Factors predicting poor survival after resection of stage IA non-small cell lung cancer

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Objective: Using a national cancer registry, we determined the postoperative survival of patients with stage IA non-small cell lung cancer in the United States from 1988 to 1997 and identified factors that affect survival.

Methods: Within the Surveillance, Epidemiology, and End Result Program database, 10,761 patients were identified as having stage IA non-small cell lung cancer and underwent curative surgical resection from 1988 to 1997. Univariate analyses were performed by the log-rank test to determine predictors of survival, and multivariable analysis was performed by a Cox regression model.

Results: Overall 5-year survival was 58%. On univariate analysis, tumor size, gender, age, and extent of resection were significant predictors of survival. Five-year survival of patients with tumors 2.1 to 3.0 cm was lower than that for patients with tumors 2.0 cm or smaller: 55% versus 60% ($P < .0001$). Men fared significantly worse than women, with a 5-year survival of 53% versus 63% ($P < .0001$). Patients older than the median age of 67 years had worse 5-year survival than had those under the median age: 52% versus 65% ($P < .0001$). Patients undergoing sublobar resections showed poorer 5-year survival than patients undergoing anatomic resections: 44% versus 61% ($P < .0001$). On multivariable analysis with a Cox regression model, all 4 variables remained statistically significant.

Conclusion: The survival of patients with stage IA non-small cell lung cancer within the United States is significantly worse than survival reported from single-institution studies. This study identifies 4 factors that may affect survival in resected stage IA non-small cell lung cancer: tumor size, gender, age, and extent of resection.

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Lung cancer is the leading cause of cancer deaths among both men and women in the United States. There are approximately 170,000 new cases of lung cancer annually and 160,000 deaths annually from lung cancer.¹ Fewer than 20% of patients diagnosed with lung cancer are candidates for surgical resection. Of those patients undergoing surgical resection, patients with stage IA disease (T1 N0 M0) have the best chance of cure. A multi-institutional study reported a 67% 5-year survival for patients undergoing resection for stage IA disease.² In contrast, single-institution studies have generally reported better 5-year survivals, ranging from 65% to 90%.³⁻⁸ There are no studies detailing the survival of patients with stage IA

Abbreviations and Acronyms

NSCLC = non-small cell lung cancer

SEER = Surveillance, Epidemiology, and End Result (database)

disease across a large population base, including both community hospitals and academic centers.

Within the stage IA designation, there may be patient characteristics that influence long-term survival. A number of investigators have reported that tumor size influences survival within the stage IA classification.^{5,8-12} Others have found no correlation between size and survival within stage IA.^{13,14} Female gender has also been found in several studies to confer a survival advantage over male patients with non-small cell lung cancer (NSCLC) across all stages.¹⁵⁻¹⁷ In several studies, patient age has been found to be a predictor of postoperative survival in stage I and II NSCLC.^{18,19} The issue of whether a sublobar resection results in worse long-term survival than that of anatomic resection has been studied by numerous investigators. Some single-institution, nonrandomized, retrospective studies have found poorer survival with sublobar resections,^{5,9} whereas other single-institution, nonrandomized studies of stage IA NSCLC showed no difference in survival between lobectomy and sublobar resections.^{6,7} A prospective, randomized, multi-institutional trial by the Lung Cancer Study Group²⁰ reported statistically significant survival advantage in favor of the lobectomy group (all causes of death, $P = .088$; P value for significance level set at 0.1 in study design). The results were later revised but did not change the conclusions of the study.²¹

This study was conducted to determine the survival of patients with stage IA NSCLC who underwent curative resection from 1988 to 1997 across a broad population base in the United States using the Surveillance, Epidemiology, and End Result (SEER) database. Furthermore, this study individually examines the impact of tumor size, gender, patient age, and extent of surgical resection on survival within this cohort. Finally, these prognostic factors are combined in a multivariable Cox proportional hazards model to determine which factors remain independent predictors of survival.

