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Factors affecting survival after anatomical lung resection in pulmonary aspergilloma: Our 10-year single institution experience

Pulmoner aspergillomada anatomik akciğer rezeksiyonu sonrası sağkalımı etkileyen faktörler: 10 yıllık tek merkezli deneyimimiz

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ABSTRACT

Background: The aim of this study was to investigate the long-term outcomes of patients who underwent anatomic lung resection for pulmonary aspergilloma and to evaluate the prognostic factors affecting early postoperative morbidity.

Methods: Between January 2007 and January 2017, we retrospectively evaluated a total of 55 patients (40 males, 15 females; mean age: 44.6 years; range, 18 to 75 years) who underwent lobectomy and pneumonectomy for pulmonary aspergilloma. All patients were evaluated for simple or complex aspergilloma based on imaging and thoracotomy findings.

Results: Thirty-two (58.2%) patients presented with hemoptysis. Seven (12.7%) patients underwent emergency surgery due to massive hemoptysis. Postoperative morbidity was observed in 15 (27.3%) patients. Prognostic factors that had an effect on morbidity were resection type, Charlson Comorbidity Index >3, and massive hemoptysis (p<0.05). There was no intra- or postoperative mortality. The five-year survival rate was 89.4%. None of the factors evaluated in the study were associated with survival.

Conclusion: The main finding of this study is the absence of mortality after surgical treatment for pulmonary aspergilloma. The success of surgical treatment depends on the management of postoperative complications.

Keywords: Aspergilloma, lung resection, morbidity, surgery.

Pulmonary aspergilloma is a rare and challenging lung disease that can be complicated by other respiratory problems. Surgery is preferred as the primary treatment for aspergilloma, as antifungal agents are not effective

ÖZ

Amaç: Bu çalışmada pulmoner aspergilloma nedeniyle anatomik akciğer rezeksiyonu uygulanan hastaların uzun dönem sonuçları incelendi ve ameliyat sonrası erken morbiditeyi etkileyen prognostik faktörler değerlendirildi.

Çalışma planı: Ocak 2007 - Ocak 2017 tarihleri arasında pulmoner aspergilloma nedeniyle lobektomi ve pnömonektomi yapılan toplam 55 hasta (40 erkek, 15 kadın; ort. yaş: 44.6 yıl; dağılım, 18-75 yıl) retrospektif olarak incelendi. Hastalar görüntüleme ve torakotomi bulgularına dayanarak basit veya kompleks aspergilloma açısından değerlendirildi.

Bulgular: Otuz iki (%58.2) hasta hemoptizi ile başvurdu. Yedi (%12.7) hastaya masif hemoptizi nedeniyle acil cerrahi uygulandı. Ameliyat sonrası morbidite 15 (%27.3) hastada gözlendi. Morbidite üzerine etkisi olan prognostik faktörler rezeksiyon tipi, Charlson Komorbidite İndeksi >3 ve masif hemoptizi idi (p<0.05). Ameliyat sırası veya sonrası mortalite gözlenmedi. Beş yıllık sağkalım oranı %89.4 idi. Çalışmada değerlendirilen faktörlerin hiçbiri sağkalım ile ilişkili değildi.

Sonuç: Bu çalışmanın ana bulgusu, pulmoner aspergilloma için cerrahi tedaviden sonra mortalitenin olmamasıdır. Cerrahi tedavinin başarısı, ameliyat sonrası komplikasyonların yönetimine bağlıdır.

Anahtar sözcükler: Aspergilloma, akciğer rezeksiyonu, morbidite, ameliyat.

inside the cavitary structures of the lungs, and lifethreatening hemoptysis is common.^[1] The main goal of surgical treatment is to prevent hemoptysis by protecting the lung parenchyma. Surgery also provides

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curative treatment of aspergilloma, including the reduction of symptoms in patients with localized lung lesions. [1,2] Although successful results have been achieved in the long-term with the advances in surgical techniques, there is no consensus on the role of surgical resection in the treatment of pulmonary aspergilloma due to high morbidity and mortality rates. Surgical treatment is usually recommended owing to lower morbidity and mortality rates in patients with simple pulmonary aspergilloma (SPA). On the other hand, there are significant mortality and morbidity rates in complex aspergilloma. Therefore, there is controversy regarding the optimal treatment strategy for complex pulmonary aspergilloma (CPA). [3]

