Original Article

Favorable Surgical Results for Patients with Nonsmall Cell Lung Cancer over 80 Years Old: A Multicenter Survey

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Background: Surgery for elderly patients, especially those over 80 years old, with primary lung neoplasms is a relatively common treatment according to the increasing elderly population. We reviewed our experiences to evaluate surgical outcomes in over-80-year-old patients with nonsmall cell lung cancer (NSCLC).

Patients and Methods: We reviewed and analyzed the clinical records of 146 consecutive over-80-year-old patients (Group 1) and 926 control patients (65 years old and younger) (Group 2) with NSCLC who underwent surgical resections from 1981 to 2006.

Results: The mean ages of Group 1 and Group 2 were 82.6 and 56.2 years old, respectively. The ratio of the clinical and pathological Stage I was higher than the Stages II–IV in Group 1, and that of pathological Stage III was higher in Group 2. Segmental and wedge resection were selected more frequently in Group 1, otherwise, pneumonectomy and lobectomy were selected more frequently in Group 2. The ratio of squamous cell carcinoma was higher in Group 1 than in Group 2. When we divided the time of surgeries into decades, the 1980s, 1990s, and 2000s, the ratio of elder to younger patients was clearly increased according to era: 6.6%, 13.7%, and 18.8%. Furthermore, incomplete operation cases were significantly decreased in the two groups. There was no difference of overall survival in either. When examined for overall survival, except for patients with incomplete resection, there was no significant difference between the two groups.

Conclusions: Surgery is the convenient treatment for elderly NSCLC patients, especially, for those who can undergo complete resection. (Ann Thorac Cardiovasc Surg 2008; 14: 154–160)

Key words: nonsmall cell lung cancer, over 80 years old, complete resection, survival

Introduction

As in many developed countries, lung cancer is now the first leading cause of cancer death in men and the third cause of death in women in Japan, in which more than 50,000 lung cancer death are being recorded annually.[1)]

Whereas the number of elderly patients with nonsmall cell lung cancer (NSCLC) who have been experiencing longer life expectancy has increased, the surgical treatment of NSCLC in elderly patients remains challenging for general thoracic surgeons. Aging results in physiological changes in the cardiovascular and respiratory systems and

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increases the frequency of other underlying diseases. Thus surgical resection for NSCLC itself has a possibility of increasing the risk of life-threatening complications; however, there is a considerable divergence of reported data about the mortality rate, ranging from 2.8% to 3.7%.[2–4)]

In this study, we retrospectively analyzed the surgical results and prognoses of patients older than 80 who underwent curative resection for NSCLC in different centers.

Patients and Methods

Patients

A total of 2,321 patients with NSCLC have been treated by pulmonary resection in three large-scale teaching medical centers (National Kyushu Medical Center, from 1991 to 2006; Matsuyama Red Cross Hospital, from 1988 to 2001; Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, from 1981 to 2004), and their cases were retrospectively analyzed in this study. These medical centers are part of Kyushu University, and the policies of indications for surgery and operation methods are almost the same. Among the patients, 146 (6.3%) were older than 80. To clarify the differences in surgical results between patients over 80 (Group 1) and younger patients, we compared the postoperative outcomes to the 926 patients (39.9%) under 65 who underwent pulmonary resection in this series (Group 2). The patient characteristics are listed in Table 1. There were 85 males (58.2%) and 61 females (41.8%) in Group 1 and 631 males (68.1 %) and 295 females (31.9%) in Group 2. The mean ages were 82.6 years (range 80 to 90) in Group 1 and 56.2 years (range 20 to 65) in Group 2.

All patients underwent a respiratory function test and an electrocardiogram. Those who were predicted to have a postoperative forced expiratory volume in 1st second ($FEV_{1.0}$) of less than 600 mL/m^2 were not indicated for surgical resection. Moreover, an echocardiogram, a cardiac scintigraphy, or a pulmonary ventilation-blood flow scintigraphy was done preoperatively, if necessary.

