GENERAL THORACIC SUGERY

DETECTION OF CIRCULATING TUMOR CELLS IN PATIENTS WITH NON–SMALL CELL LUNG CANCER UNDERGOING LOBECTOMY BY VIDEO-ASSISTED THORACIC SURGERY: A POTENTIAL HAZARD FOR INTRAOPERATIVE HEMATOGENOUS TUMOR CELL DISSEMINATION

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Objective: We prospectively tested whether circulating tumor cells can be found in the preoperative, intraoperative, and postoperative peripheral blood of patients with resectable non–small cell lung cancer who undergo video-assisted lobectomy.

Methods: We assayed for carcinoembryonic antigen messenger RNA (mRNA) by reverse transcriptase–polymerase chain reaction in the peripheral blood taken before, during, just after the completion of the lobectomy and then 2 to 3 weeks, and again 5 to 6 weeks, after the operation in 29 patients with pathologic stage I non–small cell lung cancer who underwent video-assisted lobectomy. We also analyzed the prognostic value of carcinoembryonic antigen mRNA expression pattern in an additional 57 patients with stage I non–small cell lung cancer, whose blood samples were previously assayed for carcinoembryonic antigen mRNA.

Results: Of the 29 patients, the preoperative blood samples from 18 patients were negative for carcinoembryonic antigen mRNA. Of these 18 patients, 16 (89%) had positive test results during operation, although the remaining 2 patients (11%) consistently showed negative test results. The occurrence of this change from negative to positive tests results for carcinoembryonic antigen mRNA during video-assisted lobectomy was significantly higher than in patients who underwent open lobectomy in a previous study (18 of 35 patients; 51%; $P < .001$). In the 57 patients with stage I cancer whose blood samples were previously assayed for carcinoembryonic antigen mRNA, patients with persistently positive test results for carcinoembryonic antigen mRNA before and during operation had a significantly shorter survival when compared with those patients whose test results were persistently positive.

Conclusions: Video-assisted lobectomy, as compared with open lobectomy, for non–small cell lung cancer may increase the risk of seeding tumor cells into the circulation during operation. (J Thorac Cardiovasc Surg 2000;119:899-905)

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The recent introduction of video-assisted thoracic surgery (VATS) has allowed many procedures that previously required a thoracotomy to be performed by way of this "minimally invasive approach." Lung biopsy, wedge resection of pulmonary nodules, bullectomy, and resection of mediastinal tumors have now all been successfully and safely accomplished by a VATS approach.[1-3] Well-accepted advantages of VATS include decreased postoperative pain, shortened hospital stays, and a faster return to work.[4] Recently, VATS has been adopted by some thoracic surgeons as the preferred approach over the standard thoracotomy for the curative resection of lung cancer because it is associated with less morbidity. However, the intraoperative hematoge-

Table I. *Summary of CEA mRNA expression patterns in pre-, intra-, and postoperative peripheral blood samples from 32 patients with NSCLC who underwent VATS lobectomy in terms of pathologic TNM stage*

	RT-PCR for CEA mRNA						*Pathologic TNM stage*					
	I	*II*	*III*	*IV*	*V*	*VI*	*IA*	*IB*	*IIA*	*IIIA*	*Total*	*Clinical outcome*
Initially positive group (n = 13)	+	+	+	+	+	+	4	1	0	2	7	Two patients with stage IIIA died of recurrence
	+	+	–	–	–	–	3	0	0	0	3	All patients alive, disease-free
	+	–	–	–	–	–	3	0	0	0	3	All patients alive, disease-free
Initially negative group (n = 19)	–	–	–	–	–	–	2	0	1	0	3	All patients alive, disease-free
	–	+	+	–	–	–	11	1	0	0	12	All patients alive, disease-free
	–	+	+	–	+	+	1	0	0	0	1	All patients alive, disease-free
	–	+	+	–	–	+	2	1	0	0	3	All patients alive, disease-free
Total							26	3	1	2	32	

