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ORIGINAL ARTICLE

A prospective randomized trial comparing stapler and laser techniques for interlobar fissure completion during pulmonary lobectomy

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Abstract Alveolar air leaks, often resulting from lung tissue traumatization during dissection of fissures, still remain a challenging problem in lung surgery. Several tools and techniques have been used to reduce air leakage, but none was judged ideal. This prospective, randomized trial was designed to evaluate the feasibility, safety, and effectiveness of completion of fissures during pulmonary lobectomy by using a laser system. A standard stapler technique was used for comparison; the primary goal was to reach at least a comparable result. Forty-four patients were enrolled, 22 were treated with standard technique by using staplers (S) and 22 underwent laser (L) dissection. Randomization to one of the two groups was intraoperative after evaluating the presence of incomplete fissure (grade 3–4 following Craig's classification). A Thulium laser 2010 nm (Cyber TM, Quanta System, Italy) was used at power of 40 W. Outcome primary measures were the evaluation and duration of intra- and postoperative air leaks, the rate of complications, and the hospital stay. Air leaks (2.1±4.2 vs 3.6±7.2 days; p=0.98) and chest tube duration (6.4±4.2 vs 7.5±6.3 days, p=0.44) were lower in L compared with S group even if these were not statistically significant. Complications (36.4 vs 77.3 %; p=0.006), hospital stay (6.9±3.8 vs 9.9±6.9 days; p=0.03), hospitalization costs (5,650 vs 8,147 euros; p=0.01), and procedure costs (77 % of difference; p<0.0001) were significantly lower for L group, while operative time was longer (197±34 vs 158±41 min; p=0.004). The use of laser dissection to prevent postoperative air leaks is effective and comparable with stapler technique. Aero-haemostatic laser properties (by sealing of small blood vessels and checking air leaks) allow a safe application during pulmonary lobectomy in interlobar fissure completion avoiding stapler use.

Keywords Laser · Pulmonary lobectomy · Air leaks · Thulium laser

Introduction

Postoperative air leaks during lung surgery are reported to be as high as 70 % [1, 2]. Prolonged alveolar air leaks, defined as air leaks that last more than 7 days [3], represent the most common complication (up to 25 %) in patients undergoing major pulmonary resection [4]. Prolonged air leaks have an adverse effect on postoperative course leading to a longer duration of intercostal drainage, greater pain, increased immobility, and risk of further complications such as pneumonia, empyema, and thromboembolic events [5, 6]. This causes longer hospital stay and higher health care costs [7]. Described risk factors for pulmonary leakage, reported in literature, are underlying lung diseases such as emphysema, fibrosis, tuberculosis or malignancies, presence of a lymphangioleiomyomatosis, intrathoracic adhesions, elderly patients (>75 years), and lower diffusion capacity for carbon monoxide [6, 8]. In the absence of a risk factor, during a standard lobectomy air leaks most commonly originate from

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the dissection of the interlobar fissures as a result of the trauma on lung parenchyma due to surgical maneuvers or mechanical stapling, particularly if fissures are incomplete [9]. Standard techniques widely used to complete interlobar fissures involve surgical stapling and electrocautery; however, intraoperative air leaks are commonly seen, and additional treatments such as suturing, more stapling, or the application of various surgical sealants are required to further prevent or reduce air leaks [1, 2, 10–12]. Since the 1980s, the effect on pulmonary parenchyma of various types of lasers was explored, and their possible role as a surgical tool in a range of thoracic surgical operations was evaluated [13–15]. In the following years, the use of laser (in particular Nd:YAG) has steadily increased with application in a variety of lung operations (particularly metastasectomy), with excellent results in both haemostasis and air-sealing effects [16–19]. Based on these findings, we designed a randomized prospective controlled study to evaluate the effectiveness of the application of laser to complete interlobar fissures during pulmonary lobectomy. This group was compared with a group treated by standard stapling technique.

