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SERIES "LUNG CANCER"
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Early proximal lung cancer diagnosis and treatment

A. McWilliams*, B. Lam# and T. Sutedja¶

ABSTRACT: Lung cancer remains the largest cause of cancer deaths worldwide and the overall 5-yr survival rate is only 15%. This is because the majority of the lung cancers are diagnosed at late stages and the treatment outcome is suboptimal. However, the survival of patients with early stage proximal lung cancer is excellent and with advancements in technology we are currently well equipped to diagnose and stage these lung cancers. Together with the application of local bronchoscopic therapeutic modalities that may potentially cure early stage intraluminal lesions, there is expanding interest in the further exploration of new avenues for early detection, localisation, staging, treatment and close surveillance of these high-risk patients who are suffering from chronic field carcinogenesis. The present article will deal with various issues regarding early detection, staging and treatment of centrally located early stage, mostly squamous type, lung cancer.

Lung cancer remains the largest cause of cancer deaths worldwide and the overall 5-yr survival rate is only 15%, despite many advances in imaging techniques and oncological care over the last few decades [1]. The largest gain in life expectancy in lung cancer patients has been among those with localised disease *versus* those with regional or distant metastasis [2]. However, only 19% of lung cancers are localised at the time of diagnosis [2].

Lung cancer consists of a number of histological subtypes that are preferentially located in different parts of the tracheobronchial tree, *i.e.* central bronchial cancers tend to be squamous or small cell carcinoma types, and peripheral lung cancers tend to be adenocarcinoma and neuroendocrine cell types. Squamous cell carcinoma still accounts for 40–50% of lung cancers in males and 20–30% in females [3]. Early central squamous carcinoma *in situ* (stage 0) is difficult to detect and has the additional risk of being potentially multifocal, with up to 30% patients developing synchronous or metachronous lesions [4–15]. However, the survival of patients with small central lung cancers is excellent with 5-yr survival >90% [6–10]. Despite the challenges of detecting this disease, the development of strategies to detect and treat these early stage central cancers may have an important impact on patient survival.

There has been considerable controversy regarding the invasive potential of squamous cell carcinoma *in situ* and the need for curative treatment [9, 11]. Retrospective analysis of untreated patients with radiologically occult central lung cancer has revealed much lower 5-yr survival rates compared with surgically treated cases, in whom >90% survival at 5 yrs can be achieved [4]. As squamous carcinoma *in situ* is difficult to detect and is often diagnosed by chance, only limited data are available regarding the natural history of these lesions [5]. In addition, most centres treat the lesions at the time of detection rather than await the development of invasion [7–11]. Reported progression rates to invasive cancer vary from 20% to 67% despite bronchoscopic therapy in some instances [16–19]. In one published study of observation without intervention, the overall progression of carcinoma *in situ* to invasive cancer was 21% over 4–17 months [20]. However, if lesions with completed follow-up only were evaluated, the observed progression rate was ⩾33% (data included severe dysplasia) and half of the lesions that progressed were incurable [20].

AFFILIATIONS
*British Columbia Cancer Agency and Dept of Respiratory Medicine, Vancouver General Hospital, Vancouver, BC, Canada.
#Dept of Medicine, University of Hong Kong, Hong Kong SAR, China.
¶Dept of Pulmonary Medicine, VU Academic Medical Center, Amsterdam, The Netherlands.

CORRESPONDENCE
A. McWilliams
University of British Columbia
British Columbia Cancer Agency and
Vancouver General Hospital
675 West 10th Avenue
Vancouver
BC
V5Z 1L3
Canada
Fax: 1 6046758099
E-mail: amcwilli@bccancer.bc.ca

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Therefore, the delay of treatment of these lesions seems likely to be detrimental, particularly in a patient with reasonable life expectancy.

However, early proximal lung cancer only represents a small proportion of lung cancer diagnosed in the clinical setting [21]. If more lung cancers could be diagnosed at this stage, the prognosis of lung cancer might be improved. With the advancements in technology, we are currently well equipped for the early detection and staging of these early stage proximal squamous type lung cancers. Together with application of local bronchoscopic therapeutic modalities that may potentially cure early stage intraluminal lesions [22], there is expanding interest in exploring new avenues for early detection, localisation, staging, treatment and close surveillance of these high-risk patients who are suffering from chronic field carcinogenesis. The present article will deal with various issues regarding early detection, staging and treatment of centrally located early stage, mostly squamous type, lung cancer.

