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Combined Nd-YAG laser/HDR brachytherapy versus Nd-YAG laser only in malignant central airway involvement: a prospective randomized study

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Abstract

Background: Laser debulking and prosthetic stents are useful modalities in the palliative treatment of initial inoperable or recurrent lung cancer. Recently, endobrochial brachytherapy was introduced to extend the duration of palliation and reduce the number of endoscopic treatments. This trial compares Nd-YAG laser alone and associated to high dose rated (HDR)-brachytherapy. *Patients and Methods:* From 1995 to 1998, 29 consecutive patients, with non-small cell lung cancer (NSCLC) and central airway involvement, were randomized in two groups: group 1 (15 patients) received Nd-YAG laser only; group 2 (14 patients) underwent a combined Nd-YAG laser/ HDR brachytherapy treatment. *Results:* There was no mortality or morbidity related to the treatment. The period free from symptoms was 2.8 months for group 1 and increased to 8.5 months in group 2 ($P < 0.05$). The disease's progression free period grew from 2.2 months of group 1 to 7.5 months of group 2 ($P < 0.05$) and the number of further endoscopic treatment reduced from 15 to 3 ($P < 0.05$). *Conclusion:* The results confirm the potential of brachytherapy to prolong relief from symptoms, lessen disease progression and reduce costs of treatment. A detailed analysis is presented of both groups.

Keywords: Nd-YAG laser; Brachytherapy; Lung cancer; Mini-invasive; Endoscopy; Radiotherapy

1. Introduction

The relatively limited value of any treatment for lung cancer has encouraged the development of several modalities for the palliative management of symptoms in patients with initial inoperable or

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recurrent disease [1].The palliation of malignant airway obstruction may be achieved by laser therapy and prosthetic stents [2–4]. In the last decade, the introduction of high dose rate (HDR) brachytherapy has allowed for a better control of the neoplastic airway involvement and extend the duration of palliation [5,6]. This modality, alone or associated with laser debulking, seems able to achieve the desirable objectives of each palliative treatment: it is easy, quick, effective and mini-invasive [1,5,7–10]. If compared with low dose rate (LDR) method, and with the same efficacy [5,11,12], HDR brachytherapy has allowed to reduce the treatment time, program with more accuracy the dose distributions and reduce radiation exposure to personnel. Moreover, the great variability of the series reported in literature, about the technique utilized for the treatment and the population involved in the study, has not until now allowed a complete evaluation of the potentials of this method [13]. With the aim of verifying these potentialities, the efficacy of the combined Nd-YAG laser/HDR brachitherapy versus bronchial debulking with Nd-YAG laser alone was evaluated, in a prospective randomized study treatment.

Table 1
Clinical features of all 29 patients and according to the group

Clinical features	Number		
	Group 1	Group 2	Total (%)
Previous treatments			
Surgery/radiotherapy (50–60 Gy)	6	5	11 (37.9)
Chemo/radiotherapy (50–60 Gy)	9	9	18 (62.1)
Histology			
Squamous cell carcinoma	10	11	21 (72.4)
Adenocarcinoma	4	2	6 (20.6)
Large cell carcinoma	1	1	2 (6.9)
Symptoms			
Haemoptysis	5	6	11 (37.9)
Stridor	4	5	9 (31)
Cough	15	14	29 (100)
Dyspnoea	12	9	21 (72.4)
Performance status (WHO)			
0	2	1	3 (10.4)
I	7	4	11 (37.9)
II	6	9	15 (51.7)
Radiology			
Lobar atelectasis	4	6	10 (34.4)
Pulmonary atelectasis	4	4	8 (27.6)