Materials and Methods

The SEER Program is a database of cancer incidence and survival in the United States sponsored by the National Cancer Institute. From its inception in 1973, the program has collected clinicopathologic data from population-based cancer registries and currently covers 26% of the US population. It is estimated that the SEER Program captures 98% of all cancer cases in these geographic areas.²² The cancer registries include most of California, Connecticut, Iowa, New Mexico, Utah, Hawaii, the Detroit, Atlanta, and Seattle metropolitan areas, and parts of Georgia and Arizona. The

entire state of California, New Jersey, Kentucky, and Louisiana were added in 2001. From the SEER registry spanning the years 1973 to 2000, we identified all cases of lung cancer (tumor site code 34.0 to 34.9), which totaled 414,867 patients. Additionally, using the International Classification of Diseases for Oncology-2 morphology codes, we selected only cases of NSCLC, eliminating all patients with small cell carcinoma, neuroendocrine tumor, mesothelioma, carcinoid tumor, and sarcoma.

Starting in 1988, detailed stage and extent of disease data were added to the SEER registry; therefore, we confined our analysis to 1988 and later. The coding for extent of surgery changed after 1997; therefore, we ended our analysis with the year 1997. We restricted the analysis to the following criteria: patients with diagnostic confirmation of NSCLC (SEER confirm code > 4); patients who underwent curative surgical resection (SEER reason code = 0); tumors less than or equal to 3.0 cm (SEER tumor size code ≤ 30); absence of lymph node metastasis (SEER lymph node code = 0); and absence of visceral pleural involvement or location within 2 cm of the carina or distant metastasis (SEER extension code). We identified 10,761 patients with T1 N0 M0 disease who underwent curative surgical resection. We defined curative surgical resection as any operation other than local tumor destruction or excision; thus, we included patients undergoing wedge resections and segmentectomies.

The SEER database contains a variety of patient demographic data, cancer staging data, and some treatment data. We made an a priori decision to investigate tumor size, gender, age, and extent of resection for effect on survival. We partitioned the patients by tumor size (0.1–2.0 cm or 2.1–3.0 cm), age (above or below the median of 67 years), and extent of resection (sublobar resection vs lobectomy or greater, SEER site-specific surgery code). For the univariate analyses, we constructed survival curves using the Kaplan–Meier method and compared survival between groups using log-rank tests. Multivariable analysis was performed by constructing a Cox proportional hazards model using the significant factors ($P < .05$) from the univariate analyses: tumor size, gender, age, and extent of resection. The analyses were performed with the SASv8 statistical software program (SAS Institute, Inc, Cary, NC).

Results

There were 10,761 patients who met the inclusion criteria for the study: stage IA NSCLC undergoing curative resection. The 1-, 3-, and 5-year survival rates for the entire group were 90.2%, 71.5%, and 57.8%, respectively. [Table 1](#) shows the 1- to 5-year survivals of the entire SEER group compared with the survival data reported by Mountain.² None of the 95% confidence intervals for the SEER group contain the survivals reported by Mountain, which suggests survival is worse in our study. Moreover, during the period of this analysis, 1988 to 1997, we did not observe a trend toward improvement in survival by year of diagnosis (log-rank test; $P = .69$).

The results of the univariate analyses examining the effect of tumor size, gender, age, and extent of resection are summarized in [Table 2](#), and the corresponding Kaplan–Meier survival plots are shown in [Figure 1](#). We examined

TABLE 1. Survival using the Kaplan–Meier method with 95% confidence intervals as compared with survival reported by Mountain²

	Mountain (n = 511)	SEER (n = 10,761)	
	%	%	95% CI (%)
1 y	94	90.2	89.6-90.8
2 y	86	80.3	79.5-81.1
3 y	80	71.5	70.6-72.4
4 y	73	64.3	63.4-65.2
5 y	76	57.8	56.8-58.8

CI, Confidence interval.

the effect of tumor size on survival, using tumor size as a linear continuous variable. The size of the tumor significantly affected survival with a hazard ratio of death per millimeter tumor size of 1.014 ($P < .0001$). To simplify interpretation, we dichotomized tumor size into 0.1 to 2.0 cm and 2.1 to 3.0 cm. There were 6161 patients with tumors 0.1 to 2.0 cm in size and 4600 patients with tumors 2.1 to 3.0 cm in size. Patients in the small tumor group had better 5-year survival than patients with larger tumors: 60.3% versus 54.5% (log-rank test; $P < .0001$). The hazard ratio for death for having a tumor 2.1 to 3.0 cm compared with a tumor 0.1 to 2.0 cm is 1.183. Within the small tumor group, we compared patients with tumors from 0.1 to 1.0 cm to patients with tumors 1.1 to 2.0 cm. There was no difference in survival (log-rank test; $P = .78$); therefore, these patients were grouped together.

