to the prognosis significance of the extracapsular LNI after neoadjuvant CRT. Detection and quantification of extracapsular LNI in the surgical resection specimen might be helpful not only for staging purposes but also for individualizing future adjuvant strategies.

The aim of this study was to assess the prognostic value of the extracapsular LNI in a consecutive series of patients treated with neoadjuvant CRT followed by standardized

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transthoracic esophagectomy. The relation between extracapsular LNI with histologic types and the number of positive LNs was investigated. Disease-free survival (DFS) was analyzed according to the nodal status, with special emphasis on intracapsular and extracapsular involvement, and the invaded/resected LNR.

METHODS

Patients

This retrospective study was conducted according to the current regulations for clinical research in France. There was no intent of research at the time of data collection, and all tests were proposed in the framework of medical care, with a presumed individual benefit for the patients. Patient charts were identified by screening a database into which data had been entered prospectively for any patient undergoing esophageal resection for cancer at our department.

Between January 1996 and December 2006, a consecutive series of 270 patients underwent esophagectomy for a malignancy of the esophagus or GEJ. Among them, 94 patients who presented with a tumor staged IIB ($n = 17$) and III ($n = 77$) received neoadjuvant CRT followed by a transthoracic en-bloc esophagectomy with extended two-field lymphadenectomy. There were 81 men and 13 women, with a mean age of 60 ± 9 years. Histology was squamous cell carcinoma in 46 patients and adenocarcinoma in 48 patients. Neoadjuvant therapy consisted of two (range 2–6) sessions of the association 5-fluorouracil/cisplatin concomitantly with a 43 ± 8 Gy radiation therapy.

Surgery

Operations were performed with curative intent, i.e., in the absence of local irresectability and/or distant metastases (such as tumor positive cervical LNs or irresectable celiac nodes). The histologic type and the location of the tumor dictated the choice of the surgical technique. On this basis, 63 Ivor-Lewis esophagectomies and 31 MacKeown esophagectomies were performed. All patients underwent gastric tube reconstruction in the posterior mediastinum. The esophagus was resected en-bloc with all (peri) esophageal tissue in the mediastinum, including the thoracic duct, azygos vein, ipsilateral mediastinal pleura, upper and lower mediastinal LNs. The abdominal lymphadenectomy included LNs of the hepatic artery, celiac trunk, splenic nodes, and nodes at the origin of the left gastric artery. The surgeon separately marked the LNs by location, and these nodes were analyzed separately by the pathologist.

Resected Specimen

The resected specimen was carefully palpated by the pathologist, and palpable LNs were removed and evaluated. The posttherapeutic pathologic stage (ypTNM), differentiation grade, longitudinal and circumferential clearances, total number of removed LNs, and total number of positive LNs, including their location, were recorded. Larger LNs were bisected and routine hematoxylin and eosin staining was performed using a standardized protocol. No additional immunohistochemical staining techniques to detect micrometastases were used. An experienced pathologist reexamined all positive LNs to assess extracapsular LNI. Extracapsular LNI was defined as metastatic neoplastic tissue extending through the nodal capsule into the perinodal fatty tissue and breaking the LN capsula (Figure 1). Deposits of metastatic tumor cells in the periesophageal fat without a recognizable LN were considered as extracapsular LNI. A desmoplastic reaction led the pathologist to reexamine the specimen to identify an extracapsular LNI.

