The significance of intrapulmonary metastasis in non-small cell lung cancer: upstaging or downstaging? A re-appraisal for the next TNM staging system

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Abstract

Objective: The management of patients with non-small cell lung cancer (NSCLC) with intrapulmonary metastases (PM) is controversial. In TNM classification, PM are designed as T4 when in the same lobe of the primary tumour (PM1) and M1 when in a different lobe(s) (PM2). Some authors have questioned the negative prognostic impact of PM. The present study assessed prevalence, correlation with clinico-pathologic variables and impact on survival of PM, along with a review of the literature. Methods: From January 1993 to December 2006, 2013 NSCLC patients underwent surgical resection at our institution. Of these, 74 presented with PM (39 PM1, 35 PM2). Patients with bronchioloalveolar carcinoma (BAC), carcinoid tumours, contralateral disease and preoperative chemo/radiotherapy were excluded from the analysis. A logistic regression analysis was undertaken to evaluate a relationship between the presence of PM and different clinico-pathologic variables. Survival analysis was undertaken to investigate the prognostic significance of PM. Results: PM represent 3.6% of our patient population of operated NSCLC. Metastases were multiple in 36 cases and single in 38. Thirty-six patients had node-negative disease. Among all the variables for the logistic regression analysis only vascular invasion (OR: 0.45; 95% CI 0.24–0.85, p = 0.01) and N status (OR: 0.6; 95% CI 0.43–0.82, p = 0.001) were significantly correlated with the presence of PM. Median survival rates of PM1, PM2, other T4 and other M1 patients were 25, 23, 15 and 14 months, respectively. A survival advantage was observed in patients with PM as compared to other T4/M1 patients, although the difference was not significant either overall (p = 0.21) or in the N0 disease group (p = 0.12). Conclusions: The presence of PM in NSCLC patients is a rare occurrence. Risk factors for the development of PM are a microscopic vascular invasion and a high nodal status. A survival advantage over other T4/M1 patients is evident from our experience, although not significant. The results of the literature which have been accumulating in the most recent years including ours bend to the conclusion that there is sufficient validated information to consider a downstaging in the presence of intrapulmonary metastases from NSCLC for the seventh edition of the TNM classification.

Keywords: Non-small cell lung cancer; Intrapulmonary metastases; Surgery; TNM staging system

1. Introduction

In non-small cell lung cancer (NSCLC), the presence of intra pulmonary metastases (PM) is not infrequent. In the past, PM have been variously termed as multifocal or satellite nodules, which has created some confusion in the interpretation of the results from different studies.

Additional problems arise because at present there are no definite mechanisms to differentiate on a molecular basis between multiple primary lung carcinomas and intrapulmonary metastases (PM), and in most institutions the distinction is based only on the clinical and histopathologic criteria proposed by Martini and Melamed in 1975 [1].

The most recent revision of the TNM staging system for lung cancer published in 1997 [2] considered intrapulmonary metastases (PM) as evidence of advanced disease: PM within the same lobe of the primary tumour (PM1) was designated as T4 (stage IIIb), and PM in a different lobe (PM2) as M1 (stage IV). A subsequent study by Deslauriers and colleagues [3] found a more favourable prognosis for patients with PM1 compared with those with distant metastases outside the lung. However, the sixth edition of the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) in 2002 basically confirmed the 1997 TNM proposals about PM [4,5].

Since then, a number of studies have been published about the prognostic significance of PM in lung cancer, with some conflicting results. Many studies reported a better prognosis in patients with totally resected PM without evidence of
other distant disease. Most authors therefore suggest that the current staging of patients with PM may not be appropriate, and a downsizing might be proposed in order to maintain the current staging indications to surgery.

The issue of the significance of PM in patients with NSCLC is of utmost importance in view of the forthcoming new edition of the TNM staging system, which is expected in the next few years.

The present study represents our experience about PM in resected patients with lung cancer, along with a review of the literature on this debatable issue.

