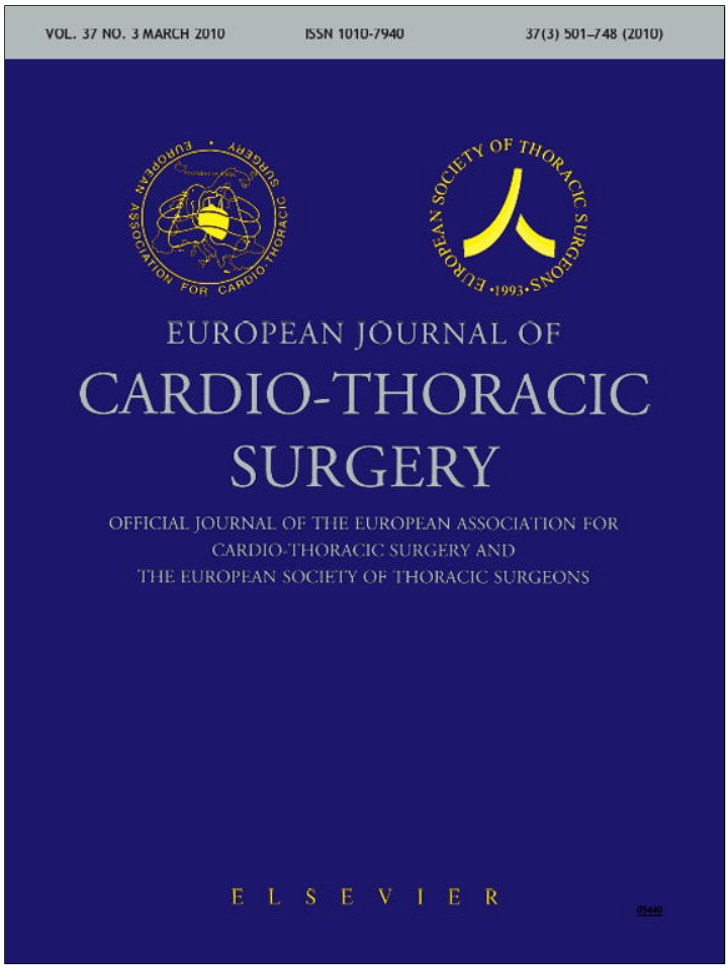

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Quality study of a lung cancer committee: study of agreement between preoperative and pathological staging

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Abstract

Objective: Accurate preoperative staging is essential to provide the best treatment for lung cancer. The objective of the present study was to determine agreement between preoperative and surgical—pathological staging and to analyse the impact of any disparity on treatment. **Methods:** This is a descriptive study of a series of 176 lung cancer cases treated by surgery between 2005 and 2007. Preoperative staging was based on clinical information and computed tomography (CT), positron emission tomography (PET), PET-CT, bronchoscopy and mediastinoscopy. In all cases, surgical—pathological staging was based on the analysis of surgical samples and the findings during surgery. Both preoperative and pathological stage determination were based on the TNM (tumour, node, metastasis) classification established in 1997. Concordance was measured by calculating agreement rates and the kappa value. **Results:** Preoperative and surgical—pathological staging agreed in 102 cases, an agreement rate of 58% and kappa value of 0.54 (95% confidence interval (CI) 0.44—0.63). The highest kappa value (0.68, 95% CI 0.53—0.82) was obtained in stage IA patients. Patients who underwent PET or PET-CT had a better kappa index (0.56, 95% CI 0.45—0.67, vs 0.39, 95% CI 0.21—0.56). Surgical—pathological staging validated surgery in 145 cases (82%), while 21 (12%) were revised to stage IIIA N2 and 10 (6%) to non-surgical stages. **Conclusions:** Global agreement between preoperative and surgical—pathological staging was moderate. The best agreement was found in stages IV and IA.

Keywords: Bronchogenic carcinoma; Neoplasm staging; Preoperative staging; Surgical—pathological staging; Surgery

1. Introduction

Accurate preoperative staging in bronchogenic carcinoma is essential in determining the true extent of disease; moreover, it is crucial if we are to provide patients with optimal treatment and a realistic prognosis. It is therefore imperative that preoperative staging coincide closely with pathological staging, which uses information obtained during surgery to provide the most accurate picture of disease extension. Preoperative and surgical—pathological staging are currently based on the revised tumour-node-metastasis (TNM) classification system established by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), which has been in effect since 1997 [1], although revised criteria have been proposed for 2009 [2]. According to the published studies, agreement rates range from 35% to 50% [3].