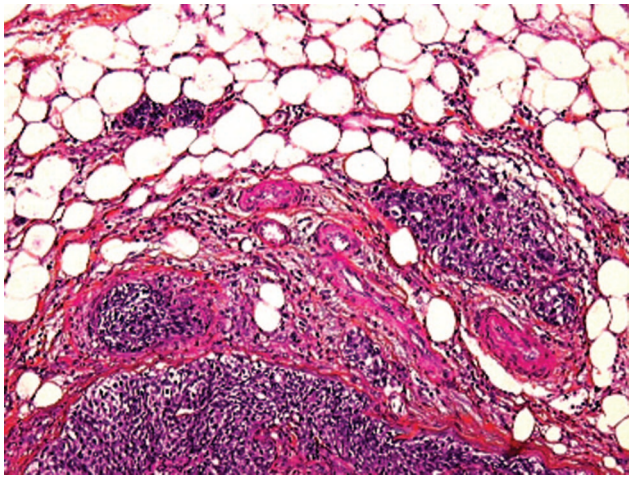

FIGURE 1. Extracapsular lymph node involvement (LNI). Extracapsular extension was defined as metastatic neoplastic tissue extending through the nodal capsule into the perinodal fatty tissue and breaking the lymph node capsula.

Statistical Analysis

All patients were seen at the outpatient clinic at intervals of 3 to 4 months during the first 2 years and every 6 months afterward. For patients lost to medical follow-up, missing data were obtained by consulting the City Hall registry. Statistical analysis included the Student's t test, the χ^2 test, and the Fisher's exact test as appropriate. Survival was measured from the date of operation, and survivorship was calculated according to the Kaplan–Meier method. Survival curves were calculated from the time of surgery to death from any cause or to the time of the last follow-up visit (at which time data were censored). Disease-free survival was counted up to the time of first relapse or death from any cause or up to the time of the last visit without a previous relapse. Survival and DFS curves were drawn up using the Kaplan–Meier method excluding the in-hospital mortality. DFS was analyzed according to the nodal status, with special emphasis on intracapsular and extracapsular involvement, and the invaded/resected LNR. Differences between curves were tested by the log-rank test. Cox logistic regression was used including uni- and multivariate analysis. Variables with a p value <0.2 were included in the multivariate analysis. Logistic regression was used to identify predictive clinical factors affecting development of extracapsular LNI. P values below 0.05 were considered to indicate statistical significance.

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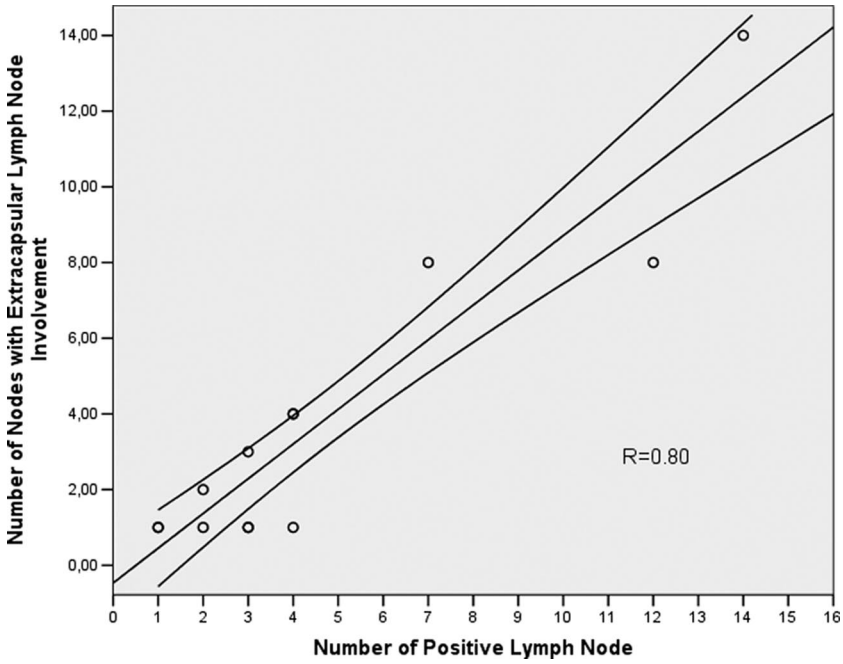

FIGURE 2. Correlation between the number of positive lymph nodes with the number of nodes with an extracapsular LNI. The number of lymph nodes with extracapsular involvement was significantly correlated with the number of positive nodes ($p = 0.01$, $R = 0.80$).

