

Surveillance for the detection of early lung cancer in patients with bronchial dysplasia

P J. George<sup>1,7</sup>, A. K Banerjee<sup>1,7</sup>, C. Read<sup>1</sup>, C. O'Sullivan<sup>2</sup>, M. Falzon<sup>3</sup>, F. Pezzella<sup>4</sup>, A. G Nicholson<sup>5</sup>, P. Shaw<sup>6</sup>, G. Laurent<sup>7</sup>, P. H Rabbitts<sup>8</sup>

<sup>1</sup>Department of Thoracic Medicine, University College London Hospitals, London, UK.

<sup>2</sup>R & D Directorate, University College London Hospitals.

<sup>3</sup>Department of Histopathology, University College London Hospitals London, UK.

<sup>4</sup>Nuffield Department of Clinical Laboratory Science, John Radcliffe Hospital, Oxford UK.

<sup>5</sup>Department of Histopathology, Royal Brompton Hospital, London, UK.

<sup>6</sup>Department of Radiology, University College London Hospitals, London, UK.

<sup>7</sup>Centre for Respiratory Research, Department of Medicine University College London, London, UK

<sup>8</sup>Leeds Institute for Molecular Medicine, University of Leeds, St James's University Hospital, Leeds LS9 7TF

Corresponding Author: Dr Jeremy George, Department of Thoracic Medicine, UCL Hospitals, Grafton Way, London WC1E 6AU.

[jeremy.george@uclh.org](mailto:jeremy.george@uclh.org), tel. (+44) 207 380 9005, fax (+44) 020 7380 9476

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## ABSTRACT

**Background:** The natural history of bronchial pre-invasive lesions and the risk of developing lung cancer in patients harbouring these lesions are not clear. Previous studies have treated severe dysplasia (SD) and carcinoma-in-situ (CIS) on the assumption that the majority will progress to invasive carcinoma.

**Aims:** To define the natural history of pre-invasive lesions and assess lung cancer risk in patients harbouring these lesions.

**Hypotheses:** The majority of pre-invasive lesions will not progress to invasive carcinoma but patients harbouring these lesions will be at high risk.

**Methods:** A cohort of patients with pre-invasive lesions underwent fluorescence bronchoscopy every 4-12 months and chest CT annually. The main endpoint was the development of invasive carcinoma.

**Results:** Twenty-two patients with 53 lesions were followed for 12-85 months. Eleven cancers were diagnosed in 9 patients. Of 36 high-grade lesions (SD and CIS), 6 progressed to invasive cancers. Five separate cancers developed at remote sites in patients harbouring high-grade lesions. All cancers were N<sub>0</sub>M<sub>0</sub> and curative treatment was given to 8/9 patients. The cumulative risk of developing lung cancer in a patient harbouring a high-grade lesion was 33% and 54% at 1 and 2 years respectively. Of 17 low-grade lesions, none progressed to invasive carcinoma.

**Conclusions:** Although the risk of malignant progression of individual preinvasive lesions is relatively small, patients harbouring high-grade lesions are at high lung cancer risk. Surveillance facilitated early detection and treatment with curative intent in the majority of patients.

## INTRODUCTION

Lung cancer continues to carry a poor prognosis<sup>1</sup>. Although 5-year survival prospects are relatively good for early stage disease<sup>2</sup>, the majority of patients are diagnosed with advanced disease when curative treatment is not feasible<sup>3</sup>. This has prompted the development and refinement of a number of sensitive diagnostic tests that will facilitate detection and treatment at earlier stages.

Fluorescence bronchoscopy has been developed to enhance the detection of pre-invasive lesions involving the large airways<sup>4,5</sup>. Pre-invasive lesions, such as severe dysplasia (SD) and carcinoma-in-situ (CIS), are believed to be precursors of squamous cell carcinoma. However, understanding of their natural history is incomplete due to the previous difficulties of detection using conventional white light bronchoscopy. With the development of fluorescence bronchoscopy, it is now possible to locate these lesions and this has created a dilemma as to how they should be managed<sup>6</sup>.

Several studies have recently been undertaken using fluorescence bronchoscopy<sup>7,8,9,10</sup> but all have treated the most severe lesions (SD and/or CIS) and this has complicated the interpretation of their natural history. Evidence from post mortem studies conducted by Auerbach and colleagues 40 years ago<sup>11</sup>, however, suggests that the majority of CIS lesions may not progress to invasive carcinoma. Serial sections obtained from the airways revealed CIS in up to 75% of individuals with heavy smoking histories<sup>11</sup>. As CIS is only implicated in the development of squamous cell carcinoma and as only 10% of heavy smokers are likely to develop lung cancer, Auerbach argued that the majority of lesions were unlikely to progress to clinically significant lung cancers<sup>11</sup>. However, patients harbouring pre-invasive lesions may still be at high risk, as they have been reported to develop cancers at other sites within their lungs<sup>12</sup>.

