Review

Surgical Treatment of Stage I Non-small Cell Lung Carcinoma

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In stage I non-small cell lung cancer (NSCLC), the cancer is localized to the lung. For this early stage NSCLC, therefore, surgery is considered to be the treatment of choice. In this report, we reviewed the surgical treatment approaches for stage I NSCLC, placing emphasis on limited resection and video-assisted thoracic surgery (VATS). In regard to limited resection, sublobar resection (wedge resection and segmentectomy) may yield a good long-term outcome in selected cases, as does lobectomy. No strong evidence to recommend this procedure has, however, been published. On the other hand, many descriptive studies have indicated that VATS may be useful for the treatment of NSCLC, although the results have not shown any statistically significant differences from those of resection by conventional open thoracotomy. In addition to the low invasiveness, the curability of NSCLC using the VATS approach has been recognized to be similar to that of the standard thoracotomic approaches in clinical practice. Well-controlled studies with strong statistical results are needed to provide strong supportive evidence for the use of VATS for NSCLC. (Ann Thorac Cardiovasc Surg 2003; 9: 283–9)

Key words: non-small cell lung cancer (NSCLC), stage I, surgery

Introduction

In stage I non-small cell lung cancer (NSCLC), the cancer is localized to the lung. In patients with such early stage NSCLC, surgical resection is considered to be the most effective curative therapeutic option. In this study, we reviewed the literature on the surgical treatment approaches employed for stage I NSCLC, focusing on limited operation and thoracoscopic surgery. This study does not, however, cover perioperative adjuvant therapy using other modalities, such as radiotherapy and chemotherapy.

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Natural History

Understanding the natural history of NSCLC is crucial for making appropriate therapeutic decisions. However, few studies have described the natural history of clinical stage I NSCLC. Vrdoljak et al.[1)] reported that the mean survival time (MST) was 17 months and the two-year survival rate was 20%, from a study of 19 untreated NSCLC patients with stage cT2N0M0 cancer according to the TNM classification. McGarry and colleagues[2)] analyzed the data of a total of 49 NSCLC patients diagnosed as having stage I or II NSCLC, and found no significant difference in the MST (14 months) between the two stages. Sobue et al.[3)] demonstrated that the MST was 25 months in 42 clinical stage I NSCLC patients in whom the disease was detected at mass screening and no surgical treatment was performed, and 13 months in 27 clinical stage I NSCLC patients in whom the disease was symptomatic but no surgical treatment was conducted. In their study, however, some of the patients received radiotherapy and/or chemotherapy.

Comparison of the Survival Rate between Clinical Stage I NSCLC and Pathological Stage I NSCLC

Many investigators[4-11] have reported postoperative results after the resection of stage I NSCLC. In these studies, the postoperative five-year survival rate was 65% in patients diagnosed to have clinical stage IA (cT1N0M0) NSCLC and 45% in those diagnosed to have clinical stage IB (cT2N0M0) cancer, while it was 70% in patients with pathological stage IA (pT1N0M0) and 55% in those with pathological stage IB (pT2N0M0) cancer. The Japanese Joint Committee of Lung Cancer Registry conducted a survey[9] on a total of 7,408 patients who underwent surgical resection for stage I NSCLC in 1994. The results revealed that the five-year survival rate was 72% in 2,618 patients with cT1N0M0 NSCLC, 50% in 1,646 patients with cT2N0M0 NSCLC, and 79% in 2,142 patients with pT1N0M0 NSCLC, and 60% in 1,488 patients with pT2N0M0 NSCLC. In this survey, all the subjects were patients with stage I NSCLC who had undergone surgical resection in 1994. This data accumulation of patients who had undergone surgical treatment over a period of one year represented one of the largest sample sizes in the world for this kind of oncological epidemiological study. By 1994, computed tomography (CT) had already begun to be widely used in the clinical setting across the country. Taking these factors into account, the survey results probably provide an almost accurate reflection of the surgical results for stage I NSCLC in present day Japan.

