Extracapsular lymph node involvement is a negative prognostic factor in T3 adenocarcinoma of the distal esophagus and gastroesophageal junction

T. Lerut, MD, PhD,^a W. Coosemans, MD, PhD,^a G. Decker, MD,^a P. De Leyn, MD, PhD,^a N. Ectors, MD, PhD,^b S. Fieuws, Msc,^c J. Moons, CNS,^a P. Nafteux, MD,^a and D. Van Raemdonck, MD, PhD,^a for the Leuven Collaborative Workgroup for Esophageal Carcinoma*

See related editorial on page 947.

From the Departments of Thoracic Surgery^a and Pathology^b and the School of Public Health, Biostatistical Centre,^c University of Leuven, Leuven, Belgium.

Read at the Eighty-second Annual Meeting of The American Association for Thoracic Surgery, Washington, DC, May 5-8, 2002.

Received for publication June 10, 2002; revisions requested July 22, 2002; revisions received April 27, 2003; accepted for publication June 9, 2003.

Address for reprints: Dr T. Lerut, Catholic University Leuven, Department of Thoracic Surgery, UZ Gasthuisberg, Herestraat 49, Belgium (E-mail: Toni.Lerut@uz.kuleuven.ac.be).

*Other members of the collaborative work group for esophageal carcinoma are: digestive oncology: E. Van Cutsem; endoscopy: M. Hiele, I. Demedts; nuclear medicine: P. Flamen; radiology: W. De Wever, S. Dymarkowski; radiotherapy: K. Haustermans.

J Thorac Cardiovasc Surg 2003;126:1121-8

Copyright © 2003 by The American Association for Thoracic Surgery

0022-5223/2003 \$30.00 + 0

doi:10.1016/S0022-5223(03)00941-3

Objective: To assess prognosis according to whether lymph node involvement is intracapsular or with extracapsular breakthrough in adenocarcinoma of the distal esophagus and gastroesophageal junction.

Materials and Methods: One hundred ninety-five consecutive patients with T3 adenocarcinoma of the distal esophagus and gastroesophageal junction between 1990 and 1999 were studied. All patients underwent primary R0 esophagectomy. The mean number of resected nodes per patient was 36.9. Survival was analyzed according to intracapsular and extracapsular involvement.

Results: In N0 patients 5-year survival was 57% and 9-year survival was 38.7%. In patients with positive nodes these figures were 26.2% and 18.1%, respectively ($P = .0069$). Intracapsular and extracapsular node involvement showed 5- and 10-year survival of 40.9% and 21.7% versus 18% and 15.7%, respectively. There was no significant difference in 5- and 10-year survival between N0 and intracapsular node involvement ($P = .43$). However, there was a significant difference in survival between N0 and extracapsular node involvement ($P = .002$) and between intracapsular and extracapsular node involvement ($P = .0001$).

Conclusions: This study shows a significant difference in survival according to whether lymph node involvement was intracapsular or extracapsular. Patients with intracapsular lymph node involvement have similar survival rates as N0 patients. Extracapsular lymph node involvement is a bad prognostic factor, independent of the number of involved lymph nodes. The number of involved lymph nodes has an additive negative effect. These data may have an impact on treatment strategies.

Lymph node involvement is considered as the main prognostic determinant in most solid organ cancers and this has been well documented for carcinoma of the esophagus and gastroesophageal junction (GEJ).¹ The importance of the number of involved lymph nodes and the location of involved lymph nodes, in particular the distant lymph node metastasis (M1_{lym}), as negative prognostic indicators has been documented.²

More recently, attention has been paid to micrometastatic lymph node involvement by using immunohistochemical staining techniques. The prognostic relevance of micrometastasis, however, is not clear because of conflicting results between different studies.³⁻⁵

TABLE 1. Univariate analysis in lymph node positive patients (n = 162)

Variables	Log rank	P values
Grading	4.15	.1256, NS
G1 vs G2	2.18	.1398, NS
G1 vs G3	2.63	.1045, NS
G2 vs G3	1.56	.2117, NS
Lymphatic vessel invasion		
L0 vs L1	1.44	.2299, NS
Venous vessel invasion		
V0 vs V1	1.83	.1757, NS
Neural invasion		
N0 vs N1	0.57	.4494, NS
Barrett		
Barrett vs non-Barrett	3.57	.0588, NS
Localization	0.54	.7626, NS
Distal vs GEJ	0.54	.4625, NS
Distal vs subcardia	0.00	.9818, NS
GEJ vs subcardia	0.15	.6985, NS
Sex		
Male vs female	0.32	.5725, NS
Age		
< or > mean age 63.2 years	1.51	.2191, NS
<70 years vs >70 years	0.45	.5014, NS
pM		
pM0-pM+LYM	1.04	.3080, NS
Extracapsular		
Extracapsular vs intracapsular	15.23	.0001
Lymph node status*		
LN negative vs LN positive	7.3	.0069

NS, Not significant.

