Risk Factors for the Development of Postoperative Complications After Bronchial Sleeve Resection for Malignancy: A Univariate and Multivariate Analysis

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Background. **This study was designed to identify risk factors responsible for postoperative complications after bronchoplastic procedures.**

Methods. **Excluding sleeve pneumonectomies between January 1994 and December 2001, 108 patients underwent bronchoplastic procedures for bronchial malignancy. Prospectively documented data were age, gender, side, type of bronchial reconstruction, extended resection, histology, TNM stage, diseased lobe, and bronchial tumour occlusion. Cardiovascular (CV) risk factors included heart disease, arterial hypertension, cerebro-occlusive disease, peripheral artery disease of the lower extremities, diabetes mellitus, and abdominal aortic aneurysm. Patients were grouped according to the presence/absence of any CV risk factor and the absolute number of CV risk factors present (zero to four). Non-CV risk factors included neoadjuvant chemotherapy, alcoholism, lung disease, sleep apnea, history of recent pneumococcal sepsis, and repeat thoracotomy. Groups were assembled according to the presence or absence of any non-CV risk factor, neoadjuvant chemotherapy, and alcoholism. Respiratory risk factors included lung function and blood gas analysis. Groups were assembled according to the absolute number of respiratory risk factors in each person (zero to three) and the combination of respiratory and CV risk factors. Complications were defined as septic (pneumonia, empyema, brochopleural fistula, colitis) and aseptic. For univariate statistical analysis, *t* test, cross-tabulation, and χ^2 test were used. All factors with a significance of $p < 0.1$ were entered into a binary backwards-stepwise logistic regression model.**

Results. **The combination of respiratory and CV risk factors ($p = 0.012$, OR = 0.165) was predictive for overall complications. Coronary artery disease ($p = 0.02$, OR = 0.062) and the combination of two respiratory risk factors ($p = 0.008$, OR = 0.062) were predictive for septic complications. Peripheral artery disease ($p = 0.024$, OR = 0.28), moderate ($p = 0.01$, OR = 0.13) and severe chronic obstructive pulmonary disease ($p = 0.018$, OR = 0.11), and extended resections ($p = 0.003$, OR = 0.017.) were predictive for aseptic complications.**

Conclusions. **Comorbidity significantly influences the postoperative complication rate and is therefore crucial for evaluation of patients for bronchoplastic procedures. Different risk factors are responsible for the occurrence of septic and aseptic complications after bronchoplastic procedures.**

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The literature dealing with postoperative complications aims to define risk groups to optimize postoperative surveillance measures or even to exclude patients with an unacceptably high risk from surgery. Whereas the surgical literature mainly investigates the incidence and causes of septic complications such as empyema and bronchopleural fistula, publications in respiratory medicine try to define risk factors for all kinds of complications without citing differences between septic and aseptic problems, thus ignoring their different pathophysiologic character. The data published so far have been derived from patients undergoing various extents of resection or focus on pneumonectomy. We found no recent reports that have investigated resections lesser than pneumonectomy. In addition, no data exist on risk factors for postoperative complications after bronchoplastic procedures. Complication rates are simply reported without any detailed analysis.

Patients and Methods

Between January 1994 and December 2001, 108 patients underwent bronchial sleeve resection for bronchial malignancy, with sleeve pneumonectomies being excluded. There were 81 men (74%) and 27 women (26%) aged between 26 and 76 years (mean, 58.06 ± 10.65). Thirty procedures (27.7%) were left sided and 78 (72.3%) were right sided. The bronchial tree was reconstructed with a

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Table 1. Definition of Respiratory and Cardiovascular Risk Factors

Chronic obstructive pulmonary disease	
Moderate	FEV_1%pred 50–70%
Severe	FEV_1%pred < 50%
Pulmonary restriction	
Moderate	VC%pred 50–80%
Severe	VC%pred < 50%
Hypoxia	
Moderate	PO_2 60–80 mm Hg
Severe	PO_2 < 60 mm Hg
Hypercapnia	
Moderate	PCO_2 45–55 mm Hg
Severe	PCO_2 > 55 mm Hg
Peripheral arterial disease	History of vascular surgery or percutaneous angioplasty, pathologic angiography, ankle brachial index < 0.7
Coronary arterial disease	History of angina pectoris, myocardial infarction, coronary surgery, percutaneous angioplasty. Pathologic stress ergometry, coronary angiography, or thallium scintigraphy, dyskinesia in heart ultrasound
Cerebro-occlusive disease	History of stroke, TIA, PRIND, internal carotid artery surgery, stenosis of the internal carotid artery > 80%, pathologic computed tomography
Cardiac insufficiency	Ejection fraction < 50%, New York Heart Association Class III, IV
Hypertension	Hypertension treatment, systolic > 160 mm Hg, diastolic > 95 mm Hg