In the present study, we aimed to evaluate the longterm outcomes of patients who underwent anatomic lung resection for SPA and CPA and to evaluate the prognostic factors affecting early postoperative morbidity and mortality.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Thoracic Surgery between January 2007 and January 2017. Data from 3,962 patients who underwent pulmonary resection in our center were obtained from a prospective database. Among these patients, 55 (40 males, 15 females; mean age: 44.6 years; range, 18 to 75 years) who underwent lobectomy and pneumonectomy for pulmonary aspergilloma were included in the study. Patients who were operated without anatomic resection and whose data could not be reached were excluded from the study. The comorbidity score was calculated according to the Modified Charlson Comorbidity Index (CCI). [4] A written informed consent was obtained

from each patient. The study protocol was approved by the Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee (date, no: 3/11/2018-1524). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Diagnosis and classification of pulmonary aspergilloma

Pulmonary aspergilloma was diagnosed based on clinical symptoms and the presence of an intracavitary mass surrounded by an air crescent on radiologic examination. Chest X-ray and thoracic computed tomography (CT) was used for radiological evaluation (Figure 1a, b). In the preoperative evaluation, bronchoalveolar lavage, fungal culture, and galactomannan samples were obtained. Cytology and a fungal cult were conducted as preoperative testing to all patients, except for patients having an emergency operation, and two patients could not tolerate bronchoscopy. Galactomannan was found positive in 16 patients, and antifungal culture was found positive in 25 (45.5%) patients. Three of the operated patients had a history of multi-drug-resistant tuberculosis.

Aspergillosis is a disease caused by aspergillus species, particularly Aspergillus fumigatus. Although tissue invasion is rare, it is frequently observed in patients with the suppressed immune system, such as hematological malignant, hematopoietic cell transplantation, and solid organ transplants.^[5] Pulmonary aspergillosis is observed in three groups such as aspergilloma, allergic aspergillosis, and invasive aspergillosis.^[6] According to the radiological aspergilloma classification developed by Belcher and Plummer,^[7] the patients were evaluated as those with

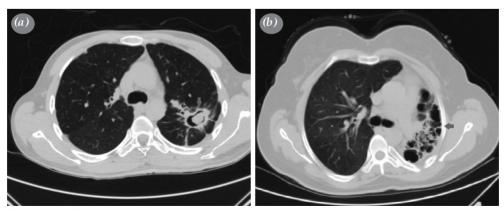


Figure 1. (a) Thoracic computed tomography showing fungus ball view in the cavitary lesion at the left lung upper lobe. (b) Thoracic computed tomography showing destroid view of the left lung.

SPA or CPA based on imaging and thoracotomy findings. Simple pulmonary aspergilloma was defined as localized, smaller than 5 cm, well-defined, thin-walled, with no surrounding atelectasis or consolidation. Complex pulmonary aspergilloma was defined as a size larger than 5 cm, thick-walled, and surrounded by atelectasis or consolidation (with bronchiectasis and tuberculosis).

For patients presenting with hemoptysis, massive hemoptysis was regarded as ≥300 mL per 24 h or ≥100 mL/h, and mild hemoptysis was <100 mL/h or <300 mL per 24 h. Seven patients underwent emergency surgery due to massive hemoptysis. Cough, shortness of breath, recurrent infections, and hemoptysis were evaluated as symptoms in the study. The most common symptom was cough complaints, which occurred in 18 (32.7%) patients.

In the study, 26 (47.3%) patients had a past history of tuberculosis. All patients with tuberculosis received antituberculosis treatment. Twenty-four patients had tuberculosis sequela on thoracic CT. In the study, pleural and mediastinal adipose tissue was used to reinforcement to bronchial stump in patients undergoing pneumonectomy. Five of these patients had a tuberculosis history.

Postoperative morbidities were classified as major (bronchopleural fistula [BPF], empyema, respiratory failure requiring mechanical ventilation, hemorrhage requiring revision, and pneumonia) or minor (prolonged air leak [PAL], arrhythmia, and surgical site infection). Air leaks persisting for seven days or longer were regarded as PAL.

