Original Article

Concordance between clinical and pathological staging in patients with stages I or II non-small cell lung cancer subjected to surgical treatment*

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Abstract

Objective: To compare clinical and pathological staging in patients with non-small cell lung cancer submitted to surgical treatment, as well as to identify the causes of discordance. **Methods:** Data related to patients treated at the Department of Thoracic Surgery of the Pontifical Catholic University of Rio Grande do Sul São Lucas Hospital were analyzed retrospectively. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated for clinical stages IA, IB, and IIB. The kappa index was used to determine the concordance between clinical and pathological staging. **Results:** Of the 92 patients studied, 33.7% were classified as clinical stage IA, 50% as IB, and 16.3% as IIB. The concordance between clinical and pathological staging was 67.5% for stage IA, 54.3% for IB, and 66.6% for IIB. The accuracy of the clinical staging was greater for stage IA, and a kappa of 0.74, in this case, confirmed a substantial association with pathological staging. The difficulty in evaluating nodal metastatic disease is responsible for the low concordance in patients with clinical stage IB. **Conclusions:** The concordance between clinical and pathological staging is low, and patients are frequently understaged (in the present study, only one case was overstaged). Strategies are necessary to improve clinical staging and, consequently, the treatment and prognosis of patients with non-small cell lung cancer.

Keywords: Neoplasm staging; Lung neoplasms/diagnosis; Lung neoplasms/surgery; Prognosis.

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Introduction

Lung cancer is the most common cause of death from malignant neoplasia, in males and females alike. In addition, it accounts for 28% of all cancer deaths, and only breast cancer has a higher incidence. There are approximately 180,000 new cases of pulmonary neoplasia in the United States each year.[1]

The prognosis of patients with pulmonary neoplasia depends on early diagnosis and accurate oncologic staging. The type of treatment used differs according to the time (stage) at which the neoplasia is diagnosed. Therefore, it is important to identify subgroups of patients with the same prognosis and define treatment strategies for each subgroup.

The current staging system for non-small cell lung cancer (NSCLC) is tumor-node-metastasis (TNM) staging,[2] which provides only a definition of the anatomic extent of the neoplasia: size, location, and extent of the primary lesion; presence and location of the locoregional lymph node metastasis; and systemic metastatic disease. This system is recognized as having significant limitations, such as that of not considering clinical aspects (including the general status of the patient, weight loss, functional capacity, and the histologic subtype of the tumor) or the influence of prognostic factors that are primarily biological (such as the mutation in the p53 gene).

From this results a special problem, understaging, which is caused by the limitations in the sensitivity of the various diagnostic methods used in the preoperative staging. The staging obtained after all tests, invasive or not, that are performed prior to pulmonary resection is designated clinical staging (CS). For patients undergoing surgery, CS is confirmed or reviewed according to the operative findings. Pathological staging (PS) is determined by the analysis of the surgical sample, and this result plays an important role in the subsequent therapeutic decisions.

Disparities between CS and PS occur frequently, thus compromising the design of clinical studies and, more importantly, the individual treatment of patients, since inadequate staging can result in losing the benefit of the neoadjuvant therapy and in failing to identify patients with advanced neoplastic disease and for whom surgery is not indicated.

The objective of this study was to determine the concordance between CS and PS, in addition to identifying the causal factors that lead to discordance between them.

Methods

Between January of 2002 and January of 2006, 125 patients, all of whom were diagnosed with NSCLC via fiberoptic bronchoscopy, percutaneous puncture, thoracoscopy, or intraoperative biopsy, underwent surgical treatment in the Department of Thoracic Surgery of the *Pontifícia Universidade Católica do Rio Grande do Sul* (PUCRS, Pontifical Catholic University of Rio Grande do Sul) São Lucas Hospital. Those patients were clinically staged by computed tomography (CT) of the chest and abdomen, CT of the skull (in the presence of neurological symptoms), or bone scintigraphy (in the presence of related symptoms). Cervical mediastinoscopy was the method used to evaluate the paratracheal and subcarinal lymph nodes. The patients with tumors located in the left upper lobe underwent parasternal mediastinotomy for the evaluation of the subaortic and aortopulmonary window stations. Thoracoscopy was used for the investigation of pleural effusion.