FEV_1 = forced expiratory volume in 1 second; PRIND = prolonged reversible ischemic neurological deficit; TIA = transient ischemic attack.

classical end-to-end anastomosis in 75 cases (69.4%), a wedge resection in 16 cases (14.8%), and a Y-sleeve (replantation of a lobar bronchus into the mainstem bronchus) in 17 (15.7%). In 15 patients (13.9%), an additional procedure was performed: angioplasty (n = 11), thoracic wall resection (n = 1), wedge resection (n = 2), and anatomic segmentectomy (n = 1). Preoperative workup included lung function testing by spirometry, chest computed tomography, (CT), and bronchoscopy. In cases of limited pulmonary functional reserves contraindicating pneumonectomy, a ventilation-perfusion scan was performed. Patients with enlarged mediastinal lymph nodes on CT scan underwent preoperative mediastinoscopy to exclude N3 disease and multilevel N2 disease. Intubation was performed with a double-lumen endobronchial tube under single-shot antibiotic prophylaxis with a second-generation cephalosporin. Surgical access was a standard posterolateral thoracotomy. After completion of the anastomosis, a check for leaks was performed by water test under manual bag inflation. (p max = 40 cm) The anastomosis was not covered with autogenous tissue flaps; a pericardial release was not necessary. At the end of the procedure, the anastomosis was routinely inspected bronchoscopically through an adapter while ventilation was maintained. The patient was extubated in the operating room. During the postoperative course, bronchoscopy was only performed in cases of atelectasis, secretion retention, or if a fistula was suspected. Therapeutic bronchoscopy was performed in 27 patients (25%).

Cardiovascular Risk Factors

Coronary artery disease (CAD), arterial hypertension, cerebroocclusive disease (COD), peripheral artery disease of the lower extremities (PAD), and diabetes mellitus were prospectively documented as cardiovascular (CV) risk factors. Additionally, diseases such as congestive heart failure, valve dysfunction, preoperative arrhythmia, and abdominal aortic aneurysm were recorded but not evaluated separately due to their small number. To include these factors into analysis, patients were further grouped according to the presence or absence of any CV risk factor and according to the absolute number of CV risk factors present in a single individual. The definition of CV risk factors is shown in Table 1.

Noncardiovascular Risk Factors

Neoadjuvant chemotherapy, alcoholism, and age > 70 years were prospectively documented as non-CV risk factors. Further, the presence of lung disease, sleep apnea, a history of recent pneumococcal sepsis, chronic lymphatic leukemia, and secondary thoracotomy was recorded. Due to the small number, these additional diseases were not evaluated separately, but included into analysis by assembling two groups according to the presence or absence of any non-CV risk factor. Alcoholism was evaluated as an extra group. A subgrouping according to the absolute number of additional risk factors in one person was not performed.

Respiratory Risk Factors

Forced expiratory volume in 1 second (FEV_1) (L), FEV_1%pred, VC (vital capacity)(L), VC%pred, O_2 (mm Hg), CO_2 (mm Hg), and FEV_1/VC were prospectively documented as respiratory risk factors. The definition of respiratory risk factors is shown in Table 1. Groups were assembled according to the absolute number of respiratory risk factors in one person. Further grouping concerned the combination of respiratory and cardiovascular risk factors.

Bronchological Risk Factors

The diseased lobe and the presence of occlusion of a bronchial or segmental bronchus were prospectively documented as bronchological risk factors.

Patients were further characterized by age, gender side, type of reconstruction of the bronchial tree (end-to-end anastomosis, wedge resection, y-sleeve), additional procedures (angioplasty, thoracic wall resection, segmentectomy, wedge resection), histology (squamous cell, adenocarcinoma, neuroendocrine carcinoma grade I, II, and III, miscellaneous), and TNM stage.

