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Tumour Review

Preinvasive disease of the airway

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ABSTRACT

Squamous cell carcinoma of the lung arises from preinvasive progenitors in the central airways. The archetypal model appears to be a stepwise morphological progression until there is invasion of the basement membrane. However, not every lesion appears to follow this course and many individuals can have stable disease, or indeed regress to normal epithelium. From our increased understanding of the molecular pathology it is becoming apparent that the respiratory epithelium accumulates progressive genetic and epigenetic insults in response to carcinogens. Still, little is known about how to predict those 'at risk' of progression, and it is likely that in the future molecular signatures will underpin prediction models of developing invasive lung cancer. Currently, autofluorescence bronchoscopy gives us the ability to follow the natural history of these lesions, with the prospect that detecting and treating lesions early may improve survival. However, treatment remains controversial, and radical therapies are offered to individuals with carcinoma in situ who may never develop invasive cancer. This has paved the way for the use of minimally invasive bronchoscopic treatments, which, while apparently effective, have not been tested in randomised controlled trials. In this paper we describe the known biology and natural history of preinvasive lesions and review the current treatment strategies.

Introduction

Lung cancer is the leading cause of cancer-related death. It accounts for nearly 1.4 million deaths worldwide every year, with a five-year survival rate of just 6%. In contrast to the steady increase in survival for most cancers, lung cancer outcome has barely changed in four decades [1,2]. Although surgical resection of early stage disease offers a prospect of cure [3], the vast majority of cases are diagnosed at a late stage with no hope of curative therapy. In contrast, prospects for patients with preinvasive or intraepithelial neoplastic lesions (stage 0), or early stage invasive cancers (Stage 1A) of the central airway, are far better, with a 5-year survival of >70% [3–6].

Squamous cell lung cancer (SQCC) is the second most common type of non-small cell lung cancer in the US and most common in the UK. It accounts for around a third of all lung cancers and commonly arises in the central airways [7,8]. While there is promise for improving survival rates by early detection of small peripheral cancers through computed tomography (CT) screening (reducing lung cancer deaths by 16–20% in smokers [9]), this may not always detect small central airway cancers or preinvasive airway disease. Preinvasive lesions are precursors of squamous cell carcinoma arising in the bronchial epithelium where the basement membrane remains intact [10]. They are readily accessible to bronchoscopic assessment and the development of autofluorescence bronchoscopy has provided a sensitive way of detecting these lesions in the airway [11].

Early detection and treatment of these lesions is critical to improving survival. Since these lesions are by definition non-invasive, one would expect them to be cured with surgical resection or radiotherapy. However, this clinical scenario is faced with 3 caveats: (i) these patients frequently have co-existing medical problems such as chronic obstructive pulmonary disease (COPD) and poor cardiopulmonary reserve making them poor candidates for surgery, (ii) they are often at high-risk of developing synchronous and metachronous lesions throughout the airway, and (iii) not all preinvasive lesions will progress to invasive cancer, with some regressing back to normal epithelium. Hence, a radical approach may not always be possible, or indeed required. Therefore, tissue-sparing bronchoscopic therapies such as photodynamic therapy (PDT) and other ablative techniques have been used to treat these lesions. An improved understanding of the natural history of preinvasive disease will however be crucial for effective risk stratification and patient selection.

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In this review we describe the natural history of preinvasive disease of the airway and its detection. We review the current understanding of molecular changes in preinvasive disease and their role as predictive biomarkers. Finally, we look at treatment approaches to preinvasive disease and current studies that are underway looking at the prevention of lung cancer.

Characteristics of preinvasive lung cancer

Qu. What pathological changes define pre-cancerous lesions of the airway?

Qu. How are preinvasive lesions classified?

Preinvasive bronchial epithelial lesions may occur over wide areas of the tracheobronchial tree and are particularly prevalent in individuals who have smoked heavily or developed synchronous invasive lung cancers [12]. These observations underpin the generally held opinion that squamous cell carcinomas (SQCC) develop through a series of morphological stages of increasing abnormality from basal cell hyperplasia, to metaplasia, dysplasia, carcinoma in situ (CIS) and then to invasive disease.

