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

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Abstract

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

**Subjects and methods:** Amongst 200 patients undergoing bronchoscopic PDT, 21 had early central lung cancer and were entered into a prospective study. Patients had standard work up 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 declining consent to operation in 3 patients. PDT method consisted of intravenous administration of Photofrin 2 mg/kg bw followed by bronchoscopic illumination 24–48 hours later.

**Results:** 29 treatments were carried out in 21 patients (23 lesions). There was no procedure-related or 30 day mortality. One patient developed mild skin-photosensitivity. All patients expressed satisfaction to treatment and had complete response for variable duration. Six patients died from 3-103 months (mean 39.3), 3 not in consequence of cancer. 15 patients are alive from 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 complimentary investigation in such cases, for diagnosis identification, of synchronous lesions and accurate illumination in bronchoscopic PDT.

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Introduction:

In the context of this paper early central lung cancer (ECLC) is defined as a malignant tumour which is:
1. Bronchoscopically visible and accessible for cyto/histological sampling.
2. Confined to the bronchial lumen and wall.
3. Radiologically occult.
4. Without mediastinal lymphadenopathy or distant metastases.

Oncologically, a patient with such an ECLC would be an ideal candidate for surgical resection, with as high as an 80% chance of surviving 5 years or more depending on tumour size.[1][2] However, in patients with limited respiratory reserve, the standard method of resection may involve an unaffordable loss of functioning lung 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 1970’s introduced a new treatment method into the arena of cancer therapy generally and central lung cancer more specifically.[3][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 compared with 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 (YLC) 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
From March 1991 to March 2005, two hundred patients with central type lung cancer received bronchoscopic PDT and were entered into a prospective study. Twenty-one (10.5%) of these patients match our criteria for ECLC and are the subject of this article. Prior to consideration
for PDT, every patient had standard clinical, laboratory, imaging and bronchoscopic investigations with cyto/histological confirmation of non-small cell lung cancer (NSCLC). The YLC being a tertiary referral centre, in the majority of cases these investigations had been carried out by the referral source and the institutional review process had been carried out by the respective multi-disciplinary team (MDT). In the remaining minority, the YLC team undertook the work-up and reviewed the treatment protocol. Unsuitability for surgical operation and selection for PDT had also been evaluated by the referring source and/or the MDT in consultation with the YLC team.

Inclusion and selection of patients for bronchoscopic PDT in this cohort was based on the following criteria:

- Patients with 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.
- Good Performance Status (PS) ≤2 of the World Health Organisation (WHO) scale.

At our centre, patients were re-evaluated through:

- Review of previous investigation and staging procedures.
- Recording of symptoms and performance status (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 LIFE (Laser Induced Fluorescence Endoscopy) Lung” system (Xillix Technologies Corp, Canada) in the last seven 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: This has previously been described in detail.[6] Briefly, it consisted of intravenous administration of the photosensitiser (Porfimer sodium: Photofrin® Axcan Pharma Inc, Canada) 2mg/kg/body weight followed by bronchoscopic illumination 24–72 hours later using 630nm laser light. The light source was initially a copper vapour/dye laser (Oxford Lasers Ltd, UK). For the past 7 years a 630nm diode laser (Diomed Ltd, UK) was used. Interstitial 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 >1cm in length or a microlens was used to project the light forward over the mucosal surface for tumours ≤1cm in diameter. All except two of our cases had surface illumination. The light dose was 150-200 J/cm of the tumour (400 mw x 375-500 seconds).

Instrumentation. In all, except for 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.[6] 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.

Assessment of results was made on the basis of:

- Mortality
- Complications
- Patient’s subjective satisfaction to treatment
- Pathological response to treatment and its duration. The following definitions were adopted:
  - Complete response (CR): macroscopic and microscopic absence of tumour in the treated area at bronchoscopy
  - Partial response (PR): bronchoscopic absence of tumour macroscopically but microscopic presence at cyto/histological sampling.
  - No response (NR): 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 six 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.

Statistics: Kaplan Meier analysis was undertaken using survival at 1 to 5 years. Also, a survival curve (censored) with a cut off at 5 years was constructed.

