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Long-term results of surgical treatment of pulmonary carcinoids

Pulmoner karsinoidlerin cerrahi tedavisinin uzun dönem sonuçları

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ABSTRACT

Background: This study aims to investigate possible factors other than lymph node invasion and cell type which may affect survival in patients with lung carcinoids over long-term follow-up.

Methods: This retrospective study included 82 patients (36 males, 46 females; mean age 43.8 years; range 16 to 19 years) operated with a diagnosis of bronchial carcinoid between February 1993 and November 2012. Factors that may affect survival were identified as age, sex, location of surgery, T status, N status, complete resection, resection width, cell type, and stage. Morbidities and mortalities were recorded according to these factors.

Results: Mean duration of follow-up was 84 months. Ten-year survival rate was 98.5%. Of patients, 49 were T_1, 29 were T_2, and four were T_3. Data showed that T status affected survival (p=0.001). According to the seventh TNM staging system, 65 of the patients were stage 1, 14 were stage 2, and two were stage 3. Surgical margins were positive in one patient. Stage of disease had an effect on survival (p=0.023). Sixty-eight patients had typical, and 14 patients had atypical carcinoids. There was no difference in survival between typical and atypical carcinoids (p=0.62). Seventy patients were N_0, 10 patients were N_1, and two patients were N_2. According to data, N status did not affect survival (p=0.72).

Conclusion: In our study, surgery performed on tumors detected at an earlier stage was found to have a better prognosis.

Keywords: Mortality; pulmonary carcinoid tumor; survival.

ÖZ

Amaç: Bu çalışmada akciğer karsinoidleri olan hastaların uzun süreli takiplerinde lenf nodu invazyonu ve hücre tipi dışında sağkalımı etkileyebilecek olası faktörler incelendi.

Çalışma planı: Bu retrospektif çalışmaya Şubat 1993 - Kasım 2012 tarihleri arasında bronşiyal karsinoid tanısı ile ameliyat edilen 82 hasta (36 erkek, 46 kadın; ort. yaş 43.8 yıl; dağılım 16-19 yıl) dahil edildi. Sağkalımı etkileyebilecek faktörler yaş, cinsiyet, cerrahinin yeri, T statüsü, N statüsü, tam rezeksiyon, rezeksiyon genişliği, hücre tipi ve evre olarak belirlendi. Morbidite ve mortaliteler bu faktörlere göre kaydedildi.

Bulgular: Ortalama takip süresi 84 ay idi. On yıllık sağkalım oranı %98.5 idi. Hastalardan 49'u T_1, 29'u T_2, dördü T_3 idi. Veriler T statüsünün sağkalımı etkilediğini gösterdi (p=0.001). Yedinci TNM evreleme sistemine göre, hastaların 65'i evre 1, 14'ü evre 2, ikisi evre 3 idi. Bir hastada cerrahi sınırlar pozitif idi. Hastalık evresinin sağkalım üzerinde etkisi var idi (p=0.023). Altmış sekiz hastada tipik, 14 hastada atipik karsinoid var idi. Tipik ve atipik karsinoidlerde sağkalımda farklılık yok idi (p=0.62). Yetmiş hasta N_0, 10 hasta N_1 ve iki hasta N_2 idi. Verilere göre, N durumu sağkalımı etkilemedi (p=0.72).

Sonuç: Çalışmamızda erken evrede tespit edilen tümörlere uygulanan cerrahide prognozun daha iyi olduğu bulundu.

Anahtar sözcükler: Mortalite; pulmoner karsinoid tümör; sağkalım.

Pulmonary carcinoid tumors constitute 1-2% of all pulmonary neoplasms,[1,2] and they have lower grades than other pulmonary malignancies.[1,3] Carcinoids are the most common type of neuroendocrine tumors, and compared with other types of tumors, they are relatively more benign. They can be classified as typical and atypical carcinoids as well as both large and small cell carcinomas.[1-3] Pulmonary carcinoids occur because

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of an increase in the number of Kulchitsky cells that are naturally present in the bronchial mucosa[1] and are classified as typical when the number of mitoses is <2/mm^2 with no associated necrosis and as atypical when the number of mitoses are 2-10/mm^2 or when there is necrosis.[4] Half of the cases are localized at the time of diagnosis, 25% have regional localization, and 25% have distant metastases. According to previous studies, the mean survival rate for surgically treated localized carcinoids is 83 months, but for those with distant metastases, it is only 16 months.[5,6] This shows the significance of the need for surgical treatment at an early stage.[7] The aim of this study was to retrospectively analyze the factors that affected survival in patients who underwent surgical treatment for carcinoid tumors.