DataSoftware used included Microsoft Excel (Microsoft Corporation, Redmond, WA) and SPSS 13.0 (SPSS Inc, Chicago, IL) statistical software.

RESULTS

Number of Lymph Nodes

Sixty-two patients were considered as N0 status (66%). LNI was identified in 32 patients (34%). Among these 32 patients, 19 had an intracapsular LNI (60%) and 13 had a documented extracapsular LNI (40%). A total number of 1778 LNs was resected and examined in the 94 patients (mean 18.9 ± 11 LNs/patient). Metastasis was detected in 120 LNs (7%). Tumor growth beyond the LN capsule was identified in a total of 49 LNs (41% of the positive nodes). Extracapsular LNI was confined to only one LN in 6 of the 13 patients (46%). The frequency of extracapsular LNI was significantly correlated with the number of positive nodes (Figure 2, $p = 0.01$).

Outcome and Survival

The in-hospital mortality rate was 10.5% (10 of 94 patients): 6 of 62 for N0 patients, 1 of 19 for ICLNI, and 3 of 13 for ECLNI. At the end of the study period, 60 patients were free of disease. Of the 24 patients who suffered from a recurrent disease, 13 patients (55%) had hematogenous recurrence and 11 patients (45%) had locoregional recurrence. The pattern of recurrence was not significantly different between patients with and without extracapsular LNI (Table 1).

Five-year DFS rates, excluding the in-hospital mortality, were 46, 36, and 11% in N0 patients ($n = 56$), intracapsular LNI patients ($n = 18$), and extracapsular LNI patients ($n = 10$), respectively ($p = 0.002$) (Figure 3). In the subgroup of intracapsular LNI patients, survival was dictated by the LNR. Intracapsular LNI patients with an LNR <0.1 ($n = 12$) and N0 patients had similar 5-year DFS figures (44 versus 46%, $p = 0.95$). Intracapsular LNI patients with an LNR beyond 0.1 ($n = 6$) and extracapsular LNI patients also showed similar DFS rates (18 versus 11%, $p = 0.69$) (Figure 4). According to the histologic type, there were no prevailing differences for adenocarcinoma or for squamous cell carcinoma.

Survival was not affected by the number of extracapsular LNI. Patients with only one positive LN had the same survival rate compared with patients with two or more nodes with extracapsular LNI. The location of the extracapsular breakthrough (peritumoral versus distant) seemed not to affect survival ($p = 0.41$). The median of DFS was 12 months when the extracapsular LNI was in a peritumoral location. The median was 9 months when extracapsular LNI was distant from the esophageal tumor.

TABLE 1. Pattern of Recurrence

	N0 $n = 56$	Intracapsular LNI $n = 18$	Extracapsular LNI $n = 10$
Free of disease	43 (76%)	12 (66%)	5 (50%)
Locoregional recurrences	7 (12.5%)	2 (11%)	2 (20%)
Abdominal	2	0	1
Chest	4	2	0
Neck	1	0	1
General recurrence (solid organ)	6 (11%)	4 (22%)	3 (30%)

The in-hospital mortality was excluded.

Of the 24 patients who suffered from a recurrent disease, 13 patients (55%) had haematogenous recurrence and 11 patients (45%) had locoregional recurrence.

The pattern of recurrence was not statistically different between N0, intracapsular LNI, and extracapsular LNI patients.

LNI, lymph node involvement.

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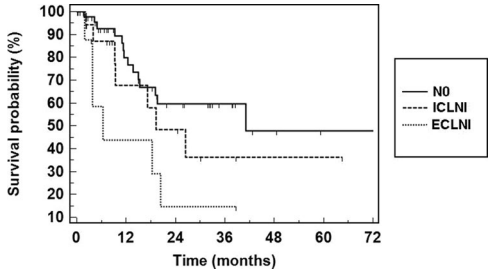

FIGURE 3. Disease-free survival according to extracapsular or intracapsular LNI. The in-hospital mortality was excluded. Five-years disease-free survival rates were 46, 36, and 11%, respectively, in N0 patients ($n = 56$), intracapsular LNI patients ($n = 18$), and extracapsular LNI patients ($n = 10$) (Log-rank test: $p = 0.002$).