The surgical procedures for Group 1 were 79 lobectomies (54.1%), 7 bilobectomies (4.8%), 1 pneumonectomy (0.7%), 17 segmental resections (11.6%), 38 wedge resections (26.0%), and 4 explorations (2.7%). For Group 2 they were 683 lobectomies (73.8%), 59 bilobectomies (6.4%), 91 pneumonectomies (9.8%), 10 segmental resections (1.1%), 47 wedge resections (5.1%), and 36 explorations (3.9%). Anatomical resection was followed by complete systemic mediastinal lymph node dissection, and segmental and wedge resection were followed by mediastinal lymph node sampling. We defined a complete resection as a macroscopically and pathologically surgical resection according to Japanese general rules for the clinical and pathological records of lung cancer.[5)] Respectively in each group, a total of 17 patients (6.6%) and 239 patients (93.4%) underwent pulmonary resection from 1980 to 1989; a total of 70 (13.7%) and 432 (86.3%) from 1990 to 1999; and a total of 59 (18.8%) and 255 (81.2%) from 2000 to 2006. In this series, incomplete resections totaled 20 cases (13.7%) in Group 1 and 164 (17.7%) in Group 2.

Clinical and pathological stagings were defined according to the TNM criteria of the International System for Staging Lung Cancer.[6)] Clinical stagings of Group 1 and Group 2, respectively, totaled 109 (74.7%) and 563 (60.8%) patients in Stage I; 14 (9.6%) and 109 (11.9%) in Stage II; 22 (15.1%) and 205 (22.1%) in Stage III; and 1 (0.7%) and 48 (5.2%) in Stage IV. Pathological stagings of Group 1 and Group 2, respectively, totaled 94 (64.3%) and 437 (47.2%) patients in Stage I; 16 (11.0%) and 117 (12.6%) in stage II; 31 (21.2%) and 308 (33.3%) in Stage III; and 5 (3.5%) and 64 (6.9%) in Stage IV. Histological typing was carried out according to the World Health Organization histological classifications.[7)] For Group 1 and Group 2, respectively, a total of 90 (61.6%) and 633 (68.4%) patients were adenocarcinoma (AD), 49 (33.6%) and 221 (23.9%) were squamous cell carcinoma (SQ), 6 (4.1%) and 47 (5.1%) were large cell carcinoma, and 1 (0.7%) and 25 (2.7%) were classified as others.

Postoperative follow-up

A follow-up examination was usually carried out every 2 months for the first 2 years and every 3 to 4 months thereafter. The follow-up included a physical examinations, tumor marker, and chest radiography. Chest computed tomography or bone scintigraphy were conducted once or twice a year after the operation.

Statistical analysis

The survival time was defined as being from the date of surgery to the latest follow-up date. Survival curves were obtained using the Kaplan-Meier method, and the prognostic influence of variables on survival was analyzed using the log-rank test. Statistical analysis was performed using chi-square and two-tailed Student tests for comparison of variables. In all statistical analyses, a *p* value

Table 1. Group 1 and Group 2 characteristics

	Group 1 (%)	Group 2 (%)	*p*-value
Age (years)			**<0.0001**
Mean ± SD	82.6 ± 2.3	56.2 ± 7.4	
Range	80–90	20–65	
Sex			**0.018**
Male/female	85 (58.2)/61 (41.8)	631 (68.1)/295 (31.9)	
Clinical stage			**0.0046**
I	109 (74.7)	563 (60.8)	0.0013
II	14 (9.6)	109 (11.9)	0.4420
III	22 (15.1)	205 (22.1)	0.0520
IV	1 (0.7)	48 (5.2)	0.0156
Pathological stage			**0.0012**
I	94 (64.3)	437 (47.2)	0.0001
II	16 (11.0)	117 (12.6)	0.5680
III	31 (21.2)	308 (33.3)	0.0037
IV	5 (3.5)	64 (6.9)	0.1106
Surgery			**<0.0001**
Pneumonectomy	1 (0.7)	91 (9.8)	<0.0001
Lobectomy	79 (54.1)	683 (73.8)	<0.0001
Bilobectomy	7 (4.8)	59 (6.4)	0.4613
Segmental resection	17 (11.6)	10 (1.1)	<0.0001
Wedge resection	38 (26.0)	47 (5.1)	<0.0001
Exploration	4 (2.7)	36 (3.9)	0.4964
Histology*			**0.0481**
AD	90 (61.6)	633 (68.4)	0.2151
SQ	49 (33.6)	221 (23.9)	0.0121
Large cell carcinoma	6 (4.1)	47 (5.1)	0.6168
Other	1 (0.7)	25 (2.7)	0.1413
Operation era			**0.0001**
1980s	17 (6.6)	239 (93.4)	
1990s	70 (13.7)	432 (86.3)	
2000s	59 (18.8)	255 (81.2)	

*AD, Adenocarcinoma; SQ, Squoamous cell carcinoma.