PATIENTS AND METHODS

In this study, a retrospective analysis was used to evaluate the surgical procedures that were used to treat pulmonary carcinoids in our thoracic surgery department for 82 patients between February 1993 and November 2012. The diagnosis was determined using information obtained from the electronic data bank or the pathology results, and the patient files or the data bank were scanned to access the relevant data.

The preoperative assessment included recording the patients' complaints and their history of the illness along with a physical examination, a biochemical evaluation, radiographic imaging, pulmonary function tests, computed tomography (CT) of the chest, fiber optic bronchoscopy findings, and a pathological diagnosis. Those who were considered to be suitable for surgical treatment then underwent either a bronchotomy, bronchial resection, lobectomy, bilobectomy, sleeve lobectomy, or pneumonectomy, depending on the preoperative and intraoperative findings. In patients with stage 1 cancer, a sublobar resection was performed. Those with a settled, narrow-based polypoid tumor underwent a bronchotomy while those with a localized, broad-based tumor underwent a bronchial sleeve resection.

All of the patients also underwent a mediastinal lymph node dissection. At least three lymph nodes from the 4th, 7th, 8th, 9th, and 10th stations in the right hemithorax and the 5th, 6th, 7th, 8th, 9th, and 10th stations in the left hemithorax were sampled. The patients were followed up in the intensive care unit (ICU) after the operation and then transferred to the ward once they were in stable condition. The mean period of hospitalization was seven days.

The disease stage was calculated based on the results of the pathological examinations. In the postoperative period, all of the patients were referred to the oncology department, but none received chemotherapy or radiotherapy. Follow-up was carried out via chest CT every six months. The factors that might have affected survival were age, gender, operation side, T status, N status, cell type, and stage, with the T status and stage being evaluated according to the seventh edition of the TNM staging system for lung cancer that was published in 2010. In addition, whether or not the patients underwent a complete resection also played a role in their survival. The morbidity and mortality of the patients were then recorded by taking into account all of these factors.

Statistical analysis

Statistical analysis was performed with the SPSS version 16.0 for Windows software program (SPSS Inc, Chicago, IL, USA). Survival rates were calculated using the Kaplan-Meier method, and survival rate comparisons were made using the log-rank test. In addition, the analysis of the relationship between age and survival was performed via the Cox proportional hazards regression model. A p value of less than 0.05 was considered to be significant. Other parameters that were analyzed were gender, operation width, operation side, pathological type, T and N statuses, and TNM stage.[8]

RESULTS

During a 19-year period, 5,150 operations were performed at our facility, and 88 of these patients were suspected of having macroscopic bronchial carcinoids after they underwent a preoperative fiberoptic bronchoscopy. Subsequent biopsies then revealed the pulmonary carcinoids. Of these patients, six were excluded from the study because of inadequate access to all of their data, and one was not included because of a diagnosis of T_4 cancer that was unresectable because it had invaded the aorta. This patient died during the fourth postoperative month. Our study group was composed of 82 patients (46 women and 36 men; mean age 43.8 years; range 16-69 years).

Sixty-eight of the patients were pathologically diagnosed with typical carcinoids while 14 were diagnosed with atypical carcinoids, and 47 patients were operated on the right side and 35 on the left. Furthermore, one patient was operated on via video-assisted thoracoscopic surgery (VATS) (a lobectomy), whereas the others underwent a thoracotomy. A lobar resection was performed on 64 patients (three pneumonectomies, 50 lobectomies, and 11 sleeve lobectomies), and 18 underwent a sublobar resection

(15 bronchotomies and three bronchial resections) (Table 1). Among the patients with typical carcinoids, one who underwent an intermediary bronchotomy developed a recurrence at the fifth year, and a right lower lobectomy had to be performed.

Number of patients in stages T_1, T_2, and T_3 were 49, 29, and 4, respectively while the numbers of N_0, N_1, and N_2 patients were 70, 10, and 2 (Table 2). All patients were M_0 before the operation. Residual disease remained at microscopic levels in one patient. Therefore, the follow-up continued for 149 months, and this patient was not included in our study. The numbers of patients in stages 1, 2, and 3 were 65, 14, and 2, respectively.