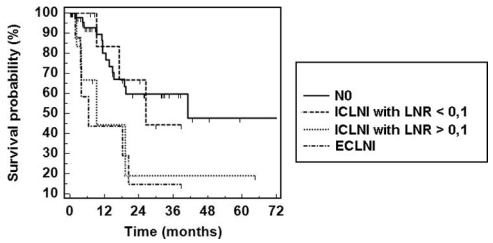

FIGURE 4. Disease-free survival according to lymph node ratio (LNR). In the subgroups of patients with intracapsular LNI, survival was dictated by the LNR. Intracapsular LNI patients with an LNR <0.1 had a similar 5-year DFS rate as N0 patients (44 versus 46%, $p = 0.95$). Intracapsular LNI patients with an LNR ≥0.1 had a similar DFS rate as extracapsular LNI patients (18 versus 11%, $p = 0.69$).

TABLE 2. Uni and Multivariate Analysis for Factor Affecting Disease-Free Survival

	Hazard Ratio (CI 95%)	*p*
Univariate		
Adenocarcinoma/SCC	1.13 (0.55–2.33)	0.720
Response to neoadjuvant therapy	0.88 (0.4–1.8)	0.73
Resection R0/R1–R2	3.2 (0.59–17.3)	0.175
pT Stage	1.09 (0.8–1.4)	0.48
Lymph node involvement (LNI)	0.4 (0.18–0.87)	0.021
Extracapsular LNI	0.14 (0.04–0.49)	0.001
Neural invasion	0.154 (0.02–1.06)	0.058
Lymph node ratio	4 (1.21–13.1)	0.022
Number of invaded LN	1.13 (1.01–1.26)	0.026
Distant/peritumoral LNI	1.68 (1.1–2.5)	0.016
Differentiation Grade	0.07–2	0.29
Multivariate		
Resection R0/R1–R2	0.59 (0.1–2.2)	0.439
Lymph node involvement (LNI)	0.56 (0.06–5.1)	0.617
Extracapsular LNI	3.9 (1.1–13)	0.026
Neural invasion	3.4 (0.7–15)	0.105
Lymph node ratio	0.4 (0.01–8.8)	0.564
Number of invaded LN	1.01 (0.8–1.2)	0.87
Distant/peritumoral LNI	1.6 (0.4–5.8)	0.443

The in-hospital mortality was excluded.

Clinical factors with a *p* value <0.2 were included in the multivariate analysis.

At multivariate analysis (Cox regression model), the sole independent predictive factor affecting disease-free survival was extracapsular LNI.

LNI, lymph node involvement; CI, confidence interval; SCC, squamous cell carcinoma.

Multivariate Analysis

Eleven factors were thought to affect the DFS and were included in the univariate analysis excluding the in-hospital mortality. In the multivariate analysis (Cox regression model), the sole independent predictive factor affecting DFS was extracapsular LNI (HR = 3.39, $p = 0.026$) (Table 2).

Eight factors were thought to predict development of extracapsular LNI and were included in a univariate analysis. On logistic regression, the number of invaded LN seemed to be the sole significant predictive factor for the development of extracapsular LNI (HR = 2.39, $P = 0.008$) (Table 3).

