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Research Article

Morbidity and mortality after pneumonectomy in smokers with NSCLC

Komplikationen und Mortalität nach Pneumonektomie bei Rauchern mit NSCLC

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Abstract

Objective: Perioperative morbidity and mortality in patients receiving pneumonectomy because of non-small cell lung cancer (NSCLC) remains quite high. The aim of this study is to identify risk factors to minimize perioperative mortality and morbidity.
Patients and method: The results of 156 Patients who received pneumonectomy between 1995 and 2004 were reviewed retrospectively. All patients had stage I or II NSCLC. In 81 cases a right sided and in 75 a left sided pneumonectomy was performed. Cardiopulmonary function tests were sufficient for pneumonectomy.
Results: Overall perioperative 30-day mortality was 7.1% (n=11), in hospital mortality 8.3% (n=13). The cause was sepsis in 6 cases, cardiac failure in 4 cases, and respiratory insufficiency in 3 cases. In univariable and multivariable regression analysis considering mortality, none of the prognostic factors reached significance. The odds ratio for postoperative death was 1.6 fold for smokers in comparison to non smokers. Complications after pneumonectomy were seen in 34.6%, with arrhythmia in 16.0%, sepsis in 1.9% and bronchopleural fistula (BPF) occurring in 6.4%. Smoking and intraoperative blood loss >500 ml were highly significant perioperative risk factors.
Conclusion: Smoking until operation and intraoperative blood loss were independent postoperative risk factors leading to complications after pneumonectomy for NSCLC. The risk for complications was 2.8-fold higher for smokers.

Keywords: pneumonectomy, risk factor, morbidity, mortality, complications, smoking

Zusammenfassung

Ziel: Nach wie vor ist die perioperative Morbidität und Mortalität bei Patienten, die sich auf Grund eines nicht-kleinzelligem Lungenkarzinoms einer Pneumonektomie unterziehen müssen, sehr hoch. Das Ziel dieser Studie ist, Risikofaktoren zu identifizieren und dadurch die Morbidität und Mortalität zu senken.
Patienten und Methode: Die Daten von 156 Patienten, die zwischen 1995 und 2004 auf Grund eines nicht-kleinzelligen Lungenkarzinoms im Stadium I und II pneumonektomiert werden mussten, wurden retrospektiv ausgewertet. In 81 Fällen wurde die Pneumonektomie rechts und in 75 Fällen links vorgenommen. Sowohl kardiale als auch pulmonale Funktionsparameter qualifizierten die Patienten für eine Pneumonektomie.
Resultate: Die 30-Tage-Mortalität betrug 7,1% (n=11), die Krankenhausletalität 8,3% (n=13). Die Ursachen waren eine Sepsis bei 6 Patienten, Herzversagen bei 4 Patienten und pulmonale Probleme bei 3 Patienten. Bezüglich der Letalität erreichte keiner der Prognosefaktoren sowohl in der univariablen als auch der multivariablen Regression statistische Signifikanz. Die Odds-Ratio, postoperativ zu versterben, betrug bei den

Rauchern 1,6. Komplikationen traten in 34,6% auf, am häufigsten Arrhythmie bei 16,0%, Sepsis in 1,9% und Bronchusstumpfinsuffizienz in 6,4%. Rauchen und intraoperativer Blutverlust >500 ml waren hoch signifikante perioperative Risikofaktoren.
Schlussfolgerung: Rauchen bis zur Operation und intraoperativer Blutverlust sind unabhängige perioperative Risikofaktoren nach Pneumonektomie bei nicht-kleinzelligem Lungenkarzinom. Das Risiko, postoperativ Komplikationen zu entwickeln, war 2,8-mal höher bei Rauchern.