NONINVASIVE DETECTION OF EARLY PROXIMAL LUNG CANCER

Sputum cytology

Sputum contains exfoliated airway epithelial cells and morphological analysis of sputum by cytology has been used for the early diagnosis of lung cancer, particularly central airway tumours, *i.e.* squamous cell carcinoma [22]. However, because of the low percentage of bronchial epithelial cells in sputum or inadequate preparatory techniques, the sensitivity is usually low [23]. Induced sputum has found to be better than spontaneous sputum [24] and the ThinPrep technique has been shown to improve diagnostic accuracy by reducing the unsatisfactory and false-negative rates by a total of 30% [25]. The other limiting factor is the skill required for identifying subtle morphological abnormalities in cells; this results in significant variation in intra- and interobserver agreement in determining cancer cells [26]. Besides the above limitations, a recently published paper demonstrated that, although sputum cytological atypia predicted incidence of lung cancer, especially squamous cell lung cancer, this was a late event as the association was stronger for samples collected within 5 months of the diagnosis of lung cancer [27].

Sputum cytometry

Malignancy-associated change (MAC) is the change in the distribution of DNA in the nuclei of cytologically normal cells in the vicinity of pre-invasive or invasive cancer [28, 29]. It has been shown that the frequency of bronchial epithelial cells expressing MAC can be used to differentiate normal from lung cancer patients [30]. Computer-assisted sputum DNA analysis is the method used to detect MAC in exfoliated cells in sputum. By using either spontaneous sputum or induced sputum, PALCIC *et al.* [31] have found that sputum cytometry was not superior to that of conventional cytology in detecting early stage squamous cell lung cancer. By using induced sputum, a European study has shown that the sensitivity of sputum cytometry was 100% for all stages of squamous cell lung cancer, while the sensitivity of conventional sputum cytology was only 10% [32]. However, in the latter study, only subjects with severe dysplasia or higher grade changes on cytological examination or grade II on DNA image cytometry were called for bronchoscopy. A selection bias might have occurred and, as longitudinal data were not available, its true sensitivity could not be defined. A recently published study has found that sputum cytometry was two times more sensitive than cytology in detecting either squamous cell lung cancer or central type of lung cancer [33]. However, as one-third of the study population were eventually found to have lung cancer, the performance of sputum cytometry could not be extrapolated to a lower risk population, *i.e.* in a screening setting. The performance of cytometry was compared with cytology in a lung cancer case finding study in radon-exposed uranium miners [34]. Sputum (spontaneous or *via* induction) were collected from 1,500 subjects. Lung cancers were found in 1.5% of the subjects and two-thirds had squamous cell lung cancer. There was no difference in either sensitivity or specificity of the two tests, though it should be noted that both the sensitivity and specificity of conventional sputum cytology in the study were very high.

MINIMALLY INVASIVE DETECTION OF EARLY PROXIMAL LUNG CANCER

The development of flexible fibreoptic white light bronchoscopy ~40 yrs ago has resulted in the availability of sophisticated tools for the assessment of the central airway mucosa [35–37]. Technological advancement has greatly improved image resolution and quality. However, early central lung cancers remain difficult to detect with white light bronchoscopy, even if it is compared with the improved images of video bronchoscopy [35]. A number of other white light imaging improvements are presently being evaluated, including optical zoom or magnifying lenses that may enhance the examination of the bronchial mucosa and improve the detection of early vascular changes that can be associated with early malignant change [36].

There are other developments that can be used along with white light imaging for localisation of pre-neoplastic lesions and early lung cancer utilising light outside the visible spectrum. These include autofluorescence-reflectance imaging, narrow band imaging and optical coherence tomography. Endobronchial ultrasound is another new technology that may assist in the evaluation of early central lung cancers.

Autofluorescence-reflectance bronchoscopy

The detection of pre-neoplastic lesions and carcinoma *in situ* is significantly increased with the use of autofluorescence imaging with white light bronchoscopy (table 1) [37–57]. Autofluorescence-reflectance bronchoscopy (AFB) has also been shown to have an important impact on the staging of potentially curable central lung cancers prior to endobronchial therapy, by enabling the bronchoscopist to obtain a more accurate assessment of the lesion size and margins [57–59].

