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Original Article / Özgün Makale

Pulmonary artery resections and reconstructions for lung cancer treatment: an anatomical-technical analysis and survival relationships

Akciğer kanseri tedavisinde pulmoner arter rezeksiyon ve rekonstrüksiyonları: Anatomik-teknik analiz ve sağkalım ilişkisi

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ABSTRACT

Background: This study aims to report the results of pulmonary arterial (PA) resections and reconstructions with either a patch or end-to-end anastomosis for lung cancer which are currently rarely used.

Methods: Between January 2005 and January 2012, 712 non-small cell lung cancer patients underwent surgery of which 32 (26 males, 6 females; mean age 62±8 years; range 39 to 80 years) had lobectomy and major reconstructive surgery for PA (14 partial, including four PA reconstructions with an autologous pericardial patch and 10 PA reconstructions with a polytetraflouroethylene graft and 18 circumferential).

Results: The median survival was 48±8 months. Five and seven-year survival rates were 27% and 9% respectively. No operative mortality was seen. Morbidity rates were 41% (minor 31% and major 10%). All patients with a right-sided resection had also a bronchial sleeve resections with a rate of 59% in the left lung (p=0.03). The rate of double sleeve resection was 47%. The median and five-year survival rates were 60±36 months and 37% in the arterial patch plasty operations respectively, whereas it was 43±13 months and 22% in circumferential resections and end-to-end anastomosis patients, respectively (p=0.38). There was no statistically significant difference in the complication rate between the circumferential resections with patch plasty operations and end-to-end anastomosis (p=0.808). Five-year survival rate was 16% in double sleeve resections and 48% in others (p=0.282). Univariate analysis of survival demonstrated no significant differences in terms of age (p=0.185), side (p=0.527), neoadjuvant treatment (p=279), N status (p=0.878), type of adjuvant treatment (p=0.978) and metastasis development (p=0.471). Female gender (p=0.05), adjuvant treatment (p=0.001) and development of postoperative complications (p=0.038) were identified as positive predictors for long-term survival.

Conclusion: Pulmonary arterial resections and reconstructions to prevent pneumonectomy are feasible and effective surgical procedures with acceptable morbidity and mortality rates. Female gender, postoperative adjuvant oncological treatment and non-complicated postoperative course appear to be potential influencing factors on long-term survival.

Keywords: Lobectomy; lung cancer; pulmonary artery; sleeve resection.

ÖZ

Amaç: Bu çalışmada günümüzde akciğer kanseri tedavisinde nadir olarak uygulanmakta olan pulmoner artere (PA) yama veya uç uca anastomoz yöntemleri ile rezeksiyon ve rekonstrüksiyon ameliyatlarının sonuçları bildirildi.

Çalışma planı: Ocak 2005 - Ocak 2012 tarihleri arasında küçük hücreli dışı akciğer kanseri nedeniyle ameliyat edilen 712 hastanın 32'sine (26 erkek, 6 kadın; ort. yaş 62±8 yıl; dağılım 39-80 yıl) lobektomi ve PA majör rekonstrüksiyon cerrahisi (dördü otolog perikard yama, 10'u da politetrafloroetilen greft ile yama olmak üzere 14'üne parsiyel ve 18'ine sirkumferensiyal rezeksiyon) uygulandı.