Prognostic Factors

T stage factor in TNM definitions–tumor diameter

The T stage factor in the TNM classification is the key to the evaluation of stage I NSCLC. In patients with stage I NSCLC, T1 tumor has been reported to carry a better prognosis than T2 tumor.[4-11] Martini et al.[7] divided 598 stage I NSCLC patients into four categories according to the tumor diameter: <1 cm, ≥1 cm to <3 cm, ≥3 cm to <5 cm, and ≥5 cm. They found that the prognosis was significantly better for NSCLC patients with a tumor diameter of <1 cm as compared to that in those with a tumor diameter of ≥1 cm but <3 cm (p=0.01). The prognosis was also significantly better in patients with a tumor diameter of ≥3 cm but <5 cm than in those with a tumor diameter of ≥5 cm (p=0.02). In a study for 289 patients with stage I lung cancer, Harpole et al.[8] noted that patients with tumors 3 cm or greater in diameter had significantly poorer prognosis, as determined by multivariate analysis.

Histological type

NSCLC is also classified by the histological type: the most frequently encountered are adenocarcinoma and squamous cell carcinoma (SCC). Among stage I NSCLC patients, no significant difference in the prognosis was noted between these two different histological types.[6-8]

Degree of cell differentiation and vascular invasion

The degree of cell differentiation is considered to be an important predictor of the prognosis of NSCLC. Ichinose and coworkers[12] demonstrated that the five-year survival rate in NSCLC patients with well-differentiated tumors was significantly better than that in those with moderately or poorly differentiated tumors (87% vs. 71%, p=0.02). In another study of NSCLC,[13] well-differentiated tumors were found to carry a better prognosis, although the differences in the results did not reach significant difference. Vascular invasion is considered to be a predictor of poor prognosis. Ichinose et al.[12] pointed out that the presence of vascular invasion was significantly correlated with a poor prognosis in NSCLC patients. Similar results were obtained by other investigators.[8,14]

Type of Surgery

Limited resection

No direct comparison between surgery and other treatment modalities has been made for stage I NSCLC patients. The postoperative five-year survival rate, as described above, is around 50% in patients with clinical stage I NSCLC and 65% in patients with pathological stage I NSCLC. Therefore, presumably, surgery would yield a better outcome as compared to other treatment modalities in cases of stage I NSCLC. If the patient is physically fit to endure the surgical procedure, surgery may be the strategy of first choice for stage I NSCLC.

In one randomized trial to compare open lobectomy and limited resection conducted in stage I NSCLC patients,[15] the results revealed that the local recurrence rate following limited operation was three times as high as that following lobectomy in the patients with pathological stage IA NSCLC. In addition, the disease-free period was significantly longer in the lobectomy group than in the limited resection group. Martini et al.[7] also reported that the five-year survival rate was significantly higher in 536 patients who underwent lobectomy or more exten-

sive surgery than in 62 patients who underwent segmental or smaller resection for stage I NSCLC (77% vs. 59%, p=0.026). Warren et al.[16] showed that the prognosis was significantly worse in 66 patients with stage I NSCLC who were treated by segmentectomy than in 103 stage I NSCLC patients who underwent lobectomy (p=0.035). They showed, however, there was no significant difference in outcome between the two different surgical approaches when the tumor was 3 cm or less in diameter (p<0.2). In one study by Landreneau et al.,[17] no significant difference in survival was noted between 102 patients with T1N0M0 NSCLC who underwent partial resection, and 117 T1N0M0 NSCLC patients who underwent lobectomy (p=0.056), although the local recurrence rate was significantly higher in the partial resection group than in the lobectomy group. For tumors 1 cm or less in diameter in stage I NSCLC patients, Miller et al.[18] compared the outcome between limited resection and lobectomy, and showed that the overall five-year survival rate was significantly higher in the 75 patients who underwent lobectomy than in the 25 patients who underwent limited resection (71% vs. 33%, p=0.03); on the other hand, no significant difference was found in the disease-specific five-year survival rate between the two groups, for the analysis of which cancer deaths alone were included (92% vs. 47%, p=0.07). Several other studies[19,20] analyzed the relationship between the tumor diameter and lymph node metastasis in patients with peripheral, small pulmonary cancer, and reported that the incidence of lymph node metastasis was generally around 20% for tumors 2 cm or less in diameter. In one study in which limited resection was performed for tumors 1 cm or less in diameter, no lymph node metastasis was found in any of the 19 patients with peripheral NSCLC enrolled in the study;[21] however, another investigation[22] showed a nodal micrometastasis rate of 36% in peripheral NSCLC patients. One study[18] reported that the nodal metastasis rate was 7% in patients treated by limited resection. These findings indicate that the tumor diameter may not be a reliable parameter for the selection of patients for limited resection of the lung.