Preoperative staging has improved markedly in recent years with the emergence of new tools such as positron emission tomography (PET), used alone or in with computed tomography (PET-CT), virtual bronchoscopy, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-guided fine-needle aspiration of the upper digestive tract (EUS-FNA).

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The aim of the present study was to determine the degree of agreement between preoperative and surgical–pathological staging in bronchogenic carcinoma and to analyse the consequences of diagnostic connection with the surgical treatment carried out. This is not a study to assess, compare or validate tools like PET, CT, mediastinoscopy or EBUS; furthermore, this study does not expect to validate predictors of the descriptors T, N or M.

This is only a quality study of the staging carried out by a hospital lung cancer board (Lung Functional Unit) and the impact of these decisions in the surgical treatment performed.

2. Material and methods

2.1. Sample

This is a descriptive study of 176 patients diagnosed with lung cancer and treated by surgery with curative intent at our hospital between July 2005 and August 2007. Of the 176 cases, 173 had no prior history of lung cancer while three were second lung tumours (two of which were metachronous and one synchronous).

2.2. Inclusion and exclusion criteria

The initial sample included 190 patients who underwent surgery with curative intent for lung cancer. Prior to surgery, all patients presented a lung nodule suggestive of malignancy or a histologically confirmed neoplasm. Exclusion criteria were as follows: inability to determine one of the TNM descriptors during preoperative or pathologic staging (five cases); complete pathological response after neo-adjuvant treatment (two cases); exploratory thoracotomy (six cases), and stage 0 (one case). During the inclusion period, six additional patients underwent surgery due to a lung tumour recurrence while one patient had surgery for lung metastasis; none of these cases were included in the study.

All 176 patients in our series underwent both preoperative and pathological staging according to the guidelines published in the 6th edition of the TNM classification of malignant tumours, accepted by the UICC and AJCC for lung cancer and in effect since 1997 [1]. In the present study, preoperative staging was performed prior to surgery with curative intent under the supervision of the lung tumour board at our hospital. The tumour committee consists of a multidisciplinary team with specialists in respiratory medicine, radiodiagnostics, nuclear medicine, thoracic surgery, pathology, medical oncology and radiation oncology. Staging was performed by evaluating data from patient medical records and physical examination, bronchoscopy, chest radiograph, contrast-enhanced CT of the chest and upper abdomen, PET in two cases (1%), PET-CT in 135 cases (77%), mediastinoscopy in seven cases (4%) and brain magnetic resonance imaging (MRI) in cases with adenocarcinoma and/or clinical suspicion of advanced stage. Bone scintigraphy was not performed because PET scans are reported to be better than scintigraphy at detecting bone metastasis [4].

To determine whether the primary tumour (T) had invaded the mediastinum, we used the following criteria for no invasion: less than 3 cm of tumour in contact with the mediastinum, presence of a fatty layer between the tumour and the mediastinum and less than 90° of circumferential contact with the aorta [5]. Cytological samples were obtained by bronchoscopic aspiration. Whenever possible, biopsy of the primary tumour was performed by bronchoscopy and/or CT-guided fine-needle aspiration (FNA) to obtain histological diagnosis prior to surgery.

For lymph node staging (N), all patients with a PET or PET-CT scan without evidence of thoracic or supraclavicular nodal uptake were considered cN0 as were patients with nodal uptake (after visual and semi-quantitative analysis and determination of the maximum standard uptake value (SUVmax)) of the radiolabelled glucose analogue fluorodeoxyglucose (FDG) at the mediastinal level but with a negative biopsy on mediastinoscopy. Evidence of uptake at the hilar level on the PET or PET-CT scan was considered sufficient for cN1 (hilar lymph node involvement) classification. Patients with positive mediastinal nodes on biopsy were considered cN2, although in certain cases we elected to perform surgery despite nodal involvement, for these cases, uptake identified by PET or PET-CT was deemed sufficient for cN2 classification.

To confirm the presence of neoplastic disease, all patients with evidence of mediastinal node uptake on PET or PET-CT underwent mediastinoscopy. If no evidence of disease was found on pathological examination of the resected samples, the patient was considered eligible for surgery, provided that assessment of the T and M descriptors supported this option. However, patients with confirmed nodal involvement were prescribed neo-adjuvant chemotherapy (with or without radiotherapy), after which restaging was performed. In cases without PET or PET-CT scan, nodal involvement detected by CT scan was considered pathological if the smallest diameter was greater than 1 cm in all nodal stations, except for the subcarinal level, where the minimum was 1.5 cm.

