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Out-patient high-dose-rate endobronchial brachytherapy for palliation of lung cancer: an observational study

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ABSTRACT: ***Out-patient high-dose-rate endobronchial brachytherapy for palliation of lung cancer: an observational study. A. Scarda, M. Confalonieri, C. Baghiris, S. Binato, R. Mazzarotto, A. Palamidese, R. Zuin, U. Fantoni.***

Background and Aim. **Out-patient high-dose-rate endobronchial brachytherapy (HDREB) is a possible option in the palliation of symptoms in patients with advanced lung cancer, but literature data is limited and the technique is still under development in Italy.**

Our aim was to evaluate safety and effectiveness of out-patient HDREB for palliation of malignant endobronchial tumours in the context of a multidisciplinary approach.

Methods. **Out-patient HDREB sessions were scheduled at weekly intervals (500-1000 cGy per session) with prior Diodi-laser resection in some cases. Response was assessed bronchoscopically, clinically and functionally at the end of treatment and one month after the last HDREB session. Inclusion criteria was: histological evidence of malignant tumour not susceptible to surgical treatment for extension or co-morbidity.**

Results. **150 outpatient HDREB sessions were carried out on consecutive 35 patients (mean age 69 yrs, M/F 29/6) with symptoms due to central airway obstruction. A short-term endoscopic response was observed in 15/28 patients. After delivering 2000 cGy dyspnoea decreased significantly. After one month cough decreased and haemoptysis disappeared. Palliation was obtained in all patients except one during. Lung function tests did not significantly improve after HDREB. No fatal complication occurred. A temporary radiation bronchitis was observed in six patients.**

Conclusions. **This non-comparative, prospective observational study showed a palliative response of HDREB in most of patients with advanced endoluminal lung cancer. The safety of the procedure was good and the rate of non-fatal serious complications was very low.**
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Keywords: Endobronchial radiotherapy, brachytherapy, high-dose-rate, palliation, lung cancer.

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Introduction

Most patients presenting with lung cancer have a locally advanced or metastatic disease: less than 30% of cases are considered operable, and only a third of these cases actually undergo definitive surgery with a high risk of subsequent local recurrence [1]. Endobronchial metastases or local recurrence after surgery and/or conventionally therapies often cause symptoms which refer to tumour stenosis in central tracheobronchial system, including haemoptysis, intractable cough, dyspnoea, and post-obstructive pneumonia. Symptomatic benefit could be achieved by bronchoscopic treatment as part of multidisciplinary treatment. The best treatment option has to be chosen according to the individual situation. High-dose-rate endobronchial brachytherapy (HDREB) has been proposed for its potential advantage to deliver a higher dose of radiation directly to reduce the tumour while sparing surrounding healthy tissues and structures [1-5]: patients with a poor performance status who have already received large doses of external-beam radiation therapy can still receive endobronchial brachytherapy provided that the catheter can be placed safely near the lesion. HDREB either alone or in combination with external beam radiotherapy (EBRT) have also been used as a curative treatment in a few cases of carcinoma in situ or early-stage Non-Small Cell Lung Cancer (NSCLC) [1, 3-9], and as a treatment option for local tumour relapse in patients already treated with surgical resection [10, 11]. Nevertheless, the role of HDREB in the management of patients with not resectable lung cancer is still under debate, and the optimal dosage and fractionation schemes are still unknown. For

this reason and due to the lack of awareness of its safety and effectiveness, HDREB is not still widely used all over the world and in Italy. The aim of our observational study is to assess the safety and palliative effectiveness of HDREB as a component of a multidisciplinary approach.

Patients and methods

Eligibility

All the consecutive patients needing palliative treatment to resolve bronchial obstruction for lung cancers were considered for HDREB on an outpatient basis. Inclusion criteria were: histological evidence of malignant tumour not susceptible to surgical treatment for extension or co-morbidity. Exclusion criteria were: impediments to correct bronchoscopic catheter insertion; poor performance status (ECOG>2) to contraindicate repetition of bronchoscopy; informed consent not granted.