Table 2. Distribution of operation number between each operation era, and the percentage of incomplete operation

Operation era	Group 1 Incomplete/total (%)*	Group 2 Incomplete/total (%)*	*p*-value
1980s	5/17 (29.4)	62/239 (25.9)	
1990s	10/70 (14.3)	74/432 (17.1)	
2000s	5/59 (8.5)	28/255 (11.0)	0.0001

*Percentage of incomplete cases with each group to total cases.

of less than 0.05 was recognized as significant.

Results

The details of the patients' characteristics are shown in Table 1. There were significant differences in sex, clinical stage, pathological stage, surgery, histology, and operation era. The ratio of male patients was about 60%–70% in each group. Group 1 had a higher ratio of clinical and pathological Stage I than Group 2 ($p = 0.0013$ and 0.0001, respectively). On the other hand, Group 2 had a higher ratio of clinical and pathological Stage III than Group 1 ($p = 0.0520$ and 0.0037, respectively). The ratio of segmental and wedge resections increased in Group 1 ($p < 0.0001$); otherwise, pneumonectomy and lobectomy increased in Group 2 ($p < 0.0001$). As for histology, the

Table 3. Difference of clinical stage and operation method devised operation era

	Group 1 (%)/Group 2 (%)			
	1980s	1990s	2000s	*p*-value
Clinical Stage*				0.4625/ 0.0024
I	13 (76.5)/125 (52.3)	48 (68.6)/258 (59.7)	48 (81.4)/180 (70.6)	
II	1 (5.9)/40 (16.7)	8 (11.4)/51 (11.8)	5 (8.5)/19 (7.5)	
III	3 (17.6)/59 (24.7)	14 (20.0)/99 (22.9)	5 (8.5)/47 (18.4)	
IV	0 (0)/15 (6.3)	0 (0)/24 (5.6)	1 (1.7)/9 (3.5)	
Operation method				0.0474/<0.0001
Pneumonectomy	0 (0)/35 (14.6)	1 (1.4)/36 (8.3)	0 (0)/20 (7.8)	
Lobectomy	12 (70.6)/158 (66.1)	42 (60.0)/336 (77.8)	25 (42.4)/189 (74.1)	
Bilobectomy	1 (5.9)/20 (8.4)	3 (4.3)/31 (7.2)	3 (5.1)/8 (3.1)	
Segmental resection	0 (0)/2 (0.8)	8 (11.4)/1 (0.2)	9 (15.3)/7 (2.7)	
Wedge resection	2 (11.8)/7 (2.9)	14 (20.0)/13 (3.0)	22 (37.3)/27 (10.6)	
Exploration	2 (11.8)/17 (7.1)	2 (2.9)/15 (3.5)	0 (0)/4 (1.6)	

ratio of Group 1 with SQ was higher than that of Group 2 ($p = 0.0121$). According to the three operation eras in each group, the proportion of elderly patients has been significantly increasing with time (6.6%, 13.7%, and 18.8%, respectively. $p = 0.0001$).

The number of incomplete resections in each group (almost all were exploration cases) has been significantly decreasing, as stratified by each decade from 1980 ($p = 0.0001$; Table 2). The proportion of incomplete resections in Group 1 in each decade was 5 cases in the 1980s (29.4%), 10 in the 1990s (14.3%), and 5 in the 2000s (8.5%), respectively. The proportion of incomplete resections in Group 2 in each decade was, respectively, 62 (25.9%), 74 (17.1%) and 28 (11.0%).

Next, we devised a clinical stage and operation method of each group into an operation era because of analyzing the bias between the 2 groups (Table 3). There was no statistical difference in the clinical stage of Group 1. The clinical Stage I of Group 2 increased according to the operation era, and clinical Stages II–IV decreased. As for the operation method, the proportion of segmental and wedge resections in each group increased according to operation era. Exploration also decreased in each group. The proportion of Stage I in Group 2 seemed to increase more than in Group 1; however, the operation method had almost no difference between the 2 groups.

There were no significant differences in overall 5-year survival between Group 1 and Group 2 (Fig. 1: 46.8% and 55.3%, respectively; $p = 0.1507$). The survival curves stratified by histological type are shown in Fig. 2. Because of the small number of cases with large cell carcinoma and other histology in both groups, the patients with AD and SQ were analyzed. There was a significant difference in 5-year survival between AD and SQ ($p < 0.0001$) in both groups (55.9% and 31.3% in Group 1, and 58.8% and 44.9% in Group 2, respectively). However, no significant difference was observed between Group 1 and Group 2, stratified by histological types.

