Original Article

Patient-related independent clinical risk factors for early complications following Nd: YAG laser resection of lung cancer

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Abstract:

INTRODUCTION: Neodymium:yttrium aluminum garnet (Nd:YAG) laser resection is one of the most established interventional pulmonology techniques for immediate debulking of malignant central airway obstruction (CAO). The major aim of this study was to investigate the complication rate and identify clinical risk factors for complications in patients with advanced lung cancer.

METHODS: In the period from January 2006 to January 2011, data sufficient for analysis were identified in 464 patients. Nd:YAG laser resection due to malignant CAO was performed in all patients. The procedure was carried out in general anesthesia. Complications after laser resection were defined as severe hypoxemia, global respiratory failure, arrhythmia requiring treatment, hemoptysis, pneumothorax, pneumomediastinum, pulmonary edema, tracheoesophageal fistulae, and death. Risk factors were defined as acute myocardial infarction within 6 months before treatment, hypertension, chronic arrhythmia, chronic obstructive pulmonary disease (COPD), stabilized cardiomyopathy, previous external beam radiotherapy, previous chemotherapy, and previous interventional pulmonology treatment.

RESULTS: There was 76.1% male and 23.9% female patients in the study, 76.5% were current smokers, 17.2% former smokers, and 6.3% of nonsmokers. The majority of patients had squamous cell lung cancer (70%), small cell lung cancer was identified in 18.3%, adenocarcinoma in 3.4%, and metastases from lung primary in 8.2%. The overall complication rate was 8.4%. Statistically significant risk factors were age ($P = 0.001$), current smoking status ($P = 0.012$), arterial hypertension ($P < 0.0001$), chronic arrhythmia ($P = 0.034$), COPD ($P < 0.0001$), and stabilized cardiomyopathy ($P < 0.0001$). Independent clinical risk factors were age over 60 years ($P = 0.026$), arterial hypertension ($P < 0.0001$), and COPD ($P < 0.0001$).

CONCLUSION: Closer monitoring of patients with identified risk factors is advisable prior and immediately after laser resection. In order to avoid or minimize complications, special attention should be directed toward patients who are current smokers, over 60 years of age, with arterial hypertension or COPD.

Key words:

Bronchoscopy, interventional pulmonology, laser resection, lung cancer, Nd:YAG laser, treatment

Neodymium:yttrium aluminum garnet (Nd:YAG) laser resection is one of the most common interventional pulmonology techniques for urgent debulking of malignant central airway obstruction (CAO). The laser beam is delivered through quartz optical fiber, which is easily adaptable for a flexible or rigid bronchoscope. It operates in the invisible range of the electromagnetic spectrum, at a wavelength of 1064 nm and thus requires a pilot light for navigation. Even though the technique was introduced into bronchology and interventional pulmonology over 20 years ago, only high volume experienced centers are performing this intervention. In hands of a skilled and experienced bronchoscopist, the technique is safe and reliable.[1-4] Over the years, this procedure showed to be beneficial in therapeutic relief of lung cancer signs and symptoms, showing potential to improve progression free survival, quality of life, and even survival in lung cancer patients.[5-11] All of the major interventional pulmonology guidelines are suggesting that Nd:YAG laser resection should be considered a part of multimodality treatment of advanced central lung cancer with endobronchial obstruction.[12-19] Nd:YAG laser resection alone or in combination with other interventional techniques demonstrated benefit in treatment of inoperable early stage lung cancer, in the treatment of benign CAO, and in multimodality treatment of central, advanced stage lung cancer.[20-27]

The complication rate after Nd:YAG laser resection depends on several factors. One of the most important is bronchoscopists skillfulness. However, the patient's general condition as well

as the characteristics of lesions, laser power settings, and other procedure-related aspects (oxygen concentration, duration of pulses) must not be neglected. The reported complication rate varies from less than 1% to over 35%, depending on the timing of occurrence and complication type.[28-31] Early complications, occurring within a few weeks after intervention, are more common than the late complications. The average complication rate is usually around 5%. Most of the published data evaluate procedure-related risk factors and complications following Nd:YAG laser resection.[32-34] That is the main reason why we intended to evaluate patient-related risk factors and complications.

