

Predicting Systemic Disease in Patients With Esophageal Cancer After Esophagectomy

A Multinational Study on the Significance of the Number of Involved Lymph Nodes

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Objective: The aim of this study was to determine whether the risk of systemic disease after esophagectomy can be predicted by the number of involved lymph nodes.

Summary Background Data: Primary esophagectomy is curative in some but not all patients with esophageal cancer. Identification of patients at high risk for systemic disease would allow selective use of additional systemic therapy. This study is a multinational, retrospective review of patients treated with resection alone to assess the impact of the number of involved lymph nodes on the probability of systemic disease.

Methods: The study population included 1053 patients with esophageal cancer (700 adenocarcinoma, 353 squamous carcinoma) who underwent R₀ esophagectomy with ≥ 15 lymph nodes resected at 9 international centers: Asia (1), Europe (5), and United States (3). To ensure a minimum potential follow-up of 5 years, only patients who had esophagectomy before October 2002 were included. Patients treated with neoadjuvant or adjuvant therapy were excluded. The impact of the number of involved lymph nodes on the risk of systemic disease recurrence was assessed using univariate and multivariate analyses.

Results: Systemic disease occurred in 40%. The number of involved lymph nodes ranged from 0 to 26 with 55% of patients having at least 1 involved lymph node. The frequency of systemic disease after esophagectomy was 16% for those without nodal involvement and progressively increased to 93% in patients with 8 or more involved lymph nodes.

Conclusions: This study shows that the number of involved lymph nodes can be used to predict the likelihood of systemic disease in patients with esophageal cancer. The probability of systemic disease exceeds 50% when 3 or more nodes are involved and approaches 100% when the number of involved nodes is 8 or more. Additional therapy is warranted in these patients with a high probability of systemic disease.

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Systemic disease is a common cause of death after resection of esophageal cancer. Reducing the risk of systemic disease requires effective systemic therapy either before or after esophagectomy. In published trials of neoadjuvant and adjuvant therapies, patients were treated without stratification according to the stage of disease.^{1–8} In this situation, it is possible that administering chemotherapy to patients at low risk for systemic disease may obscure the benefit of the therapy in the subgroup of patients who are at high risk for systemic disease. This concept is supported by studies that on the one hand show a survival disadvantage when neoadjuvant therapy is given to patients with early stage disease⁹ and on the other hand show a benefit for adjuvant therapy in the subgroup of patients with involved lymph nodes.⁵

Nodal involvement (N1) as defined by the tumor-node-metastasis (TNM) staging system, is a strong predictor of survival in esophageal cancer, and it has been suggested that the number of involved lymph nodes may be a better predictor of outcome.^{10–12} We hypothesize that this is so because the number of involved lymph nodes may be related to the

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TABLE 1. Operative Approach and Details of Resection

	En Bloc (n = 636)	Transhiatal (n = 187)	Ivor Lewis (n = 112)	Transthoracic (n = 84)	Thoracoabdominal (n = 32)	Other (n = 2)
No. nodes removed*	33 (24, 48)	21 (17, 28)	20 (17, 25)	20 (18, 25)	20 (16, 28)	20
No. nodes involved*	1 (0, 4)	2 (0, 6)	0 (0, 2)	2 (0, 2)	0 (0, 3)	3

*Median (interquartile range).

TABLE 2. Final Pathology

	All Patients (n = 1053)	Adenocarcinoma (n = 700)	Squamous (n = 353)
Location of tumor*			
Proximal 1/3	55 (6%)	14 (3%)	41 (12%)
Middle 1/3	206 (24%)	51 (10%)	144 (47%)
Distal 1/3	440 (51%)	313 (60%)	127 (38%)
GEJ†	156 (19%)	147 (28%)	9 (3%)
No. nodes removed‡	27 (15–115)	29 (15–115)	24 (15–106)
No. involved nodes‡	1 (0–26)	1 (0–26)	0 (0–20)
Node status			
N0	476 (45%)	289 (41%)	187 (53%)
N1	577 (55%)	411 (59%)	166 (47%)
Depth of invasion			
T1	242 (23%)	167 (24%)	75 (21%)
T2	176 (17%)	98 (16%)	78 (22%)
T3	635 (60%)	435 (62%)	200 (57%)

*Location of tumor not specified in 196 patients.

