Treatment Outcomes of Patients With Different Subtypes of Large Cell Carcinoma of the Lung

Yung-Han Sun, MS,* Shih-Wei Lin, PhD,* Chih-Cheng Hsieh, MD, Yi-Chen Yeh, MD, Cheng-Che Tu, MD, and Kuan-Jeng Chen, PhD

Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei; Graduate Institute of Business and Management and Department of Information Management, Chang Gung University, Taoyuan; Institute of Clinical Medicine, National Yang-Ming University, Taipei; and Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

Background. Although large cell neuroendocrine carcinoma (LCNEC) and lymphoepithelioma-like carcinoma (LELC) are the variants of large cell carcinoma (LCC) of lung, there are a few studies comparing them. The aim of this study was to compare the clinical characteristic and treatment outcomes of LCNEC, LELC, and classic LCC.

Methods. Patients with LCNEC, LELC, or classic LCC were identified in a prospectively collected database, and their data were analyzed.

Results. A total of 46 patients with classic LCC, 30 with LCNEC, and 18 with LELC, who received surgical resection with curative intent, were identified and included in the analysis. Patients with LELC were younger, and the frequency of nonsmokers was greater than in patients with classic LCC or LCNEC. In patients with LCNEC or LELC, most lesions were located on the left side. There were 5 surgical deaths, and the median follow-up time of the surviving patients was 44.1 months. The 5-year disease free survival among the three subgroups was similar (p = 0.601), but patients with LELC had a significantly better overall survival than the other two subgroups (LELC vs classic LCC, p = 0.009; LELC vs LCNEC, p = 0.002). Multivariate analysis showed tumor location site, tumor stage, and LELC were independent prognostic factors of overall survival.

Conclusions. The clinical manifestations and treatment outcomes of LCNEC, LELC, and classic LCC are different. LCNEC has a poor survival, and survival is not different than that of classic LCC. LELC is associated with younger age and a higher frequency of nonsmokers, and the treatment outcomes are better than those of other subtypes.

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*Yung-Han Sun and Shih-Wei Lin contributed equally to this article.

Address correspondence to Dr Hsieh, Division of Thoracic Surgery, Department of Surgery, Taipei Veterans General Hospital, 201 Shih-Pai Rd, Sec 2, Beitou, Taipei, Taiwan; e-mail: cchsieh2@vghtpe.gov.tw.

Lung cancer is the leading cause of cancer death worldwide, with more than 1.6 million new cases in 2008 representing one-eighth of all cancers [1]. Lung cancer is a serious problem in developing countries, and the incidence is increasing by 0.5% annually. The incidence and mortality rates are highest in North and South America, Europe, Australia, New Zealand, and Eastern Asia, including Taiwan. In 2009 more than 10,000 new cases of lung cancer were diagnosed in Taiwan [1, 2].

Lung cancer is diagnosed pathologically by a histologic and cytologic approach. The major issue for pathologists in the diagnosis of lung cancer is to differentiate between small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC), with NSCLC including squamous cell carcinoma, adenocarcinoma, large cell carcinoma (LCC), and some less frequent subtypes [3, 4].

The definition of LCC by the World Health Organization (WHO) classification is an undifferentiated NSCLC without the cytologic and architectural features of SCLC or glandular or squamous differentiation. Some special entities included in LCC by the WHO classification are large cell neuroendocrine carcinoma (LCNEC), lymphoepithelioma-like carcinoma (LELC), clear cell LCC, basaloid LCC, and LCC with rhabdoid features [4–6]. However, most cases are categorized as classic LCC because it may represent the end point of undifferentiation of various lung tumors [4–6].

Literature reviews have usually compared LCNEC with typical/atypical carcinoid and SCLC because of their neuroendocrine patterns. However, carcinoid tumors are usually treated surgically, whereas SCLCs are not [7, 8]. The treatment of LCNEC is debatable and is still categorized as a variant of LCC due to its undifferentiated morphology [9, 10].

LELC was first reported in 1987 with morphology similar to that of undifferentiated nasopharyngeal carcinoma. Because of close relationship to Epstein-Barr virus, the diagnosis of LELC is not difficult, and it is still categorized as a variant of LCC because of its undifferentiated morphology [11, 12]. LELC, however, is typically discussed alone and not compared with other subtypes of NSCLC. The aim of this study was to compare the clinical characteristic and surgical treatment results of LCNEC and LELC with classic LCC, and identify factors influencing survival.
Patients and Methods

The Taipei-Veterans General Hospital Institutional Review Board approved this study. Because of the retrospective nature of the study, the requirement of patient informed consent was waived.

