Photodynamic therapy (PDT) in early central lung cancer: a treatment option for patients ineligible for surgical resection

Keyvan Moghissi, Kate Dixon, James Andrew Charles Thorpe, Mark Stringer, Christopher Oxtoby

Objective: To review the Yorkshire Laser Centre experience with bronchoscopic photodynamic therapy (PDT) in early central lung cancer in subjects not eligible for surgery and to discuss diagnostic problems and the indications for PDT in such cases.

Methods: Of 200 patients undergoing bronchoscopic PDT, 21 had early central lung cancer and were entered into a prospective study. Patients underwent standard investigations including white light bronchoscopy in all and autofluorescence bronchoscopy in 12 of the most recent cases. Indications for bronchoscopic PDT were recurrence/metachronous endobronchial lesions following previous treatment with curative intent in 10 patients (11 lesions), ineligibility for surgery because of poor cardio-respiratory function in 8 patients (9 lesions) and declined consent to operation in 3 patients. PDT consisted of intravenous administration of Photofrin 2 mg/kg followed by bronchoscopic illumination 24–48 h later.

Results: 29 treatments were performed in 21 patients (23 lesions). There was no procedure-related or 30 day mortality. One patient developed mild skin photosensitivity. All patients expressed satisfaction with the treatment and had a complete response of variable duration. Six patients died at 3–103 months (mean 39.3), three of which were not as a result of cancer. Fifteen patients were alive at 12–82 months.

Conclusion: Bronchoscopic PDT in early central lung cancer can achieve long disease-free survival and should be considered as a treatment option in those ineligible for resection. Autofluorescence bronchoscopy is a valuable complementary investigation for identification of synchronous lesions and accurate illumination in bronchoscopic PDT.

early central lung cancer (ECLC) is defined in this paper as a malignant tumour which is bronchoscopically visible and accessible for cyto/histological sampling; confined to the bronchial lumen and wall; radiologically occult; and without mediastinal lymphadenopathy or distant metastases. Oncologically, a patient with such an ECLC would be an ideal candidate for surgical resection, with a chance of surviving 5 years or more of up to 80% depending on tumour size.2,3 However, in patients with limited respiratory reserve, the standard method of resection may involve an unavoidable loss of functioning tissue unless the topography of the tumour, in relation to the anatomy of the bronchial tree, is favourable for parenchyma-saving bronchoplastic operations. Also, standard resection may adversely affect the quality of survival. Of the non-operative standard treatments, radiotherapy and chemotherapy are not sufficiently target-orientated for these well localised cancers and are attended by unwanted side effects as well as collateral injuries leading to gradual deterioration of pulmonary function. In recent years attention has been focused on endobronchial methods to treat these localised lesions. A number of options such as bronchoscopic Nd:YAG laser application, electrocautery, argon coagulator, cryotherapy and brachytherapy are now available, each with its proponents. The advent of photodynamic therapy (PDT) in the 1970s introduced a new treatment method into the arena of cancer therapy generally, and central lung cancer more specifically.4,5 PDT is a treatment modality which requires a chemical photosensitiser (drug) that is activated by light of a specific wavelength. In the presence of oxygen, interaction between drug and light generates singlet oxygen and other cytotoxic species leading to tissue necrosis. PDT for central lung cancer is carried out bronchoscopically as a two-phase process:

1. Tissue sensitisation: the photosensitising drug is administered intravenously to the patient. Time is allowed for it to be distributed in the body and retained at a higher concentration in the cancer tissue than in the healthy surrounding tissue.

2. Illumination: the pre-sensitised cancer tissue is bronchoscopically exposed to a laser light whose specific wavelength matches the absorption band of the drug. This prompts the photodynamic reaction and necrotic process of the tumour.

In this paper we review the Yorkshire Laser Centre experience in a series of patients with lung cancer whose disease was confined to endobronchial lesions and whose tumour characteristics matched the ECLC definition. They were technically operable with resectable cancers but otherwise ineligible for surgical operation. In the light of this experience, we discuss the diagnostic problems and current indications of such cases.