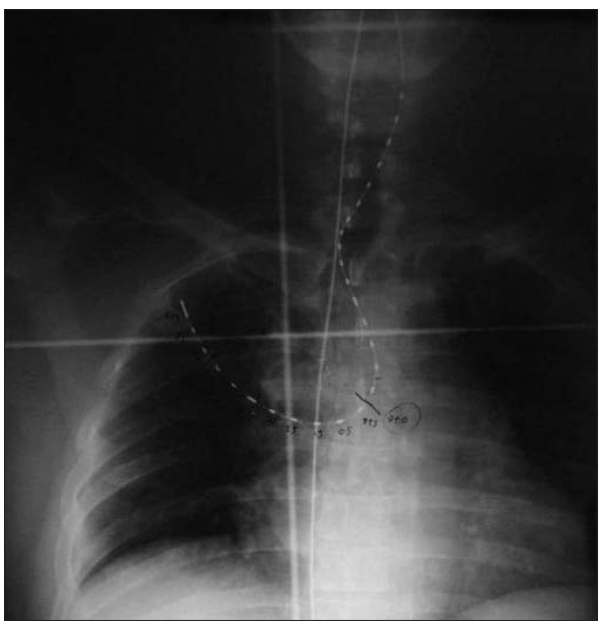

Fig. 1. - Radiograph after catheter positioned to calculate the target area.

Bronchoscopic procedures and palliative treatment

A preliminary flexible bronchoscopy was performed in all patients to localise the tumour region and to assess an individual therapeutic approach.

Each patient was prepared for the procedure with cortisone i.v. and atropine i.m. to control secretions, to minimise bronchial spasms and to stop vaso-vagal reflexes.

An endobronchial brachytherapy was performed under sedation (midazolam 2.5 mg + propofol 1.5-2.5 mg/kg ev) using flexible fiberoptic bronchoscope introduced through the nostril. A 995-mm long by 2-mm section teflon afterloading catheter was positioned through the suction channel of the bronchoscope adjacent to the lesion and the bronchoscope was removed. The guide wire was replaced with a simulation probe (graduated radio-opaque markings 1 cm apart along its length). The catheter was secured in place with adhesive tape on the patient's nose. The position of the catheter was verified by fluoroscopy and a treatment plan taking carina as reference point going up from the end of catheter was established by means of a postero-anterior radiograph (figure 1). Then, the catheter was attached to the Microselectron HDR remote afterloading unit that contains the iridium-192 radioactive source. Patients were treated in an adjacent, shielded room and contact was maintained with personnel through a closed circuit television system (figure 2). In the case of multiple endobronchial locations, two catheters were inserted into bronchi to treat the tumour (figure 3).

In the case of a complete or nearly complete obstruction of the bronchus a Diodi-laser disobliteration was done for initial re-canalisation of the main airway, to place afterloading catheter under direct visualization of bronchoscope over the lesion and to achieve a more lasting response. HDREB was used jointly with others procedures, as part of multidisciplinary treatment of chemo- and external radiotherapy.

Routinely, four HDREB sessions were carried out at 1-week intervals in which a dose per session of 500 cGy was applied at a depth of 1 cm from the

Fig. 2. - **A.** The patient into the bunker of treatment: catheter connected to an Ir-192 source (Microselectron HDR remote afterloading). **B.** The course of treatment is controlled on the monitor outside the bunker.