Bulgular: Medyan sağkalım 48±8 ay idi. Beş ve yedi yıllık sağkalım oranları sırasıyla %27 ve %9 idi. Ameliyata bağlı mortalite görülmedi. Morbidite oranı %41 (minör %31 ve majör %10) idi. Sağ taraflı ameliyat olan hastaların tümünde bronşiyal sleeve rezeksiyon da uygulanır iken, sol tarafta bu oran %59 idi (p=0.03). 'Double sleeve' rezeksiyon oranı %47 idi. Pulmoner artere yama cerrahisi yapılan hastalarda medyan sağkalım oranı 60±36 ay, beş yıllık sağkalım oranı ise %37 iken, sirkumferensiyal rezeksiyon ve uç uca anastomoz yapılan hastalarda medyan sağkalım 43±13 ay, beş yıllık sağkalım oranı ise %22 bulundu (p=0.38). Yama uygulaması ile sirkumferensiyel rezeksiyon ve uç uca anastomoz grubu arasında komplikasyon açısından istatistiksel olarak anlamlı fark yoktu (p=0.808). 'Double sleeve' rezeksiyon uygulanan hastalarda beş yıllık sağkalım oranı %16 iken, diğerlerinde bu oran %48 idi (p=0.282). Ayrıca sağkalımın tek değişkenli analizinde yaş (p=0.185), taraf (p=0.527), neoadjuvan tedavi (p=279), N durumu (p=0.878), adjuvant tedavi seçimi (p=0.978) ve metastaz gelişimi (p=0.471) açısından anlamlı bir fark görülmedi. Kadın cinsiyeti (p=0.05), adjuvan tedavi (p=0.001) ve ameliyat sonrası komplikasyon gelişimi (p=0.038) uzun dönem sağkalım için pozitif öngördürücüler olarak bulundu.

Sonuç: Pnömonektomiden sakınmak için uygulanan PA rezeksiyonları ve rekonstrüksiyonları, düşük morbidite ve mortalite oranları ile uygulanabilen uygun ve etkili cerrahi işlemlerdir. Kadın cinsiyeti, ameliyat sonrası adjuvan onkolojik tedavi ve ameliyat sonrası süreçte komplikasyon gelişmemesinin uzun dönem sağkalımı etkileyebileceği görünmektedir.

Anahtar sözcükler: Lobektomi; akciğer kanseri; pulmoner arter; sleeve rezeksiyon.

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A pneumonectomy is considered to be the classic resection technique for lung cancers when the main bronchus, the main or interlobar pulmonary artery (PA), or both pulmonary veins are involved.[1-3] However, this procedure not only has high morbidity and mortality rates but also causes a reduction in quality of life (QoL).[1,3] Within the past two decades, many studies have confirmed the feasibility and efficacy of bronchial sleeve lobectomies,[4-8] but PA resections and reconstruction have not developed as much as bronchial sleeve resections and have not been as popular due to the high complication rate and insufficient long-term survival.[9,10] A heterogeneous group of surgical PA resection techniques, including tangential resections and primary repairs, resections and reconstruction with a patch, and circumferential resections and reconstruction by end-to-end anastomosis have been studied, and synthetic grafts have also been used in the replacement of the resected PA. However, due to the heterogeneity of the population, concerns regarding the complexity of the technique and the presence of fatal complications, such as bronchovascular fistulae, the issue of long-term survival remains a problem.

The aim of our study was to evaluate the vascular and bronchial technical preferences with respect to anatomic and pathological conditions as well as the morbidity, mortality, and long-term survival rates.

PATIENTS AND METHODS

Between January 2005 and January 2012, we operated on 712 non-small cell lung cancer (NSCLC) patients, and 32 (26 males, 6 females; mean age 62±8 years; range 39 to 80 years) of these underwent major reconstructive surgery of the PA. Fourteen patients underwent patch plasty reconstruction (4 with autologous pericardial patch and 10 PA reconstructions with a polytetraflouroethylene graft) and 18 patients underwent circumferential resection of PA and end-to-end anastomosis. We reviewed the prospectively collected clinical records.

The preoperative workup included pulmonary function tests, a blood gas analysis, electrocardiography, Doppler echocardiography (when the patient had a history of cardiac disease), fiber-optic bronchoscopy, 18-fluoro-deoxyglucose positron emission tomography (FDG-PET), and brain magnetic resonance imaging (MRI) to exclude occult brain metastasis. The primary indication for PA reconstruction was anatomic feasibility; therefore, the procedure was also performed on patients who had no functional contraindications for a pneumonectomy. In addition, at least one of the invasive staging procedures, such as a mediastinoscopy, endobronchial ultrasonography, or transbronchial biopsy, was performed even when the FDG-PET results were negative for the mediastinum. Patients with positive N2 nodes in the paratracheal area were sent for neoadjuvant treatment, but further invasive investigations, such as a mediastinotomy or video-assisted thoracic surgery (VATS), were not carried out on patients with suspected station 5 or 6 positivity in the left lung.