*LN negative (n = 33) versus LN positive (n = 162).

However, little or no attention has been paid to the prognostic value of the presence or absence of extracapsular lymph node involvement. Yet its relevance as a negative prognostic factor has been well documented in several other types of cancer (eg, hypopharynx, stomach, breast⁶⁻⁸) and may have an impact on therapeutic strategy.⁸

We therefore studied the prognostic significance of the mode of lymph node involvement according to whether it was intra- or extracapsular. The study specifically focused on patients presenting with adenocarcinoma of the esophagus and GEJ⁹ because of the rising incidence of adenocarcinoma (currently the most frequent type of tumor).

Materials and Methods

Between 1990 and 1999, 822 patients with carcinoma of the esophagus and cardia were treated in the Department of Thoracic Surgery. Four hundred ninety patients presented with an adenocarcinoma (59%); of them, 429 patients underwent resection. To obtain a homogenous cohort of patients out of this group, this retrospective study concentrated on 195 patients presenting with T3 tumors of the distal esophagus and GEJ who underwent a complete resection (R0). Reasons for exclusion were: induction chemoradiotherapy (n = 10), microscopic residual disease (R1) (n = 60) and macroscopic residual disease (R2) (n = 18) resections,

organ metastasis (n = 8), no lymphadenectomy due to comorbidity (n = 23), and all remaining R0 T stages (n = 115). There were 163 men and 32 women, with a mean age of 63.6 years.

Survival was analyzed according to intracapsular (IC) or extracapsular (EC) extension. Patients with involvement of at least 1 EC lymph node were assigned to the EC group, whereas patients with positive lymph nodes without evidence of EC breakthrough were assigned to the IC group.

The surgical technique has been described elsewhere in detail. In brief, a left thoracophrenotomy was performed with a wide peritumoral resection combined with extensive lymphadenectomy of the upper abdominal compartment, so-called "DII resection," and posterior mediastinum was performed in all patients. Bilateral cervical lymphadenectomy was performed in 68 patients (35%).

Lymph nodes were fixed in formalin and stained with hematoxylin and eosin. Lymph nodes have an investing capsule. Afferent lymphatic vessels penetrate the convex surface of the gland and drain into the subcapsular and medullary sinus. Once in the lymph node, tumor cells will adhere to and proliferate in the sinuses (IC); with time, tumoral expansion will outgrow the lymph node and extend beyond the capsule (EC). A reexamination of lymph node specimens was performed by 1 of the authors and responsible pathologist (N.E.).

Statistical Analysis

Univariate analysis by proportional hazard model was performed for all node-positive patients. Log-rank test and *P* values are reported. Cox regression analysis was used to verify the effects of different covariates and factors on survival. This was done for each predictor separately as well as for combinations of predictors.

Hazard ratios and their 95% confidence intervals are reported. To determine the functional form to be used for a given covariate (the number of positive nodes) to best explain its effect on survival through a Cox proportional model, the Martingale residuals of a Cox model without that covariate are plotted against that covariate. A smoothed fit of the scatter plot is then added, giving an indication of the functional form.¹¹

Survival statistics were obtained by the Kaplan-Meier method.^{12,13} All analysis were performed with the statistical packages SPSS (version 10) and SAS (version 8.01). The alpha level was set at 5%.

Results

One hundred ninety-five patients with a T3 adenocarcinoma of the distal esophagus underwent primary surgery with an R0 resection. The mean number of resected nodes was 36.9 (median 35; range 10-95). The mean number of resected nodes in the IC group was 41.6 (median 35; range 10-95) and in the EC group was 39.2 (median 35; range 10-95), which are not significantly different (*P* = .32). One hundred sixty-two patients had lymph node involvement (83%).