Study Design

In this cohort study, the medical records of patients treated for LCC at the Division of Thoracic Surgery, Taipei-Veterans General Hospital, from January 1991 to March 2013 were retrospectively reviewed. Records were identified from the prospectively collected database by using text-mining techniques, and clinical information was collected from the medical records. Histologic subtypes were classified according to the criteria of the 2004 WHO classification of lung cancer by a pathologist who did not know the patient’s clinical information.[3]

Only patients who received complete resection of major LCC histology were included. Rare histologic subtypes of LCC, such as clear cell LCC or LCC with rhabdoid features, were excluded. Tumor staging was determined according to the Union for International Cancer Control/American Joint Committee on Cancer (7th Edition) TNM staging system [13].

Disease-free survival (DFS) was calculated from the day of the operation to the time of the first relapse (recurrence or metastasis). Postrecurrence survival was calculated from the time of the first relapse to the date of death as a result of disease recurrence. The disease-specific survival was calculated from the day of the operation to the date of death from disease recurrence. Overall survival (OS) was calculated from day of the operation to the date of death from any cause.

Statistical Analysis

Categoric variables were analyzed by the Pearson $\chi^2$ test. Continuous variables were analyzed with Kruskal-Wallis test. Survival was estimated using Kaplan-Meier plots and compared with the log-rank test. Significance levels and estimates of relative risks and their 95% confidence interval were calculated with a Cox regression model. The statistical analyses were performed using SPSS 17.0 software (SPSS Inc, Chicago, IL). A $p$ value of less than 0.05 was considered statistically significant.

Results

A total of 3,883 patients who were treated for NSCLC from January 1991 to March 2013 were identified in the lung cancer database; of these, 114 patients were diagnosed as having LCC. The study excluded 20 patients, and the remaining 94 patients who received a curative surgical resection were enrolled (Fig 1). The histopathologic subtypes of these patients were 46 (48.9%) with classic LCC, 30 (31.9%) with LCNEC, and 18 (19.1%) with LELC.

The demographic characteristics of the patients in the three subgroups are reported in Table 1. The 94 patients (81.9% men) were a mean age of 65.3 years (range, 31 to 85 years), and 55.3% were smokers. A preoperative tissue diagnosis was made in 41 patients (43.6%), most of which were diagnosed with nonspecific cell types, including 18 (43.9%) with NSCLC, and 9 (22.0%) with poorly differentiated carcinoma. Only 14 patients had a specific cell type diagnosis preoperatively, including 7 adenocarcinomas, 6 squamous cell carcinomas, and only 1 LCC.

Tumors were located in the upper lobes in 55 of 94 patients (58.5%), and the right side was predominant (55 of 94 [58.5%]), including 2 patients with right hilar tumors. The surgical approach was through an open thoracotomy in 82 of 94 patients (87.2%) because video-assisted thoracoscopic surgery (VATS) was introduced late in the study period. Lobectomy was performed in 83 patients, and the other 11 underwent wedge resection or segmentectomy only because of poor pulmonary function. More resections were performed because of tumor invasion or other small lesions in other lobes in 27 patients, including 17 wedge resections, 5 bilobectomies, and 5 pneumonectomies. In addition, 6 patients also required partial chest wall resections. Dissections of mediastinal lymph nodes were performed routinely, and the average number of removed lymph nodes was 24.4 (range, 6 to 53).

Most patients had a complete (R0) resection, and only 3 patients (3.2%) had a microscopic residual tumor. By pathologic stage, 39 patients (41.5%) had stage I disease, 32 had stage II disease, and 22 had stage III disease. One patient had stage IV disease because the patient had undergone craniotomy for adenocarcinoma of the brain 3 years before LCC of the lung was diagnosed.

Age, gender, smoking, tumor location, and surgical approach were different in the three patient subgroups. Patients with LELC were younger, there were more nonsmokers compared with patients with classic LCC or LCNEC, and there were fewer men compared with patients with LCNEC (all $p < 0.05$). Compared with those with classic LCC, patients with LCNEC or LELC had more left-side tumors (classic LCC vs LCNEC, $p = 0.007$; classic LCC vs LELC, $p = 0.026$). The left upper lobe was the predominant lobe in patients with LCNEC (13 of 30 [43.3%]), but the left lower lobe was the predominant lobe in patients with LELC (8 of 18 [44.4%]). Because most LELC cases were collected in the last 5 years of the study interval, and VATS was also introduced in the last 5 years of the study, the percentage of LELC patients treated with VATS was greater than the percentage of those treated with VATS in the other 2 subgroups ($p = 0.010$). No difference was found in tumor stage distribution or the resection procedure among the three subgroups. Patients who received lobectomy and sublobar resection were also not different among the subtypes ($p = 0.570$).

