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Surgical assessment of malignant pleural mesothelioma: have we reached a critical stage?☆

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Abstract

Objective: The International Mesothelioma Interest Group (IMIG) classification is the most widely used staging system but is based on post-resectional parameters. We aimed to test the association between clinical and pathological staging and to identify possible discrepancies. **Methods:** We identified 164 consecutive patients (144 males and 20 females, with mean age 58 years) who underwent radical surgery (114 extrapleural pneumonectomy; 50 radical pleurectomy/decortication) for malignant pleural mesothelioma (MPM). The patients were clinically staged with CT ± MRI (CT, computed tomography; MRI, magnetic resonance imaging). **Results:** Clinical T (cT) stage proved to be the same as pathological T (pT) stage in 44%; understaged in 46% and overstaged in 10%. Clinical N (cN) stage proved to be the same as pathological N (pN) stage in 56%; understaged in 31% and overstaged in 13%. Disease-free interval (DFI) was associated with cT stage (median DFI 29 months, SE 13, 95% CI 3—54 months for cT1; median 5, SE 3, 95% CI 3—6 months for cT4, $p = 0.02$) but not clinical N stage (median DFI 12 months, SE 1, 95% CI 9—15 months for cN0; median DFI 11 months, SE 0.3, 95% CI 10—12 months for cN2, $p = 0.5$) and was associated with both pT (median DFI 31 months, SE 17, 95% CI 0—64 months for pT1; median DFI 8 months, SE1, 95% CI 6—11 months for pT4, $p = 0.03$) and pN stage (median DFI 14 months, SE 3, 95% CI 9—20 months for pN0; median DFI 10 months, SE 1, 95% CI 8—13 months for pN2, $p = 0.02$). Overall survival was associated with cT stage (median survival 25 months, SE 3, 95% CI 20—30 months for cT1; median survival 11 months, SE 3, 95% CI 10—11 months for cT4, $p = 0.01$) but not cN stage (median survival 15 months, SE 2, 95% CI 11—19 months for cN0; median survival 15 months, SE 2, 95% CI 12—19 months for cN2, $p = 0.49$) and pN stage (median survival 22 months, SE 3, 95% CI 19—27 months for pN0; median survival 14 months, SE 1, 95% CI 12—17 months for pN2, $p = 0.01$) but not pT stage (median survival 27 months, SE 4, 95% CI 19—35 months for pT1; median survival 12 months, SE 2, 95% CI 9—15 months for pT4, $p = 0.06$). Pathological IMIG stage was associated with DFI and overall survival; however, preoperative IMIG stage was less useful. **Conclusions:** There are deficiencies in the current staging system for MPM and discrepancies between clinical and pathological systems. Future improvements are needed in clinical descriptors of nodal status and pathological descriptors of T stage. Subsequent IMIG stage grouping also needs revision.

Keywords: Malignant pleural mesothelioma; Surgery; Staging

1. Background and objectives of the study

The most widely used system for clinical and pathological staging for malignant pleural mesothelioma (MPM) is the one proposed by the International Mesothelioma Interest Group (IMIG) in 1995 [1] and subsequently adopted by the Union Internationale Contre le Cancer (UICC) and American Joint Committee on Cancer (AJCC) and published in their staging manuals [2,3].

Previous research conducted in our department has highlighted the discrepancies between clinical and pathological nodal staging [4] and emphasised the importance of accurate staging before radical resection.

Our aim in the present study was to examine the association between clinical and pathological staging in a cohort of patients that underwent radical resection for MPM in the two surgical departments participating in this study and identify possible discrepancies between staging based on imaging and the one derived from post-resectional parameters.

We also aimed to examine whether clinical and pathological stage was associated with incidence of incomplete resection, disease-free interval (DFI), pattern of recurrence and overall survival.

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2. Methods

From a cohort of 207 consecutive patients that underwent radical surgery (extrapleural pneumonectomy or radical pleurectomy decortication) over 9 years, we identified 164 cases with full staging data on file.