Postoperative mortality was defined as deaths that occurred within the first 30 days after surgery or those that occurred due to any surgical complication that required long-term hospitalization. In the postoperative period, the patients were consulted for antifungal treatment by a pulmonologist. Fifty-one patients took antifungal treatment, but four patients refused medical treatment.

The patients' preoperative symptoms and findings, presence of any underlying lung disease, surgical procedure, morbidities and/or mortality during postoperative follow-up, length of postoperative hospital stay, length of stay after readmission, if applicable, and long-term follow-up results were recorded.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk,

NY, USA). Continuous variables were presented in mean \pm standard deviation (SD) or median (min-max), while categorical variables were presented in number and frequency. Demographic and clinical characteristics of the patients, such as age and length of hospital stay, were tested for normal distribution using the Kolmogorov-Smirnov test. The t-test was used to compare group means for these variables, while the chi-square test was used to compare morbidity between the two groups. Survival analysis was conducted using the Kaplan-Meier method, and curves were compared using the log-rank test. A p value of <0.05 was considered statistically significant.

RESULTS

Of the patients, 32 (58.2%) presented with hemoptysis, 17 of these patients had massive hemoptysis, and 15 patients had mild hemoptysis. Pulmonary aspergillomas were most commonly located in the right and left upper lobes (n=44, 80%). Twenty-two (40%) patients had simple, and 33 (60%) had CPA. Fungus ball was detected in thoracic CT in 23 (69.7%) of the CPA patients. Forty-eight (87.3%) patients underwent lobectomy and seven (12.7%) underwent pneumonectomy. Pneumonectomy was performed in four patients with destroyed lung and three patients whose lesion invaded in the other lobe. The mean operating time was 253±113 min, and the mean intraoperative blood loss was 499±441 mL. Demographic characteristics of the patients and aspergilloma types are shown in Table 1.

Seven patients underwent emergency surgery due to massive hemoptysis. Embolization was performed on 13 of 32 patients with hemoptysis. Postoperative morbidity was observed in 15 (27.3%) patients. There were major complications in seven (12.7%) patients and minor complications in 11 (20%) patients. Six patients had PAL, which was treated with blood pleurodesis in five patients and resolved spontaneously in one patient. Five patients had an arrhythmia that was corrected with medical treatment. Two patients underwent postoperative revision due to surgical site infection, and two others underwent revision due to postoperative hemorrhage. Two patients with early postoperative respiratory failure were supported with non-invasive mechanical ventilation. One patient who underwent thoracotomy for massive hemoptysis was supported with invasive mechanical ventilation due to postoperative respiratory failure and was extubated on postoperative Day 4. One patient developed BPF after lobectomy and underwent complementary pneumonectomy, and another patient developed BPF after pneumonectomy and underwent open-window thoracostomy followed by observation. Three patients developed pyothorax postoperatively. The factors affecting morbidity were CCI >3 and massive hemoptysis (p<0.05). No statistically significant difference was found between other demographic characteristics and morbidity (Table 2).

The mean length of hospital stay was 8.8 ± 6.0 days. There was no statistically significant difference between patients with SPA and CPA in terms of length of stay (p=0.621). The presence of tuberculosis was not associated with a significant difference in length of stay (p=0.139). There was no intraoperative or postoperative mortality. The patients were followed up a median 59 months, and the five-year survival rate was 89.4% (mean: 116 ± 6.8 months). None of the factors

