Prognostic role of lymph node involvement in lung metastasectomy

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Objective: The impact of lymph node involvement in lung metastasectomy from extrapulmonary malignancies is uncertain. We assessed the prognostic value of lymph node status in lung metastasectomy and the prevalence of unexpected mediastinal lymph node involvement after lymph node sampling or dissection.

Methods: From May 1998 to October 2005, 388 patients underwent 430 pulmonary metastasectomies with curative intent. The clinical records of all patients who underwent radical lymph node dissection or sampling were reviewed retrospectively. Survival was evaluated using the Kaplan–Meier method and comparison of survival curves by log–rank test.

Results: A total of 124 patients (61 men, mean age 59 years) underwent 139 pulmonary metastasectomies (56 wedge resections, 30 segmentectomies, 49 lobectomies, and 4 pneumonectomies with radical lymph node dissection [88] or sampling [51]). Means of 9.4 lymph nodes and 2 lung metastases per intervention were removed. The median disease-free interval from primary treatment to lung metastasectomy was 49 months. Lymph node involvement was present in 25 patients (20%), in 10 (8%) at N1 stations (hilar or peribronchial) and in 15 (12%) at N2 stations (mediastinal), and in 7 (12.5%) after atypical resection and in 19 (23%) after typical resection. In 15 patients (12%) (60% of N+ patients), lymph node involvement was unexpected. Estimated overall 5-year survival was 46%: It was 60% for subjects with no lymph node metastasis and 17% and 0% for those with N1 and N2 disease, respectively ($P = .01$).

Conclusions: Lymph node involvement heavily affects prognosis after pulmonary metastasectomies. In most patients, lymph node involvement was not revealed by preoperative workup.

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Although the efficacy of surgical removal of lung metastases has been demonstrated, fewer than 40% of patients benefit.[1-5] For this reason there is great interest to identify criteria and prognostic factors to improve selection of surgical candidates and plan further therapeutic approaches. The main factor predicting survival is complete surgical removal of all metastases[2]; others are the disease-free interval, number of metastases, primary tumor type, presence of extrathoracic metastases, and levels of biological markers, such as carcinoembryonic antigen for gastrointestinal cancers and alpha-fetoprotein for germ cell-cancers.[1-8]

Lymph node staging was recently introduced as a prognostic factor for patients with resectable lung metastases.[9-11] However, few data are available in the literature on the prevalence of nodal involvement in these patients and its prognostic significance, so there is no agreement whether lymph node dissection should be routinely performed as part of metastasectomy.[6-10,12]

Abbreviations and Acronyms
CI = confidence interval
HR = hazard ratio
PET = positron emission tomography

The aim of the present study was to determine the prevalence of occult regional lymph node metastasis and the prognostic value in a retrospective series of patients who underwent radical lymph node dissection or sampling during lung metastasectomy.

Materials and Methods

From May 1998 to October 2005, 388 patients underwent 430 lung metastasectomies with curative intent at the European Institute of Oncology. The records of all patients who received radical lymph node dissection or lymph node sampling were reviewed. Age, sex, disease-free interval, primary tumor type, type of resection, number and size of lung metastases, number of lymph nodes resected, presence of hilar and mediastinal node metastases, and length of follow-up were abstracted and analyzed.

Indications for lung metastasectomy were controlled: primary tumor, absence of extrapulmonary metastasis or local recurrence at the preoperative staging, and complete lung resection considered possible from chest computed tomography.

Positron emission tomography (PET) scan was not available during the entire time frame of the study period. All lesions that were suitable for nonanatomic resection on the basis of their size and position were removed by a wedge resection or tumorectomy; in all other cases (large or centrally located metastases), an anatomic resection was performed (segmentectomy, lobectomy, or pneumonectomy). Videothoracoscopy was not used because a manual palpation of all lungs was routinely performed. The standard approach was lateral muscle-sparing thoracotomy. Only in case of apical chest tumors with suspicious invasion of cervicothoracic junction structures was a transmanubrial approach or hemiclamshell performed.