LCC in 8 patients was combined with other cell types, including 5 with adenocarcinoma and 3 with squamous cell carcinoma. In 6 of the 8 patients (4 with adenocarcinoma and 2 with squamous cell carcinoma) the associated cell type was the LCNEC subtype and all were in the same lobe. The other two cases were in the classic LCC subgroup, and both were in the different lobes.
The surgical mortality rate of the 94 patients who received curative resection for LCC was 5.3% (n = 5). The causes of death were cardiac complications in 2 patients, pneumonia with sepsis in 2, and hypoxic encephalopathy in 1. All of the deaths occurred before 2003. There were 12 complications in the entire cohort, including 3 patients with respiratory failure requiring ventilator support, 2 wound infections, 2 with atelectasis, and 2 with prolonged air leakage with chemical pleurodesis.

Forty-six patients (51.7%) received postoperative adjuvant treatment. Twelve patients received radiotherapy, including 9 patients with positive mediastinal/hilar lymph nodes and 3 with incomplete surgical margins. Thirty-six patients underwent postoperative chemotherapy using a platinum-based regimen. There were 8 patients with stage I disease, 12 with stage II disease, and 16 with stage III disease. Postoperative adjuvant therapy was correlated to tumor stage (p < 0.001) but was not related to the histologic subtypes (p = 0.392).

The median follow-up time of the 89 surviving patients was 44.1 months (interquartile range, 16.7 to 86.1 months). At the end date of the study, tumor relapse had occurred in 44 patients, including 5 with local/regional recurrence and 39 with distal metastases. DFS rates were 56.4% at 3 years and 47.0% at 5 years and were similar among the three subgroups (p = 0.601). DFS was better in patients with right-sided tumor, early-stage, and no postoperative adjuvant therapy. Multivariate analysis for DFS showed tumor location and no postoperative adjuvant treatment were independent prognostic factors (Table 2). In the 44 patients with tumor relapse, 29 received adjuvant treatment. There were 23 patients who received chemotherapy, 11 patients received radiotherapy for brain or local/regional metastasis, 4 received local resection for isolated metastasis, and 1 received radiofrequency ablation for liver metastasis. A platinum-based regimen was still the most commonly used chemotherapy in 15 patients.
The median postrecurrence survival time of patients with classic LCC, LCNEC, and LELC were 10.5, 6.9, and 28.4 months, respectively, and the differences among the subgroups were significant ($p = 0.005$). LELC metastasis occurred in 4 patients, and 2 received pemetrexed plus platinum regimen, 1 received pemetrexed only, and the other patient received docetaxel for further chemotherapy.

Within the follow-up period, 47 patients (52.8%) died, including 18 who died of causes other than lung cancer. The OS rates were 63.6% at 3 years and 59.2% at 5 years, and there were significant differences among the three subgroups ($p = 0.011$; Fig 2). Patients with LELC had better survival than those in the other two subgroups (LELC vs classic LCC, $p = 0.009$; LELC vs LCNEC, $p = 0.002$), whereas there was no significant difference between the classic LCC and LCNEC subgroups ($p = 0.488$). Multivariate analysis showed tumor location site and tumor stage were independent prognostic factors for OS. In addition, LELC was also a prognostic factor considered in the multivariate analysis.