Schlüsselwörter: Pneumonektomie, Risikofaktor, Morbidität, Mortalität, Komplikationen, Rauchen

Introduction

Lung cancer remains the leading cause of cancer death throughout the world with 1.2 million new cases annually. Complete resection continues to be the only way to eliminate lung cancer. Because of improved surgical technique and perioperative care, the outcome after pulmonary resection has greatly improved throughout recent years [1]. However, pneumonectomy results in the highest morbidity and mortality of thoracic procedures with pneumonectomy necessary for complete resection of non-small cell lung cancer (NSCLC) in about 10–30% of resectable cases [2], [3]. The perioperative 30-day mortality has been reported as high as 25–40% in recent scientific literature [4], [5], [6]. The most common cause for perioperative mortality is postoperative bronchopleural fistula (BPF). The use of monofilament absorbable sutures for closure of the bronchial stump decreases the rate of BPF significantly [7]. Buttressing the bronchial stump with viable material like pericardium or different muscles could give additional security [8]. Several studies dealing with pre- and perioperative risk factors of patients requiring pneumonectomy reach different conclusions [3], [9], [10], [11], [12], [13]. The different conclusions are due to a low number of patients and inappropriate statistic methods in most studies which leads to contradictory results with some minor impact for clinical work. Mortality rates could be decreased 6–15% with proper selection of procedures [14], [15]. Therefore, we have reviewed the role of smoking and other risk factors in patients requiring pneumonectomy because of NSCLC over the past 10 years. To exclude factors related to advanced cancer, only patients with early stage lung cancer were included. Cigarette smoking is a significant and preventable cause of morbidity and mortality and has also been implicated as a risk factor for postoperative pulmonary complications [5]. Previous studies have found that current smokers are two to four times more likely to develop postoperative complications [16].

Patients and methods

All patients undergoing pneumonectomy for stage I and II lung cancer at Schillerhöhe Hospital between January 1995 and June 2004 were retrospectively identified and reviewed. Patients with stage-III NSCLC have received neoadjuvant chemoradiotherapy since 1995 in our hospital. Despite additional factors related to advanced cancer treatment, related morbidity and mortality played a major role in these patients and we decided not to consider them in this study.
All data were analyzed for pre- or intraoperative factors related to an increase in postoperative morbidity and mortality. Mortality was defined as death within 30 days after pneumonectomy. All postoperative complications which required treatment were documented. The following demographic data were collected for all patients: Age, sex, weight, stage, number of additional diseases, smoking, ASA score, side of operation, operation time, and intraoperative blood loss. According to the guidelines of the German Society for Thoracic Surgery, all patients had sufficient cardio-pulmonary reserves for pneumonectomy. The preoperative evaluation included a complete history, physical examination, blood cell count, biochemical profile, chest X-ray, ECG and pulmonary function tests. Preoperative staging required bronchoscopy, CT thorax, CT brain, bone scan, and ultrasound of abdomen. Resection was standardized in all patients with posterolateral thoracotomy following dissection of the hilar structures confirming resectability. After resection, free margins at the bronchial stump were documented by frozen section and the bronchial stump was closed by interrupted 3.0 and 4.0 PDS sutures in all patients. Buttressing was not done routinely. Complete lymphadenectomy of sections 2–4, 7–9, and 10 in right sided and 4–10 in left sided tumors was done routinely. All patients were monitored at ICU for a minimum of 5 days.
Statistics were accomplished using the software R (http://www.r-project.org/). For comparison of significances, a Fisher exact test was used for categorical variables. Univariable and multivariable regression analysis was used for exploring significant prognostic factors before the odds ratio was calculated.

Results

Between 1995 and 2004, 156 patients (125 male, 31 female) with stage I or II NSCLC underwent pneumonectomy. Median age was 63 years; Karnofsky Index was 100 in 79%; and 84% had no major comorbidity with only one having an additional disease. ASA score was 3 in

82% and 4 in 15%. 52% (n=81) of the patients had right side and 48% (n=75) left side tumors (Table 1).

Table 1: Demographic data (n=156)

	n	%
Age (average in years ± SD)	63	
Age ≤60 years	63	40
Age >60 years	93	60
Male	125	80
Female	31	20
Smoker	92	59
Nonsmoker	64	41
OP side right	81	52
OP side left	75	48
Days of treatment in hospital (pre- and postoperative)	21 days (5–55)	
Complications	54	35
Death	13	8.3
Alive	143	91.7

59% (n=92) of the patients smoked until operation. During this time, no program for smoking cessation was offered at our hospital. 57 patients had more than 30 pack years. Smoker data are shown in Table 2.