Results

Table 1 shows the characteristics of the patients and their lesions.
There were 21 patients; 16 male, 5 female aged 53 – 86 years (mean 66.2). Most patients presented with cough or dyspnoea. Bloodstaining of sputum was recorded in 3 patients. The ineligibility for surgical resection and reasons for referral to PDT consisted of:

- 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 patients had: external beam radiotherapy (EBR) (1), bronchoscopic YAG laser treatment + EBR (1), brachytherapy (1) and YAG laser therapy (1).

- 11 patients were either unsuitable for surgery (8) or declined surgical resection (3).

Twenty-three lesions were identified in the 21 patients. Five lesions were classified by the histopathologist as carcinoma in situ (CIS). Twenty-nine bronchoscopic treatments were undertaken in the 21 patients; 14 patients had one treatment, 6 had two and 1 had three treatments respectively. 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 or 30 days mortality. One patient presented with 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 to the treatment.

CR was recorded in all patients for a duration between 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 between 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 between 3-103 months (mean survival of 39.3 months), 3 from non-cancer related causes (patients 1, 7, 12 respectively). 15 patients are alive between 12 and 82 months. Table 2 presents survival at 1-5 years.

Table 2

<table>
<thead>
<tr>
<th>Survival as at:</th>
<th>Number who died</th>
<th>Mean survival at each time point</th>
<th>95% Confidence Interval for survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>21</td>
<td>11.57</td>
<td>10.75 - 12.39</td>
</tr>
<tr>
<td>2 years</td>
<td>21</td>
<td>22.55</td>
<td>20.04 - 25.07</td>
</tr>
<tr>
<td>3 years</td>
<td>21</td>
<td>32.12</td>
<td>28.09 - 36.14</td>
</tr>
<tr>
<td>4 years</td>
<td>21</td>
<td>41.36</td>
<td>35.30 - 47.42</td>
</tr>
<tr>
<td>5 years</td>
<td>21</td>
<td>50.61</td>
<td>42.30 - 58.91</td>
</tr>
</tbody>
</table>

Figure 1 shows the Kaplan Meier survival curve up to 5 years. It is evident from Table 2 that confidence interval associated with mean survival data increases significantly from year 1 to 5. This is a consequence of the small number of patients in the study overall and the smaller numbers contained within each time period.

**Discussion**

We adopted the term “early central lung cancer” for a heterogeneous group of patients in whom the common denominator was localised 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, early central lung cancer 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 akin to ours. Kato et al introduced a cut off lesion size of <1cm 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 fitted with our definition of ECLC. This is because our method of illumination for lesions >1cm 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 nevertheless...
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.[17][18]

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.[19]

The work up and staging procedure in our patients were carried out as per British Thoracic Society guidelines, which recommend WLB and CT scanning.[20] Until recently clinicians had to rely on chest radiography, CT of thorax and standard white light bronchoscopy with multiple biopsies to diagnose early endobronchial cancer. In recent years development in AFB, endobronchial ultrasonography (EBUS) and Positron Emission Tomography (PET) scanning have contributed in better defining the extent of endobronchial pre-invasive lesions and in determining the depth of cancer invasion into the bronchial wall, thus providing more accurate staging of lesions.

AFB exhibits more accurately the extent of mucosal pre and early neoplastic changes than WLB. It has higher discriminative power than WLB and allows intelligent sampling as well as more accurate lesion targeting for endobronchial treatment such as bronchoscopic PDT.[15][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 visualised by WLB in two patients.

Although EBUS was first described over 10 years ago, it is not yet in widespread use.[13][23] PET scan has been shown to be superior than CT in lung cancer staging.[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.[25] We believe AFB and PET scan should be an integral part of investigations for patients undergoing endoscopic treatment for ECLC.

Indication for PDT in our series was, essentially, that of 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 patients with ECLC (lesion <1cm in diameter), long term CR is such that PDT could be considered as a primary treatment option.[8][16] Also, Cortese et al carried out bronchoscopic PDT as an alternative to surgery in 21 patients (23 lesions) with early superficial cancer who were eligible for surgery.[9] Following PDT the patients underwent close endoscopic follow up; 10 patients subsequently needed resection of whom 3 had N1 disease in the resected specimen. Nine patients (nearly 45%) were spared surgical resection within the mean follow up duration of 68 months. We believe that this policy is problematic since, firstly, one cannot identify those patients who have a good prognosis and in whom surgery can be avoided. Also, some patients will, inevitably, develop disease and become inoperable whilst under surveillance.

