European Journal of Cardio-Thoracic Surgery 45 (2014) 882–887
doi:10.1093/ejcts/ezt478 Advance Access publication 29 September 2013

ORIGINAL ARTICLE

The N2 paradox: similar outcomes of pre- and postoperatively identified single-zone N2a positive non-small-cell lung cancer[†]

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Received 23 May 2013; received in revised form 13 August 2013; accepted 21 August 2013

Abstract

OBJECTIVES: Resection of N2a non-small-cell lung cancer (NSCLC) diagnosed preoperatively is controversial but there is support for resection of unexpected N2 disease discovered at surgery. Since the seventh TNM edition, we have intentionally resected clinical N2a disease. To validate this policy, we determined prognostic factors associated with all resected N2 disease.

METHODS: From a prospective database of 1131 consecutive patients undergoing elective resection for primary lung cancer over a period of 8 years, we identified 68 patients (35 females (51.4%), mean age 66 years, standard deviation (SD) 9 years) who had pathological N2 disease. All patients had positron emission computed tomography (CT-PET) staging and selective mediastinoscopy. A Cox-regression analysis was performed to identify prognostic factors.

RESULTS: At a median follow-up of 38.7 months (standard error 10, 95% confidence interval (CI) 19.0–58.4), the overall median survival was 22.2 months (95% CI 14.6–29.8) with 1-, 2- and 5-year survival rates of 63.3, 46.6 and 13.2%, respectively. Survival after resection of pN2 disease is adversely affected by the need for pneumonectomy, multizone pN2b involvement and by non-compliance with adjuvant chemotherapy. Pathological involvement of the subcarinal zone but no other zone appears to be associated with an adverse prognosis (hazard ratio (HR) 1.87, $P = 0.063$). Importantly, long-term survival is not different between those patients who have a negative preoperative PET-CT scan and yet are found to have pN2 *after* resection, and those who are single-zone cN2a positive *before* resection on PET-CT scan (HR 1.37, $P = 0.335$).

CONCLUSIONS: Our results support a policy of intentionally resecting single-zone N2a NSCLC identified preoperatively as part of a multimodality therapy.

Keywords: Lung cancer • Mediastinum • Lymph nodes • Staging • Single zone

INTRODUCTION

The role of surgery for Stage IIIA-N2 non-small-cell lung cancer (NSCLC) remains undetermined. In the seventh edition of the TNM staging system, the relatively favourable prognosis of single pathological zone N2 disease (N2a) was identified but could not be formally validated. Nevertheless, resection of N2a NSCLC diagnosed preoperatively is not universally accepted, whilst paradoxically there is support for resection of unexpected N2 disease discovered intraoperatively rather than closing without resection [1]. Since the publication of the seventh TNM edition in May 2009 [2], we have intentionally resected clinical N2a disease with a prospective analysis of outcomes. The aim of this study was to validate our policy by comparing the postoperative outcomes of patients with clinical N2a with those clinically staged cN0 or cN1 on preoperative positron emission computed tomography (PET-CT), but who were found to have pN2 disease.

[†]Presented at the 21st European Conference on General Thoracic Surgery, Birmingham, UK, 26–29 May 2013.

MATERIALS AND METHODS

From a prospective histological database of 1131 consecutive cases of NSCLC resected over 8 years (May 2004–January 2012), we identified 68 patients [33 males; 35 females, mean age 65.9 (standard deviation, SD 9.3) years] who underwent resection for pathological N2 disease. All patients had clinical nodal staging with PET-CT and a selective mediastinoscopy was performed on patients with either PET positive mediastinal lymph nodes or when the multidisciplinary team required exclusion of multizone N2 disease. Intraoperative staging comprised a lobe-specific systematic mediastinal lymph node dissection [3].

Ten patients had received neoadjuvant chemotherapy (CT) prior to surgical resection and adjuvant treatment was given as

follows: 14 patients (20.5%) received and completed adjuvant chemotherapy only with cisplatin-based regimens, 4 patients (5.8%) received postoperative radiotherapy (RT) only and 9 patients (13.2%) received combined RT and chemotherapy postoperatively. No adjuvant chemoradiotherapy was given to 41 patients.

Data were collected from the hospital's electronic patient records, case notes and our Trust's web-deployable imaging management software.