Although our previous experience indicated that 14% of patients undergoing lung metastasectomy had lymph node involvement,[13] regional lymph node dissection in clinically negative cases was not performed routinely but according to the preference of each surgeon.

We considered a lymph node sampling to be the exploration of all ipsilateral mediastinal stations with lymph node biopsy at the level of at least 2 of them. We considered a radical lymph node dissection to be performed at the following stations: R2, R4, 7, and R9 for right lung metastasis and 5, 6, 7, and L9 for left lung metastasis.

The institutional review board was notified of our study, and informed consent to treat clinical data for research was obtained from the patients at the time of surgical resection.

Statistical Analysis

Time to death was defined as the time from surgery until death from any cause. All patients alive at last follow-up were right censored. Survival curves were estimated by the Kaplan–Meier method, and the log–rank test was used to compare survival between groups. The chi-square or Fisher exact test was used to analyze associations between categoric variables. A Cox proportional hazards model was used to identify independent predictors of survival, with adjustment for relevant clinical covariates. All statistical tests were 2-sided. The analyses were performed with the SAS statistical package version 8.2 (SAS Institute, Cary, NC).

Results

Mediastinal lymph node dissection or sampling was performed in 124 patients. The mean age was 59 years (range 24-82 years); 61 were men and 63 were women. The median disease-free time from primary tumor resection to first pulmonary metastasectomy was 49 months (range 2-371 months). A total of 139 pulmonary metastasectomies were performed in these patients: 56 wedge resections, 30 segmentectomies, 49 lobectomies, and 4 pneumonectomies. Radical lymph node dissection was performed in 88 procedures, and sampling was performed in 51 procedures. A mean of 9.4 (1308/139) lymph nodes were removed per operation (4.6 lymph nodes for sampling and 12.1 lymph nodes for radical dissection). A mean of 2 lung metastases were resected per operation. Table 1 shows the frequency of lymph node metastases and other characteristics. Lymph node involvement was found in 25 patients (20%); 10 patients (8%) had hilar station and 15 patients (12%) had mediastinal station involvement (among these, 7 patients had both hilar and mediastinal metastases). In 10 of these cases, involvement (hilar 6, mediastinal 4) was suspected from the presurgical workup, and in 15 of these cases (12%), lymph node metastasis was not revealed by staging procedures and was totally unexpected. Another 5 patients had clinically positive lymph nodes (among the group with pathologic negative lymph nodes). Overall, there were 109 patients with clinically negative lymph nodes, and the true rate of occult nodal involvement was 13.7% (15/109). Even if a small number of patients were available for each tumor type, we could observe that the frequency of nodal involvement varied significantly according to primary site (Table 1). Patients with lung metastases from breast cancer, germ cell cancers, and epithelial gynecologic cancers had significantly higher frequencies of nodal involvement than those with metastases from colon cancer. Nodal metastases were found in 7 of 56 (12.5%) atypical lung resections and in 19 of 83 (22.9%) typical resections (per procedure analysis; $P = .18$). Peribronchial or hilar node (N1) metastases occurred in 3.5% and 9% of atypical and typical resections, respectively, whereas mediastinal node metastases occurred in 9% and 12% of atypical and typical resections, respectively. Fifteen (4.9%) of the 303 lymph nodes removed during atypical resection were metastatic, compared with 71 (6.7%) of the 998 lymph nodes removed by typical resection ($P = .29$).

The prevalence of nodal metastasis was not significantly correlated with the size of resected metastasis ($P = .17$).