Complications were classified as major (fatal outcome, emergent intensive care unit admission, or reoperation) and minor. Further complications were defined as septic when an infection occurred (ie, pneumonia, empyema, brochopleural fistula, colitis) and aseptic (gastrointestinal bleeding, tachyarrhythmia, postoperative pneumothorax, cerebral infarction, mesenteric embolism, ileus, postoperative hemorrhage, atelectasis).

Statistical Analysis

Statistical analysis was performed with SPSS for windows 10.0.7 (SSPS Inc., Chicago, IL). All summary statistics are presented as means ± standard deviation for continuous variables and as percentages for categoric variables. Differences in continuous variables were evaluated performing a t test for independent samples. Cross-tabulation and χ^2 test were used for comparison of categorical variables. To identify significant independent predictors of overall complications, and septic and aseptic complications, all factors with a significance < 0.1 were entered into multivariate analysis. Odds ratio (OR) and their 95% confidence intervals were calculated using a binary backwards-stepwise logistic regression estimates. The combination of independent variables giving the best explanation of the outcome (using R^2 statistic) was adopted. Results were considered to be significant at a p value less than 0.05.

Table 2. Risk Factors in Patients Undergoing Bronchoplastic Resection

Risk Factors	No. of Patients
Cardiovascular risk factors: 52 patients (49.1%)	
PAD	5
CAD	18
COD	4
Arterial hypertension	34
Diabetes mellitus	10
Diet	3
Tablets	6
Insulin	1
Abdominal aortic aneurysm (operated)	2
Cardiac insufficiency	2
Mitral regurgitation II–III	1
Preoperative arrhythmia	2
Noncardiovascular risk factors: 18 patients (16.7%)	
Neoadjuvant chemotherapy	7
Miscellaneous additional noncardiovascular risk factors[a]	11
Chronic ethylism	12
Age > 70 years: 15 patients (13.9%)	
Respiratory risk factors: 84 patients (77.8%)	
COPD moderate	31
COPD severe	3
Restriction moderate	27
Restriction severe	0
Hypoxia moderate	59
Hypoxia severe	1
Hyperkapnia moderate	3
Hyperkapnia severe	0

[a] Secondary thoracotomy (n = 1), diffuse interstitial lung disease (n = 1), active tuberculosis (n = 1), sleep apnea (n = 2), history of recent pneumococcal sepsis (n = 2), history of tuberculosis (n = 2), chronic lymphatic leukemia (n = 1), history of pulmonary embolism (n = 1).

CAD = coronary arterial disease; COD = cerebro-occlusive disease; COPD = chronic obstructive pulmonary disease; PAD = peripheral arterial disease.

Results

FEV_1 ranged from 1.32 to 4.28 I (mean, 2.58 ± 0.63 L). FEV_1%pred ranged from 46% to 119% (mean, 77.32% ± 14.71%). VC ranged from 1.88 to 6.93 L (mean, 3.68 ± 0.78 L). VC%pred ranged from 53% to 122% (mean, 89.69% ± 14.98%). FEV_1/VC ranged from 0.4 to 2.11 (mean, 0.71 ± 0.19), pO_2 from 58 to 97 mm Hg (mean, 77.17 ± 8.66 mm Hg), and pCO_2 from 29 to 54 mm Hg (mean, 37.83 ± 4.08 mm Hg).

Risk Factors

Eleven patients (10.2%) presented without any risk factor, and 52 (48.1%) presented with one or more CV risk factors (Table 2). Of these, 31 patients (28.7%) had a single risk factor, 16 (14.8%) had a combination of two, 3 (2.8%) had a combination of three, and 2 (1.9%) had a combination of of four.

Eighty-four (77.8%) patients had one or more respiratory risks. One risk factor was present in 37 cases (39.4%), two in 21 (19.4%), and three in 12 (11.1%). In 14 patients (13%), the absolute number of respiratory risks could not be evaluated due to incomplete data. In 36 cases (33.3%), a combination of CV and respiratory risk factors was seen.

Eighteen patients (16.6%) presented with non-CV risk factors.