Surgical technique

Resectability and operability were evaluated by frozen section examinations of the lymph nodes, bronchus, pulmonary artery, and veins. The surgical technique that we used for vascular reconstruction of a patch defect with an autologous pericardial patch or a synthetic patch has been described in detail by Rendina et al.[11] The major difference in our experience was the timing of the PA reconstruction. In the literature, vascular reconstruction is usually recommended after the completion of the bronchial anastomosis so as to minimize the manipulation of the vessel and evaluate the exact location after the bronchial reconstruction. However, in this study, we preferred to do the arterial reconstruction first to avoid additional heparin administration because of the prolonged clamping time.

Division of the ductus arteriosus was done in the left chest in cases where a circumferential sleeve resection was performed in order to mobilize the proximal part of the left PA, although it was not recommended as a routine; in patch reconstruction, such division was not needed. After the intravenous injection of 3,000 to 5,000 IU of heparin sodium (depending on the weight of the patient), the PA was clamped at its origin. Before the clamping of the artery, bronchial dissection should have been ready for division or bronchotomies if the patient was a candidate for a bronchial sleeve resection. The residual lobe pulmonary vein, rather than the distal pulmonary artery, was clamped. Pulmonary vascular reconstruction was performed using Prolene™ polypropylene 5/0 or 6/0 sutures (Ethicon, Inc., Somerville, NJ, USA), with 6/0 being preferred when a more distal artery was involved. Polytetraflouroethylene (PTFE) (Goretex®, W. L. Gore & Associates Inc., Newark, NJ, USA) was the preferred synthetic material for patch plasties. Four patients had patch plasties using autologous pericardial graft. No neutralization for heparin was done in all patients. The clamp on the pulmonary vein was released after de-airing, and viable material was always inserted between the

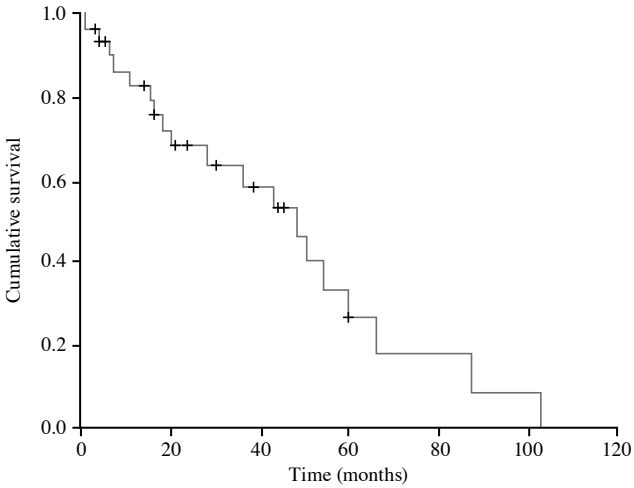

Figure 1. Survival analysis of all the patients.

bronchus and the artery when a bronchial sleeve was applied. This was an intercostal muscle flap when the patient underwent neoadjuvant treatment, but for the others, the thymus, pleura, or pericardium were preferred. In addition, routine postoperative control angiography was not performed, but the patients who developed pulmonary symptoms, underwent contrast-enhanced computed tomography angiography (CTA). Subcutaneous fractionated heparin was also given in the early postoperative period, and the patients were advised to take acetylsalicylic acid at 100 mg/day afterwards.