TABLE 1. Prevalence of nodal involvement in lung metastasectomies in relation to primary cancer site, type of resection, number of lymph nodes removed, number of lung metastases, and maximum diameter of lung metastasis

	No. of procedures (patients)	No. with involved nodes (%)*	*P* value	Extent of involvement	
				Hilum only (N1) (%)*	Mediastinum (N1 + N2 or N2) (%)*
Total	139 (124)	26 (18.7%)		11 (7.9%)	15 (10.8%)
Atypical resections (%)*	56 (47)	7 (12.5%)		2 (3.6%)	5 (8.9%)
Typical resections	83 (77)	19 (22.9%)	.18	9 (10.8%)	10 (12.0%)
No. of metastases removed					
1	80 (73)	14 (17.5%)		4 (5.0%)	10 (12.5%)
≥2	59 (51)	12 (20.3%)	.67	7 (11.9%)	5 (8.5%)
Size of lung metastasis†					
0-1 cm	7 (7)	1 (14.3%)		1 (14.3%)	0 (0.0%)
1-2 cm	42 (34)	7 (16.7%)		5 (11.9%)	2 (4.8%)
2-3 cm	38 (33)	5 (13.2%)		1 (2.6%)	4 (10.5%)
3-4 cm	22 (21)	5 (22.7%)		1 (4.6%)	4 (18.2%)
>4 cm	29 (28)	8 (27.6%)	.18	3 (10.3%)	5 (17.2%)
Primary tumor site					
Colon	61 (54)	6 (9.8%)	Reference	2 (3.3%)	4 (6.6%)
Sarcoma	17 (15)	1 (5.9%)	1.00	1 (5.9%)	0 (0.0%)
Head/neck	10 (8)	1 (10.0%)	.51	0 (0.0%)	1 (10.0%)
Urinary tract	17 (16)	3 (17.6%)	.34	2 (11.8%)	1 (5.9%)
Breast	12 (11)	6 (50.0%)	<.001	2 (16.7%)	4 (33.3%)
Gynecologic	9 (8)	3 (33.3%)	.04	1 (11.1%)	2 (22.2%)
Melanoma	6 (6)	2 (33.3%)	.11	1 (16.7%)	1 (16.7%)
Germ cell	3 (3)	3 (100%)	.001	1 (33.3%)	2 (66.7%)
Other/unknown	4 (3)	1 (25.0%)	.24	1 (25.0%)	0 (0.0%)

*Percentages calculated on the number of procedures. †Largest diameter of lung metastasis determined by pathologic exam.

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Survival

The mean postoperative follow-up was 31 months (range 2-82 months). Estimated 5-year survival was 46% overall, 60% in N0, 17% in N1, and 0% in N2 (or N1 + N2) cases ($P = .01$; Figure 1). Estimated 5-year survival was 47% in those with 1 lung metastasis, 57% in those 2 lung metastases, and 31% in those with 3 or more metastases ($P = .024$; Figure 2).

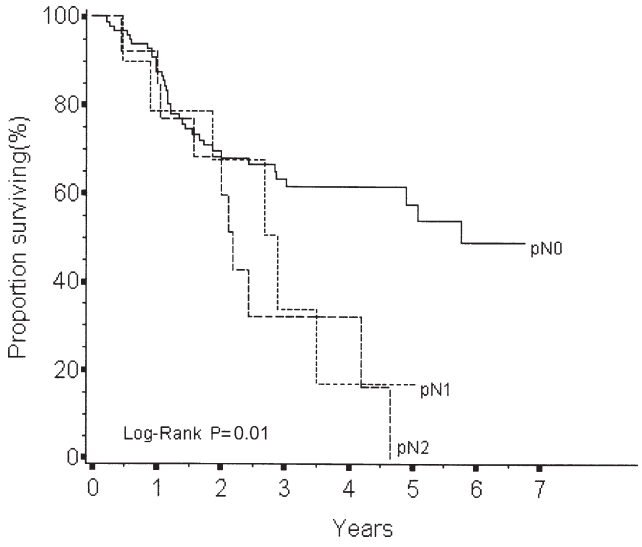

Figure 1. Survival according to lymph node status after lung metastasectomy.