Patients were analysed in two groups: patients with PET-CT positive N2 nodes preoperatively (group PETP) and patients with CT-PET negative N2 nodes (group PETN). The groups were compared with respect to age, gender, T stage, preoperative forced expiratory volume (FEV1), histology, rate of R0 resection, recurrence rate, receipt of chemotherapy and survival.

All patients were followed up in regular intervals postoperatively (3, 6, 9, 12, 24, 36, 48, 60 m) with regular clinic appointments, chest radiographs and/or CT scan if there was a clinical or radiological suspicion of recurrence. Patients receiving adjuvant therapy were also followed up with a CT scan organized between surgical and oncology teams after completion of their chemo- or RT sessions. Additional information was obtained, where required, from Oncology departments.

Statistical analysis

We used the IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp. for analysis: continuous data were analysed using Student's unpaired *t*-test and categorical data with Fisher's exact test. Survival curves were estimated using the Kaplan–Meier method. Follow-up was quantified with the reverse Kaplan–Meier estimator. Univariate analysis of survival was performed using the log-rank test. The prognostic factors shown statistically significant on univariate analysis were included in a multivariate analysis, using Cox-regression models. A probability value <0.05 was considered statistically significant.

RESULTS

A preoperative mediastinoscopy was only performed in 14 out of 30 patients who were staged cN2 on preoperative PET-CT scan. Two of them were positive confirming the presence of NSCLC in lymph nodes with avid standardized uptake value on preoperative scan (station 4L for a left upper lobe tumour and 7 for a right lower lobe tumour, respectively). No mediastinoscopies were performed on patients with cN0–N1 on PET.

There were no significant intergroup differences in any of the clinical or pathological characteristics of the 68 patients [Tables 1 and 2]. There were four in-hospital deaths (5.8%). The mean hospital stay for all patients was 10.3 days (SD 12.5 days). The overall median follow-up was 38.7 months [standard error 10, 95% confidence interval (CI) 19.0–58.4].

The anatomical resections performed included: lobectomy in 29 patients, bilobectomy in 5, sleeve lobectomy in 10, segmentectomy in 9 and pneumonectomy in 15. Of the 68 patients who underwent resection for pN2 NSCLC in this study, 30 patients were clinically staged as N2 on preoperative PET-CT (group PETP), whilst 38 patients were clinically staged as N0 or N1 (group PETN). In group PETP, 28 patients had single-zone disease on PET-CT staging (cN2a), whilst 2 had multizone cN2b disease (1 patient with positive stations 4L and 5 and the other one positive in stations 7 and 8). In group PETN, 16 patients had cN1, whilst 22 were cN0.

Analysis of the resected pathological data showed that 55 of the 68 cases were proven to have pN2a (single zone) disease: 30 subcarinal, 17 aortopulmonary, 6 upper mediastinal and 2 lower mediastinal. In the remaining 13 cases of pN2b (multizone) disease, only one had preoperative cN2b disease but had a negative mediastinoscopy. Three further patients in this group had cN2a disease but the majority had cN0/1 disease: 7 were cN0 and 2 cN1.

Survival

There was no significant difference in progression-free survival (PFS) between group PETP (median PFS 14.4 months, 95% CI 6.4–22.4) and group PETN (median PFS 17.6 months, 95% CI 1.5–33.5, $P = 0.16$) [Fig. 1].

Analysis of overall survival (OS) has also shown no intergroup difference: PETP (median survival 22.2 months, 95% CI 10.9–37.1) and PETN (median survival 24 months, 95% CI 10.9–33.9, $P = 0.33$) [Fig. 2].

In the subgroup of patients that had proven single-zone pN2a, the survival was significantly better than for the patients with resected multizone pN2b disease (median OS 26.5 months vs 5.4 months, $P = 0.005$) [Fig. 3].

