LUNG CANCER

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

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Objectives: 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 cardiorespiratory 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.[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 1970s introduced a new treatment method into the arena of cancer therapy generally, and central lung cancer more specifically.[3–5]

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

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Abbreviations: AFB, autofluorescence bronchoscopy; EBR, external beam radiotherapy; EBUS, endobronchial ultrasonography; ECLC, early central lung cancer; PDT, photodynamic therapy; PET, positron emission tomography; WLB, white light bronchoscopy

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 auto-fluorescence 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.[6] Briefly, it consisted of intravenous administration of the photosensitiser (Porfimer 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. 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 >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.[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.

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

Table 1 Characteristics of the patients and their lesions

			Lesion				PDT			
No	Age	Sex	Site	No	Cytology/ histology	TNM	Previous treatment	No of treatments	Date of 1st treatment	Survival (months)
1	71	F	(L) UL and (L) M	1	AD	T2N0M0	YAG	1	15/04/1992	D 103
2	69	M	(L) UL	1	AD	T1N0M0	EBR	2	08/09/1997	D 35
3	62	M	(L) UL	1	SQ	TISN0M0	None	3	20/04/1998	D 63
4	53	M	(R) UL	1	SQ	T1N0M0	None	1	23/03/1999	A 82
5	63	M	(R) LL	1	SQ	TISN0M0	None	1	13/04/1999	A 81
6	69	M	(R) UL	1	SQ	TISN0M0	LBY	1	14/09/1999	A 75
7	73	M	(R) UL	1	SQ	T1N0M0	None	1	22/11/1999	D 3
8	67	F	(R) M + UL	1	SQ	T1N0M0	YAG + EBR	1	26/06/2001	D 16
9	54	M	(R) MidL + I	1	SQ	T1N0M0	None	2	24/07/2001	A 52
10	74	M	(L) UL	1	SQ	T1N0M0	None	1	23/04/2002	A 46
11	63	F	(L) UL + M	2	Carcinoid	T2N0M0	None	1	27/05/2002	A 44
12	86	M	(L) M	1	SQ	T2N0M0	LBY + EBR	2	24/06/2002	D 16
13	67	M	(R) I	1	SQ	T1N0M0	PNY	2	25/06/2002	A 43
14	67	F	(R) UL + M	1	SQ	T1N0M0	None	2	25/06/2002	A 43
15	79	M	(L) UL	1	SQ	T1N0M0	None	1	01/07/2002	A 43
16	71	M	(L) UL	1	SQ	T1N0M0	None	1	12/08/2003	A 26
17	55	M	(L) LL	2	SQ	T1N0M0 + TISN0M0	PNY + EBR	1	20/04/2004	A 21
18	67	F	(L) UL	1	SQ	T1N0M0	BCY	1	07/05/2004	A 20
19	65	M	(R) I	1	SQ	TISN0M0	None	1	28/09/2004	A 15
20	67	M	(R) UL	1	SQ	N0M0	PNY	2	09/11/2004	A 14
21	73	M	(L) LL	1	SQ	T1N0M0	LBY	1	11/01/2005	A 12

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; MidL, middle lobe bronchus; PNY, pneumonectomy; (R), right; SQ, squamous cell carcinoma; TIS, carcinoma in situ; UL, upper lobe bronchus; YAG, Nd:YAG laser.

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 are alive at 12–82 months. Table 2 shows the survival at 1–5 years.

Figure 1 shows the Kaplan-Meier survival curve up to 5 years. It is evident from table 2 that the 95% CI associated with the 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.[7] 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.[4 8–15] Kato et al introduced a cut off lesion size of <1 cm in their definition of ECLC.[16]

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 >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 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 investigation 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 scanning of the thorax and standard WLB with multiple biopsies to diagnose early endobronchial cancer. In recent years, developments in AFB,

Table 2 Survival at 1–5 years

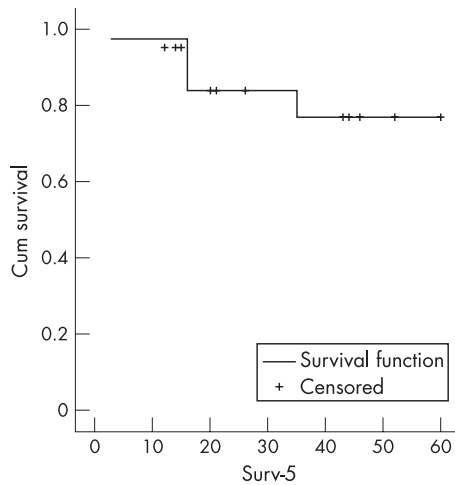|	No	No of deaths	Mean survival	95% CI for survival
1 year	21	1	11.57	10.75 to 12.39
2 years	21	3	22.55	20.04 to 25.07
3 years	21	4	32.12	28.09 to 36.14
4 years	21	4	41.36	35.30 to 47.42
5 years	21	4	50.61	42.30 to 58.91

Figure 1 Survival function up to 5 years for 21 patients undergoing bronchoscopic photodynamic therapy for early central lung cancer.