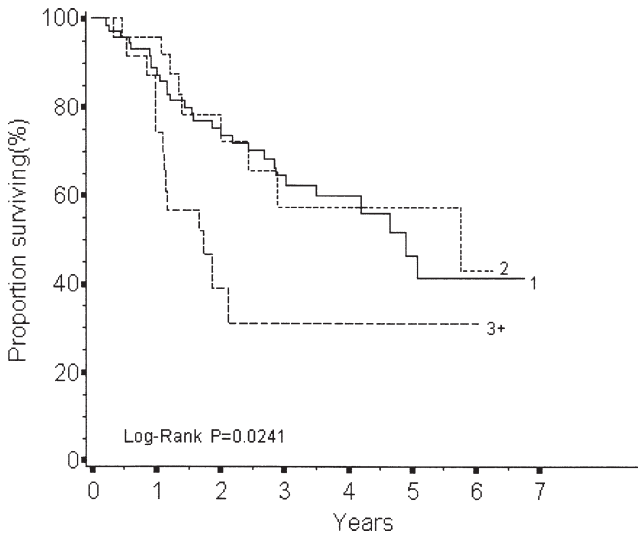

Figure 2. Survival according to number of lung metastases removed.

TABLE 2. Univariate and multivariate analysis of 124 patients undergoing 139 lung metastasectomies with lymph node sampling

	No. of patients	Dead	HR of death (95% CI) univariate	HR of death (95% CI) multivariate
Age (y)				
<50	28	15	1.00	1.00
50-59	31	9	0.47 (0.21-1.08)	0.71 (0.27-1.90)
60-69	33	17	0.84 (0.42-1.69)	1.22 (0.52-2.85)
70+	32	11	0.56 (0.26-1.23)	1.27 (0.46-3.50)
Sex				
Men	61	28	1.00	1.00
Women	63	24	0.88 (0.51-1.51)	1.16 (0.53-2.51)
Size of mets (cm)				
≤2.2	59	20	1.00	1.00
>2.2	64	31	1.43 (0.81-2.51)	1.32 (0.65-2.69)
pN status				
pN0	100	36	1.00	1.00
pN+	24	10	2.18 (1.20-3.97)	2.62 (1.14-6.01)
No. of mets				
1	73	29	1.00	1.00
2	26	9	0.94 (0.44-1.99)	0.88 (0.35-2.22)
3+	25	14	2.28 (1.19-4.37)	5.83 (2.35-14.5)
Type of resection				
Atypical	47	14	1.00	1.00
Typical	77	38	1.52 (0.82-2.81)	1.93 (0.89-4.17)
Mets + pN				
pN0 with 1 or 2 mets	78	24	1.00	1.00
pN+ or ≥3 mets	46	28	3.11 (1.78-5.42)	5.19 (0.55-10.6)
Disease-free interval				
<24 mo	36	12	1.00	1.00
24-48 mo	43	23	1.75 (0.87-3.52)	1.82 (0.81-4.10)
>48 mo	42	15	0.86 (0.40-1.83)	0.72 (0.29-1.79)
Site of primary				
Colon	54	21	1.00	1.00
Breast	11	5	1.16 (0.44-3.07)	0.78 (0.21-2.86)
Melanoma	6	4	2.25 (0.77-6.59)	2.03 (0.57-7.24)
Head/neck	8	1	0.29 (0.04-2.18)	0.24 (0.03-2.01)
Urinary tract	16	8	1.31 (0.58-2.97)	1.52 (0.56-4.09)
Gynecologic	8	3	0.93 (0.28-3.13)	0.48 (0.09-5.28)
Germ cell	3	1	0.92 (0.12-6.86)	0.29 (0.02-3.57)
Other	3	2	2.28 (0.53-9.79)	2.19 (0.21-23.2)
Sarcoma	15	7	1.75 (0.74-4.12)	1.58 (0.60-4.21)

HR, Hazard ratio; *CI,* confidence interval; *mets,* metastases. Largest diameter of lung metastases determined pathologically.