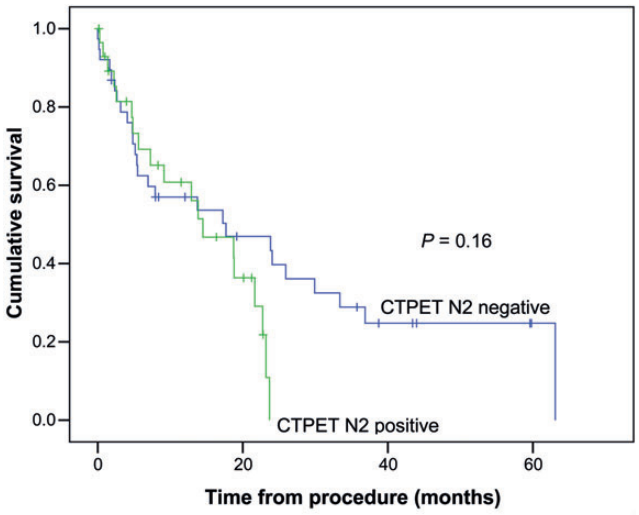
Table 1: Clinical characteristics

	Overall	PETP	PETN	*P*-value
No. of patients	68	30 (44%)	38 (56%)	
Age (mean)	65 (SD 9.4)	64 (SD 9.6)	66 (SD 9.2)	0.32
Gender (M : F)	33 : 35	11 : 19	22 : 16	0.094
Pre-FEV1 (mean)	71%	70% (SD 23.6)	72% (SD 21.5)	0.73
Cardiac comorbidities	14 (21%)	5	9	0.55
Pneumonectomy	13 (19%)	6	7	0.78
Intrapericardial pneumonectomy	2 (3%)	1	1	
Lobectomy	29 (43%)	11	18	
Bilobectomy	5 (7%)	2	3	
Sleeve lobectomy	10 (15%)	4	6	
Segmentectomy	9 (13%)	6	3	

Table 2: Pathological characteristics

	Overall	PET N2+	PET N2−	*P*-value
Tumour (mean) size mm	49.2 (SD 26.1)	46.3 (SD 25.9)	51.5 (SD 26.2)	0.41
Cell type				
Adenocarcinoma	41 (60%)	18	23	0.45
Squamous cell carcinoma	23 (34%)	9	14	
Miscellaneous	4 (6%)	3	1	
Resection margin				
R0	45 (66%)	20	25	0.95
R1	15 (22%)	6	9	
R2	2 (3%)	1	1	
Rx	6 (9%)	3	3	
Recurrence rate	32%	40%	26%	0.29
Loco-regional[a]	11.7%	16.6%	7.8%	0.27
Distant	19.1%	20%	18.4%	0.86
Adjuvant chemotherapy	33.8%	40%	28.9%	0.34

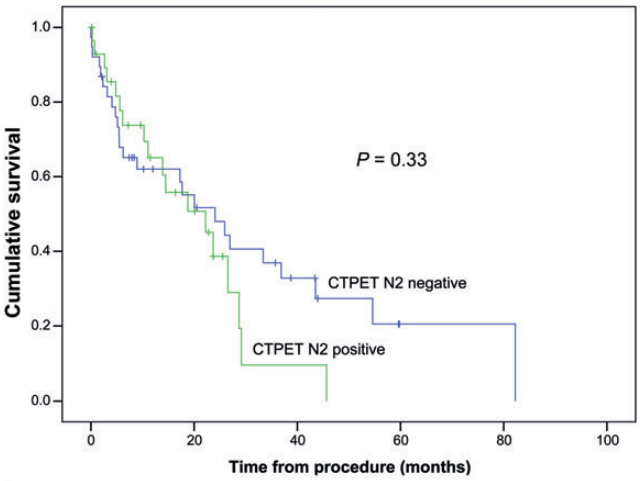
[a]'Loco-regional' recurrence includes proper loco-regional recurrence after initial R0 resection and progressive disease after R1 and R2 resection.



Number at risk

Time (months)	12	18	24
PET N2 negative (38)	17	13	11
PET N2 positive (30)	12	8	0

Figure 1: Progression-free survival comparison between CT-PET N2 negative and CT-PET N2 positive groups.



Number at risk

Time (months)	12	18	24	36
PET N2 negative (38)	18	15	13	8
PET N2 positive (30)	14	13	5	1

Figure 2: Overall survival of 68 resected cases of N2 NSCLC: CT-PET N2 positive group vs CT-PET N2 negative group.

The results of univariate analysis of clinical and pathological related features [Table 3] showed the following variables to be associated with a poorer prognosis: multizone pN2b ($P = 0.007$), pneumonectomy ($P = 0.005$) and no adjuvant chemotherapy ($P = 0.012$). No difference in survival was associated with: gender, CT-PET positive cN2, lower mediastinal zone pN2, upper mediastinal zone pN2 or aortopulmonary zone pN2. There was a non-significant trend between adverse prognosis and pathological involvement of subcarinal zone pN2 ($P = 0.063$).