Both bronchotomy sides in bronchial sleeve resections and the lobar bronchus in standard resections were analyzed by frozen section pathologic examinations. The pulmonary vascular margins were also analyzed in frozen section examinations (the circular margin for arterial patch patients and the both margins for sleeve resections). When positivity was diagnosed in the arterial margins, completion pneumonectomy was done proximal to the graft.

The patients with an N1 disease underwent adjuvant chemotherapy while those with an N2 disease were advised to undergo chemo- and radiotherapy of the mediastinum. The routine postoperative follow-up

Table 1. Patient data and a comparison according to the pulmonary arterial reconstructive surgery

Variables	Total (n=32)				Circumferential resection and anastomosis (n=18)				Patch plasty (n=14)				
	n	%	Mean±SD	Range	n	%	Mean±SD	Range	n	%	Mean±SD	Range	*p*
Age (years)			62±8	39-80			61±9	39-72			63±6	52-80	0.619
Gender													0.196
Male	26	81			13	72			13	93			
Female	6	19			5	28			1	7			
Side													0.96
Right	9	28			5	28			4	29			
Left	23	72			13	72			10	71			
Neoadjuvant treatment													0.79
Yes	28	87.5			16	90			12	86			
No	4	13.5			2	10			2	14			
Bronchial sleeve													0.062
Yes	22	69			15	83			7	50			
No	10	31			3	17			7	50			
N status													0.301
N_0	10	31			7	39			3	21			
N_1	17	53			9	50			8	57			
N_2	5	16			2	11			3	22			
Complications													0.808
None	19	60			12	67			7	50			
Minor	10	31			4	22			6	43			
Major	3	9			2	11			1	7			
Adjuvant treatment													0.536
CT	12	63			11	61			9	64			
CT+RT	20	31			6	33			4	29			
No	2	6			1	6			1	7			
Metastasis													0.252
No	24	75			15	83			9	64			
Yes	8	25			3	17			5	36			
Follow-up (months)			31±25	1-103			36±27	4-103			25±21	1-60	0.196

SD: Standard deviation; CT: Chemotherapy; RT: Radiotherapy.

included a chest CT every six months for the first three years, but after this three-year period, a yearly follow-up with a chest CT was sufficient.

Statistical analysis

All data analyses were done using the SPSS for Windows version 16 (SPSS Inc., Chicago, IL, USA) software program. The data was presented as a mean ± standard error of the mean. A between-group comparison of the continuous numerical data was done using either Student's t-test or the Mann-Whitney U test, and the non-continuous (categorical) data was compared using either a chi-square test or Fisher's exact test. The patients' survival was expressed using the Kaplan-Meier method (univariate analysis) with the day of the operation representing time zero and the end point representing the time of death (when applicable). Furthermore, the differences in survival were determined using a log-rank test at the time of the univariate analysis. A *p* value of less than 0.05 was considered to be statistically significant.

RESULTS

The median survival time of all patients was 48±8 months, and the five and seven year survival rates were 27% and 9%, respectively (Figure 1). The mortality and morbidity rates were 0% and 41%, respectively while 31% had minor complications and 10% had major complications.

The demographic characteristics are listed in Table 1. Complication rates of patch plasty reconstructions and circumferential resections were 50% and 33% respectively (p=0.808).

The demographic characteristics of the patients who had also bronchial sleeve resections are listed in Table 2. The rate of bronchial sleeve resection was 69% of all patients and who had right sided resections had also bronchial sleeve resections, where as this rate was 59% in left lung resections (p=0.03). The most commonly applied procedure was the double sleeve resection (47%). Complication rates for resections with bronchial sleeve and without

Table 2. Patient data and a comparison of the patients according to the presence of bronchial sleeve resections