We have undertaken a longitudinal study of patients with bronchial dysplasia and CIS in which we have maintained combined surveillance with fluorescence bronchoscopy and chest computed tomography (CT). Treatment was given as soon as a diagnosis of invasive carcinoma was made.

The main aims were to define the natural history of pre-invasive lesions and assess the risk of developing lung cancer in patients harbouring these lesions. Our hypothesis was that the majority of lesions would not progress to invasive carcinoma but that patients bearing these lesions would be at high risk of lung cancer. Preliminary findings from this study have already been reported.<sup>13</sup>

## **METHODS**

The study protocol is summarised in figure 1 and was approved by the UCL Hospitals Medical Ethics Committees.

### **Patient selection**

A total of 84 patients received fluorescence bronchoscopy of whom 22 met the study entry criteria. The majority were referred from other hospitals for assessment of conditions listed in table 1. All patients with pre-invasive lesions underwent spiral CT of the chest with the intention of excluding tumour adjacent to the pre-invasive lesion and at remote sites within the lung. Only patients without such evidence of invasive disease entered the study.

The significance of pre-invasive lesions and treatment options were discussed and informed consent was obtained at study entry. Patients were ineligible for the study if they had any disorder affecting their short-term prognosis or ability to tolerate bronchoscopy and/or biopsy.

### **Fluorescence bronchoscopy**

The initial fluorescence bronchoscopy was performed under general anaesthetic by passing the bronchoscope (D-Light autofluorescence bronchoscope; Karl Storz GMBH) inside a rigid bronchoscope. The bronchial tree was first inspected under white light and then blue light. All areas that appeared abnormal were initially documented and sampled when the bronchoscopic examination had been completed. Samples for cytology were obtained using a bronchial brush and saline washings. Bronchial biopsies for histology were then obtained using flexible

disposable forceps, a minimum of 5 biopsies being taken from each site to minimise the risk of overlooking foci of invasive disease. Control biopsies were obtained from areas negative for both modalities. Separate forceps were used for each site to eliminate the risk of cross-contamination. Although rigid bronchoscopy has the potential to miss lesions within the sub-glottic trachea, this technique enables biopsies to be obtained from multiple sites without additional patient discomfort.

Subsequent bronchoscopies were performed under sedation with intravenous Midazolam and topical lignocaine. Bronchial biopsies, brush specimens and washings were obtained from sites that appeared abnormal and from sites of previously documented pre-invasive lesions. Additional sites were recorded as distinct lesions when separated by normal mucosa. The same operator (PJG) performed all surveillance bronchoscopies and biopsies to facilitate consistency of sampling throughout the study.

Patients with mild to moderate dysplasia underwent bronchoscopy every 6-12 months as reported elsewhere<sup>8,9,10</sup> (figure 1). In patients with CIS and SD, bronchoscopic surveillance was performed every 4-6 months on the assumption that these intervals would be sufficient to identify progression to invasive carcinoma without compromising the possibility of curative treatment.

### **Imaging**

Annual low-dose non-enhanced spiral CT scan of the thorax was performed to check for the development of incidental cancers within the lung parenchyma. Patients were scanned with a Siemens' Sensation 4 Channel detector multi-slice scanner. The dose was reduced by decreasing the tube current to 50-70 mA. Solitary pulmonary nodules of  $\leq 1$ cm in diameter were investigated by repeat CT after an interval of 3-4 months to check for a change in shape or size that might suggest a malignant aetiology. Lesions of  $\geq 1$  cm in diameter were imaged by positron emission tomography (PET).

## **Endpoints**

The main study endpoint was the development of invasive carcinoma. Although this was based primarily on histological evidence, clinical suspicion was also accepted. In patients with lesions involving the large airways, histological evidence was obtained. However, clinical diagnoses were made in patients with peripheral lesions who were not fit to undergo tissue biopsies and were based upon interval CT scans demonstrating an increase in lung nodule size in association with abnormal uptake on PET. Patients who developed lung cancer were treated promptly after discussion in a multi-disciplinary lung cancer clinic and remained under surveillance if their treatment was given with curative intent. Surveillance was discontinued if they developed evidence of recurrent invasive disease.