Autofluorescence imaging utilises the spectral differences in fluorescence and absorption properties of normal and dysplastic bronchial epithelium. These differences have been the basis for the design of several autofluorescence imaging devices [40, 43, 47]. More recently, these devices have used a combination of reflectance and fluorescence for imaging [42, 54, 59, 60].

AFB was first developed at the British Columbia Cancer Research Centre (Vancouver, BC, Canada) and became commercially available in 1998 [46]. The original LIFE-Lung® system (Xillix Technologies, Vancouver, BC, Canada) used a helium–cadmium laser for illumination (442 nm) and detected

TABLE 1 Multicentre trials and randomised studies of autofluorescence bronchoscopy

Study	System	Subjects n	Sensitivity %		Specificity %	
			WLB	AFB	WLB	AFB
LAM [38]	LIFE-Lung	173	9	66	90	66
ERNST [39]	D-Light	293	11	66	95	73
EDELL [40]	Onco-LIFE	170	10	44	94	75
HIRSCH [41]	LIFE-Lung	55	18	73	78	46
HÄUSSINGER [42]	D-Light	1173	58	82	62	58

WLB: white light bronchoscopy; AFB: addition of autofluorescence bronchoscopy. LIFE-Lung® system is manufactured by Xillix Technologies, Vancouver, BC, Canada; D-Light® system: Karl Storz Endoscopy of America, Culver City, CA, USA; Onco-LIFE®: Novadaq Technologies, Richmond, BC, Canada.

the emitted red and green autofluorescent light with two image-intensified charge-coupled device (CCD) cameras. Normal areas appear green and abnormal areas appear reddish brown, owing to reduced green autofluorescence in pre-neoplastic and neoplastic lesions.

Subsequent technological improvements made it possible to use non-image intensified CCD cameras and further development included the combination of fluorescence and reflectance imaging, in order to enhance contrast between normal and abnormal tissues. The Pinpoint system (previously Onco-LIFE®; Novadaq Technologies, Richmond, BC, Canada) uses a combination of reflectance and fluorescence imaging. Blue light (395–445 nm) and small amount of red light (675–720 nm) from a filtered mercury arc lamp is used for illumination. A red reflectance image is captured in combination with the green autofluorescence image (fig. 1) [40]. Another system utilising fluorescence and reflectance imaging is the D-Light® system (Karl Storz Endoscopy of America, Culver City, CA, USA) which consists of a RGB CCD camera and a filtered Xe lamp (380–460 nm). It combines an autofluorescence image from wavelengths >480 nm with a blue reflectance image [42]. Frame averaging is used to amplify the weak autofluorescence signal.

These earlier autofluorescence systems were designed to be used with fibreoptic bronchoscopes. Autofluorescence systems that can be used with video bronchoscope systems have now been developed. The Pentax SAFE-3000® system (Pentax Corp., Tokyo, Japan) uses a semiconductor laser diode that emits 408 nm wavelength light for illumination and detects autofluorescence using a single high-sensitivity colour CCD sensor in the fluorescence spectrum (430–700 nm). Reflected blue light is used to generate a fluorescence-reflectance image. The white light and fluorescence images can also be made displayed simultaneously (figs 2 and 3) [59]. The Olympus autofluorescence video bronchoscope (AFI-Lucera® system; Olympus Corp., Tokyo, Japan) uses blue light (395–445 nm) for illumination. An autofluorescence image (490–700 nm), as well as two reflectance images, one green (550 nm) and one red (610 nm), are captured sequentially and integrated by a video processor to produce a composite image [60].

There is a reduction in specificity associated with the increased sensitivity for detection of early lesions by autofluorescence imaging (table 1). This increase in false-positive biopsies has an impact on the cost-effectiveness of this technique. However, there are some recent data to suggest that areas with abnormal autofluorescence but benign histopathology contain increased chromosomal aberrations, and that the presence of multiple areas of abnormal autofluorescence may be an indicator of increased lung cancer risk [61, 62]. Recently, the use of a quantitative score during autofluorescence examination has been shown to improve specificity [63].