METHODS

Patients

From March 1991 to March 2005, 200 patients with central type lung cancer received bronchoscopic PDT and were entered into a prospective study. Twenty-one (10.5%) of these patients matched our criteria for ECLC and are the subject of this paper. Before consideration for PDT, every patient had standard clinical, laboratory, imaging and bronchoscopic investigations with cyto/histological confirmation of non-small cell lung cancer (NSCLC). As the Yorkshire Laser Centre is a tertiary
referral centre, in most cases these investigations had been carried out by the referral source and the institutional review process had been carried out by the respective multidisciplinary team. In the remaining minority, the Yorkshire Laser Centre team undertook the investigations and reviewed the treatment protocol. Unsuitability for surgical operation and selection for PDT had also been evaluated by the referring source and/or the multidisciplinary team in consultation with the Yorkshire Laser Centre team.

Inclusion and selection of patients for bronchoscopic PDT in this cohort was based on the following criteria: (1) ECLC ineligible for surgical resection on account of poor general condition, cardio/respiratory function insufficiency, metachronous endobronchial tumour after previous pneumonectomy and/or not consenting to surgical resection; (2) good performance status (PS) ≤2 on the World Health Organisation (WHO) scale.

Patients were re-evaluated at our centre by:

- Review of previous investigation and staging procedures.
- Recording of symptoms and PS using the WHO scale.
- General clinical examination and spirometry.
- Chest radiographs and CT scans.
- Bronchoscopy, in which location and extent of the tumour in length and its projection into the bronchial lumen were noted. Availability of the Xillix Laser Induced Fluorescence Endoscopy (LIFE) Lung system (Xillix Technologies Corporation, Canada) in the last 7 years permitted autofluorescence bronchoscopy (AFB) in addition to white light bronchoscopy (WLB). In all cases biopsy and/or brush sampling of lesions and areas of abnormal fluorescence for cyto/histological examination accompanied bronchoscopic assessment.

Every patient was fully informed and counselled on the risks and benefits of PDT, including possible adverse events. An informed consent form was signed by all patients prior to PDT.

**PDT protocol**

The PDT protocol has previously been described in detail. Briefly, it consisted of intravenous administration of the photosensitisiser (Porflimer sodium: Photofrin; Axcan Pharma Inc, Canada) 2 mg/kg body weight followed by bronchoscopic illumination 24–72 h later using 630 nm laser light. The light source was initially a copper vapour/dye laser (Oxford Lasers Ltd, UK). For the past 7 years a 630 nm diode laser (Diomed Ltd, UK) was used. Intestinal illumination was used when the tumour was clearly visible at bronchoscopy projecting into the bronchial lumen. In this case the diffusing end of the light delivery fibre was inserted into the substance of the tumour. Surface illumination was used for superficial tumours, when the light delivery fibre/diffuser was placed in the lumen of the bronchus (intraluminal illumination) for lesions >1 cm in length or a microlens was used to project the light forward over the mucosal surface for tumours ≤1 cm in diameter. All except two of our cases had surface illumination. The light dose was 150–200 J/cm of the tumour (400 MW × 375–500 s).

**Instrumentation**

In all except two cases, bronchoscopic PDT was carried out under general anaesthesia using both the rigid instrument for ventilation and the flexible fibreoptic instrument for localisation of the tumour and target illumination. The latter is achieved by introducing the optical light delivery fibre into the biopsy channel of the flexible bronchoscope so that it can be directed to the appropriate site for illumination.

**Outcome**

Assessment of results was made on the basis of:

- Mortality.
- Complications.
- Patient’s subjective satisfaction with treatment.
- Pathological response to treatment and its duration using the following definitions:
  - Complete response: macroscopic and microscopic absence of tumour in the treated area at bronchoscopy.
  - Partial response: bronchoscopic absence of tumour macroscopically but microscopic presence at cyto/histological sampling.
  - No response: no change in macroscopic appearance and positive cyto/histology for malignancy.

- Patient survival expressed in months.

Patients were followed up at 6 weeks, 3 months and 6 months after treatment and 6-monthly thereafter until death. On each occasion, chest radiography and bronchoscopic assessment were carried out. Patients with evidence of endobronchial lesions/recurrence were re-treated by PDT or had other treatment methods as appropriate.

**Analysis of data**

Kaplan-Meier analysis was undertaken using survival at 1–5 years. A survival curve (censored) with a cut off at 5 years was also constructed.