Univariate analysis was performed in all patients with positive lymph nodes (Table 1). Lymph node status (*P* = .0069) and EC lymph node involvement (*P* = .00001) were the 2 parameters with a highly significant prognostic value. Five- and 10-year cancer-specific survival of N0 patients was 57% and 38.7%, respectively. For N+ patients the

Figure 1. Survival according to lymph node status.

figures were 26.2% and 18.1%, respectively (Figure 1). Calculating survival according to IC versus EC node involvement showed 5- and 10-year survival of 40.9% and 21.7% versus 18% and 15.7%, respectively (Figure 2). There was no significant difference between pN0 and IC involvement ($P = .4334$). The difference between pN0 versus EC ($P = .0002$) and IC versus EC ($P = .0001$), on the contrary, was highly significant. The effect of intra- versus extracapsular lymph node involvement on survival is furthermore highlighted ($P = .01$) in the subgroup of patients with involvement of only a single positive lymph node, where a 5-year survival rate of 85.7% for IC involvement is noted versus 33.3% for EC involvement (Figure 3).

In a subsequent step the number of involved nodes was analyzed by plotting the Martingale residuals versus the number of positive nodes, as described earlier (Figure 4). The figure suggests that the number of positive nodes has a linear effect in the Cox model, as long as the number of nodes is smaller than or equal to ~ 12 . Once the number of positive nodes is higher than 12, the risk does not appear to increase anymore. To capture this trend, the effect of the number of positive nodes is entered into the Cox model as a linear spline with a knot at 12 nodes. This implies that the effect of the number of nodes is separated in 2 intervals: an effect in the range of 0 to 12 nodes, where there is a

cumulative negative effect on survival for each added lymph node, and an effect in the range of >12 nodes, where there is no further effect on survival.

From the results of the univariate analysis, we derived in a first step a model to verify the effects of number of lymph nodes and extracapsular involvement including influence of time (Table 2). In this model the interaction has been checked, as well as the proportional hazards assumption. The figures obtained from these calculations showed that there is no significant interaction between “extracapsular” and number of lymph nodes ($P = .37$), which implies that both effects are independent and the effects can be considered additive. The effect of “extracapsular” decreases significantly with time ($P = .01$). The effect of “number of lymph nodes” does not change significantly with time ($P = .93$).

The model shows a hazard ratio or relative risk of 3.37 for the EC group. The value 1, which means equal risks in both groups, is not included in this interval, and the conclusion is that there is a 2.37-fold (237%) increased risk in the EC group compared with the IC group and this increase is statistically significant at the 5% level. This risk decreases in time by about 2.9% per month ($0.971 - 1 = -0.029$). The second effect, the number of positive lymph nodes, adds a relative risk of about 8.6% ($1.086 - 1 = 0.086$) per

Figure 2. Survival according to lymph node capsular status.

Figure 3. Survival in patients with exactly 1 positive lymph node.

positive node (up to about 12 positive nodes, after which this effect no longer increases).

In a second step the significant variables of the additive model (Table 2) were extended with the other covariates from the univariate analysis. This was done predictor by predictor, due to the large number of predictors. The only aim of this extension was to verify if the obtained model

still holds when correcting for the influence of another variable. No further significant effects were found in the examined covariates. The ranges for the additive model are reported (Table 3).

In summary this statistical analysis indicates 3 effects that have a significant influence on survival. These effects are additive. (1) The involvement of EC lymph nodes in-

Figure 4. Fitted curve on plot of number of positive lymph nodes.

TABLE 2. Multivariate model

Effect	β	SE	P value	Hazard ratio	95% confidence interval	
					Lower limit	Upper limit
Extracapsular	1.22	0.335	.0003	3.37	1.75	6.49
Number of lymph nodes						
0-12	0.086	0.029	.0145	1.086	1.03	1.15
>12	−0.027	0.026	.31	0.973	0.93	1.02
Extracapsular × time	−0.0299	0.012	.012	0.971	0.95	0.99