Of the 164 patients, 20 were females and 144 males with a mean age of 57.6 (14–75) years. As many as 120 patients (73%) had epithelioid, 39 (23.8%) had biphasic and 5 (3%) had sarcomatoid disease.

All these patients have been staged clinically with computed tomography (CT) of the thorax and abdomen. Magnetic resonance imaging (MRI) was used in selected cases only. Of the 164 patients, 14 (8.5%) were clinical IMIG stage I, 52 (31.7%) stage II, 88 (53.7%) stage III and 10 (6.1%) stage IV.

114 (69.5%) of the patients underwent pleuropneumonectomy (EPP) and 50 (30.5%) radical pleurectomy decortication (radical P/D) with the removal of the diaphragm and pericardium.

Clinical staging data were collected from the CT/MRI reports, and pathological staging data from the histopathological reports on file. Recurrence and survival data were collected from the information stored in the patients' records, the electronic patients' records management system and from telephone communications with the patients' general practitioners. Accurate staging data for both clinical and pathological stages were retrieved for 164 out of 207 patients who underwent radical resections; therefore, only these patients were included in the study.

We tested for possible links between stage and incomplete resection, recurrence and pattern of recurrence (local, distal or both) using the Fisher's exact test.

We tested for possible links between stage and incidence of disease recurrence and then for association between stage and pattern of disease recurrence as to whether advanced T, N or IMIG stage was linked to a specific pattern: local, distal or both local and distal recurrence.

To test for possible associations between stage and time to progression of disease (or DFI), we did not include the patients who died within the first 90 postoperative days. This brought the population tested for DFI to 146 patients.

Survival analysis was performed using the Kaplan–Meier method, and comparison of survival and disease-free period after the resection was tested with the log rank test. The DFI was calculated as the time interval between the radical procedure and the time of the first clinical and radiological evidence of disease progression. Overall survival was calculated as the time between histopathological confirmation of the disease and the time of death or last review of the patient by a clinician.

All statistical analyses were performed using the SPSS software, version 16 (SPSS Inc, Chicago, IL, USA).

3. Results

3.1. Clinical and pathological T, N and IMIG stages

The distribution of clinical and pathological stages is detailed in Table 1.

3.1.1. T stage

In 44% of the patients, pathological T (pT) stage was the same as clinical T (cT) stage. In 10%, pT proved to be earlier than cT: imaging had overstaged the disease. In the remaining 46%, pT proved to be more advanced than cT: disease was clinically understaged.

3.1.2. N stage

In 56% of the cases, pathological N (pN) stage was the same as clinical N (cN). In 13%, pN proved to be earlier than cN. In the remaining 31%, pN proved to be more advanced than cN: disease was clinically understaged.

3.1.3. IMIG grouping

Pathological IMIG stage (pIMIG) was the same as clinical (cIMIG) in 44.5% of the patients and falsely understaging the disease in the same proportion (44.5%). Only in 11% of the cases, clinical staging proved to be pessimistic and overstaged the extent of the disease.

Table 1
Clinical and pathological TNM stage and IMIG grouping, $n = 164$.

	Clinical staging, n =	Clinical staging, %	Pathological staging, n =	Pathological staging, %	c = p	c <p	c >p
T							
1	17	10.4	13	7.9			
2	67	40.9	32	19.5	$n = 72$	$n = 76$	$n = 16$
3	71	43.3	74	45.1	43.9%	46.3%	9.8%
4	9	5.5	45	27.4			
N							
0	109	66.5	78	47.6			
1	5	3	11	6.7	$n = 92$	$n = 51$	$n = 21$
2	48	29.3	75	45.7	56.1%	31.1%	12.8%
3	2	1.2	0	0			
IMIG							
I	14	8.5	11	6.7			
II	52	31.7	18	11	$n = 73$	$n = 73$	$n = 18$
III	88	53.7	90	54.9	44.5%	44.5%	11%
IV	10	6.1	45	27.4			

c = p: pathological stage same as clinical stage; c <p: pathological stage more advanced than clinical stage; and c >p: pathological stage earlier than clinical stage.