All patients underwent thoracotomy with standard resection for NSCLC, according to respiratory function, with systematic lymph node dissection (paratracheal, subcarinal, and hilar lymph nodes on the right side; and subaortic, aortopulmonary window, subcarinal, and hilar lymph nodes on the left side). The postoperative anatomopathological analysis revealed a particular PS, which was then compared to the CS in order to identify where there was discordance.

There were 92 patients with CS I or II, data collection being performed retrospectively. Patients with incomplete CS or PS, those with histology other than NSCLC, those with CS III or IV submitted to surgical treatment, and those submitted to neoadjuvant therapy were excluded. This study was approved by the Ethics in Human Research Committee of the PUCRS São Lucas Hospital.

The data related to the patients were analyzed using Microsoft Office Excel 2003, and the statistical analysis was performed using the R for

Windows software.[3] Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated for CS IA (T1N0M0), CS IB (T2N0M0), and CS IIB (T3N0M0). None of the patients with CS IIB were found to present T2N1M0 preoperative staging. Cohen's kappa index was used to determine the power of concordance between CS and PS in the stages studied.[4]

Results

Of the 92 patients studied, 65 (70.6%) were male and 27 (29.4%) were female. The mean age was 63.2 years (median, 67 years). Table 1 shows that pulmonary lobectomy (76.1%) was the surgical procedure most commonly used, followed by pneumonectomy, conservative segmentectomy, bilobectomy, and wedge resection. The predominant histological type was adenocarcinoma (in 38% of the cases), followed by epidermoid carcinoma (in 33.7%). Most of the neoplasms were located in the left upper lobe in 32.6% of the patients and in the right upper lobe in 27.5% of the patients.

Table 1 - Characteristics of the patients.

	n(%)
Gender	
Male	65 (70.6)
Female	27 (29.4)
Procedures	
Lobectomy	70 (76.1)
Segmentectomy	6 (6.5)
Pneumonectomy	9 (9.8)
Bilobectomy	5 (5.4)
Wedge resection	2 (2.2)
Histology	
Adenocarcinoma	35 (38.0)
Epidermoid carcinoma	31 (33.7)
Adenosquamous carcinoma	9 (9.8)
Bronchial-alveolar carcinoma	3 (3.3)
Large-cell carcinoma	6 (6.5)
Others	8 (8.7)
Site affected	
Right upper lobe	25 (27.2)
Middle lobe	3 (3.3)
Right lower lobe	15 (16.3)
Left upper lobe	30 (32.6)
Left lower lobe	15 (16.3)
More than one lobe	4 (4.3)

With regard to CS, 33.7% of the patients were classified as IA, 50% as IB, and 16.3% as IIB (Table 2). All patients classified as IIB were so classified because tomographic findings led to the suspicion of thoracic wall or parietal pleura invasion, since there were no patients with CS IIB - T2N1M0.

In relation to CS IA, the concordance between CS and PS was 67.5%. There were 4 patients who migrated to PS IB due to visceral pleura invasion, 1 who migrated to IIA due to the presence of a metastatic hilar lymph node, 1 who migrated to IIB due to parietal pleura invasion, 2 who migrated to IIIA due to the presence of metastatic disease in ipsilateral mediastinal lymph node, 1 who migrated to IIIB because there was another lesion in the same lobe, and 1 who migrated to IV due to the presence of a lesion in another lobe. In the group of patients classified as CS IB, in which most of the changes occurred, the concordance was 54.3%, and there were 12 patients who migrated to PS IIB, 9 due to the presence of pathological N1 lymph nodes and the remaining 3 due to previously undetected parietal pleura invasion. However, there were 9 patients who migrated to PS III, 8 to stage IIIA because there was metastasis in N2 ganglia and 1 to IIIB due to the presence of another lesion in the same lobe. In the group of patients classified as CS IIB, the concordance was 66.6%, and there was 1 patient who migrated to PS IB since no parietal pleura invasion was found. Of the remaining patients, 2 migrated to IIIA (neoplasia with costal invasion and presence of a metastatic N1 lymph node), 1 migrated to IIIB, again due to the presence of another lesion in the lobe resected, and 1 migrated to IV, also due to the presence of another lesion, albeit in another lobe (Table 2 and Figure 1).

A classification of CS IA had a sensitivity of 100%, specificity of 85%, positive predictive value of 67%, negative predictive value of 100%, and a quite high accuracy (89%). The power of concordance, calculated using the kappa index, was 0.74.