Table 2: Smokers and nonsmokers in comparison

	Smoker		Nonsmoker	
	N=92	% 59	N=64	% 41
Age >60 years	56	60.8	37	57.8
Age ≤60 years	36	39.2	27	42.2
Male	76	82.6	49	76,6
Female	16	17.4	15	23,4
OP side right	52	56.4	29	45.3
OP side left	40	43.5	35	54.7
Complications	39	42.4	15	23.4
No Complications	53	57.6	49	76.6
Death	9	9.8	4	6.2
Alive	83	90.2	60	93.8

Mortality

30-day mortality was 7.1% (n=11) (9 male, 2 female) and hospital mortality was 8.3% (n=13). The cause was sepsis in 3.2% (n=6) because of advanced pneumonia or bronchopleural fistula, cardiac failure in 2.6% (n=4) and pulmonary failure in 1.2% (n=1).

Table 3 presents the results of univariable regression analysis. In the group of smokers, hospital mortality was 9.8% (n=9) while mortality in non smokers was 6.2% (n=4) which was not significant in χ^2 test ($p< 0.56$). The Odds ratio (OR) to die within 30 days after pneumonectomy was 1.6 for smokers. Other prognostic factors – ASA score, age, intraoperative blood loss and operation time – did not reach significance.

Table 3: Univariable regression analysis: mortality
OR = Odds ratio, ASA = ASA score

	OR	95% confidential intervall	P	Decision
Age >/<60 years	2.4	0.5–14.1	0.24	ns
Smoker	1.6	0.4–7.5	0.56	ns
OP side	0.6	0.1–2.4	0.5	ns
OP time (>240 min)	3.1	0.8–13.1	0.08	ns
Gender	1.4	0.2–13.6	1.0	ns
ASA	1.8	0.3–8.0	0.4	ns
Intraoperative blood loss (>500 ml)	2.8	0.7–11.4	0.13	ns

ns = nonsignificant, * = significant

Morbidity

Postoperative complications occurred in 34.6% (n=54) patients. As shown in Table 4, the most common problems which required treatment were arrhythmia in 16.0% (n=25), BPF in 6.4% (n=10), sepsis in 5.7% (n=9), haemorrhage which required reoperation in 3.8% (n=6), and recurrent nerve palsy in 2.5% (n=4).

Table 4: Incidence of postoperative complications

Complication	Number	Percent (%)
Arrythmia	25	16.0
Sepsis	9	5.7
Pneumonia	13	8.3
Bronchus stump fistula	10	6.4
Bleeding	7	4.4
Paralysis of the recurrent nerve	4	2.5

Age over 60 years, and operation time >4 hours were significant risk factors for developing postoperative complications. Intraoperative blood loss over 500 ml and smoking were highly significant prognostic factors for postoperative complications (Table 5). Postoperative complications occurred in 39 (42.4%) smokers and in 15 (23.4%) nonsmokers, this was significant in χ^2-test ($p=0.01$). This means that smokers have an OR of 2.4 for developing postoperative complications. When intraoperative blood loss was more than 500 ml the OR for developing postoperative complications was 2.6.

Arrhythmia, sepsis and postoperative haemorrhage appeared significant more often in smokers than in nonsmokers (Table 6). BPF appeared in 8 smokers and in only 2 nonsmokers with an OR of 1.3.

Table 5: Univariable regression analysis: complications
OR = Odds ratio, ASA = ASA score

	OR	95% confidential intervall	p	Decision
Age >/< 60 years	2.0	0.9 – 4.4	0.05	*
Gender	1.3	0.5 – 3.6	0.5	ns
Smoker	2.4	1.1 – 5.2	0.01	**
OP side	1.1	0.5 – 2.2	0.7	ns
Intraoperative blood loss > 500 (ml)	2.6	1.13 – 4.9	0.01	**
ASA	2.3	0.8 – 6.4	0.06	ns
OP time >240 min	2.0	0.1 – 4.1	0.04	*

ns = nonsignificant, * = significant, ** = highly significant

Table 6: Multivariable regression analysis: complications considering smoking
OR = Odds ratio