When stratified by complete and incomplete resections, there were significantly better 5-year survivals in patients who had undergone complete resections in both Group 1 and Group 2 ($p < 0.0001$; Fig. 3). However, there were no significant differences in 5-year survivals between Group 1 and Group 2 (Fig. 3) patients, who had undergone complete (53.8% and 64.0%, respectively. $p = 0.0623$) or incomplete resections (0% and 14.4%, respectively, $p = 0.4865$).

Discussion

The proportion of elderly people with lung cancer had been increasing, and one reason for this seems to be a consequence of the prolonged life expectancy in Japan. Recent studies demonstrated the effectiveness and safety of surgery for elderly patients with early stage NSCLC.[4,8,9] However, elderly patients have a tendency to have more underlying morbidities than younger patients do. In this study, we focused on patients more than 80 years old with NSCLC to investigate whether it contributed to prolonging their survival, since surgical procedures for these patients was still challenging to thoracic surgeons.

In this series, the overall survival curves of Group 1 and Group 2 had no significant difference between one another (Fig. 1). The 5-year survival of Group 1 and Group 2 was 46.8% and 55.3%, respectively. Elderly patients with NSCLC tend to undergo radiotherapy, but not sur-

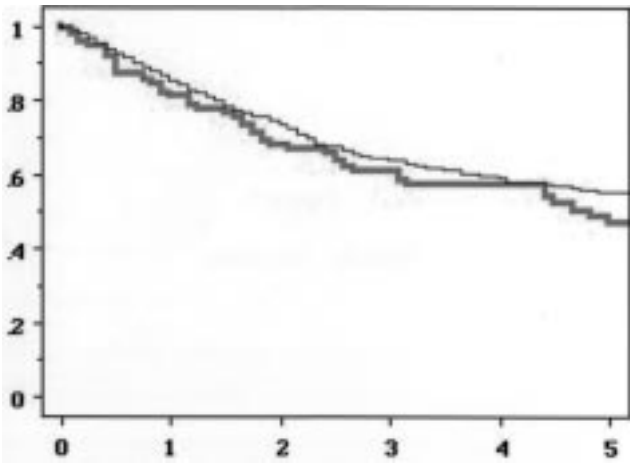

Fig. 1. Survival curves of overall survival. Thick line, Group 1; thin line, Group 2. Comparison between groups: $p = 0.1507$. Five-year survival rates for Group 1 and Group 2 were 46.8% and 55.3%, respectively.

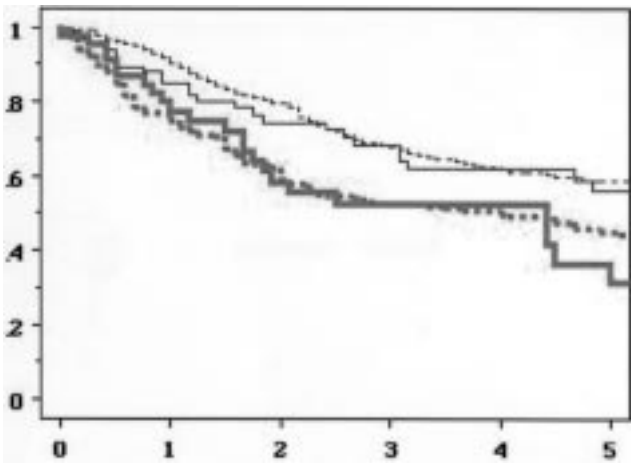

Fig. 2. Survival curves of histology. Thin line, Group 1 with adenocarcinoma; dotted thin line, Group 2 with adenocaricinoma; thick line, Group 1 with squamous cell carcinoma (SQ); dotted thick line, Group 2 with SQ.

gery or chemotherapy, because of poor physical function including pulmonary and cardial functions, and moreover because of perioperative morbidity. Moreover, chemotherapy for patients older than 80 was generally considered inadequate in Japan. The survival benefits of radiation for elderly patients with stage I NSCLC were reported to be 23%–42% in 5-year survival;[10,11] however, radiation for stages I-IIB NSCLC was 7%-17% of 5-year survival.[12,13] Although radiation for elderly patients with early stage NSCLC seemed useful, surgery is considered one of the beneficial treatments for operable elderly patients.