PET or PET-CT scans were used to assess distant metastasis (descriptor M). If FDG uptake suggestive of malignancy was detected in any region of the body, a comprehensive physical examination—including additional imaging tests and extraction of histological material (generally with fine-needle aspiration)—was performed. Other tests to rule out distant metastasis were performed in certain cases. In this study, all cases included with metastasis underwent resection of the metastatic tumour prior to thoracic surgery.

Patients at preoperative stages I, II and IIIA with hilar node involvement were deemed surgical candidates. Under certain conditions, other patients were also accepted for surgery: stage IIIA patients with mediastinal node involvement (major haemoptysis or involvement of a single station on PET or PET-CT with reduced metabolic activity of the affected nodes after neo-adjuvant treatment); stage IIIB cases with a diseased satellite node in the same lobe or vertebral involvement without mediastinal node involvement; stage IV patients with a single resectable brain metastasis; and patients with a single resectable suprarenal metastasis.

The 176 cases in our study underwent thoracotomy, lung resection and hilar and mediastinal lymphadenectomy. The lymphadenectomy was more than sampling [6,7]; all lymph nodes that were seen during surgery were removed. At least, lymph node stations must be explored and the lymph node

removed at the anatomic level of the hilum and mediastinum (topographic) that correspond to the specimen (the lobe with the tumour) or lung section to be extirpated; at least three hilar lymph nodes and three mediastinal lymph node stations from these levels should be evaluated pathologically.

Fourteen patients (8%) received chemotherapy prior to surgery.

To assess the resected samples for pathology, all lymph nodes were individualised, fixed in 10% formaldehyde and completely embedded in paraffin. The paraffin blocks were cut into numerous 3-μm sections (from two to eight sections per block) and then subjected to deparaffination and rehydration followed by conventional haematoxylin and eosin staining. Histological evaluation was performed by a single observer. Pathological staging, which followed the same TNM classification system used for preoperative staging, took into consideration information gathered during surgery.

2.3. Data collection

A rigorous protocol which included the following information: administrative data, demographic data, toxic habits, co-morbidities, additional tests performed, treatments prior to surgery, preoperative staging, surgery performed, pathological staging, histology and tumour location was developed for patient data collection.

2.4. Statistical analysis

Statistical analysis included descriptive statistics and agreement analysis. To compare the results of preoperative and pathological staging, the kappa index and the agreement rate (the number of cases in which preoperative and pathological staging coincided divided by the number of cases that underwent preoperative staging) were calculated. We have calculated global kappa and κ individual kappas for each category, named weighted kappa by Cohen [8].

According to published criteria, a kappa value less than 0 implies poor agreement; 0–0.2 indicates slight agreement; 0.21–0.4, fair; 0.41–0.6, moderate; 0.61–0.8, substantial and greater than 0.8 almost perfect agreement [9]. Statistical analysis was performed with SPSS® 12.0 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA). All patients signed the informed consent form and our institutional ethics committee on human research approved the study.

3. Results

Descriptive analysis of the population revealed 158 men (90%) and 18 women (10%), with a mean age of 62 years and a median age of 63 (range, 40–81 years) and a standard deviation of ±9.4 years. Of these 176 patients, 89% were current or previous smokers and 1% were passive smokers. In addition, 47% had a prior history of respiratory disease and 46% a history of cardiocirculatory problems. Sixteen percent of the sample had a prior history of cancer. The remaining characteristics are described in Table 1. All patients underwent both preoperative and pathological staging (Table 2).

Table 1
Patient characteristics.

		n[a]	%[b]
Histology	Adenocarcinoma	66	38
	Squamous cell carcinoma	58	33
	Bronchioloalveolar adenocarcinoma	17	10
	Large-cell carcinoma	16	9
	Small-cell carcinoma	4	2
	Miscellaneous	15	8
Tumour location	Upper left lobe	56	32
	Upper right lobe	53	30
	Lower left lobe	36	21
	Lower right lobe	25	14
	Main and intermediate bronchi	4	2
	Middle lobe	2	1
Resection performed	Segmentectomy	7	4
	Standard and extended lobectomy	144	82
	Bilobectomy	7	4
	Standard and expanded pneumonectomy	18	10

[a] *n*, number of patients.
[b] %, percentage of patients.