By univariate analyses, age, sex, primary tumor site, disease-free interval, type of resection, type of lymph node dissection, and size of the largest metastasis had no impact on survival (Table 2).

Among patients with positive nodes, no significant difference in overall survival was observed in cases of radical lymph node dissection or sampling ($P = .36$).

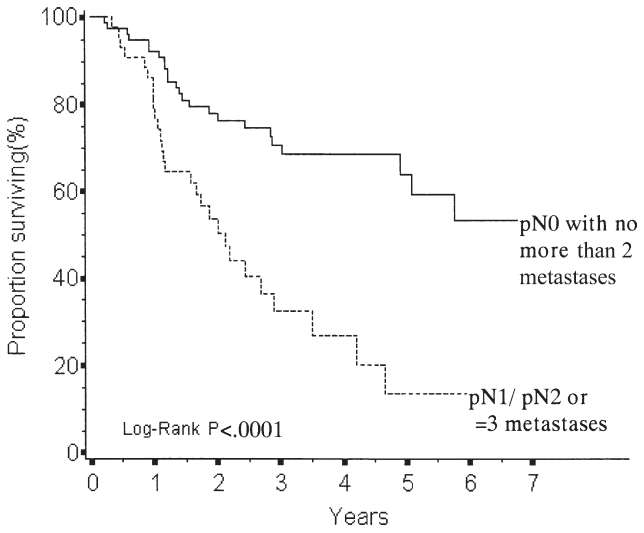

Figure 3. Survival according to combination of the 2 independent prognostic variables (pN status and number of metastases).

The multivariate analysis showed that the nodal status and number of lung metastases were independent prognostic factors for overall survival. For involved nodes, the hazard ratio (HR) for death was 2.62 (95% confidence interval [CI] 1.14-6.01) for 3 or more lung metastases, and the HR of death was 5.83 (95% CI 2.35-14.5) (Table 2). The combination of nodal status and number of lung metastases produced 2 groups of patients with markedly differing prognoses: Those with pN0 and 1 or 2 metastases had a 5-year survival of 55%; those with pN+ and 3 or more metastases (most with 1 had the other) had a 5-year survival of 12% ($P < .0001$, log rank; HR of death 3.1, 95% CI 1.78-5.4, Figure 3).

Discussion

The role of lymph node dissection in lung metastasectomy and the prognostic role of nodal involvement are still controversial (Table 3). In a series of 100 patients with colon cancer who underwent routine lymph node dissection during lung metastasectomy, involved lymph nodes were associated with poorer prognosis (5-year survival 7% vs 50% in those with no positive nodes).[6] Similarly, in a series of 70 lung metastasectomies with complete lymph node dissection,[9] the 3-year survival of patients with negative nodes was 69%, but only 38% in those with positive nodes ($P < .001$); nodal status was the only prognostic factor for survival in this series. Lymph node metastasis was also an independent predictor of survival in the studies of Pfannschmidt and colleagues.[12,14] In contrast, the recent study of Loehe and colleagues[10] found that lymph node status had no effect on survival in a series of 71 lung metastasectomies from various primaries, 14.5% of which had mediastinal metastasis. Kamiyoshihara and associates[15] found no

TABLE 3. Lymph node involvement in patients with lung metastases and impact on survival in published series

First author	Year	Primary site	5-y survival N+	5-y survival N−	Percentage positive LN
Webb	1979	Melanoma			50%
Okumura	1996	Colon			15%
International Registry	1997	Mix	14%	45%	5%
Inoue	2000	Colon	14%	49%	
Loehe	2001	Mix	*22 mo	32 mo	14%
Saito	2002	Colon	6.2%	53.6%	15%
Ercan	2004	Mix no sarcoma	20%	60%	29%
Pfannschmidt	2006	Mix	20 mo	64 mo	37%
Veronesi	2006	Mix	9%	57%	20%

LN, Lymph node. *Median survival.

survival difference between patients with and without lymph node involvement in a retrospective review of 28 patients undergoing lung metastasectomy and nodal dissection.