In our series, there was a remarkable difference between the surgical managements of Group 1 and Group 2. In Group 1, the ratio of limited resections, i.e., segmental and wedge resections, had significantly been increased when compared with those of Group 2 (Table 1). However, stratified with the operation era, the change of operation methods showed almost the same in both groups (Table 3). Recently, video-assisted thoracic surgery and limited resection are becoming more popular and known as a useful technique for elderly patients at high risk in early-stage NSCLC,[14] and this is one of the reasons why limited resection for not only elderly patients, but also for younger ones is increasing.[15] Further, operation cases in 2000s for Group 1 have increased more than those of 1980s and 1990s.

Recently, management for the prevention of postoperative complications has been undertaken by the use of various methods. At the Kyushu Medical Center, we introduced preoperative examinations such as electrocardiography and spirometry, and also by ultrasonic cardiogram and ultrasonic carotidgram, for all operation cases since 1998. Furthermore, we tried perioperative management to prevent operative complications, such as early ambulation, elastic stockings, and intermittent positive pressure of the lower extremity. These maintenance efforts might remarkably reduce postoperative complica-

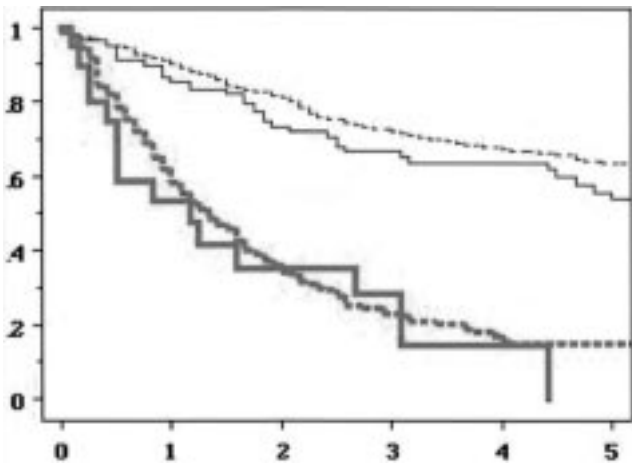

Fig. 3. Survival curves of complete and incomplete resection. Thin line, Group 1 with complete resection; dotted thin line, Group 2 with complete resection; thick line, Group 1 with incomplete resection; dotted thick line, Group 2 with incomplete resection. Comparison between complete and incomplete resection: $p < 0.0001$. Five-year survival rates for Group 1 and Group 2 with complete resection were 53.8% and 64.0%, respectively ($p = 0.0623$).

tions (data not shown). We considered that notable advances have been made in surgical techniques, anesthetic management, and perioperative care with a modern trend of a decreased perioperative risk. On the other hand, incomplete resection in 2000s was significantly decreased more than that of 1980s and 1990s (Table 2). This reason seemed to take part in the improvement of preoperative diagnostic techniques that enable us to make more accurate diagnoses preoperatively, thus reducing exploration.

As for histology, patients with AD have better prognoses than those with SQ in this series (Fig. 2); however, no significant difference was found between Group 1 and Group 2 when stratified with histological types. On the other hand, in our series the ratio of AD, both male and female, was obviously increased according to the operation era: 1980s, 66.3%; 1990s, 71.4%; 2000s, 79.8% (p = 0.0018, data not shown) Especially, the ratio of male to female with AD was significantly increasing: 1980s, 57.4%; 1990s, 62.0%; 2000s, 71.1% (p = 0.0024, data not shown). However, these tendencies were not recognized in Group 1. One possible reason was that the number of male smokers in Japan, who have a risk factor of SQ, had been decreasing gradually, and alternatively, the number of female smokers has been increasing.[16,17)]

The overall survival rate for each group with incomplete and complete resection is shown in Fig. 3. Group 1 with complete resection accepted almost the same survival rate as Group 2 with complete resection. In these data, Group 1, which is able to undergo complete resection and experience tolerable function for perioperative invasiveness, has an indication for surgery similar to young patients. However, our patients' characteristics are different between the elderly and younger patients, and the simple comparison of their survival might be meaningless. So we also analyzed whether there was bias in the stage and operation methods (Table 3). There might be bias for the clinical stage in each group; however, the operation method seemed not to be statistical different stratified with the operation era in each group. In such a background, it seems that the prognoses of young patients are almost equal to those of elderly patients who tend to undergo limited resections.

In conclusion, our observations suggest that overall survival for elderly patients with complete resection was the same as that for younger patients with complete resection, whereas chemotherapy and/or radiotherapy was inadequate for elderly patients. Surgery is the useful treatment for elderly patients with NSCLC who are carefully and specially selected as being tolerable to operation and possibly to complete resection.

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