Variables	Total (n=32)				Presence of a bronchial sleeve (n=22)				Without bronchial sleeve (n=10)				
	n	%	Mean±SD	Range	n	%	Mean±SD	Range	n	%	Mean±SD	Range	*p*
Age (years)			62±8	39-80			62.2±6.5				61.8±10		0.900
Gender													0.346
Male	26	81			19	87			7	70			
Female	6	19			3	14			3	30			
Side													0.030
Right	9	28			9	41			0	0			
Left	23	72			13	59			10	100			
Neoadjuvant treatment													0.632
Yes	4	12.5			3	14			1	10			
No	28	87.5			19	86			9	90			
Vasculer resection													
Vasculer sleeve	18	56			15	68			3	30			0.062
Vasculer patch plasties	14	44			7	32			7	70			
Double sleeve resection													0.000
Yes	15	47			15	68			0	0			
No	17	53			7	32			10	100			
N status													0.562
N_0	10	31			6	27			4	40			
N_1	17	53			15	68			2	20			
N_2	5	16			1	5			4	40			
Complications													0.467
No	19	59			12	54.5			7	70			
Yes	13	41			10	45.5			3	30			
Adjuvant treatment													**0.036**
CT	20	63			17	77			3	30			
CT+RT	10	7			4	18			6	60			
Yok	2	30			1	5			1	10			
Metastasis													0.660
No	24	75			16	73			8	80			
Yes	8	25			6	27			2	20			

SD: Standard deviation; CT: Chemotherapy; RT: Radiotherapy.

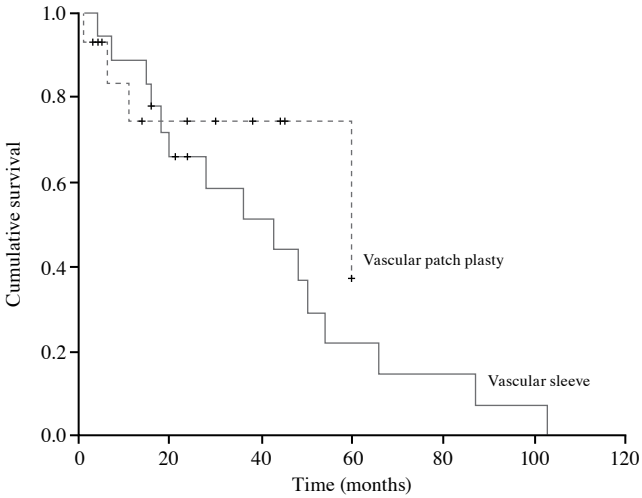

Figure 2. Survival analysis of all vascular resections and reconstructions.

bronchial sleeve were 45.5% and 30% respectively (p=0.467, Table 2).

Only 32% of the patients were shown to be N_0 cases; the rest were found to have N_1 (53%) and N_2 (16%) disease. N_1 positivity was a common finding in patients with bronchial sleeve resections (68%). Furthermore, N_1 positivity was more common in those who had a double sleeve resection (68%).

The most commonly used adjuvant treatment in patients who had bronchial sleeve resections was chemotherapy (77%) while chemoradiotherapy was reserved for those who did not undergo this procedure (60%). This difference was statistically significant (p=0.036) and can be seen in Table 2.

The median survival time was 60 months and the five-year rate was 37% in the arterial patch plasty operations, whereas it was 43±13 months and 22% in both the patients who had the circumferential resection and end-to-end anastomosis (p=0.38) (Figure 2 and Table 3).

The patients who also underwent bronchial sleeve resections had a median survival time of 48 months and a five-year survival rate of 16%, whereas these figures were 87 months and 68% for those who did not have additional bronchial sleeve resections (p=0.613) (Table 3 and Figure 3). Moreover, the patients who had double sleeve resections had a five-year survival rate of 16% while the rate was 48% for those who did not undergo this procedure (p=0.282) (Table 3 and Figure 4).