nous dissemination of tumor by this technique is a potential hazard. One limitation of the VATS technique is that lung tumors are often not visualized at all or, if visualized, are detected only as a distortion of the visceral surface and are palpable only with the fingertips. Therefore, the surgeon may inadequately identify the margins of the malignant tumor by VATS, as compared with the standard thoracotomy operation. In addition, compared with the open lobectomy procedure, the surgeon may need more frequent and stronger traction and more manipulation of the pulmonary lobes containing the tumor on all sides by forceps to get a better field of vision and to ligate the lobar bronchovascular pedicles. These technical problems of the VATS procedure raise concerns that VATS techniques may be more likely to disseminate malignant tumors than the type of manipulation that occurs during an open thoracotomy. However, in contrast to the many claims of benefits from the VATS procedure, there have been few studies to address this issue.

Although the presence of circulating tumor cells does not necessarily predict the subsequent appearance of clinical systemic disease, such tumor cells have the potential to establish metastases and so may have a negative influence on patient prognosis. Because the number of circulating cells may be very small, methods for their detection must be both sensitive and specific. Morphologic features, flow cytometry, conventional cytogenetics, and immunocytochemistry have been used to detect circulating tumor cells. However, these techniques are relatively insensitive, and some depend on the interaction of antibodies with tumor-associated cell-surface antigens.[5,6] Recent developments in molecular technology, including the advent of the polymerase chain reaction (PCR), have permitted the sensitive detection of circulating tumor cells in the peripheral blood.[5,7] We and others[8-11] have used the carcinoembryonic antigen (CEA) as the target gene because CEA messenger RNA can be detected in almost all epithelial cells, including cancer cells, but not in nonepithelial cells. If CEA mRNA is detected in blood samples, this implies the presence of ectopic epithelial cells and presumably cancer cells. The reverse PCR (RT-PCR) amplification method for CEA mRNA is an efficient means of detecting cancer cells in peripheral blood with a high sensitivity. This technique can detect 10 malignant cells in up to 10^7 normal cells.[12] The technique is also highly specific because no control blood samples from healthy volunteers were positive for CEA mRNA.[12]

In this study, we have detected, by means of an RT-PCR assay before, during, and after operation, the presence of CEA mRNA in the peripheral blood of patients with resectable non–small cell lung cancer (NSCLC) who underwent VATS lobectomy. In addition, to examine whether CEA mRNA expression pattern in the peripheral blood during the procedure is associated with the prognosis of patients with NSCLC, we performed a survival analysis for an additional 57 patients with resectable NSCLC who underwent a curative lobectomy with a standard open thoracotomy and whose blood samples were previously assayed for CEA mRNA.[11] Because insufficient time has elapsed to analyze the prognosis in patients in the present study, we were unable to determine the prognostic significance of CEA mRNA detection in patients who underwent resection by VATS.

Patients and methods

Patients. During the 24-month period starting in July 1997, 36 patients with confirmed or what, before the operation, was thought to be stage IA (T1 N0 M0) or stage IB (T2 N0 M0) NSCLC were entered into this study after informed consent had been obtained in accordance with the ethics committees of our institutions. During the same period, 68

patients with stage I NSCLC underwent open lobectomy on patient request. The 2 populations of patients resemble each other with respect to age, sex, smoking history, histologic type, and pathologic TNM classification. Two of the 36 patients in this study proved to have nonmalignant disease at the time of operation and were therefore excluded from the study. Two additional patients required conversion to a standard posterolateral open thoracotomy because there was some difficulty in safely dissecting the interlobar pulmonary artery or because of incomplete fissures; these patients were therefore also excluded from the study. This left 32 patients with NSCLC who underwent VATS lobectomy (Table I). Of these 32 patients, 1 had postoperative pathologic N1 disease and 2 had postoperative pathologic N2 disease. Consequently, this study includes 26 patients with stage IA (T1 N0), 3 patients with stage IB (T2 N0), 1 patient with stage IIA (T1 N1), and 2 patients with stage IIIA (T1 N2 and T2 N2), according to the newly revised classification of the American Joint Committee on Cancer and the Union Internationale Contre le Cancer.[13] There were 10 men and 22 women, with an age range of 37 to 83 years (mean, 63 years). The histologic distribution of the resected tumor specimens was 29 adenocarcinomas, 2 squamous cell carcinomas, and 1 carcinoid, based on the World Health Organization Histologic Typing of Lung Tumors.[14] The median follow-up period was 12 months (range, 1-24 months).