The aims of the study were to determine the rate of early complications following Nd:YAG laser resection in a high volume respiratory endoscopy unit with experienced bronchoscopists, and to identify potential patient-related risk factors for these complications. Identification of independent patient-related clinical risk factors was the primary aim of the study. We hypothesized that thorough examination of the patients' current condition and medical history could reveal risk factors significantly related to complications after laser resection. Determination of these risk factors could improve patient selection and decrease the complication rate.

Methods

We analyzed patient-related clinical risk factors for early complications following Nd:YAG laser resection in 464 patients who were eligible according to the inclusion and exclusion criteria, in the period from January 2006 to January 2011. Hospital, endoscopy, anesthesiology, and patient medical charts were reviewed to determine age, gender, tumor histology, smoking status, site of the tumor, and previous therapy. The potential clinical risk factors were recorded for multivariate analysis. The risk factors were determined as myocardial infarction occurring over 6 months ago, controlled hypertension, controlled chronic arrhythmias, chronic obstructive pulmonary disease (COPD), controlled cardiomyopathy, previous external beam radiotherapy (EBRT), previous chemotherapy, and previous interventional pulmonology procedures. Early complications of laser resection, occurring within 3 weeks after intervention, were defined as severe hypoxemia, global respiratory failure, arrhythmia requiring treatment, hemoptysis (over 250 mL), pneumothorax, pneumomediastinum, pulmonary edema, tracheoesophageal fistulae, and death. Patients were monitored for complications during intervention, immediately after laser resection, and daily during first 5 days. In following 2 weeks, patients were monitored once a week, unless there was a need for more often clinical examination.

The study was approved by the ethical and scientific boards of the Institute for Pulmonary Diseases of Vojvodina, Serbia. All of the patients who decided to participate in the study have been informed about the procedure, potential benefits, and risks, and all of them had signed an informed consent form. Major inclusion criteria were endobronchial laser resection (endobronchial tumorous lesions causing significant intraluminal obstruction, not more than 4 cm of length, with functional distal lung tissue), Eastern Cooperative Oncology Group (ECOG) performance status ≤3, ability to tolerate general anesthesia, and the absence of general contraindications for bronchoscopy. The exclusion criteria were ECOG ≥ 4, recent myocardial infarction, unresolved coagulopathies, platelet (PLT) $N_o < 50$, unstable angina pectoris, chronic heart failure (New York Heart Association – NYHA, class ≥ 3), uncontrolled arrhythmia or hypertension, and allergy to anesthetics.

Technique

Nd:YAG laser resection was carried out via a combination of rigid and flexible bronchoscopy. Intervention was performed under general anesthesia. Vital parameters, (heart rate, rhythm, arterial blood pressure, and oxygen saturation) were followed in real time on the monitor. The patients were intubated with the rigid bronchoscope. A flexible bronchoscope was introduced through the rigid instrument, while the laser fiber was introduced through the working channel of the bronchoscope. We used a Sharplan-3000 Nd:YAG laser machine (Laser Industries Ltd., Israel). Initial laser power applied was 40 W; average power used was 50–60 W, with 1–2 s pulses. Average duration of procedures was 60 min.

Statistical analysis

The continuous variables were described as mean and standard deviations (SDs). The discrete variables were described as frequencies and proportion and compared, using the Pearson χ^2-test. The logistic regression analysis was performed to evaluate dependency between potential clinical risk factors and occurrence of complications. All probability values were calculated by assuming a two-tailed α value of 0.05 with confidence intervals at the 95% level. All statistical analyses were performed using the SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL) software. After identification of risk factors in univariate analysis, all the parameters that reached statistical significance were inputted in multivariate analysis. True independent risk factors were derived from multivariate analysis.

Results

There were 464 patients included in the study, 353 (76.1%) male and 111 (23.9%) female patients. The average age of the patients was 59 ± 9 years. Among the patients, 355 (76.5%) were current smokers, 80 patients (17.2%) were former smokers, and only 29 (6.3%) were nonsmokers. The majority of the patients had stage IV lung cancer (61.6%), stage IIIB was determined in 22.2% of the patients, while 16.2% had stage IIIA disease. Lung cancer types and tumor localizations are given in Table 1. Risk factors and the corresponding frequencies are shown in Table 2 while complications and their frequency are listed in Table 3. As visible from Table 2, most common risk factors as defined per protocol were previous treatment interventions: chemotherapy, radiotherapy, and previous interventional pulmonology treatment. The majority of patients were without complications (91.6%), among patients with complications most common were hypoxemia and hemoptysis [Table 3].