†Median (range).

‡GEJ indicates gastroesophageal junction.

risk of systemic disease. The aim of this study was to determine whether the number of involved lymph nodes can predict the risk of systemic disease after esophagectomy for cancer.

METHODS

Study Population

This study is a retrospective analysis of patients with esophageal cancer who had R₀ resection at 1 of 9 international esophageal cancer surgery centers, including 5 from Europe, 3 from North America, and 1 from Asia. A database was constructed that included demographic characteristics, type of operation, tumor cell type, depth of invasion, the number of lymph nodes found in the specimen, and the number of lymph nodes containing metastases based on hematoxylin and eosin staining. Each center was provided a template for the database with definitions for each field.

Patients with adenocarcinoma or squamous cell carcinoma were included. All patients underwent esophagectomy before 2002 to allow sufficient time for systemic disease to develop and were followed by clinical examination every 3 months for the first year, every 3 to 6 months for the second year, and 6 to 12 months thereafter. Imaging studies were performed at regular intervals that varied across centers. Evidence of metastatic disease on imaging studies was confirmed by histology whenever possible. Systemic metastases

occurring either alone or in the presence of local recurrence were defined as systemic disease. Local recurrence was defined as a recurrence within the field of the resection and lymphadenectomy. The median duration of follow-up of surviving patients was 87 months (interquartile range [IQR]: 62, 117).

The type of esophagectomy performed varied and included approaches with and without thoracotomy (Table 1). Patients with T4 tumors, involved celiac lymph nodes or known systemic disease, and those treated with neoadjuvant or adjuvant therapy were excluded. To ensure adequate node sampling, a minimum number of lymph nodes were required to be removed for inclusion in the study. At present, there is no universally accepted minimum threshold for the number of nodes to be removed. The American Joint Committee on Cancer (AJCC) suggests, but does not require, removal of a minimum of 6 lymph nodes. Higher thresholds ranging from 12 to 18 nodes have been proposed.^{13–16} In this study, we chose the threshold of 15 lymph nodes.

A total of 3651 patients were submitted from the 9 centers. From this total, 76 patients were excluded because of T4 disease, 354 because of involved celiac nodes or existing systemic metastases, 918 because they received adjuvant/neoadjuvant therapy, 942 because less than 15 lymph nodes were removed, and 308 because of incomplete database information. This gave a final study population of 1053 patients. The study was approved by the Institutional Review Board of the University of Southern California.

Statistical Analysis

Univariate analysis was performed using chi square and Wilcoxon 2 sample tests, as appropriate, to determine factors associated with the development of systemic disease. A Cox regression analysis was performed to determine independent predictors of the risk of development of systemic disease. Statistical significance was defined as $P < 0.05$.

RESULTS

Of the 1053 patients who met the inclusion criteria, 700 had adenocarcinoma and 353 had squamous cell carcinoma. There were 835 men and 218 women with a median age of 63 years (IQR: 56, 70). Operative approach and final pathology are shown in Tables 1 and 2. The median number of lymph nodes removed was 27 (range: 15–115). A total of 577 patients (55%) had involved lymph nodes.

Isolated local recurrence occurred in 94 of 1053 patients (9%). Combined systemic disease and local recurrence occurred in 75 patients (7%). In most patients, systemic disease (204 [19%]) occurred in the absence of local recurrence.