Bronchology

The tumor was located in the upper, middle, and lower lobes in 81 (75%), 3 (2.8%), and 15 (13.9%) cases, respectively, in the upper and middle lobes in 6 (5.6%), and lower and middle lobes in 3 (2.8%). In 49 patients (45.4%), a lobar or segmental orifice was occluded by the tumor.

Histology and Staging

Histology and stage are shown in Table 3. Two patients underwent thoracotomy after successful radiotherapy of a single brain metastasis. In 6 patients (5.6%), the resec-

Table 3. Histology and TNM Stage

Stage	Adenocarcinoma	Squamous Cell Carcinoma	NEC I	NEC II, III	Miscellaneous[a]	Total
I	8	18	8	7	5	46 (42.6%)
II	3	17		2	7	29 (26.8%)
IIIA	11	6			4	21 (19.4%)
IIIB	1	3		1		5 (4.6%)
IV					2	2 (1.8%)
Total	23	44	8	10	18	103

Undifferentiated ca (n = 3), large cell ca (n = 5), bronchoalveolar ca (n = 3), adenoid cyst ca (n = 2), metastasis of extrapulmonary tumor (n = 2), carcinosarcoma (n = 2), malignant papilloma (n = 1), malignant histiocytoma (n = 1), mucoepidermoid ca (n = 1), polymorphocellular ca (n = 1).

ca = carcinoma.

tion was not radical. In 5 patients, no tumor stage was given.

Postoperative Complications

The overall morbidity was 26.8% and mortality was 5.5%. There were 18 (16.7%) major and 11 (10.2%) minor complications. Details are shown in Table 4. Aseptic complications occurred in 12 patients (11.1%), with a mortality of 25%, and septic complications in 17 patients (15.7%), with a mortality of 17.6%.

Statistic Evaluation

The following risk factors did not show any influence on the occurrence of postoperative complications: gender, side, COD, diabetes, neoadjuvant chemotherapy, the presence of non-CV risk factors, T,N tumor stage, negative margin resection, technique of bronchial reconstruction, and the location of the diseased lobe. The p values for those risk factors showing a statistical trend or significance in univariate analysis (χ^2 test, t test) are shown in Table 5.

The results of multivariate analysis revealed several risk factors for septic and aseptic complications, as shown in Table 6.

Comment

Since the first description by Price-Thomas in 1956 [1], the reported number of bronchoplastic procedures has increased nearly fourfold in the 1980s [2]. Nowadays, bronchial sleeve resections have become an established procedure for the operative treatment of bronchial malignancies. The achieved results are comparable with those of classical resections such as pneumonectomy and lobectomy in benign [2] and malignant lesions [3]. Compared with pneumonectomy, which is the only alternative to achieve local radicality, functional lung tissue is preserved, mortality and long-term morbidity are reduced [4], and reoperation is possible in selected cases of recurrence. However, the complication rate of bronchoplastic surgery exceeds that of classical resections lesser than pneumonectomy due to possible anastomotic problems. These may result in bronchovascular or bronchopleural fistula and secretion retention as a result of local anastomotic edema.

The most consistent finding in the literature is that the more lung tissue removed, the higher are postoperative mortality and morbidity, with pneumonectomy being the most dangerous intervention. The postoperative complication rate after bronchial sleeve resections has been extensively reviewed by Tedder and associates [3]. Still, it remains difficult to evaluate the given numbers due to a great number of methodic flaws in the literature, because so far, a standardized definition of postoperative complications is still missing. Therefore, the reported numbers heavily depend on subjective criteria.

Some authors consider atelectasis requiring bronchoscopy as a pulmonary complication [3, 5, 6]. On the other

Table 4. Postoperative Complications After Bronchial Sleeve Resection

Severity	Aseptic	Septic
Minor	Supraventricular tachyarrhythmia (n = 1)	Empyema (n = 1)
	Pulmonary expansion deficit requiring redrainage (n = 3)	Pneumonia (n = 4)
	Gastrointestinal bleeding, conservative management (n = 2)	
Major	Lethal	
	Mesenterial infarction (n = 1)	Anastomotic leakage (n = 1)
	Stroke (n = 1)	Pneumonia (n = 2)
	Gastrointestinal bleeding (n = 1)	
	Reoperation	
	Ileus (n = 1)	Anastomotic leakage (n = 2)
	Intercostal artery bleeding due to erosion by a fractured rib (n = 1)	Empyema (n = 2)
	Intensive care unit treatment:	
	Massive secretion retention (n = 1)	Pneumonia (n = 5)