3.2. Association between stage and positive resection margins

Both cT and pT were associated with incidence of positive resection margins: R1/2 incidence increased from 17.6% in cT1 to 49.3% in cT2, 63.4% in cT3 and to 66.7% in cT4 ($p = 0.007$). There was a similar increase in the R1/2 incidence for pT from 15.4% in pT1 to 43.8% in pT2, 55.4% in pT3 to 66.7% ($p = 0.005$).

Both cN and pN failed to demonstrate an association with positive resection margins $p = 0.75$ and $p = 0.61$, respectively. cIMIG also did not correlate with R1/2 ($p = 0.08$) but pIMIG did ($p = 0.004$).

3.3. Association between stage and disease recurrence

Neither clinical nor pathological T, N or IMIG stage demonstrated any association between incidence or pattern of recurrence with p values above 0.3 for all tests.

3.4. Association between stage and DFI

Advanced cT stage was associated with decreased DFI: from a median of 29 months for cT1 down to 5 months for cT4 ($p = 0.02$). cN stage did not associate well ($p = 0.5$) and clinical IMIG approached but did not achieve statistical significance: median DFI was 29 months for cIMIG I dropping to 8 months for cIMIG IV ($p = 0.08$; Table 2, Fig. 1).

All advanced pathological stages were associated with decreased DFI: from median of 31 months for pT1 to 8 months for pT4 ($p = 0.03$), 14 months for pN0 to 10 months for pN2 ($p = 0.02$) and from 31 months for pIMIG I down to 8 months for pIMIG IV ($p = 0.03$; Table 2, Fig. 2).

3.5. Association between stage and overall survival

Advanced cT stage was associated with decreased survival from a median of 25 months for cT1 down to 11 months for cT4 ($p = 0.01$; Table 2). However, cN was not similarly associated ($p = 0.5$). Clinical IMIG narrowly achieved statistical significance: median survival 25 months for cIMIG I, 18 for cIMIG II, 15 for III and 11 for IV ($p = 0.05$; Table 2, Fig. 3).

Although survival decreased from a median of 27 months for pT1 to 18 months for pT2, 15 months for pT3 and to 12 months for pT4, the log rank test did not demonstrate any significant difference between the pT stages ($p = 0.06$; Table 2).

Both pN and IMIG fared better with median survival decreasing from 22 months for pN0 to 14 months for pN2 ($p = 0.01$) and from 27 months for pIMIG I to 12 months for pIMIG IV ($p = 0.03$; Table 2, Fig. 4).

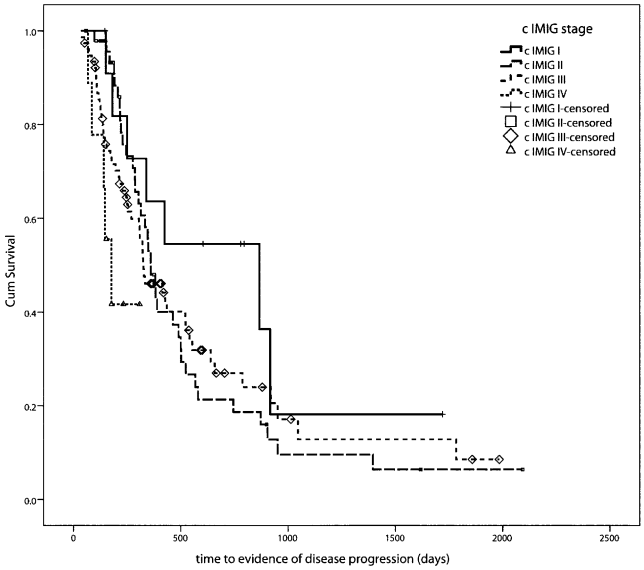

Fig. 1. Association between clinical IMIG stage and disease-free interval.

Table 2
Association between stage, disease-free interval and overall survival from diagnosis of disease (Kaplan—Meier estimates).