Table 1. Patient Demographic Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Classic LCC (n = 46)</th>
<th>LCNEC (n = 30)</th>
<th>LELC (n = 18)</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.9 ± 10.7</td>
<td>69.2 ± 11.0</td>
<td>57.3 ± 11.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.033</td>
</tr>
<tr>
<td>Male</td>
<td>39 (84.8)</td>
<td>27 (90)</td>
<td>11 (61.1)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7 (15.2)</td>
<td>3 (10)</td>
<td>7 (38.9)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Yes</td>
<td>28 (60.9)</td>
<td>20 (66.7)</td>
<td>4 (22.2)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18 (39.1)</td>
<td>10 (33.3)</td>
<td>14 (77.8)</td>
<td></td>
</tr>
<tr>
<td>Preoperative diagnosis</td>
<td></td>
<td></td>
<td></td>
<td>0.870</td>
</tr>
<tr>
<td>Yes</td>
<td>20 (43.5)</td>
<td>14 (46.7)</td>
<td>7 (38.9)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>26 (56.5)</td>
<td>16 (53.3)</td>
<td>11 (61.1)</td>
<td></td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Right lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>21 (45.7)</td>
<td>8 (26.7)</td>
<td>1 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>2 (4.3)</td>
<td>1 (3.3)</td>
<td>2 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>10 (21.7)</td>
<td>3 (10)</td>
<td>5 (27.8)</td>
<td></td>
</tr>
<tr>
<td>Left lobe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>10 (21.7)</td>
<td>13 (43.3)</td>
<td>2 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>2 (4.3)</td>
<td>4 (13.3)</td>
<td>8 (44.4)</td>
<td></td>
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<tr>
<td>Surgical method</td>
<td></td>
<td></td>
<td></td>
<td>0.009</td>
</tr>
<tr>
<td>VATS</td>
<td>5 (10.9)</td>
<td>1 (3.3)</td>
<td>6 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Open thoracotomy</td>
<td>41 (89.1)</td>
<td>29 (96.7)</td>
<td>12 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Resection procedure</td>
<td></td>
<td></td>
<td></td>
<td>0.172</td>
</tr>
<tr>
<td>Wedge/segmentectomy</td>
<td>4 (8.7)</td>
<td>5 (16.7)</td>
<td>2 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Lobectomy</td>
<td>26 (56.5)</td>
<td>16 (53.3)</td>
<td>14 (77.8)</td>
<td></td>
</tr>
<tr>
<td>Lobectomy + wedge</td>
<td>7 (15.2)</td>
<td>8 (26.7)</td>
<td>2 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>4 (8.7)</td>
<td>1 (3.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>5 (10.9)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td>0.557</td>
</tr>
<tr>
<td>I</td>
<td>18 (39.1)</td>
<td>13 (43.3)</td>
<td>8 (44.4)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>19 (41.3)</td>
<td>9 (30)</td>
<td>4 (22.2)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>9 (19.6)</td>
<td>7 (23.3)</td>
<td>6 (33.3)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>1 (3.3)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Continuous data are presented as mean ± standard deviation and categoric data as number (%).

LCC = large cell carcinoma; LCNEC = large cell neuroendocrine carcinoma; LELC = lymphoepithelioma-like carcinoma; VATS = video-assisted thoracoscopic surgery.

Table 2. Multivariate Analysis of Prognostic Factors Influencing Disease-Free Survival After Surgical Resection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk (95% CI)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1 (Referent)</td>
<td>0.007</td>
</tr>
<tr>
<td>Left</td>
<td>2.335 (1.263–4.319)</td>
<td></td>
</tr>
<tr>
<td>Post-op adjuvant therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (Referent)</td>
<td>0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>2.918 (1.510–5.636)</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval.
factor for OS (relative risk, 0.064; 95% confidence interval, 0.008 to 0.496, \( p = 0.009 \); Table 3).

Comment

On the basis of the 2004 WHO classification, LCC is a diagnosis of exclusion in patients with NSCLC that has no differentiation of adenocarcinoma, squamous cell carcinoma, or SCLC [3]. LCC has several variants, including LCNEC, LELC, and other minor subtypes. Even with advances in diagnosis methods, LCNEC and LELC are still categorized as LCC because their undifferentiated characteristics.

The incidence of LCC in our series was 2.8% of all NSCLC patients in our database. The incidence was similar to that reported in the Surveillance, Epidemiology and End Results database before 2011 [14] but lower than that reported by Battafarano and colleagues [9]. There are several possible reasons for this. Some patients with unresectable disease were included in our database. However, LCC is often reclassified as adenocarcinoma, poorly differentiated squamous cell carcinoma, or adenosquamous carcinoma using immunohistochemical markers [15], thus influencing the incidence. This series also showed the percentages of LCNEC and LELC in the LCC group were 31.9% (30 of 94) and 19.1% (18 of 94), respectively. However, studies have shown that the incidence of LCNEC was only 3.1% in Japan, and the incidence of LELC was about 1% of all lung cancers in Southern China, frequencies that are higher than in our series. These differences may be due to regional effects and the close association with Epstein-Barr virus infection [4, 6, 12, 16–22].

In our series, patients with LCNEC had a similar age as those with classic LCC or NSCLC, but patients with LELC were a mean of 10 years younger than those with LCNEC or classic LCC (Table 1). These results are the same as reported in other studies from Taiwan and Hong Kong, but studies in China have reported a slightly younger age than that in our report [21–25]. In our series, 90% of patients with LCNEC were male, and this male predominance was reported in other studies [4, 20, 26]. However, 38.9% of the patients in our series with LELC were female. This result was comparable with other series, although some studies have shown a slight female predominance [6, 21, 22, 25]. Studies have shown that the frequency of smokers is higher in patients with LCNEC, whereas the frequency of non-smokers is higher in patients with LELC [6, 20, 22, 24, 25]. The results in our series were similar to these prior studies, and we found a significant difference in smokers between the LELC group and the other two subgroups.