**RESULTS**

There were 21 patients (16 men) of mean age 66.2 years (range 53–86). Most patients presented with cough or dyspnoea. Blood staining of sputum was recorded in three patients. The ineligibility for surgical resection and reasons for referral to PDT were as follows:

- 10 patients had had previous treatment for lung cancer with curative intent. Of these:
  - 6 had undergone pulmonary resection, 5 of whom had tumour recurrence at the bronchial stump and one had an endobronchial metachronous tumour 17 years after pneumonectomy.
  - 4 had external beam radiotherapy (EBR) (n = 1), bronchoscopic YAG laser treatment + EBR (n = 1), brachytherapy (n = 1) and YAG laser therapy (n = 1).
  - 11 patients were either unsuitable for surgery (n = 8) or declined surgical resection (n = 3).

Twenty-three lesions were identified in the 21 patients. Five lesions were classified by the histopathologist as carcinoma in situ. The characteristics of the patients and their lesions are shown in table 1.

Twenty-nine bronchoscopic treatments were undertaken in the 21 patients; 14 patients had one treatment, 6 had two, and 1 had three treatments. All treatments were carried out as a day case procedure and no patient needed re-admission to hospital following PDT other than pre-arranged visits. There was no procedure-related or 30 day mortality. One patient presented with a mild photosensitivity skin reaction (skin burn) with slight erythema of hands and face that settled after 3 days. Every patient, including the one who had skin burn, expressed satisfaction with the treatment.

Complete response was recorded in all patients for 2 months to >5 years (the 2 month response was in patient 7 who died...
from myocardial infarction 3 months after treatment). Seven patients had local recurrence of their tumour at 6–15 months after the first PDT, all of whom were treated by a second (one by a third) bronchoscopic PDT. Six patients have died at 3–103 months (mean survival 39.3 months), three from non-
cancer related causes (patients 1, 7, and 12). Fifteen patients were alive at 12–82 months. Table 2 shows the survival at 1–5 years.

**DISCUSSION**

We adopted the term ‘early central lung cancer’ for a
determinant group of patients in whom the common
localisation of neoplastic lesions confined to the
bronchial lumen and wall with no lymph node involvement or metastases. We acknowledge that the adjective ‘early’ does not
express a clear pathological definition and, as such, contravenes
the conventional rules of staging based on the existing Tumour
Node Metastases (TNM) classification. Nevertheless, ECLC
does represent a subset of endobronchial tumours which, by
reason of their heterogeneity in location within the bronchial
tree, extent and number of lesions, cannot be accommodated in
the existing TNM grouping. Notwithstanding its imperfection,
the term has been used in relation to bronchoscopic PDT since
1982 by many authors, some of whom have provided
definitions similar to ours. Kato et al introduced a cut off
lesion size of <1 cm in their definition of ECLC.

We have not considered the size or number of mucosal
lesions as exclusion criteria as long as the lesion characteristics
are fitted with our definition of ECLC. This is because our method
of illumination for lesions >1 cm is to use an appropriate
intraluminal cylindrical diffuser whose length matches the
length of the lesion, which is placed over the whole extent of
the cancer. This method allows efficient illumination of a
mucosal lesion irrespective of its length within the range of 1–5
cm (available range of cylindrical diffusers). We do never-
theless acknowledge the relevance of the size of the mucosal
lesion in relation to the extent of lymph node involvement and
the depth of bronchial wall infiltration.

It is important to point out that both the definition and the
diagnosis of ECLC are governed by diagnostic tools which are
available at any time to map out the extent of tumour on the
surface and in the depth of bronchial wall and to determine the
degree of lymph node involvement. This is well expressed in a
review article by Pasic et al which highlights the problems
associated with clinical staging and definition of ‘earliness’ of
central lung cancer.

The investigation and staging procedure in our patients were
carried out as per British Thoracic Society guidelines, which
recommend WLB and CT scanning to diagnose early
endobronchial cancer. In recent years, developments in AFB,

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**Table 1** Characteristics of the patients and their lesions

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<th>Sex</th>
<th>Site</th>
<th>No</th>
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<th>TNM</th>
<th>Previous treatment</th>
<th>PDT</th>
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<td>1</td>
<td>11/01/2005</td>
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A, alive; AD, adenocarcinoma; BCY, brachytherapy; D, died; EBR, external beam radiotherapy; I, intermediate bronchus; [L], left; LL, lower lobe bronchus; LBY, lobectomy; M, main bronchus; Med, middle lobe bronchus; FNY, pneumonectomy; [R], right; SQ, squamous cell carcinoma; TIS, carcinoma in situ; UL, upper lobe bronchus; YAG, Nd:YAG laser.