2. Materials and methods

2.1. Patient selection

The following inclusion criteria were required for enrollment: non-small cell lung cancer (NSCLC) involving central airway and not eligible for further surgical, chemotherapeutic or external beam radiation treatment; an expectation of life of at least 2 months; a performance status score (according to WHO) ≤ 2. The protocol was approved by the Hospital Ethical Committee and written informed consent was obtained from all patients. From December 1995 to December 1998, we enrolled 29 patients with NSCLC who had already undergone a previous conventional treatment (11 with surgery followed by external beam radiation therapy, 18 with chemo/radiotherapy). The patients were randomized in two groups. Fifteen patients (Group 1) underwent Nd-YAG laser debulking only and 14 (Group 2) laser debulking followed by HDR brachytherapy. There were 23 males and six females with a mean age of 61 years (range 47–76). Twenty-one patients had a squamous cell carcinoma, six had an adenocarcinoma and two an undifferentiated large cell carcinoma (Table 1). The lesion involved the trachea in six cases, the carina and both mainstems in six, the carina and a mainstem in seven, a mainstem in seven and a lobar bronchus in three (Table 2). Airway obstruction grade was calculated according to Speiser's obstruction score method [12] (Table 3).

2.2. Evaluation

They underwent a standard protocol management: complete history and physical examination; pulmonary function tests; arterial blood gas assessment; chest radiograph; fiberoptic bron-

Table 2
Endoscopic features and involvement of the central airway

Involvement of tracheobronchial tree	No.			Speiser's index*			Lesion's length*		
	G1	G2	T	G1	G2	T	G1	G2	T
Trachea	4	2	6	5.1	5.7	5.4	2.3	2.7	2.5
Carina and both mainstems	3	3	6	6.5	6.1	6.3	4.9	4.1	4.5
Carina and one mainstem	3	4	7	6.7	7.9	7.3	1.9	2.5	2.2
Mainstem	3	4	7	7.7	7.5	7.6	2.4	2.2	2.3
Lobar bronchus	2	1	3	6.0	6.0	6.0	0.9	1.3	1.1

* Mean value; G1, Group 1, G2, Group 2, T, total.

choscopy. These examinations were repeated 14 days after the laser debulking and from 30 to 45 days after HDR brachytherapy. A radiological (chest film and CT scan) and endoscopic follow-up was performed every 2 months. Morbidity produced by intraluminal radiotherapy was assessed according to Gollins's scoring system [14] (Table 4).

2.3. Nd-YAG laser debulking technique

The delivery fiber for laser debulking was always introduced through the channel of a rigid bronchoscope (Wolf or Effer–Dumon), under general anesthesia. An energy of 25–45 W, using pulses up to 1.2 s, was used for a mean total amount of 1850 J (range 1400–2200 J). Particular attention was paid to preserving as much as possible the bronchial wall by an exclusive use of tangential laser beams and an extreme caution in mechanically removing the residual tumor mass.

2.4. HDR brachytherapy technique

Group 2 patients underwent HDR brachytherapy 15–18 days after Nd-YAG laser debulking, on an outpatient basis. All patients received anticholinergic and sedative premedication (atropine 1 mg and morphine 10 mg im), then topical anesthesia (lidocain 2–10%). A 19 mm diameter afterloading catheter (Nucletron) was advanced beyond the stenosis through the working channel of a fiberoptic bronchoscope (Pentax FB18X), and its correct position verified both endoscopically and radiologically. The bronchoscope was withdrawn and the catheter taped to the nose. A metal wire with radio-opaque marker pellets was introduced into the afterloading catheter to perform an accurate planning of the treatment field

Table 3
Obstruction scores according to Speiser's semiquantitative method [12]

	Obstruction and score		
	>50%	10–50%	<10%
Trachea	10	5	2
Mainstem	6	3	1
Lobar bronchus	2	1	0
Pneumonia	2 per lobe		
Atelectasis	2 per lobe		

Table 4
Gollins's index for radiation bronchitis [14]

Description	Score
No reaction, normal mucosa	0
Mild inflammation, with white collagenous slough occupying part of the endobronchial circumference	1
More marked inflammation with white collagenous slough occupying the whole of the endobronchial circumference at some point	2
A degree of fibrosis associated with the inflammatory response, causing narrowing but not complete occlusion of the bronchus	3
Complete occlusion of the bronchus at some point due to marked fibrotic reaction	4

