Lung Cancer 74 (2011) 233–238

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Coexisting pulmonary nodules in operable lung cancer: Prevalence and probability of malignancy

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ARTICLE INFO

Article history:
Received 17 December 2010
Received in revised form 7 March 2011
Accepted 21 March 2011

Keywords:
Lung cancer
Pulmonary nodule
Diagnosis
Surgery
Computed tomography scan

ABSTRACT

Introduction: Coexistence of pulmonary nodules in operable non small cell lung cancer (NSCLC) may influence the therapeutic indication. The aim of this study was to evaluate prospectively the prevalence and the probability of malignancy of pulmonary nodules in operable lung cancer.
Methods: From a prospective database, all surgically treated patients diagnosed with NSCLC from 1998 to 2003 were retrospectively reviewed. Patients presenting pulmonary nodule(s) were identified.
Results: Two hundred thirty nine patients had a complete resection for a NSCLC and 56 patients (24%) presented altogether 88 nodules on thoracic CT. Twenty-four of these nodules (27%) were malignant, 28 (32%) benign and 36 (41%) of undetermined nature. Five factors associated with nodule's malignancy were identified: tumour histology (non-squamous (non-SCC) 44% vs. SCC 7%, $p = 0.001$), localization of the nodules in an upper lobe (vs. other lobe, $p = 0.004$), co localization in the same lobe as the NSCLC (vs. another lobe, $p = 0.03$), nodule size ($p = 0.05$) and shape (speculated vs. non spiculated, $p = 0.02$). From these factors, a probability score was assessed with a malignancy rate in SCC of 0% in nodules presenting $\leq$1 feature, 33% with 2 features and 100% with $\geq$3 features and in non-SCC of 40% with 1 feature, 82% with 2 features and 100% with 3 $\geq$ features.
Conclusion: Diagnosis of satellite nodules associated with early stage NSCLC is common. We developed a predictive score to estimate the probability of malignancy which may be a precious aid in the management of pulmonary nodules associated to a NSCLC.

1. Introduction

Recent advances in thoracic imaging with the widespread use of computed tomography (CT) has improved the management of non-small cell lung cancer (NSCLC) [1]. However, the sensitivity of this technique has increased and the detection of small pulmonary nodules is common during the staging evaluation for patients with lung cancer. In patients with an operable lung cancer, the coexistence of satellite lesions may change TNM status and influence the therapeutic indication. If a nodule is considered as malignant, NSCLC may be classified as stage T4 (nodule in the same lobe) or M1 (nodule in another lobe), or as synchronous multiple lung cancer in the 1997 classification [2] and T3 (nodule in the same lobe), T4 (ipsilateral nodules in different lobes) or M1a (controlateral pulmonary nodules) in the 2009 classification [3]. As prognosis is significantly better in patients with stage I (T1-2N0M0) or synchronous primary lung cancer than those with stage IIIB (T4N0M0) or stage IV (T1-2N0M1), the existence of malignant pulmonary nodules could be considered as a contraindication to surgery. Thus, to obtain a differential diagnosis between metastases and benign lesions is essential to choose the best therapeutic strategy.

Few studies have focused on pulmonary nodules in lung cancer patients. However, the diagnosis of these nodules coexisting with a known primary lung cancer remains a diagnostic challenge. Fiberoptic bronchoscopy is not often helpful in the diagnosis of peripheral pulmonary nodules [4] and the diagnostic sensibility of CT guided transthoracic needle aspiration is conflicting. For certain authors, transthoracic needle aspiration is less accurate in small pulmonary nodules [5], whereas other authors report a good diagnostic value, but a high rate of pneumothorax [6]. Interest in non-invasive procedures as 18F-fluorodeoxyglucose positron

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doi:10.1016/j.lungcan.2011.03.012

emission tomography (PET-FDG) is high, because of a good sensitivity (96%) and specificity (73%) [7]. However pulmonary nodules which are less than 1 cm in size or show ground glass opacities on CT cannot be evaluated accurately by PET [8].

The aim of this study was to evaluate prospectively the prevalence of pulmonary nodules coexisting in operable lung cancer, the rate and the probability of malignancy of these nodules.

2. Patients and methods

2.1. Patients

All patients diagnosed with lung cancer are registered in a prospective database. Data from surgically treated patients diagnosed with NSCLC between 15/08/1998 and 15/08/2003 were retrospectively reviewed to identify patients presenting at least one pulmonary nodule coexisting with lung cancer on initial thoracic CT.

