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Stage I Non-Small Cell Lung Cancer: Recurrence Patterns, Prognostic Factors and Survival

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1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Surgical resection is the treatment of choice for early-stage non-small cell lung cancer (NSCLC).[1,2] Five-year survival in patients with resected stage I NSCLC ranges between 55% and 80%.[3-6] Tumor recurrence is the most common cause of death, and thus the main obstacle for long-term survival after resection.[4-10] The postoperative recurrence rates in stage I NSCLC range between 22% to 38%.[4-8] The incidence of local or regional recurrence in stage I NSCLC after surgical resection has been reported between 7% to 15%,[4-6] while distant metastasis been reported between 14% and 23%.[4-8] Post-recurrence survival in resected stage I NSCLC is poor.[7,10-12]

The fifth edition of the TNM staging system for lung cancer was published in 1997, and stage I NSCLC was subdivided into IA (T1N0M0, tumor size ≤ 3 cm) and IB (T2N0M0, tumor size > 3 cm).[3] In addition to tumor size greater than 3 cm, the T2 descriptor also includes tumors that invade the visceral pleura regardless of size, tumors that involve the main bronchus ≧ 2 cm distal to the carina, and tumors that result in associated atelectasis and obstructive pneumonitis that extends to the hilar region but does not involve the entire lung radiographically.[3] In the sixth edition of the TNM classification (TNM 6)[13] for lung cancer published in 2002, no change was made to the previous edition.[3] The seventh edition of the TNM classification (TNM 7) for lung cancer has been published in 2009.[14,15] The changes to the TNM 6 for lung cancer were based upon the proposals from the International Association for the Study of Lung Cancer (IASLC). In the seventh edition, T1 descriptor has been classified into T1a (≤ 2 cm) and T1b (> 2 to ≤ 3 cm), while size-based T2 descriptor has been classified into T2a (> 3 to ≤ 5 cm), T2b (> 5 to ≤ 7 cm), and T3 (> 7 cm).[16] Stage I NSCLC was subdivided into IA (T1aN0M0, T1bN0M0) and IB (T2aN0M0).17 T2bN0M0 was reclassified as stage IIA.[17]

This review focuses on recurrence patterns of stage I NSCLC after surgical resection, survival after recurrence, and its prognostic factors. Predictors for local recurrence and distant metastasis are analyzed and discussed separately. Recent reports in the literature aiming at recurrence patterns and survival in stage I NSCLC (TNM 7) were also reviewed and included.

2. Prognostic factors for stage I NSCLC

The prognostic factors of stage I NSCLC (TNM 6) have been widely reported in the literature.[4-6,18,19] Martini et al[4] reported that T2 status and sublobar resection were the prognostic factors for poor overall survival in resected stage I NSCLC. Harpole et al[15] reported that presence of symptoms, vascular invasion, visceral pleural invasion and tumor size greater than 3 cm were the factors affecting overall survival in resected stage I NSCLC. Sawyer et al[18] reported that factors predicting poor overall survival included fewer than 15 lymph nodes dissected and tumor size greater than 3 cm. Varlotto et al[19] also reported that lymphadenectomy was associated with improved overall survival and disease-free survival in resected stage I NSCLC. Many other reports also demonstrated the prognostic value of tumor size in stage I NSCLC.[6,20] The number of mediastinal lymph nodes dissected/sampled alternatively represents the quality of lymphadenectomy and affects the survival rate for patients with resected stage I NSCLC.[19,21] Our previous studies[21,22] also showed that number of mediastinal lymph nodes dissected/sampled was a predictor of survival in stage I NSCLC. Cigarette smoking has been shown to be another prognostic factor in patients with NSCLC in the literature.[23-26] Hanagiri et al[23] reported that smoking was a significant postoperative prognostic factor in patients with NSCLC. Bryant et al[24] reported that 5-year survival rate was significantly better for never smokers compared to smokers in stage I NSCLC (TNM 6).

Only few studies reported the prognostic factors of stage I NSCLC (TNM 7).[25-28] In the report by Maeda et al, [27] 5-year overall survival rates for stage IA and IB (TNM 7) were 89.9% and 72.3%, respectively. They also demonstrated that older age, intratumoral vascular invasion, and visceral pleural invasion were poor prognostic factors in stage IB NSCLC.[27] In the report by Maeda et al,[27] 5-year disease-specific survival rates for stage IA and IB NSCLC (TNM 7) were 93.1% and 72.3%, respectively. They also demonstrated that intratumoral vascular invasion and visceral pleural invasion were poor prognostic factors for cancer-specific survival in stage IB NSCLC.[27] Maeda et al[25] reported that overall survival and recurrence-free survival in never smokers were significant better than those of ever smokers in patients with stage I NSCLC (TNM 7). Maeda et al[26] also discovered that a greater smoking extent was associated with the presence of solid components in stage I lung adenocarcinoma, which may have more aggressive biological features resulting in poorer outcomes.