TABLE 3. Multivariate analysis: ranges after correcting for other variables

Effect	β	SE	P value	Hazard ratio	95% confidence interval	
					Lower limit	Upper limit
Extracapsular	1.22 (1.182-1.309)	0.335 (0.33-0.34)	.0003 (.0001-.0005)	3.37 (3.25-3.703)	1.75 (1.675-1.908)	6.49 (6.341-7.187)
Number of lymph nodes, 0-12	0.086 (0.076-0.097)	0.029 (0.028-0.03)	.0145 (.0013-.0083)	1.086 (1.079-1.102)	1.03 (1.02-1.038)	1.15 (1.142-1.169)
Extracapsular × time	−0.0299 (−0.03-0.029)	0.012 (0.011-0.012)	.012 (.009-.0128)	0.971 (0.97-0.971)	0.95 (0.948-0.949)	0.99 (0.993-0.994)

creases the risk of dying by 237% but (2) this risk decreases by 2.9% per month, and (3) there is an effect of number of positive lymph nodes: up to 12 positive lymph nodes, each positive lymph node increases this risk with 8.6%. Patients with 13 or more positive lymph nodes have the same risk as patients with 12 positive lymph nodes.

Discussion

Over the last few decades it has been shown by several authors that lymph node involvement is the foremost important factor in determining prognosis in patients suffering from carcinoma of the esophagus and GEJ.^{1,10,14-16} It has also been well established that there is a direct correlation

between depth of invasion of the tumor and the incidence of lymph node involvement. In T3 tumors approximately 80% (in our series 83%) of patients will have lymph node involvement.^{14,17} Over the years, especially since the introduction of endoscopic ultrasound (EUS), accuracy of T staging has greatly improved,¹⁸ so much so that today some authors are using T staging as a decisive factor in setting up therapeutic strategies, systematically advocating induction therapy in case of T3 or T4 cases.¹⁹

Other groups have clearly demonstrated that the equation is not that simple. In fact, it seems that both number of involved lymph nodes and location of involved lymph nodes have a major prognostic impact as well.²⁰⁻²²

From their studies it appears that a limited number of lymph nodes (ie, less than 4 to 6 according the different studies) carry a relative good prognosis with a significantly better survival as compared with a higher number of positive nodes. Therefore, some groups prefer the use of lymph node ratio rather than absolute numbers.²⁰ Furthermore, it seems that if lymph node involvement is confined to the peritumoral region, prognosis is significantly better than if lymph node involvement is located in more distant lymph nodes.²¹

Because a substantial number of patients with pN0 disease will still die of a recurrent metastatic disease, much attention has been paid to the use of immunohistochemical staining techniques to detect micrometastasis on routine hematoxylin and eosin staining in patients with otherwise N0 disease.³⁻⁵ Some studies have indicated a negative impact in patients showing micrometastasis⁴; others did not find any difference in outcome.³

Surprisingly, despite the well-known effect of extracapsular lymph node involvement in other cancers (eg, stomach, hypopharynx, breast⁶⁻⁸), little attention has been paid to this finding in cancer of the esophagus and GEJ.

Tachikawa and colleagues²³ suggested that prognosis is significantly worse in patients with extracapsular lymph node involvement in esophageal squamous cell carcinoma irrespective of other pathologic factors such as depth of invasion, lymphatic invasion, or number of involved nodes. In their study, however, the population consisted of patients with a mixture of different therapeutic regimens (ie, induction therapy, surgery alone, surgery followed by adjuvant therapy) and also of different depths (T stage) of tumor.

The present study deals with a homogeneous cohort of T3 adenocarcinoma treated by primary surgery and R0 resection. From our analysis it appears that extracapsular lymph node involvement is an independent negative prognostic factor. Its negative impact in our experience seems to equal the negative impact of distant lymph node metastasis (M1_{lym}).

On the other hand, intracapsular lymph node involvement seems to have a prognosis that is near that of N0 patients, with 5- and 10-year survival of 40.9% and 21.7%, respectively.

The number of involved lymph nodes, up to 12, also has an additive negative impact on survival. The only cutoff point that was found was around 12 positive nodes, after which no significant increase in risk was noted.