All surgical procedures were performed after the patient had been given a general anesthetic and with the use of single-lung ventilation through a double-lumen endotracheal tube (Broncho-Cath; Mallinckrodt Medical Inc, St Louis, Mo). Patients were placed in the lateral decubitus position with arms extended on an arm rest. VATS lobectomy was performed by techniques previously described, which included a 6- to 8-cm access thoracotomy, through which standard thoracic instruments were introduced without rib spreading.[15,16] The operations performed for the 32 patients with NSCLC were right upper lobectomy in 11, right middle lobectomy in 1, right lower lobectomy in 8, left upper lobectomy in 6, and left lower lobectomy in 6. Pulmonary vessel mobilization and ligation and hilar and mediastinal lymph node dissection were performed in a manner similar to those used in the conventional thoracotomy approach. All the surgical procedures were uniformly and successfully performed by the same 2 authors (J.Y. and N.F.). All the patients had uneventful postoperative recoveries.

Blood samples. During the operation, a polyethylene catheter (Becton Dickinson, Sandy, Utah) was inserted into the radial artery of the contralateral arm (opposite the lobectomy side) for monitoring the heart rate and blood pressure. Blood samples were taken from this line just before the operation (point I); 5 minutes after the ligation of the pulmonary vein or the pulmonary artery (point II); 5 minutes after both the pulmonary artery and pulmonary vein were ligated (point III); and 5 minutes after the completion of the lobectomy (point IV). Blood samples were also taken from the radial artery after 2 to 3 weeks (point V) and at 5 to 6 weeks (point VI) after the operation. In case of blood sampling at points V and VI, the first sampling blood was abandoned to avoid contamination from skin.

Table II. *Summary of CEA mRNA expression patterns before and during operation in the peripheral blood samples from 57 patients with stages IA or IB NSCLC who underwent open lobectomy*

	*RT-PCR for CEA mRNA pattern (I, II, III, IV)**	*No. of patients (% per subtotal)*	*% Per total*
Initially positive group (n = 22)	A (++++)	6 (27)	11
	B (++ – –, + – – –)	16 (73)	28
Initially negative group (n = 35)			
	C (– ++ –)	18 (51)	30
	D (– – – –)	17 (49)	32
Total		57 (100)	

*I, II, III, and IV represent the 4 blood sampling points in each patient, as described in the text.

RT-PCR for CEA mRNA. The RT-PCR for CEA mRNA was performed as described previously.[11] This RT-PCR assay could detect CEA mRNA at a cell frequency as low as 10 EBC-1 cells per 10^7 peripheral blood leukocytes in an in vitro model.[12] In addition, none of the preoperative or postoperative blood samples from 15 patients with interstitial pulmonary fibrosis who underwent an open-lung biopsy for the histologic diagnosis nor any of 32 control blood samples obtained from healthy volunteers were positive for CEA mRNA by RT-PCR.[12]

Survival analysis. An important unresolved question is whether the patients with positive CEA mRNA findings might have more metastases, shorter survivals, or shorter disease-free intervals than those who did not have positive findings. However, in this series of patients, insufficient time has elapsed to perform the survival analysis, and none of the 29 patients with stages IA or IB NSCLC experienced recurrence, although both patients with stage IIIA died of recurrence (Table I). Therefore, to determine whether there is a correlation between the CEA mRNA expression pattern in the peripheral blood samples and prognosis of patients with NSCLC, we performed disease-free and overall survival analyses in the previously reported 57 patients. These patients had pathologic stage I NSCLC (32 patients with stage IA and 25 patients with stage IB) and underwent a curative lobectomy by a conventional open thoracotomy procedure,[11] accompanied by pre- and intraoperative CEA mRNA determinations in peripheral blood. Blood samples were not taken from these patients at the time of 2 to 3 weeks (point V) or 5 to 6 weeks (point VI) after the operation.

