Metastasectomy for Synchronous Solitary Non-Small Cell Lung Cancer Metastases

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Background. Surgical treatment of patients with limited metastatic lesions from non-small cell lung cancer (NSCLC) remains controversial; however, reports suggest that a subset of patients may benefit from complete resection including metastasectomy.

Methods. Between 1997 and 2009, 99 patients underwent complete solitary synchronous NSCLC metastasis resection in a single center. Only patients who met the potentially curative operation criteria (ie, primary NSCLC and metastasis resection of a solitary pulmonary or solitary extrapulmonary metastases) were included for retrospective analyses within this study.

Results. The overall 5-year survival rate was 38%. A significantly longer survival was observed in patients without mediastinal (N2 or N3) lymph node involvement (median, 50.0 months) compared with patients who had mediastinal lymph node metastases (median, 19.0 months survival; \( p = 0.015 \)). In patients with a solitary metastasis in the ipsilateral (not ipsilobar) or contralateral lung, we observed a 5-year survival rate of 48.5%, whereas the rate was 23.6% in patients with extrapulmonary metastases (\( p = 0.006 \)). In univariate analysis, a trend for a more favorable long-term survival rate was observed for patients with a histologic grade of G1 or G2 versus G3 primary NSCLC (\( p = 0.058 \)).

Conclusions. We conclude that metastasectomy for synchronous oligometastatic disease in NSCLC can be performed in selected patients. It appears reasonable that such patients should be considered as surgical candidates if mediastinal lymph node involvement is excluded.


Primary lung cancer ranks among the most commonly occurring malignancies and is the leading cause of cancer-related deaths worldwide. Of the patients who exhibit non-small cell lung cancer (NSCLC), approximately 30% to 50% will present with metastatic disease. The condition of most patients with metastatic disease on presentation or with recurrent lesions is not controllable with a curative treatment approach. However, the treatment of patients with limited NSCLC metastatic lesions remains controversial [1]. Several studies of local therapy by surgical resection or radiation therapy of solitary metastases have demonstrated that highly selected patients can achieve long-term survival if the primary NSCLC is also resectable or has been curatively treated [2]. To emphasize the importance of surgical resection in stage IV NSCLC, one must realize that without therapy, the median survival in stage IV disease is between 3 and 4 months and up to 12 months with systemic therapy alone [3]. Several case series reported 5-year survival rates of approximately 15% after solitary brain metastasis resection [4, 5]. Surgical isolated adrenal metastasis resection can result in up to 40% long-term survival [6].

This report was initiated to summarize our single-center experience for curative treatment of patients with synchronous oligometastatic NSCLC. Our aim is to identify patient characteristics, prognostic survival, and predictive factors after a curative treatment approach.

Patients and Methods

Patients

We analyzed the database of patients who underwent NSCLC surgical resection between 1997 and 2009 at the Heckeshorn Lung Clinic. Of those, 99 patients were retrospectively identified who experienced synchronous oligometastatic disease (ie, solitary pulmonary or solitary extrapulmonary metastases) and were treated for a solitary metastasis. The institutional review board waived the need for registration because data were gathered for internal quality control. All of the patients gave their informed consent to use their data for scientific research. In all of the patients, the primary NSCLC was treated by curative resection. Solitary hematogenous metastasis diagnosis within 3 months after primary NSCLC surgery was considered to be synchronous metastatic disease presentation. Patients with additional tumor nodules in the primary NSCLC lobe were excluded from the study. Patients were evaluated by physical examination, chest roentgenographs, chest computed tomographic (CT) scans, brain CT or magnetic resonance imaging (MRI),
abdomen ultrasonography, and bone scans. In the most recent period (since 2008), positron emission tomography–CT scan was incorporated in preoperative staging. Only patients who met the criteria for potentially curative operation were included. The preconditions valid for potentially curative hematogenous metastasis operation were as follows:

1. The metastases were technically resectable.
2. The general and functional risks were tolerable.
3. The primary NSCLC was completely resected (R0), and a systematic lymph node dissection was additionally intended.
4. There was synchronous onset of the metastatic disease.
5. No further metastatic lesions were detected (solitary metastasis).