TABLE 3. Univariate Analysis for Predictors of Systemic Disease

Factor	Systemic Disease (n = 279)	No Systemic Disease (n = 774)	P
Age*	63 (56, 70)	63 (56, 70)	0.8725
Gender			0.0427
Male	233 (28%)	602 (72%)	
Female	46 (21%)	172 (79%)	
Depth of invasion			<0.0001
T1	8 (3%)	234 (97%)	
T2	38 (22%)	138 (78%)	
T3	233 (37%)	402 (63%)	
Node status			<0.0001
N0	49 (10%)	427 (90%)	
N1	230 (40%)	347 (60%)	
No. nodes removed*	27 (20, 42)	27 (19, 38)	0.2149
No. involved nodes*	3 (1, 7)	0 (0, 2)	<0.0001
Cell type			<0.0001
Adenocarcinoma	212 (30%)	488 (70%)	
Squamous cell carcinoma	67 (19%)	286 (81%)	

*Median (interquartile range).

TABLE 4. Cox Regression Analysis for Independent Predictors of Systemic Disease

Factor	Hazard Ratio	95% Confidence Interval	P
Node status	2.297	1.599, 3.299	<0.0001
Depth of invasion	2.107	1.634, 2.716	<0.0001
No. involved nodes*	1.099	1.071, 1.127	<0.0001
Cell type	0.614	0.608, 1.090	0.1670
Male	1.219	0.883, 1.682	0.2284
Age	1.004	0.992, 1.017	0.4844
No. nodes removed*	0.998	0.991, 1.005	0.5453

*Hazard per node.

The results of univariate analysis for factors associated with the development of systemic disease are shown in Table 3. The number of involved lymph nodes was a significant predictor of systemic disease. Other significant predictors of systemic disease included depth of invasion and node status.

The results of a Cox regression analysis are shown in Table 4. The number of involved lymph nodes was an independent predictor of systemic disease when adjusted for depth of invasion and node status.

To focus on the relationship between the number of involved nodes and the risk of developing systemic disease, we calculated the frequency of systemic disease at 5 years based on the number of involved lymph nodes in the operative specimen (Fig. 1). These calculations excluded patients who died of noncancer causes and patients with only local recurrence. Systemic disease occurred in 16% of patients without nodal involvement and was progressively more likely

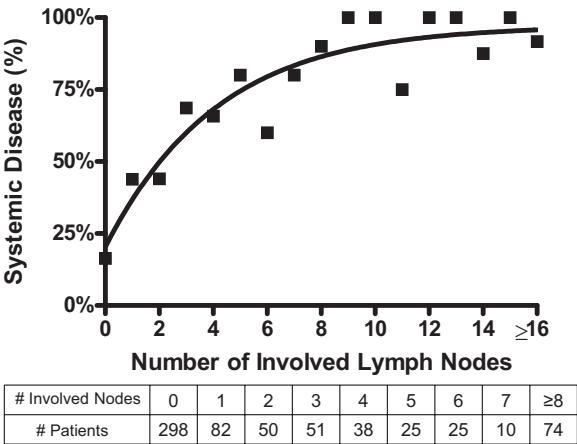


FIGURE 1. Relationship between the number of involved lymph nodes and the frequency of systemic disease in patients with carcinoma of the esophagus (n = 653).

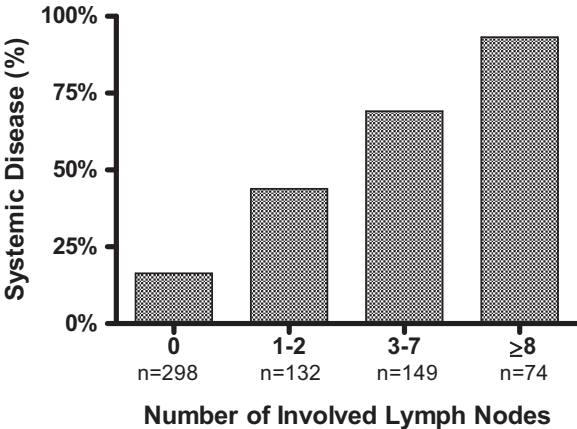


FIGURE 2. Frequency of systemic disease in patients with esophageal carcinoma. Patient groups defined by the number of involved lymph nodes (n = 653). $P < 0.0001$, chi square test for trend.

as the number of involved lymph nodes increased. When 8 or more lymph nodes were involved, systemic disease was essentially universal (93%).