Additionally, univariate analysis demonstrated that age (p=0.185), side (p=0.527), neoadjuvant treatment (p=279), N status (p=0.878), and metastasis were not statistically significant determinants of survival (p=0.471). However, we determined that female gender (p=0.05), the use of adjuvant treatment (p=0.001), and

Table 3. Univariate and multivariate analysis of patient variables used to predict five-year survival after pulmonary arterial reconstructive surgery

Variables	Five-year survival %	Univariate *p*
Age (years)		0.185
x <60	62	
60-70	12	
x >70	27	
Gender		0.05
Male	16	
Female	67	
Side		0.527
Right	0	
Left	33	
Neoadjuvant treatment		0.279
Yes	75	
No	22	
Bronchial sleeve		0.613
Yes	16	
No	64	
Pulmonary artery		0.380
Patch plasty (+)	37	
Circumferential	22	
Double sleeve		0.282
Yes	16	
No	48	
N status		0.878
N_0	28	
N_1	19	
N_2	25	
N status		0.711
N_0	28	
N_{1-2}	23	
Complications		0.038
No	35	
Minor	39*	
Major	0*	
Adjuvant treatment		<0.001
CT	28	
CT+RT	35	
No	0	
Adjuvant treatment		0.978
CT	28	
CT+RT	35	
Metastasis		0.471
Yes	0	
No	32	

* Indicates four-year survival; CT: Chemotherapy; RT: Radiotherapy.

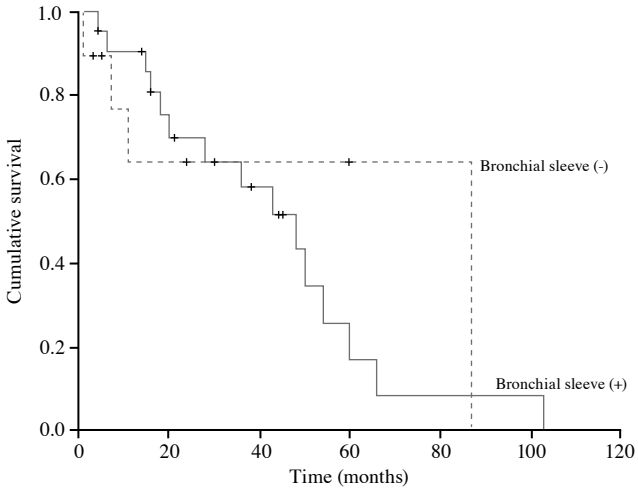

Figure 3. Survival analysis of the patients who underwent bronchial sleeve resections.

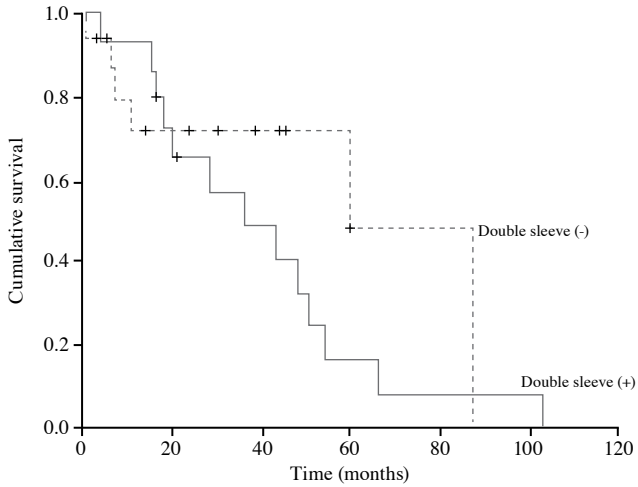

Figure 4. Survival analysis of the patients who underwent double sleeve resections.

an uncomplicated postoperative course (p=0.038) were positive predictors for long-term survival.

DISCUSSION

Allison[12] cited pulmonary angioplasty surgery in 1954, and Wurnig[13] described a tangential resection technique of the PA in 1967. In 1971, Pichlmaier and Spelsberg[14] published a report on four successful cases of combined bronchial and vascular sleeve resections. Later, in 1974, Vogt-Moykopf[15] reported on 39 cases of angioplastic lung resection, and in 1981, Vogt-Moykopf et al.[16] also determined that there was a mortality rate of 17% in combined procedures and 11% in angioplastic resections, and a five-year survival rate of 14% in combined procedures.