To differentiate between second primary lung cancer and NSCLC pulmonary metastasis, the pivotal questions were different histology and synchronous onset. Only patients in whom the pathologic results (ie, histology and immunohistochemistry) were in accordance with a metastasis of the primary NSCLC were included in the study.

Data Processing and Statistical Analysis
All of the patients were analyzed for demographic data, resection location and type, resection completeness, 30-day mortality, and overall long-term survival. For patients who underwent recurrent metastasectomy, the date of the last operation was used as the beginning of the observation period. Survival data were updated every 3 months, and patient survival data were censored according to this date because the patients were still alive then.

Disease-specific items included histology and grading, pathologic T and N descriptors, perioperative chemotherapy or radiation therapy, ipsilateral and contralateral lung metastasis, resection type (pneumonectomy versus others), and metastasis site.

Univariate survival analyses were performed with Kaplan-Meier statistics reporting the group median and the 95% confidence interval (CI). Log-rank analyses were used for comparison between groups. Variables with a significant trend (p < 0.1) in univariate survival analyses qualified for the multivariable approach. For the multivariable analysis, the Cox-Hazard regression model (forward selection p<0.1; p > 0.05) was used, and the following variables were tested: N descriptor (pN0/pN1 versus pN2/pN3), grading (G1/G2 versus G3), perioperative radiation therapy (none versus any), and metastasis type (pulmonary versus extrapulmonary).

Probability values less than 5% were regarded as significant. All of the data were analyzed and processed using IBM SPSS Statistics version 19.0 (IBM Corp, Armonk, NY) on a Windows 7 operating system (Microsoft Corp, Redmond, WA).

Results
A total of 99 patients with a median age of 62 years at resection (range, 36 to 84 years; 64 of 99 male patients; 65%) were included in the study. Tumor characteristics of the study population are summarized in Table 1. Adenocarcinoma was the predominant histologic type (68 of 99, 69%) and 18 of 99 patients had an initial pT descriptor of T3 or greater (19%). In 2 of 9 patients after neoadjuvant chemotherapy, the operative tumor size was rated ypTx because of effective chemotherapy (22%). The pN descriptor included 3 pN3 cases (3 of 99, 3%) and 5 cases with unknown operative pN status (5 of 99; 5%).

Table 2 summarizes the metastasis site at primary resection and the extent of pulmonary resection at the initial procedure. Lobectomy or bilobectomy was necessary in 73 of 99 patients (74%), the majority of patients had pulmonary metastasis (57 of 99; 58%), and 21 of 99 patients presented with brain metastasis (21%). The treatment sequence in 21 of 99 patients with brain metastasis (21%) was brain metastasectomy first in 17 of 22 patients (77%), and adrenal metastasis adrenalectomy before

Table 1. Histologic Type, T Descriptor, and N Descriptor

<table>
<thead>
<tr>
<th>Histology</th>
<th>(n)</th>
<th>(%)</th>
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<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>68</td>
<td>68.7</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>22</td>
<td>22.2</td>
</tr>
<tr>
<td>Large-cell carcinoma</td>
<td>6</td>
<td>6.1</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>3.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N Descriptor</th>
<th>pTy (n)</th>
<th>pT1 (n)</th>
<th>pT2 (n)</th>
<th>pT3 (n)</th>
<th>pT4 (n)</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0</td>
<td>2</td>
<td>12</td>
<td>25</td>
<td>6</td>
<td>1</td>
<td>46 (46.5%)</td>
</tr>
<tr>
<td>pN1</td>
<td>0</td>
<td>3</td>
<td>12</td>
<td>2</td>
<td>2</td>
<td>19 (19.2%)</td>
</tr>
<tr>
<td>pN2</td>
<td>0</td>
<td>7</td>
<td>14</td>
<td>1</td>
<td>4</td>
<td>26 (26.3%)</td>
</tr>
<tr>
<td>pN3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3 (3.0%)</td>
</tr>
<tr>
<td>pNx</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>5 (5.1%)</td>
</tr>
<tr>
<td>Total (n)</td>
<td>2 (2%)</td>
<td>25 (25.3%)</td>
<td>54 (54.5%)</td>
<td>11 (11.1%)</td>
<td>7 (7.1%)</td>
<td>99 (100%)</td>
</tr>
</tbody>
</table>
primary NSCLC resection in 9 of 10 patients (90%).