## **Histology**

Multiple sections from all biopsies were examined by two histopathologists (FP or MF) and verified by a reference pathologist (AGN) who reviewed the same slides. The diagnosis of the reference pathologist was accepted in cases of disagreement. The histological appearances were classified according to the WHO criteria<sup>14</sup>. Biopsies from sites of previous lesions that showed no abnormality or a lesser grade of dysplasia on at least two consecutive occasions were considered to indicate regression of the lesion.

## **Analysis**

Pre-invasive lesions were subdivided into high-grade (CIS and SD) and low-grade lesions (mild and moderate dysplasia). Data were censored when follow-up ceased or when a patient received treatment that might affect the natural history of that lesion. The probability of a patient developing an invasive carcinoma was estimated with the Kaplan Meier analysis. Some patients developed more than one invasive carcinoma during surveillance but the analysis was confined to the time that the first tumour was detected.

## RESULTS

### Patients, lung cancer risk factors and clinical presentations

Twenty-two patients (mean age 64 years; 19 males) entered the study and were followed for 12-85 months (median 23 months). All but one gave significant smoking histories. Their demographics, clinical presentations and circumstances leading to the discovery of pre-invasive lesion(s) are summarised in table 1. Six patients had low-grade lesions only, while the remaining 16 had both high- and low-grade lesions. Nine patients had been successfully treated for a previous lung cancer, whereas 13 had no such history; there were no marked differences between these groups except that patients with only low-grade lesions at study entry were most frequently in the “no previous lung cancer” category (figure 2).

Thirty-six high-grade lesions (7 SD and 29 CIS) were identified in 16 patients: 23 were detected with fluorescence bronchoscopy at study entry, while 11 new lesions developed during surveillance in sites that had previously been judged to be normal. A further 2 high-grade lesions were detected in 2 patients at conventional bronchoscopy before study entry, and subsequently verified by independent histological review of their biopsies, but regressed by the time of the initial fluorescence bronchoscopy.

Six of 36 high-grade lesions progressed to invasive squamous cell carcinoma at intervals ranging from 4-17 months, while 7, including 2 lesions detected before study entry, appeared to regress to normal or to a lesser grade of dysplasia (figure 3). The remaining 23 lesions persisted with unchanged histology for 6-50 months, though follow-up ceased in 18 lesions when patients received treatments that might have affected their behaviour (table 3).

Seventeen low-grade lesions were detected in 9 patients (figure 3). Three patients had synchronous high-grade lesions and the remaining 6 patients had only low-grade lesions. Twelve low-grade lesions were detected at study entry and 5 developed during surveillance at sites that had previously appeared normal. None progressed to invasive carcinoma, while 14

spontaneously regressed to normal. The remaining 3 lesions (all in the same patient) remained indolent though follow-up ceased after 12 months as a result of deteriorating lung function.

### **Incidental lung cancers detected during surveillance**

Five patients (all harbouring high-grade lesions) developed incidental lung cancers at remote sites and were detected by CT (figure 2 and table 2). Three patients underwent surgery and were found to have squamous cell carcinomas. The remaining two patients developed mass lesions that were judged to be primary lung cancers, on the basis of their CT and PET appearances, but could not be biopsied nor removed surgically, and so a histological diagnosis was not obtained. None of the 6 patients with only low-grade lesions developed incidental cancers during surveillance.

### **Clinical outcomes in patients with invasive lung cancers**

Eleven lung cancers were detected in 9 patients, all of whom were known to have high-grade lesions (table 2). Although the risk of developing a lung cancer was negligible in patients with only low-grade lesions, it was estimated to be 33% at one year and 54% at two years (figure 4). All tumours were N<sub>0</sub>M<sub>0</sub> at the time of diagnosis, and all were stage 1a with the exception of a patient with a primary tracheal tumour, which was stage 111b (patient 1 in table 2). It was possible to offer potentially curative treatment to all patients with the exception of one who had previously undergone a pneumonectomy and who developed a second primary cancer in the periphery of the remaining lung (patient 10 in table 2). This patient received supportive care and has now died. Of the remaining 10 lung cancers in eight patients, 4 have recurred in 4 patients of whom 3 have died. There is no evidence of recurrent disease in the remaining 4 patients after 14-60 months.

## **DISCUSSION**

The present study supports the hypothesis that the majority of high-grade pre-invasive lesions do not progress to invasive carcinoma but that patients bearing these lesions are at extremely high risk of developing lung cancer (figure 4). Our findings also demonstrate the potential of

surveillance with fluorescence bronchoscopy and chest CT to detect lung cancers in such high-risk patients at early stages when treatment with curative intent is feasible.