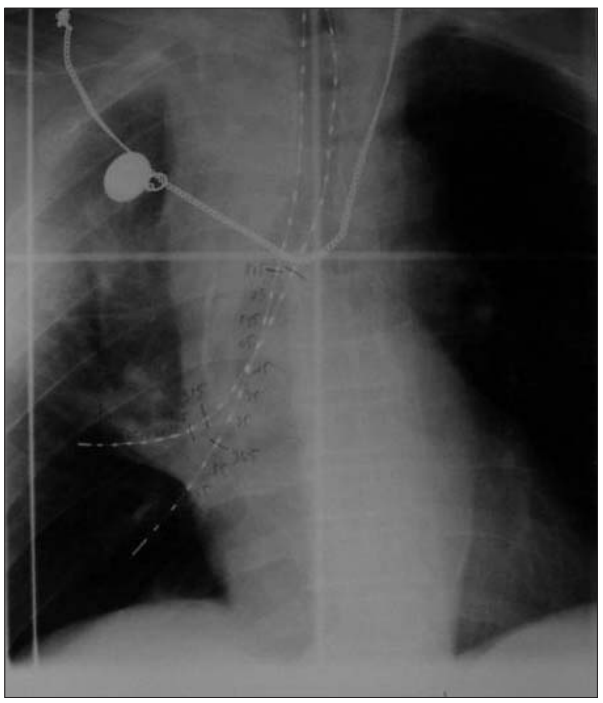

Fig. 3. - Radiograph: two endobronchial catheter inserted.

long axis of the catheter. When the performance status of the patient was low a reduced number course of HDREB sessions was scheduled with the application of 1000 cGy per session instead of 500 cGy. Otherwise, some patients could need supplemental HDREB applications to obtain a satisfying palliative result.

Therapy results Evaluation and Follow-up

Patients were evaluated bronchoscopically, functionally, and clinically after each HDREB session and followed-up after 1 month from the conclusion of a complete HDREB course to assess appearance of complications, and the overall palliative effect. The endoscopic response was considered to be complete if lesions disappeared with negative biopsy one month after the last session; partial if there was a bronchoscopic evidence of a greater than 50% improvement in patency; absent if there was no change or an improvement in patency less than 50%.

The clinical response to treatment was based on a qualitative assessment of the patient's improvement for symptoms such as fatigue, anorexia, chest pain, fever, and especially for cough, dyspnoea and haemoptysis. Lung Cancer Symptom Scale (LCSS) was used to score pre-therapy and post-therapy assessment using a four-point scale: 0, none; 1, mild; 2, moderate; 3, severe (table 1).

Following suggestions of the MRC Cancer Trials Office, palliation was defined in terms of improvement (a reduction of moderate or severe symptoms to mild or moderate), control (no deterioration in mild-moderate symptoms), and prevention (no deterioration in those with no symptoms) [12]. At each control for each negative symptom endpoint was assigned a score of 0 and for positive endpoint 1, giving a range of scores 0-7. Without the intention of weighing up the degree or the duration of palliation, a total score of 0-3 was considered to be poor palliation and 4-7 good palliation [13].

Spirometric analysis for assessment of lung function included maximal expiratory flow-volume loops, lung volumes and, if possible, total lung capacity (TLC). Following GOLD Guide Lines, $FEV_1/FVC<70\%$ confirmed the presence of airflow limitation; the degree of airflow limitation

Table 1. - Chart used for symptomatic assessments [Lung Cancer Symptom Scale, modified]

☐ **Cough**
0. None.
1. Mild: occasionally, not troublesome; no medicines needed.
2. Moderate: daily, troublesome, leads to shortness of breath on occasion.
3. Severe: nearly constant, troublesome, disturb sleep and other normal functioning.

☐ **Dyspnoea**
0. None.
1. Mild: noticed only with major activity, does not limit usual activities.
2. Moderate: present when walking at a normal pace and with minimal activity; supplemental oxygen used occasionally.
3. evere: present even at rest; supplemental oxygen required most of the time.

☐ **Hemoptysis**
0. None.
1. Mild: blood in sputum, less frequently than daily.
2. Moderate: blood in sputum at least daily.
3. Severe: sputum is often purely bloody on a daily basis.

☐ **Fever**
0. None.
1. Mild: occasionally.
2. Moderate: nearly daily.
3. Severe: high fever nearly daily.

☐ **Astenia**
- None.
- Mild: occasionally.
- Moderate: nearly daily.
- Severe: marked, nearly constant.