3. Recurrence patterns

For stage I NSCLC (TNM 6), Martini et al[4] reported that the 2- and 5-year recurrence-free rates were 84% and 76%, respectively. Sixty percent of patients developed recurrence within the first 2 years after operation. Sawyer et al[18] reported that 5-year of local recurrence-free and distant metastasis-free rates were 85% and 83%, respectively, in patients with resected stage I NSCLC. In the study by Varlotto et al [29] regarding tumor recurrence in patients with resected NSCLC (including 82% of patients with stage I NSCLC), the 2- and 5-year local recurrence-free rates were 84% and 68%, respectively. The 2- and 5-year distant metastasis-free rates were 87% and 79%, respectively.

Martini et al[4] reported the overall incidence of recurrence in patients with resected stage I NSCLC was 27% (local or regional 7%, systemic 20%). In the study by Harpole et al,[5] the

initial location of recurrence of stage I NSCLC after surgical resection was at a distant site in 19%, within the ipsilateral hemithorax in 11% or at both locations in 6% of patients. Distant recurrence rates between 14% to 23% in stage I NSCLC after surgical resection have also been reported in the literature.[6-8] Our studies[11,12] demonstrated that overall incidence of recurrence was 31.0% (distant only in 17.8%, local only in 7.9%, local and distant in 5.3%) in stage I NSCLC after surgical resection. The patterns of local recurrence included local only in 60.2%, local with distant in 15.4%, local before distant in 19.5% and distant before local in 4.9% of patients. Approximately 78% of patients with local recurrence occurred within the first 2 years after operation. We also showed that approximately 84% of patients with distant metastases occurred within the first 2 years after operation. A major proportion of patients (62%) died within one year after distant metastasis.

Most distant metastases appear as multiple foci in multiple organs after treatment of original cancer.[30] Martini et al[4] reported that the most common site of distant metastasis in patients with resected stage I NSCLC was the brain. Yoshino et al[31] demonstrated that pulmonary metastasis was most common in NSCLC patients with recurrence at distant organs, followed by bone metastasis. Our study[12] revealed that bone (32.1%) was the most common site of single organ metastasis in patients with resected stage I NSCLC, followed by the brain (29.2%). We further demonstrated that the patterns of distant metastasis included single and multiple organ metastases in approximately 64% and 36% of patients, respectively.

The recurrence-free rate of stage I NSCLC (TNM 7) has also been reported in the literature.[28,32,33] Maeda et al[32,33] reported that the 5-year recurrence-free rate in patients with stage IA NSCLC (TNM 7) ranges between 84 to 87%. In another article by Maeda et al,[28] they reported that 5-year recurrence-free rate in patients with stage I NSCLC (TNM 7) was 84.2%.

4. Predictors of recurrence

The predictors for recurrence in resected stage I NSCLC (TNM 6) has been well demonstrated in the literature.[4,5,18,29] In the report by Martini et al,[4] the factors having adverse effects on recurrence in resected stage I NSCLC included lesser resection than lobectomy, no lymph node dissection, T2 tumor, and greater tumor size. In the study by Harpole et al,[5] the factors affecting early recurrence in resected stage I NSCLC included presence of symptoms, vascular invasion, visceral pleural invasion, and tumor size greater than 3 cm. Although both Martini et al[4] and Harpole et al[5] performed elegant analysis demonstrating the factors influencing tumor recurrence in resected stage I NSCLC, they did not analyze local recurrence and distant metastasis as separate end-points. Only few studies evaluated the risk factors for local recurrence and distant metastasis separately. Varlotto et al[29] reported that local recurrence in resected NSCLC was associated with lymphatic or vascular invasion, the use of chemotherapy, and diabetes. Distant metastasis in resected NSCLC was significantly higher in patients with non-squamous cell histology, those undergoing pneumonectomy and those with more advanced TNM stage.[29] In the report by Sawyer et al,18 the factors independently predicting local recurrence in resected stage I NSCLC included fewer than 15 lymph nodes dissected and T2 tumor. Tumor size greater than 5 cm and non-squamous histology independently predicted a poor distant metastasis-free rate in resected stage I NSCLC.[18]

The predictors for recurrence in resected stage I NSCLC (TNM 7) has not been widely investigated in the literature. In the reports by Maeda et al,[28,33] they demonstrated that histologic differentiation, intratumoral vascular invasion, and visceral of pleural invasion were significant predictors for recurrence in stage I NSCLC (TNM 7).

5. Postrecurrence survival

In our previous study,[11] the 1- and 2-year post-recurrence survival rates for resected stage I NSCLC patients with local only recurrence were 48.7% and 17.6%, respectively. Tumor size and treatment for initial recurrence were significant predictors for post-recurrence survival in patients with local only recurrence in univariate analyses. The hazard of death was greater in patients with larger tumor size. Treatment for initial recurrence was still significant prognostic indicator in multivariate analysis. Patients underwent re-operation after local recurrence survived longer than those with chemotherapy or/and radiotherapy and those without treatment.