There were 5320 women and 5441 men in the study group (Table 2). Examining the effect of gender on survival, we found women had superior 5-year survival compared with men: 63.0% versus 52.8% (log-rank test; $P < .0001$). The hazard ratio of death for being male was 1.328. On average, women had slightly smaller tumors (1.98 cm vs

2.05 cm) and were younger than men (median age 67 years vs 68 years).

The effect of age on survival after surgical resection was examined (Table 2). We performed the analysis using age as a linear continuous variable and found it to be statistically significant (hazard ratio 1.034; $P < .0001$; results not shown). For ease of interpretation, we dichotomized age by the median age 67 years. There were 4936 patients under the median age of 67 and 5825 patients aged 67 or greater. Patients under the median age had better 5-year survival than patients over the median: 65.2% versus 51.5% (log-rank test; $P < .0001$). The hazard ratio for death for being in the older age group was 1.664. On average, the older patients had slightly larger tumors than the younger patients: 1.97 cm versus 2.06 cm.

We analyzed the survival of patients who underwent sublobar resection (wedge resection and segmentectomy) compared with patients who underwent lobectomy (or greater resection). Of the 10,761 patients in the study group, 8527 patients underwent lobectomy or greater resections, and 2234 patients underwent sublobar resections (Table 2). The lobectomy group had better 5-year survival than the sublobar group: 61.4% versus 44.0% (log-rank test; $P < .0001$). The hazard ratio for death for having a sublobar resection was 1.621. On average, patients undergoing lobectomy had larger tumors (2.07 cm vs 1.82 cm) but were younger (median age 67 vs 69) than the patients undergoing sublobar resections. These data need to be interpreted with caution inasmuch as the SEER database does not contain comorbidity data or pulmonary function tests, which may have influenced the choice of operation by the treating physician. Therefore, the sublobar group may have risk factors, not contained within this database, that influence their long-term survival after resection. Additionally, patients with sublobar resections may not have undergone

TABLE 2. Univariate analysis

Patient characteristic	n	Survival*					P value†	Hazard ratio‡
		1 y (%)	2 y (%)	3 y (%)	4 y (%)	5 y (%)		
Size of tumor								
0.1-2.0 cm	6161	91.4	82.0	73.9	67.0	60.3		
2.1-2.9 cm	4600	88.5	78.1	68.3	60.8	54.5	<.0001	1.183
Gender								
Female	5320	92.4	83.6	75.6	69.1	63.0		
Male	5441	88.0	77.1	67.5	59.7	52.8	<.0001	1.328
Age								
<67 y	4936	92.7	84.4	77.5	71.0	65.2		
≥67 y	5825	88.0	76.9	66.5	58.7	51.5	<.0001	1.664
Extent of resection								
Lobe +	8527	90.5	82.1	74.0	67.5	61.4		
Sublobar	2234	88.7	73.4	62.0	52.2	44.0	<.0001	1.621

*Kaplan–Meier survival estimates. †Log-rank test. ‡Cox proportional hazard model containing 1 variable.

Figure 1. A, Kaplan–Meier survival estimates comparing patients having tumors 0.1 to 2.0 cm with patients having tumors 2.1 to 3.0 cm. B, Kaplan–Meier survival estimates comparing women with men. C, Kaplan–Meier survival estimates comparing patients younger than 67 years old with patients 67 years or older. D, Kaplan–Meier survival estimates comparing patients undergoing lobectomy with patients undergoing sublobar resection.

mediastinal or hilar lymph node dissection and, therefore, the stage may be underestimated.

To determine whether all 4 variables remain significant in a multivariable analysis, we created a Cox proportional hazards model with the 4 significant variables: gender, tumor size, age, and extent of resection. All 4 variables remained statistically significant with P values $< .0001$. The hazard ratios, 95% confidence intervals, and P values are summarized in Table 3.