☐ **Loss of appetite**
- None.
- Mild: occasional loss of appetite that does not interferes with food intake.
- Moderate: occasional loss of appetite that occasionally interferes with food intake.
- Severe: frequent loss of appetite that interferes with food intake; medical intervention for feeding is needed.

☐ **Thoracic pain**
- None.
- Mild: pain control with not narcotic meds.
- Moderate: codeine or codeine-containing oral medications needed.
- Severe: narcotic medications required.

was based on value of FEV_1 as % of the predicted value. A restrictive disventilatory pattern was defined as reduced of TLC or FVC with a normal or only modestly reduced FEV_1/FVC ratio. Measures of CO gas transfer were done when possible with single-breath DLCO.

Adverse effect of HDREB were regularly checked during each session and follow-up.

Statistical Analysis

Data is presented as an absolute number, a median (min.-max. range) or a mean ± SD. Results of the palliative treatment were compared with Wilcoxon's test (no parametric test for paired data). For proportion of repeated observations, the comparison was made with McNemar's symmetry test. Statistical significance was defined as $p<0.05$. (95% confidence interval).

Results

Patients characteristics

From November 2004 to August 2005, 150 day hospital HDREB sessions were carried out on 35 patients with signs and symptoms of central airway obstruction. Patients' median age was: 69 years (range 50-82); M/F 29/6. Primary tumours were twenty-four (22 patients with TNM III-IV); the four metastatic lesions corresponded to three carcinomas of the colon and one renal carcinomas; in eight patients local recurrence of a previously surgically treated tumour or residual malignant lesion on the bronchial resection surface. Only in the two cases of limited invasive primary tumours without nodal involvement and in three cases of residual malignant lesion on the bronchial resection surface after surgical excision, HDREB was carried out with curative intent. All the patients were in ECOG performance status 0-2. Cough, dyspnoea and haemoptysis were present respectively in 34, 30 and 15 patients before treatment. In 12 patients the lesion was located in trachea and/or main stem bronchi (central location, 34.3%); in sixteen patients at level of lobar and/or segmental bronchi (peripheral location, 45.7%); seven patients (20%) with extensive endobronchial lesion. The upper lobe bronchus, endobronchial site of the tumour with highest risk for haemoptysis [1, 14-16], particularly in the case of recurrences [14], was interested in over 37% of cases. Bronchoscopic tumour appearance was: twelve endophytic lesions (34.3%), fourteen submucosal infiltration/extrinsic compression (40%); nine lesions characterised endoscopically as endoluminal projection and submucosal infiltration (25.7%). The main characteristics of the patients are detailed in table 2. HDREB was used as first-line palliation of symptom in eleven patients, and as second-line palliation treatment for persistence of symptoms in 24 patients who underwent conventional therapies (EBR, chemotherapy, etc.). Treatments administered in addition to HDREB as a part of multidisciplinary approach are summarised in table 3.

Treatment response and follow-up

All but seven patients concluded HDREB therapy and follow-up (four patients were lost at the end of brachytherapy and three one month after the last session).

Endoscopic response: was observed in 15/28 patients after 2000 cGy: reduction of endobronchial obstruction <50%, 51-75% and >75% in 5, 6 and 4 patients, respectively. No patient showed a complete endoscopic response one month after the last session of HDREB (CR). In table 4 are

Table 2. - Characteristics of patients undergoing HDREB

N° of patients	35
Male/Female	29/6
Median age (years, range)	69 (50-82)
Tumour (n)	
– NSLC	20
– small cell	4
– metastatic	4
Local tumour recurrency (n)	7
Endobronchial location (%)	
– central	34.3
– peripheral	45.7
– central-peripheral	20
Bronchoscopic appearance (%)	
– endophytic	34.3
– infiltration/compression	40
– endophytic-infiltration	25.7
Symptoms (n)	
– cough	34
– dispnoea	30
– haemoptysis	15

Table 3. - Treatments administered to the patient population before HDREB. Data is presented as a sum of treated patients (total number = 35)

Initial brachytherapy (4 with prior laser therapy)	11
External irradiation	3
Chemotherapy	7
Chemotherapy + External irradiation	6
Surgery	5
Surgery + External irradiation	1
Surgery+ External irradiation + Chemotherapy	2

Table 4. - Endoscopic response at 1 month with respect to type and site of lesion (n=21).