These findings may have important consequences in determining therapeutic strategies, as the EC group consisted of a significant subset of patients, 102 (52%). It seems therefore of paramount importance to be able to discriminate between this group by clinical staging. However, it is quite difficult to stage adequately lymph node involvement even in the era of EUS and positron-emission tomography (PET). In our series, even after introducing PET scan, accuracy of lymph node staging was only 73.8%. Moreover, it seems at this point that there is no clinical staging modality that can discriminate between IC and EC. The only data available are on the use of nuclear magnetic resonance, which shows no benefit whatsoever.²⁴

From the findings in the present study, it is difficult to draw any conclusions as to the therapeutic implications. However, one could speculate that patients showing intracapsular node involvement should not be treated by induction therapy as only half of such patients will show measurable response, thus jeopardizing the chances of the nonresponders or minimal responders by losing precious time or by higher postoperative mortality. On the other hand, patients with a limited number of positive nodes but with extracapsular involvement may be better candidates for induction therapy. Whether invasive staging methods like laparoscopy and video-assisted thoracoscopic surgery will enable us to easily detect extranodal involvement remains an open question. This may indeed require extensive mobilization and extensive node sampling in a great number of these patients. For these reasons it seems that the debate between proponents of induction therapy in all patients with any positive nodes and the advocates of radical primary surgery remains open, and the findings of negative prognostic impact of extracapsular lymph node or conversely the good survival figures in patients with intracapsular lymph node involvement may even further complicate the decision-making strategy toward initiating induction therapy.

Because of the difficulty of discrimination by clinical staging between intracapsular and extracapsular node involvement, it may be worthwhile to investigate the systematic use of adjuvant therapy, preferentially chemoradiotherapy, in patients with extracapsular node involvement, especially in adenocarcinoma. Indeed, recent studies have indicated a significant survival advantage of such regimens in gastric adenocarcinoma, including GEJ tumors and adenocarcinoma of the distal esophagus, for patients who ap-

peared to have lymph node involvement at pathologic staging.^{25,26} It may well be that patients with extracapsular lymph node involvement will be a subset of patients benefiting from such adjuvant regimen.

References

1. Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. *Ann Surg*. 1994; 220:364-72.
2. Roder JD, Stein HJ, Siewert JR. Prognostic markers in patients with carcinoma of the esophagus. *Eur J Gastroenterol Hepatol*. 1994;6: 663-9.
3. Glickman JN, Torres C, Wang HH, et al. The prognostic significance of lymph node micrometastasis in patients with esophageal carcinoma. *Cancer*. 1999;85:769-78.
4. Natsugoe S, Mueller J, Stein HJ, Feith M, Höfler H, Siewert JR. Micrometastasis and tumor cell microinvolvement of lymph nodes from esophageal squamous cell carcinoma: frequency, associated tumor characteristics and impact on prognosis. *Cancer*. 1998;83:858-66.
5. Izbicki JR, Hosch SB, Pichlmeier U, et al. Prognostic value of immunohistochemically identifiable tumor cells in lymph nodes of patients with completely resected esophageal cancer. *N Engl J Med*. 1997;337: 1188-94.
6. Di Giorgio A, Botti C, Sammartino P, Mingazzini P, Flammia M, Stipa V. Extracapsular lymph node metastases in the staging and prognosis of gastric cancer. *Int Surg*. 1991;76:218-21.
7. Brasilino de Carvalho M. Quantitative analysis of the extent of extracapsular invasion and its prognostic significance: a prospective study of 170 cases of carcinoma of the larynx and hypopharynx. *Head Neck*. 1998;20:16-21.
8. Fisher BJ, Perera FE, Cooke AL, et al. Extracapsular axillary node extension in patients receiving adjuvant systemic therapy: an indication for radiotherapy? *Int J Radiat Oncol Biol Phys*. 1997;38:551-9.
9. Pera M. Epidemiology of esophageal cancer, especially adenocarcinoma of the esophagus and esophagogastric junction. *Recent Results Cancer Res*. 2000;155:1-14.
10. Lerut T, De Leyn P, Coosemans W, et al. Surgical strategies in esophageal carcinoma with emphasis on radical lymphadenectomy. *Ann Surg*. 1992;216:583-90.
11. Klein JP, Moeschberger ML. Survival analysis. New York: Springer; 1992.
12. Cox DR. Regression models and life tables (with discussion). *J R Statist Soc B*. 1972;34:187-220.
13. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *JASA*. 1958;53:457-81.
14. Hagen JA, DeMeester SR, Peters JH, Chandrasoma P, DeMeester T. Curative resection for esophageal adenocarcinoma. Analysis of 100 en bloc esophagectomies. *Ann Surg*. 2001;234:520-31.
15. Collard JM, Otte JB, Fiasse R, et al. Skeletonizing en bloc esophagectomy for cancer. *Ann Surg*. 2001;234:25-32.
16. Altorki N, Skinner D. Should en bloc esophagectomy be the standard of care for esophageal carcinoma? *Ann Surg*. 2001;234:581-7.
17. Rice TW, Zuccaro G Jr, Adelstein DJ, Rybicki LA, Blackstone EH, Goldblum JR. Esophageal carcinoma: depth of tumor invasion is predictive of regional lymph node status. *Ann Thorac Surg*. 1998;65: 787-92.
18. Kelly S, Harris KM, Berry E, et al. A systematic review of the staging performance of endoscopic ultrasound in gastro-oesophageal carcinoma. *Gut*. 2001;49:534-9.
19. Rice TW, Blackstone EH, Goldblum JR, et al. Superficial adenocarcinoma of the esophagus. *J Thorac Cardiovasc Surg*. 2001;122:1077-90.
20. Holscher AH, Bollschweiler E, Bumm R, Bartels H, Hofler H, Siewert JR. Prognostic factors of resected adenocarcinoma of the esophagus. *Surgery*. 1995;118:845-55.
21. Skinner DB. En bloc resection for neoplasms of the esophagus and cardia. *J Thorac Cardiovasc Surg*. 1983;85:59-71.
22. Peracchia A, Bonavina L, Ruol A, Stein H. Esophageal cancer: a European perspective. Recent results. *Cancer Res*. 2000;155:119-22.
23. Tachikawa D, Inada S, Kotoh T, Futami K, Arima S, Iwashita A. An evaluation of malignancy and prognostic factors based on mode of lymph node metastasis in esophageal carcinoma. *Surg Today*. 1999; 29:1131-5.
24. Steinkamp HJ, Beck A, Werk M, Felix R. Extracapsular spread of cervical lymph node metastases: diagnostic value of magnetic resonance imaging. *Rofo Fortschr Geb Rontgenstr N*. 2000;174:50-5.
25. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001;345:725-30.
26. Bedard EL, Incullet RI, Malthaner RA, Brecevic E, Vincent M, Dar R. The role of surgery and postoperative chemoradiation therapy in patients with lymph node positive esophageal carcinoma. *Cancer*. 2001;91:2423-30.

