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Lactate dehydrodgenase levels predict pulmonary morbidity after lung resection for non-small cell lung cancer

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Abstract

Objective: The prevention of pulmonary complication after pulmonary resection for non-small cell lung cancer may minimize postoperative mortality rates and hospitalization period. The purpose of this study was to identify preoperative factors associated with the development of pulmonary complications after lung resections to help predict which patients are at increased risk for morbidity. **Methods**: From January 2000 to June 2003, 108 consecutive pulmonary resections were performed for non-small cell lung cancer in our institution. The following information was recorded: demographic, clinical, functional, and surgical variables. We evaluated all complications, which arose after pulmonary resection during hospitalization. The risk of complication was evaluated using univariate and multiple logistic regression analysis to estimate odds ratio. **Results**: Sixty-six lobectomies, 31 pneumonectomies, 11 bilobectomies and four wedge resections were done. Forty-nine complications were realized in all patients. A logistic regression analysis on relevant variables showed that only the increased serum lactate dehydrogenase (LDH) levels (>320 U/l) was a significant predictor of a pulmonary complication ($P = 0.03$). Age, side of resection, low FEV_1, stage of the disease, low partial arterial oxygen pressure, low partial arterial carbon dioxide pressure, cigarette smoking and concomitant disease were not significant predictors of morbidity. **Conclusion**: Patients who have higher serum LDH levels are at increased risk for developing postoperative morbidity. Postoperative physical therapy and medical care might be intensified in those patients at high risk.
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Keywords: Lung cancer; Complication; Morbidity; Lactate dehydrogenase

1. Introduction

For patients with non-small cell carcinoma presenting as localized disease, surgical resection remains the only potentially curative option. Lung resection can be a high-risk procedure in patients with severe underlying cardio-pulmonary disease. Pneumonectomy in an otherwise healthy patient will be associated with a mortality rate of 4–5% but may rise to greater than 20% in those elderly patients with severe heart or lung disease [1]. A wide range of tests has been evaluated to aid the identification of patients at high risk for developing complications after lung resection. These tests have included spirometry, arterial gas measurement, exercise testing, and radio-nuclide lung scanning. Male sex, older age, greater extent of surgical resection and a reduced forced expiratory volume in first second (FEV_1) have been associated with increased postoperative morbidity and mortality in most but not all studies [2,3]. Exercise capacity and ventilatory reserve have been associated with postoperative compli-cations, but the clinical usefulness of this test is controversial [2,3].

The purpose of this study was to identify preoperative factors associated with the development of pulmonary complications after lung resections to help predict which patients are at increased risk for morbidity.

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2. Patients and methods

From January 2000 to June 2003, 108 consecutive pulmonary resections were performed for non-small cell lung cancer in our institution. Subjects who underwent exploratory thoracotomy were excluded from the study. Routine blood tests included hemoglobin, alkaline phosphatase and serum calcium estimations. All patients underwent postero-anterior and lateral chest radiographs and bronchoscopy. CT scans of the thorax, abdomen (or abdominal ultrasonography), and cranium, all body bone scintigraphies were done in all patients for pretreatment staging. Fiberoptic bronchoscopies were performed in all patients. Potentially resectable patients (cT1–cT4) were deemed to be candidates for surgery and underwent preoperative staging procedures.

Mediastinal lymph node samplings from the lymph nodes using cervical mediastinoscopy were carried out in all patients. The mediastinal exploration was supplemented by a left anterior mediastinotomy or extended mediastinoscopy in patients whose tumor lay in the left upper lobe or left main bronchus and in patients with enlarged (>1 cm) anterior mediastinal and/or aorticopulmonary lymph nodes. The following patients were excluded: (1) patients who underwent partial resection or segmentectomy; (2) patients with multiple lung tumors; (3) patients with low-grade malignancy, such as bronchial carcinoid; (4) patients who were found to have mediastinal nodal tumor involvement and underwent neoadjuvant therapy. Preoperative pulmonary evaluation included partial arterial oxygen pressure (Pa_{O2}), partial arterial carbondioxide pressure (Pa_{CO2}); and spirometry forced expiratory volume in 1 s (FEV_1) was also expressed as percent of prediction using standard prediction formulas. The following information was recorded: demographic, clinical, functional, and surgical variables. The 19 variables including age, sex, presence of concurrent disease, alkaline phosphatase, hemoglobin, oxygen saturation, operative procedure, operated site, surgical pathologic T stage (pT), surgical-pathologic N stage (pN), histologic type, % predicted vital capacity (%VC), % forced expiratory volume in one-second (%FEV_1), PaO_2, $PaCO_2$, serum albumin, serum lactate dehydrogenase (LDH), arterial oxygen saturation, total cigarette smoking (pack/year) were evaluated Patients who had lower than 2 l or 60% of predicted preoperative FEV_1 underwent perfusion lung scintigraphy and patients who were calculated to have more than 0.8 l or 40% of predicted postoperative FEV_1 were planned to undergo resectional surgery. All patients were operated on by five thoracic surgeons in a tertiary care thoracic surgery hospital. A posterolateral thoracotomy through the fifth intercostal space was accomplished with patient under general anesthesia and in the lateral decubitus position. Analgesia was provided with intramuscular narcotic analgesics and non-steroid anti-inflammatory drugs. All patients underwent a uniform and the latest staging protocol [4] in construction of a final surgical-pathologic stage (pTNM).