The World Health Organization (WHO) summarized the pathological grading of these progenitor airway lesions in the Histological Typing of Lung and Pleural Tumours by Travis et al. [10]. These were later revised in 2004, where the various grades of dysplasia and CIS were more clearly distinguished [13]. The pathological grades are summarized as per the latest edition in both Fig. 1 and Table 1 [14]. Squamous dysplasia may be mild, moderate, or severe, with severity being based on the progressive cytological aberration, loss of maturation and increasing involvement of the full thickness of the epithelium. The most important of these lesions is CIS, which sits on the extreme end of the spectrum where cytological aberration is extreme, mitoses occur at all levels, and maturation is absent. The usual form of CIS does not cause epithelial thickening, however a more unusual form exists where the lesion develops into an exophytic papillary growth that can cause mechanical airway obstruction, but remains free of mucosal invasion [15]. Although the WHO guidelines have been useful in distinguishing between the higher grades of dysplasia and CIS, there can be significant inter- and intra- observer variability in grading of specific preinvasive lesions, even amongst experienced pulmonary pathologists [16,17]. This is as a result of considerable overlap between the categories and in any particular sample a range of grades may be seen. Furthermore, such lesions are not frequently encountered by pathologists, and may be incorrectly graded due to small biopsy size. Consequently, many investigators [18–20] have categorized lesions into "high-grade" and "low-grade". This may minimize the risk of observer error in the histopathological reporting, and as described later seems to correlate to their risk of progression to invasive cancer.

Diagnosis and screening for preinvasive lesions and early cancers in the central airway

Sputum cytology

Qu. Is sputum cytology useful in detection and screening of preinvasive lesions?

The potential of sputum cytology as a non-invasive test for lung cancer was first raised by the longitudinal studies of Saccomanno et al. [21]. Sputum samples collected from uranium workers at high risk were found to contain cells with increasingly malignant features in those individuals who subsequently developed lung cancer [21]. When preinvasive lesions form throughout the respiratory epithelium as a consequence of carcinogenic exposure, exfoliated cells are consequently detected in the sputum. However, sputum gives no information on specific lesions in the airway, especially when they are multifocal. Further problems include poor sensitivity and variation in pathologist agreement [22]. Three large randomized controlled trials have evaluated screening with sputum cytology; despite increased detection of early stage lung cancers they failed to show improvement in overall survival [23–25]. However, there remains ongoing interest in this field in screening high-risk populations. Patients with COPD are at increased risk of developing lung cancer if they have abnormal sputum, and in a cohort of 2550 patients, 17.7% who were found to have at least moderate cytological atypia had a cumulative lung cancer incidence of 10% at 3 years and 20% at 6 years [26]. Ongoing screening trials in these high-risk subjects have combined sputum cytometry with bronchoscopy examination and are soon to report their findings [27].

Autofluorescence bronchoscopy

Qu. What is value of autofluorescence over white light bronchoscopy?

Qu. Can autofluorescence bronchoscopy be used for screening for early lung cancer?

The precise localization of microinvasive carcinomas and preinvasive lesions is difficult as they are not easily visualized with conventional white light bronchoscopy (WLB) [28]. Autofluorescence

Table 1
Summary of pathological changes occurring in preinvasive lesions of the airway.

Histological grade	Pathology
Low-grade lesions	
Mild dysplasia	Mild cellular atypia limited to lower ⅓ of airway epithelium Mild anisocytosis and pleomorphism Mitoses absent or very rare
Moderate dysplasia	More severe cytological disarray of lower ⅔ of airway epithelium Moderate anisocytosis and pleomorphism Mitotic figures confined to lower ⅓
High-grade lesions	
Severe dysplasia	High degree of cellular atypia and minimal cell maturation Disarray extends entire depth of epithelium, but without reaching the surface Mitotic figures confined to lower ⅔
Carcinoma in situ (CIS)	Extreme cytological aberration and chaos Uneven chromatin, variable nuclear size and shape, multiplicity of nucleoli and dyskariosis that extend throughout airway epithelium Mitotic figures through full thickness No infiltration of the basement membrane

Description: Categorizing lesion as either low- or high- grade lesions enables distinction of two groups of individuals that have noticeably different malignant potentials.
Footnotes: Summary of pathological descriptions based on Histological Typing of Lung and Pleural Tumours by Travis et al. [13].