TABLE 3. Hazard ratios, 95% confidence intervals, and P values for the 4 variables entered into the Cox proportional hazards model

	Hazard ratio	95% CI	P value
Male vs female	1.335	1.261, 1.406	$< .0001$
Tumor 2–3 cm vs 0–2 cm	1.202	1.140, 1.267	$< .0001$
Age ≥ 67 y vs < 67 y	1.595	1.512, 1.683	$< .0001$
Sublobar resection vs lobe+	1.611	1.517, 1.710	$< .0001$

CI, Confidence interval.

To address the issue of understaging the disease in patients who underwent sublobar resections, we investigated the percentage of patients who had at least 1 lymph node sampled during their curative resection. Of the patients undergoing lobectomy, 89% had at least 1 lymph node submitted for pathologic examination, whereas in the sublobar group, only 39% had at least 1 lymph node submitted (χ^2 test; $P < .0001$). When a dichotomous variable representing the number of lymph nodes examined (0 or 1+) was added to the Cox proportional hazards model, all 4 variables remained statistically significant (Table 4). With the addition of the lymph node variable, the hazard ratio for gender, tumor size, and age did not change, indicating that the lymph node variable is not a confounder of the effect of gender, tumor size, and age. However, the hazard ratio for extent of resection decreased by 10% with the addition of the lymph node variable, suggesting this variable is a confounder of the effect on survival of extent of resection. Therefore, the lymph node variable explains some of the effect of extent of resection on survival; however, even with

TABLE 4. Hazard ratios, 95% confidence intervals, and *P* values for the 5 variables entered into the Cox proportional hazards model

	Hazard ratio	95% CI	<i>P</i> value
Male vs female	1.336	1.268, 1.407	<.0001
Tumor 2–3 cm vs 0–2 cm	1.208	1.114, 1.273	<.0001
Age ≥67 y vs <67 y	1.587	1.504, 1.674	<.0001
Sublobar resection vs lobe+	1.452	1.354, 1.557	<.0001
Zero nodes sampled	1.233	1.150, 1.322	<.001

CI, Confidence interval.

the lymph node variable in the model, extent of resection remains statistically significant.

Of the 10,761 patients, we compared two subgroups to investigate the two extremes of survival within our cohort of patients. There were 1201 favorable prognosis patients who were female, had tumors 2.0 cm or less, were less than 67 years old, and underwent a lobectomy or greater resection. In contrast, there were 251 poor prognosis patients who were male, had tumors between 2.1 and 3.0 cm, were 67 years old or older, and underwent a sublobar resection. In a univariate analysis comparing these two groups, the 5-year survival of the favorable prognosis subgroup was 74.3% compared with 29.7% for the poor prognosis subgroup (log-rank test; $P < .001$). The hazard ratio of death for being in the poor prognosis group compared with the favorable prognosis group is 4.047.

Discussion

This study examines the survival of patients with stage IA disease within a large percentage of the US population and includes the largest cohort of patients with stage IA NSCLC treated with curative surgical resection in the literature. These data provide a snapshot of the survival that is being achieved across the United States, rather than at single specialized institutions. We investigated patient characteristics that would predict poor survival within this group. We found tumors 2.1 to 3.0 cm, age greater than or equal to the median of 67 years, male gender, and sublobar resection to be statistically significant predictors of poor survival. The hazard ratio is largest for age and extent of resection (1.664 and 1.621, respectively) and smallest for size of tumor (1.183). Analysis with a Cox proportional hazards model showed all 4 predictors remained independent predictors of survival.

Curative surgical resection is the most effective therapy for patients with stage IA NSCLC. Most series report 5-year survivals between 60% and 90%, with single-institution results generally much better than multi-institution studies. Mountain² published a large series evaluating the survival of patients after surgical resection, using the revised staging system. In Mountain's series there were 511 patients with

pathologic stage IA NSCLC. Survival was found to be 67% at 5 years.² The overall 5-year survival of our cohort of patients is 57.8%, which was worse than we expected. This difference may be explained by understaging. The data for the Mountain's report came from The M. D. Anderson Cancer Center and the institutions of the Lung Cancer Study Group, and the pathologic slides were reviewed at a single pathology center. Staging in this study was likely more accurate and more uniform than in our study, despite the patients being treated one decade earlier than the patients in our study. The SEER data are compiled from multiple state cancer registries, which in turn contain a compilation of hospital pathology reports. The heterogeneity of these data sources and heterogeneity of clinical practice across thousands of physicians likely results in understaging and would lead to poorer long-term survival.