	Clinical staging								Pathological staging							
	Median DFI (months) $n = 146$	SE	95% CI	Log rank $p =$	Median survival (months) $n = 164$	SE	95% CI	Log rank $p =$	Median DFI (months) $n = 146$	SE	95% CI	Log rank $p =$	Median survival (months) $n = 164$	SE	95% CI	Log rank $p =$
T																
1	29	13	3—54		25	3	20—30		31	17	0—64		27	4	19—35	
2	13	1	11—14	0.02	18	2	13—22	0.01	12	4	5—19	0.03	18	4	10—25	0.06
3	11	1	8—14		13	2	9—17		11	0.4	10—12		15	2	11—19	
4	5	1	3—6		11	3	10—11		8	1	6—11		12	2	9—15	
N																
0	12	1	9—15		15	2	11—19		14	3	9—20		22	3	17—27	
1	26	0	—	0.5	19	3	12—25	0.5	16	1	14—18	0.02	18	7	5—32	0.01
2	11	0.3	10—12		15	2	12—19		10	1	8—13		14	1	12—17	
3	5	—	—		12	—	—		—	—	—		—	—	—	
IMIG																
I	29	12	6—51		25	4	18—32		31	16	0—62		27	5	17—37	
II	12	1	11—13	0.08	18	3	12—23	0.05	17	4	9—25	0.03	23	4	15—30	0.03
III	11	2	7—15		15	1	12—18		11	1	9—12		15	2	12—18	
IV	8	1	3—8		11	0.6	9—12		8	1	6—11		12	2	9—15	

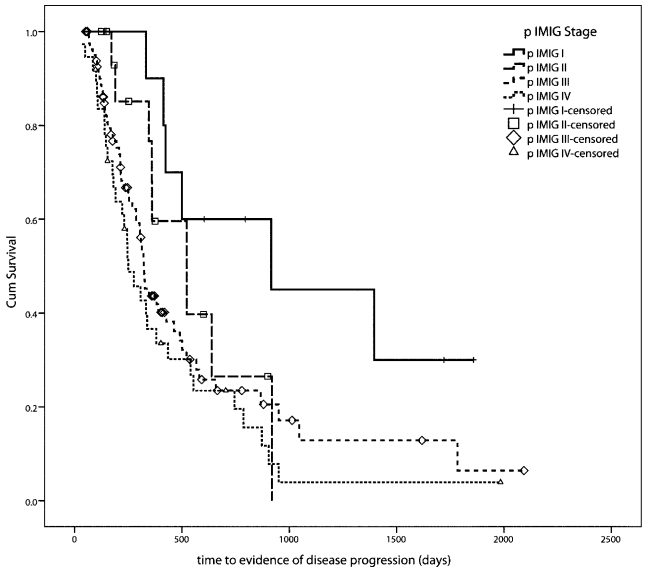

Fig. 2. Association between pathological IMIG stage and disease-free interval.

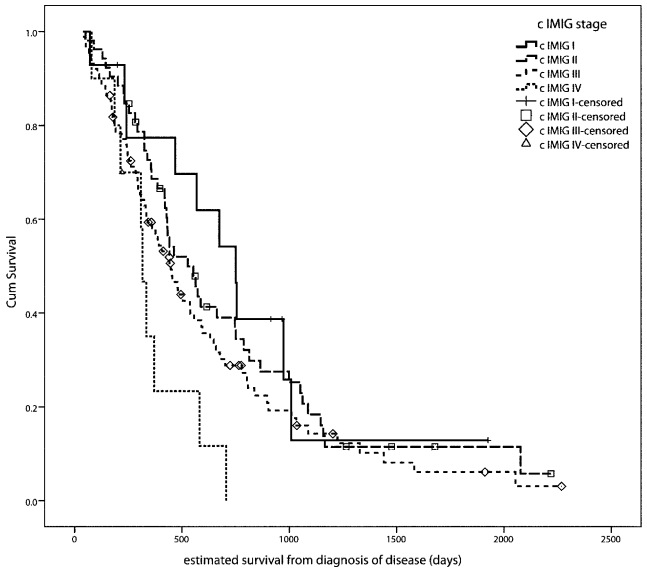

Fig. 3. Association between clinical IMIG stage and survival.