Table 5. Results of Univariate Analysis

Risk Factors	Complication (Y/N)	Aseptic Complications	Septic Complications
Age > 70 years	NS	0.012	NS
Cardiovascular risk			
Cardiovascular risk factor (Y/N)	0.009	0.006	NS
Number of cardiovascular risk factors	0.014	0.006	NS
CAD	0.015	0.043	0.056
PAD	0.087	0.026	NS
Hypertension	0.07	0.026	NS
Noncardiovascular risk			
Chronic alcoholism	NS	NS	0.085
Respiratory risk			
Number of risk factors	0.067	NS	0.02
Obstruction	NS	0.021	NS
Restriction	NS	NS	0.047
Hypoxia	0.074	NS	NS
Presence of cardiovascular and respiratory risk	0.003	0.001	0.052
Tumor risk			
Histology	0.068	NS	NS
Surgical risk			
Additional procedure (including all procedures)	NS	0.007	NS
Additional angioplasty	NS	0.008	NS
Bronchological risk			
Bronchial tumour obstruction	0.024	0.082	0.092

NS = $p > 0.1$.

CAD = coronary arterial disease; PAD = peripheral artery disease of the lower extremities.

hand, surgeons tend to perform bronchoscopy routinely during the postoperative course [7] or perform bronchoscopy if auscultation and chest roentgenogram are suggestive of secretion retention [8], which is also the policy of our department. The different strategies make a differentiation between routine bronchoscopy, therapeutical bronchoscopy, and bronchoscopy due to atelectasis nearly impossible. Because we prefer aggressive bronchoscopic management during the postoperative course, we do not consider postoperative bronchoscopy a complication.

Another problem is the diagnosis of postoperative pneumonia. Stephan and associates [6] regard a positive sputum culture as crucial for the diagnosis of nosocomial pneumonia. Bernard and associates [9] define pneumonia as a new infiltrate on chest roentgenogram, fever > 38°C, and purulent sputum. Wang and associates [10] include any new radiological infiltrate accompanied by fevers necessitating intravenous antibiotics. Busch and associates [5] need a positive sputum culture or a clinically significant infiltrate on chest roentgenogram, or the need for repeated bronchoscopy. Jagoe and associates [11] require a new infiltrate on chest roentgenogram, purulent sputum, and antibiotic treatment for diagnosis. Kearny and coworkers [12] do not provide any definition at all. The pneumonia rates differ significantly in all papers. Stephan, postulating a bronchoscopic evaluation, reports 6.5%; Wang, being more generous, 25%; Busch, 22%; Jagoe, 24.5%; and Kearney, without any definition, the lowest rate of 2%. This suggests that there is an overestimation of postoperative pneumonia rates when no strict bacteriological criteria are applied, and an underestimation when no criteria are given at all. We considered any new infiltrate accompanied by a rise of oxygen consumption and a decline of oxygen saturation as diagnostic for pneumonia. Our rate of 10.1% lies in the lower range and may be a result of aggressive bronchoscopic intervention if radiological signs of secretion retention are suspected.

Table 6. Results of Multivariate Analysis

	p	O.R.	CI (95%)
Complication Y/N ($R^2 = 0.4$)			
Presence of cardiovascular and respiratory risk factor	0.012	0.165	0.04–0.677
Septic complications ($R^2 = 0.28$)			
CAD	0.02	0.117	0.019–0.712
Two respiratory risk factors	0.008	0.062	0.008–0.481
Aseptic complications ($R^2 = 0.57$)			
PAD	0.024	0.28	0.001–0.632
Moderate obstruction	0.01	0.13	0.00–0.351
Severe obstruction	0.018	0.11	0.00–0.465
Additional procedure	0.003	0.017	0.001–0.248

CAD = coronary arterial disease; PAD = peripheral artery disease of the lower extremities.