Sensitivity for stage IB was 98%, with a low specificity of 35%, positive predictive value of 66%, and negative predictive value of 93%. Accuracy was 70%, and the kappa index was 0.33.

Finally, the patients with CS IIB presented low sensitivity (43%) and high specificity (92%).

Table 2 - Concordance between clinical and pathological staging.

Clinical staging	Pathological staging								% of total	Probability CS = PS
	IA	IB	IIA	IIB	IIIA	IIIB	IV	Total		
IA	21	4	1	1	2	1	1	31	33.7	67.54
IB	0	25	0	12	8	1	0	46	50.0	54.34
IIB	0	1	0	10	2	1	1	15	16.3	66.6
Total	21	30	1	23	12	3	2	92	100.0	62.82

CS: clinical staging; and PS: pathological staging.

Positive predictive value was 66%, and negative predictive value was 83%, with an accuracy of 80%. Concordance, using the kappa index, was 0.41 (Figure 2).

Discussion

The PS is the most important factor in the prognostic evaluation of patients with NSCLC submitted to surgical treatment. As some studies have shown, the benefits of the neoadjuvant treatment, especially in relation to the increased survival of patients with stage IIIA, the preoperative identification of this subgroup of patients has acquired greater significance.[5,6]

The importance of the preoperative identification of those patients who, in the PS, proved to belong to stage IV should also be stressed, since those patients did not benefit, at any time, from the surgical procedure they were submitted to.[7] In this sense, studies that determine the concordance between CS and PS are of utmost importance.

However, a clinical pathological comparison is only valid for T and N, since thoracotomy, with the subsequent analysis of the surgical sample, does not typically alter the M factor. In general, what is found is that this concordance deteriorates as T and N increase. Even with an appropriate CS, the rate of exploratory thoracotomy or incomplete resection ultimately ranges from 8 to 10%.[8]

This objective has been given considerable weight, as have and the refinement of CS and PS. However, one group of authors,[9] in a series of 11,668 patients submitted to surgical treatment for NSCLC, found that only 27% had been submitted to cervical mediastinoscopy and that, of this group, only 46% had undergone lymph node biopsy. In addition, only 60% of the patients had been submitted to mediastinal lymph node sampling or dissection during surgery, and this compromised the PS. Most patients received surgical treatment only, and it is important to emphasize that, in stages II, III, and IV, no adjuvant treatment was used in 61, 38, and 37%, respectively. It becomes evident that there is lack of consensus on this point.

In our study, 32.2% of the patients with CS IA were reclassified as being in more advanced stages when the PS was analyzed. It is important to highlight that 6.4% of the patients were reclassified as PS II, and that, despite having undergone the standard treatment for the stage, those patients clearly have a worse prognosis, as has been demonstrated by other researchers.[10] However, 12.9% of the patients were found to be in PS III or IV and, in this context, lost the benefits of the multimodal treatment or had no indication for surgery at any time during treatment. Patients with small (T1) tumors are hardly ever understaged, and, when this occurs, the tumors are usually reclassified as T2 due to undiagnosed visceral pleura invasion in the CS.

With regard to stage IB, the concordance between CS and PS was slightly lower (approximately 54%). In this group, 26% of the patients migrated to PS IIB, the main reason for this being the presence of hilar lymph nodes affected by the disease, whereas 19.5% of the patients migrated to stages in which surgery was not the first therapeutic option. Approximately 43% of the T2 patients were reclassified as being in more advanced stages because they presented lymph node metastasis in N1 or N2 stations. We observe, therefore, a deficiency in the evaluation of nodal metastatic disease during CS using the methods currently available.

The reason why 16.3% of the patients evaluated were classified as CS IIB was the suspicion of thoracic wall or parietal pleura invasion, and the

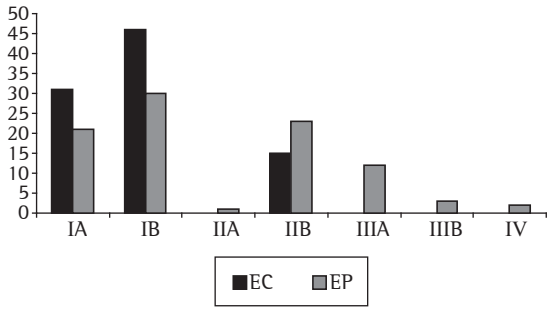

Figure 1 - Results of the comparison between clinical staging (CS) and pathological staging (OS).