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**Table 2** Survival at 1–5 years

<table>
<thead>
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<th>Year</th>
<th>No of deaths</th>
<th>Mean survival</th>
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<td>21</td>
<td>4</td>
<td>32.12</td>
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<td>4 years</td>
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<td>4</td>
<td>41.36</td>
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<tr>
<td>5 years</td>
<td>21</td>
<td>4</td>
<td>50.61</td>
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endobronchial ultrasonography (EBUS) and positron emission tomography (PET) scanning have contributed to a better definition of the extent of endobronchial preinvasive lesions and determination of the depth of cancer invasion into the bronchial wall, thus providing more accurate staging of lesions.

AFB exhibits more accurately the extent of mucosal preneoplastic and early neoplastic changes than WLB. It has a higher discriminative power than WLB and allows intelligent sampling as well as more accurate lesion targeting for endobronchial treatment such as bronchoscopic PDT.\cite{21, 22} AFB was used in 12 patients in this series and allowed the discovery of carcinoma in situ synchronously and in addition to the lesions already visualized by WLB in two patients.

Although EBUS was first described over 10 years ago, it is not yet in widespread use.\cite{23} PET scanning has been shown to be superior to CT scanning in lung cancer staging.\cite{24} Its value in ECLC for definition of T factor and bronchial wall infiltration has also been tested in a small number of cases with encouraging preliminary results.\cite{25} We believe that AFB and PET scanning should be an integral part of investigations for patients undergoing endoscopic treatment for ECLC.

The indication for PDT in our series was essentially an identifiable ECLC in patients ineligible for surgical resection or those who had declined surgical operation. This follows the current generally accepted principle that resectional surgery should be the primary treatment of choice for all patients who are oncologically suitable and are otherwise fit and accept the undertaking. Japanese authors suggest that, in selected lesions and clearly indicated that an overall majority of carcinoma in situ lesions (28 of 32) persisted or progressed in a 2 year period.\cite{31} Similar observations have been recorded by other authors.\cite{22, 31} Considering that PDT is a non-invasive therapy, from the patient’s perspective there is more to be gained by treating carcinoma in situ by PDT than by leaving it to the chance that it might not become an invasive carcinoma or that it could regress. We therefore believe it to be prudent to continue the practice of treating patients with carcinoma in situ with PDT. It is important to bear in mind that PDT is one of a number of bronchoscopic treatments and that, as yet, there has been no comparative study to suggest its relative therapeutic value when set against an other endobronchial treatment. A study by Mathur \textit{et al.}\cite{14} based on a literature review of endobronchial therapies for early superficial bronchial carcinoma, suggests the advantages and effectiveness of PDT compared with other methods (ie, Nd:YAG laser, electrosurgery, cryotherapy and brachytherapy).

The cost effectiveness of the various endobronchial methods in ECLC is an issue of increasing relevance to the current...
economic climate of healthcare finance which needs evaluation. The comparative cost effectiveness of PDT set against other endobronchial therapies has not been evaluated. At first sight it seems that the high cost of photosensitizer would make PDT more expensive than others. However, this requires evaluation in the light of clinical effectiveness in a properly conducted trial. Kato et al have compared the cost effectiveness of PDT in early stage lung cancer with surgical resection. Their findings suggest that the cost of surgery is 1.3 times higher than PDT.

There is an urgent need for a phase III multicentre trial to determine the relative value of bronchoscopic PDT in patients with ECLC compared with other endobronchial treatment. However, in the era of patient choice and in the ongoing economic climate, the prospect of such a trial seems fairly remote. In the meantime, we believe that patients with inoperable ECLC should be given the choice of bronchoscopic PDT as a treatment option while effort is being made to achieve properly designed trials.

In conclusion, this study indicates that a subset of patients with ECLC confined to the bronchial tree can be treated safely by PDT with curative intent. AFB and PET scanning are an important part of the investigation. Patients treated by bronchoscopic PDT need to enter into a programme of surveillance which includes chest radiography and endoscopy using standard WLB as well as AFB. An appropriate planned phase III multicentre study is warranted, taking into account the cost compared with other endobronchial therapies and surgery. In the meantime, PDT should be offered to suitable patients as a treatment option.

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