Editorial on Early Stage Lung Cancer: Sublobar Resections are a Choice?

Early stage lung cancer: pathologist's perspective

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Presurgical diagnosis

Albeit considered less relevant in comparison to stage IV cancer, obtaining a cytological presurgical diagnosis of early lesion is strongly recommended whenever feasible (1).

The most common procedure used in clinical practice are represented by bronchoscopy, endobronchial ultrasound and CT-guided biopsy.

Those techniques demonstrated, in the recent years, satisfying rate of diagnostic adequacy and to provide enough material also for molecular testing (2-4).

When dealing with small (<1 or 1.5 cm) lesions several authors advise that performing CT-guided fine-needle aspiration can produce high diagnostic reliability rates (5-8).

Considered the increasing incidence of lung cancer diagnosed at early stage, the pathologist should be aware of the essential information's he is asked to provide for the correct management of the patient.

Prior to the 2000s, lung cancer was classified into the following two major groups: small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) (encompassing squamous cell carcinoma, adenocarcinoma (ADC), large cell lung carcinoma and sarcomatoid carcinoma).

Nowadays the new WHO classification of lung tumors (9) no longer supports this strategy, stressing the use of the specific terminology of ADC and squamous cell carcinoma (SCC) (versus SCLC) as much as possible.

The use the nomenclature "non-small cell lung carcinoma not otherwise specified" (NSCLC-NOS) should be saved for selected cases when a more precise diagnosis is not achievable considering both cytomorphology and immunohistochemistry.

Morphology

Morphological clues of glandular differentiation in ADC are expressed cytologically in different features: papillae with central fibrovascular cores, pseudopapillae, group of cells organized in flat sheets or three-dimensional structures, clusters with acinar structures with picket fence or honeycomb-like arrangement (10-13).

Cytologically cytoplasms in ADC usually are basophilic with homogeneous, granular or foamy appearance. Frequently cytoplasmic vacuoles can also be spotted.

Nuclei are usually eccentrically located with delicately granular, hyperchromatic or uniform chromatin arrangement. Macronucleoli represent a common finding.

On the other hand, squamous differentiation must be suspected with evidence of keratinization, pearls and intercellular bridges.

Cells usually show opaque or dense cytoplasm, less translucent compared to other NSCLC hystotypes. Cellular contours generally have rounded, ovoid or streched shape and nuclei are usually central, hyperchromatic, with rectangular outlines and squared-off edges.

Not infrequently chromatin is pyknotic meanwhile nucleoli are usually non-evident (10-13).

Unfortunately, morphology alone is frequently not a straightforward tool for a specific cytological differentiation, in this contest immunohistochemistry play the major role in distinguishing ADC versus SCC.

Immunohistochemistry

Limited immunohistochemical panel are strongly suggested in order to spare as much material as possible for

subsequent molecular analysis (14-16).

Several authors suggest to start the initial evaluation with TTF-1 and p40 antibodies, considered the most specific markers for ADC and SCC, respectively (13,17,18).

Specific stain for mucin (such as diastase–periodic acid-Schiff, mucicarmine, or Alcian blue) may also be useful to confirm the glandular nature of suspected ADC together with the expression of napsin A.

Other markers for squamous differentiation, namely cytokeratin 5/6, cytokeratin 7, 34βE12, and S100A7, can also be useful albeit qualified by less sensitivity and specificity (13).

In the commonly used diagnostic algorithm positive cases for TTF-1 and/or mucin with a negative p40 expression should be categorized as ADC, and those that are positive for a p40 and negative ADC marker should be defined as SCC.

Albeit TTF-1 and p40 are considered mutually exclusive exceptions can occur since some ADC could express squamous marker. In those cases, if tumor cells express TTF-1 the diagnosis should be NSCLC, favor ADC regardless of any positivity for squamous marker.