Table 1. Demographic and surgical features of aspergillomas patients

	SPA			СРА			
Variables	n	%	Mean±SD	n	%	Mean±SD	p
Age (year)			46.0±13.7			43.6±10.1	0.450
Sex							0.216
Male	18	81.8		22	66.7		
Female	4	18.2		11	33.3		
Smoking habit (package/year)			30.5±15.6			26.7±17.8	0.454
CCI							0.186
0-2	14	63.6		15	45.5		
>3	8	36.4		18	54.5		
Underlying lung diseases							0.005
Tuberculosis	5	22.7		21	63.6		
Bronchiectasis	3	13.6		6	18.2		
Emphysema	3	13.6		2	6.1		
Malignancy	0	0		1	3		
None	11	50		2	6.1		
Symptoms							0.332
Asymptomatic	8	36.4		8	24.2		
Symptomatic	14	63.6		25	75.8		
Hemoptysis							0.036
Mild	9	69.2		6	31.6		
Massive	4	30.8		13	68.4		
FEV1 (L)			2.7 ± 1.1			2.7 ± 0.9	0.392
FEV1 (%)			78.9 ± 28.6			65.6±19.6	0.187
Preoperative embolization	2	9.1		11	33.3		0.038
Resections							
RUL	12	54.5		18	54.5		
RLL	1	4.5		0	0		
RBS	6	27.3		7	21.2		
LUL	2	9.1		1	3		
LLL	1	4.5		0	0		
Pneumonectomy	0	0		7	21.2		
Operation time (min)	302.7±79.1				0.012		
Amount of intraoperative bleeding (mL)			244.1±213.2			670.3±473.8	< 0.001
Duration of pleural drainage (days)			5.5 ± 2.6			5.8±3.3	0.881

SPA: Simple pulmonary aspergilloma; CPA: Complex pulmonary aspergilloma; SD: Standard deviation; CCI: Charlson Comorbidity Index; FEV1: Forced expiratory volume in 1 sec; RUL: Right upper lobectomy; RLL: Right lower lobectomy; RBS: Right bilobectomy superior; LUL: Left upper lobectomy; LLL: Left lower lobectomy; Bold values indicate statistical significance (p<0.05).

Table 2. Evaluation of factors affecting morbidity

	Morbidity (None)			Morbidity (Yes)			
Variables	n	%	Mean±SD	n	%	Mean±SD	p
Age (year)			43.5±11.8			47.7±10.8	0.400
Sex							0.458
Male	28	70		12	30		
Female	12	80		3	20		
Side							0.435
Right	22	68.8		10	31.3		
Left	18	78.3		5	27.5		
Symptoms							0.510
Asymptomatic	13	81.3		3	18.8		
Symptomatic	27	69.2		12	30.8		
Preoperative embolization							0.697
No	30	71.4		12	28.6		
Yes	10	76.9		3	23.2		
Type of aspergilloma							0.216
Simple	18	81.8		4	18.2		
Complex	22	66.7		11	33.3		
FEV1 (%)			75.1±22.8			59.0±22.9	0.102
Resection							0.013
Lobectomy	38	79.2		10	20.8		
Pneumonectomy	2	28.6		5	71.4		
CCI							0.018
0-2	25	86.2		4	13.8		
>3	15	57.7		11	42.3		
Hemoptysis							0.435
No	18	45		5	33.3		
Yes	22	55		10	66.7		
Hemoptysis type							0.040
Mild	13	59.1		2	20		
Massive	9	40.9		8	80		
Operation time (min)			276.6±103.8			264.1±102.6	0.691
Intraoperative bleeding (mL)	350			450			0.232

SD: Standard deviation; FEV1 Forced expiratory volume in 1 sec; CCI: Charlson Comorbidity Index, Bold values indicate statistical significance (p<0.05).

evaluated in the study were associated with survival (Table 3).

DISCUSSION

In pulmonary aspergilloma, surgical treatment is performed, when lesions are localized and resistant to antifungal therapies. Patients with aspergilloma often present with chronic infections and episodes of hemoptysis. Most patients are symptomatic at the time of presentation.^[8,9] Invasive aspergillosis is frequently seen in patients with a suppressed immune system. It particularly occurs in patients with solid and stem cell transplantation.^[6] Lejay et al.^[1] argued that surgery was

the main treatment for aspergilloma and emphasized that surgery was less risky in asymptomatic patients. This is because, in addition to reducing patients' symptoms, surgical treatment improves survival in asymptomatic patients. [10-12] Similar to the literature, 29.1% of the patients in our study were asymptomatic. The asymptomatic patients were not found to have an effect on morbidity and survival rates.