After surgery, all patients were cared for in a specialized intermediate care unit by thoracic surgery advice. The electrocardiogram was monitored continuously during first postoperative day and every abnormality noticed by medical staff was recorded. Emphasis is placed on aggressive pulmonary care, early ambulation, and pain control to minimize postoperative pulmonary complications. Postoperative complications were determined by a review of the hospital record and chest radiographs. It is acknowledged that retrospective identification of postoperative complications is subject to the detail and completeness of the medical record. To minimize this factor, the analysis was limited to postoperative complications thought to be clinically significant and thus unlikely to be omitted from the medical record. We evaluated all complications, which arose after pulmonary resection during hospitalization. Potential risk factors for a complication were identified by univariate logistic regression analysis. Factors with $P < 0.25$ were considered as potential risk factors in the forward multivariate model. To avoid multicollinearity, only one variable set of variables with a correlation coefficient >0.5 was used in the multivariate analysis. Adjusted odds ratios (OR) were calculated.

3. Results

Three patients died (2.8%). The reasons were stroke (embolism), respiratory insufficiency and acute myocardial infarction. Sixty-one minor or major complications were recorded. There were 72 (66.7%) patients with squamous cell carcinoma, 22 patients (20.6%) with adenocarcinoma, one patient with large cell carcinoma. In thirteen patients, no histologic subtype was found but non-small cell lung

Table 1
Postoperative complications in patients who underwent anatomic resection for NSCLC

Type of morbidity	Number of patients (%)
Major morbidities	
Prolonged air leak	13 (12.0)
Empyema	6 (5.5)
Respiratory insufficiency	5 (4.6)
Bronchopleural fistula	5 (4.6)
Hemorrhage	4 (3.7)
Pulmonary infection	3 (2.8)
Myocardial infarction	1 (0.9)
Pulmonary embolism	1 (0.9)
Minor morbidities	
Supraventricular dysrythmia	9 (8.3)
Wound infection	8 (7.4)
Atelectasis	3 (2.8)
Transient ischemic attack	2 (1.9)
Dysphonia	1 (0.9)

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Table 2
Univariate analysis to identify preoperative predictors of major pulmonary complications seen in 49 patients

Presence of complication	Variable examined	Significance
	Age (years ± SD)	
No	57.3 ± 10.6	
Yes	55.5 ± 10.1	0.35
	Sex (M/F)	
No	43/3	
Yes	57/5	0.98
	Presence of concurrent systemic disease	
No	11	
Yes	14	0.56
	Alkaline phosphatase (IU/l) (Mean ± SD)	
No	191.1 ± 104.6	
Yes	209.3 ± 86.1	0.06
	Hemoglobin (g/dl) (Mean ± SD)	
No	13.3 ± 1.5	
Yes	13.1 ± 1.5	0.09
	Oxygen saturation (%Mean ± SD)	
No	95.9 ± 1.5	
Yes	95.7 ± 1.9	0.73
	Operative procedure (pneumonectomy/ bilobectomy/lobectomy)	
No	16/7/23	
Yes	15/4/39	0.37
	Operated site (Right/Left)	
No	28/18	
Yes	38/24	0.89
	Surgical-pathologic T stage (T1/T2/T3/T4)	0.39
No	6/20/17/3	
Yes	13/27/15/5	
	Surgical-pathologic N stage (N0/N1/N2)	
No	25/14/7	
Yes	27/23/12	0.57
	Surgical pathologic stage (stage I/II/IIIA/IIIB)	
No	17/14/14/1	
Yes	19/21/15/7	0.60
	Histologic type (squamous cell/ non-squamous cell)	
No	31/15	
Yes	39/23	0.62
	%VC (%Mean ± SD)	
No	87.4 ± 20.2	
Yes	87.5 ± 17.5	0.69
	%FEV1 (%Mean ± SD)	
No	80.9 ± 18.7	
Yes	80.1 ± 18.3	0.71
	Arterial pCO_2 (mean mmHg ± SD)	
No	37.6 ± 3.8	
Yes	38.7 ± 3.4	0.21
	Arterial pO_2 (Mean mmHg ± SD)	
No	84.5 ± 12.7	
Yes	84.1 ± 11.3	0.99
	Serum Albumin	
No	4.2 ± 0.4	
Yes	4.1 ± 0.6	0.68
	Serum LDH (mean IU/L)	
No	238.1 ± 82.0	
Yes	398.5 ± 164.4	0.03
	% Saturation (in room air) (Mean ± SD)	
No	95.9 ± 1.5	
Yes	95.7 ± 1.9	0.84
	Smoking (mean pack.year ± SD)	
No	43.6 ± 26.0	
Yes	46.7 ± 30.2	0.76

SD, standard deviation; VC, vital capacity; FEV_1, forced expiratory volume in 1 s; LDH, lactate dehydrogenase; IU, international unit.

carcinoma was (i.e. not-otherwise specified). Sixty-two patients underwent lobectomy while 31 patients underwent pneumonectomy and 11 and 4 patients had undergone bilobectomy and wedge resections, respectively. The number of patients who had stage IA, IB, IIA, IIB, IIIA and IIIB patients were 13, 23, 6, 29, 29 and 8, respectively. The incidences of postoperative complications are shown in Table 1. Total of 61 complications were seen in 49 (45.3%) patients.