Stage IB was the most common preoperative stage and stage IA the most common pathological stage. Mean time between preoperative staging and surgery was 21 days, with a median of 20 days (range, 2–66 days).

Preoperative and pathological staging coincided in 102 cases (Table 2) for an overall agreement rate of 58% and kappa value of 0.54, 95% CI 0.44–0.63. The agreement rate and kappa value for each stage are shown in Table 3. Stage IV had the highest agreement (100%), followed by stage IA (75%), although the best kappa index was observed in stage IA (0.68, 95% CI 0.53–0.82).

Preoperative understaging occurred in 53 cases (30%) and overstaging in 21 cases (12%). Of the 53 understaged cases, pathological examination confirmed that 22 (41% of that group) were surgical stages, while 21 (40%) were stage IIIA with mediastinal node involvement and 10 (19%) were stages IIIB or IV. All the overstaged cases were surgical candidates.

Preoperative and pathological staging for the descriptor T (primary tumour) coincided in 127 cases, for an agreement of

Table 2
Distribution by preoperative and pathological staging.

	cTNM[a]							Total	%[d]
	IA	IB	IIA	IIB	IIIA[c]	IIIB	IV		
pTNM[b]									
IA	38	10	0	0	0	0	0	48	27
IB	4	33	0	4	2	0	0	43	25
IIA	1	0	1	1	1	0	0	4	2
IIB	1	15	0	18	1	2	0	37	21
IIIA	5	8	1	8	6	0	0	28	16
IIIB	0	0	0	1	2	1	0	4	2
IV	2	2	0	1	1	1	5	12	7
Total	51	68	2	33	13	4	5	176	100
%[d]	29	39	1	19	7	2	3	100	

[a] cTNM, preoperative staging.
[b] pTNM, surgical–pathological staging.
[c] The 13 cases at preoperative stage IIIA include 3 patients with hilar node involvement and 10 with diseased mediastinal nodes. The 28 cases at pathological stage IIIA include 2 with affected hilar nodes and 26 with mediastinal node involvement.
[d] Percentage of cases.

Table 3
Agreement by stage.

Stage	Agreement rate (%)	Kappa value	95% confidence intervals
IA	75	0.68	0.53–0.82
IB	49	0.42	0.28–0.56
IIA	50	0.32	0.18–0.46
IIB	55	0.39	0.25–0.54
IIIA	46	0.21	0.08–0.34
IIIB	25	0.23	0.09–0.38
IV	100	0.57	0.44–0.70

72% and a kappa value of 0.61 (95% CI 0.50–0.71). For the descriptor N (nodal involvement) agreement between preoperative and pathological staging was confirmed in 123 cases, an agreement of 69% and kappa index of 0.34 (95% CI 0.23–0.44).

For the group of patients who underwent a PET scan (PET alone or PET-CT), in 137 cases, agreement was 57% with a kappa value of 0.56 (95% CI 0.45–0.67). In contrast, agreement for those who did not undergo PET (39 cases) was 62%, with a kappa value of 0.39 (95% CI 0.21–0.56). Taking CIs into consideration, the differences between these two groups were not significant; $p > 0.05$.

After establishing the histological type of the resected tissue, we assessed agreement between preoperative and pathological staging as a function of tumour histology. Agreement between pre- and postoperative histological type was not assessed. The highest agreement (100%) and kappa values (1) were observed in bronchioloalveolar adenocarcinoma. Large-cell carcinoma had the second highest agreement (75%) and kappa values (0.74, 95% CI 0.42–1). Agreement rates for squamous cell carcinoma and adenocarcinoma were 55% and 47%, respectively, with kappa values of 0.55 (95% CI 0.38–0.72) and 0.42 (95% CI 0.26–0.57).

The lowest kappa value (0.14, 95% CI 0.01–0.26) occurred in the group that included the few patients with small-cell lung cancer. Of these four patients, there were three patients with localised small lung nodule without affected lymph nodes and without metastasis prior to surgery and one patient in whom the histology of small-cell lung cancer was discovered after surgery.

Tumours located in the lower right lobe gave a higher agreement (68%) and the highest kappa value, 0.67 (95% CI 0.41–0.93). The lowest kappa value (0.39, 95% CI 0.21–0.58) was observed in tumours of the lower left lobe. The 162 patients who did not receive neo-adjuvant chemotherapy presented a higher kappa value (0.53, 95% CI 0.43–0.62, vs 0.24, 95% CI 0.04–0.53) than those who received chemotherapy prior to surgery.