Materials and methods

This was a randomized, prospective, open-label, parallel group study carried out at two Thoracic Surgery Centers (University Hospital of Padova, Italy and Carlo Poma Hospital, Mantova, Italy) and designed to compare two different techniques for interlobar fissure completion during pulmonary lobectomy. The patients enrolled were assigned to the two groups: the L group, in which laser was used for precision dissection of the fissures, and the S group, in which an approved routine surgical procedure with staplers was carried out. The trial conformed to the ethical principles of the Declaration of Helsinki and was in accordance with guidelines for Good Clinical Practice. Informed consent was obtained from each patient included in the trial before the operation.

Patient selection

The trial population included patients aged ≥18 years with lung cancer scheduled for elective pulmonary lobectomy with planned antero- or posterolateral incision and systematic lymphadenectomy. Exclusion criteria were: previous lung surgery (on the same side), chemotherapy or radiotherapy (within the previous 3 or 4 weeks, respectively), preexisting advanced obstructive pulmonary disease [forced expiratory volume in 1 s (FEV1), <40 %], the need for adhesiolysis, pneumonectomy, wedge or sleeve resection. Patients undergoing video-assisted thoracoscopic lobectomies as well as lobectomies for nonmalignant reasons were excluded from the study. After thoracotomy, interlobar fissures were defined according to Craig's classification as follows: grade 1, complete fissure with entirely separate lobes; grade 2, complete visceral cleft but parenchymal fusion at the base of the fissure; grade 3, visceral cleft evident for part of the fissure; and grade 4, complete fusion of the lobes with no evident fissural line [20]. Only patients with fissures in grades 3 and 4 were deemed eligible for the study and entered in the randomization. Entry to the trial and randomization took place in the operating room once it was established that the fissure was of Craig's grade 3 or 4. The assignment to one of the two treatments was performed using closed envelopes containing notes reading either "L" for laser resection or "S" for conventional treatment with staplers.

Surgical procedure and protocol

A Cyber TM Thulium surgical laser system (Quanta System S.p.a., Solbiate Olona, Italy), wavelength 2,010 nm, 150 W maximum power, and touch-screen display, was used (Fig. 1). The energy was delivered in a continuous mode, by a 550-μm sterile optical fiber, equipped on a stainless steel handpiece with tips of various lengths (up to 20 cm) and activated by a footswitch. A high-performance smoke evacuation system was also used during the procedures to eliminate the vaporization fumes. All surgeons, anesthesiologists, and nurses were equipped with protection goggles to protect the eyes from laser radiation. Standard lobectomy was performed via lateral or posterolateral thoracotomy according to the surgeon's preference. For the L group, the fissures were dissected with the lung moderately inflated, by using a laser power of 40 W in a non-contact mode to obtain a precise cutting and coagulative effect (tissue average distance, 2 mm, divergence, 24°; fluence at 40 W, 26 J/mm^2, spot size 1.54 mm^2). The dissection was carried out until hilar vessels were identified, legated, and sectioned (Fig. 2). After completion of lobectomy, with the lung inflated, the dissected surface of the residual lobe was newly treated by a second laser irradiation with lower power (20 W) in a defocused mode in order to achieve a perfect aero-haemostatic effect on lung parenchyma. For the S group, the vessels in the fissures were isolated by a bipolar dissector or by blunt dissection and then legated and sectioned; therefore, the fissure was completed by using standard staplers. At the end of the surgical procedure, patients were tested for the presence of air leaks by a water submersion test under standard airway pressure of 25 cm H_2O and the intensity of air leaks graded according to Macchiarini's scale as 0 (no leakage), 1 (mild, countable bubbles), 2 (moderate, stream of bubbles), or 3 (severe, coalescent bubbles) [21]. Patients with