Statistics. Differences in the occurrence of CEA mRNA expression pattern in the blood samples were calculated by the χ^2 test or the Fisher exact probability test. The disease-free survival and overall survival curves were generated by the Kaplan-Meier method.[17] The univariate Cox regression model was used to test for survival differences.

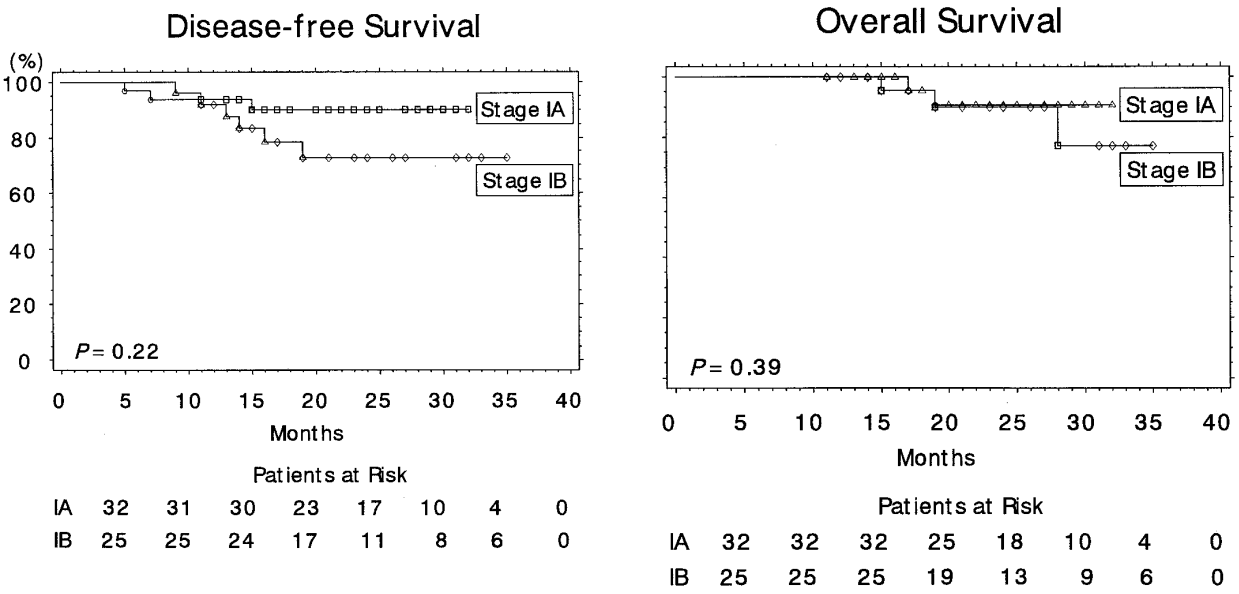

Fig 1. Disease-free and overall survival in 57 patients with NSCLC who underwent conventional open lobectomy in terms of pathologic TNM stage during operation.