For patients with single organ metastasis, the 1- and 2-year post-recurrence survival rates were 30.2% and 15.1%, respectively.[12] The most common site of single organ metastasis was the bone, followed by the brain. Disease-free interval > 16 months and treatment for distant metastasis (including re-operation, chemotherapy and/or radiotherapy) were significant predictors of better post-recurrence survival in resected stage I NSCLC with single organ metastasis. Post-recurrence survival was not significantly different between single and multiple organ metastases groups of patients. Multiplicity of metastatic organ sites is not a significant prognostic factor in these patients. Yoshino and coworkers[31] reported that the 2-year survival rate of NSCLC patients with postoperative recurrence at distant organs was 15.7 %. Their result is similar to that in our study.

Surgical resection offers a good chance of cure for patients with stage I NSCLC.[3,5,20] However, the outcome of surgical treatment in resected stage I NSCLC after local recurrence have rarely been reported. Walsh et al[34] reported that complete surgical resection or high-dose radiotherapy with curative intent significantly prolonged post-recurrence survival in NSCLC. Sugimura et al[10] demonstrated that whether surgery or combination chemotherapy with radiation significantly improved post-recurrence survival over both no treatment and radiation alone in resected NSCLC after local recurrence. Voltolini et al[35] reported that 5-year survival after re-operation for locally recurrent bronchogenic carcinoma was 15.5%. The 5-year post-recurrence survival in our patients undergoing re-operation after local recurrence was 15%.

Treatment for recurrent NSCLC significantly prolongs overall survival and post-recurrence survival.[10,34] Yoshino et al[31] reported that patients who underwent metastatectomy for recurrence in distant organs had significantly longer survival while those with chemotherapy had marginally prolonged survival. Nakagawa et al[7] reported that treatment for the initial recurrence prolonged survival in stage I NSCLC after recurrence. In our study,[12] treatment for distant metastasis (including surgery and chemotherapy and/or radiotherapy) had a favorable survival in resected stage I NSCLC after distant metastasis than without treatment. There was no significant difference in post-recurrence survival between patients undergoing re-operation and those treated with chemotherapy and/or radiotherapy. However, there were two postoperative deaths due to respiratory failure after

pulmonary resection. If the two patients were excluded, patients undergoing re-operation had significantly better post-recurrence survival than those receiving chemotherapy and/or radiotherapy ($P = 0.021$). The differences of therapeutic effects of surgery and chemotherapy and/or radiotherapy need larger series for further investigation.

Disease-free interval has also been shown to be a significant prognostic factor of post-recurrence survival in NSCLC. Longer disease-free interval was associated as with better post-recurrence survival in NSCLC after complete pulmonary resection.[10,34,36] Walsh et al[34] reported that disease-free interval greater than 12 months was a favorable predictor of post-recurrence survival in NSCLC after complete resection. Our study[12] showed that disease-free interval > 16 months was a significant predictor for better post-recurrence survival in patients with stage I NSCLC after distant metastasis.

Although some reports in the literature had tried to figure out the impact of specific distant metastatic organ sites on post-recurrence survival in resected NSCLC, small cohorts or mixtures with local and distant metastasis made it difficult to acquire definite results. Sugimura et al[10] reported that initial recurrence confined to the lung was associated with better post-recurrence survival in resected NSCLC. Yoshino et al[31] demonstrated that intra-pulmonary metastasis was a favorable factor for postrecurrence survival of resected NSCLC, while bone metastasis was a marginally unfavorable factor. Liver metastasis has also been reported as a worse prognostic factor in NSCLC after recurrence.[7,36] In our study, patients with distant metastases confined within the contralateral lung have significantly better post-recurrence survival than those with distant metastases outside the contralateral lung. We further showed that for patients with distant metastases outside the contralateral lung, those with bone metastasis had significantly worse post-recurrence survival.

6. Conclusion

Treatment for initial recurrence is a prognostic predictor for post-recurrence survival in resected stage I NSCLC with local recurrence. Longer disease-free interval and treatment for distant metastasis are indicators for better post-recurrence survival in resected stage I NSCLC with single organ metastasis. Complete surgical resection should be considered in selected candidates with resectable local recurrent disease. Aggressive treatment for distant metastasis in selected patients with longer disease-free interval may prolong the post-recurrence survival.

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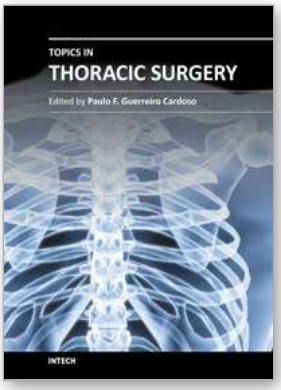

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