All patients underwent surgery, as described in Section 2.2. The pathology report confirmed that surgery was correctly indicated in 91 stage I cases, 41 stage II cases and two stage IIIA cases with nodal involvement at the hilum; this in addition to the selected cases at non-surgical stages that were accepted for surgery and confirmed the stage pathologically: five at stage IIIA with mediastinal lymph node involvement, one at stage IIIB and five at stage IV. In other words, 145 cases (82%) correctly underwent surgery according to their final pathological stage. Of the remaining 31 cases, 21 were pathological stage IIIA with diseased mediastinal nodes (12% of all cases) and 10 were stage IIIB or IV (6% of the total) (Fig. 1).

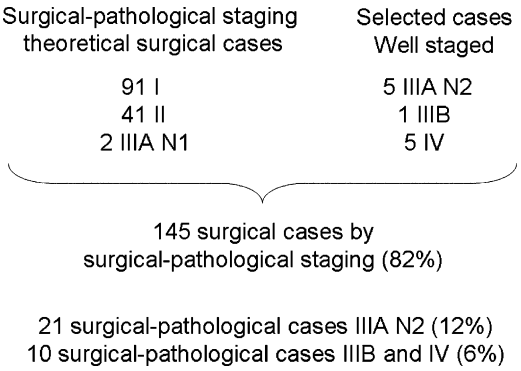

Fig. 1. Distribution of cases by pathological stage and clinical impact.

4. Discussion

In lung cancer, a preoperative staging that approximates the real anatomical extent of disease allows, *a priori*, each patient to receive optimal treatment. Moreover, with proper staging, the prognosis is realistic. Pathological staging, which includes information gathered during surgery, is the current gold standard in determining disease extension and is one of the main prognostic factors. As a result, obtaining good agreement between preoperative and pathological staging—that is, a high number of cases in which preoperative staging reflects reality—is essential.

The characteristics of the patients included in this study are similar in many ways to those we find in our daily practice in Spain, as evidenced by comparing our sample with the patient data provided by the member hospitals of the Bronchogenic Carcinoma Cooperative Group (GCCB-S) of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) [3]. Our sample is similar to the GCCB-S group in many respects: men account for a large percentage of patients in both groups, the mean age (62 years vs 64 years in the GCCB-S) is similar, as is the percentage of current or past smokers (89% vs 87%), and both groups have high rates of respiratory or cardiocirculatory co-morbidities. In addition, distribution among early and late stages is similar in both series, with stage IB being the most common group on preoperative staging in both series. However, differences can be found in histological type—adenocarcinoma was the most common cancer in our study—and in the distribution of lung resections, with a lower percentage of pneumonectomies and more lobectomies in our series [3].

A review of the literature shows that overall agreement between preoperative and pathological staging is low, with reported rates ranging from 22% to 47% [3,10–13] and a kappa value of approximately 0.25 [3]. However, most of these studies did not use a PET scan or PET-CT fusion for preoperative staging. A PET or PET-CT was performed on most patients in our series, mostly as a consequence of the increasingly routine use of such scans at our hospital. The overall agreement (58%) and kappa index (0.54, 95% CI 0.44–0.63)—both of which indicate moderate agreement—observed in our study are better than the figures reported

in other studies. While it is true that agreement was slightly higher in those group patients who did not undergo PET than in those who did, results of the derived kappa index show better agreement in the PET group (0.56, 95% CI 0.45–0.67, vs 0.39, 95% CI 0.21–0.56), although this difference was not significant. This study was not designed to compare PET or PET-CT versus no PET with regard to agreement between preoperative and surgical–pathological staging.

Although PET can be used to assess nodal stations throughout the body, fusion with CT makes more precise determination of the anatomical location. This is possible because fusion scans provide both morphological and metabolic information while CT alone is exclusively morphologic. In addition, with PET-CT, it is possible to identify disease in locations that were not initially suspected of involvement, especially nodal groups. Previously, our group carried out a preliminary study of 68 patients evaluated by PET-CT fusion and we found a high specificity (94%) and a negative predictive value (97%) in mediastinal staging with no association between SUVmax and mediastinal involvement by either PET-CT or surgery. However, some groups have found SUVmax to be a prognostic factor in lung cancer; with a higher SUVmax associated with a worse survival index [14]. Attempts have also been made to establish a specific SUVmax cut-off point that would indicate a higher probability of malignancy [15].