Results

CEA mRNA expression in blood before, during, and after VATS. The CEA mRNA expression pattern in the peripheral blood samples before, during, and after operation for the 32 patients with NSCLC who had undergone VATS lobectomy as it relates to pathologic TNM stage is summarized in Table I. The blood samples of both patients with stage IIIA NSCLC were consistently positive (ie, positive at all sampling points). The blood samples of 1 patient with stage IIA disease (carcinoid) were consistently negative at all sampling points. When we analyzed CEA mRNA expression pattern in patients with stage IA or IB disease, the preoperative blood samples from 11 of 29 patients (38%) were positive for CEA mRNA. Of these 11 patients, 5 patients (45%) showed consistently positive CEA mRNA during and after operation (ie, positive at all sampling points), although the remaining 6 patients (55%) were found to have negative samples during and after the operation (ie, at sampling points III-VI or II-VI). On the other hand, in 18 patients with preoperative negative CEA mRNA blood samples, 16 patients (89%) had detectable CEA mRNA in peripheral blood during or after operation (ie, positive at points II and III, II, III, V and VI, or II, III, and VI), although samples from the remaining 2 patients (11%) were consistently negative at all sampling points.

We compared the occurrence of each CEA mRNA expression pattern in 29 patients with stage IA and IB NSCLC who underwent VATS lobectomy in this study to 57 patients who underwent open lobectomy and whose blood samples were assayed for CEA mRNA by RT-PCR at sampling points I, II, III, and IV in our previous study.[11] The treatment groups were comparable in terms of baseline characteristics, such as age, gender, smoking history, and histologic type (data not shown). Table II shows the summary of CEA mRNA expression patterns in the 57 patients with stages IA or IB NSCLC. Those are pattern A (persistently positive for CEA mRNA at all sampling points; positive at points I-IV), pattern B (preoperative positive CEA mRNA, which was negative during the operation; positive only at sampling points I and II or I), pattern C (before the operation, negative for CEA mRNA but positive when sampled during the operation; positive only at points II and III), and pattern D (consistently negative for CEA mRNA; negative at all 4 sampling points).

In the present VATS group, the preoperative blood samples from 11 of 29 patients (38%) with stage I NSCLC were positive for CEA mRNA, which is almost the same occurrence in the 57 patients in our previous study (22/57 patients; 39%). Of these 11 patients, 5 patients (45%) showed consistently positive CEA mRNA during and after operation, although the remaining 6 patients (55%) were negative for CEA mRNA during the operation and remained negative after the operation. The occurrence of patients with a consistently positive pattern during the opera-