Table 5
Objective results and statistical comparison between the two groups

	Group 1		Group 2		*P*
Disease's progression free period (months)	2.2		7.5		<0.05
Further endoscopic treatments (Laser/Stent)(number)	15		3		<0.05
Median survival (months)	7.4		10.3		ns
Lung function tests	Pre	Post	Pre	Post	
FEV_1 (l)	1.35 (±0.7)	2.16 (±0.6)	1.43 (±0.6)	2.32 (±0.4)	
FEV_1 (%)	52.4 (±10.7)	63.4 (±12.3)	53.2 (±11.2)	65.4 (±12.1)	
FVC (l)	2.08 (±0.6)	3.34 (±0.6)	2.11 (±0.8)	3.47 (±0.7)	ns
FVC (%)	60.9 (±14.1)	74.2 (±12.8)	62.8 (±13.5)	77.0 (±14.6)	
FEF_{50}/FIF_{50}	0.51 (±0.7)	0.86 (±0.7)	0.55 (±0.8)	0.91 (±0.5)	
Arterial blood gas analysis					
PaO_2(mmHg)	63.7 (±8.4)	74.6 (±9.6)	65.4 (±6.7)	75.6 (±7.1)	ns
Bronchoscopy					
Speiser's index	6.4 (±0.7)	3.0 (±0.8)	6.9 (±0.7)	2.7 (±0.9)	ns

under radiographic control (chest radiographs at 0, +30, −30, +90, −90°). The metal wire was removed and the patient transferred to the radiation bunker where the catheter was connected to a microSelectron-HDR (Nucletron). Using 5 mm steps, the system advanced a 1.1 mm diameter high radioactive Iridium-192 source (10 Ci) along the treatment field, under remote control. The dose prescription was 5 Gy at 0.5 cm, with a total exposition time variable from 10 to 15 min. The treatment was repeated three times every 7 days, for a total dose of 15 Gy.

2.5. Statistics

Accrual goals for the study were determined on the basis of the primary end point to increase the disease progression free period from 2 to 8 months. Setting $\alpha = 0.05$ (two-tail) and power = 90%, a sample size of 28 patients (14 patients per treatment arm) was calculated. Survival plots were determined according to the product limit method of Kaplan and Meier and compared by log rank test. For statistical comparisons between the two groups χ^2 test was used for median survival and Fisher's exact test for the proportions of events. A P value of less than 0.05 was considered significant [15,16].

3. Results

At the time of this analysis (May 1999) 11 patients were still alive and four free from endobronchial relapse. The median follow-up was 17.8 months (range 9–35 months). During the observation period, 13 patients died of local progression of the disease and five patients of distant metastasis. One patient, with local progression and endobronchial relapse, died of massive hemoptysis 12 months after the combined treatment. Overall actuarial median survival was 9.2 months, without significant statistical difference between the two groups (Table 5).

3.1. Subjective responses

After Nd-YAG treatment an improvement in symptoms was obvious in all patients with hemoptysis and stridor, in 16 of 21 patients (76%) with dyspnoea, in 14 of 29 patients (48%) with cough. No patient showed an impairment of symptoms after the treatment, except for six patients who had a transient increase of cough. The period free from symptoms in the responsive patients was 2.8 months for Nd-YAG treatment alone and 8.5 months for combined Nd-YAG/HDR treatment (overall 5.4 months), with a statistically significant difference ($P < 0.05$).

3.2. Objective responses

Twelve of 18 patients (66.6%) showed a radiological disappearance or reduction of a pulmonary atelectasis, in 16 cases immediately afterlaser debulking and in two cases as consequence of brachytherapy.

Pulmonary function tests, before and after laser treatment, were available for 25 patients. A significant improvement of forced expiratory volume in the first second (FEV1), of forced vital capacity (FVC) and of the ratio between the forced expiratory and inspiratory flow at 50% of vital capacity (FEF_{50}/FIF_{50}) was measured in group 1 patients. The same way, arterial blood gas analysis showed an increase of PaO_2. Group 2 patients showed a further improvement of these parameters but without statistical significance (Table 5).

