Topics in thoracic oncology: from surgical resection to molecular dissection

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Thoracic malignancies include tumours of the lung, pleura and mediastinum. Among those, lung cancer is by far the most frequent entity, and represents the first cause of cancer-related death worldwide. The vast majority of patients are diagnosed with advanced disease, preventing curative treatment (mostly consisting of surgical resection with or without adjuvant chemotherapy) from being performed [1]. Until recently, the treatment of these patients was confined to cytotoxic chemotherapy, which, over the past years, has been optimised through histology-driven decision making of regimens, combination with anti-angiogenic agents and development of maintenance strategies [1, 2]. The median overall survival of patients has been improved from an abyssal 8 months in the late 1990s to 15 months in the most recent phase III trials of the 2010s, but novel strategies are clearly needed [2].

Meanwhile, major progress has been achieved in the understanding of the molecular bases of lung cancer. Data from genomic, expression, mutational and proteomic profiling studies have emerged, first for lung adenocarcinoma and more recently for squamous cell carcinoma [3]. While being considered obscure and out of touch with the overall poor reality of cancer care in the clinical setting, these data led to the identification, among the numerous background molecular alterations observed, of specific oncogenic mutations being necessary and sufficient to drive tumour formation and maintenance, the so-called “addictive” mutations [3]. With the development of agents specifically designed to target these key signalling pathways, the paradigm is changing from the traditional view of chemotherapy, which, even if binding specific proteins, aims at destroying cancer cells as “massive destruction weapons”, thus producing toxicities to the non-tumoural tissues, leading to the potential inhibition of causative carcinogenesis processes by targeted, better tolerated agents.

Such an approach requires the accurate selection of patients based on the molecular characterisation of individual tumours, as these targeted agents are highly effective, both in terms of response rate and survival, but in specific molecularly defined subsets of tumours. Lung adenocarcinoma harbouring epidermal growth factor receptor mutations are the best illustration of the therapeutic relevance of such a strategy [4, 5]. More recently, anaplastic lymphoma kinase rearrangements have emerged as another driver of molecular alteration, predicting the clinical efficacy of specific inhibitors [5].

These developments actually complicate the physician’s decision-making process, especially when acquired resistance to these agents ultimately emerges, often after months of initially efficacious treatment and dramatic tumour response. Besides molecular switch towards other oncogenic pathways, histologic so-called “trans-differentiation” of lung adenocarcinoma tumours to small cell carcinoma has been reported, alternatively explained by treatment-induced selection of a sub-clone within the initial tumour. This unexpected dynamic of tumour cells, which has not been described in other tumour locations, remains to be molecularly better understood. Moreover, isolated extrathoracic metastasis, potentially driven by growth of dormant micrometastasis, may represent a frequent pattern of recurrence in patients receiving targeted therapies, bringing the issues raised by the management of oligometastatic disease back up to date. Some of the historical paradigms in lung cancer treatment may be disregarded, including the immediate switch of regimen at time of radiological progression, or the absence of re-challenge of one anti-tumoural agent during disease management.

Furthermore, while our knowledge has been increasing with regard to oncogenic mutations, the tumour microenvironment is emerging as a major player in lung carcinogenesis, both in the primary tumour and its metastases [6]. Beyond the classical analysis of invasion, metastatic and angiogenesis processes, inflammation and immune responses may represent potentially relevant therapeutic targets, as shown by recent therapeutic results of antibodies targeting signalling pathways that negatively regulate immune reactions against cancer cells. Thus, new prognostic and predictive biomarkers are emerging, both for early-stage and advanced tumours.

Other intrathoracic malignancies could also benefit from these conceptual progresses. The management of thymic epithelial tumours is a paradigm of cooperation between clinicians, surgeons and pathologists from establishing the diagnosis to organising the multimodal therapeutic strategy [7]. Surgery is the mainstay of the curative-intent treatment, as complete resection represents the most significantly favourable prognostic factor on overall survival. Similar to lung cancer, novel strategies are
needed, especially for refractory, recurrent tumours and thymic carcinomas, which carry a poor prognosis. Personalised approaches are currently being developed as potentially druggable molecular targets and are emerging from recent integrated genomic analyses.

Taken together, these developments led us to begin a series on thoracic oncology in the *European Respiratory Review* [8]. We aim at providing the reader with a complete viewpoint of the hottest topics, especially regarding the molecular characterisation of lung cancer, while including comprehensive reviews on landmark areas, such as surgery and echo-endoscopy. Ultimately, our objective is to highlight the variety of questions and answers that make the management of thoracic malignancies a model of implementation and achievement in respiratory medicine and oncology.

**STATEMENT OF INTEREST**
Conflict of interest information can be found alongside the online version of this article at err.ersjournals.com

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