Type of lesion	**Response***
endophytic (n=9)	7/9 (77.8%)
submucosal infiltration (n=8)	6/8 (75%)
infiltration/endophytic (n=4)	3/4 (75%)
Site of lesion	
central (n=7)	6/7 (85.7%)
peripheral (n=10)	7/10 (70%)
central-peripheral (n=4)	3/4 (75%)

* Bronchoscopic evidence of a greater than 50 percent improvement in patency.

showed the endoscopic responses at one month after the last session of HDREB with respect to site (central or peripheral locations) and type (endophytic lesion or submucosal infiltration). All the four patients previously treated with laser-therapy showed an endoscopic response at two days of 25-50%.

Clinical response: dyspnoea decreased after delivering of 2000 cGy (Wilcoxon test, p=0.049), and remained significantly improved (p=0.049) after 1 month. Haemoptysis completely disappeared after one month from the last HDREB session (χ^2 McNemar=4.9; p=0.027). Cough decreased significantly (Wilcoxon test, p=0.019) only after one month. Palliation according to the MRC Cancer Trial Office was obtained in all patients except one.

Lung Function Tests response: obstructive spirometric pattern before treatment was present in 28.6%; restrictive and mixed (obstructive-restrictive) patterns in 31.4% and 28.6%. DLCO was reduced in 77.3% (in 17 patients out of 22 in which a measure of CO gas transfer was carried out). No lung function test index improved significantly at the end of HDREB or after one month following the last session. In the four patients treated also with laser therapy the mean basal values (± SD) were: FVC 3.1±0.88 L, FEV_1/FVC (%) 74.84±11.29, FEV_1 2.36±0.62 L, TLC 5.05±0.89 L; after two days the laser-treatment lung function test did not show an evident change: FVC 2.91±0.86 L, FEV_1/FVC (%) 76.32±8.97, FEV_1 2.16±0.52 L, TLC 5.53±1.67 L.

Complications: no death was related to HDREB treatment. No major complication related to HDREB occurred. A temporary radiation bronchitis without altered canalisation of the bronchial lumen was observed in six patients.

Discussion

In our series of 35 consecutive patients needing palliative treatment for not resectable lung cancer, we found that HDREB can relieve the symptoms related to endobronchial obstruction by lung tumours with a low rate of non-fatal complications. In our study we observed a partial response in 81 % of cases, similarly to the overall endoscopic response of 74-87% reported in the literature [7, 9, 15].

