Patterns of survival and recurrence after surgical treatment of early stage non–small cell lung carcinoma in the ACOSOG Z0030 (ALLIANCE) trial

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Objective: Surgical resection has been the mainstay of curative treatment of early stage lung cancer in selected patients. We evaluated survival and patterns of recurrence after surgical resection for early stage lung cancer from the American College of Surgeons Oncology Group Z0030/Alliance trial.

Methods: One thousand eighteen patients enrolled in the Z0030 trial were analyzed according to clinical T stage. Differences between groups were compared using the 2-sample rank test or χ^2 test. Log rank test and Cox proportional hazards regression were used to compare survival and recurrence. To compare patients who underwent open versus video-assisted thoracoscopic surgery (VATS) resections, propensity-score matched analysis was performed. Seven hundred fifty-two patients (66 undergoing VATS and 686 undergoing open surgery) were classified into 5 equal-sized propensity-score groups. Proportional hazards regression was used to compare these outcomes.

Results: There were 578 patients with cT1 tumors and 440 patients with cT2 tumors. Median follow-up was 6.7 years. Median overall survival was 9.1 years (stage T1) and 6.5 years (stage T2). Overall survival at 5 years was 72% (stage T1) and 55% (stage T2). Local recurrence-free survival at 5 years was 95% (stage T1) and 91% (stage T2) ($P = .015$). Among patients with stage T1 cancer, 4.2% (23 out of 542) had local recurrences, whereas 7.3% (30 out of 409) of those with stage T2 tumors had local failure. There was no difference in the development of new primary tumors between stage T1 and stage T2 groups. In the propensity-score matched analysis of VATS versus open lobectomy patients, there was no difference in overall survival, disease-free survival, and freedom from development of a new primary tumor.

Conclusions: Results of patients with resected early stage non–small cell carcinoma from a large-scale, multicenter trial serve as benchmarks against which to compare nonsurgical therapies for early stage lung cancer. Propensity-score matched analysis shows no difference in survival between patients undergoing VATS and open lobectomy. (J Thorac Cardiovasc Surg 2014;147:747-53)

Surgical resection has been the gold standard for curative treatment of early stage lung cancer in appropriately selected patients. However, over the past decade, new technologies for treating early stage non–small cell lung carcinoma (NSCLC) have emerged as alternatives for patients who may be poor or marginal operative candidates. Outcomes of surgical treatment are needed to serve as reference points against which to compare the outcomes of these nonsurgical therapies in early stage lung cancer.

We performed a secondary analysis of a large-scale multicenter, randomized trial to determine the long-term clinical outcomes of patients undergoing surgical treatment for early stage NSCLC. The American College of Surgeons Oncology Group (ACOSOG) Z0030 (Alliance) trial was a prospective, randomized, multi-institutional clinical trial that was designed to determine the effect on survival of lymph node sampling versus mediastinal lymph node dissection in patients undergoing complete resection of early stage NSCLC.[1] Once the primary endpoints of the study were reached, we secondarily analyzed the data to determine overall survival and patterns of recurrence. The advantages of this dataset include the rigor and uniformity with which the trial was conducted regarding eligibility criteria, staging procedures, data collection, and surgical techniques as well as the fact that these data were audited. The long-term results derived from this study serve as benchmark data against which to compare the results of more recent nonsurgical therapies for the treatment of early stage lung cancer.

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Abbreviations and Acronyms

ACOSOG = American College of Surgeons Oncology Group
NSCLC = non–small cell carcinoma
VATS = video-assisted thoracoscopic surgery

METHODS

Details of the study design, eligibility requirements, and the morbidity and mortality of patients enrolled in the ACOSOG Z0030 (Alliance) trial have been previously reported.[1,2] The protocol was approved by a central institutional review board in addition to the institutional review board at each participating institution. All patients provided written informed consent before trial enrollment. In summary, eligible patients were required to be older than age 18 years, to have an Eastern Cooperative Oncology Group performance status lower than 3, and a tissue diagnosis of NSCLC clinical stage T1 or T2, N0 or non-hilar N1, M0 before randomization. Eligible patients had to be candidates for resection by means of pneumonectomy, lobectomy, bilobectomy, or segmentectomy. The type of resection (video-assisted thoracoscopic surgery [VATS] vs open) was recorded in the dataset. Patients with N2 metastases were excluded from randomization.