Multivariate analysis using Cox regression showed multizone pN2b involvement (hazard ratio (HR) 2.34, 95% CI 1.01–5.40, $P = 0.047$) and receipt of adjuvant chemotherapy (HR 0.42, 95% CI 0.21–0.85, $P = 0.016$) to be significant prognostic factors [Table 4].

DISCUSSION

Summary of results

Our study showed a low incidence of resected pN2 (68 out of 1131 patients, 6%) that can be attributed to the efficacy and wide

use of PET-CT in the preoperative assessment of patients. Only 2 patients were identified as cN2b preoperatively and 1 of them had a negative mediastinoscopy subsequently.

The analysis of the International Association for the Study of Lung Cancer database showed that median survival for the two subgroups of surgically treated pN2 disease was 35 months for pN2a compared with 19 months for pN2b disease [4]. Our results show a lower survival (26.5 months for pN2a vs 5.4 months for pN2b) especially for the multizone N2 group that can be attributed to the small non-randomized nature of the study as well as poor compliance with adjuvant chemotherapy.

The heterogeneity of the subgroup of patients with Stage IIIA-N2 NSCLC with regard to prognosis and treatment has not allowed for a consensus on the management of the disease. Numerous investigators have focused on recognizing clinical and pathological prognostic factors [5–7]. Large multi-institutional studies [8] have also described correlation between clinical N status, number of N2 stations involved and survival. In the latest revision of TNM staging, there were three distinct prognostic groups among patients undergoing resection without induction therapy: single pathological N1 zone, multiple pathological N1 zones *or* single pathological N2 zone, and multiple pathological N2 zone disease. However, analysis of the above N categories in conjunction with each T category (e.g. T1N1a, T1N1b, T1N2a, T1N2b, etc.) identified insufficiently large numbers to yield statistically valid analysis. Therefore, the change of N descriptors was not recommended [4]. Nevertheless, the preoperative finding of N2 in multiple levels is related with poor prognosis, similar to Stage IIIB, but the presence of incidental N2a (cN0–N1) depicts a subgroup with good prognosis.

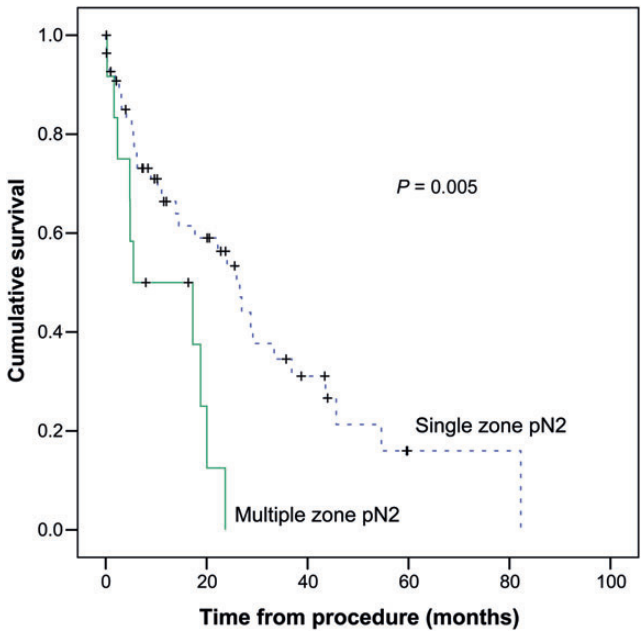


Figure 3: Overall survival by number of pN2 zones with involvement.

