Role of estrogen and progesterone receptors in pathogenesis of gastroenteropancreatic neuroendocrine tumors

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Objectives
Gastroenteropancreatic tumors may present as metastatic disease without known primary site. Although the morphologic pattern and hormone production may be indicative of the primary site, surgical exploration may be necessary and successful. A positive expression of estrogen receptors has recently been demonstrated in pancreatic neuroendocrine tumors as well as in non-neoplastic islet-cells. This prompted us to systematically analyze the expression of both estrogen and progesterone receptors in a series of gastroenteropancreatic (GEP) neuroendocrine tumors (NET) as well as the proliferation and the morphologic pattern[1][2].

Material
We analyzed 159 neuroendocrine tumors (102 foregut GEP, including 56 pankreatic NET, 48 midgut GEP and 9 hindgut GEP). Furthermore we evaluated 92 metastases (27 hemagenous metastases and 65 lymph node metastases) from 49 cases.

Methods
The proliferation was evaluated by Ki67 and the morphologic pattern by HE-stain. The estrogen and progesterone receptors were evaluated by a consensus immunoreactivity score (IRS) according to Remmel (0-12). An IRS ≥ 2 was regarded as positive.

Results
There was a high correlation of primary tumor and metastases related to the proliferation (correlation coefficient r=0.826, which was more pronounced in lymph node metastases (r=0.879) than in hemagenous metastases (r=0.859). The morphologic pattern gave no indication of the primary site (p=0.053). Whereas non-pancreatic NET (primary tumor) were significantly more often estrogen receptor (ER) positive than pancreatic NET (p=0.001), we could not verify this result concerning the metastases (p=0.284) (Fig.1-3). However, pancreatic NET compared to non-pancreatic NET were significantly more often progesterone receptor (PR) positive (76.8% vs. 7.8%, p=0.000001). Even if we compared pancreatic NET with non-pancreatic foregut GEP (76.8% vs. 6.5%, p<0.000001), midgut GEP (76.8% vs. 8.3%, p=0.000001) and hindgut GEP (76.8% vs. 11.1%, p=0.0000092) a statistically significant difference was shown. Non-pancreatic NET metastases showed a positive PR-expression in only 2 lymph node metastases (3.4%) and in 15 pancreatic NET metastases (45.5%) (p=0.0000001) (Fig. 4-6).

Conclusions
• The proliferation showed a higher correlation between primary tumor and lymph node metastases than between primary tumor and hemagenous metastases.
• The progesterone receptor expression in GEP metastases is highly specific for pancreatic NET (specificity 96.6%, positive predictive value 88.2%). Therefore the PR-expression analysis may be of help in case of unknown primary site.
• The estrogen receptor expression of metastases gives no indication of primary site.

References

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