	OR	95% confidential intervall	p	Decision
Arrhythmia	2.0	0.9–4.4	0.05	*
Bronchopleural fistula	1.3	0.5–3.6	0.5	ns
Sepsis	2.4	1.1–5.2	0.01	**
Pneumonia	1.1	0.5–2.2	0.7	ns
Haemorrhage	2.3	1.13–4.9	0.01	**

ns = nonsignificant, * = significant, ** = highly significant

Discussion

Pneumonectomy continues to be an important routine resection procedure in lung cancer surgery. In a study involving 1905 operated patients with lung cancer, the percentage of patients undergoing pneumonectomy was 16.5% [17]. Improvements in surgical technique, anaesthesia, and perioperative care resulted in a decrease in morbidity and mortality rates in major pulmonary resections. Despite these improvements, pneumonectomy persistently has the highest rates of morbidity and mortality of pulmonary resections.

The present study examined the postoperative course of patients undergoing pneumonectomy for stage I and II NSCLC and evaluated the importance of perioperative risk factors as predictors for postoperative death and complications. We found that postoperative complications occurred in 35% and mortality was 8.3%. Considering perioperative death, none of the perioperative risk factors reached significance within our cohort of 156 patients. Surprisingly, the OR was only a moderate increase in smokers and, against our expectations, smoking until surgery had no major impact on 30-day mortality after pneumonectomy in NSCLC. Perioperative mortality following pneumonectomy ranges from 3 to 33% in different publications [18]. [19]. In a study on the quality of surgery in lung cancer carried out in various German clinics, the mortality rate following pneumonectomy varied from 4 to 33% [14]. Ginsberg found an increase in mortality rate in patients older than 70 years [20]. In contrast, Cui found no correlation between mortality in 1738 patients with age >60 years [18].

Smoking, age, intraoperative blood loss and operation time had a significant impact on morbidity in the univariate regression analysis ($p<0.05$). Patients who smoked up to the time of operation had 2.8-fold higher morbidity and a 1.6-fold higher mortality. However, we could not select any of the preoperative risk factors responsible for mortality after pneumonectomy in smokers.

Only a few reports have dealt with smoking as a perioperative risk factor. Algar et al. determined the effect of smoking on perioperative mortality in 267 patients but was unable to show a significant relationship ($p =0.28$) [21]. Licker et al, in a study with 193 patients, showed that smoking status in univariate analysis had a significant impact although it could not be confirmed in multivariate analysis [19]. Other studies have also been unable to demonstrate that smoking has an effect on perioperative mortality [4], [22]. Our study could conclude that smoking has a deteriorating effect on postoperative morbidity – but not on mortality after pneumonectomy.

Considering perioperative complications as well the incidence of cardiac arrhythmias (25% versus 7%, $p<0.01$), as the rate of bronchopleural fistulas was higher in smokers than in nonsmokers (9.7% versus 4.6%). We have not done any protective medication to prevent arrhythmias nor routinely buttressing the bronchial stump. Orthopaedic surgeons in a randomised study have observed that the healing of wounds and fractures in smokers after hip and knee surgery is impaired (deterioration of wound healing in 31% versus 5% for smokers and nonsmokers respectively, $p<0.001$) [23]. Healing of anastomoses in abdominal surgery is also deteriorated for smokers [24]. Barrera observed postoperative pulmon-

ary complications in nonsmokers in 8% and in smokers in 23% [25].

The problems in wound healing for smokers could be the result of reduced cellular repair processes and a decrease in tissue oxygenation. Smoking is also a risk factor for pulmonary infections, probably because of its adverse effect on respiratory defence processes [26]. Vaporciyan showed in a retrospective analysis of 257 pneumonectomies that patients who stopped smoking one month before the operation had significantly less pulmonary complications (p=0.03) [27].

It can be concluded from our investigation that nicotine abstinence prior to operation probably reduces mortality and morbidity after pneumonectomy. However, we did not find the expected differences between smokers and nonsmokers considering perioperative complications. All methods available for assisting smoking cessation and nicotine withdrawal (nicotine substitution, psychosocial therapy) should be employed to stop smoking as early as possible before lung resection. We have recognised the importance of this approach and have established a professional nicotine cessation program to improve the success rate of surgery for lung cancer. The program consist a smokers hot line, professional psychological guided groups and nicotin substitution and medical support. However, we stop short of postponing patients from surgery if they are still smokers.

Notes

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Conflicts of interest

None declared.

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