Preoperative mediastinoscopy

Detailed mediastinal nodal staging has resulted in several studies confirming the superiority of PET-CT over CT [9–11]. Whilst cervical mediastinoscopy is superior to both CT and PET-CT, it should not be employed in all cases. Its non-selective use amongst Stage 1 NSCLC has not been proven to be cost-effective [12]. Other invasive techniques for sampling of mediastinal stations not accessible by cervical mediastinoscopy, such as videothoracoscopy, have also been suggested [13]. One of our main conclusions is that preoperative mediastinoscopy should be used to confirm N2a disease by showing that the other mediastinal lymph node zones are negative. Recently Yasufuku *et al.* [14] found that endobronchial ultrasound-guided trans-bronchial needle aspiration (EBUS-TBNA) and oesophageal ultrasound-guided fine needle aspiration (EUS-FNA) were highly effective in the radiologically normal mediastinum with a sensitivity of up to 68% and a negative predictive value (NPV) of 91%. However, we prefer mediastinoscopy to the less invasive techniques of EBUS-TBNA or EUS-FNA since in the potential surgical patients with suspected N2 disease on a PET-CT scan the conclusions are different as shown in two recent papers, where EBUS-TBNA and EUS-FNA had an NPV of 79% and sensitivity of only 57% but mediastinoscopy had better results with 88% sensitivity, 93% NPV and 95% accuracy [15, 16].

The majority of our pN2 patients had pathologically proven involvement of the subcarinal zone (41/68, 60.3%). Eleven out of these patients had mediastinoscopy with only 1 showing positive subcarinal lymph nodes. This finding highlights the technical challenges of this procedure as well as the importance

Table 3: Results of univariate analysis of overall survival

Factors	*n*	HR	95% CI	*P*-value
PET cN2	30	1.37	0.73–2.59	0.33
Multizone pN2 involvement	13	2.83	1.32–6.06	0.007
Subcarinal zone pN2	41	1.87	0.97–3.62	0.063
Lower zone pN2	6	1.40	0.49–4.02	0.52
Upper zone pN2	14	0.77	0.34–1.76	0.53
AP zone pN2	19	0.99	0.49–1.98	0.96
Adjuvant chemotherapy	23	0.42	0.22–0.83	0.012
FEV1 (<50%)	11	1.93	0.85–4.40	0.11
Pneumonectomy	15	2.70	1.36–5.35	0.005
Gender (male)	33	1.69	0.91–3.13	0.098

n: number of subjects.

Table 4: Results of Cox-regression analysis of overall survival

Factors	*n*	HR	95% CI	*P*-value
PET cN2	30	1.20	0.85–1.68	0.28
Multizone pN2 involvement	13	2.34	1.01–5.40	0.047
Adjuvant chemotherapy	23	0.42	0.21–0.85	0.016
Pneumonectomy	15	1.88	0.93–3.80	0.078

n: number of subjects

of video mediastinoscopy, which facilitates better access to difficult areas and a complete lymphadenectomy rather than subtotal sampling.

Intraoperative staging

In view of the above results, we recommend systematic mediastinal lymph node dissection, especially when N2 disease has been identified preoperatively, to achieve an accurate nodal staging and guide the therapeutic strategy. However, we recognize that this approach does not hold a survival advantage over systematic sampling [17, 18].

Detterbeck [1] has shown in his study no demonstrably different quality of life nor significantly increased perioperative mortality between exploratory thoracotomy and lobectomy when assessing the appropriateness for resection of what he describes as 'surprise N2 disease'. Our results though support his conclusion that one should proceed with resection only in pN2a but not pN2b disease.

We acknowledge that alternative strategies need to be considered especially for patients who would not tolerate a surgical approach. Randomized studies have recently shown no benefit in survival between induction chemoradiation vs induction chemotherapy alone prior to subsequent surgical resection [19]. Albain *et al*. [20] have also shown in their Phase III study significantly improved PFS but not OS when comparing concurrent CT and RT (C/R) vs C/R followed by surgical resection on selected patients with histologically or cytologically proven Stage IIIA-N2 NSCLC. None of these studies, however, quoted specific survival data for pN2a and pN2b disease, making direct comparison difficult.

Limitations

The small number of this series, 68 patients with pathological N2 disease, is a definite limitation of the study. Also, its retrospective nature meant that, during the 8 years (2004–2012) reviewed, three different TNM classifications as well as different imaging modalities (CT, PET-CT) were used, the technical aspects of which have changed. The clinical staging followed in our study, consisting of lobe-specific systematic mediastinal lymph node dissection, resulted in failure to identify clinical N2b disease in 13 patients, who subsequently underwent lung resection with very poor survival (overall median survival was 5.4 months). In retrospect, our pN2 might have been higher if a systematic nodal dissection was applied. We would also like to highlight the fact that 13 of the patients underwent pneumonectomy, which is known to be associated with a high rate of delayed cardio-respiratory complications. Therefore, our mortality rates could have been lower if a different end point had been applied other than death from any cause.