Patients with contralateral lobe metastasis (14 of 99, 14%) underwent a bilateral staged thoracotomy after primary lung cancer resection.

For patients with pulmonary metastases, lobectomies (n = 3), pneumonectomies (n = 7), and wedge resections (n = 33) were done concurrently with the resection of the primary NSCLC. In 14 patients, pulmonary metastases of the contralateral site were resected for oligometastatic disease, and this was done by wedge resections without systematic lymph node dissection. Systematic lymph node dissection was performed in all patients for the primary NSCLC except for 5 patients who had wedge resections because of a limited functional reserve. The number and type of all surgical procedures, including primary solitary metastases and in case of multiple operations for recurrent locoregional disease, are summarized in Table 3.

We defined a primary metastasis as a synchronous detected solitary metastasis, which was also the first resected metastasis. The median interval between the primary resection and the metastases resection was 0 days (95% CI, 0 to 165 days). The surgical approach was chosen according to the metastasis site. All of the patients underwent curative surgical primary lung cancer and metastatic site resections. For 57 patients with pulmonary metastasis, 71 thoracotomies or thoracoscopies were performed as the initial surgical resection, and 8 thoracotomies as a second operation were performed on patients detected after regular follow-up for NSCLC. They experienced a recurrent pulmonary metastasis after curative resection for the first pulmonary metastasis. Recurrent metastasis was defined in this study as a locoregional event amenable for a second local treatment option.

Platinum-based combination chemotherapy was performed preoperatively in 5 of 99 patients (5%), a post-operative adjuvant chemotherapy was used in 56 of 99 (57%) patients, and preoperative and postoperative therapy was used in 4 of 99 (4%) patients. No perioperative chemotherapy was given to 29% (29 of 99) of all patients, and no perioperative chemotherapy data were available in 5% (5 of 99) of patients.

In total, 48% (14 of 29) of patients with pN2/pN3 disease received adjuvant mediastinal radiotherapy, whereas 90.5% (19 of 21) of patients who had surgery for brain metastasis received adjuvant whole brain radiation therapy. No adjuvant radiation therapy was applied in 61 patients, and no data on adjuvant radiation therapy were accessible for 7 patients.

Within our cohort, 1 patient experienced rapid postoperative brain metastasis progression with cranial pressure symptoms and subsequent death (30-day mortality rate, 1 of 99; 1%). All of the other patients left the hospital and were followed up for a median of 36 months, ranging from 1 to 157 months. During this observation period, 68 of 99 patients died (69%; 31% survival rate), and the 5-year patient survival rate was 37 of 99 (38%). Figure 1 demonstrates Kaplan-Meier plots for the entire cohort.

In the univariate survival analyses, age, sex, histology, pathologic T descriptor, ipsilateral and contralateral lung metastasis, and perioperative chemotherapy were not significantly associated with better survival.

There was not a significant trend toward worse survival among patients who received radiotherapy (Fig 2) and those with low grading in the initial histologic assessment (Fig 3). We observe significant differences in estimated survival in patients with lower N descriptors (pN0/pN1; Fig 4) and pulmonary metastatic disease (Fig 5). The median survival time for patients with pN0/pN1 disease was 50.0 months (95% CI, 34.7 to 65.2) versus 19.0 months (95% CI, 0.0 to 42.3) for patients with pN2/pN3 (p = 0.017) disease. Additionally, the difference in long-term survival was also significant between patients with pN0 and a median survival of 53.0 months (95% CI, 10.7 to 95.3) versus patients with pN1 through pN3 lymph node involvement and a median survival of 31.0 months (95% CI, 6.9 to 55.1; p = 0.011). Median survival for patients with intrapulmonary metastatic disease was 56.0 months.