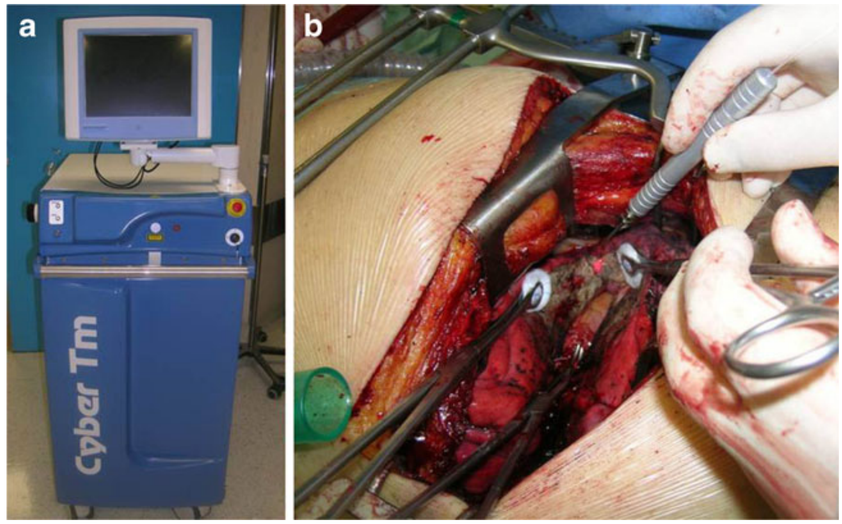

Fig. 1 **a** The Cyber TM laser system. **b** Intraoperative view of a dissection of fissure

grade 1 or 2 leakage did not receive any further treatment. Patients with grade 3 air leaks underwent a “rescue” treatment in order to reduce air leaks, by using restapling (for S group), new defocused laser treatment (for L group), parenchymal suturing, or application of sealants (allowed for both groups), followed by repeat submersion test until the evidence of downgrading of leakage. Standard double drainage of the chest cavity was performed using two 28 Charrier drains connected to a Sentinel Seal chest drainage unit. Continuous suction at 15–20 cm H2O was applied for 3 days. After 3 days, drainage could be maintained using water seal without suction. Air leakage was assessed at rest and under provocation by coughing. If no air bubbles appeared in the water reservoir, air leakage was considered absent. Postoperative air leakage was assessed on the evening of the day of operation and subsequently twice daily (morning and evening) until chest drain removal. Chest tubes were removed when there was no more clinical evidence of air leaks and routine chest X-ray showed no major pneumothorax. In addition, the volume of drained fluids was required to be less than 200 ml during the preceding 24-h period. The estimated daily cost of hospitalization per patient was 800 euros. Patients were followed-up for at least 3 months with clinical visit and chest X-ray at 1 and 3 months after surgery.

Efficacy and safety end points

The primary efficacy end point was the duration of postoperative air leakage. Secondary efficacy parameters evaluated were: (a) the percentage of patients’ air leak-free at the intraoperative water submersion test and remaining air leak-free at discharge from the surgical ward, (b) the mean time to chest drain removal, (c) the mean time to hospital discharge, and (d) the incidence and severity of complications and their relationship with the experimental and standard procedures. Moreover, the costs of the procedures and hospitalization were calculated and compared.

Statistical methods

This was a pilot study, and no attempts have been made to calculate a sample size to obtain a statistical power sufficient for confident evaluation of the results. Descriptive statistics were applied to primary and secondary outcome measures for all the patients. The variables were compared by the unpaired *t* test or Wilcoxon’s two-sample test applied to discrete or continuous data, and by the chi-square test or Fisher exact test when appropriate, applied to dichotomous or categorical data. Continuous data were presented as mean ±standard deviation. The normality of data distribution was