There were 1023 eligible patients who were evaluated for the following long-term outcomes: local, locoregional, distant recurrence, disease-specific, and overall survival (5 were excluded because clinical stage was not reported in the database). Thus in this study we evaluated 1018 patients by clinical T classification: 578 patients with T1 tumors and 440 patients with T2 tumors. Based on the Z0030 dataset definitions, recurrence was defined as local if it occurred in the adjacent lung parenchyma, bronchial stump, or the hilum adjacent to the bronchial stump. It was defined as regional if it occurred in the hilum (separate from bronchial stump), mediastinum, chest wall, or ipsilateral pleura. Recurrence was defined as distant if it occurred in a separate lobe of ipsilateral lung, contralateral thorax, supraclavicular lymph nodes, or distant organ.

Statistical Methods

Differences between groups with regard to clinical and tumor characteristics were compared using the 2-sample rank test or χ^2 test as appropriate. Cumulative survival probabilities were estimated using the Kaplan-Meier method. The log rank test and Cox proportional hazards regression were used to compare survival and recurrence across groups.

As an additional analysis, we evaluated the Z0030 dataset based on propensity-score matching to compare patients who underwent open versus VATS anatomic lung resections.[3] Clinical and tumor characteristics were used to build a propensity score for choice of treatments. These variables included age, sex, histology, performance status, tumor location, and clinical T classification (T1 vs T2). Propensity scores were developed to estimate the adjusted risks of perioperative outcomes associated with the approach of treatment (VATS vs open). Logistic regression was used to estimate the probability of VATS versus open given the previously listed risk factors. Patients were classified into 7 groups based on their propensity scores. Two hundred eight thoracotomy patients had lower scores than the lowest score of any VATS patient treated (group 0); 4 open lobectomy patients had higher scores than the highest VATS patient treated (group 6). Patients from these 2 groups were omitted from further analysis.[3] The remaining 752 patients (66 in the VATS group and 686 in the open lobectomy group) were classified into 5 equal-sized propensity score groups (groups 1-5). Proportional hazards regression with 5 strata (propensity score groups 1-5) was used to compare long-term outcomes between patients undergoing VATS and those undergoing an open procedure.

TABLE 1. Characteristics of patients in the American College of Surgeons Oncology Group Z0030/Alliance trial by clinical classification (n = 1023)

Clinical classification	n	%
T stage		
cT1	578	57
cT2	440	43
Pathologic stage		
IA	423	41
IB	418	41
IIA	37	4
IIB	97	9
IIIA	26	3
IIIB	19	2

RESULTS

Overall Survival

There were 1018 patients who were evaluated by clinical T classification: 578 patients with T1 tumors and 440 patients with T2 tumors. The stratification by clinical T classification is shown in Table 1. Median follow-up was 6.7 years in the entire cohort. The median overall survival for patients with T1 tumors was 9.1 years, whereas that for those with T2 tumors was 6.5 years. Overall survival and disease-free survival for clinical T1 and T2 patients are shown in Table 2.

The 5-year overall survival was 72% for T1 patients and 55% for T2 patients ($P < .001$) (Figure 1). Disease-free survival at 5 years was 77% for patients with T1 tumors and 58% for those with T2 tumors ($P < .001$) (Figure 2).

Local and Locoregional Recurrence

The 5-year local recurrence-free survival for the T1 cohort was 95% and for T2 group 5-year local recurrence-free survival was 91% ($P = .015$).

The 5-year locoregional recurrence-free survival was 88% for T1 patients, 84% for T2 patients ($P = .044$). The 5-year distant disease-free survival for the T1 patients was 83% and for the T2 patients was 66% ($P < .001$) (Table 2).

Of 542 patients with T1 tumors assessed for recurrence, 4.2% had local recurrences and 17.3% had distant metastases. Among patients with T1 tumors who were reported to develop recurrent tumor (125 patients), 6% of total recurrences were local alone, whereas 75.2% of recurrences were distant in nature (Table 3).

Of 409 patients with T2 tumors assessed for recurrence, 7.3% had local recurrences and 30.8% had distant metastases. Among patients with T2 tumors who developed recurrent tumor (156 patients), 8% of total recurrences were purely local, whereas 80.8% of recurrences included distant metastases (Table 3).