The risk factors associated with complications after bronchial sleeve resections have not been analyzed so far. Besides the above-mentioned problem of missing

definitions, we have no clues concerning the comorbidity of the patients either. Our comorbidity rate of 89.8% seems relatively high; however, an overall comorbidity rate is only given in Bernard's publication, who reported a rate of 79% [9]. Our distribution of risk factors is comparable with the numbers given by Licker and associates [17], but very different from other papers. Whereas Romano and associates [13] describe a rate of drug abuse and alcoholism of 0.9%, we found 11%. Hypertension was present in 31.5% of our patients, diabetes in 9.2%, and chronic heart disease in 20%; whereas Romano reports 12.1%, 4.6%, and 19.4%, respectively. Förster and associates [14] described a cardiocirculatory comorbidity rate of 22.2%, compared with 38.8% in our series. This suggests that the selection criteria are extremely different. Thus, a higher complication rate does not necessarily mean inferior management, but probably a cumulation of patients with high comorbidity. Given the fact that surgery is the only chance of cure for lung cancer, we try to offer operations to as many patients as possible, even in the case of a high-risk situation. This is justified due to the desperate situation in the nonsurgical treatment of lung cancer.

Our numbers include our learning curve, and there was no mortality since 1999. Even so, our overall morbidity rate of 27% is comparable with the literature, which reports 25% [6, 8] to 32.4% [15, 18]. Our results show that complex thoracic procedures can be performed in a patient group with a high comorbidity rate with acceptable risk.

To allow multivariate analysis, complications are classified according to subjective criteria. They are defined as life-threatening/non–life-threatening [15, 16], organ-related such as respiratory and cardiac [5, 9, 12], severe/not severe [8], or fatal/nonfatal, life-threatening [17]. Jagoe and associates [11] used the categories septic, pulmonary, and miscellaneous. We partly adopted this idea but disregarded outcome because outcome depends not only on the patients' preoperative condition but also heavily on complication management. While a bronchovascular fistula is usually lethal, the successful management of a bronchopleural fistula or empyema requires a very experienced surgical unit, a quick diagnosis, and immediate intervention. Thus, trying to evaluate our complications from a pathophysiological point of view, we divided them into infectious and noninfectious events.

Only the combination of cardiovascular and respiratory disease was predictive of the overall occurrence of complications. Although we used a rather different definition of complications, the results of multivariate analysis are confirmed by the literature. Extended resections, being predictive of aseptic complications, have been identified by numerous other publications [5, 9, 13, 15], as was the grade of COPD [13], the presence of respiratory risk [9, 13, 18], peripheral artery disease of the lower extremities [18], and coronary artery disease [17]. Still, a comparison of data remains questionable because the cited publications included various kinds of resections into their analysis. The rate of postoperative arrhythmias is very low compared with the literature. Our analysis covers a period of more than 7 years, and makes it difficult to find an explanation. One reason might be that the pericardium was never opened during bronchial sleeve resections. Because bronchoplastic procedures represent only a small percentage of all resections, and we are confronted with postoperative arrhythmias quite frequently after conventional resections, the low rate of arrhythmias in this study could have also been achieved by mere chance.

When divided into septic and aseptic complications, a more sophisticated result was obtained. No risk factors could be identified for both types of complications. This suggests that septic and aseptic complications have different causes. The logistic regression model proved to be fairly good for aseptic complications ($R^2 = 0.57$), but much less satisfactory for septic complications ($R^2 = 0.28$). Therefore, we must assume that the data collected are not the main predictors of septic complications, and further research needs to be done.

Conclusions

Exact definitions of postoperative complications are missing. It is desirable that stringent criteria defining the diagnosis of clinical entities are introduced to allow for comparison of published data. If complication rates are published, at least an exact definition of the criteria applied by the authors should be provided.

Comorbidity significantly influences the rate of postoperative complications. If comparisons of complication rates of different centers are to make sense, the comorbity rate is essential to exclude bias caused by patient selection. Due to the still disastrous prognosis of lung cancer, as many patients as possible should undergo surgical treatment if criteria of operability are met. Inoperability due to comorbidity should be an exemption, except that survival due to underlying nonneoplastic diseases falls below survival due to cancer.

Different risk factors are responsible for the occurrence of septic and aseptic postoperative complications. Whereas promotors of aseptic problems are confirmed by the literature and well known, the reasons for septic complications remain obscure.

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