Editorial

Cytological Ki-67 in pancreatic endocrine tumors: a new "must"?

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Abstract: In the last decades, the incidence of neuroendocrine tumors (NETs) has been rising and this might be due to more awareness, improved diagnostic tools and a change in definition. The histopathological type of the tumor, its Ki-67 or MIB-1 proliferation index, size and location, as well as the age of the patient, seems to be the most important factor that affects prognosis and survival. In 2008, in one of our studies, we concluded that the cytological Ki-67 may improve the preoperative assessment of pancreatic NETs (pNETs), helping the clinician choosing the optimal therapeutical approach". Although the literature reports discordant opinions on the value of tumor proliferation markers in predicting a patient's prognosis, many studies have then reinforced the idea that Ki-67 expression in histological sections obtained from pNETs is an important predictor of their biological behaviour. The WHO classification of pNETs includes Ki-67 expression in the list of parameters (together with distant metastases, organ infiltration, dimension, angio/neuroinvasion, number of mitosis) determining the patient's prognosis. In conclusion we think that any study aimed to assess the correct biology and proliferative pattern of NETs contributes to the already known but still unclear attempt to define the correct individualized therapeutic strategy for each patient before surgery or any other therapeutic approach.

Keywords: Pancreas; neuroendocrine tumor (NET); endoscopic ultrasound (EUS)-guided fine needle aspiration; grading; Ki-67

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The cancer story: from its understanding to the targeted therapy

Many changes have occurred in medical science and practice over the last 50 years.

Especially, there has been much progress in genomics and in the understanding of the molecular pathways of cancer in the ten years since a draft sequence of the human genome was published. Opportunities for understanding health and disease are now unprecedented, as advances are harnessed to obtain robust foundational knowledge about structural, functional and biological mechanisms of tumors.

And since we're learning more about gene and biology changes that occurs in cells that cause cancer, we are increasingly able to develop therapies that target these changes, in the attempt to individualize medical strategies depending on the single patient and the single type of tumors.

The neuroendocrine tumors (NETs) story: from rare tumors to new classification systems

NETs are a heterogeneous group of rare neoplasms that account for 0.5% of all malignancies, with an incidence that is approximately 2/100,000 per year.

However, in the last decades, the incidence has been rising and this might be due to more awareness, improved diagnostic tools and a change in definition.

The largest and most recent analyses of the epidemiology of NETs have examined data from the USA [the surveillance, epidemiology and end results (SEER) programme] and Norway [the Norwegian registry of cancer (NRC)] (1-3). The USA data cover nearly five decades and—demonstrate a steady increase in the incidence, or reporting, of stomach and rectal tumors and a decrease in that of appendiceal NETs (1,3). There are reported ethnic differences in NET

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incidence, with African-Americans having the highest overall value at 6.5 per 100,000 per year (1). The overall incidence of NETs in Caucasians is 4.44 per 100,000 persons per year in the USA and 3.24 per 100,000 persons per year in Norway. Another analysis of the SEER dataset suggests that the rate of increase in the incidence of NETs has been from 1.09 to 5.25 per 100,000 persons per year between 1973 and 2004 (3).

Whatever the precise incidence of NETs, it appears that the number of patients presenting with these tumors has been steadily increasing (4). Indeed, since many NETs are slow-growing or of uncertain malignant potential, with even malignant NETs associated with prolonged survival, the prevalence of NETs is relatively high (4).

These increased numbers contribute to the development of new classifications and increasing knowledge of these tumors, which slowly allows clinician to individualize therapies as for the most common type of tumors. In particular, evaluating prognosis before surgery or any other type of therapy is mandatory for a correct individualized therapeutic approach.

The histopathological type of the tumor, its Ki-67 or MIB-I proliferation index, size and location, as well as the age of the patient (age >50 years is associated with a poor prognosis), seems to be the most important factor that affect prognosis and survival (4,5).

Length of survival is directly related to both the extent of the disease at the time of diagnosis and the degree of differentiation of the tumor. According to the SEER data, the 5-year survival of patients with well or moderately well-differentiated tumors was:

- 82% for local spread;
- 68% for regional spread;
- 35% for distant spread.