Table 2. Site of Metastasis and Types of Pulmonary Resection for Primary Non-Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>(n)</th>
<th>(%)</th>
</tr>
</thead>
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<tr>
<td>Site of metastasis</td>
<td></td>
<td></td>
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<tr>
<td>Lung</td>
<td>57</td>
<td>57.6</td>
</tr>
<tr>
<td>Brain</td>
<td>21</td>
<td>21.2</td>
</tr>
<tr>
<td>Adrenal</td>
<td>10</td>
<td>10.1</td>
</tr>
<tr>
<td>Bone</td>
<td>4</td>
<td>4.0</td>
</tr>
<tr>
<td>Hepatic</td>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>Mediastinal/thymus</td>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>Pleura</td>
<td>1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Types of pulmonary resection for the primary NSCLC

<table>
<thead>
<tr>
<th>Procedures</th>
<th>(n)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracotomy with resection of the primary NSCLC</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Thoracotomy with resection of the primary NSCLC together with resection of ipsilateral pulmonary metastasis</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Thoracotomy for contralateral metastasis</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Thoracotomy for recurrent pulmonary metastatic disease</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Brain metastasectomy (operations for the primary solitary brain metastasis)</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Adrenalectomy (operations for the primary solitary metastasis)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Other resection locations: bone, liver, diaphragm, pleura (operations for the primary solitary metastasis)</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

NSCLC = non-small cell lung cancer.
(95% CI, 37.2 to 74.8; \( p = 0.001 \)), with a 5-year survival rate of 48.5% versus 18.0 months (95% CI, 8.5 to 27.5) and 23.6% for patients with extrapulmonary metastasis, respectively. Of patients with extrapulmonary disease, there were 4 patients with bone metastases. Although metastasis of the bone is generally considered as having systemic disease, long-term results for surgical resection were as follows: in 2 patients who had rib metastases on the ipsilateral site of the primary tumor, the median survivals were 5 and 14 months. The other 2 patients presented initially with pathologic femoral fractures, which led to the diagnosis of NSCLC. Median survivals of these patients were 5 and 36 months.

Cox regression analysis revealed a high N descriptor (pN2/pN3; risk ratio, 2.0; 95% CI, 1.1 to 3.4; \( p = 0.015 \)) and extrapulmonary metastasis (risk ratio, 1.1; 95% CI, 1.1 to 3.4; \( p = 0.006 \)) as independent worse outcome predictors. Use of radiotherapy (\( p = 0.912 \)) and the initial histologic grade (\( p = 0.391 \)) were not significantly associated within multivariable analysis and were thus excluded from the model.

To transfer the results into clinically applicable prognostic categories, we assigned each patient a risk score from 0 to 2 depending on the presence of the prognostic factors (eg, pN2/pN3 plus extrapulmonary metastatic site yields a risk score of 2). According to this assignment, we found no risk factors in 41 of 99 (41%), 1 risk factor in 44 of 99 (44%), and both risk factors in 14 of 99 (14%) of our patients. Figure 6 demonstrates the patient group survival curves. There was a strong association between survival and the numbers of risk factors present (Fig 6). Patients without one of these risk factors had a median survival of 61 months (95% CI, 36.0 to 82.4 months) compared with patients who had either one risk factor (31 months; 95%
CI, 18.7 to 43.3 months) or those with both risk factors who survived for a median of 13 months (95% CI, 10.6 to 15.5 months; \( p < 0.001 \)).