Similar to other studies,[16-19] arterial resection and reconstruction were applied to our patients more frequently for left-sided tumors (75% of the patients), which could be explained by the proximal character of the tumors and the different anatomy of the PAs on the right and left sides. In our series, partial PA involvement as well as partial resection and reconstruction were less common than the aforementioned series. We believe that arterial resection alone and patch plasty may be sufficient to radically deal with the disease. In addition, 18 of our study participants (56%) underwent circumferential resection with end-to-end anastomosis, which contrasts with the results of previous reports.[17,18] Our experience was similar to that of Rendina et al.[11] probably because our inclusion criteria was similar to theirs (only patch reconstruction and circumferential resections were evaluated). In their series, 15 PA sleeve resections, 34 PA reconstructions via a pericardial patch, and three PA reconstructions via a pericardial conduit were performed. The reconstructive procedure in their study was associated with a bronchial sleeve lobectomy in 33 patients (including a bilobectomy in two) and a standard lobectomy in 19 others, which actually reflects the results of our study comprised of 22 patients (69%) who underwent a bronchial sleeve resection and 10 (31%) who did not. Furthermore, all of their patients underwent an upper lobectomy except for one who had a left lower sleeve lobectomy and patch reconstruction of the lower aspect of the PA. This was similar to a patient in our series at the right lower lobe (Figure 5).[11]

The perioperative morbidity and mortality rates in our study [41% (minor 31% and major 10%) and 0, respectively] could have been higher if there were compared with the current rates for standard lobectomies; however, we considered complications to be any condition requiring a hospital stay of longer than seven days, including incisional infections. It should also be noted that patients who undergo arterial resections have an increased postoperative risk because of the locally more advanced disease. However, we did not experience any revision or death after performing this procedure. In one patient, not only did they undergo a double sleeve resection, but superior vena cava (SVC) replacement was also performed for a right upper lobe tumor (Figure 6).[20]

The data in the literature is quite variable, with mortality and morbidity rates ranging from 0-17% and 7-40%, respectively,[9,16,19] which probably reflects the heterogeneity of the study populations and perioperative treatments. In our experience, no major

Figure 5. Operative view of a right lower lobectomy in which vascular sleeve resection and patch reconstruction were used to save the posterior ascending artery and middle lobe artery.

complications (major bleeding, pulmonary infarction, or bronchovascular fistulae) were related per se to the arterial resection, although all these complications have been reported in this setting.[9,17] Sufficient lumen preservation combined with a proper application of vascular surgical techniques and the use of a pedicled flap, especially when contact between the arterial and bronchial sutures is visible, are the key elements to prevent such mortal complications.

In addition, the survival rates associated with in the PA resection and reconstruction patients in our study were similar to those of Rendina et al.,[11] and in one of their earlier series, they identified that cancer stage was the most important factor when determining survival rates. Their patients had an overall five-year survival rate of 38.3%, but it was 83% for stage 1, 56% for stage 2, 22% for stage 3A, and 11% for stage 3B. With respect to the N factor, the five-year survival rate was 56% for N_0, 37% for N_1, and 19% for N_2. Furthermore, Cerfolio and Bryant[18] reported an overall five-year survival rate of 60% in a recently published study featuring different side preferences (two right upper lobectomies and 40 left upper lobectomies) and vascular techniques (only four circumferential resections). Most of their patients (55%) received neoadjuvant treatment, and 86% were at pathological stages 0 and 2. They concluded that a circumferential resection with end-to-end anastomosis of the pulmonary artery was rarely required and claimed that partial resection was not only safe, but that it did not impede blood flow and