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 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 scanning has been shown to be superior to CT scanning 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 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 patients with ECLC (lesion <1 cm in diameter), the long-term complete response 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, 3 of whom had N1 disease in the resected specimen. Nine patients (nearly 45%) were spared surgical resection during the mean follow-up period of 68 months. We believe that this policy is problematic since 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 while 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 complete response. In most cases, long disease-free survival is achievable. This accords with the observations of other authors and literature reviews.[8 16 26 27] Following bronchoscopic PDT in ECLC, patients should be followed up for life with periodic bronchoscopic examinations because complete response is unpredictable. Also, with the recent use of fluorescence bronchoscopy, many investigators find synchronous or metachronous superficial endobronchial tumours pointing to field cancerisation. Early diagnosis of these could offer the potential for their eradication by endoscopic methods.[28–30] We believe such multifocal lesions constitute a major indication for bronchoscopic PDT. In this series the use of AFB revealed two 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 multimodal treatments (chemotherapy/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 nine cases of recurrence after PDT in 77 lesions.[31] Interestingly, all the lesions treated were initially <1 cm in diameter.[31]

In all our cases we used Photofrin (Porfimer sodium) since the drug is licensed 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 (table 1). These treatments were based on the strong indication that at least some such preinvasive lesions, including carcinoma in situ, will progress to invasive cancers in the course of time.[22 33] Also, one should consider that a biopsy sample showing carcinoma in situ may not be representative of the lesion(s) as a whole. Nevertheless, the natural history of pre-cancerous lesions (including carcinoma in situ) 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 carcinoma in situ lesions (28 of 32) persisted or progressed in a 2 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 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 et al,[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, electrocautery, crytherapy 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 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[35] 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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REFERENCES
1 **Koike T**, Terashima M, Takizawa T, et al. Surgical results for centrally located early stage lung cancer. Ann Thorac Surg 2000;**70**:1176–9.
2 **Terzi A**, Pelosi G, Falezza G, et al. Early hilar lung cancer – clinical aspects and long term survival. Identification of sub group of stage IA patients with more favourable prognosis. Lung Cancer 2000;**27**:119–24.
3 **Dougherty TJ**, Kaufman JE, Goldfarb A, et al. Photoradiation therapy for the treatment of malignant tumours. Cancer Res 1978;**38**:2628–35.
4 **Hayata Y**, Kato H, Konaka C, et al. Photoradiation therapy with haematoporphyrin derivative in early and stage I lung cancer. Chest 1982;**81**:269–77.
5 **Balchum OJ**, Doiron DR, Huth GC. Photoradiation therapy of endobronchial lung cancers employing the photodynamic action of the haematoporphyrin derivative. Lasers Surg Med 1984;**4**:13–30.
6 **Moghissi K**, Dixon K, Stringer M, et al. The place of bronchoscopic photodynamic therapy in advanced unresectable lung cancer: experience 100 cases. Eur J Cardiothorac Surg 1999;**15**:1–6.
7 **Mountain CF**. Revisions in the International System for staging lung cancer. Chest 1997;**111**:1710–7.
8 **Furuse K**, Fukuoka M, Kato H, et al. A prospective phase II study on photodynamic therapy with Photofrin II for centrally located early-stage lung cancer. J Clin Oncol 1993;**11**:1852–7.
9 **Cortese DA**, Edell ES, Kinsey JH. Photodynamic therapy for early stage squamous cell carcinoma of the lung. Mayo Clin Proc 1997;**72**:595–602.
10 **Lam S**, Haussinger K, LeRoy M, et al. Photodynamic therapy (PDT) with Photofrin, a treatment with curative potential for early stage superficial lung cancer. Proceedings 34th Annual Meeting of the American Society of Clinical Oncology. Los Angeles, 1998.