4. Discussion

4.1. Background

The first staging system for diffuse MPM was proposed by Butchart et al. in 1976 [5]. It was based on post-resectional parameters from a group of 29 patients that underwent pleuropneumonectomy for diffuse MPM between 1959 and 1972. In the following 19 years, at least four more staging systems have been proposed by: Mattson in 1982 [6], Chahinian in 1983 [7], Sugarbaker in 1993 [8] and the UICC in 1993 [9]. None of these systems were completely validated or universally accepted. The increase in incidence and the availability of new therapeutic modalities for MPM by the mid-1990s led to increased pressure for a more accurate staging system that would allow for more accurate

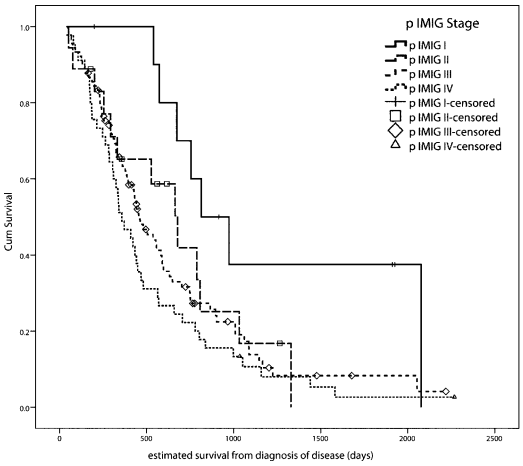

Fig. 4. Association between pathological IMIG stage and survival.

stratification of patients into groups with similar prognosis [1]. The IMIG held a consensus meeting in 1994 and as a result the new International TNM Staging System for MPM was proposed in 1995 [1]. This system used descriptors based on surgical and pathological findings and became subsequently almost universally accepted. What this system was not designed to do was to take into account the reality of contemporary cross-sectional methodology [10]. The resolution of the CT/MRI available in the late 1990s was not adequate to distinguish between some descriptors, for example, visceral from parietal pleural involvement. Moreover, as reported by Heelan et al. in 1999, both CT and MRI failed to diagnose regional nodal disease [11]. Another study published in 2004 by Pilling et al. [4] showed that lymph node size on cross-sectional imaging did not correspond with regional lymph node infiltration and advocated the use of routine invasive mediastinal staging before radical surgery for mesothelioma.

4.2. Rationale for the study

Before we embarked on the retrospective research, we were fully aware that the IMIG staging system was not developed to be used for clinical staging but it could prove to be relevant [1]. The importance of surgical staging and the impact of stage on survival has been emphasised on numerous studies [12,13]; therefore, it becomes obvious that we are in need of a system that will stage the disease as accurately as possible before the operation.

4.3. Findings

The first finding from our study was that clinical stage did not link well with pathological stage: clinical staging underestimated the disease extent in 46.3% of the patients for T stage and 31.1% for N stage, subsequently understaging the IMIG stage in 44.5% of the patients (Table 1). This can be explained by the limitations of imaging: descriptors as visceral or parietal pleura invasion, transmural pericardial or diaphragmatic invasion can be difficult to assess with current imaging modalities. Furthermore, where nodal staging is

concerned, lymph node size does not correlate well with lymph node infiltration [4].

One would expect that the more advanced the T stage, the higher the possibility of leaving malignant cells behind would be. This was the reason that we tested the hypothesis that not only T, but also N and IMIG stage could potentially be associated with microscopically (R1) or macroscopically (R2) infiltrated resection margins.

Although previous research by Mineo et al. did not find an association between advanced T stage and increased incidence of positive resection margins [14], in the present study advanced clinical and pT stage was associated with incomplete resection. The aforementioned researchers commented on their paper that perhaps surgeons were performing a 'less radical' clearance of margins in earlier disease [14] and this was the reason that more advanced T was not associated with incomplete resection.

