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Diagnosis and management of typical and atypical lung carcinoids

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ABSTRACT

An estimated 20% to 30% of all neuroendocrine tumours originate in the bronchial tree and lungs. According to the 2015 World Health Organization categorization, these tumours are separated into four subtypes characterized by increasing biological aggressiveness: typical carcinoid, atypical carcinoid, large-cell neuroendocrine carcinoma and small-cell carcinoma. Although typical and atypical lung carcinoids account for less than 1–5% of all pulmonary malignancies, the incidence of these neoplasms has risen significantly in recent decades. Surgery is the treatment of choice for loco-regional disease but for advanced lung carcinoids there is no recognized standard of care and successful management requires a multidisciplinary approach. The aim of this review is to provide a useful guide for the clinical management of lung carcinoids.

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1. Introduction

Neuroendocrine tumours (NETs) are a group of neoplasms that arise from cells of the neuroendocrine system which are found in most organs of the human body (Klimstra et al., 2010). Lung NETs include a wide range of diseases and are traditionally classified into four subtypes characterized by increasing biological aggressiveness: typical carcinoids (TCs), atypical carcinoids (ACs), large-cell neuroendocrine carcinomas (LCNECs) and small-cell lung cancers (SCLCs). However, based on recent clinical and molecular data two categories can be distinguished: typical or atypical NETs also called lung carcinoids (LCs) and high-grade NETs (LCNECs and SCLCs) (Volante et al., 2015; Travis, 2014; Travis et al., 2015). Lung NETs account for approximately 20–30% of all NETs and represent about 25% of lung cancers. Of these, SCLC represents 15–20% and LCNEC 3–5%. LCs are rarer, representing only 1–5% of all lung malignancies, with an incidence rate of 5–10/1,000,000 person-years (Yao et al., 2008a; Modlin et al., 2003; Naalsund et al., 2010; Travis, 2009). The incidence of LCs has increased over the past 30 years when there has been greater effort to better characterize these neoplasms which require complex multidisciplinary approach. Whilst the management of high-grade NETs has been largely standardized over the past years, there is considerably less knowledge regarding the optimal management of LCs, particularly when there is advanced disease. Compared with non-small cell lung cancers (NSCLCs) and high-grade lung NETs, LCs are less aggressive and generally follow an indolent course. In these cases, surgery is the recommended approach where feasible, due to their low sensitivity to chemotherapy and radiotherapy (Yao et al., 2008a; Naalsund et al., 2010; Travis, 2010). Survival is generally favourable, with an estimated 5-year overall survival (OS) rate of 61–88% for ACs and 90% for TCs (Travis, 2010). For patients with resectable LCs surgery is the gold standard but treatment options are very limited for patients with metastatic or unresectable disease. In advanced cases prognosis is poor (5-year survival rate approximately 27% with a median OS of 17 months) and no standard treatment approaches exist (Klimstra et al., 2010; Yao et al., 2008a; Naalsund et al., 2010; Travis, 2010; Raz et al., 2015). Here we review the literature about available treatment strategies for LCs.

2. Methods

We performed an extensive review of the scientific literature concerning LCs. In particular, we investigated histopathological features, biochemical evaluation, radiological assessment and treatment strategies in the management of patients with LCs. We searched digital databases including Pubmed, EMBASE, Clinical trials.gov and the Cochrane Library using relevant keywords. The search was carried out using the following keywords: “lung carcinoids”; “lung typical carcinoids”; “lung atypical carcinoids”; “lung neuroendocrine tumours” associated with “prognosis”; “treatment”; “diagnosis”; “epidemiology”; “histopathology”; “biochemical evaluation”; “radiological assessment”; “carcinoid syndrome”; “surgery”; “somatostatin analogues”; “peptide receptor radiotherapy”; “chemotherapy” and “target therapy”. We used no restrictions in first instance. Subsequently we restricted the search to English language publications. In this review we did not include animal studies. The majority of the studies were excluded based on the publication title and content of abstract. Reference lists of the most important papers were also examined and some authors were contacted by e-mail for further information about their work. In the selection process we have favoured randomized clinical trials; meta-analyses; systematic reviews and cohort studies than case-control studies; case reports and case series. Abstract communications from the most important conferences on lung NETs have been considered. We analyzed the full text of all relevant scientific papers (abstracts were considered when extended version of the work was not available) and we evaluated the relevant information for the management of LCs. In particular; we focused on sample size; type of treatment regimens used; time of clinical follow-up and number of LCs reported.

Using the search criteria described, we examined 11,357 papers and abstracts and excluded 11,260 because irrelevant or of minor importance. The remaining 97 studies were considered in their full text versions.

3. Diagnosis

The vast majority of patients with LCs are asymptomatic and diagnosed incidentally. When symptoms are present, they involve directly the broncho-pulmonary tree and may include obstructive pneumonia, atelectasis and wheezing due to central airway obstruction. There is an equal male to female distribution and these tumours may occur at any age from 5 to 90 years (Hauso et al., 2008). Appropriate diagnosis of LCs requires biochemical evaluations, imaging and pathological assessment.

Functioning LCs are relatively infrequent (about 10–15% of cases) but if subclinical secretion is considered this rate increases to approximately 25% of cases (Ferolla et al., 2009). The most common hormonal syndrome associated with LCs is due to adrenocorticotropic hormone (ACTH) secretion and about 10–15% of all ACTH-dependent Cushing’s syndrome is ectopic. LCs are one of the most common causes of ectopic secretion of ACTH and account for approximately 1% of all patients diagnosed with Cushing’s syndrome (Isidori et al., 2006). The carcinoid syndrome, mainly due to serotonin or histamine secretion, is uncommon in LCs (overall 2–3% of cases) (Öberg et al., 2012; Vinik et al., 2000–2014). Symptoms may also be due to secretion of other hormones such as growth hormone (GH), growth hormone-releasing hormone (GHRH), antidiuretic hormone (ADH) and parathyroid hormone (PTH) (Isidori et al., 2006; Filosso et al., 2015a; Öberg et al., 2012; 2000–2014). Key features of the most important syndromes produced by functioning LCs are described in Table 1.

3.1. Biochemical evaluation

In the diagnostic process and follow-up of LCs the biochemical evaluation should be limited to plasma chromogranin A (CgA) measurement, blood count, electrolytes, liver and kidney function always associated with other diagnostic procedures (Ferolla et al., 2008). Specific tests must be performed only when there are symptoms suggesting hormonal secretion syndromes. Urinary dU-5-hydroxy indol-acetic acid determination is useful in patients with carcinoid syndrome. Serum cortisol, 24 h urine free cortisol, and ACTH level determination are performed in patients with Cushing’s disease. Plasma GHRH and insulin growth factor (IGF)-I are used in patients with signs of acromegaly (Isidori et al., 2006; Filosso et al., 2015a; Öberg et al., 2012; Ferolla et al., 2008; Vinik et al., 2010; Caplin et al., 2015).

3.2. Radiological assessment

The gold standard for radiological detection of LCs is contrast computed tomography (CT), despite more than 40% of cases may

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