The main finding of our study is that involved lymph nodes identified during radical lymphadenectomy or sampling as part of lung metastasectomy for extrapulmonary primaries had a major impact on survival: The nodal status and number of lung metastases were independent prognostic factors. The combination of these 2 factors defined 2 groups with different prognoses: those with 1 or 2 metastases and no nodal involvement (5-year survival, 60%) and those with 3 or more lung metastases and nodal involvement (5-year survival, 12%). An important issue in patients proposed for lung metastasectomy is the frequency of nodal involvement, particularly in view of the finding by most studies that nodal involvement has a strong negative impact on survival. The frequency was 5% in the International Registry Report[3] and approximately 15% in most reports,[6,10,11] but sometimes higher (28.6% and 37%).[9,12] Twenty percent of our patients (18% of procedures) had lymph node involvement. More revealing, however, is the frequency of unexpected (not identified in preoperative workup) lymph node involvement, which was 13.5% in our study.

The incidence of lymph node metastasis was significantly influenced by primary tumor site, being low for colorectal cancer and sarcoma (9% and 6.6%, respectively), moderate for head and neck and urinary tract tumors (12% and 18%, respectively), and high for melanoma, gynecologic tract cancers, breast cancers, and germ cell cancers (33%, 38%, 54% and 100%, respectively). Even if a small number of cases are reported for each tumor type, these findings are in line with previous experience of high rates of lymph node involvement in lung metastases from melanoma[16,17] and gynecologic tract tumors[10] and a low rate for sarcoma.[9,18]

We found that the frequency of nodal involvement did not correlate with the number of resected lung metastases as reported by others[9,10] or the maximum diameter of the lung lesions. In contrast, the frequency of nodal involvement tended to be higher for typical resections (23%) than for atypical resections (12%) ($P = .18$). In particular, patients undergoing typical resections had a higher frequency of N1 metastases than those who received atypical resection (11% vs 3.5%, respectively), suggesting differences in the extent of lymph node resection at hilar, lobar, or segmental stations by the 2 procedures (no segmental and peribronchial lymph node can be removed in case of wedge resection). In fact, when the number of positive nodes is divided by the total number of resected lymph nodes in the 2 groups of patients (typical vs atypical resection), a similar proportion of involved nodes was found at N1 and N2 stations.

Conclusions

Although our study is limited by its retrospective nature and the absence of evaluation of preoperative PET results, it provides strong evidence that N2 and N1 node involvement in patients undergoing lung metastasectomy has a significant impact on survival. The implication is that preoperatively confirmed involvement is a relative contraindication for lung metastasectomy. Our second major finding was that at least 13% of patients undergoing metastasectomy had lymph node metastases that were not suspected from preoperative workup and that the frequency of involvement correlated with the primary site.

More accurate and sensitive preoperative staging procedures are required. There is evidence that PET or computed tomography/PET may partially fulfill this requirement,[13] although this requires confirmation by prospective study with the aim to avoid useless surgery and to identify patients who are candidates for multimodality treatments that may offer longer survival. Mediastinoscopy can also be considered in some histologic subtypes. Considering the standard methods of staging available today, we can affirm that the pathologic examination of regional lymph nodes offers patients with resectable lung metastasis a more accurate staging and better determination of prognosis with the possibility to administrate potentially beneficial multimodality treatment.

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Discussion

Dr Vallieres *(Seattle, Wash).* Dr Veronesi, thank you for this review and for sending me all the material way ahead of time. That was appreciated.