From the analysis of survival and DFI, the most striking findings are the failure of cN stage to show a relationship with either, as well as the failure of clinical IMIG to associate with DFI and, surprisingly, pT to associate with survival (Table 2).

The pathologist in our group has highlighted various problems that pathologists face when staging the disease, the most important being the involvement of the endothoracic fascia, which is not easily identifiable in the specimen, the invasion of the pericardium and the multifocal invasion of the chest wall: how exactly would we classify the infiltration of the biopsy site(s) or drain(s)? According to the existing classification, it should be classed as T4, but further clarification is required for this descriptor.

Where N disease is concerned, we already know that the size of lymph nodes does not correspond to invasion from malignant cells; [4] therefore, the failures of cN staging in our study do not come as a surprise to us.

It appears that T stage descriptors are more accurate than N or IMIG grouping: only pT failed marginally ($p = 0.06$) to associate with disease survival. On the other hand, cN and pN failed to associate with incidence of R1/2 resections ($p = 0.75$ and 0.6, respectively) and cN failed to associate with DFI and survival as well ($p = 0.5$ and 0.5, respectively).

Subsequently, cIMIG failed to associate with incidence of incomplete resection and DFI and marginally ($p = 0.05$) associated with survival.

4.4. Study limitations

We acknowledge a number of limitations in this study: it is a retrospective study with relatively small numbers, especially in the early stage groups. Data were incomplete for 43 patients (25%) who had to be excluded from the study.

One might argue that there are also other confounding factors influencing DFI and survival, most important of which is trimodality treatment (chemotherapy and radiotherapy as adjuncts to surgery). This study though is not about survival, is about staging. In addition, if we start exploring the effect of adjuvant treatment in stage adjusted survival, we will need to look at the effects of different chemotherapeutic agents, whole hemithorax or wound-only radiotherapy and so on. This would only fragment our study population in tiny subgroups making any attempt to extract meaningful statistical results futile.

4.5. Future directions

Flores et al. [13] reported in 2008 the impact of multiple lymph node station infiltration on survival and recommended changes in the current IMIG system: they suggested that N1 disease should be classified as lower stage and multilevel N2 as higher one.

Edwards et al. [17] reported that the number of positive nodes correlated with survival, although the number of involved stations and their anatomic location did not, and that the classical anatomic location was not as important as the scatter of nodal involvement.

It may be that we need to incorporate new diagnostic modalities in a revised staging system: there are reports that fluorodeoxyglucose positron emission tomography (FDG PET) can predict survival in malignant MPM [15] and that maximum standardised uptake value (SUV max) on PET may be prognostic.

There are reports that total glycolytic volume (TGV), a volume-based measure of total glycolysis, is superior to SUV max and to CT measurements in predicting survival in the patients who receive chemotherapy [18]. This could potentially prove to be of benefit in the clinical staging of mesothelioma.

Alternatively, it may be that we need to look at the information provided by diagnostic modalities that we have been using for more than a decade under a new angle: Pass et al. [16] reported in 1998 that increased preoperative tumour volume is associated with outcome in MPM. Preoperative tumour volume was associated with survival, positive nodes, and T and IMIG stages.

4.6. Conclusions

It appears that there are deficiencies in the current staging system for MPM and discrepancies between clinical and pathological systems. Clinical descriptors of nodal status and pathological descriptors of T stage appear to be less accurate; therefore, future improvements in these parameters are needed. Subsequent IMIG stage grouping also needs revision.

The IASLC Mesothelioma staging project is ongoing and will lead to an evidence-based revision of the TNM staging for mesothelioma within the next 3 years.

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Appendix A. Conference discussion

Dr T. Treasure (*London, United Kingdom*): An analysis will show association between factors and outcomes with their *p* values. But we're more interested as clinicians in the factors which separate groups of patients, as we have in lung cancer, in whom we can give a probability of cure, 90%, 80% or 50%. Using the postoperative pathological findings in a prediction model is, if you like, an oxymoron. The predictor is of no use if it's after the event.