Excellent results of limited resection were obtained in other studies. In one study of patients with T1N0M0 NSCLC conducted by Kodama et al.,[23] no significant difference in the five-year survival rate was detected between the limited resection group (46 patients) and the lobectomy group (77 patients) (93% vs. 88%, p=0.86). Furthermore, multivariate analysis showed no significant correlation between the outcome and the type of surgery. Through their study of pathological stage I lung cancer, Pastorino et al.[24] compared limited resection and lobectomy in patients with stage I lung cancer. They found no significant difference in the five-year survival rate between the limited resection group (61 patients) and the lobectomy group (411 patients) (55% vs. 49%). Even when patients with T1 tumor alone were included in the analysis, no significant difference in the survival rate was found between the two different surgical groups. Sagawa et al.[25] performed segmentectomy of the lung in 58 patients with roentgenographically occult bronchogenic SCC. The results were remarkable. The overall five-year survival rate was 82.6% when all causes of death were included in the analysis, while the disease-specific five-year survival rate was 96.8% when cancer deaths alone were included in the analysis. Yoshikawa et al.[26] conducted a prospective study of extended segmentectomy based on intraoperative diagnosis of lymph node metastasis in 55 patients with a small lung tumor 2 cm or less in diameter, and again obtained remarkable results: they found that the overall five-year survival rate was 81.8% when all causes of death were included in the analysis, and the disease-specific five-year survival rate was 91.8% when cancer deaths alone were included. Taking into consideration all of these findings, it appears that limited resection for stage I lung cancer may yield excellent results in selected patients with stage I NSCLC.

Video-assisted thoracic surgery (VATS)

No well-controlled randomized studies have been performed to compare the five-year survival rate between stage I lung cancer patients undergoing VATS resection or resection by the standard thoracotomy procedure. One randomized study,[27] although the sample size was relatively small, showed that the outcome was similar for the two different surgical approaches. Many other case studies have also indicated that the outcome following VATS was as good or better than that following standard thoracotomy in lung cancer patients.[28-33]

Concerning the extent of lymph node dissection, there have been sample data from a number of case series. In most of these studies, no significant difference in the potential extent of lymph node resection was found between VATS and the standard thoracotomic approach.[34-37] A prospective study to examine the effectiveness of the VATS approach for lymph node dissection in lung cancer patients showed that the percentage of lymph nodes that remained was 2-3%.[38] This figure may be a good estimate of the per-

centage of remaining lymph nodes after VATS.

Based on several large case series, recurrence at thoracoscopic port sites was reported in one per several hundred patients who underwent VATS.[29,33,34,39] No significant difference in the recurrence pattern was found between VATS and standard thoracotomy.[27] One study suggested that circulating tumor-derived mRNA level in the serum may increase in NSCLC patients during VATS,[40] but the clinical significance of such intraoperative mRNA overexpression of tumor cells during VATS procedures has remained unclear. In many studies, no significant difference in blood loss was noted between VATS and standard thoracotomy.[27,30,34-37,41-43]

The severity of postoperative pain was similar in VATS performed without the use of rib spreaders and muscle-sparing thoracotomy,[41] but patients undergoing VATS had less postoperative pain than those undergoing standard thoracotomy, which is a more invasive procedure than muscle-sparing thoracotomy.[30,35-37,42] As to the time required for surgery, one study reported that VATS required a longer time than standard thoracotomy,[42] but many other studies have reported that there is no significant difference between the two surgical approaches in respect of the time taken for the procedure.[27,34,41,43] Concerning the length of hospital stay, numerous studies have shown that there is no significant difference in the duration of hospitalization between patients undergoing VATS and those undergoing standard thoracotomy.[29-36,41,42,44] The postoperative quality of life was better in patients who underwent VATS without rib spreaders than in those who underwent posterolateral thoracotomy.[45] In addition, VATS was associated with less perioperative changes in the circulating cytokine profiles in the blood than posterolateral thoracotomy;[27,32,36,37,46,47] however, the clinical significance of this phenomenon has not yet been clarified.