Muniappan et al.^[13] reported that treatment prior to aspergilloma surgery reduced postoperative recurrence. Similarly, guidelines of the Infectious Diseases Society of America (IDSA) states that preoperative antifungal

Table 3. Evaluation of factors affecting survival

Variables	5 year survival (%)	Median survival (Month)	95% CI	p
Side				0.807
Right	85.1	104	90-119	
Left	95	118	100-136	
Symptoms				0.211
Asymptomatic	93.3	125	111-136	
Symptomatic	87.6	111	95-128	
Hemoptysis				0.966
Mild	77.8	114	88-140	
Massive	92.9	111	89-132	
Location of aspergilloma				0.570
Upper lobe	89.5	118	104-132	
Mid or lower lobe	88.9	94	68-119	
CCI				0.191
0-2	96.6	123	106-140	
>3	79.2	96	77-114	
Underlying lung diseases				0.823
Tuberculosis	89.8	103.1	86-120	
Nontuberculosis	89.5	118.4	101-135	
Resection				0.300
Lobectomy	90.4	119	106-113	
Pneumonectomy	83.3	89	60-119	
Type of aspergilloma				0.765
Simple	85.9	119	101-137	
Complex	92.4	102	86-117	

CI: Confidence interval; CCI: Charlson Comorbidity Index.

therapy is effective in preventing postoperative recurrence.^[14] However, there are publications suggesting surgery instead of preoperative antifungal therapy after the diagnosis of aspergilloma.^[15,16] In particular, Chen et al.^[16] recommended surgical treatment due to life-threatening complications that might occur during medical treatment.

Hemoptysis is among the main risk factors for mortality in cases of aspergilloma and occurs in 20% of cases. [17,18] Akbari et al. [12] and Okubo et al. [10] reported that the recurrence of hemoptysis was reduced after surgical resection. The prevalence of massive hemoptysis in our study was 30.9%. Massive hemoptysis was significantly more common in patients with CPA. One patient with CPA who underwent surgery for massive hemoptysis developed recurrent hemoptysis at the postoperative 18th month and underwent bronchial arterial embolization. Bleeding of the patient was caused by bronchiectasis in the opposite lung. Bronchial arterial embolization was

performed due to the low lung reserve of the patient. Of note, PAL, persistent pleural space, emphysema, pneumonia, surgical site infection, BPF, respiratory failure, and massive hemorrhage may occur after aspergilloma resection.[11] Morbidity rates of up to 60% were reported in earlier series. Infiltration of surrounding tissue, indurated hilar structures, pleural adhesions, and poor expansions led to postoperative complications.[10] Although these rates are lower in the current series, the average morbidity remains around 24%. This can be mostly attributed to the heterogeneity of aspergilloma. In particular, greater morbidity is seen in CPA. [19] Table 4 shows the morbidity and mortality rates of the patients with aspergilloma. Accordingly, the average mortality rate in the literature ranges from %1 to 3, and the morbidity rate is around 20%. In our study, a comparison of the operating times and blood loss in simple and complex aspergillomas clearly showed greater operative difficulties occurring with complex aspergillomas. Risk factors associated

Table 4. Evaluation of pulmonary aspergilloma literature

			CPA	SPA	Mortality	Morbidity
Authors	Publication year	n	%	%	%	%
Kim et al. ^[24]	2005	88	72	16	1.1	27
Akbari et al.[12]	2005	60	14	46	3.3	33.3
Demir et al.[20]	2006	41	-	-	2.4	24.4
Okubo et al.[10]	2007	18	-	-	41.6	5.55
Brik et al.[17]	2008	42	12	30	3.3	0.3
Lee et al.[11]	2009	135	33	102	4.4	30
Lejay et al.[1]	2011	33	4	29	0	24.2
Muniappan et al.[13]	2014	60	47	13	3.3	30
Aydogdu et al.[28]	2015	77	37	40	3.3	23.3
Komori et al.[3]	2018	35	26	9	0	32

CPA: Complex pulmonary aspergilloma; SPA: Simple pulmonary aspergilloma.

with morbidity were CCI >3, presence of massive hemoptysis, and resection type. The most important factor in surgical morbidity is the extrapleural resection, if there were adhesions in the apical region during the operation. We also believe that patients undergoing pneumonectomy, bronchial stump reinforcement with live tissue (mediastinal fat tissue or pleura) to reduce the risk of BPF.