Moreover, if those markers are express differently in 2 morphological separate populations of cell the pathologist should be awarded that this could represent an adenosquamous carcinoma, despite this diagnosis can only be performed on resected sample (13).

When those markers are equally negative and when there is no clear-cut morphological evidence of squamous or glandular differentiations, further stains should be performed in order to confirm the epithelial nature of the lesion (such as pan cytokeratin markers), or to exclude other epithelioid tumors (melanoma, lymphoma, malignant mesothelioma, epithelioid hemangioendothelioma or metastasis).

Diagnostic challenges

Diagnostic error on cytology is estimated to occur in 15% of patient with lung cancer (19).

Reactive atypia basically represent the main source of false positive on this sample: inflammatory lesion, especially granulomatous inflammation, could sometimes elicit striking epithelial atypia resulting in incorrect over-diagnosis (20).

On the other hand, common reason for false negative results are represented by sampling error, particularly for small lesions. In this setting on-site evaluation of the sample by pathologist could minimize this problem (21).

Finally specimen from low-grade ADC cells, particularly those from ADC *in situ*, may be wrongly identified as histiocytes (22).

To date the IASLC/ATS/ERS histological subtyping applied on resected specimen for lung ADC (namely acinar, solid, lepidic, papillary, and micropapillary) (23), is not currently employed for cytological specimens.

Some Authors tried to classify those lesions also on cytological material but the majority of these articles failed in this attempt, also due to the mixed histotype frequently observed on the subsequent resected specimen (24-27).

More data are needed before grading on small biopsies and cytology can be formally recommended.

Diagnosis on surgical specimens

Early lung cancer potentially amenable to sublobar resection correspond radiologically to ground-glass opacification (GGO).

Since it has been demonstrated how this radiological finding usually correspond to early form of ADC (28), we will focus on this particular histotype in the following section.

ADC represent the most common histotype in NSCLC characterized by high clinical and microscopical heterogeneity.

During the last decades, several efforts have been made in order to create a reliable prognostic subtyping.

Those studies culminate in 2011 with a comprehensive update of the histologic classification included in the 2015 World Health Organization (WHO) classification (9).

The new classification confers different prognostic meaning to the five invasive subtypes. The best prognosis was assigned to lepidic predominant tumors while the poorest was allocate to solid and micropapillary predominant tumors.

Lesion exhibiting papillary and acinar predominant architecture were designated as tumors having an intermediate prognosis. Several subsequent studies confirmed this evidence (29-32).

In this classification, tumors entirely composed by the so-called lepidic pattern of growth (consisting in neoplastic cells expanding along the alveolar structures) were labeled as adenocarcinoma in situ (AIS) thus replacing the nomenclature of bronchioloalveolar carcinoma.

Moreover the new terminology of minimally invasive adenocarcinoma (MIA) was also proposed (9).

According to this new classification, lesions radiologically presenting as GGO on CT are to date considered to indicate a tumor composed essentially by lepidic component, suggestive therefore for AIS or MIA.

In detail AIS is defined as a localized small (≤3 cm) ADC with exclusive lepidic growth, lacking stromal, vascular, alveolar space or pleural invasion. Those ADC should be staged as pT1a and an extensive sampling is strongly recommended in order to avoid under-staging risks by missing any invasive component (33) due to the heterogeneity of these tumors (34).

However, this diagnosis is not free from diagnostic challenges since it should be discriminated from the atypical adenomatous hyperplasia (AAH), considered a premalignant lesion. This distinction can be difficult and pathologists should remember that even if AAH is usually smaller than 0.5 cm, larger lesions can also occur and, at the same time, that AIS can be smaller than 0.5 cm.

Tips for histological differential diagnosis should be searched once more morphologically: AIS typically is composed by more packed homogeneous cuboidal or columnar cells with more abrupt transition to adjacent alveolar lining cells (33).