Figure 2 shows the frequency of systemic disease for patients grouped by the number of involved lymph nodes. The node groupings used were selected post hoc to include patients with similar rates of systemic disease. Patients with 1 or 2 involved lymph nodes were significantly less likely to develop systemic disease than those with 3 to 7 involved lymph nodes (44% vs. 69%, $P < 0.0001$). A similar relationship between the number of involved lymph nodes and the risk of systemic disease was present when patients with adenocarcinoma and squamous cell carcinoma were analyzed separately (Fig. 3 and 4).

Figure 5 shows the effect of T status on systemic disease in the absence of involved lymph nodes and the additive effect of involved lymph nodes.

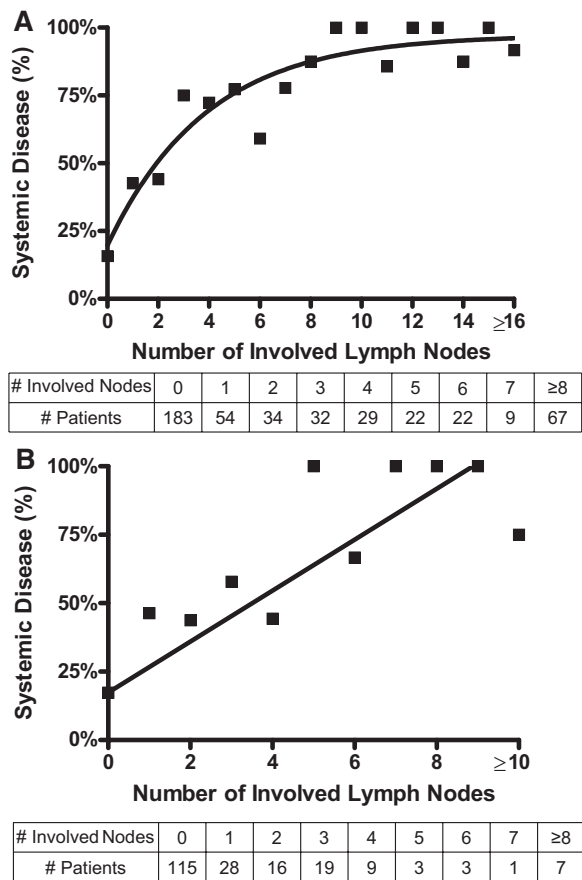


FIGURE 3. Relationship between the number of involved lymph nodes and the frequency of systemic disease in patients with (A) adenocarcinoma of the esophagus ($n = 452$) and (B) squamous cell carcinoma ($n = 201$).

Figure 6 shows the Kaplan Meier estimates of all-cause mortality and freedom from systemic disease for all 1053 patients.

DISCUSSION

In this study, involving patients from 9 esophageal centers from around the world, we clearly demonstrated using Cox regression analysis that the number of involved lymph nodes was an independent predictor of systemic disease after surgical resection. Further, we were able to stratify the risk of systemic disease based on the number of involved lymph nodes. We found that patients with ≤ 2 involved nodes were at low risk of developing systemic disease, whereas those with ≥ 8 involved nodes were at high risk. These findings correspond to previously published data reporting survival rates based on the number of nodes removed, showing better survival when 2 or less lymph nodes were involved¹⁷ and poor survival when 8 or more lymph nodes were involved.^{18,19}

Our results refute the prevailing concept that esophageal cancer is a systemic disease, at the time of diagnosis. In this multinational study, two-thirds of patients were found to have limited node involvement (0–2 involved lymph nodes), and in these patients the frequency of systemic disease after