Previous studies of pre-invasive lesions have treated SD and CIS due to concerns that a large proportion would progress to invasive carcinoma<sup>7,8,9,10,15</sup>. In the present study, treatment was withheld until there was histological or radiological evidence of progression to invasive carcinoma in order to evaluate their malignant potential as precisely as possible. Although the outcome of high-grade lesions was variable, only a minority progressed to invasive carcinoma in the first 2 years (figure 3). A similar proportion of high-grade lesions regressed to normal, while the remainder persisted with unchanged histology for long periods of time (figure 3). In addition, new lesions have appeared during the course of surveillance and it has not been possible to predict which lesion is destined to progress to invasive carcinoma from the initial histology.

These findings differ from those of Sutedja and colleagues who reported that all CIS lesions progressed to squamous cell carcinoma<sup>7,10</sup>. However, comparison between studies may be complicated by the classification of pre-invasive lesions. We have found that sequential biopsies from the same site may be scored as SD or CIS (unpublished observations). In addition to intra- and inter-observational variation, it is possible that there is morphological heterogeneity within lesions. Furthermore, we have found no difference in the outcomes of lesions classed as SD or CIS at initial presentation<sup>16</sup>. We therefore find it appropriate to group these two grades together.

In our study no low-grade lesions progressed to carcinoma (figure 3) or to a higher grade (results not shown) unlike those observed in the study of Breuer et al<sup>10</sup> who described a 9% progression rate (6/64) for mild-moderate dysplasia followed for a median of 21 months. The reasons for these discrepancies are unknown but could be elucidated in a large multi-centre study with longer follow-up.

Our study has two important limitations. Firstly, it has been assumed that pre-invasive lesions

in patients with previous histories of lung cancer behave similarly to those in patients with no such histories. Although there is no apparent difference between these two groups (figure 2), a larger study with longer follow-up is needed to establish whether this assumption is correct. Secondly, it is assumed that biopsies taken from pre-invasive lesions do not influence the outcome of that lesion. However, it has been suggested that bronchial biopsies may completely remove some lesions<sup>7</sup>. Although this possibility cannot be discounted, this is unlikely as the majority of lesions appeared considerably larger than the area sampled by biopsy. This could be addressed in a future study by using non-invasive techniques, such as endobronchial ultrasound and optical coherence tomography. It is likely, however, that treatment given to invasive carcinomas will have affected the behaviour of pre-invasive lesions adjacent to these carcinomas. Follow-up data from these lesions were therefore censored at the time of treatment (table 3). Although a significant proportion of data were discarded, our assessments of the behaviour of pre-invasive lesions are consistent with the conclusions made by Auerbach<sup>11</sup>.

Despite this relatively low rate of malignant progression of individual lesions (figure 3), we have found that patients harbouring high-grade lesions are at extremely high risk of developing invasive carcinoma (figure 4). This high risk is due to the multifocal distribution of lesions and to the development of incidental cancers at remote sites within the lung. These findings are consistent with the “field cancerisation” concept in which the entire bronchial epithelium is exposed to the carcinogenic effects of tobacco smoke and therefore at risk of progressing to invasive carcinoma<sup>17</sup>.

The observation of multi-focal disease and the large proportion of patients developing incidental cancers at remote sites within their lungs raise important questions as to how high-grade lesions and patients should be managed clinically. Treatment options presently include surgery and a variety of endobronchial treatments. Surgery undoubtedly provides the most effective method of eradicating lesions but is associated with significant morbidity and mortality, which is difficult to justify for a condition that may not necessarily progress to malignancy. Furthermore, there is

a risk that it may render the patient unfit for curative treatment if an invasive carcinoma subsequently develops within the remaining lung(s).

Endobronchial treatments have the advantage of conserving lung tissue and are used more widely. However, their efficacy is difficult to evaluate given the unpredictable nature of high-grade lesions and the observation that patients harbouring these lesions are just as likely to develop incidental cancers at remote sites within their lungs. Ultimately, systemic treatments aimed at preventing the progression to invasive carcinoma may be more appropriate for such a field-change disease.

The advantage of maintaining combined surveillance with CT and bronchoscopy has been to ensure that definitive treatment has been directed to the most appropriate site within the patient's airway and that incidental lung cancers have been diagnosed and treated early. Nevertheless, 4/8 patients developed metastatic disease despite receiving treatment with curative intent. Three cancers progressed from known pre-invasive lesions (table 2) and it could be argued that pre-emptive treatment would have prevented this. However, three studies have reported significant rates of tumour progression, ranging from 17-67%, despite endobronchial treatment<sup>7,9,15</sup>, and underline the importance of conducting randomised controlled clinical trials to evaluate different treatment strategies.