The WHO criteria for MIA allow to defines as such solitary lesions smaller than 3 cm, with a predominantly lepidic pattern and ≤5 mm of invasion, without lymphatic or blood vessels invasion, pleural involvement, necrosis or spread through alveolar spaces (9).

The evaluation of the invasion foci could be difficult particularly if multiple foci are spotted in the same tumor. In this contest, recent data suggest to sum the percentage area of the invasive components and multiply the result for the main tumor diameter. If the result is ≤5 mm then the diagnosis of MIA should be formulated (35). Those tumors are to date classified as T1mi.

In a minority of cases GGO correspond histologically to invasive carcinoma, more frequently with lepidic, acinar or papillary pattern (36).

For those tumors, the main dimension represents one of the crucial predictors of outcome, causing it to be one of the most important elements of TNM staging.

Even if more evidences are still needed to confirm that, it is recommended to evaluate only the invasive component to assess the TNM staging, irrespective of the size and extent of the lepidic area (33).

The pathological precise discrimination between lepidic and invasive components is still a matter of challenging. On the other hand, the new classification demonstrated to have high reproducibly among pathologists, supporting the adoption of the "predominant pattern" strategy for subtyping invasive ADC (37).

Tumor spread through air spaces

Tumor spread through air spaces (STAS) was portrait as tumor cells present within air spaces of the parenchyma outside the tumor border. This phenomenon may occur morphologically with micropapillary structures (small papillary structures without fibro-vascular stalk), solid nests of tumor cells or even scattered discohesive single cells (38).

This evidence is now identified as a pattern of invasion in lung ADC particularly tricky since not visible on gross examination and without radiological method of detection.

Moreover, STAS is mostly overlooked on microscopic review also for the difficulties in its differentiation from alveolar macrophages.

To avoid misinterpretations pathologist should look for pigmented or foamy cytoplasms and for small regular uniform nuclei without atypia, peculiar for histiocyte.

The distinction of STAS from artifacts is also a demanding task: presence of cells in clusters often casually scattered over tissue or at the border of the tissue section, clusters with jagged edges, linear strips of cells lifted off of alveolar walls all represent feature favoring artifact rather than STAT (38).

Despite interpretation difficulties, detection of this pattern of invasion is particularly important for early stage lung carcinoma since it has been associated with higher incidence of loco-regional recurrence in patient treated with sub-lobar resection and also represent an independent prognostic factor for both recurrence-free survival and overall survival (39,40).

Pleural invasion

Pleural invasion remains to be an important prognostic factor for NSCLC able to reduce, when present, the survival rates.

Previous studies have shown that patients with visceral pleural invasion (VPI) yield significantly worse survival rates than patients without, therefore according to 8th edition of the TNM classification for NSCLC its presence increases the T descriptor from T1 to T2 and upstages a tumour from stage IA to stage IB, even if smaller than 3 cm in size (41).

Also in early stage lung cancer, the prognostic relevance of this feature has been demonstrated (42,43) although not

predictable by radiographic study and usually reported in low rate of patients (44).

Nevertheless, one study assessed the meaning of VPI in patient who underwent a sublobar resection (45) stating how completion lobectomy seem unnecessary for patient with VPI.

To date a careful examination of the visceral pleura is always suggest in order to collect all the prognostic information and formulate a thorough pathological report.

Molecular analysis

Since large trial showed no benefit using adjuvant targeted therapies in early stage lung cancer, molecular analysis is usually not required on these specimens.

Adjuvant immunotherapy trials employing anti-PD-1 and anti PD-L1 checkpoint inhibitors in stage I to III adjuvant setting are ongoing (1,46).

Recently several studies have explored prognostic prediction models by using molecular biomarkers from single omics data, in order to identify patients with heterogeneous prognoses.

Aim of these studies is to better stratify patients in order to select who may benefit from adjuvant therapy, nowadays proposed only to patients with resected stage IB disease and a primary tumor >4 cm (47-49).

To date large-scale, multicenter and prospective studies are still necessary to validate those promising models.

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