Discussion

Dr Mark Krasna (Baltimore, Md). I congratulate Dr Lerut and his colleagues for an excellent presentation and thank them for forwarding their manuscript to me. This study retrospectively reviewed 195 patients with T3 esophageal cancer undergoing R0 resection over a 10-year period. Sixty-eight of these also underwent neck dissection as part of a radical 3-field esophagectomy; 83% of these patients had positive lymph nodes. In fact, 1 of the pathologists on this study reviewed approximately 6000 lymph node specimens to determine evidence of extracapsular versus intracapsular lymph node invasion in these lymph nodes. Your group has shown a remarkable 5- and 9-year survival of 57% and 38% for N0 patients and 26% and 18% for N1 patients. These results are truly admirable. Your group has consistently shown that esophagectomy can be done with low mortality and excellent 5-year survival. More importantly, you have shown the significance of lymph node involvement as an independent prognosticator in patients with esophageal cancer.

Dr F. Henry Ellis and I, in a review of over 450 patients at the Lahey Clinic, found that lymph nodes were the single most important prognostic indicator in patients with esophageal cancer.¹ Moreover, we, too, found that the number of involved nodes was important. Dr Tom Rice has also shown the paramount importance of lymph node spread in esophageal cancer. He has demonstrated as well the very important relationships between the T and N classifications. Finally, Dr Skinner and later DeMeester have demonstrated the significance of lymph node positivity and the importance of the numbers of lymph nodes involved and proposed a new so-called "WNM classification" that included an N1 and N2 classification.

It seems therefore that we have 2 challenges regarding staging of esophageal cancer: first, to modify the existing lymph node N stage to better reflect the significance of multiple lymph node involvement and consider celiac and cervical lymph nodes, which are being resected together with other lymph node stations; second, to optimize the methods of staging lymph nodes in esophageal cancer patients' pretreatment.

I have 3 questions for you, Dr Lerut: (1) Do you have data on lymph node involvement, meaning intracapsular versus extracapsular, by the lymph node level according to the lymph node map, or at least can you define them by chest involvement, neck involvement, and abdomen involvement? (2) This was a highly selected group of 195/429 patients with adenocarcinoma undergoing R0 resections at your institution. How did the other 236 patients fare? (3) Finally, and practically, how should we use the