Comment
Since Martini and Melamed [7] published the first article to address the definition of multiple primary NSCLC and solitary metastatic disease in 1975, and later Hellmann and Weichselbaum [8] described the term “oligometastases” as a restricted locoregional tumor load, treatment for isolated distant metastases is gaining more and more momentum in the oncologic literature. There have been numerous retrospective case studies including NSCLC patients suggesting that some of these patients may be effectively treated with primary tumor resection and local therapy for metastatic lesions [1, 9]. However, the metastatic potential of NSCLC limits local treatment options to metastases of a less biologically aggressive tumor stage in which a solitary metastasis that is located to a single organ site remains stable over time. More restricted than the definition of Hellman and Weichselbaum [8], we defined oligometastatic disease in NSCLC patients as metastatic disease with a solitary metastasis located in one site. The present study was conducted to describe criteria for selecting patients with oligometastatic disease in an attempt to identify patients who would benefit from surgical resection of the tumor and synchronous metastasis.

A complete resection was performed in all cases, and the 5-year survival probability was 38%. In a multivariate analysis of a series of 170 surgical procedures in 99 patients, the results indicate that the presence or absence of intrapulmonary or extrapulmonary metastatic disease and the detection of thoracic lymph node involvement are independent significant prognostic factors for survival after metastasectomy. Using univariate analysis, the primary NSCLC histologic grading nearly retained significance for survival.

Studies concerning surgery for synchronous metastasis from NSCLC are scarce, and median overall survival ranged between 13.5 and 20.5 months [10–12]. However, in the present study, our survival data after complete resection were more favorable with a survival median of 41 months [10–12].

Most surgical series reporting on patients with oligometastatic NSCLC have focused on brain and adrenal metastases. Treatment of patients with brain metastasis was staged brain first before the primary lung cancer was resected, but in many studies, patients with adrenal metastasis and preserved adrenal function had primary NSCLC resection before adrenalectomy. Nevertheless, we preferred adrenal metastasis resection before lung resection to confirm stage IV disease and local metastasis resectability. A recently published review on NSCLC adrenalectomy demonstrated a median survival of 12 months for patients with synchronous onset of adrenal metastasis [13], which is comparable to our results of 13.0 months of median survival (95% CI, 5.2 to 20.7). Interestingly, Raz and colleagues [14] determined that besides mediastinal lymph node involvement, adrenal metastasis ipsilateral to their primary NSCLC were prognostic factors associated with inferior survival. However, within our study we could not confirm adrenal metastasis laterality as prognostically relevant.

Billing and coworkers [15] published a retrospective review of 28 patients with curative NSCLC treatment and synchronous brain metastasis, which revealed a median survival of 24 months. In their study, mediastinal or hilar lymph node metastases were a significant adverse prognosticator for long-term survival. Bonnette and colleagues [16] corroborated in a study of 103 patients with synchronous oligometastatic brain disease; the median survival after resection of the primary site...
Fig 4. (A) Overall survival of the cohort with data available for N-descriptor (pN0/pN1 [blue line] versus pN2/pN3 [green line]; n = 94). Log-rank analysis (p = 0.017). (B) Overall survival of the cohort with data available for N-descriptor (pN0 [blue line] versus pN1–pN3 [green line]; n = 94). Log-rank analysis (p = 0.011).

Fig 5. Overall survival of the cohort separated for pulmonary [blue line] versus extrapulmonary [green line] metastasis (n = 99). Log-rank analysis (p = 0.001).
and brain metastases was 12.4 months. Of the factors analyzed, adenocarcinoma histology was a significant prognostic factor for better survival. In a series of 42 patients who underwent gamma knife stereotactic radiotherapy for synchronous brain metastasis, Flannery and associates [17] reported a median survival rate of 26.4 months in 26 patients who received definitive therapy. Karnofsky performance status and definitive thoracic therapy were identified as prognostic factors by multivariate analysis. In our series, survival in 21 patients with synchronous brain metastasis was 23.0 months (95% CI, 16.2 to 29.7), which was comparable with the published literature.