2. Materials and methods

From January 1993 to December 2006, a total of 2013 patients with primary NSCLC underwent curative resection at our institution. Among these patients, 74 (3.6%) were pathologically diagnosed to have ipsilateral pulmonary metastases (PM) at the time of operation, either in the same lobe (PM1) or in different lobes (PM2).

PM were defined as independent parenchymatous lesions separate from the primary tumour and usually smaller, yet having the same histopathologic features as the primary lesion. PM were differentiated from synchronous multiple primary lung cancers according to the criteria established by Martini and Melamed [1]. Patients with bronchioloalveolar carcinoma (BAC), carcinoid tumours, patients who had been previously treated for lung cancer, patients with contralateral disease, and patients who had received preoperative chemo or radiotherapy were excluded from the analysis.

All cancers were staged according to the 1997 revision of TNM for lung cancer, which was subsequently updated by the UICC and the American Committee on Lung Cancer (AJCC) to form the sixth edition of the TNM staging System in 2002. Investigative criteria for staging included CT scan of the chest and upper abdomen, PET or PET-CT (since 2000), bronchoscopy and invasive mediastinal staging with mediastinoscopy or anterior mediastinotomy in case of CT-enlarged or positive mediastinal lymph nodes at PET-CT. Most patients were pathologically diagnosed to have ipsilateral pulmonary metastases (PM) as an incidental finding at the time of surgery. In a minority of cases, the nodules were identified preoperatively.

All patients received resection of the primary tumour and the associated PM (either by resection of the lobe in case of PM1, or by one or more wedge resections in case of PM2), along with a complete mediastinal lymph node dissection.

Follow-up information on all patients was obtained through clinic follow-up notes, direct patient or family contact, or contact with the patient’s primary care physician.

In order to investigate the relationship between some possible causal (independent) variables and the presence/absence of PM (considered as binary output variable), a logistic regression model was employed, with the assumption that the events were independent and the relationship plausibly log-linear. The \( p \) value was calculated on the Wald statistic and confidence intervals (95% CI) were provided.

Cumulative survival rates were calculated by the Kaplan—Meier method [6], using the date of surgical resection as the starting point and the date of death or the latest follow-up date as the endpoint. The difference in survival rates was determined by log-rank analysis. A \( p \) value less than 0.05 was considered statistically significant. All statistical analysis was undertaken using software packages (STATISTICA, release 7.1, 2005, StatSoft, Italy).

The study was approved by our institutional review board. Individual patient consent was waived.

3. Results

Table 1 shows the demographic and clinico-pathologic characteristics of the patient population. Seventy-four patients operated upon for primary NSCLC were identified to have ipsilateral pulmonary metastases (PM) at operation, of which 39 were in the same lobe (PM1) and 35 in different lobe (PM2). They represent 3.6% of our entire patient population of resected NSCLC patients. Metastases were multiple in 36 cases, and single in 38. Types of operation are summarised in Table 1. A radical resection was performed in 69 cases (93%); causes of non-radical resection were positive pleural effusion in 4 cases, and pleural carcinosis in 1 case. Most patients (63%, 47/74) had adenocarcinoma at final histology. Histopathologic characteristics including tumour size, grading, vascular invasion, perineural invasion and tumour infiltrating lymphocytes (TIL) are illustrated in

<table>
<thead>
<tr>
<th>Stage (disregarding PM)</th>
<th>Total</th>
<th>PM1</th>
<th>PM2</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1N0</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>T2N0</td>
<td>19</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>T3N0</td>
<td>6</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>T1N1</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>T2N1</td>
<td>10</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>T3N1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>T1N2</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>T2N2</td>
<td>17</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>T3N2</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>T4N0 (pleural effusion)</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>T4N2 (pleural effusion)</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of resection</th>
<th>PM1</th>
<th>PM2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Segmental/wedge</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radicality of resection</th>
<th>Total</th>
<th>PM1</th>
<th>PM2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete*</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Positive pleural effusion [4], pleural carcinosis [1].
Table 2. Provisional staging, disregarding the presence of PM, includes 26 stage I, 18 stage II, 25 stage IIIa and 5 stage IIIb (pleural effusion/carcinosis) patients. Thirty-six patients (48%) had node-negative disease.