The reported complication rate of VATS ranges from 5% to 32%.[29-33,43,44] One study showed that the postoperative complication rate of VATS performed without the use of rib spreaders was lower than that of muscle-sparing thoracotomy,[41] whereas another reported no significant difference in the complication rate between the two surgical approaches.[42] The reported operative mortality rate of VATS ranges from 0% to 6.8%.[29,30,32,33,43,44] One study reported that there was no significant difference in the operative mortality rate between VATS and standard thoracotomy.[42] The postoperative pulmonary functions after VATS and open thoracotomy procedures were similar.[28,34,37,42]

No large-scale well-controlled randomized trial has been performed to compare the outcome of patients undergoing VATS or standard thoracotomy for clinical stage I lung cancer. One randomized study conducted on a relatively smaller number of patients, however, reported that the outcome was similar for the two different surgical approaches.[41] Numerous case series have demonstrated that the outcome in patients undergoing VATS was as good or better than that of those undergoing standard thoracotomy. In regard to the potential extent of lymph node dissection, many researchers have shown that there is no significant difference between VATS and standard thoracotomy, however, a definitive conclusion has still not been arrived at. Concerning the low invasiveness of VATS, descriptive studies reported that VATS was associated with markedly reduced perioperative pain. In a randomized trial, however, the difference in the results did not reach statistical significance, perhaps because their sample sizes were too small.[41] Small randomized controlled trial and descriptive studies have shown that the perioperative safety of patients undergoing VATS is as good or superior to that those undergoing standard thoracotomy. Intraoperative hemorrhage or unexpected organ injury requiring emergency treatment can occur during VATS, but there are few data available about these events, as there is probably a tendency not to publicize adverse events. Thus, while there is not sufficient evidence to indicate the definitive superiority of VATS over open thoracotomy techniques, many descriptive studies have suggested that VATS may be very useful for the treatment of early stage lung cancer.

In clinical practice, VATS has already been used as a low invasive approach in the treatment of early stage NSCLC, as the curability of this cancer has been shown to be similar for VATS and open thoracotomy approaches. Well-controlled studies with strong statistical results need to be performed to provide strong evidence to support the use of VATS over conventional surgical techniques for NSCLC.

Recurrence

In patients with stage I lung cancer who underwent surgery, 60% of the postoperative deaths were attributed to recurrence of the disease, and 10% to multiple lung cancer.[7,8,48-51] In patients with pathological stage I NSCLC, 30% had recurrence after undergoing surgery for NSCLC. In these cases with recurrence, metastasis accounted for 70%.[7,8,48-51]

Postoperative Follow-up

In one follow-up study conducted employing imaging modalities, imaging diagnosis was found to be useful for the detection of recurrence that was asymptomatic in patients who had undergone surgery for NSCLC. The three-year survival rate was better in patients in whom the recurrence had been detected at an asymptomatic stage by imaging than in those in whom the recurrence was detected because of symptoms.[52] On the other hand, other studies showed no significant difference in the survival rate between these two patient groups.[53,54] Whole-body FDG-PET scan is expected to be useful for the detection of recurrence,[55] but further studies are required to clarify its possible benefits in the detection of recurrence in NSCLC patients who have undergone surgery. Walsh et al.[50] followed up 358 patients (including 190 patients with stage I lung cancer) who underwent complete resection of lung cancer. They showed that the detection rate of recurrent disease in the asymptomatic stage was only 24%. In addition, multivariate analysis revealed that the relapse-free survival duration was a significant predictive factor of survival after the recurrent malignancy appeared. They further indicated that the detection of recurrent disease in the asymptomatic stage did not favor the overall survival rate or the cost-effectiveness. An ideal follow-up program has still not been established for patients undergoing surgery for early stage NSCLC. Consideration in terms of the cost-effectiveness will also be necessary.

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