A preoperative diagnosis of LCC is difficult because the diagnosis of LCC is by exclusion, and a biopsy specimen or cytologic specimen may not be representative of the entire lesion [6]. In our series, only 1.1% of LCC cases were diagnosed before surgical resection, and the preoperative diagnosis in most patients was poorly differentiated carcinoma or NSCLC. The frequency of preoperative diagnosis was relatively low compared with the 17% reported by Liang and colleagues [25].

With respect to tumor location, most lesions in patients with classic LCC were on the right side, but most lesions in patients with LCNEC or LELC were on the left side. Although LCNEC and LELC were both predominant on the left side, LCNEC patients had more left upper lobe lesions, and LELC patients had more left lower lobe lesions. Han and colleagues [21] found no difference in the frequency of LELC lesions between the left and the right side. Several researchers have explored the relationship between survival and tumor location side. The survival rate of patients with a right-side tumor was not significantly different from that of patients with a left-side tumor. The lymph nodes in the left higher mediastinum were more difficult to approach than those in right side.
from the surgical technical considerations [27, 28], with the result that patients with a left-side tumor were more likely understaged. The reason might be that left-side tumor was a poor prognostic factor to predict DFS and OS survival in this study.

Surgical approach and resection range did not affect the survival rate in our study. That only fewer patients (11.7%) received sublobar resection may be one reason; however, some recent reports also showed no survival difference between lobectomy and sublobar resection, regardless of histologic subtype [29, 30].

The National Comprehensive Cancer Network guideline for NSCLC recommends postoperative adjuvant treatment for stage II or higher and for some stage Iib in high-risk patients [31]. More than 50% patients in this study received postoperative adjuvant treatment, and the treatment was highly correlated to tumor stage. Thus, the postoperative adjuvant treatment was a better prognostic factor than tumor stage for predicting DFS. The 5-year OS of patients with LCC was 59.2% in our series, which was better than the OS reported by Battafarano and colleagues [9]. This may have been due to differences in the percentages of the different subtypes. Reports have shown that the 5-year survival of LCNEC ranged from 13% to 57% and that the survival of patients with LCNEC was poorer than those with classic LCC or other NSCLCs [4, 9, 32, 33]. In this series, the 5-year OS was 44.8% for patients with LCNEC and 55.4% for those with classic LCC, but the difference was not significant (p = 0.488). Stage distribution might have influenced this result.

Most studies have shown that the survival of patients with LELC is higher than the survival of patients with other types of NSCLC [21, 25]. The results of our series are consistent with these prior reports. The main difference was the longer postrecurrence survival time of patients with LELC. This may be due to the lower malignancy of LELC or a higher response rate with chemotherapy. Patients with LCNEC in our series received NSCLC chemotherapy regimens, and the results were poor. Better results may be obtained by using a chemotherapy regimen that is typically used for SCLC because of the neuroendocrine characteristics of LCNEC [34].

In conclusion, there are many subtypes of LCC, and the clinical manifestations and treatment results are different. LCNEC has a poor survival, has some special properties, and survival is not different than that with classic LCC. LELC is a distinct entity of NSCLC and is associated with a younger age and is more likely to occur in nonsmokers. The treatment outcomes of LELC are better than those of other subtypes of LCC.

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References


The Society of Thoracic Surgeons: Fifty-First Annual Meeting

Mark your calendar for the 51st Annual Meeting of The Society of Thoracic Surgeons (STS) to be held at the San Diego Convention Center in San Diego, California, January 24-28, 2015. The STS Annual Meeting offers you a chance to meet the experts, network with colleagues from around the world, and participate in a dynamic learning experience.

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An advance program with information about housing and registration will be mailed to STS members this fall. Nonmembers may contact the Society to receive a copy of the printed advance program; however, detailed up-to-date meeting information will be available on the STS website at www.sts.org/annualmeeting.

I hope to see you in San Diego.

Keith S. Naunheim, MD
Secretary
The Society of Thoracic Surgeons
633 N Saint Clair St, 23rd Floor
Chicago, IL 60611-3658
Telephone: (312) 202-5800
Fax: (312) 202-5801
E-mail: sts@sts.org
Website: www.sts.org