A logistic regression analysis was performed using the presence/absence of PM as dependent variable, and the following independent variables: sex, age, tumour size, grading, vascular invasion, perineural invasion, TIL, N factor (Table 3). Among all the independent variables, only vascular invasion (OR: 0.45; 95% CI 0.24—0.85, \(p = 0.01\)) and N status (OR: 0.6; 95% CI 0.43—0.82, \(p = 0.001\)) were significantly correlated with the presence of PM.

Survival analysis was conducted on the overall population and on the patient population with N0 disease. Cumulative survival proportions are shown in Figs. 1 and 2. Three and 5-year survivals were 29% and 20% in PM1 and 35% and 10% in PM2 patients. In N0 population, 3- and 5-year survivals were 33% and 33% (4 years) in PM1 and 45% and 16% in PM2 patients. Although a trend towards a better survival in PM1 and PM2 patients as compared to other T4 and M1 disease was observed, the difference was not significant either overall (\(p = 0.21\)) or in the node-negative population (\(p = 0.12\)). Median survivals were 25 and 23 months for the PM1 and PM2 groups, respectively, as compared to 15 and 14 months for other T4 and M1 disease.

4. Discussion

In the present study, we analysed our population of patients resected for non-small cell lung carcinoma (NSCLC) who presented associated intrapulmonary metastases (PM) either in the same lobe (PM1) or in different lobe(s) (PM2) to assess their prevalence, correlation with clinico-pathologic variables and impact on survival and review the literature on the subject.

The results of our study indicate that: (1) the prevalence of PM in patients operated on for NSCLC is quite low (3.6%); (2) there is a relationship between the presence of PM and some clinico-pathologic variables such as N status and microscopic vascular invasion; (3) the presence of PM is associated with a moderate survival advantage over other T4/M1 disease which however did not reach a statistical significance.

The most recent update of the TNM staging system for lung cancer dates back to 1997 [2], subsequently validated in 2002 by the sixth edition of the UICC and the AJCC [4,5]. This system classifies PM in the primary lobe (PM1) as T4, and PM in different lobes (PM2) as M1, thus considering PM as a sign of advanced disease. Since the first report of Deslauriers and colleagues in 1989 [3], however, it has been clear that this subgroup of patients may behave differently from those presenting with other signs of advanced disease, and considerable debate has arisen on this issue ever since.
The presence of additional nodules in patients with NSCLC arouses confusion about whether the lesions represent metastases of the primary tumour, multiple primary NSCLC, or even benign lesions [7,8]. An estimated 16% of potentially resectable patients with stage I through IIIa NSCLC have additional nodules identified preoperatively, most of which are indeed benign [9]. Most cases, however, have additional pulmonary nodules identified at operation or as incidental findings at histologic examination. The differentiation between synchronous multiple primary NSCLC and PM is difficult. The criteria proposed by Martini and Melamed in 1975 [1] are still the most widely used by pathologists, although there have been some experimental trials for the discrimination of multiple primary lung cancer from PM using immunohistochemistry or molecular biology [10—13].

PM have been reported to account from as low as 3% to as high as 10% of all surgically treated patients with NSCLC [14—16] and the prevalence among surgical series partly depends upon how carefully the pathologists look for them, as well as upon the prevalence of bronchioloalveolar carcinoma which, in its multifocal form, may mimic the presence of PM and may influence the survival results because of its known favourable prognosis. Our study excluded patients with pure BAC, thus avoiding possible misinterpretation of the results. From all the reports, however, it may be suggested that the presence of a preoperative or intraoperative nodule(s) should not be regarded per se as an absolute contraindication to surgery [17].

