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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

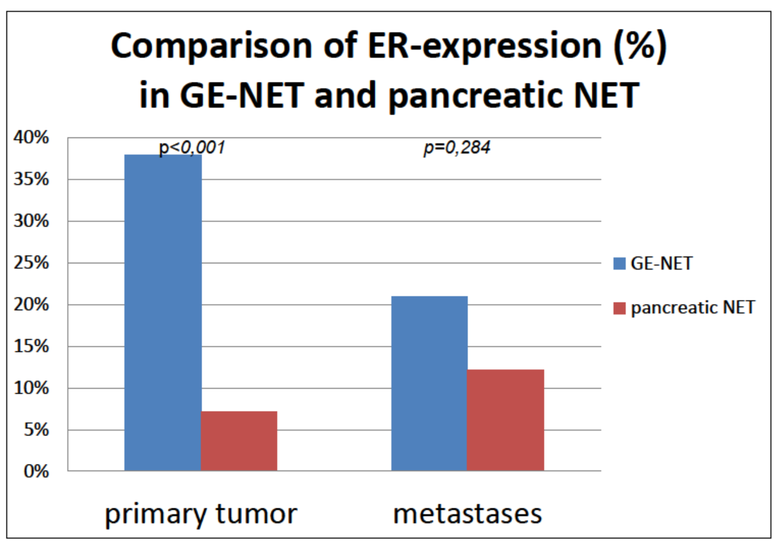
We analyzed 159 neuroendocrine tumors (102 foregut GEP, including 56 pankreatic NET, 48 midgut GEP and 9 hindgut GEP). Furthermore we evaluated 92 metastases (27 hematogenous metastases and 65 lymph node metastases) from 49 cases.

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 hematogenous metastases (*r=0,659*). 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 varify 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=0,000092*) 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<0,000001*) (Fig. 4-6).



ER positive (%)	primary tumor	metastases
GE-NET	39 (37,9 %)	13 (21%)
pancreatic NET	4 (7,1%)	4 (12,1%)

Fig. 1: Comparison of ER-expression in GE-NET and pancreatic NET and their metastases

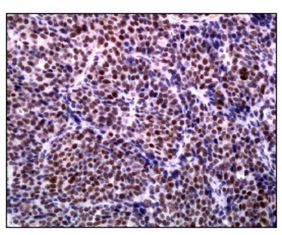


Fig. 2: ER positive stomach NET (IRS=8), original magnification, x 200

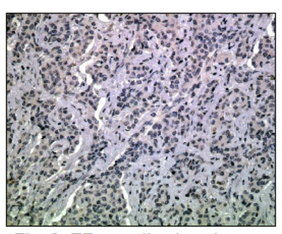
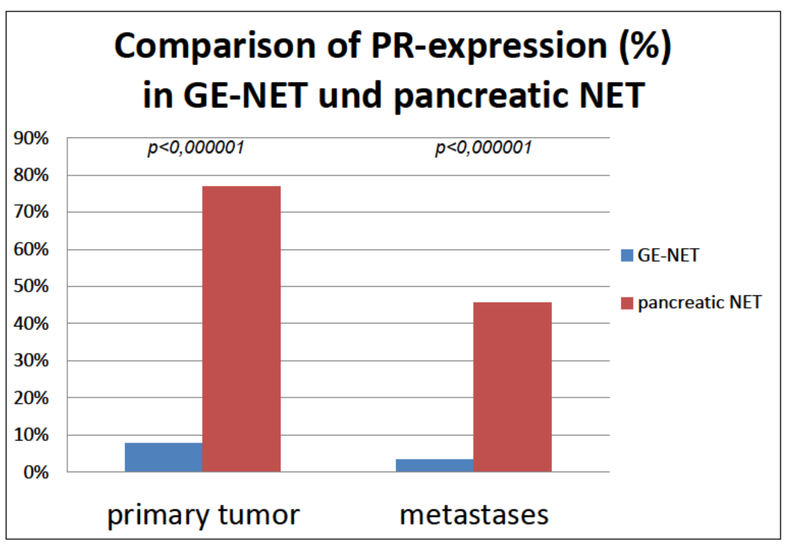


Fig. 3: ER negative lymph node metastasis of stomach NET (IRS=0), original magnification, x 200



PR positive (%)	primary tumor	metastases
GE-NET	8 (7,8%)	2 (3,4%)
pancreatic NET	43 (76,8%)	15 (45,5%)

Fig. 4: Comparison of PR-expression in GE-NET and pancreatic NET and their metastases

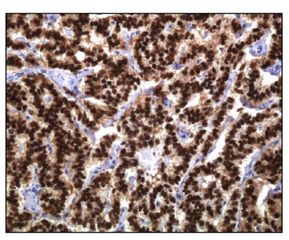


Fig. 5: PR positive pancreatic NET (IRS=12), original magnification, x 200

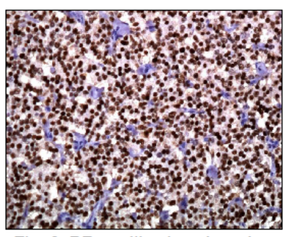


Fig. 6: PR positive lymph node metastasis of pancreatic NET (IRS=12), original magnification, x 200

Conclusions

- The proliferation showed a higher correlation between primary tumor and lymph node metastases than between primary tumor and hematogenous 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 unknowen primary site.
- The estrogen receptor expression of metastases gives no indication of primary site.

References

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