There were no postoperative deaths. Two patients developed postoperative bronchopleural fistulas after a lobectomy. In the other patient, an endobronchial stent was inserted because of the presence of empyema. Postoperative atelectasis developed in five patients who had undergone a lobectomy, and these were treated medically.

The mean length of follow-up was 84 months (range 1-212 months), and one patient died four years after the operation due to liver metastasis. The five-year overall survival rates was 98.6% (Figure 1), and 27 are still being followed up.

Table 1. Patient profiles in progress

	n	%	p
Age			
<40	32	39.020	
40-60	39	47.560	0.243
>60	11	13.414	
Gender			
Female	46	56.097	0.415
Male	36	43.902	
Cell type			
Typical	68	82.926	0.622
Atypical	14	17.073	
Side			
Right	47	57.316	0.380
Left	35	42.682	
Surgery			
Sublobar	18	21.951	0.582
Bronchotomy	15		
Bronchial resection	3		
Lobar	64	78.048	
Extended	1		
Pneumonectomy	2		
Lobectomy	50		
Sleeve lobectomy	11		

The T level and stage significantly affected the survival rate, which decreased as the T level increased (p=0.001). When the stages were compared, there was a statistically significant difference between the survival rates in stages 1 and 2 (p=0.023), whereas there was no such difference between stages 2 and 3 (p=0.76) as shown in Table 2. Since there were no deaths in the patients with stage 1 and stage 3 disease, a comparison could not be made. We also found no statistically significant differences with respect to N status (p=0.72), age (p=0.243), gender (p=0.415), operation side (p=0.380), pathological type (p=0.622), or lobar and sublobar resections (p=0.582).

DISCUSSION

Carcinoid tumors, although the most common type of neuroendocrine neoplasms are rare in comparison with other pulmonary neoplasms.[1-3] In addition, carcinoids diagnosed and operated at an early stage have a better prognosis compared with those managed at a late stage.[5-7] Therefore, determining the factors that affect survival and analyzing the results are vital components of successful treatment.

Data exists which indicates that the coexistence of advanced age and atypical carcinoids is associated with poor survival rates.[9] In our study, age and the presence of atypical cells did not have a significant effect, and the mean age was five years lower in the patients who underwent sublobar resections. The reason for this was thought to be an early manifestation of the tumor symptoms and the preference for sublobar resections in the treatment of T_1 tumors. The fact that gender and the operation side had no effect on survival was in accord

Table 2. Postoperative T, N status and stages of patients

	n	%	p
T status			
T_1	49	59.755	0.001
T_2	29	35.365	
T_3	4	4.878	
N status			
N_0	70	85.365	0.720
N_1	10	12.195	
N_2	2	2.439	
Stage			
1a	43	52.438	0.023
1b	22	26.829	
2a	3	3.658	
2b	11	13.414	
3a	2	2.439	0.768
3b	0	0	

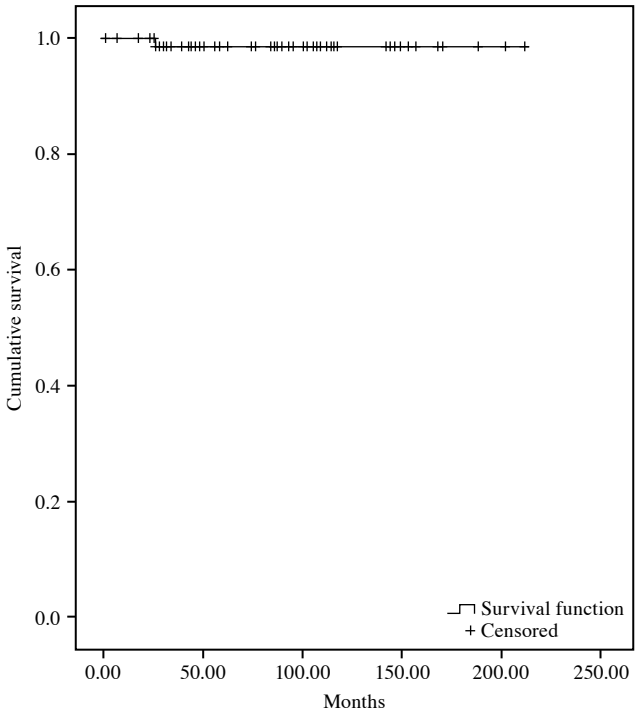

Figure 1. Survival curve.

with previous data.[9] Another factor which possibly can affect survival is the atypical carcinoid subtype.[9,10-12] In our study, there were no differences in survival between the typical and atypical subtypes, but the patient with a residual tumor, the one who died because of liver metastasis, and the two with N_2 disease had typical carcinoids, which was surprising. Cao et al.[9] compared patients with typical and atypical carcinoids and found that the former were significantly younger. However, in our study, there were no differences with regard to age.