A number of authors report a poor survival in patients with PM. The search for identifiable prognostic factors to the development of PM recently led Nakagawa and colleagues [18] to analyse several clinicopathologic characteristics in patients with resected NSCLC and associated PM. They found that, although overall survival of patients with PM was similar to that of other T4/M1 patients, a complete resection, a tumour less than 30 mm, and a pathological absence of nodal metastases (N0) were independent prognostic factors, thus raising the issue of whether these patients should be assigned to a less TNM determinant. Our results show, using a logistic regression model, that there is a relationship between the presence of PM and either microscopic vascular invasion or N status, in accordance to what already reported in the literature [19,20].

The prognostic significance of the presence of additional nodules to the primary tumour has been a very controversial point in the TNM classification and several series have shown contradictory results in the past [21,22]. Table 4 summarises the survival results of the most recent series.

Battafarano and colleagues [23], on 44 patients with nodes-negative (N0) PM, reported a 66% 3-year survival rate, comparable, although not significantly, with stage I disease. Most Japanese authors, conversely, did not find any difference between PM patients and other T4/M1 patients. In a recent report, Okumura and colleagues [14] over 1534 patients, of whom 123 had PM, found similar survival rates in PM patients and other T4/M1 disease, even in the N0 subgroup.

The two largest series to date addressing the issue of PM in NSCLC patients are those from the Japanese Committee of Lung Cancer Registry (JCLCR) and the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project both published in 2007 [24,25].

The JCLCR study from Nagai and colleagues retrospectively collected data over 303 institutions for a total of 6525 patients. Of these, there were 445 patients with PM of which there were 317 PM1 and 128 PM2. Five-year survival rates were 27% and 22% respectively (46% and 42% in N0 disease).

**Table 4**
Survival data of patients with NSCLC and PM from different series

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>No/total (%)</th>
<th>PM1/PM2</th>
<th>5Yr%&lt;sup&gt;a&lt;/sup&gt; PM1/PM2</th>
<th>5Yr%&lt;sup&gt;a&lt;/sup&gt; N0</th>
<th>5Yr%&lt;sup&gt;a&lt;/sup&gt; OtherT4/M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okada (1999)</td>
<td>89/889 (10%)</td>
<td>48/41</td>
<td>30%/23%</td>
<td>45%</td>
<td>N.S. &lt;sup&gt;b&lt;/sup&gt;/11%</td>
</tr>
<tr>
<td>Okumura (2001)</td>
<td>123/1534 (8%)</td>
<td>105/18</td>
<td>34%/11%</td>
<td>37%</td>
<td>34%/6%</td>
</tr>
<tr>
<td>Battafarano (2002)</td>
<td>44/504 (9%)</td>
<td>27/17</td>
<td>66%/63%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>54%</td>
<td>31%/28%</td>
</tr>
<tr>
<td>Nakagawa (2005)</td>
<td>48/1198 (4%)</td>
<td>31/17</td>
<td>30%</td>
<td>48%</td>
<td>58%</td>
</tr>
<tr>
<td>Port (2007)</td>
<td>53</td>
<td>53</td>
<td>27%/22%</td>
<td>46%/42%</td>
<td>18%/21%</td>
</tr>
<tr>
<td>Nagai (2007)</td>
<td>445/6525 (7%)</td>
<td>317/128</td>
<td>28%/22%</td>
<td>45%/48%</td>
<td>22%/N.S.</td>
</tr>
<tr>
<td>Rami-Porta (IASLC, 2007)</td>
<td>543/18198 (3%)</td>
<td>363/180</td>
<td>35%/33%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>44%/32%</td>
<td>18%/8%</td>
</tr>
<tr>
<td>Oliaro (2007)</td>
<td>74/2013 (3.6%)</td>
<td>39/35</td>
<td>35%/33%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>44%/32%</td>
<td>18%/8%</td>
</tr>
</tbody>
</table>

<sup>a</sup> 5Yr%: 5-year survival rate.
<sup>b</sup> N.S.: not stated.
<sup>c</sup> 3-year survival rate.
Survival among other T4 and M1 patients were 18% and 20%, respectively. The authors concluded that there is no survival differences between PM1 and PM2; survival of PM1 was significantly better than that of other T4 patients, lying somewhere between that of T3 and other T4 disease.