Optical coherence tomography

Optical coherence tomography (OCT) is a promising endoscopic imaging method that enables micron-scale resolution of the bronchial epithelium. It may become an imaging modality that helps address the relatively high false-positive rate of autofluorescence imaging. OCT is a noncontact method that delivers near-infrared light to the endobronchial tissue *via* a small probe *via* a bronchoscope. It allows imaging of cellular and extracellular structures from analysis of the back-scattered light with a spatial resolution of 3–15 μm and a depth penetration of ~2 mm to provide near-histological images in the bronchial wall [64–75]. Early studies have shown that dysplasia can be distinguished from metaplasia, hyperplasia or normal tissue and that

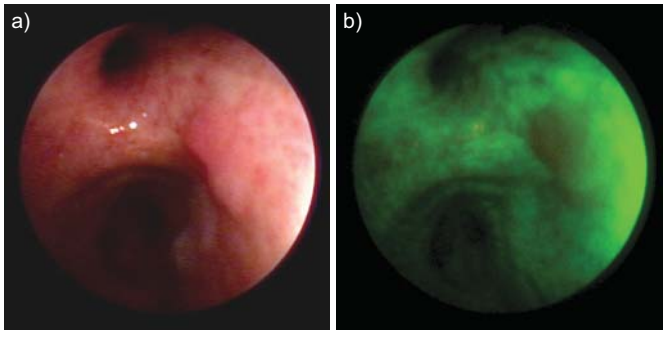

FIGURE 1. Right main bronchus carcinoma *in situ* under a) white light imaging and b) autofluorescence imaging with Pinpoint system® (Novadaq Technologies, Mississauga, ON, Canada).

FIGURE 2. Pentax SAFE 3000® (Pentax Corp., Tokyo, Japan) autofluorescence bronchoscopy system.

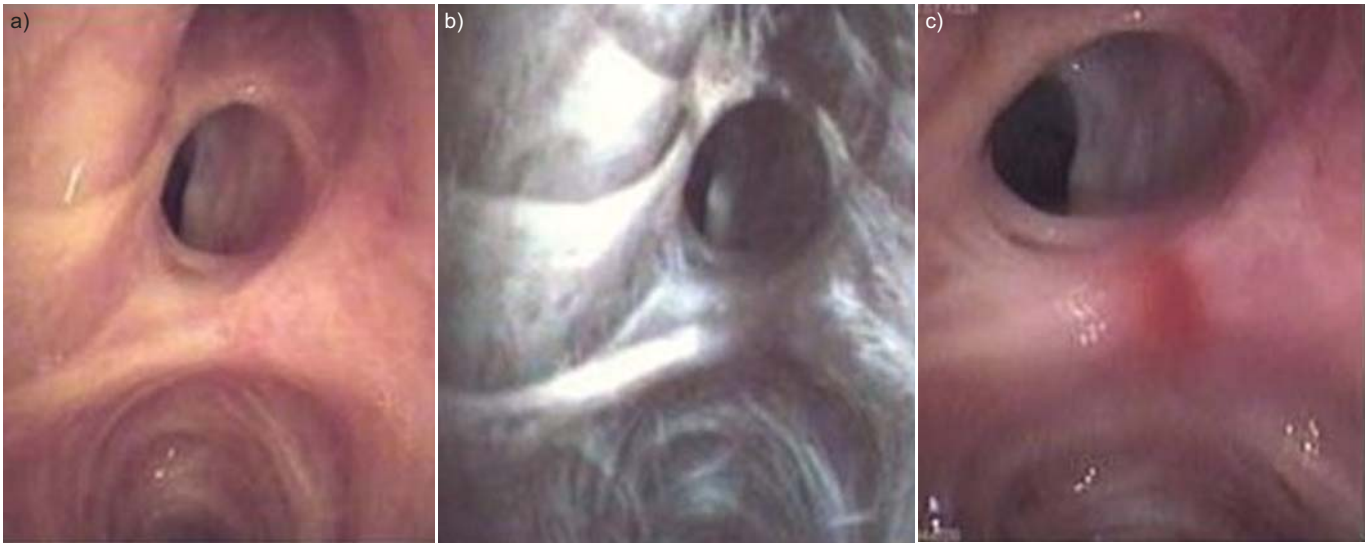

FIGURE 3. An area of carcinoma *in situ* at the left upper lobe carina seen using the Pentax SAFE 3000® system (Pentax Corp., Tokyo, Japan). a) White light imaging alone, b) autofluorescence imaging and c) dual imaging.

carcinoma *in situ* can be distinguished from invasive cancer [68, 69]. Severity of the histopathology grade was associated with a progressive increase in the epithelial thickness and the nuclei of the cells also became darker and less light was scattered. The basement membrane became disrupted or disappeared with invasive carcinoma (fig. 4) [69].