The demonstration of variable outcomes in pre-invasive lesions also highlights the need to identify reliable markers of tumour progression. We have established an archive of blood, sputum and bronchoscopic specimens so that it is now possible to conduct molecular biological studies on histologically identical lesions with different clinical outcomes<sup>18</sup>. In addition to identifying markers of disease progression, this study should also provide new insights into the biology of the invasion process.

Although the main aim of this study was to study the natural history of pre-invasive lesions, the finding of such a high lung cancer risk in patients with SD and CIS suggests that they have potential as disease bio-markers. The clinical value of fluorescence bronchoscopy may therefore

lie in its ability to identify patients at especially high risk of developing lung cancer by detecting these lesions. Although bronchoscopy is too invasive and time-consuming to be developed as a screening tool, there is some evidence to suggest that patients with pre-invasive lesions may be identified non-invasively with sputum cytometry<sup>19</sup>. Screening with sputum cytometry, combined with surveillance, may therefore facilitate the diagnosis of lung cancers at earlier stages when curative treatment is feasible in high-risk groups.

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There are no author conflicts of interests with this paper.

### **ABBREVIATIONS**

SD, severe dysplasia; CIS, carcinoma in situ

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## FIGURES AND TABLE LEGENDS

### Figure 1 Surveillance protocol

Surveillance protocol for patients with pre-invasive lesions involving the bronchial epithelium. Fluorescence bronchoscopies were performed at 4-12 monthly intervals depending upon the grade of the pre-invasive lesion: patients with high-grade lesions (severe dysplasia and carcinoma in situ) underwent bronchoscopy at 4-6 monthly intervals, while patients with low-grade lesions (mild to moderate dysplasia) had bronchoscopies at 6-12 monthly intervals.

### Figure 2 Distribution of histological outcomes

In this study of 22 patients there were 9 with previous lung cancer (N=9) and 13 with no previous cancer (N=13). Each group is divided into patients that showed [1] local progression from a pre-invasive lesion to carcinoma (local prog<sup>n</sup>), [2] patients that developed a carcinoma at a site remote from the detectable pre-invasive disease (remote ca.) [3] patients with both local progression and a remote carcinoma (local prog<sup>n</sup> and remote ca.) and [4] patients with no progression of their pre-invasive disease. The numbers of each are shown in the lowest tier of boxes together with the patients' study numbers; these cross reference with the study numbers in tables 1 and 2. Those in italics are patients with low grade lesions at study entry.

Since this study was closed, patient, 012 designated \*, has developed local progression to carcinoma; patient, 004 designated \*\*, has developed carcinoma at a remote site.

### Figure 3 Outcomes of pre-invasive lesions

Outcomes of surveillance in 36 high-grade (black bars) and 17 low-grade (grey bars) pre-invasive lesions. A large number of lesions persisted with unchanged histology during surveillance though follow-up ceased in some of these patients when treatments were given to adjacent carcinomas that may have influenced their behaviour.

**Figure 4 Kaplan Meier plot**

A Kaplan Meier plot is shown indicating the estimated probability of invasive lung cancer developing at any site in the lungs of patients harbouring high-grade lesion(s).



**Table 1 Patient characteristics**

Patient demographics, lung cancer risk factors and the circumstances leading to the detection of pre-invasive lesions are listed for each patient enrolled into the surveillance study. Patients are numbered from 1-22. Abbreviations are as follows: COPD – chronic obstructive pulmonary disease, SCLC – small cell lung cancer, NSCLC – non small cell lung cancer, CIS – carcinoma in situ, SD – severe dysplasia.