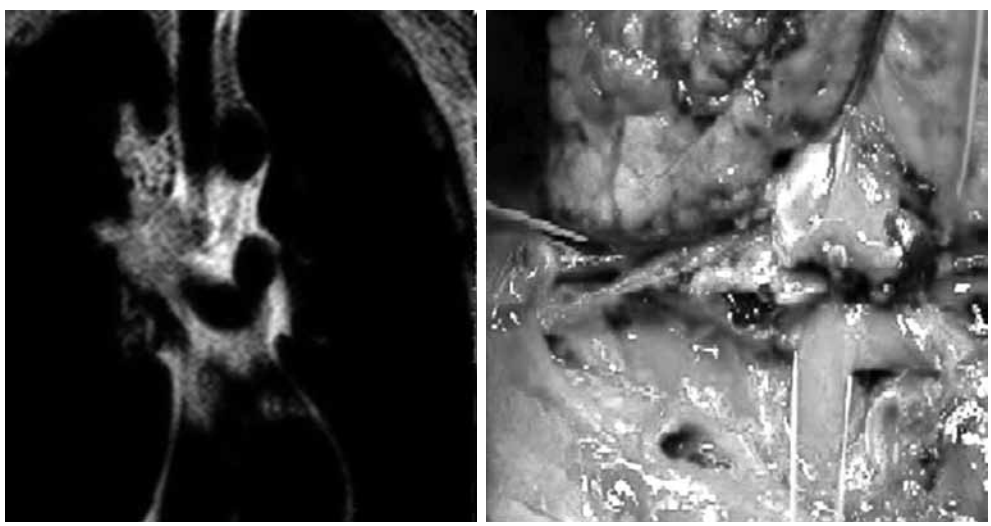

Figure 6. Computer tomographic and operative views of a double sleeve resection with superior vena cava replacement for a right upper lobe tumor. The patient survived for five and a half years without adjuvant treatment.

did not compromise local recurrence rates. In another recent study by Alifano et al.,[19] they reported a median survival of 40 months, and three- and five-year overall survival rates of 59.6% and 39.4%, respectively. This report was similar to Cerfolio and Bryant study[18] in that it had a very limited percentage of circumferential PA resections. In our study, the median survival was 48 months, and the five- and seven-year survival rates were 27% and 9%, respectively. In addition, we found similar survival rates in the patients who underwent PA vascular resection and reconstruction only when there was no associated bronchial sleeve. Hence, it is possible that degree of invasion is the factor that determines survival. Our patients mostly underwent circumferential resections. In a 2007 meta-analysis by Ma et al.,[21] the five-year survival rate was 38.7%, which is similar to that of our patients who did not undergo bronchial sleeve resections but higher than ours who had this procedure. However, there were markedly fewer numbers of stage 1 and 2 patients in our study than in other studies.

Obviously, comparisons between these studies are difficult to make. In the study by Alifano et al.,[19] a multivariate analysis showed that the size of the primary tumor and the presence of vascular emboli were independent factors that indicated a poorer outcome, whereas nodal status was not a prognostic factor in either the univariate or multivariate analysis. In our study, female gender was an important prognostic factor, but we could not find any sufficient explanation for this finding. For this reason, further studies that focus on gender as it relates to these procedures are needed. Nodal involvement, side, histology, and bronchial sleeve resections did not influence survival rates in our study, probably because of the heterogeneity of our population. However, we did identify that the use of adjuvant oncological treatment ($p=0.001$) and an uncomplicated postoperative course ($p=0.038$) were positive predictors for long-term survival.

Our study had a few limitations. This series involved the analysis of prospectively collected data; thus, randomization was unfeasible. Hence, a multicenter study might have been more meaningful. In addition, the number of patients, while comparable to most similar series, was still small, making comparisons difficult and causing the creation of smaller groups in our detailed analyses.

Conclusion

Our study population was comprised of 4.49% of all lung cancer patients operated on during the same time period at our facility. Our findings showed that PA resections and reconstructions to prevent pneumonectomies are feasible and effective surgical procedures with acceptable morbidity and mortality rates. We also found that female gender, postoperative adjuvant oncological treatment, and an uncomplicated postoperative course were potential factors that could affect long-term survival.

Declaration of conflicting interests

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