TABLE 3. Uni and Multivariate Analysis for Predictive Factors of Extracapsular LNI

	Hazard Ratio (CI 95%)	*p*
Univariate		
Adenocarcinoma/SCC	2.46 (0.59–10)	0.21
Response to neoadjuvant therapy	0.34 (0.06–1.7)	0.19
Resection R0/R1–R2	0.25 (0.02–3)	0.27
pT Stage	1.48 (0.85–2.5)	0.16
Neural invasion	5.91 (0.85–40)	0.094
Number of invaded LN	2.81 (1.6–4.8)	<0.0001
Number of resected LN	0.99 (0.94–1.05)	0.87
Distant/peritumoral LNI	5.3 (2.1–13)	0.0003
Multivariate		
Response to neoadjuvant therapy	0.8 (0.02–78)	0.94
pT stage	1.4 (0.7–2.8)	0.356
Neural invasion	0.55 (0.02–11)	0.703
Number of invaded LN	2.39 (1.2–4.5)	0.008
Distant/peritumoral LNI	1.8 (0.5–6.8)	0.345

Clinical factors with a *p* value <0.2 were included in the multivariate analysis.

On the logistic regression model, the sole independent predictive factor of extracapsular LNI is the number of invaded LN.

LNI, lymph node involvement; CI, confidence interval; SCC, squamous cell carcinoma.

DISCUSSION

Lymphatic dissemination is the most important predictor for survival in patients with cancer of the esophagus or GEJ.[1–4,14,15] The probability of lymphatic dissemination increases with the depth of the primary tumor.[16,17] The number of positive LNs, their localization, and the LNR gives important prognostic information.[18,19] A recent review of literature[7] has demonstrated that an extracapsular extension of nodal metastasis was also a significant prognostic factor for carcinomas of different organs, including gastric, esophageal, and colon cancer.

Only a limited number of studies have been published on extracapsular LNI in esophageal cancer. In squamous cell

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carcinoma of the esophagus, Tachikawa et al.[20] analyzed an inhomogeneous cohort of patients (with or without neoadjuvant CRT). They concluded that the prognosis was significantly worse in patients with extracapsular disease, irrespective of other pathologic factors. In adenocarcinoma of the esophagus, Lerut et al.[5] included patients with a T3 adenocarcinoma of the esophagus or GEJ. Within this uniform group of 195 patients treated with surgery alone, extracapsular LNI was a negative prognostic indicator affecting survival. Moreover, extracapsular LNI was independent of the number of positive LNs which was shown to be an additional negative factor. Lagarde et al.[6] also reported the negative impact of the extracapsular LNI on survival in a consecutive series of 266 LN-positive patients treated with surgery alone for adenocarcinoma of the distal esophagus or GEJ. The extracapsular LNI together with LNR and pT-stage were independent prognostic parameters for survival in LN-positive patients.

Patients who received preoperative CRT for advanced esophageal cancer and underwent subsequent surgery, the posttherapy pathologic status (ypTNM),[9–11] the number of positive LNs, and the LNR are independent prognostic factors affecting survival.[11–13] Surprisingly, despite the well-known effect of extracapsular LNI in adenocarcinoma of the esophagus, little attention has been paid to this pathologic feature after neoadjuvant CRT and according to the histologic type.

Our results show a significant difference in DFS depending on whether LN involvement is intracapsular or extracapsular for advanced esophageal cancer previously treated with neoadjuvant CRT. The extension of tumor cells through the nodal capsule is not rare and may concern approximately 40% of the LNs-positive patients. For patient with an intracapsular LNI, the prognosis was dictated by the LNR. The extracapsular LNI acted as an independent negative factor affecting the DFS in our Cox logistic regression model. According to the histology, the difference did not appear significant for adenocarcinoma or for squamous cell carcinoma, probably because of the small number of patients.

The progression from one node with extracapsular involvement to two or more LNs had no significant impact on survival in our study. However, a clear correlation existed between the number of positive LNs and the number of LNs with extracapsular extension, reflecting a locally aggressive behavior of the tumor cells through the capsula. Lagarde et al.[6] have shown that patients with two or more LNs with extracapsular disease have a very limited chance for definite cure after surgical therapy, and considered extracapsular LNI as highly lethal biologic behavior of the tumor. They proposed a theoretical explanation, the so-called "metastases of metastases," whereby extracapsular disease can generate new hematogenous metastases. Our study was not powered enough to suggest that the localization of the extracapsular LNI might be an element affecting the survival. Respective median values of DFS were 12 months when the extracapsular LNI was in a peritumoral location and 9 months when extracapsular LNI was distant from the esophageal tumor ($p = 0.41$).