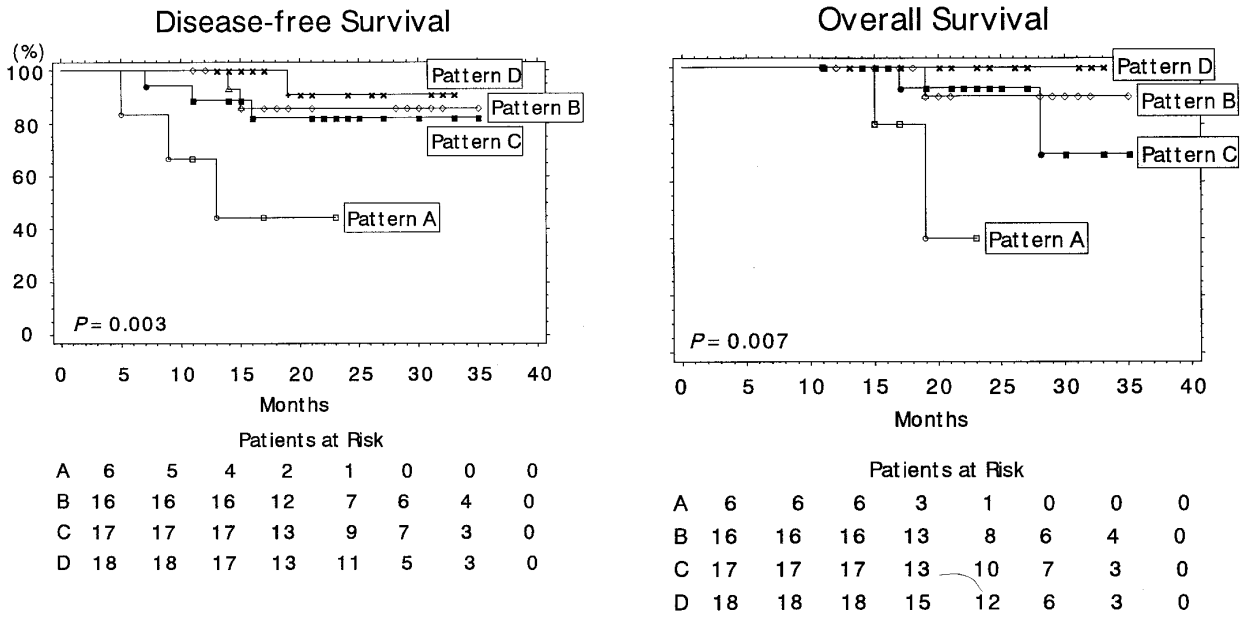

Fig 2. Disease-free and overall survival in 57 patients with NSCLC who underwent conventional open lobectomy in terms of CEA mRNA expression pattern during surgery. At sampling points I through IV: *Pattern A*, + + + +; *Pattern B*, + + – – or + – – –; *Pattern C*, – + + –; *Pattern D*, – – – –.

tion tended to be higher in the present VATS lobectomy group (5/11 patients; 45%) than in the open lobectomy group (6/22 patients; 27%; $P = .09$). However, when compared with patients with initially negative samples for CEA mRNA, 16 of 18 patients (89%) with initially negative CEA mRNA blood samples were positive for CEA mRNA during operation (ie, positive at sampling points II and III in the present study). The occurrence of this change (89%) was significantly higher than that in the open lobectomy study (18/35 patients; 51%; $P < .001$).

Prognostic analysis of CEA mRNA expression pattern in patients with NSCLC who underwent open lobectomy. To examine whether the CEA mRNA expression pattern in the peripheral blood during operation is associated with the prognosis of patients with NSCLC, we analyzed the prognostic value of CEA mRNA expression pattern in the 57 patients with stage IA or IB NSCLC whose blood samples were previously assayed for CEA mRNA by RT-PCR at sampling points I, II, III, and IV.

Fig 1 shows disease-free and overall survival curves that are stratified by pathologic TNM stage in the peripheral blood during the operation. There is no statistical difference in disease-free and overall survival between patients with stage IA and stage IB NSCLC. However, when the patient prognosis was analyzed in terms of CEA mRNA expression pattern in the peripheral blood during the operation, patients with pattern A (ie, positive at all 4 sampling points) had a significantly shorter disease-free and overall survival when compared with those patients with the other 3 patterns for CEA mRNA expression during operation (Fig 2). With respect to overall survival, patients with pattern C (ie, positive only at sampling points II and III) are likely to have a poorer prognosis when compared with those patients with patterns B (positive before operation only) and D (negative at all sampling points). However, there was no statistical difference in overall survival between patterns C and B and patterns C and D.

Discussion

Current imaging techniques allow the operating surgeon to see only the visceral and parietal pleural surfaces of the thoracic cavity, with palpation of tissues limited to what can be reached by fingertips inserted between ribs. This limitation of VATS procedure raises concerns that VATS techniques may be more likely to disseminate malignant tumors than the type of manipulation that occurs during an open thoracotomy. Pulling the tumor mass by instruments through relatively small incisions may disrupt the tumor. It may even be possible that the assisting surgeon may accidentally grasp the tumor directly. It is also possible that

hematogenous cancer cell dissemination could result from frequent attempts to pull the pulmonary lobe containing the tumor from all sides by forceps to get a better field of vision and to ligate the lobar bronchovascular pedicles through a small chest incision. All these technical limitations of VATS do not allow surgeons to perform a "gentle handling" of the malignant tumor as compared with the standard open surgery.