The overall complication rate was 8.4%. There was a significant correlation between the age and the complication rate (P= 0.001). Statistically significant clinical risk factors for complications were actual smoking status (P= 0.012), duration of smoking status (PCKY) (P=0.009), arterial hypertension (P<0.0001), chronic arrhythmia (P= 0.034), COPD (P<0.0001),

and stabilized cardiomyopathy (P<0.0001). There was also a significant correlation between previous chemotherapy and complications (P=0.031). Additional statistical analysis revealed independent clinical risk factors. Statistically significant independent factors were age over 60 years (P=0.026), arterial hypertension (P<0.0001), and COPD (P<0.0001). The results of multivariate logistic regression are shown in Table 4.

Discussion

Although majority of the patients undergoing laser resection of endobronchial malignancy have impaired respiratory function and significant comorbidities, the incidence of complications is surprisingly low. The most common complications following Nd:YAG laser resection of endobronchial tumors include hemorrhage (hemoptysis), pneumothorax, pneumomediastinum, respiratory failure, cardiac arrest, and myocardial infarction. The most feared, and nowadays a very rare complication, is airway fire.[1-10] However, there are some inconsistencies in the reporting of complications. Majority of the studies that evaluated safety of laser resection in palliation of lung cancer reported the overall complication rate with special attention on technique-related risk factors (power settings, pulls duration, oxygen concentration, bronchoscopists experience, or characteristics of the lesion).[11-15] Only few studies reported exact complications and the complication rate, and none of these studies evaluated patient-related risk factors. A large number of studies confirm the low complication rate, with range from less than 5% to 5–10%.[27] The overall complication rate in our study was 8.4%. It is slightly higher than in the most recent studies. However, this result could be attributed to the large number of patients in stage IV lung cancer. The incidence of acute hemorrhage is reported to be between 1 and 10%, pneumothorax up to 3%, and transient deterioration of gas exchange up to 80%.[27] Data from our study show the rate of hemoptysis 2.6%, pneumothorax 0.9%, and prolonged hypoxemia 2.4%. We did not observe fatal hemorrhage. There was one fatal outcome in our data series, and it was related to the cardiac arrest. In Han *et al*.'s study,[28] the overall complication rate was 6.5%; study population was very similar to ours as well as the tumor stage and characteristics. The reported complication rate is in consistency with data obtained from our study. As shown in Venuta *et al*.'s study,[29] the complication rate remains low even when Nd:YAG laser resection is used as a bridge to surgery. The complication rate (calculated per patient) for bleeding and hypoxia in their study was 2.56% and 1.83%, respectively. The largest study on Nd:YAG laser resection published up until today by Cavaliere and Cavaliere[30,31] evaluated results of 5049 bronchoscopies with the overall complication rate of 2.35%. Their data showed the complication rate for hemorrhage 0.67%, pneumothorax 0.5%, pneumomediastinum 0.31%, respiratory failure 0.42%, cardiac arrest 0.34%, and myocardial infarction 0.09%. The corresponding values from our data series are completely in consistency with the results from Cavaliere's study [Table 3]. However, when compared to the analysis of complications in 7000 bronchoscopies that showed an overall rate of 0.99%, as published in Ernst's state of the art paper, our complication rate (8.4%) remains higher than usual. In two of our previous

Table 1: Lung cancer types and tumor localizations identified in our patient group

	Frequency	Percent
Lung cancer types		
Squamous cell lung cancer	326	70.2
Small cell lung cancer	85	18.3
Adenocarcinoma	16	3.3
Carcinoid	6	1.2
Meta from lung primary	21	4.4
Other metastases	10	2.6
Total	464	100
Tumor localization		
Trachea	95	20.5
RM	180	38.8
RUL	48	10.3
LM	105	22.6
LUL	36	7.8
Total	464	100

RM, right main bronchus; RUL, right upper lobe bronchus; LM, left main bronchus; LUL, left upper lobe bronchus.