Patient	Age	Sex	Smoking / pack yrs	Additional risk factors	Previous malignancy	Reasons for referral
1 (001)	75	M	90	COPD	None	Haemoptysis
2 (002)	73	F	40	None	CIS of breast excised 1 year previously	Haemoptysis
3 (003)	69	M	40	COPD	None	Persistent cough
4 (004)	62	M	106	COPD	None	Haemoptysis
5 (005)	54	M	38	None	None	Persistent cough
6 (006)	61	M	141	None	None	Pneumonia
7 (007)	67	M	104	Asbestos exposure, COPD	None	Persistent cough
8 (008)	62	M	96	COPD	None	Haemoptysis
9 (009)	66	M	88	COPD	SCLC - chemo/radiotherapy 8 years previously	Persistent cough
10 (010)	74	M	60	Asbestos exposure, COPD	NSCLC - pneumonectomy 2 years previously	Persistent cough, abnormal sputum cytology
11 (011)	75	M	80	COPD	NSCLC - lobectomy 2 years previously	Haemoptysis
12 (012)	61	M	60	None	NSCLC - lobectomy 3 years previously	Haemoptysis
13 (013)	53	F	96	None	NSCLC - lobectomy 6 months previously	CIS at resection margin
14 (014)	74	M	62	Asbestos exposure, COPD	NSCLC - lobectomy 6 months previously	CIS at resection margin
15 (015)	57	F	22	None	NSCLC - lobectomy 6 months previously	SD at the resection margin
16 (016)	60	M	40	COPD	SCLC - chemo/radiotherapy 6 months previously	Persistent cough
17 (017)	67	M	47	Asbestos exposure, COPD	NSCLC - lobectomy 6 months previously	CIS at resection margin
18 (018)	62	M	48	COPD	None	Pneumonia
19 (019)	70	M	120	COPD	None	Persistent cough
20 (020)	54	M	45	None	None	Persistent cough
21 (021)	49	M	62	Asbestos exposure	None	Haemoptysis
22 (022)	60	M	0	Asbestos exposure	None	Persistent cough, abnormal sputum cytology

## **Table 2 Treatment and patient outcomes**

Details of 11 lung cancers diagnosed in 9 patients during the surveillance study. Staging is according to the international staging system<sup>2</sup>; (C) denotes clinical staging while (S) denotes surgical staging. Abbreviations are as follows: RUL – right upper lobe, RML - right middle lobe, RLL– right lower lobe, LUL – left upper lobe, LLL – left lower lobe, sq cell ca – squamous cell carcinoma, FB - fluorescence bronchoscopy, CIS - carcinoma in situ, CT – computed tomography, PET - positron emission tomography, PDT – photodynamic therapy, RT – radiotherapy

Patient	Time to diagnosis (months)	Tumour site	Histology	How diagnosed	Stage	Treatment	Outcome following treatment
1 (001)	3 11	Trachea RUL	Sq cell Ca	FB: Progressed from known CIS	(C) T4N0M0	Photodynamic therapy (PDT)	Eradicated: no evidence of recurrence
			Sq cell Ca	FB: Progressed from new CIS	(C) T1N0M0	Radical RT	Progressive disease
2 (002)	15	LLL	Sq cell Ca	Clinical suspicion: Progressed from known CIS	(S) T1N0M0	Surgery	Alive: no evidence of recurrent disease after 5 years
3 (003)	5	RML	Sq cell Ca	FB: Progressed from known CIS	(C) T1N0M0	Radical RT (PDT unsuccessful)	Progressive disease
5 (005)	8	RUL	Not known	CT surveillance followed by PET:CT scan	(C) T1N0M0	Radical RT	Alive: no evidence of recurrence after 3 years
6 (006)	19	LLL	Sq cell Ca	CT surveillance followed by PET scan	(S) T1N0M0	Surgery	Alive: no evidence of recurrence after 1 year
7 (007)	6	RUL	Sq cell Ca	CT surveillance followed by PET scan	(S) T1N0M0	Surgery	Progressive disease Alive after 1 year
9 (009)	4	LUL	Sq cell Ca	FB: Progressed from known CIS	(C) T1N0M0	PDT: refused surgery and ineligible for radical RT	Progressive disease
10 (010)	17	LLL	Not known	CT surveillance	(C) T1N0M0	Symptomatic: unfit for surgery/ RT due to previous pneumonectomy	Progressive disease
11 (011)	14	LL lobectomy stump	Sq cell Ca	FB: Progressed from known CIS	(C) T1N0M0	Radical brachytherapy	Eradicated: no recurrence after 1 year
	14	RLL	Sq cell Ca	CT surveillance followed by PET:CT scan	(S) T1N0M0	Surgery	No evidence of recurrence after 1 year

**Table 3 Circumstances leading to the censorship of high-grade pre-invasive lesions during surveillance**

Surveillance was discontinued in 18 high-grade pre-invasive lesions when patients received treatment that might influence the outcome of the lesion. The duration of follow-up and the reasons for censorship are shown in each case.