2.2. Preoperative evaluation and follow up

All patients presented histological proven NSCLC according to the World Health Organization guidelines and tumour stage was defined by the 7th TNM classification [2,9]. Preoperative assessment included fiberoptic bronchoscopy, thoracic CT, abdominal CT, cerebral CT or MRI, and bone scan if bone metastases were suspected. Realization of 18F-fluorodeoxyglucose positron emission tomography (PET-FDG) was recommended but not mandatory, as access to this investigation was difficult at that time. Postoperative follow up included clinical examination and chest X-ray every three months and clinical examination and thoracic CT every six months during the first two years, and clinical examination and chest X-ray every six months and clinical examination and thoracic CT every year during the three following years.

2.3. Investigation of pulmonary nodules

The diagnostic procedures recommended for nodules coexisting with NSCLC depend on their localization with regard to the tumour. For pulmonary nodules situated in the same lung as the tumour, resection was considered. Contralateral nodules with a size $\leq$10 mm were evaluated by thoracic CT during follow up. Contralateral nodules with a size >10 mm were assessed by PET-FDG. If PET-FDG shows metabolic hyperactivity, resection was recommended. PET-FDG negative controlateral nodules were monitored during follow up.

2.4. Analyzed parameters

For each patient, the following characteristics were analyzed: age, sex, smoking status, performance status, personal history of cancer, tuberculosis (active or sequela) or pneumoconiosis, tumour histology, clinical and post operative TNM tumour stage (established without considering the pulmonary nodule(s)), type of surgery, localization of the tumour, PET-FDG results concerning the tumour, number of pulmonary nodules identified on thoracic CT and patient's outcome.

For each pulmonary nodule, its anatomical localization (upper lobe, lower lobe and middle lobe), its localization with regard to the tumour (same lobe, different lobes in ipsilateral or controlateral lung), its size, rate of calcifications, shape, and PET-FDG results were noted. During postoperative follow up, any modification in size of the nodule on thoracic CT was mentioned.

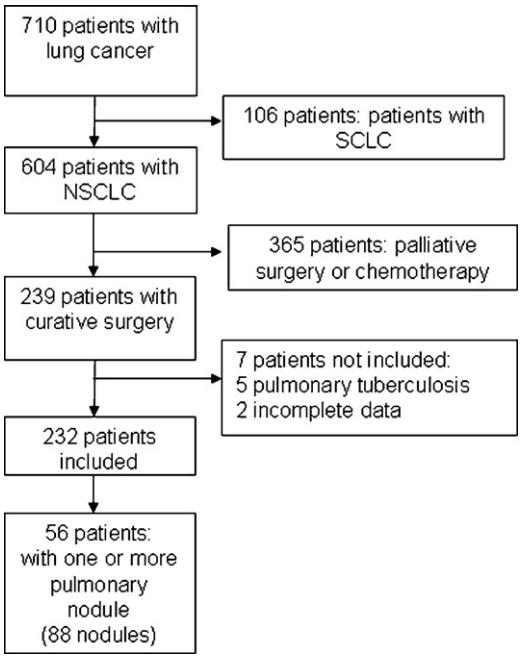

Fig. 1. Study algorithm.

2.4.1. Classification of pulmonary nodules and definition of patient groups

Three groups of pulmonary nodules according to their histological nature: benign, malignant or undetermined were considered. The diagnosis of malignancy of a nodule was established on histological analyses obtained by surgery, fiberoptic bronchoscopy or CT-guided transthoracic needle aspiration. A nodule was considered as benign when its benignity was histologicaly proven or when a nodule spontaneously disappeared or was stable in size over a period of at least 24 months. A nodule was considered of undetermined nature if the nodule cannot be clearly identified by the pathologist in the resected lobe when the nodule was in the same lobe or in the ipsilateral nodules in different lobes biopsied during the thoracotomy.

Furthermore, three groups of patients were identified according to the histological nature of the nodule(s): group of patients with malignant nodules, group of patients with benign nodules and a group of patients with nodules of undetermined nature. Patients presenting several nodules were put into the group of patients with malignant nodules if at least one nodule was malignant.

2.4.2. Statistical analyses

Statistical analyses for comparisons between groups were realized using Mann–Whitney's *U* test for continuous variables and Fisher's exact test for proportions. A value of $p < 0.05$ was considered statistically significant. The date of point was December 30, 2007.

3. Results

3.1. Patient's characteristics

Between 15/08/1998 and 15/08/2003, 604 patients were diagnosed with NSCLC and 239 patients had complete resection. Seven of these patients were not included (five presented active pulmonary tuberculosis with multiple pulmonary nodular lesions, and data of two patients were incomplete).

Fifty-six patients (24%) presented at least one pulmonary nodule coexisting with NSCLC on initial thoracic CT (Fig. 1). No signifi-