However, differentiation between high-grade dysplasia and carcinoma *in situ* could not be made with OCT. To further advance this technology, systems with higher resolution and Doppler capability that can measure both tissue microstructures in greater detail and microvascular blood flow may be useful [70]. Doppler OCT systems already exist that can detect very slow blood flow (<20 μm·s^{-1} in blood vessels as small as ~15 μm diameter). OCT technology could prove useful for structural and functional assessment of suspicious lesions, staging (invasion of basement membrane) and feedback during endobronchial therapy [68, 70, 71].

High-magnification video bronchoscopy

High-magnification bronchoscopy (Exera®; Olympus Optical Corp., Tokyo, Japan), combines both fibreoptic and video bronchoscope technologies to produce 100–110× better magnification of the bronchial wall compared with standard video bronchoscopes [72]. This technique enables the visualisation of microvascular networks in the bronchial mucosa. Increased vessel density in the bronchial submucosa is often present in squamous dysplasia and may play an early role in cancer pathogenesis [73]. Angiogenic squamous dysplasia is believed to be a potentially more aggressive pre-neoplastic lesion characterised by a collection of blood vessels juxtaposed to and projecting into an area of epithelial dysplasia. Increase in microvascular density can be seen under high magnification in the majority of areas of abnormal autofluorescence and enables better discrimination from mucosal inflammation [72].

Narrow band imaging

Narrow band imaging (NBI®; Olympus Optical Corp.) is a novel system that also utilises the changes seen in the microvascular network. This technique uses a narrow band filter rather than the conventional broad RGB filter used in standard video bronchoscopes. The conventional RGB filter uses 400–500 nm (blue), 500–600 nm (green) and 600–700 nm (red). NBI uses three narrow bands: 400–430 nm (blue; covers haemoglobin absorption at 410 nm), 420–470 nm (blue) and 560–590 nm (green). Blue light has a short wavelength, reaches into the bronchial submucosa and is absorbed by haemoglobin. On evaluation of airway lesions that were abnormal under autofluorescence imaging, this technique provided more accurate images of microvessels compared to high-magnification video bronchoscopy using broadband RGB technology. NBI, in comparison to standard white light video bronchoscopy, seemed to improve the detection of dysplasia/malignancy when used as an adjunct to white light in a small study [74]. Direct comparisons between narrow band imaging and autofluorescence bronchoscopy, in order to determine their relative merits, have not been conducted.

The choice of patients to investigate with these new imaging techniques, outside a research setting, remains under consideration. There is no current comprehensive lung cancer screening programme for asymptomatic smokers in Europe and North America, except in a research setting. At present, high-risk patients considered for further clinical assessment include those with sputum atypia and those with a previous, suspected or known lung cancer, particularly squamous cell carcinoma [9, 62, 75]. The accurate prediction of those patients who are at greatest risk and those who will develop progression of pre-malignant lesions to invasive cancer will be an important clinical tool. Currently, it appears that the presence of autofluorescence abnormalities may itself be a marker of field carcinogenesis and overall lung cancer risk [20, 62]. The presence of chromosomal aneusomy or a number of immunohistochemical markers in pre-invasive lesions may also be useful in prediction of lesion progression and lung cancer risk [76–80].

In summary, minimally invasive bronchoscopy-based technologies are currently available and are being further developed in