Results of our study confirm the palliative effectiveness of HDREB on symptoms [7, 17-21], resulting haemoptysis to be reduced more quickly in most patients [7, 8, 15, 22-24], and dyspnoea to be controlled after four weeks of HDREB [19]. Previous studies reported subjective improvement following brachytherapy in 20 to 100 percent of patients, depending upon the series and the pre-procedure symptom complex [19-24]. One study of 50 patients who were treated with HDR endobronchial brachytherapy showed a relief of hemoptysis in 24 of 28 patients, breathlessness in 21 of 33, and a cough in 9 of 18 patients [25]. Hemoptysis improves most readily, with a greater than 90 percent response rate in many series. Cough and dyspnea improve less reliably, probably because they frequently are due in part to underlying conditions such as chronic obstructive pulmonary disease, metastatic lymphangitis, or radiation fibrosis [8, 22-26]. A recent systematic review of the literature supported the recommendation of HDREB for symptomatic patients with recurrent endobronchial obstruction previously already treated with external beam radiotherapy (EBR), given that HDREB plus EBR seems to provide better symptom relief than EBR alone [19]. Furthermore, in comparative studies EBR showed to be more effective than HDREB for symptom palliation [19]. In our observational non-comparative study we used HDREB as an initial palliative treatment in a minority of patients with good results. However, most of our patient series received HDREB after EBR or other treatments for lung cancer. Thanks to this multidisciplinary approach most of the patients had a satisfying symptom relief. The choice to use HDREB alone for palliation or in conjunction with other therapies was made on a clinical basis judgment. In fact, our study was not designed to compare HDREB with EBR nor to evaluate the better treatment regimen in strictly selected patients. Furthermore, according to other Authors [5, 7, 8], we treated with HDREB patients who also had oat-cell tumours, who were excluded from other published patient series [1, 19]. In the literature the optimal total dose and its fractionation remain to be determined [1, 3, 4, 7, 19-24, 27], but we found a favourable response to a fractionated 4 weeks HDREB-regimen with a total dose of 2000 cGy. Lung function test did not significantly improve after HDREB in our patient series, consistently with previous reports [28]. Goldman *et al*. [29] showed that FEV_1 and CVF can significantly increase six weeks after brachytherapy (15 Gy at 1 cm in a single fraction), but the greatest improvement were obtained only in patients with tumour occluding a main bronchus, and not in patients with obstruction of the lobar bronchi. Among the endobronchial techniques, only laser photoresection showed improvement of lung function tests [30, 31] after treatment of centrally located lung cancers. Nevertheless, Gelb and co-workers [32], in agreement with our data, found that lung function tests did not reflect the bronchoscopically-visualised improvement in large airway diameter following laser-resection of tumour lesions. However, when indicated, a combination of laser resection and HDREB could strengthen the effect of single techniques in selected cases [19]. In fact, HDREB can stabilize the re-canalising effect of laser-therapy.

HDREB showed to be safe in our patient case histories: no catheter had to be removed as a result of patient's intolerance and no treatment was discontinued for catheter-placement problems. Although the optimal dose and its fractionation remain to be determined, our protocol of 4 sessions at 1-week intervals with a 500 cGy dose per session showed to be safe without severe complications, such as massive haemoptysis and fistulas [1, 17, 22, 23]. The overall incidence of acute complications (hemoptysis, pneumothorax and perfora-

tion) is extremely low in literature [1, 4, 19, 21]. Performed by an experienced endoscopist, HDR brachytherapy has the same acute side-effects as routine bronchoscopy and, therefore, can be easily applied in an outpatient setting.

Limitations of the study

A major limitation of this study is the non-comparative observational design. Moreover, the patient population was not large, but it was one of the largest case series of HDREB from Italy. This study included either patients who underwent HDREB alone and others treated with combined external beam radiotherapy plus HDREB, so making interpretation of results more difficult in term of evaluation of the additional advantage of brachytherapy. Lastly, the reported outcomes (symptom related scores, performance status, lung function tests, endoscopic evidence) could less precisely represent the improvement of quality of life than a designed questionnaire (e.g. EORTC QLQ-30). Nevertheless, this study could give reliable information on the clinical safety and effectiveness of HDREB in the daily practice, in a context of multidisciplinary approach for the palliation of symptoms due to lung cancer.

We conclude that HDREB as a part of a multidisciplinary approach is a good palliative treatment for patients with endoluminal lung cancer in advanced stage, effectively alleviating symptoms in many cases. It also has a good tolerance and a low complication rate.

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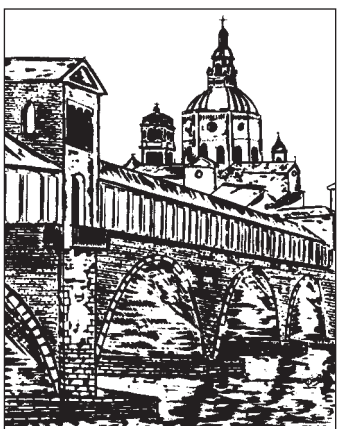

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