Conclusion

Our results have shown no significant difference in survival between those patients with negative preoperative PET-CT who are found to have pN2 disease after resection and those who are single-zone cN2 positive before resection. Therefore, the answer to the paradox is that if the surgeon would proceed to resection for intraoperatively detected N2 disease, then he is justified to proceed to resection for preoperatively identified single-zone N2a disease. However, confirmatory mediastinoscopy should be routinely performed in this treatment schedule. Also surgery should be part of a multimodality treatment with adjuvant chemotherapy as has been demonstrated in our study.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

Dr A. Turna *(Istanbul, Turkey)*: You obviously operated on some patients with N2 disease disclosed by mediastinoscopy. What was your strategy for these patients, because we all know that multiple zone N2 disease patients, or preoperatively proven N2 disease patients, do not survive beyond five years. So you reached those conclusions again? In our institution, we concluded that the five-year survival of multiple N2 disease patients had no survival beyond five years. So what will be your strategy after this study?

Dr Tsitsias: Our strategy initially included performing a preoperative mediastinoscopy for CT PET positive N2 patients, especially for patients that were multizone positive on the preoperative PET. Of course, in the patients that were found negative, we proceeded to curative resections. As I mentioned, there were two patients that were proven to be single zone preoperatively on mediastinoscopy, and, again, we proceeded to resection. And this also varied depending on the oncology team that supported us in the different multidisciplinary meetings that we attend that supported proceeding to resection without preoperative mediastinoscopy when single zone disease was suspected on the preoperative CT PET. After the results of this study, we think that if the suspicion from the CT PET preoperatively is for a single zone involvement, we should proceed without mediastinoscopy.

Dr T. Sioris *(Tampere, Finland)*: Do I understand correctly that the patients for the study were all operable N2, meaning intracapsular N2, and then you later on went on to see how many were PET positive and PET negative? So you are actually talking about intracapsular N2 disease, not such that it is growing out of the lymph node and thus unresectable? So this is a study on minimal N2 disease, actually.

Dr Tsitsias: This is my understanding. I don't know if Mr. Waller has anything to add.

Dr Sioris: So then it would make sense that if you have intracapsular N2 and single station, if it can be operated radically, then it is a good idea to take it out whether or not you see it pre or post?

Dr Tsitsias: Yes, absolutely, preoperatively.

Dr Sioris: But not if it grows out of the capsule, if it is invasive N2 and not minimal N2?

Dr. Tsitsias: This is not something that we particularly looked at in this paper and my expertize cannot answer this question. I will let Mr. Waller answer.

Mr D. Waller *(Leicester, UK)*: Just to answer that question for Thomas, yes, of course, these were all resectable N2 as opposed to bulky or extracapsular N2. So they were assessed preoperatively on CT and CT PET and were deemed to be resectable in that the nodes could be removed. So it did exclude bulky N2 or extracapsular invasion.

Dr I. Opitz *(Zürich, Switzerland)*: Just a quick final question. What were the T stages of the tumour? You just provided the tumour size in your presentation. Given the fact that you had quite a number of extended resections, I guess that were quite a number with higher stages of disease.

Dr Tsitsias: We didn't have that many higher stage regarding the size of the tumour, but on analysis of the data, the size of the tumour was also assessed and it wasn't a prognostic factor.

Dr R. Rami-Porta *(Terrassa, Spain)*: I think this is the first attempt that I have listened to trying to validate in the clinical staging setting the pathological staging from where the nodal zones were derived. The survival graphs that you showed derived from pathological staging. Those were patients who underwent resection and a very thorough intraoperative lymph node evaluation. This is very well described in the paper.

I think that if you want to assess preoperatively a single N2 zone in order to operate up front, if you do mediastinoscopy, you have to go beyond the minimal requirements that are stated by the ESTS guidelines, first, and, second, if you rely only on PET scan, you will probably miss nodes that are not PET avid. You can find other N2 nodes besides the one that uptakes, and you may miss N3 disease. So I would say that if you are planning to resect presumably clinical single zone N2, your preoperative evaluation must have the highest thoroughness that you can provide in your institution.

Dr Tsitsias: I totally agree that thoroughness of the mediastinoscopy is something that has to be taken into great consideration in this case.