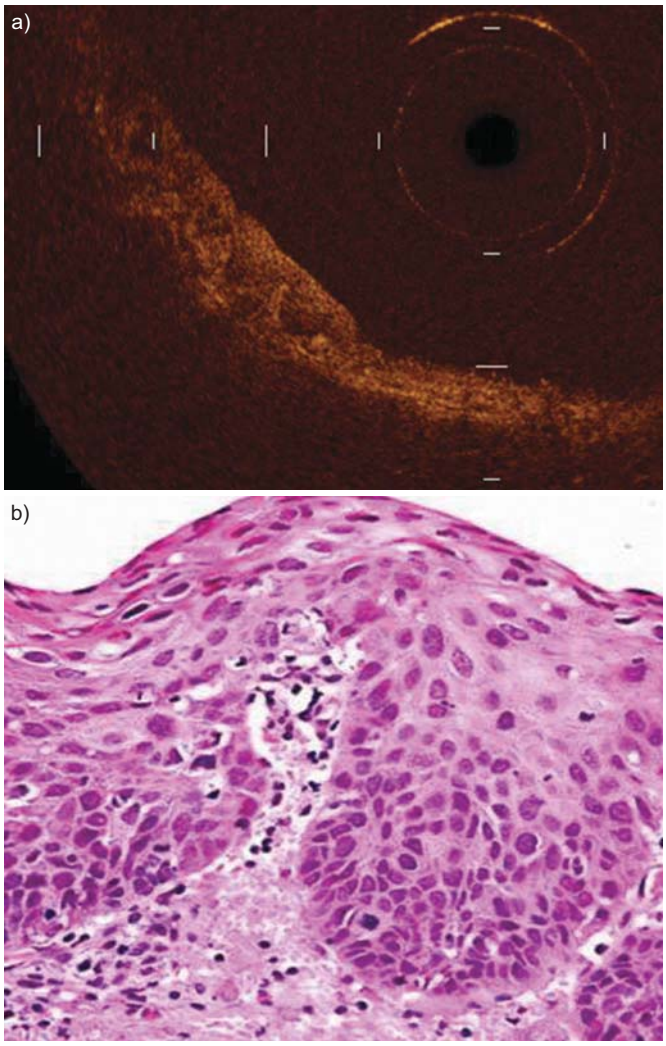

FIGURE 4. Optical coherence tomography image of a) an area of carcinoma *in situ* and b) corresponding haematoxylin and eosin stained histology section. Reproduced from [69] with permission from the publisher.

order to improve the accuracy for early detection of minute mucosal lesions that are clonally and potentially cancerous [5, 9, 18, 73]. Increased interest in the study of the natural history of these lesions, for the accurate prediction of those patients at highest risk, will continue to expand our ability to comprehensively approach the dynamic processes involved in early field carcinogenesis by exploiting the potentials of various optical imaging techniques [69, 81, 82]. Together with the advancements of single-fibre endoscopy combined with more accurate four-dimensional navigation beyond the visible spectrum, and distally towards the lung parenchyma, new technologies will even expand our ability to monitor disease processes that are, as yet, still out of bronchoscopic reach [83, 84].

STAGING FOR EARLY PROXIMAL LUNG CANCER PRIOR TO TREATMENT

Lesions that have invaded into the bronchial cartilage or wall are unlikely to be curable by bronchoscopic intraluminal therapy alone [7, 11, 57]. Surgical series and clinical trials with photodynamic therapy have been helpful in identifying lesions that are amenable to curative bronchoscopic therapy [7, 8, 11, 85]. Factors predicting the response of endobronchial therapy include intraluminal tumour growth, depth of invasion and lymph node involvement. Combined imaging and diagnostic technologies should be applied in the assessment of these lesions and assist in the choice of optimal treatment. The use of autofluorescence bronchoscopy, radial transducer endobronchial ultrasound for assessing deeper tumour infiltration, high-resolution thin-slice computed tomography and ^{18}fluorodeoxyglucose (FDG) positron emission tomography (PET), in addition to clinical assessment of patients and their comorbidities, may all influence management before choosing the optimal treatment strategy [85].

Bronchoscopic appearance

For bronchoscopic therapy, bronchoscopically accessible flat superficial lesions of $\leqslant$10 mm diameter with clear tumour margins are potential candidates. AFB is the best imaging modality for the assessment of these features, which cannot be adequately evaluated with white light imaging alone [57, 58]. AFB has the additional benefit of detecting the potential presence of synchronous lesions, which are relatively common in subjects with centrally located squamous cell carcinoma. Up to 20% patients may have a synchronous carcinoma and up to 45% patients may have other lesions of moderate or severe dysplasia [12–15, 38, 86].