11 **Vermylen P**, Pierard P, Roufosse C, et al. Detection of bronchial pre-neoplastic lesions and early lung cancer with fluorescence bronchoscopy: a study about its ambulatory feasibility under local anaesthesia. Lung Cancer 1999;**25**:161–8.
12 **Sutedja TG**, Postmus PE. Photodynamic therapy for treating early stage lung cancer. Monaldi Arch Chest Dis 2001;**56**:128–31.
13 **Herth F**, Becker HD. New aspects in early detection and local staging of early lung cancer. Lung Cancer 2001;**34**:S7–11.
14 **Mathur PN**, Edell E, Sutedja TG, et al. Treatment of early stage non small cell lung cancer. Chest 2003;**123**:176–80S.
15 **Zeng H**, McWilliams A, Lam S. Optical spectroscopy and imaging for early lung cancer detection: a review. Photodiagn Photodyn Ther 2004;**1**:111–2.
16 **Kato H**, Okunaka T, Shimatani H. Photodynamic therapy for early stage bronchogenic carcinoma. J Clin Laser Med Surg 1996;**14**:235–8.
17 **Nagamato N**, Saito Y, Ohta S, et al. Relationship of lymph node metastasis to primary tumour size and microscopic appearance of roentgenographically occult lung cancer. Am J Surg Pathol 1989;**13**:1009–13.
18 **Usuda K**, Saito Y, Nagamato N, et al. Relation between bronchoscopic findings and tumour size of roentgenographically occult bronchogenic squamous cell carcinoma. J Thorac Cardiovasc Surg 1993;**106**:1098–103.
19 **Pasic A**, Postmus PE, Sutedja TG. What is early lung cancer? A review of the literature. Lung Cancer 2004;**45**:267–77.
20 **British Thoracic Society and Society of Cardiothoracic Surgeons of Great Britain and Ireland**. Guideline on the selection of patients with lung cancer for surgery. Thorax 2001;**56**:89–108.
21 **Lam S**, Kennedy T, Unger M, et al. Localisation of intraepithelial neoplastic lesions by fluorescence bronchoscopy. Chest 1998;**113**:696–702.
22 **Venmans BJ**, van Boxem TJ, Smit EF, et al. Outcome of bronchial carcinoma in situ. Chest 2000;**117**:1572–6.
23 **Miyazu Y**, Miyazawa T, Kurimoto N, et al. Endobronchial ultrasonography in the assessment of centrally located early-stage lung cancer before photodynamic therapy. Am J Respir Crit Care Med 2002;**165**:832–7.
24 **Pieteman RM**, Van Putton JW, Meuzelaar JJ, et al. Pre-operative staging of non small cell lung cancer with positron-emission tomography. N Engl J Med 2000;**343**:254–61.
25 **Pasic A**, Brokx HA, Comans, et al. Detection and staging of pre-invasive lesions and occult lung cancer in the central airway with 18F fluorodeoxy glucose positron emission tomography a pilot study. Clin Cancer Res 2005;**11**:6186–9.
26 **Kato H**, Furukawa K, Sato M, et al. Phase II clinical study of photodynamic therapy using mono-L-aspartyl chlorine 6 and diode laser for early superficial squamous cell carcinoma of the lung. Lung Cancer 2003;**42**:103–11.
27 **Moghissi K**, Dixon K. Is bronchoscopic photodynamic therapy an option in lung cancer? Eur Respir J 2003;**22**:535–41.
28 **Pierard P**, Vermylen P, Bosschaerts T, et al. Synchronous roentgenographically occult lung cancer in patients with resectable primary lung cancer. Chest 2000;**117**:779–85.
29 **van Rens MT**, Schramel FM, Elbers JR, et al. The clinical value of lung imaging fluorescence endoscopy for detecting synchronous lung cancer. Lung Cancer 2001;**32**:13–8.
30 **Moghissi K**, Dixon K. Photodynamic therapy for synchronous occult bronchial cancer 17 years after pneumonectomy. Interact Cardiovasc Thorac Surg 2005;**4**:327–8.
31 **Furukawa K**, Kato H, Konak CA, et al. Locally recurrent central type early stage lung cancer <1.0 cm in diameter after complete remission by photodynamic therapy. Chest 2005;**128**:3264–75.
32 **Radu A**, Grosjean P, Fontolliet CH, et al. Photodynamic therapy for 101 early cancers of the upper aerodigestive tract, the esophagus and the bronchi: a single institution experience. Diagn Ther Endosc 1999;**5**:145–54.
33 **Bota S**, Auliac JB, Paris C, et al. Follow up of bronchial pre-cancerous lesions and carcinoma in situ using fluorescence endoscopy. Am J Respir Crit Care Med 2001;**164**:1688–93.
34 **Moro-Sibilot D**, Jeanmart M, Lantuejoul S, et al. Cigarette smoking, pre-invasive bronchial lesions and autofluorescence bronchoscopy. Chest 2002;**122**:1902–8.
35 **Kato H**, Okunaka T, Tsushida T, et al. Analysis of cost-effectiveness of photodynamic therapy in early stage lung cancer. Diagn Ther Endosc 1999;**6**:9–16.