concordance between CS and PS was 66.6%, which reflects, in our study, the precision of chest CT in identifying this impairment. Here, the loss of the benefits of the neoadjuvant therapy or even the absence of surgical indication occurred in 26.6% of the cases due to the migration of patients to stages IIIA, IIIB, or IVB. There was only one patient who was downstaged, being reclassified as IB. The kappa index shows that the concordance for CS IA (0.74) was much better than that found for CS IB (0.33). Typically, concordance decreases as CS increases. In our study, the kappa for stage IIB was greater than that for stage IB, probably because the former only evaluates the T factor, since there were no patients presenting CS IIB - T2N1M0.

The relatively low positive predictive values and the relatively high negative predictive values found corroborate the results of other studies and demonstrate that CS typically understages patients, rarely overstaging them. On group of authors,[11] in a study of 2994 patients with pulmonary neoplasia submitted to surgical treatment, found a concordance of 75% for stages IA and IB and of 23.5% for stage IIB, although, in that study, the patients were submitted to cervical mediastinoscopy only in the presence of lymph nodes greater than 1 cm in diameter.

Another group of authors,[12] by means of a retrospective analysis of 180 patients with NSCLC submitted to surgical treatment between 1994 and 2000, in whom cervical mediastinoscopy was performed only in the presence of lymph nodes greater than 1 cm in diameter, found that the concordance between CS and PS was 77% for stage IA, 51.6% for IB, 48.2% for IIB, and 33.3% for IIIA. In the analysis of the mediastinal lymph nodes, 26% of the patients were classified as presenting clinical N0, when, in fact, they were patients with pathological N2. Nevertheless, in the subgroup of patients with pathological N2, 46.3% were found to have been correctly staged, and, of those, only 3 had been submitted to preoperative cervical mediastinoscopy.

Other researchers,[13] by means of a prospective analysis of their patients using chest CT, found that the concordance between CS and PS was 66% for stage I, 82% for stage II, and 69% for stage III.

The benefits of highly accurate staging in defining prognosis should always be emphasized, since the most appropriate therapy for the patient is thereby determined. In this sense, the evaluation of the nodal extent of the NSCLC plays an important role. The removal of all mediastinal lymph nodes allows the extent of the disease to be evaluated with high accuracy, as well as being associated with lower recurrence and better survival, since it provides the appropriate PS.[14]

In the study of nodal metastatic disease, its presence in the hilar groups has been highlighted as another factor with prognostic importance, showing that the group of N1 patients is heterogeneous. The involvement of the hilar groups is associated with a 39% five-year survival, being significantly lower if compared to the involvement of the interlobar, lobar, and segmental groups.[15] Some authors[16] have also demonstrated that the prognosis is better for patients in whom the lobar N1 was resected than for those in whom the hilar N1 was resected.

As currently performed, CS has its problems. In general, the limitations of chest CT and those of cervical mediastinoscopy ultimately contribute to decreasing the accuracy of CS. The concordance between CS and PS in the evaluation of metastatic disease in mediastinal lymph nodes using chest CT is low, with a false positive rate of 44% and a false negative rate of 17%.[17] Cervical mediatinoscopy, despite having advantages over chest CT, since it determines the presence of N1 or N3 and provides histological diagnosis, has its range restricted to the upper lymph node groups and does not fully approach the subcarinal station,[18] as well as having risks and accompanying complications. Therefore, new procedures have helped to optimize CS.

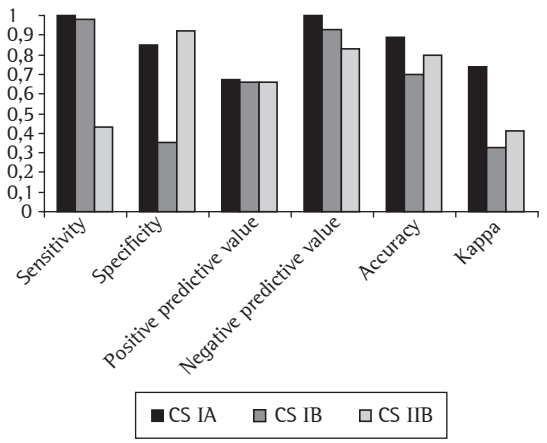

Figure 2 - Statistical evaluation of the clinical staging (CS).