In the present study, we have determined the percentage of patients with resectable NSCLC who underwent VATS lobectomy and who have detectable levels of tumor cells in their circulation before, during, and after operation; RT-PCR was used to detect CEA mRNA. We have compared the occurrence of CEA-expressing cells to that of patients with NSCLC who had undergone open lobectomy in our previous study.[11] A surprising difference in the CEA mRNA expression pattern between the present VATS lobectomy group and the previously studied open lobectomy group was observed in patients who tested negative for CEA mRNA before operation. In 18 patients with stage I NSCLC with initially negative CEA mRNA blood samples in the present study, 16 patients (89%) had detectable CEA mRNA in the circulation during the operation. The occurrence of this change (89%) was significantly higher than that in the open lobectomy study (18/35 patients; 51%).

It is not clear why the rate of intraoperative positive CEA mRNA was higher in the initially negative group than in the initially positive group. One possible explanation is that sampling errors may be occurred. In this study, we performed single-point blood sampling. However, because cancer cells may be shed intermittently into the bloodstream,18 patients who have negative blood results might have circulating tumor cells intermittently at another time or under other circumstances. Future study is necessary regarding whether sampling errors occur when only single-point blood samples are taken.

Although the number of patients is small, there were 4 patients whose CEA mRNA expression pattern was initially negative, was detectable during but not immediately after the operation, and then was positive again several weeks after the operation (points V and/or VI). The meaning of this finding is unclear. It is generally believed that most of the cancer cells shed into the bloodstream of the tumor will be destroyed ultimately by natural defense mechanisms and that very few tumor cells succeed in establishing secondary tumors.[19] However, a possible explanation for our finding is that some tumor cells that were shed into the bloodstream by the surgical manipulation may survive in a selected subset of patients. These could succeed in establishing secondary tumors, which could in turn shed tumor cells into the bloodstream at some interval after the operation.

To date, it is not clear whether the technical problems of VATS lobectomy will lead to an increased risk of recurrence or metastasis. In 57 patients with stage I NSCLC, although they had undergone open lobectomy but not VATS lobectomy, patients who have persistently positive blood samples during operation showed significantly worse prognoses than any other expression patterns for CEA mRNA. Thus patients who have persistently positive blood samples during operation may be considered at highest risk for systemic relapse. However, it remains unclear (in patients with NSCLC who have undergone VATS lobectomy) whether patients who have persistent evidence of circulating tumor cells by RT-PCR for CEA mRNA or who have detectable CEA mRNA both during and several weeks after the operation show worse prognoses than those patients with no evidence of circulating tumor cells a few weeks after the procedure.

We realize that the participants in this study have had less experience with the VATS lobectomy procedure compared with their extensive experience with open lobectomy. Lewis,[20,21] McKenna,[22] and their associates reported a larger series of VATS lobectomies for lung cancer with favorable prognoses. There may be possible differences related to learning curve issues and more manipulation in the early going in our hands versus more experienced investigators. Therefore it may be too early to try to draw definite conclusions. However, our findings should alert surgeons, at least at this time and at least for inexpert surgeons, to the possible danger of tumor dissemination during a VATS lobectomy for NSCLC and suggest that this type of operation has the potential to adversely influence long-term survival of patients with NSCLC. The long-term follow-up of our patient cohort will provide data on the prognostic relevance of circulating tumor cells and will also answer the important question of whether the technical problems of VATS lobectomy will actually lead to an increased risk of systemic disease as compared with open lobectomy.

The long-term control of disease, particularly malignant disease, is of far more importance to the patient than short-term goals such as pain control and length of hospital stay.[23-25] In many institutions, insufficient time has elapsed to report on the 5-year survival of patients with NSCLC after VATS lobectomy, the ultimate criterion in the management of lung cancer. The potential short-term benefit or the surgeon's ability to perform a VATS procedure is of little value to the patients with lung cancer if the goal of long-term survival is compromised. Before the widespread adoption of VATS

procedures for the curative resection of lung cancer, future long-term follow-up studies are needed.

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