For poorly differentiated tumors these values were lower:

- 38% for local spread;
- 21% for regional spread;
- 4% for distant spread.

Newer pathological classifications aid in the prognostication of survival (6,7). Thus, the 5-year survival rates for grades 1, 2 and 3 tumors are 96%, 73% and 28%, respectively. Similarly, using the recommended TNM staging system, 5-year survival rates for stages I, II, III and IV are 100%, 90%, 79% and 55%, respectively, demonstrating the utility of such newer classifications.

According a recent study, both the 2010 WHO classification and the ENETS staging system are valid instruments for GE-NENs prognostic assessment, with TNM-based stage appearing to be the best available choice for clinicians, both alone and in association with other classifications (i.e., the 2010 WHO classification plus ENETS staging had a higher c-index) (8).

The beginning in 2008: Ki-67 in PETs

This attempt to determine tumor characteristics and biology before surgery or any other therapeutic approach seems to be mandatory since prognosis is extremely different for G1, G2 and G3 tumors, but even more because therapeutic strategies for those tumors are completely different.

In 2008 in a study performed in our institution we wrote: "*The cytological Ki-67 expression measured on cytological samples collected by endoscopic ultrasonography-guided fine needle aspiration cytology (EUS-FNAC) may provide pre-operative indications for pancreatic neuroendocrine tumors (pNETs) management. The aim of our study was to assess reliability of Ki-67 expression measured on cytological samples obtained by EUS-FNAC in patients with pNETs. Eighteen patients with pNETs underwent EUS-FNAC before surgery. Ki-67 expression was measured on FNACs and on histological sections. Using a cut-off of 2%, percent agreement of Ki-67 expression on cytological and histological samples was 89% [k-statistic: 0.78, 95% confidence intervals (95% CI): 0.5-1.0]. Using cut-off values of 2% and 10%, percent agreement was 78% (k-statistic: 0.65, 95% CI: 0.3-0.9). Ki-67 expression measured on cytological samples obtained by EUS-FNAC before surgery showed good agreement with that measured on histological samples*".

In that study we concluded that the cytological Ki-67 may improve the preoperative assessment of PETs, helping the clinician choose the optimal therapeutical approach (9).

New evidences

Although the literature reports discordant opinions on the value of tumor proliferation markers in predicting a patient's prognosis, many studies have then reinforced the idea that Ki-67 expression in histological sections obtained from pNETs is an important predictor of their biological behaviour (10-15). The WHO classification of pNETs includes Ki-67 expression in the list of parameters (together with distant metastases, organ infiltration, dimension, angio/neuroinvasion, number of mitosis) determining the patient's prognosis (16). Furthermore, some authors have demonstrated that Ki-67 index is associated with a patient's outcome, i.e., patients with pNETs with Ki-67 index >2% have a significant increased mortality compared with those with a Ki-67 index <2% (HRZ 11.7; 95% CI: 1.98-72.3) (12).

Conclusions

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Since the EUS-FNAC is a relatively noninvasive procedure, Ki-67 expression measured on cytological samples could be easily obtained in all patients with PETs before surgery. The preoperative availability of Ki-67 expression, combined with number and size of lesions, site of the tumor, expression of somatostatin receptors, peripancreatic infiltration, presence of distant metastases or multiple tumors, patients' performance status and clinical symptoms, may help the clinician choosing the best therapeutic approach. In the case of a single pancreatic lesion, the preoperative availability of Ki-67 expression may help in selecting the best surgical intervention between atypical resection (enucleation or middle pancreatectomy) and typical resection (pancreaticoduodenectomy or distal pancreatectomy). In patients with MEN-1 syndrome, who often have multiple pancreatic lesions arising at different times over the years, preoperative availability of Ki-67 expression may help with optimizing both extension and timing of surgery.

In conclusion we think that any study aimed to assess the correct biology and proliferative pattern of NETs contributes to the already known but still unclear attempt to define the correct individualized therapeutic strategy for each patient before surgery or any other therapeutic approach.

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