Table 2: Risk factors and their frequency

Risk factor	*N* (%)
Acute myocardial infarction over 6 months before treatment	19 (4.1)
Arterial hypertension	20 (4.3)
Chronic arrhythmia	9 (1.9)
Chronic obstructive pulmonary disease (COPD)	41 (8.8)
Stabilized cardiomyopathy	31 (6.7)
Previous external beam radiotherapy	76 (16.4)
Previous chemotherapy	329 (70.9)
Previous interventional pulmonology treatment	127 (27.4)

Table 3: Complications and their frequency

Complications	n (%)
Without complications	425 (91.6)
Prolonged hypoxemia	11 (2.4)
Global respiratory failure	3 (0.6)
Cardiac arrhythmia	2 (0.4)
Hemoptysis	12 (2.6)
Pneumothorax	4 (0.9)
Pneumomediastinum	1 (0.2)
Pulmonary edema	4 (0.9)
Tracheoesophageal fistulae	1 (0.2)
Death	1 (0.2)
Total	464 (100)

Table 4: The results of logistic regression showing independent risk factors for complications after laser resection

Risk factor	β	*P* value	(e^{β}) Odds ratio	95% Confidence interval	
				Lower	Upper
Age over 60 years	1.201	0.026	3.323	1.150	9.600
Arterial hypertension	4.192	<0.0001	66.173	18.167	241.043
COPD	4.852	<0.0001	127.999	41.428	395.476
Constant	-5.203	<0.0001	–	–	–

β-beta value, *P*-value (statistical significance), odds ratio and 95% confidence interval.

papers that evaluated efficacy of Nd:YAG laser resection in treatment of lung cancer, the overall complication rate was under 5%, even though we did not analyze complications in the mentioned paper and the number of patients was significantly lower than in this study.[32,33] There are studies, but with low number of patients, which show the absence of complications after laser resection of centrally located advanced stage lung cancer.[34]

Our primary goal was not only determination of complications and the complication rate. We were mainly interested in evaluation of patient-related risk factors which could be related to complications. Among demographic data, smoking status (actual smokers) and duration of smoking presented as pack-years (PCKY) were found to be significant risk factors for complications. This could be explained by the fact that smoking seriously impairs lung function, especially in lung cancer patients with concomitant COPD. Heavy smoking could be defined as a special risk, having in mind that in this study smoking over 60 PCKY was found to be an independent risk factor for complications of laser resection. The age was found to be a significant risk factor in general; however, age over 60 years was found to be an independent risk factor for complications, implicating that special attention should be directed toward that population. Special attention should be also paid to the group of patients with cardiovascular risks. Arterial hypertension, chronic arrhythmia, and stabilized cardiomyopathy were found to be statistically significant risk factors. With the increase in number of patients with lung cancer and cardiovascular comorbidities, this particular population could be more often admitted for interventional pulmonology treatment. In our study, 13% of the patients had lung cancer and cardiovascular comorbidity. COPD was expected to be a significant risk factor, more or less majority of patients with lung cancer have chronic bronchitis or emphysema, but in multivariate analysis COPD was identified as an independent risk factor. That result should alert physicians to pay attention to patients with COPD prior and after the laser treatment. The significant risk factor for complications was previous chemotherapy. However, since 70% of the patients received chemotherapy prior Nd:YAG laser resection that result may be a pitfall of study design, rather than actual risk factor. Nevertheless we cannot neglect the results we obtained, and previous chemotherapy should be regarded at least as a potential risk factor. Determination of independent risk factors for complications following Nd:YAG laser resection enables us to define the target population which is at risk. That might be the way to decrease the incidence of complications and provide better care for patients undergoing Nd:YAG laser resection of advanced stage lung cancer.

Conclusion

Determination of independent patient-related risk factors for complications following Nd:YAG laser resection of lung cancer facilitates detection of patient population with high risk for complications. Patients over 60 years of age, especially ones with COPD and arterial hypertension, as well as smokers over 60 PCKY should be thoroughly monitored prior and after laser resection. Thorough examination of patients with risk factors prior laser resection and active monitoring after the procedure could prevent complications and lead to a decrease in complication incidence.

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