<b>Patient identity code</b>	<b>Reasons for censorship</b>	<b>Number of pre-invasive lesions affected</b>	<b>Duration of surveillance</b>
007	Upper lobectomy for synchronous carcinoma in same lobe	1	19 months
005	Radical external radiotherapy to synchronous carcinoma in same lung	2	8 months
003	Photodynamic therapy (PDT) to synchronous carcinoma in same lung	3	6 months
003	Chemotherapy for recurrent cancer in contralateral lung	1	10 months
002	Lower lobectomy for synchronous carcinoma in same lung with sleeve resection and re-implantation of upper lobe after removing proximal pre-invasive lesions	4	19 months
001	PDT to adjacent synchronous carcinoma	1	4 months
014	Surgery to correct post-operative bronchial stricture with removal of lesion	1	11 months
010	Radical external radiotherapy to synchronous carcinoma in same lung	4	22 months
011	Radical endobronchial radiotherapy to synchronous carcinoma in same lung	1	20 months

**Figure 1**

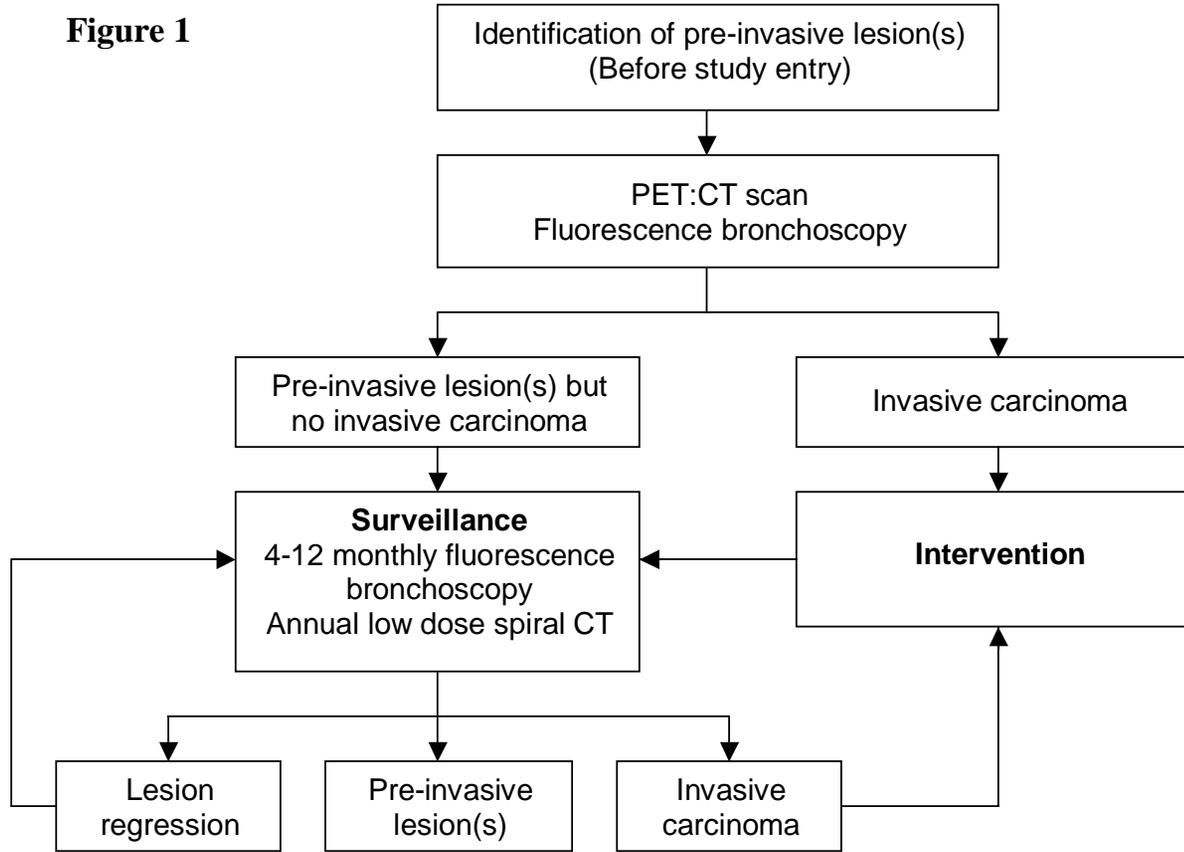


Fig. 2

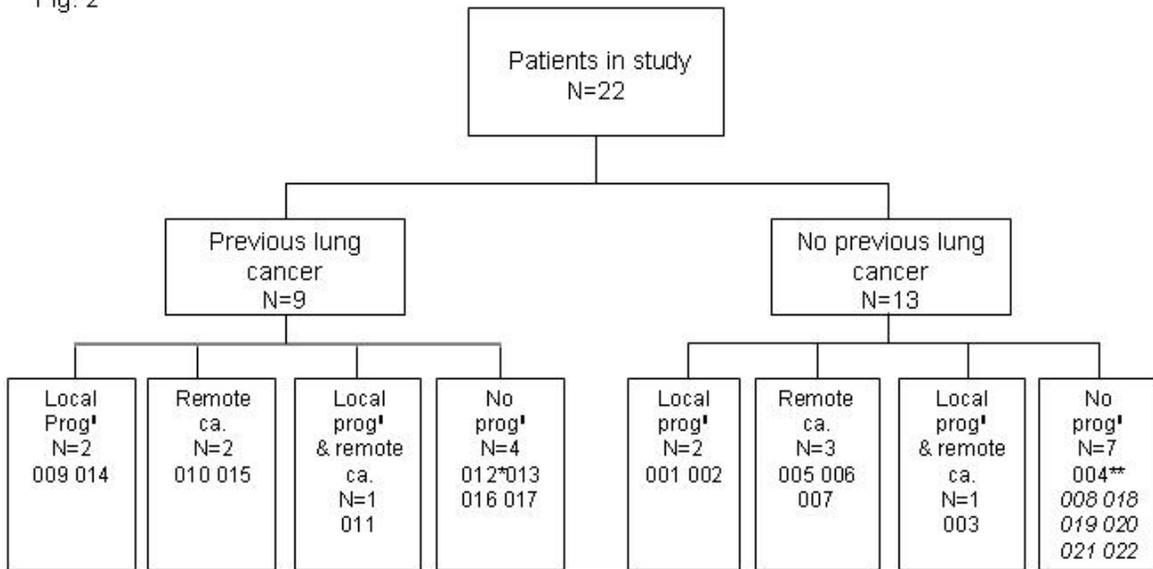


Figure 3 Outcomes in pre-invasive lesions

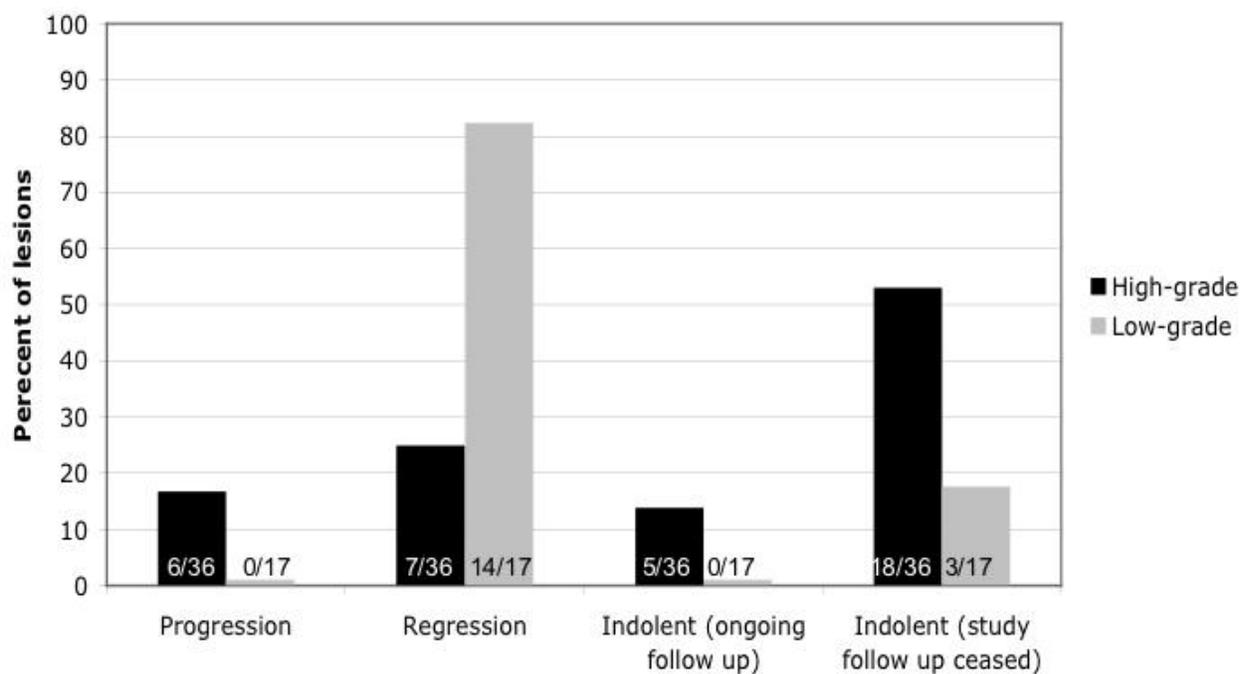


Fig 4