In addition, Cao et al.,[9] determined that the atypical subtype had an effect on survival. In our study, the mean follow-up was 84 months, which is similar as previous studies.[5,9,13,14] It is also important to note that while the five- and 10-year overall survival rates were reported in Cao et al.[9] and Kyriss et al.[14] studies as 93.7%, 81.7% and 90%, 83% respectively. The survival rate for both of these time periods was 98.5% in our study.[9,12]

Fox et al.[5] and Ferguson et al.[12] evaluated resection width and compared lobar resections with sublobar resections in different studies and found that the survival rates were similar. Moreover, they stated that the patients who underwent sublobar resections were older and had other comorbidities, but these factors were not significant. Furthermore, they found that resection width also did not affect the patients' survival rates. In contrast, the mean age of the patients in our study who underwent sublobar resections was five years less than in their studies.

Two of our patients also developed bronchopleural fistulas as a major morbidity, and five developed atelectasis as a minor complication. All of these patients had undergone lobectomies. On the other hand, the patients who underwent sublobar resections did not develop any postoperative complications. However, there was one patient who developed a recurrence during the postoperative fifth year, so a lobectomy was performed. Since the sublobar resections did not cause any significant differences in the survival rates in our study, we preferred this procedure for our patients with comorbidities.

Endobronchial carcinoid tumors that manifest relatively early due to increased tumor diameters can cause obstructive pneumonia, and this can lead to early diagnosis and treatment. Therefore, the possibility of performing a sublobar resection increases while the risk of complications decreases.[5] It has been reported that tumors which are not treated with early surgery and those that have increased diameters are associated with a poor prognosis.[6] In fact, McCaughan stated that the prognosis was worse with larger tumor diameters.[15] In our study, we also found that the patients' chance of survival decreased as the T stage increased. One patient who was not included in the study because of an inoperable condition and died during the postoperative fourth month had a T_4 (aortic invasion) tumor, which corresponds with the aforementioned information regarding tumor diameter.

Contrary to what we expected, the N status did not have an effect on survival in our study.[9,13,14] This may be due to the meticulous preoperative patient selection that resulted in only 1.2% of the patients who had surgery being diagnosed with N_2 disease. Thus, in spite of our long follow-up period, the low number of patients treated who had N_2 disease might be a weakness of this study. Detterbeck[7] recommended performing a mediastinoscopy for atypical carcinoids, but none of our patients who were suitable for surgical treatment underwent this procedure. All of our patients underwent mediastinal lymph node sampling along with lobar or sublobar resections, as has been recommended in other studies,[12-16] and we found that it was necessary to get samples from three to five lymph node stations to obtain accurate results. In our study, there were no differences between the two patients who were diagnosed as N_2 (both with typical carcinoids) and the 10 who were

assessed as N_1, which led us to consider whether radiological studies might be used to adequately evaluate operability instead mediastinoscopies.

Cao et al.[9] stated that the presence of a residual tumor had no effect on survival, and our findings led to the same conclusion. In this retrospective study that encompassed 19 years, the pathology results of the patients were reevaluated according to the seventh edition of the TNM staging system for lung cancer.[8] When we compared stages 1 and 2, the survival rates was affected, which corresponded with the results of Cao et al.[9] Unexpectedly, the survival rates between stages 2 and 3 were unaffected. In addition, because adjuvant therapy is controversial,[17-19] we concluded that none of the patients should receive this type of therapy.

Conclusion

This retrospective study demonstrated the success of surgical techniques in the management of pulmonary carcinoids. Among the factors that we expected to affect the prognosis, only an advanced T status and a higher stage decreased the rate of survival. Furthermore, we found no significant differences with respect to typical and atypical cell differentiation, N status, age, gender, operation side, or resection size. Our results also showed that patients diagnosed at an earlier stage who have smaller tumor diameters will benefit from surgery to a greater extent than those without these characteristics and that sublobar resections should be the first choice of treatment for patients with high preoperative risk.

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