Positron emission tomography (PET) scan, due to its capacity of detecting areas with greater metabolic activity in the human body, in addition to helping differentiate between malignant and benign pulmonary nodules, has also allowed better selection of patients for surgical treatment, improving CS, since it has higher accuracy to evaluate mediastinal lymph nodes than does chest CT, especially in relation to specific lymph node groups such as those of the subaortic, aortopulmonary window, and subcarinal stations.[19] The PET scan does not replace mediastinal lymph node biopsy, and surgical treatment should not be denied to any patient based exclusively on this test. However, its significance lies in selecting areas to be sampled, and this often leads to the identification of lymph node disease that was previously unsuspected. Another testing modality that has participated in this sense is endoscopic endosonography with fine-needle aspiration. Through the esophagus, an echoendoscope is used to access the posterior mediastinum and adjacent lymph nodes (aortopulmonary window, subcarinal, paraesophageal, and pulmonary ligament lymph nodes), sampling these stations. It is a safe method of evaluating the stations cited above, with an accuracy of 97%, avoiding exploratory procedures in approximately 57% of the patients,[20] a percentage that is greater than that achieved through chest CT or PET scan. Usingh this test, one group of researchers[21] found the presence of mediastinal lymph node metastasis in 42% of the patients in whom chest CT findings were normal.

Endoscopic ultrasonography, a procedure that has been introduced in the evaluation of patients with pulmonary neoplasia, has contributed to better CS evaluation. It can visualize the layers of the trachea and bronchi in detail, thereby distinguishing neoplastic invasion from extrinsic compression, as well as making it possible to evaluate the relationship between extraluminal pulmonary lesions and adjacent vessels. It can also facilitate biopsy of mediastinal and hilar lymph nodes as well as of parenchymal lesions.[22]

Thoracoscopy has been used in order to increase CS accuracy. One group of authors,[23] analyzing patients with negative cervical mediastinoscopy results whose T and N were evaluated with the aid of thoracoscopy, through pleural lavage cytology, in addition to biopsy of paraesophageal lymph node groups and of the pulmonary ligament in tumors located in lower lobes (when possible, biopsy of the interlobar or intersegmental groups was performed, and the subcarinal and paratracheal lymph nodes were only sampled if they had a pathological aspect), found that thoracoscopy presented no complications, being considered more accurate than chest CT since it staged 88% of the cases correctly, compared with 42% for CT. Its greatest benefit was staging the factor T correctly in 96% of the cases.

The factor N was staged correctly in 74% of the cases, revealing metastatic disease in paraesophageal and pulmonary ligament lymph nodes in patients with negative cervical mediastinoscopy results. Despite the limitation of thoracoscopy in relation to the evaluation of the aortopulmonary window in patients with large lesions in the left upper lobe, it was found that it can identify malignant pleural effusion that is too small for visualization on chest CT, evaluate thoracic wall invasion, in addition to sampling posterior subcarinal lymph nodes, as well as pulmonary ligament and paraesophageal lymph nodes, which is very important in patients with negative cervical mediastinoscopy results.

Considering the mean difference of 35% between CS and PS, it is very difficult to compare a study that uses CS to one that uses PS. It is always important to remember that each invasive staging method has the potential to better evaluate different lymph node stations. It is essential that

these methods be used in conjunction in order to achieve greater concordance between CS and PS.

For ideal intrathoracic staging, we suggest the following measures:

1) a better definition of tomographic criteria for the presence of pathological N1 lymph nodes and visceral pleura invasion;
2) performance of cervical mediastinoscopy in all patients, even in those whose preoperative tests show no mediastinal adenopathy, as well as systematic evaluation of the paratracheal and subcarinal stations; and
3) performance of thoracoscopy also in all patients for the evaluation of the parietal and visceral pleurae, as well as for the evaluation of the subcarinal lymph nodes, especially when they are not accessible through cervical mediastinoscopy, in addition to the paraesophageal group and the pulmonary ligament.

In the present study, the concordance between CS and PS was substantial for stage IA, decreasing for IB and IIB. The patients were understaged, except in one case, in which the patient was overstaged. The main source of discordance was the difficulty in the preoperative evaluation of metastatic lymph node involvement. It is necessary that tomographic criteria for N1 be defined and that staging using surgical methods be systematically indicated in order to increase CS yield. Therefore, we expect to optimize the treatment and improve the prognosis of patients with NSCLC.

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