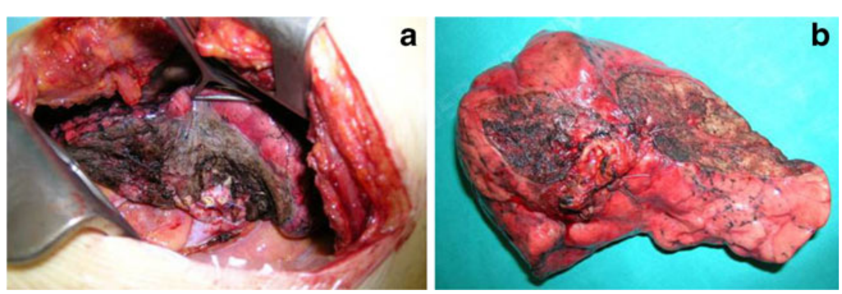

Fig. 2 **a** Intraoperative view after a left lower lobectomy. The fissure is dissected by laser, and a perfect haemostatic result is evident. **b** Specimen of a resected lobe in which the fissure was completed by laser

assessed by the Shapiro–Wilk test. Differences have been considered significant if p was ≤0.05. All of the statistical procedures described were performed with the SAS package (SAS, version 9.1.2; SAS Institute Inc, Cary, NC).

Results

Between November 2010 and May 2011, a total of 44 consecutive patients were included in the study, 22 were randomized to receive laser dissection (group L) and 22 stapler completion of fissures (group S). The characteristics of study population are reported in Table 1: no differences between the two groups were recorded. The surgical results are shown in Table 2: no differences were seen either in the class of fissures or in the distribution of the types of lobectomy. In the L group, the median time of laser use was 7 min (range, 3–16 min), with a median energy output of 16,100 J (range, 4,840–36,000 J). In the S group, a median of three loads were used (range, one to four loads). The surgical procedure was significantly longer in the L group compared with the S group (197±34.5 vs 158±41.7 min; p=0.004).

Air leaks evaluation

After the completion of lobectomy, the intraoperative evaluation of air leaks demonstrated a significant lower rate of air leaks (grade 1 to 3) in the S group than L group (50.1 vs 86.4 %; p=0.01). Grade 3 air leaks requiring a rescue treatment were observed in four (18.2 %) cases in S group and in seven (31.8 %) in L group (p=0.29).

Table 1 General characteristics of patients enrolled in the study

	S group	L group	p value
Gender (male %)	63.6	72.7	0.51
Age (years ± SD)	63±16.7	68.7±9.9	0.32
Height (cm ± SD)	169.8±6.9	168±6.2	0.37
Weight (kg ± SD)	69.8±11.1	74±11.9	0.23
Smoking history (n)			
Former smoker	8	10	0.79
Ex-smoker	11	10	
Nonsmoker	3	2	
FEV1 (l±SD)	2.3±0.8	2.3±0.5	0.62
FEV1 (%pred ± SD)	85.2±19.1	87.6±17.3	0.67
FVC (l±SD)	3±0.9	2.9±0.5	0.84
FVC (%pred ± SD)	89.6±14	91.8±19.7	0.68
DLCO (ml/min ± SD)	19.9±13.4	15±7.2	0.31
DLCO (%pred ± SD)	71.3±19.4	67.9±16.6	0.57

Table 2 Intra- and postoperative results

	S group	L group	p value
Craig's class of fissure (n)			
Class 3	21	18	0.15
Class 4	1	4	
Type of lobectomy (n)			
Upper right	11	12	
Middle	1	0	
Lower right	3	3	
Upper left	4	4	
Lower left	3	3	
Intraoperative air leaks (Macchiarini test)			
Grade 0	9	3	
Grade 1	7	7	
Grade 2	2	5	
Grade 3	4	7	
Operative time (min)	158±41	197±3	0.004
Air leak duration (days)	3.6±7.2	2.1±4.2	0.98
Air leak duration (h)	87.9±172.9	53.7±98.2	0.77
Daily amount of fluid leak (ml)	316±130	346.7±106	0.17
Chest tube duration (days)	7.5±6.3	6.4±4.2	0.44
Hospital stay (days)	9.9±6.9	6.9±3.8	0.03
Complications (%)	77.3 %	36.4 %	0.006

Interestingly, the significant difference in air leakage rate observed intraoperatively was inverted postoperatively since the first postoperative day and maintained for the entire postsurgical period (Fig. 3). Postoperatively, the L group had a shorter duration of air leaks compared with S group (2.1±4.2 vs 3.6±7.2 days; p=0.98), but this difference was not statistically significant. Prolonged air leaks were recorded in two (9.1 %) patients of L group and three (13.6 %) patients of S group (p=0.99). The incidence of dead pleural space was lower in the L group (9.1 vs 27.3 %; p=0.09), with a tendency towards a statistical significance.