A number of investigators have examined tumor size, gender, age, and extent of resection as predictors of survival in patients with NSCLC. This study examines these predictors individually and together in a multivariable model in patients with stage IA NSCLC across a broad population database. We found all 4 factors to be statistically significant predictors of survival, both individually and in the multivariable model. Given the potential of understaging within this database, the results need to be interpreted with caution. However, the analyses of the gender and age differences are likely to be valid even if the disease is understaged. We would predict that understaging would be as common in men as in women and in patients older and younger than 67 years. Therefore, we conclude that female gender and younger age are independent predictors of improved long-term survival.

The analysis of tumor size and extent of resection are more likely to be affected by understaging than by gender and age. Larger tumors are more likely to have regional or distant metastasis; therefore, the patients in the 2.0- to 3.0-cm tumor group are more likely to harbor occult metastasis. However, even in carefully performed single-institution studies where the patients' tumors are thoroughly and uniformly staged, investigators have found a difference in survival between small T1 and large T1 tumors.^{5,8-10,12}

In an attempt to address the issue of understaging in patients who received sublobar resections, we added a dichotomous variable representing number of lymph nodes submitted for pathologic examination. Not surprisingly, 89% of the lobectomy patients had at least 1 lymph node submitted, whereas only 39% of the sublobar patients had at least 1 lymph node submitted (χ^2 test; $P < .0001$). When this lymph node variable is added to the Cox proportional hazards model, the hazard ratio of extent of resection decreased but remained statistically significant, suggesting that lymph node examined is a confounder of the effect of extent of resection on survival. Because the SEER database

does not contain comorbidity data, there may be other unmeasured confounders that may reduce the effect of extent of surgery on survival.

We showed that patients with all 4 negative prognostic factors have very low 5-year survival compared with patients with all 4 positive prognostic factors. These results highlight the great disparity in survival even within the stage IA designation. Patients in the poor prognosis subgroup may benefit from consideration of alternate forms of therapy. Furthermore, patients in this subgroup would be a logical choice in whom novel nonsurgical primary therapy or adjuvant forms of therapy could be studied.

The limitations of this study are in the reliability of the staging data and lack of comorbidity data. Since the pathologic data are compiled from reports from hundreds of hospitals, there is a lack of uniformity in reporting and interpretation. Furthermore, there is no uniformity in how invasively the disease is staged—choice of radiographic staging studies, decision to perform mediastinoscopy, thoroughness of mediastinal lymph node dissection, and completeness of pathologic examination of the surgical specimen. Therefore, it is likely that a higher percentage of the patients in this study have understaged disease, compared with small single-institution studies. Additionally, without patient comorbidity data, we have no method to look for other significant predictors of survival, nor can we look for significant confounders of our 4 significant variables. However, this study does provide a snapshot of postoperative survival of patients with NSCLC staged as IA across the United States at the community level during a contemporary 10-year time period.

In the future, investigators will continue to refine the TNM staging system and identify important patient characteristics to more precisely determine prognosis and identify patients at risk for poor outcome. Patients in the poor outcome subgroups would be logical candidates for adjuvant therapy or alternatives forms of therapy.

Conclusions

In the largest series of surgically treated patients with stage IA NSCLC in the literature compiled from a national cancer registry, we found that tumor size between 2.1 and 3.0 cm, male gender, age greater than 67 years, and sublobar resection are predictors of poor 5-year survival. These results were statistically significant in both univariate and multivariable analyses. Patients with all 4 negative predictors have very poor 5-year survival.

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Discussion

Dr Alex G. Little (*Dayton, Ohio*). I think we would all agree that any collection of this large number of patients deserves to be analyzed and thought about carefully. That said, I am going to get to three areas in which I have some questions. One is to make a statement with which I know you agree because of having had the opportunity to read your manuscript and your identification of the limitations. The statement is that the validity of any clinical review of patients with IA disease really is dependent on the accuracy of the staging process that classified those patients. That being said, I do not think the concern of some patients with actual stage III or II disease being included weakens your conclusions, because presumably on a random basis the patients would have been evenly distributed. However, I think it really undermines to the point of negating any observations about long-term survival of patients with IA disease because we just do not know that this is really a clean collection of patients with stage IA disease. Would you comment on that, please?