Previous studies have suggested that the incidence of the extracapsular LNI was higher in patients who underwent a transthoracic resection.[6] This can be explained by the fact that more LNs are removed by transthoracic esophagectomy than through a transhiatal approach. To avoid this confounding criterion, only patients who underwent a transthoracic esophagectomy were included in this study to obtain a homogeneous cohort of patients with a standardized surgical approach. The mean number of removed LNs was 18 LNs per patient, thus reflecting adequate lymphadenectomy with accurate postoperative staging.[21] These results plead for an extensive LN dissection. This is in accordance with a previous report on the optimal extent of lymphadenectomy for adenocarcinoma.[22–24] The more LNs are removed, better are staging and survival.

Detection and quantification of extracapsular LNI in the surgical resection specimen might be helpful to individualize postoperative therapeutic strategies in the adjuvant setting. Our results suggested that in the subgroup of patients with intracapsular LNI, outcome is dictated by the LNR. Survival of patients with intracapsular LNI and an LNR ≥ 0.1 is similar to survival of patients with extracapsular LNI, whereas survival of patients with intracapsular LNI and an LNR < 0.1 is similar to survival of N0 patients. On the basis of the present study, one may hypothesize that adjuvant therapies are expected for patients with an extensive LN disease, i.e., extracapsular LNI or with an intracapsular LNI with an LNR ≥ 0.1. In contrast, abstention and surveillance seem sound for patients with intracapsular LNI and an LNR < 0.1, as for N0 patients. These statements deserve their prospective evaluation.

To facilitate a tailored approach in the neoadjuvant setting, it would be necessary to discriminate preoperatively between positive nodes with and without extracapsular LNI. In this respect, the diagnostic accuracy of endosonography, computer tomography, and magnetic resonance imaging has only been tested in limited studies, without convincing results so far.[25–27] The effect of preoperative CRT on the presence and extent of extracapsular LNI remains unclear, because these studies did not include patients who received such therapy. Soon others modalities, such as positron-emission tomography (PET), may be able to help distinguish LNI with or without extracapsular disease. However, even after introducing PET scan, accuracy of LN staging is only 73.8%.[5] The limit of this promising technique is that fluorodeoxyglucose -PET cannot rule out residual microscopic diseases. In contrast, surgery should remain indicated even if the post-CRT imaging modalities show positive hyperfixation.

For other malignancies, such as breast cancer, extracapsular LNI is an important factor included in the TNM classification as a specified subcategory. For esophageal cancer, some authors have pleaded for a revised staging system, including not only the number of positive nodes and the LNR, but also the presence of an extracapsular LNI.[5,27–30] Recently, Lagarde et al.[31] elaborated a prognostic nomogram to predict disease-specific survival after esophagectomy, including the T stage, the LNR, and the extracapsular LNI. The use in clinical practice of this simple model was more reliable than the current TNM staging. The LN status (intracapsular versus extracapsular) should be routinely incorporated in every pa-

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thology report in addition to the number of involved LNs and the LNR. Thus, the posttherapeutic ypTNM classification system could be modified to categories such as residual positive lymph nodes (ypN1) and residual positive lymph nodes with extracapsular disease (ypN1extracapsular).

CONCLUSION

Despite its small size, this study suggests a difference in DFS depending on whether LN involvement is intracapsular or extracapsular for advanced esophageal cancer treated with neoadjuvant CRT, transthoracic en-bloc esophagectomy, and two-field lymphadenectomy. Extracapsular invasion appeared as an independent negative prognosticator, the presence of which seemed related to the number of invaded LN. Pathologists should be aware of this biologic feature and should incorporate it into every postoperative pathologic report. However, these data have to be validated by further prospective multicenter studies.

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