I am not sure that the term 'pleurectomy/decortication' is the best to use. Decortication is a word that comes from empyema surgery; pleurectomy is a word that comes from the management of pneumothorax. Neither apply well to surgery for mesothelioma. There is a growing view, not just mine, of calling it lung-sparing total pleurectomy. The important difference is whether you aim for the total ablation of disease as in EPP, or you shift your emphasis to sparing the lung. Now, once you have shifted your emphasis to sparing the lung, whether you should be taking the pericardium or the diaphragm and so on becomes a debatable point. So rather than arguing about whether the operation you do is the same as what somebody else does, I think it's more important to say what is the intention of treatment: to spare the lung, to reinflate it, and to restore function as well as possible for as long as possible. In my view saying, 'Oh, you're not in our group because you don't patch the diaphragm' misses the point.

So it's really those two points. Don't worry about the analysis because I think you can't answer that today, but can you help us towards a phrase or would you agree to a phrase which shifts the emphasis from total eradication towards lung-sparing? And the other one was recognising that preoperative staging is really all that matters to the clinician because that's the staging on which you advise the patient and plan your operation.

Dr Nakas: I couldn't agree more that the preoperative staging is the most important, because that's what we're going to tell the patient that we cannot cure him or her, but we can offer prolongation of life. We need to get it right, so that we will quote accurate figures. We are not going to operate on patients who might not do well. I think that when I published the paper last year, I used the term 'parenchymal-sparing surgery' and its role in the management of mesothelioma. So the emphasis that we put as a group in Leicester all these years was that radical pleurectomy/decortication, as we called it, or parenchymal-sparing pleurectomy/decortication, or EPP by sparing the lung, to paraphrase it a bit, is an operation that oncologically can be as sound as an EPP because it aims to remove all macroscopic disease. There is a paper in progress now where we're actually comparing the patterns of recurrence and the incidence of incomplete resection. Our findings suggest that with radical pleurectomy/decortication, you can remove all macroscopic disease. My reservation about your comments regarding the removal of the pericardium and the diaphragm is only that if you can't remove all macroscopic disease by any other means, then you should do an EPP. In the diaphragm, sometimes we find out that you can spare quite a lot if you only decorticate the portion which has got most of the disease, but with mesothelioma, the odds are that more people are going to have more disease in the diaphragm and in the pericardium than anywhere else, so that's why we say that most probably on all occasions you will need to remove it. I don't know if anybody else thinks that that's unreasonable. But I agree that we should spare the lung, and that's very important, because then we do only one big operation. Pneumonectomy is a disease in itself. That's not my quote. An American surgeon said this a lot of years ago.

Dr Treasure: On the point of whether or not you can clear all disease, there is a paper I would recommend by Hasani, Alvarez and others [19]. They have done a meticulous prospective analysis of all patients referred to them from a captive population in Western Australia, where there is the highest incidence in the world of mesothelioma. In not a single case were they able to demonstrate R0 resection. In all cases, the pathologists were always able to demonstrate that the disease had crossed the resection margin. So to remove the diaphragm and to remove the pericardium in the hope of achieving R0 is probably illusory. Because it adds so much to an operation, for which the intention has shifted now to quality of life and improved breathing, you have to seriously ask what is the purpose of the surgery.

Dr W. Weder (*Zurich, Switzerland*): I think despite this point, Tom, the topic of this talk is slightly different. The topic of this talk is not what is the best treatment. The topic of this talk is: Is clinical staging and pathological staging in the current staging system adequate?

Dr Treasure: I take your point.

Dr Weder: I think we should focus some of the questions to this very important issue, otherwise the value of this paper, which I think is very important, doesn't get enough credit if we always discuss the same other issues.

So I will stimulate the discussion by two questions in this regard. I think it's not surprising for those who are doing clinical staging to observe that the pathological T stage differs, because by looking at the CT scan, and this is the best that we have, and occasionally we have some information from thoracoscopy, but often we get the referral with a biopsy and we have a CT scan, and at least for us, and even if we add PET or whatever, it's absolutely impossible to decide between T1, T2, and even sometimes T3. So we do it in a random way. We do not take the time as we do in lung cancer. We just say it's T2.