Univariate and multivariate analysis revealed that, LDH was the only and independent prognostic factor predicting postoperative morbidity (Tables 2 and 3). The threshold for high LDH was calculated as 320 U/l. The patients who had higher LDH levels had 4.3 times more likely experienced pulmonary complications (Table 3). There was no statistically significant relationship between LDH and any other variables. Other variables did not have any statistically important impact on pulmonary complications.

Table 3
Multivariate analysis of the preoperative variables predicting postoperative complication independently

Variable	Odds ratio (95% CI)	*P* value
LDH	4.3 (2.0–7.4)	0.03

CI, Confidence interval.

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Having categorized morbidities as 'major morbidities' and 'minor morbidities', high LDH level was found to predict major as well as minor morbidities (OR: 6.0 and 3.1, respectively).

4. Discussion

Pulmonary resection for lung cancer is associated with morbidity of 12–50% and mortality of 2–12% [1,2]. In addition to defining the clinical stage of the lung cancer, preoperative evaluation has the goal of the estimating the risk of planned surgery. For this reason, accurate prediction of the complication risk after the resectional surgery in patients with non-small cell lung cancer (NSCLC) is an important issue. Patients with lung cancer who undergo evaluation for lung resection are usually smokers and therefore often have concomitant chronic obstructive pulmonary disease (COPD) with impaired lung function. This puts them at increased risk for development of postoperative complications. Apart from the evaluation of tumor stage and histologic features, the functional assessment of the cardiorespiratory reserves of these patients is thus very important.

Previous reports have identified a wide variety of factors associated with overall morbidity and mortality after lung resection [5–8]. Recently, Beckles and his colleagues, published a guideline for preoperative evaluation for the patients with resectable NSCLC [9]. They stated that, a predicted postoperative FEV_1 or DLCO $<40\%$ indicated an increased risk for perioperative complications, including death, from lung cancer resection. However, in our study, low FEV_1 was not found to be an important risk factor using univariate or multivariate analyses.

We found that, higher serum LDH level was the only predictor for postoperative complication. High LDH level more powerfully predicted major postoperative complications (OR:6.0) than it predicted minor ones (OR:3.1). In patients with lower LDH levels (i.e. <320 U/l) could be offered a standard postoperative care and less invasive monitoring which could lead to reduce the hospital cost and labor loss, whereas intensive care could be prolonged for one day in patients with higher LDH levels.

The reduction of pyruvate by NADH to form lactate is catalyzed by LDH [10]. In humans, there are five isozymes and the existence of isozymes permits the fine-tuning of metabolism to meet the particular needs of a given tissue inflammation or remodeling [10]. A high LDH level indicates interstitial fibrosis of the lung following alveolar damage and it has been proposed as a disease activity marker in fibrosing alveolitis and extrinsic allergic alveolitis [11]. In our series, high LDH may indicate minimal interstitial damage of the lung, which is not seen radiographically. It also may be associated the higher inflammatory status of the parenchyma.

Previously only two reports declared the impact of LDH on complication [12,13]. Uramoto and colleagues reported that three factors in addition to Residual Volume/Total lung capacity ratio and PaO_2 levels, serum LDH levels might be associated with pulmonary complications in patients undergoing a lobectomy for NSCLC. However, their number of analyzed patients was relatively small [12]. Any of our patients had known or demonstrable interstitial lung disease or radiological pattern. Nevertheless LDH is related to the inflammatory and tissue-remodeling properties and it can be speculated that, it could be associated anti-tumoral immunity or pulmonary connective tissue destruction proceeded by tumor. We were unable to investigate the isozymes of LDH, which could have given more insight about inflammatory reactions. Mitsudomi et al. found LDH levels as a predictive factor in pneumonectomy patients only [13]. We defined the high LDH level as a morbidity predictor in all anatomically resected patients. We also recorded postoperative LDH levels of the patients. However, patients with morbidity, as well as ones without morbidity were found to have high LDH levels (data not shown). Tissue hypoxia and inflammatory processes due to thoracotomy and resectional procedures may play a role in increased postoperative LDH levels.

We suggest that measurement of LDH level, as a widely available and quick method seemed to have the potential to predict the occurrence of pulmonary complications. Although the *modus operandi* of the effect yet to be determined and larger studies are warranted, patients with higher LDH levels deserves more attention in terms of postoperative morbidity following pulmonary resection for lung cancer.

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