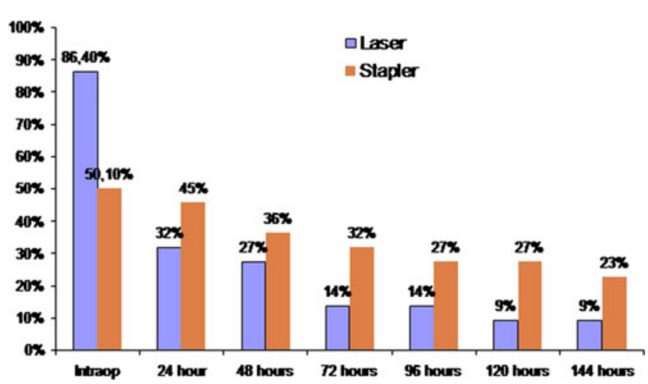

Fig. 3 Incidence of intra- and postoperative air leaks in the two groups

Other evaluations

The daily amount of pleural fluid leaks and the chest tube duration were similar between the groups. No perioperative mortality was observed. The incidence of overall complications was significantly lower in the L group (36.4 vs 77.3 %, $p=0.006$). No adverse effects were observed intraoperatively or postoperatively regarding the use of laser. No patients required a reoperation; in the S group, one patient had bleeding requiring blood transfusion, and another patient had a pneumothorax after removal of chest drain that was repositioned. Details of complications are reported in Table 3. The mean hospitalization length of the two procedures was significantly different, being shorter in the L group than the S group (6.9±3.8 vs 9.9±6.9 days; $p=0.03$).

Analysis of costs

The mean cost of the stapler procedure was significantly higher than that of the laser procedure (a mean of 77 % increased cost; $p<0.0001$) when considering the cost of disposable materials. An estimated number of 300 procedures should be carried out to recover the fixed cost of the laser system. An equal significant result was found for the mean cost of hospitalization: 8,147±5,785 euros for S group vs 5,650±3,063 for L group; $p=0.01$.

Discussion

Intra- and postoperative air leaks are a common problem following lung resection [4], having a rate between 48 and 70 % in main series [1, 10, 11]. Prolonged air leaks persisting over 7 days complicate 15–18 % of cases [21, 22]; as a result, these patients require prolonged chest tube drainage time, with increased risk of pleuropulmonary infections, pulmonary embolism, respiratory distress, associated pain, and consequently longer hospital stay [5, 6]. Several studies in the routine lung resection population have found a clear association between air leaks and hospital stay or cost [4, 5, 7]. These studies have found that air leaks prolong hospital stay by between 4 and 13.1 days. Although significant efforts have been made to reduce the incidence of parenchymal air leaks following lung resection, an ideal surgical technique or tool to reduce or prevent this complication has not been identified yet, and standard techniques do not result in adequate sealing in the majority of patients. The standard resection technique for lung parenchyma nowadays is the use of stapling devices. Following mechanical principles, they try to overcome bleeding and air fistulae by pressing the lung tissue between two rows of clamps. The routine use of surgical staplers, even buttressed by strips, for division of parenchyma has significantly improved the primary closure of resection lines; however, when interlobar fissures are incomplete, the risk of postoperative air leaks increases. Potential sources of air leaks are the areas of parenchymal traumatization and dissection, not only along the stapled borders of the lung but especially in the hilar region where staplers cannot seal the parenchyma and a local rescue treatment is difficult. In 1967, Minton et al. [23] demonstrated the effects of Nd:YAG laser on pulmonary parenchyma and excised a tumor in an experimental model. In the following years, various authors demonstrated the aero-haemostatic effects on lung tissue and particular usefulness of the laser for excision of pulmonary nodular lesions. Since that time, the use of laser surgery in resections of lung parenchyma widely increased, and various applications were explored, with particular emphasis on parenchyma-sparing surgery (mainly metastasectomy) [16–19]. The rationale of the use of laser in pulmonary surgery stems from the specific properties of this device and its effects on lung parenchyma. Due to its parenchymal tissue having a typical water content of 80 % but a very low tissue density, a very low heat capacity and a variable air content, the lung is an ideal organ for photothermal laser applications [24]. The use of a laser with a powerful coagulation capability in addition to excellent cutting properties is required when resecting lung parenchyma, given the high vessel density. Rolle et al. [14] and Moghissi et al. [15], moreover, found that in addition to the combination effect—cutting plus coagulation—laser irradiation determines, as a welcome side effect, a strong lung tissue shrinkage, which provides two additional advantages: mechanical reinforcement of the coagulation effect and sealing of alveoli avoiding parenchymal fistula responsible for air leaks. Lo Cicero et al. [13] described the mechanism of this sealant effect: laser irradiation seals by means of the progressive collapse of alveolar septa that yields a thick, multilayered, air-proof