Salah and coworkers [18] published a systematic review on extracranial, extraadrenal NSCLC solitary metastases including 51 articles with 62 patients who were eligible for review. Poor prognosis was significantly related to mediastinal lymph node involvement, with a hazard ratio of 8.2 (95% CI, 2.1 to 32.5). In our subgroup of patients with extracranial, extraadrenal metastatic sites, 4 patients had bone metastases and a median survival of 5.0 months, which was significantly worse than the group containing 7 patients who had metastasis at other sites, which was 40.0 months.

In clinical practice it seems difficult to differentiate between second primary lung cancer and pulmonary metastasis when pulmonary lesion morphology and histology are similar. The criteria first popularized by Martini and Melamed [7] can safely be applied in metachronous disease or autopsy specimens, but strict selection criteria for synchronous multiple primary NSCLC are needed.

To differentiate between a second primary lung cancer and a lung metastasis, we endorsed the American College of Chest Physicians’ panel suggestion to use an experienced multidisciplinary team of collective judgment considering all necessary radiologic and pathologic information [19, 20]. We believe that tumor differentiation should be based on histologic criteria, lymph node status, and the interval between primary NSCLC detection and pulmonary metastasis.

In this context, a pooled analysis for patients with synchronous lung cancers in multiple lobes revealed that even when it is unknown whether the cancers are multiple primary lung cancers or metastatic disease by similar histology, surgical resection may be an appropriate treatment option [21, 22]. In a retrospective series on 234 patients, Riquet and associates [23] reconsidered that a second pulmonary tumor is more likely a metastasis than a second primary cancer.

The studies by Riquet and colleagues [23] and other large series demonstrated no significant correlation with 5-year survival and histologic classification. They also found a 5-year survival rate of 26.3% (median survival, 17 months) for patients with synchronous multiple lung cancer of similar histology and different lobe locations [23]. In a population-based study by Rostad and coworkers [24], 5-year survival for patients with synchronous primary NSCLC of the same histology was 23.2% for adenocarcinomas and 31.4% for squamous cell carcinomas. We report in our study a 5-year survival rate of 48.5% after resection of a synchronous second pulmonary lesion located in a different lobe that had been defined as pulmonary metastasis by histology and immunohistochemistry.

Another interesting result from our data is the finding that the 5-year survival of patients who underwent repeated oligometastasis resections did not differ significantly from that observed in patients who had only one resection. These results most likely represent a selection bias, in that patients who succumbed rapidly to their disease or who were no longer amenable to surgery because of rapid disease progression were no longer considered for repeated metastasectomy.

Our observations indicate that a highly selective group of patients may benefit from repeated metastasectomy. However, our study has important limitations. Its retrospective design, limited number of patients, long time frame, and lack of data on relevant biomarkers for a more definite understanding of the oligometastatic state and the absence of suitable control subjects limit our conclusions. Despite this, the paucity of voluminous clinical data regarding metastasectomy in oligometastatic NSCLC.

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**Fig 6.** Overall survival of the cohort separated by the number of risk factors (RF; 0 [blue line], 1 [green line], and 2 [gold line]; n = 99). Log-rank analysis \(p < 0.001\).
makes our investigation an interesting starting point for further studies.

With more and better imaging techniques as well as the development of more effective systemic therapies, the number of patients with remaining oligometastatic deposits will increase and treatment strategies have to be adopted. Better and earlier detection of subclinical disease will have utmost significance for interdisciplinary decision-making and patient selection. Thus, we conclude that in selected patients, synchronous solitary metastasis resection may provide longer palliation or result in long-term survival. However, in selected patients, solitary bone metastasis resection may provide longer palliation in the best case, whereas surgical resection was most advantageous in patients with pulmonary metastasis irrespective of ipsilateral or contralateral location. Using a probability model for predicting overall survival, the patients with the best combination of prognostic factors had a 5-year survival rate of 52.5%.

To summarize, oligometastatic disease resection in NSCLC is safe and effective, with missing N status and pulmonary location of the metastasis being independent prognostic factors for long-term survival.

References