Considering all this, we can deduce that one factor that allows us to achieve a closer approximation to the real extent of the disease is the routine use of PET-CT for preoperative staging [16]. Although PET-CT is not a substitute for other tests, it can serve as a guide for other exploratory techniques that obtain histological material from the mediastinum and the hilum, such as mediastinoscopy and endobronchial ultrasound and endoscopic ultrasound of the upper digestive tract, serving to increase the yield of these techniques. The aim of such techniques is to serve as a complement to improve preoperative staging.

The highest levels of agreement were found at stage I, especially stage IA, with our results similar to those reported in the literature: there was agreement of approximately 60% for stage I and 75% for stage IA [17,18]; with kappa index of approximately 0.70 for stage IA [19]. On the other hand, agreement in more advanced stages—such as stage III—was worse. Stage IV is a special situation because extirpation of the metastasis prior to thoracic surgery influences agreement.

An analysis of the descriptors T and N show higher levels of agreement for T than for N, a fact previously described in the literature, with agreement rates of approximately 70% for the descriptor T and 50% for N [10]. In terms of the kappa index, the results presented here are better than previously reported series in terms of T and N [3]. A limitation of this type of study is the ethical impossibility of fully examining the pathological expression of metastasis since only those organs with a clinical suspicion of metastasis are examined.

It is worth pointing out that agreement analysis of all variables shows the best agreement in patients who did not receive neo-adjuvant chemotherapy and in those with bronchioloalveolar adenocarcinoma of the lower right lobe. The excellent agreement achieved in the 17 cases of bronchioloalveolar adenocarcinoma is surprising given the considerable reported rate of false negatives on PET scans in such tumours [20]. It would be interesting to see if this agreement is maintained when we have a larger series of patients.

Surgery with curative intent in small-cell lung cancer is a matter of controversy. In this study, the few patients with small-cell lung cancer were selected cases with localised neoplasm or patients in whom the histology of small-cell lung cancer was discovered after surgery.

In cases with no agreement between preoperative and pathological staging, our analysis showed that the tendency was for preoperative understaging, a fact described previously in the literature [3,17]. Notably, about 60% of understaged cases in our series were, in the end, either non-surgical or initially non-surgical, mostly stage IIIA with mediastinal node involvement. When analysing false negatives on PET scans, it is important to keep in mind the poor sensitivity such scans have for detecting nodes smaller than 8 mm, necrosis or cystic components and certain histological types such as bronchioloalveolar adenocarcinoma. All of the overstaged cases were surgical candidates and so staging differences did not affect the therapeutic approach.

Despite the battery of modalities and the use of a variety of different techniques over the years, the information presented here demonstrates that some disease remains undetected. The increasing adoption of virtual bronchoscopy, endobronchial ultrasound and endoscopic ultrasound of the upper digestive tract with FNA as well as tools such as molecular markers should be considered as additional modalities to evaluate the true extent of disease [18,21,22]. Moreover, given the low rate of preoperative overstaging, few surgical candidates are excluded from surgery owing to doubts about resectability.

The most important aspect of the present study is to determine how lack of agreement influences patient treatment [18]. Despite the fact that the level of agreement (58%) in our study was only moderate, 82% of patients received the appropriate treatment. In many cases, stage migration occurred within surgical stages. However, post-surgical evaluation identified 12% of patients in our sample at stage IIIA with mediastinal node involvement who should have received neo-adjuvant treatment followed by subsequent restaging. In addition, 6% of patients should not have undergone surgery at all because they were pathological stage IIIB or IV (Fig. 1).

In terms of possible bias, the inclusion of patients with and without preoperative PET and patients who received neo-adjuvant treatment gave us a heterogeneous group of patients. However, such a diverse sample provides us with a broad view of preoperative and pathological agreement in surgically treated lung cancer.

In conclusion, agreement analysis of preoperative and pathological staging in lung cancer reveals the crude reality: despite our best efforts, preoperative staging is incorrect in approximately half of all patients. Nevertheless, the introduction in recent years of new imaging modalities and techniques has helped—and will continue to help—improve staging. Fortunately, our analysis of the impact of differences between preoperative and pathological staging on patient treatment allows us to make a relatively benign conclusion: surgery is appropriately indicated in most cases and only a

small portion of patients should have received a different treatment, at least in regards to the initial treatment. We believe that efforts aimed at extending and standardising newly emerging techniques should continue, and information that such techniques provide should be added to data collected by current techniques and should also included in staging protocols [23]. Moreover, more research needs to be done to discover new and better ways to assess disease extent and complement the information currently obtained by pathological staging.

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