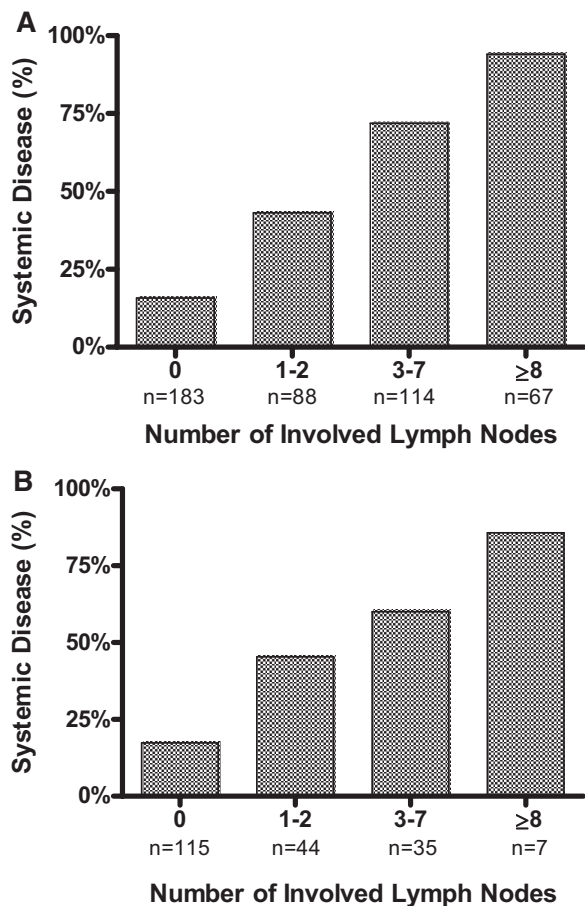


FIGURE 4. Frequency of systemic disease in patients with esophageal carcinoma. Patient groups defined by the number of involved lymph nodes. Includes patients with (A) adenocarcinoma ($n = 452$) and (B) squamous cell carcinoma ($n = 201$). ($P < 0.0001$, chi square test for trend).

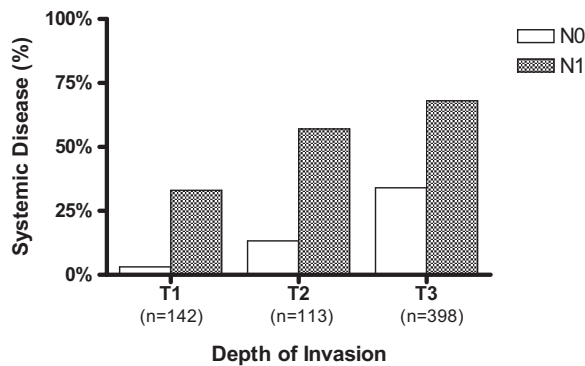


FIGURE 5. The effect of depth of invasion on the frequency of systemic disease in patients with esophageal carcinoma with and without lymph node involvement ($n = 653$).

surgical resection alone was only 25%. This confirms the effectiveness of surgical resection alone as curative therapy for early stage disease. In patients with more extensive node disease, systemic disease can be expected after surgical

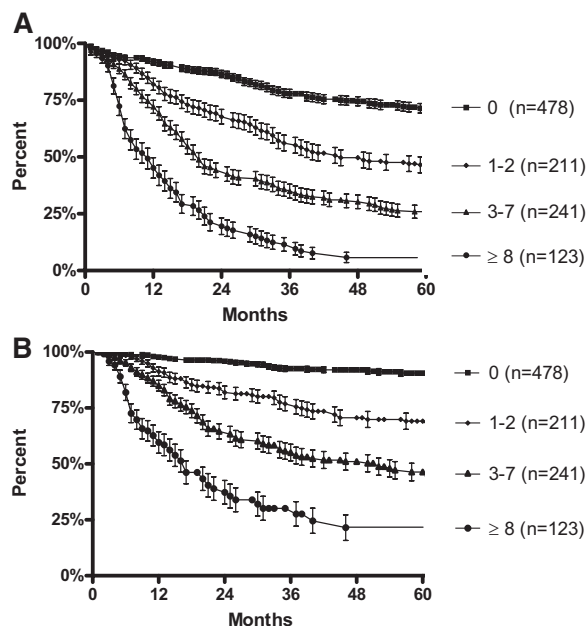


FIGURE 6. Kaplan Meier estimates of (A) all-cause mortality and (B) freedom from systemic disease ($n = 1053$). ($P < 0.0001$).