The IASLC study from Rami-Porta and colleagues analysed databases from four different geographic areas including Europe, North America, Asia and Australia. Out of 18,198 patients there were 543 patients with PM (363 PM1 and 180 PM2). Five-year survival rates were 28% and 22%, respectively (45% and 48% in N0 disease). By comparison, other T4 patients had a 22% 5-year survival rate, significantly worse than that of PM1 and similar to T3 tumours. The authors concluded that PM1 tumours should be reclassified as T3 and PM2 tumours should be reclassified as T4 in the future update of TNM staging system for NSCLC.

The discrepancies among the different series in the past may be attributable either to the very large range in the number of patients (from 48 to 543) or to the different criteria adopted by the authors to discriminate between PM and multiple primary lung carcinomas. A further source of misinterpretation of the results may be the inclusion of BAC in the patient population, which are known to show a multifocal growth mimicking PM. Further, the omission of reporting the confidence intervals associated with the estimated survival rates at a given time may lead to misinterpretation of the real survival differences among groups in most studies.

Our results lie somewhere in the middle of the spectrum of those reported in the literature: a moderate survival advantage in PM1 and PM2 over other T4/M1 disease was evident, although not significant. Our findings, although not sufficient per se to alter the current staging system, may add to other larger contributions in support of a reconsideration for a downstaging of PM in the next TNM edition.

In the present study we relied on the 3-year survival rate instead of the more used 5-year one, because the number of patients at risk was lower than five at 5 years. The observed lower survival advantage in the population of patients with PM as compared to other series may be attributable to the relatively small number of patients, with a consequent reduction of the statistical power of the study. Also, our population of PM patients is very selected since neuroendocrine tumours, patients receiving induction therapy and bronchioalveolar carcinomas were excluded from the analysis. Despite the relatively small number of patients, however, our population may be considered one of the most selected among the published series and our results may be of interest in the discussion of this particularly debatable issue.

When all of the aforementioned considerations are taken into account, some points of interest emerge from the literature and from our experience about the issue of PM in NSCLC.

First, it looks clear that most of the series including the two multi-institutional studies, point to the fact that patients with NSCLC and intrapulmonary metastases (PM) should be considered for a downstaging in the next TNM staging system which is expected to be published in 2009.

Second, most authors agree that the site of intrapulmonary metastases namely in the same lobe of the primary tumour (PM1) or in a different lobe(s) (PM2) is prognostically important, the first possibly being an expression of a local progression, while the second being a form of distant hematogenous spread and this should be taken into consideration in the staging classification.

In conclusion, the presence of intrapulmonary metastases in NSCLC patients otherwise suitable for surgical resection remains a point of controversy. However, the bulk of data from the literature that has been accumulating in the most recent years including ours bend to the conclusion that there is sufficient validated information to consider a downstaging in the presence of intrapulmonary metastases for the seventh edition of the TNM classification.

References


Appendix A. Conference discussion

Dr R. Rami-Porta (Barcelona, Spain): I didn’t stand up because the comment that I made in the previous presentation also applies to yours.

Dr Oliaro: Yes, I agree with you, our series is not very big and we ought to increase with other people.

Dr P. Darteevele (Le Plessis Robinson, France): But in the other group, it’s possible it’s not a primary lung cancer? Why do you say it is a metastasis?

Dr Oliaro: We follow the criteria proposed by Martini and Melamed, and our pathologists are, I think, sure it is metastasis and not a second primary lung cancer.