After laser debulking, Speiser's index dropped from 6.8 to 3.0 ($P < 0.001$) in group 1 patients. HDR brachytherapy allowed a further reduction of the obstruction score (not statistically significant) and a complete endoscopic clearance of the lesion in eight of 12 patients (66.6%). In seven of these cases bronchial biopsies showed a complete anatomicopathological disappearance of the disease. At follow-up, these results supported the statistical difference between the two groups both for the period free from disease progression (7.5 ± 1.6 months for the combined treatment versus 2.2 ± 0.4 months for laser debulking alone, $P < 0.05$) and for the number of further endoscopic treatments, Nd-YAG or stent (3 vs. 15, $P < 0.05$). Moreover, this last result produced a reduction of treatment costs per patient. On average they decreased from 2834 Euro (€), for each patients of group 1, to 1446€ for the patients of group 2.

3.3. Complications

Neither morbidity nor mortality related to the treatment have been observed. Five patients experienced a grade II and one patient a grade III of actinic bronchitis. This last patient required a dilatation by rigid Dumon–Effer's bronchoscope.

4. Discussion

Forty percent of patients with advanced lung cancer have an intrathoracic relapse in spite of a first line treatment based on external beam irradiation only or associated to surgery and/or chemotherapy [17–19]. The planning of a therapeutic strategy is particularly difficult in these patients, both for the limited options of treatment and for the significant manifestations related to the tracheobronchial involvement. The patient, who previously underwent external beam irradiation, in fact, cannot profit by such treatment again because of the overcoming of tissue tolerance threshold [20–22]. In these cases Nd-YAG laser debulking allows an immediate improvement of pulmonary symptoms [2–4]. But the necessity of repeated treatment reduces the quality of life of the patient and increases health costs [4]. Schray and Suh's retrospective study [9,23] underlined how laser debulking followed by brachytherapy prolonged airway opening and symptoms palliation. Other authors stressed the high risk of complications associated to the combined treatment and contested the real therapeutic effectiveness [20,21,24,25]. The authors were intrigued to conduct a randomized prospective study with the expectation to assess the real significance of combining Nd-YAG laser with HDR brachytherapy treatment.

Symptom control was excellent in both groups of the study — an improvement in 100% of patients was obtained with hemoptysis and stridor, and in 70% of patients with dyspnoea — in agreement with literature [26–29]. The same has been reported about objective response regarding either pulmonary function tests or endoscopic findings (Speiser's Index) [8,12]. As could be expected, a statistically significant difference was found at follow-up with a period free from symptoms and progression which was longer in the second group [9,23]. No early complications were experienced in either group. Late complications, related to brachytherapy, were acceptable

and no mortality related to the treatment was experienced.

Probably, several factors contributed to achieve such results. In most of the cases, debulking was carried out mechanically by the blade of the rigid bronchoscope and Nd-YAG laser utilized for hemostasis by tangential beams to the bronchial wall, reducing the risks of a direct perforation. Moreover, according to Zajac, Nori and Kohek [30–32], brachytherapy started at least 2 weeks after laser debulking and each patient underwent three afterloading sessions at weekly intervals with an endobronchial irradiation dose of 5 Gy per session, observing absolute limits of safety. Besides, recent data published by Macha [33,34] has reassessed the risk of massive hemoptysis following the combined treatment. He analyzed the high percentage of mortality associated with this complication, reported by several authors [20,21,24,25], and suggested it could be attributable to the type and topography of the treated lesions, rather than to a direct effect of the treatment. Furthermore, an extension of survival in patients with a central invasive tumor may explain the enhancement of the probability of a fatal hemoptysis.

The efficacy of the palliative endoscopic treatment has now been largely assessed and currently it seems to be an important factor in the increasing attention paid by clinical oncologists to the quality of life in patients with advanced disease. The findings confirm again the benefit of brachytherapy in stabilizing the effect of laser debulking and prolonging the improvement in symptoms, but also reducing the necessity of further endoscopic interventions and, as a consequence, the mean costs of treatment per patient. This is the same for those patients who already underwent an external beam radiation treatment [27,31].

Although Nd-Yag laser debulking and endobronchial afterloading can only be regarded as palliative methods, it could be considered a standard procedure for non-resectable NSCLC of the central bronchial tree thanks to its low invasive nature and the feasibility of performing it on an outpatient basis.

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