resection alone and additional therapy is needed for cure. This underscores the importance of performing a systematic lymphadenectomy with the esophagectomy to ensure adequate node sampling to identify these patients.

The clear relationship between the number of involved lymph nodes and the development of subsequent systemic disease suggests the following treatment strategy. If extensive node disease is encountered after surgical resection, adjuvant therapy should be given in an attempt to prevent the development of systemic disease. However, previous studies have not shown a convincing benefit for adjuvant therapy.^{5–8} This may be due to administering adjuvant therapy irrespective of the stage of disease. A recent report suggests that focusing adjuvant therapy on patients at increased risk of systemic disease (N1 patients) may be beneficial.⁵ Our results indicate that the use of adjuvant therapy should be focused further. One-third of our N1 patients had limited lymph node involvement and a low frequency of systemic disease. This implies that adjuvant therapy should be limited to patients with 3 or more involved lymph nodes where the risk of systemic disease exceeds 50%. In these patients, the risk/benefit ratio favors the use of adjuvant therapy.

When extensive node disease is identified on preoperative evaluation, the patient can be considered for neoadjuvant therapy. Currently, endoscopic ultrasound is the most widely used instrument to stage T and N, but its ability to determine the number of involved nodes remains in question.²⁰ Future advances in imaging, such as fusion positron emission tomography/computed tomography (PET-CT) and magnetic resonance imaging with iron contrast agents, may improve the ability to identify the number of lymph nodes involved before surgery.^{21–23} Neoadjuvant therapy could then be given selectively to patients with a high probability of systemic disease

based on the number of involved lymph nodes. This approach would reduce the number of patients exposed to the toxic effects of chemotherapy and avoid delaying primary, curative surgical resection in patients with a low risk of systemic disease (≤ 2 involved lymph nodes).^{24–26}

Our findings also underscore the need to modify the current staging system for esophageal cancer. Classifying lymph node involvement as either present or absent is not sufficient for stratifying patient outcome. Previously, we found that survival after en bloc esophagectomy was significantly impaired when 5 or more lymph nodes were involved.^{10,12} The current multinational study includes patients from 9 institutions, using a variety of surgical techniques to remove the esophagus, including resections with limited lymphadenectomy. This data shows that outcome after esophagectomy is best stratified by dividing the extent of lymph node involvement into 3 groups: N1 (1–2 involved lymph nodes), N2 (3–7 involved lymph nodes), and N3 (8 or more involved lymph nodes).

We understand that there are a number of limitations to the current study. The study is retrospective and the database consists of pooled information from 9 centers. The surgical technique and protocol for follow-up varied across centers. To counter these limitations, we made an effort to limit their impact on our findings. We minimized variability in the database by providing the investigators with definitions for each variable collected. The centers chosen were focused on esophageal disease, had a large volume of patients with esophageal cancer, and maintained a prospective database. Follow-up after esophagectomy was thorough at each center, with patients being seen at 3-month intervals for the first year, every 3 to 6 months for the second year, and every 6 to 12 months thereafter. Even though a variety of resection techniques were used, this potential limitation is also a strength in that the surgical approaches used in this study were representative of the types of resections performed around the world, thus making our findings broadly applicable.

CONCLUSION

This study shows that the number of involved lymph nodes can be used to predict the likelihood of systemic disease in patients with esophageal cancer. The probability of systemic disease exceeds 50% when 3 or more nodes are involved and approaches 100% when the number of involved nodes is 8 or more. Additional therapy is warranted in these patients with a high probability of systemic disease.