Dr Chang. Yes, I agree. If you look at the entire cohort, it is difficult to reach the conclusion that 5-year survival is 58% because of this issue of understaging. I think some of the predictors we looked at probably are valid. For example, there is no reason to think that the men were understaged more than the women, so that difference probably remains valid even if the numbers themselves may be slightly higher in a carefully staged population of patients.

Dr Little. With that in mind, you might think about modifying your manuscript and not being too declarative about the survival of just patients with IA disease.

The second question has to do with the issue of the wedge resections. There are wedge resections and then there are wedge resections. Do you have any information about whether or not there were frozen section analyses done of the margins? Do we really know that those were “good” wedge resections?

Dr Chang. No, the database does not contain information on margin status.

Dr Little. I do not think any of us really wants to stoutly defend that being the ideal choice for lung cancer; nonetheless, the results might have been better had those wedge resections been quality-controlled.

Dr Chang. That is absolutely correct.

Dr Little. Finally, there is an old saying: A difference to be a difference must make a difference. What difference does it make to us as clinicians to have this information? Would you suggest that patients with some number of these negative prognostic factors should be treated differently—not operated on, operated on with smaller operations, receive multimodality therapy, either adjuvant therapy or neoadjuvant? What can we take home from this that will affect our patient care?

Dr Chang. We do not suggest that these results are the best that are achievable. Looking at carefully controlled and staged single-institution studies would give us a better idea of what is the best possible practice. What this does show is the current state within the United States of patients who are deemed to have stage IA disease, and I think these results raise the issue that many patients are probably not being staged properly. I think understaging accounts mostly for the difference in survival between this study and single-institution studies.

Dr Little. I agree. Thank you.

Dr Nasser K. Altorki (*New York, NY*). I enjoyed your presentation.

I have two questions. First, have you had an opportunity to look at the effect of cell type, squamous versus nonsquamous histologic types? Second, you have presented us, I presume, with overall survival/all-cause mortality. Have you had an opportunity to look at lung cancer–specific deaths?

Dr Chang. Thank you for your question. The data on cell type are available in the SEER database. There were about 42% adenocarcinomas and about 25% squamous cell carcinomas. However, we did not look at the impact of histology on survival. With regard to all-cause mortality, there is a variable within the database indicating the cause of death, but we believed that this was probably a fairly unreliable variable because it is abstracted from death certificates. Often, the cause of death on a death certificate is listed as cardiac arrest or multisystem organ failure without any autopsy data. We thought that that was probably a fairly unreliable way to look at survival. Therefore, you are absolutely correct; this is all-cause survival.

Dr Todd Demmy (*Buffalo, NY*). Regarding age, why did you use 67 as your age dichotomizing cut point? Did you look at the population of early emerging lung cancer? There have been reports of patients presenting in their 40s and 50s with lung cancer having a worse biological disease. Did you look at your data for the young group of patients presenting with lung cancer?

Dr Chang. Thank you for your question, Dr Demmy. We did not specifically look at the younger populations. We did analyze age as a continuous variable, and age was a significant predictor of survival. We chose to dichotomize age to make interpretation of the results easier. But we did not go through and look at multiple quintiles and specifically focus on the younger patients. However, you are correct in that with a cohort of this size, we do have the power to examine survival in the very young patients. This additional analysis would be very worthwhile.

Dr David H. Harpole, Jr (*Durham, NC*). I know that the SEER data are localized. Did you look at any volume determinants versus survival? In other words, did you look in the SEER set to see the sites that were low volume versus high volume and see whether that translated into a long-term survival difference? Along the same vein, I think some SEER data have universal physician identification numbers (UPIN). I do not know how much of that information you have. Could you drill it down to type of surgeon? We have thought about doing this in administrative databases where you can look at the type of surgery done by the UPIN-derived surgeon to see whether you could separate actually who did the operation, because you may find that some of these wedges were actually not high comorbid but maybe were not necessarily done by a thoracic surgeon. That could be interesting data as well if you are able to get that.

Dr Chang. Thank you for your question and comment. I am not aware that the UPINs are available in the SEER database. I do know that the hospital where the procedure was performed is not available in the SEER database. Hospital identification information is available in the SEER–Medicare database, which we have not looked at. The downside of the SEER–included Medicare database, of course, is that patients under age 65 are not in the SEER–Medicare database.