Table 3 Complications stratified by type of treatment

	S group	L group
Overall	17 (77.3 %)	8 (36.4 %)
Dead pleural space	6 (27.3 %)	2 (9.1 %)
Prolonged air leaks	3 (13.6 %)	2 (9.1 %)
Transient cerebral ischemia	0 (0 %)	1 (4.5 %)
Fever	1 (4.5 %)	1 (4.5 %)
Pleural effusion	1 (4.5 %)	1 (4.5 %)
Respiratory distress	0 (0 %)	1 (4.5 %)
Pneumonia	1 (4.5 %)	0 (0 %)
Chylothorax	1 (4.5 %)	0 (0 %)
Atrial fibrillation	2 (9.1 %)	0 (0 %)
Bleeding	1 (4.5 %)	0 (0 %)
Pneumothorax	1 (4.5 %)	0 (0 %)

membrane. These effects are more evident when a defocused irradiation is carried out. For this reason, our protocol provided a first dissection of the fissure by using the laser at high power (40 W) exploiting its cutting (evaporation) effect and a second application over the dissected area at low power (20 W) in a defocused mode to enhance the aero-haemostatic (sealing of small blood vessels and checking air leaks) properties. In our study, we used a new generation laser system: the 2,010-nm wavelength emitted by Cyber TM Thulium laser is strongly absorbed by water resulting in an outstanding coagulation (low coagulation depth of only 0.2 mm, up to ten times less than with other laser techniques) and aero-hemostatic effects with preservation of the surrounding tissue. Our pilot study was designed to evaluate the effectiveness of laser in comparison with standard stapler technique to dissect the fissure during a pulmonary lobectomy in patients affected by NSCLC. In order to avoid significant biases, a population without risk factors predictive for prolonged air leaks was selected (i.e., patients with emphysema, low DLCO, pleural adhesions, and previous induction treatments were excluded). In addition, to have a reliable evaluation of the efficacy of the new surgical tool and to have a homogeneous study population, only patients with incomplete or absent fissures (Craig's classes 3 or 4) were randomized. To our knowledge, this is the first study exploring the application of laser during pulmonary lobectomy for the completion of fissures. The studies of Droghetti et al. [12] and Rena et al. [25] had a similar design, but they compared the standard stapler technique with electrocautery dissection and application of a collagen patch coated with human fibrinogen and thrombin. In particular, in these studies, the poor aero-haemostatic effect of electrocautery after the incision of the inflated lung was evident that frequently resulted in intraoperative bleeding and considerable air leaks, reduced only after the application of the patch. Thus, deep penetration into the tissue for strong coagulation which is observed as a function of laser irradiation and shrinking of alveoli with sealing of air leaks are not achieved by electrocautery alone. These studies demonstrated a relative reduction in length of postoperative air leaks for the group treated with electrocautery and patch, even if they were unable to demonstrate an advantage in reducing hospital stay and costs. In our pilot study, the mean duration of the occurrence of air leaks was shorter in the L group (2.1 vs 3.6 days, $p=0.98$); however, these data were not statistically significant, probably for the limited number of enrolled patients. We observed a significantly greater incidence and severity of intraoperative air leaks in the L group, but we demonstrated a relevant reduction of these on postoperative day 1 after the stabilization of the laser effect with an inversion of percentage of air leak-free patients in favor of the L group. Moreover, the L group showed a daily trend toward reduction in the proportion of patients with leakage. The observation of a significant longer hospital stay and costs for the S group in our trial was probably related to the higher rate of complications that prolonged the hospitalization, more than to the longer duration of postoperative air leaks. We noticed some advantages of laser dissection of lung parenchyma: (a) the minimal deformity or damage of the surrounding parenchyma both for reduced penetration (the necrotic damage is about 0.2 mm, Fig. 4) and for significant reduction of postoperative photothermal edema due to the lower heat exposure time (parenchyma-sparing procedure), (b) the preservation of elasticity along the resection site, (c) the aero-haemostatic effect, and (d) the respect of the major bronchi and vessels with low risk of injury during the dissection. In our experience, all these characteristics allowed for safe dissection and quick expansion of the residual lobe with a better capacity to fill the thoracic cavity that is one of the prerogatives for a rapid resolution of air leaks. This led to a minor incidence of complications such as dead pleural space in the L group.