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Discussions

B. WALTHER: Regarding the methodology, there is a case mix of patients and many surgeons involved in your study who are using different methods, including, I imagine, transhiatal esophagectomies. The incision is described as an abdominal incision, but I imagine it involves the neck and abdomen. Concerning the case mix, a statistical method for ruling out or diminishing the impact of individual variation is to create a ratio. Why did you use just a count instead of creating a ratio when you have this individual variation?

How do you define esophageal carcinoma or the included GE junction carcinoma? GE junction carcinoma can be described according to the Siewert classification with I as normal, Barrett's Carcinoma. In that circumstance, celiac nodes are M nodes and according to your paper you did not resect the M patients. Although we all know that M is more dangerous if it spreads to the organ instead of lymph nodes. How was systemic recurrence defined? With the frequency of postmortem examination, it is hard to discriminate between systemic diseases at least in the beginning.

My last comment and question is how were the nodes harvested? Was it the surgeon who dissected the nodes labeled these and turned them over to the pathologist, or was the specimen sent to the pathologist and examined there? We all know it can be very difficult to discriminate between the left gastric artery nodes and the celiac nodes.

C. G. PEYRE: We believe that the variety of operations performed is the strength of this study and reflects the practice of esophageal cancer surgery around the world, making our results broadly applicable. Our analysis did not focus on the type of resection, but was designed to analyze the impact of involved lymph nodes.

We are aware of the use of the lymph node ratio, which has the advantage of keeping the number of involved nodes in the context of the number of nodes removed. We limited our population to those with a minimum of 15 nodes removed, reducing the potential benefit of using the lymph node ratio.

To answer your remaining questions, we included all esophageal cancers, including GE junction tumors. Subcardial gastric cancers were excluded. Patients with involved celiac nodes were also excluded. Systemic recurrence was identified by imaging studies and confirmed by histology whenever possible. In some centers, the nodes were harvested by the pathologist and in others by the operating surgeon.

P. M. SCHNEIDER: I have 2 questions, the first relates to the recently published study by Hofstetter et al from the MD Anderson Cancer Center. If I remember correctly, more than 1000 esophagectomies were analyzed with regard to the number of lymph node metastases and prognosis. How do your data compare with those results and do you see essentially the same results when you look at systemic metastases? My second question is how do we deal with celiac trunk metastases? Interestingly, in the MD Anderson study, number 9 nodes on the celiac axis were not of prognostic importance. It was the absolute number of involved nodes. Did you include those celiac nodes in your analysis?

C. G. PEYRE: In the MD Anderson series, they classified node metastases as regional and nonregional and used a threshold of 1 to 3 involved nodes, proposing 4 groups for nodal staging. Their end point was survival. We chose to focus on the risk of systemic disease and its relationship to the number of involved nodes. Debate continues regarding the prognostic importance of celiac node metastases. As a consequence, we chose to exclude these patients from our analysis.

J. IZBICKI: The question I would like to ask refers to the criterion the TNM committee usually uses, that is, the number of nodes available for histologic examination – which is 6 lymph nodes. In our institution, we have shown that the number of nodes harvested during the operation bears a tremendous prognostic impact on the outcome of an operation. Not only the lymph node ratio but also the pure number of nodes harvested even if you are dealing with an N0 disease. I wonder whether you had the same experience in your material.

C. G. PEYRE: We agree that there are a minimum number of nodes that need to be removed to ensure adequate node sampling. At present there is no universally accepted minimum threshold. As you point out, the TNM committee suggests, but does not require, a minimum of 6 lymph nodes. Higher thresholds ranging from 12 to 18 nodes have been proposed. In this study, we chose the threshold of 15 lymph nodes. We made similar observations regarding the number of lymph nodes removed in this multi-institutional study and this is the subject of another publication.