Some authors have indicated that postoperative pulmonary rehabilitation is important in preventing complications. Okuba et al. prevented the development of complications in aspergillomas through preoperative pulmonary rehabilitation. In our previous study on pulmonary aspergilloma, the morbidity rate was 24.4%. We believe that the increase in the rate of morbidity in this study is mainly due to the higher proportion of pneumonectomies. In addition, the difference between SPA and CPA in our study is due to the fact that fewer pneumonectomies were performed for simple aspergillomas.

In the treatment of aspergilloma, less aggressive surgeries are preferred over pneumonectomy. Non-anatomic resections could be performed in patients with aspergilloma with inadequate lung capacity. However, pneumonectomy is performed in cases of destroyed lung or multiple lobe involvement. Similar to previous studies, we had high complication rates in patients who underwent pneumonectomy. The incidence of postoperative BPF and empyema is higher among patients undergoing pneumonectomy for CPA. Kim et al. [24] reported the development of postpneumonectomy empyema after two of their

three pneumonectomies. Regnard et al.^[25] detected postpneumonectomy empyema in two of 10 patients who underwent pneumonectomy. Shiraishi et al.^[22] reported one patient who developed empyema out of 11 patients who underwent pneumonectomy. In our study, one of the seven patients who underwent pneumonectomy developed BPF and empyema. Infection control was achieved by thoracostomy. The patient did not consent to carinal resection and was instead followed after tracheal stent placement.

Pulmonary aspergilloma is usually associated with lung diseases such as tuberculosis, bronchiectasis, bronchial cysts, bullae, neoplasm, pulmonary infection, and sarcoidosis. [26,27] Tuberculosis is the most common comorbidity associated with aspergillomas.^[23] Pulmonary tuberculosis is very common in developing countries, and its coexistence with aspergilloma has been reported in 13 to 89% of patients.[17,27] The large cavities created by tuberculosis create a suitable environment for the growth of Aspergillus. Therefore, aspergillomas occur in the same areas as tuberculosis, namely in the apical parts of the upper lobe and in the superior segments of the lower lobe. In our study, 47.3% of pulmonary aspergillomas occurred concurrently with tuberculosis, and the disease was most commonly located in the upper lobes. Thirteen of the patients with aspergilloma had no underlying disease, and these were predominantly patients with SPA (p=0.001).

It is argued that pulmonary arterial embolization is effective for preventing recurrent infections, reducing intraoperative hemorrhage, and preventing postoperative morbidity in patients with massive preoperative hemoptysis. Survival rates are 70 to 85% in patients who undergo surgical treatment. Lee et al.^[11] and Okubo et al.^[10] determined 10-year survival rates of 84.8% and 79.4%, respectively. In our study, the long-term results of surgical treatment of CPA were found to be successful. The survival rates of patients with mild hemoptysis and massive hemoptysis were similar in our study (77.8% vs. 92.9%, respectively). The five-year survival rate was 85.9% in SPA and 92.4% in CPA.

Due to the technical risks of aspergilloma surgery, postoperative outcomes are complicated. The mortality rate is 5% in the literature. Akbari et al. Italian found that the mortality rate in cases of CPA was 4.3%, whereas in their series the overall mortality rate was 3.3%. However, there are also series in the literature with no mortality. In our previous series, the mortality rate between 1988 and 2003 was 2.4%. However, there was no intra- and postoperative mortality in our current series. Our mortality outcomes are similar to some other series in the literature. We attribute this to the thorough preoperative evaluation of the patients, and our increased experience in the operative management of post-aspergilloma complications.

The main limitations of our study include its retrospective design, the fact that surgical treatment was performed in selected patients, and the inability to evaluate patients' general preoperative condition.

In conclusion, the key finding of this study is the absence of mortality after surgical treatment of pulmonary aspergilloma. The success of surgical treatment depends on preventing postoperative complications. The results of our study showed that high Charlson Comorbidity Index scores, massive hemoptysis, and extended resections were important prognostic factors in postoperative complications. Surgical resection showed acceptable results for patients with pulmonary aspergillosis despite few comorbidities and a high surgical risk. Although complex aspergillomas were more symptomatic than the simple aspergillomas, the morbidity rates were similar in this study. Therefore, surgery should be preferred in these patients.

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