Dr Nakas: It's resectable.

Dr Weder: It's resectable. So T1, T2, and T3 sometimes, but it's often not distinguishable. So this is not a surprise to me. Could you comment on this, on the T stage first?

Dr Nakas: We feel that it is important to see if you have unresectable disease. What we really need to pick are the T4s. The problem arises, I believe, when it comes to the prognostic value of the staging system. I mean for me personally, it's more worrisome if we cannot accurately stage the lymph node invasion without invasive staging. If I can expand on this a bit, there is a paper published by Flores which looks at the role of N1 disease, and the recommendation from this one is that N1 should actually be downstaged to IMIG stage II and not III, because the prognosis of these patients is completely different than the prognosis of the patients with N3 disease. So I agree with you that it wouldn't make a huge difference to me if it's T1 or T2 and that nodal disease is more important in mesothelioma, but because of the decrease in survival across the stages, it's rather significant, and if you reach stage III, IMIG

III as it is now, your survival is not really much different to what survival is without any treatment, and that's why I think that getting the clinical staging more accurately is important.

Dr Weder: So we go to the N stage, and I think this finding is even more important. In many studies, in smaller studies, it has been shown that N2 disease is much worse than N1 disease, and therefore in the guidelines they say as soon as you have an N2 disease, don't touch the patient, and you found no difference in survival. We have exactly the same observation in absolutely the same number of patients, 115 patients, exactly the same, and we never observed a difference in survival between intrapulmonary lymph node metastasis or the so-called N2 lymph node disease. But this is not a surprise. They are adjacent to the tumour. They are either in the lung or the mediastinum, but they are adjacent to the tumour. So we found exactly the same. But, for example, the group in Toronto, Marc de Perrot, they presented in the *Journal of Clinical Oncology* a huge difference in a small patient series. It's difficult for me to interpret these data. How do you interpret that some groups demonstrate a difference, and we, who have a relatively large series, couldn't see it?

Dr Nakas: To start with, this study is not about survival, because, as I mentioned at the beginning, there were nearly 210 patients, but only three-quarters of them actually made it to the study because we had full clinical staging data for them. So what happened to the patients that we excluded, we don't know. It's not like we took a consecutive case series. We published beforehand about the survival of N2 with EPP, and we said that if you do an EPP on patients with N2, they don't do very well, but then we found that if you do a radical decortication, they do well. I wouldn't do an EPP on somebody with N2 disease, but I would do a radical decortication.

Dr E. Pompeo (*Rome, Italy*): I would like a comment from my colleague on the N stage. We have seen that since we routinely perform thoracoscopy in patients with pleural effusion, when we discover early stage mesotheliomas, and we perform talc pleurodesis, we have seen that sometimes mediastinal lymph nodes enlarge postoperatively and they become PET-positive. Do you have some experience with that?

Dr Nakas: Well, we don't do PET on any of the patients as part of the routine preoperative staging. I mentioned a paper that was published by our department in 2004 where the size of the lymph nodes did not correlate with the pathologic infiltration on mediastinoscopy, and that was the paper that made the case for routine cervical staging mediastinoscopy before you do EPP on somebody. There's another issue with the lymph nodes also. There are papers coming out that suggest that it's not only the number of lymph nodes but it is the scatter of the spread to the lymph node stations that has a prognostic value in patients with mesothelioma. As far as PET is concerned, I'm not quite sure about PET and the role in nodal staging. There's at least one paper that says that PET is not very good in assessing locoregional disease, that it's only good in assessing distant disease, but there's also another paper from the Memorial Sloan-Kettering group which says that PET has prognostic value on the basis of the SUV. So that changes things a bit, and maybe toward the new staging, we're going to move in that direction.

Dr Weder: But the point you made that talc pleurodesis strongly influenced the PET outcome is true. We have investigated this and found many hot-spots which were false-positive due to mast cells which were active in reacting to the talc.