Depth of invasion and lymph node assessment

Previously, prediction of depth of invasion and lymph node involvement have depended on the bronchoscopic appearance and relatively insensitive older generation computed tomography (CT) scan machines. Endobronchial ultrasound (EBUS) can assist in the depth assessment of tumour invasion, in addition to the current sophistication of multidetector CT scans, by using a radial transducer 20 MHz ultrasound probe inserted through the working channel of a flexible bronchoscope. This can delineate the layers of the bronchial wall apart from tumour invasion [87–89]. EBUS resulted in a change in management in 36% of tumours thought to be curable by bronchoscopic therapy after white light bronchoscopy and thoracic CT, and can be used as an adjunct to AFB in order to improve prediction of malignancy in lesions with significantly abnormal autofluorescence [90].

Thoracic CT scan can detect bronchial wall thickening, peribronchial extension and lymph node enlargement, and has been shown to alter clinical management in 22–35% of cases being considered for curative endobronchial therapy. It is also useful to exclude synchronous peripheral parenchymal cancers that may alter management [91]. The sensitivity and specificity of thoracic CT scans for the detection of lymph node metastasis is limited, at 50–70% and 66–89%, respectively [92, 93]. FDG-PET scan has been shown to perform better than thoracic CT scan for the detection of lymph node metastases, with sensitivity 67–91% and specificity 82–96% [92, 93]. A recent study comparing systematic sampling with EBUS-transbronchial needle aspiration (TBNA) with CT and PET scan showed that the sensitivities of CT, PET and EBUS-TBNA were 77, 80 and 92%, respectively; specificities were 55, 70 and 100%, respectively; and diagnostic accuracies were 61, 73 and 98%, respectively. The positive predictive values of CT, PET and EBUS-TBNA were 37, 47 and 100%, respectively; negative predictive values were 88, 92 and 97%, respectively [94].

Therefore, it is clear that the combined use of non- and minimally invasive imaging technologies are required to stage early proximal lung cancer adequately prior to choosing the optimal treatment strategy.

TREATMENT OF EARLY PROXIMAL LUNG CANCER

Surgery is currently still regarded as the accepted approach for the treatment of carcinoma *in situ* and results in 80–90% 5-yr survival rate [6–10]. However, it remains relatively wasteful, as significant normal lung parenchyma tissue also has to be removed. To obtain a cure, up to 30% of patients with early proximal lung cancer will require bilobectomy or pneumonectomy, and the remaining 70% require lobectomy [8]. Segmentectomy has been used in small series with good 5-yr survival rates (>90%) [7]. Synchronous lesions can be detected in up to 20% of patients and further metachronous lesions may develop in 14–30% of patients with central squamous cell carcinoma [4–15]. Therefore, surgery is not necessarily the only and primary choice based on considerations of significant comorbidities in this cohort of patients, owing to their smoking history, the chronic field carcinogenesis with potential developments of subsequent primaries and the necessity to conserve lung parenchyma for quality of life. Hence, there is significant interest in the use of various bronchoscopic modalities for the treatment of early central lung cancers and the reservation of surgical resection for lesions that are considered too locally advanced or those that have failed the initial bronchoscopic treatment attempt [11, 57].

Published comparisons of surgical resection to bronchoscopic therapy for carcinoma *in situ* and microinvasive squamous cell cancers do not exist and are unlikely to be performed in the near future, largely due to the infrequent occurrence of these lesions, which are often found by chance. Local bronchoscopic treatment is a straightforward and relative simple procedure, which does not hamper subsequent surgical resection in the case of treatment failure [57]. The similar outcome of early proximal lung cancers treated with bronchoscopic therapy or surgery are encouraging [9, 10, 57, 95, 96].

The cost of treatment and follow-up of bronchoscopically treated small stage 1A cancers in inoperable patients was 30% of the cost of standard surgery in matched operable patients in one published cost effectiveness analysis; obviously, surgical procedures are associated with greater morbidity [97].