In this retrospective review covering 124 patients over a period of 7 years, I think you have convincingly shown that the presence of nodal metastasis in patients undergoing pulmonary metastasectomy carries a dismal prognosis, as others have previously suggested but generally with less numerous series. From your survival data, it appears that the role of pulmonary metastasectomy is probably limited to nonexistent in the presence of N2 disease. Your article brings 2 issues to discuss relating the role of nodal sampling or dissection: first, the staging issues, and second, the potential of any therapeutic issue of removing lymph nodes at the time of pulmonary metastasectomy.

First I'd like you to address a few questions regarding the staging issue. Considering your data and a 0% 5-year survival in patients with N2 disease, what is your practice now? Do you recommend routine mediastinal staging with mediastinoscopy despite normal imaging? Do you restrict that only for patients with breast, gynecologic, melanoma, or germ cell tumor primaries? What do you do now in Milan for these patients?

Dr Veronesi. One limitation of the study was that the role of PET scan was not well indicated in this series, but in a previous work I personally analyzed the role of PET scan in lung metastasectomy and found that most N-positive patients were identified at PET scan. In that series we excluded some patients with nodal involvement because of the PET scan, but I think that, as was recently reported in patients with lung cancer, PET with its high negative predictive value will be able to limit the role of mediastinoscopy. So in case of a PET-negative mediastinum with a computed tomography contrast negative at that level, we do not use mediastinoscopy. In the case of PET-positive mediastinum, I think the mediastinoscopy is a good tool to exclude disease at that level. The problem of N1 disease remains because both PET and mediastinoscopy are not precise tools to evaluate this level of disease, so in these cases I think that thoracotomy is the only possibility.

Dr Vallieres. You showed that there was no survival difference relating to the size of the metastases. What about the presence or absence of nodal involvement correlating to the size of the metastases?

Dr Veronesi. We did not find a significant correlation between nodal involvement and size of metastasis. However, we found that the lesion larger than 4 mm had a prevalence rate of nodal involvement of 30% more than smaller lesions, so it may suggest that in large lesions such as this, larger than 4, sampling should be made.

Dr Vallieres. Do you mean 4 mm or 4 cm?

Dr Veronesi. Centimeters.

Dr Vallieres. As you have stated in your discussion by doing an atypical resection, either a wedge or a tumorectomy, we understage many of the patients. Would you thus advocate that we now routinely stage N1 and N2 nodes when we are doing a video-assisted thoracic surgery wedge or an open-wedge metastasectomy?

Dr Veronesi. I am not convinced that in all cases we have to do sampling or dissection (radical lymph node dissection). Maybe in a small lesion, a peripheral PET-negative metastasis, maybe from a patient with sarcoma, we can avoid lymph node sampling because there are some other disadvantages to this procedure, such as difficult to redo a thoracotomy, for example, for recurrent metastasis.

Dr Vallieres. I'd like to explore the therapeutic role of nodal dissection/resection. Your data suggest that nodal sampling or dissection in these patients definitely allows for better staging of their disease. Is there also a potential therapeutic effect, benefit, of nodal dissection versus sampling in this scenario of metastasectomy? Did you look at the survival difference in patients with node-positive disease, whether they'd had a nodal dissection versus just sampling? I understand that the numbers are small.

Dr Veronesi. We performed a separate analysis in the population evaluating the role of radical versus sampling lymph nodes dissection, and no difference was found. Even regarding . . . (end of cassette).

Dr Vallieres. During the study period did you perform mediastinoscopies in patients who had clinical N disease and as such eliminate these patients from the cohort you have just presented? If you did, did you look at the survival of the individuals in whom you had identified N2 disease and did not operate versus those who were found to have N2 disease at surgery? Did they behave the same, or did the metastasectomy have an impact?

Dr Veronesi. This is a good question. We certainly performed mediastinoscopy and excluded patients from surgery, but I have no data about their survival outcome.

Dr Vallieres. I enjoyed your presentation. I certainly encourage you and your colleagues in Milan in continuing to prospectively accrue information on these patients so that some of these questions will be answered in the future.