Some disadvantages related to the laser use were:

1. The technique is time-consuming and potentially tedious. In our experience, the median time of the total laser irradiation on lung parenchyma capable to permit the completion of the fissure was only 7 min. However, this was only the median time of the laser application, an estimated time of 30 to 40 min was necessary to complete the fissure, leading, in our study, to a significant longer procedural time (about 40 min) for the L group.
2. The initial financial investment for the system. We have calculated a number of procedures (250–300) which are needed to recover the fixed expense.
3. The need for staff education and training in security and handling of this special technology.

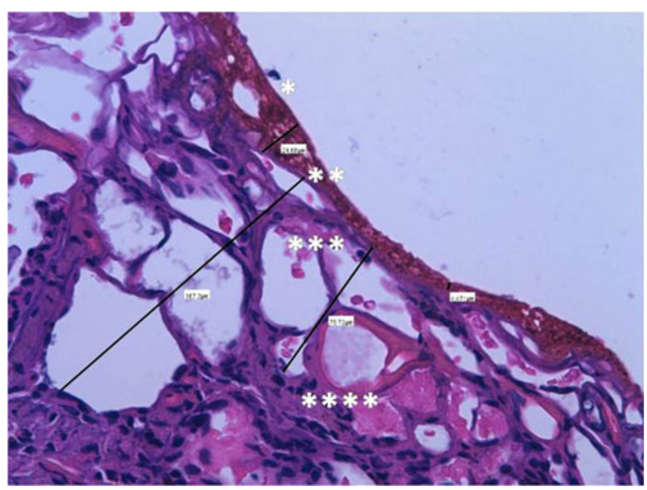

Fig. 4 Histological changes on the surface of the lung parenchyma dissected by laser: * area receiving maximum power with tissue evaporation, ** area with coagulative necrosis, *** area with partial necrosis, but the gross structure of the tissue is still preserved, **** area with slight alteration (edema and disorganization) in the structure of the lung; this area has received a minimal laser beam radiation. The maximal damaged area is no more than 0.2 mm

4. The additional need of a high-performance smoke evacuator system.
5. The obligatory use of protection goggles.

Conclusions

This study demonstrates that the laser may be a useful and safe tool alternative to the standard stapling technique. The optimal aero-haemostatic property, the minimal tissue damage with maximal preservation of the elasticity of normal parenchyma, and rapid expansion of the residual lung are effects determinant for a quick resolution of air leaks and a low rate of procedure-related complications. Results of larger trials are necessary to better define the clinical benefit of this new technology.

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