For the present time, we continue to believe that surgical resection should be considered as the first treatment option. We do, however, feel that with progress in refining diagnostic tools and molecular methods the attitude of “surgical resection as the first option” will change. We are already witnessing such a change in cases of ECLC and synchronous lesions shown through AFB for which we advocate that bronchoscopic PDT should be the preferred treatment option.
since, in many of these, bronchoplastic procedures without loss of parenchyma are technically unfeasible.

Our results show that patients with ECLC respond to PDT for variable periods of CR. In the majority of cases, long disease-free survival is achievable. This accords with the observations of other authors and literature review.[8] [16] [26] [27] Following bronchoscopic PDT in ECLC, patients should be followed up for life with periodic bronchoscopic examinations; the reason being that the duration of CR is unpredictable. Also, with the recent use of fluorescence bronchoscopy, many investigators find synchronous or metachronous superficial endobronchial tumours pointing to field cancerization. The early diagnosis of these could offer the potential for their eradication by endoscopic methods.[28] [29] [30] We believe such multifocal lesions constitute a major indication for bronchoscopic PDT. In this series, the use of AFB revealed 2 separate lesions in two patients which were both successfully treated by PDT.

The management of local recurrence of tumour following bronchoscopic PDT should be tailored to the individual circumstances of the case using multi-modal therapies (chemo/radiation or other bronchoscopic methods). Considering the ineligibility of our patients for surgical resection and the fact that all our cases of tumour recurrence responded to initial PDT, we repeated the treatment. Furukawa et al used additional PDT, surgical resection (in resectable cases) and/or brachytherapy in 9 of the cases of recurrence after PDT in 77 lesions.[31] Interestingly, all the lesions treated were initially <1cm in diameter.[31]

In all our cases we used Photofrin® (Porfimer Sodium) since the drug is licenced in the UK for endoscopic PDT in lung cancer and we are accustomed to its use.[6] [27] [30] Some authors have used other newer photosensitisers for bronchoscopic PDT for ECLC but these are not in general use in the UK.[26] [32]

Five lesions in our series were carcinoma in situ (CIS) (Table 1). These treatments were based on the strong indication that at least some such pre-invasive lesions, including CIS, will progress to invasive cancers in the course of time.[22] [33] Also, one should consider that a biopsy sample showing CIS may not be representative of the lesion/s as a whole. Nevertheless, the natural history of pre-cancerous lesions including that of CIS is not totally clear. Bota et al reported on the follow up of 416 bronchial intraepithelial lesions and clearly indicated that an overall majority of CIS lesions (28 of 32) persisted or progressed in a two-year period.[33] Similar observations have been recorded by other authors.[22] [34]. Considering that PDT is a non-invasive therapy, from the patient’s perspective there is more to be gained by treating a CIS lesion by PDT rather than 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 other endobronchial treatment. A study by Mathur et al based on literature review of endobronchial therapies for early superficial bronchial carcinoma tends to suggest the advantages and effectiveness of PDT compared with other methods; that is Nd:YAG laser, electrocautery, cryotherapy and brachytherapy.[14] However, the cost-effectiveness of the various endobronchial methods in ECLC is an issue of increasing relevance to the current economic climate of health care finance which needs evaluation. Comparative cost effectiveness of PDT set against other endobronchial therapies has not been evaluated. At first sight it seems that the high cost of photosensitiser 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 compared with surgical resection.[35] This suggests 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 whilst effort is being made to achieve properly designed trials.

**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 scan are an important part of the work up. 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 multi-centre 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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**Notes**
None of the authors have any competing interest.

Ethical Committee approval was not necessary for this study.

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**Figure Legends**

**Figure 1** Survival function out to 5 years for 21 patients undergoing bronchoscopic PDT for early central lung cancer.
References


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