Bronchoscopic treatment modalities

Treatment success with bronchoscopic techniques strongly depends on accurate staging, as has been discussed. Selected

TABLE 2 Early proximal cancer in the central airways treated with curative intent using various intraluminal bronchoscopic treatment methods

Study	Technique	Stage	Size cm	Lesions n	Complete response
Tokyo Medical University [96, 99–102]	PDT (HpD/Photofrin)	Stage 0 (n=185) Stage 1 (n=79)	<2	264	84.8% 93% ⩽1 cm 45% >1 cm
Sutedja [103]	PDT (Photofrin)	Stage 0 (n=17) Stage 1A/1B (n=22)	NA	39	72% Stage 0 100% Stage 1A/1B 50%
Cortese [104]	PDT (HpD)	Endobronchial	<2	23	65% 88% ⩽ 1 cm 33% > 1 cm
Kato [105]	PDT (NPe-6)	Stage 0 (n=23) Stage 1 (n=22)	<2	45	84.6%
Usuda [106]	PDT (NPe-6)	Stage 0 (n=37) Stage 1A (n=1)	<2	38	94% ⩽ 1 cm 80% > 1 cm
Deygas [107]	Cryotherapy	Stage 0/1A	NA	41	91%
van Boxem [108]	EC	Stage 0 (n=2) Stage 1A (n=13)	⩽1	15	80%
Vonk Noordegraaf [109]	EC/PDT/YAG laser	Stage 1A	⩽1	32 26 (EC) 5 (PDT) 1 (YAG)	97%
Pérol [110]	HDR brachytherapy	Endobronchial	⩽1	21	75%
Marsiglia [111]	HDR brachytherapy	Endobronchial	NA	34	85%
Cavaliere [112]	Nd:YAG laser	Stage 0	NA	38	63%

PDT: photodynamic therapy; HpD: haematoporphyrin derivative; NPe-6: *N*-aspartyl chlorin e6; EC: electrocautery; YAG: yttrium-aluminium-garnet; HDR: high dose rate; NA: information not available. Photofrin is manufacturered by Axcan Pharma, Mont-Saint-Hilaire, QC, Canada.

lesions should be limited to mostly flat-type squamous cell carcinoma *in situ* and microinvasive cancer of <1 cm with clearly visible distal tumour margins under AFB examination, while tumour invasion can be accurately excluded by EBUS. It is also obvious that lesions with nodal involvement cannot be regarded as early stage proximal lung cancer.

In the field of interventional pulmonology, many bronchoscopic therapeutic alternatives are currently applicable using various fibres and applicators through the working channel of the flexible bronchoscope. Consensus guidelines exist and have been previously published, and will therefore not be further described in detail [9, 22, 98]. Treatment techniques include: photodynamic therapy (PDT) using photosensitisers in combination with laser excitation; thermal coagulation using electrocautery, argon plasma coagulation or Nd:YAG (neodymium-doped yttrium-aluminium-garnet) laser; and cryotherapy using repetitive freezing and slow thawing and intraluminal irradiation or brachytherapy (mostly high dose rate). In general, the cure rate after these bronchoscopic techniques is in the range of 43–97% (table 2). A significant number of lesions may recur after treatment or require a second treatment to obtain cure [19, 86, 104]. However, failures are usually due to more extensive disease than seen on the original assessment [86, 108]. Many of the published series with these techniques include larger stage 1A tumours rather than limiting treatment to carcinoma *in situ* or microinvasive disease. In addition, many were performed without the assistance of more recent technologies, such as EBUS, AFB and PET imaging to assess lesion suitability. The success is clearly dependent on the stringent application of selection criteria for appropriate lesions, with a better response seen to correspond with lesions of smaller size (table 2) [113]. Less airway scarring and stenosis has been seen with electrocautery compared with PDT or YAG laser therapy [95]. These alternative bronchoscopic treatments emerged from the extensive experience of immediate palliative tumour debulking in dealing with imminent suffocation and larger airway obstruction. Their established role in lung cancer care have provided us with safe, quick and effective treatment alternatives for early proximal lung cancers that are intraluminally located [57, 98].

Previous reports have dealt with relatively small numbers of patients treated bronchoscopically as the majority of early proximal lung cancers are accidental findings. These lesions are often diagnosed during the clinical surveillance of high-risk individuals with various smoking-related (co)morbidities and in those after curative treatment of previous aerodigestive cancer [9]. This in itself is a valid argument for careful assessment of alternative treatment options prior to the consideration of surgical resection as the primary therapeutic choice. Bronchoscopic strategies are clearly less morbid and less toxic even if compared with radiotherapy [114]. For selected early central lung cancers, simple techniques such as electrocautery, argon plasma coagulation and cryotherapy can be conducted safely and quickly under local anaesthesia in the outpatient setting and provide superior cost-effectiveness [97].

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