Comparison between MDCT post-contrastographic pattern and microvascular density (MVD) in pancreatic neuroendocrine tumors (PNET): correlation with the neoplasms nature

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Purpose

At the state of the art, the role of imaging in the identification of signs of malignancy of neuroendocrine pancreatic neoplasms (PNET) is based quite only on nodular dimension (according to the WHO-World Health Organization-classification system) and on the presence of local and distant spreading [1].

The aim of our study was firstly to demonstrate that a further criterion to suspect the lesion nature may be represented by their post-contrastographic behaviour.

Considering that authors [2,3] demonstrated a significant inverse correlation between the microvascular density (MVD) and the biological aggressiveness of the lesions, we supposed that the enhancement pattern may be related to lesion MVD and consequently significantly related to the biological aggressiveness of the tumour.

Therefore, the further aim of our study was to correlate multidetector CT (MDCT) post-contrastographic patterns of PNET with their MVD and biological behaviour (adenomas, borderline tumors and carcinomas: ADN, BRD and WDC, respectively).
Methods and Materials

The study included 12 cases of PNET and particularly 2 adenomas, 5 borderline tumours and 5 well differentiated carcinomas submitted to MDCT study and surgical resection.

All preoperative CT examinations were performed by a multidetector CT (Light Speed Plus, GE Medical System, Milwaukee USA or Light Speed VCT, GE Medical System, Milwaukee USA). Studies were performed by acquiring basal as well as post-contrastographic scans, after intravenous administration of high-concentration iodinated contrast medium (Iomeron® 400). Post-contrastographic study included 4 phases: early arterial phase (delay 15-20"); pancreatic phase (delay 35"); venous phase (delay 70") and late phase (delay 180"). At MDCT three different patterns of enhancement were defined (Fig.1): pattern A, including lesions showing an early enhancement (during early arterial or pancreatic phase) and a rapid wash-out (Fig.2) on page 6; pattern B, including lesions showing wash-in in the early arterial or pancreatic phase with no wash-out nor in the late phase (pattern B1) (Fig.3) on page 7, and lesions showing enhancement only in the venous and/or late phases (pattern B2) (Fig.4). on page 8

Fig.: Patterns of enhancement. After the iv injection of contrast material 3 different curves of enhancement were identified: pattern A: enhancement in the early arterial or pancreatic phase and a rapid wash-out; pattern B1: wash-in in the early arterial or
pancreatic phase with no wash-out nor in the late phase; pattern B2: enhancement only in the porto-venous and/or late phases.

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At MDCT, the greatest lesion dimension was also measured.

Pathological examination after surgery confirmed the suspicion of PNET.

Moreover, a quantitative evaluation of microvascular density was also performed on histological specimens of all 12 patients (4 for each post-contrastographic pattern) (Fig.5).

![Radiological Pattern vs Histology](image)

**Fig.** After surgical resection, pathological analysis demonstrated 2 adenomas, 5 borderline tumours and 5 well-differentiated carcinomas. All 2 ADN were associated with pattern A. Three out of 4 lesions showing a pattern B1 were classified as BRD at histological examination. Three out of 4 lesions with a pattern B2 resulted to be WDC at pathology. The remaining nodules were 1 borderline tumour and 1 well differentiated carcinoma, showing pattern A.

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Surgical specimens were fixed in formalin and then included in paraffin to obtain, once paraffin got cold and solidified, blocks for the cut microtome to get thin sections of 1-5 µm; tissutal sections were then posed on elettrostatically charged slides.

These slides were used for the immunohistochemical examination to highlight the presence of proteins into the tissue by means of specific antibodies, previously binded with an enzyme (usually a peroxidase) transforming substratum and coloring the tissue of brown. Then, the entire sectional surface was covered by using a monoclonal primary antibody (anti-CD34, diluted 1:1000).

We analyzed the slides by means of a computed system (Olympus BX-51, software AnalySIS^B) consisting of a microscope and a calculator connected by a high resolution digital camera that permitted to obtain variable grade of enlargement (4X, 10X, 20X and 40X). We evaluated six fields for each patient obtaining a surface of 0.588 mm$^2$ for each field. The software AnalySIS^B allowed to automatically calculate the vascular surface identifying the brown areas (corresponding to CD34 immunoreactivity); the relative vascular surface (MVD) was obtained from the ratio of coloured brown surface and total section surface.

For WDC also the presence of fibrosis was evaluated at pathology.
Fig. 0: Patterns of enhancement. After the iv injection of contrast material 3 different curves of enhancement were identified: pattern A: enhancement in the early arterial or pancreatic phase and a rapid wash-out; pattern B1: wash-in in the early arterial or pancreatic phase with no wash-out nor in the late phase; pattern B2: enhancement only in the porto-venous and/or late phases.

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**Fig. 0:** Pattern A-After contrast medium injection, the neuroendocrine lesion located in the tail of the pancreas shows a vivid enhancement during the early arterial phase; the wash-in is still evident during the pancreatic phase, while the lesion appears as isodense in the porto-venous and late phase.

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Fig. 0: Pattern B1-After contrast medium injection, the neuroendocrine pancreatic neoplasm shows vivacious enhancement yet during the early arterial and pancreatic phase; the lesion still appears as hyperdense in respect to the surrounding parenchyma in the venous and late phases.

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Fig. 0: Pattern B2-The lesion of the pancreatic head appears as isodense in respect to the parenchyma in the early arterial and pancreatic phases. Only during the porto-venous phase the lesion shows a mild enhancement, that becomes really evident in the late phase.

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Fig. 0: After surgical resection, pathological analysis demonstrated 2 adenomas, 5 borderline tumours and 5 well-differentiated carcinomas. All 2 ADN were associated with pattern A. Three out of 4 lesions showing a pattern B1 were classified as BRD at histological examination. Three out of 4 lesions with a pattern B2 resulted to be WDC at pathology. The remaining nodules were 1 borderline tumour and 1 well differentiated carcinoma, showing pattern A.
Results

After surgical resection, pathological analysis demonstrated 2 adenomas, 5 borderline tumours and 5 well-differentiated carcinomas.

We demonstrated that all 2 ADN were associated with pattern A. Three out of 4 lesions showing pattern B1 were classified as BRD at histological examination while 1 out of 4 resulted to be a WDC. Three out of 4 lesions with pattern B2 resulted to be WDC at pathology, while 1 out of 4 was a BRD. The remaining nodules were 1 borderline tumour and 1 well differentiated carcinoma, showing pattern A (Fig. 1).

![Radiological Pattern vs Histology](image)

**Fig.**: After surgical resection, pathological analysis demonstrated 2 adenomas, 5 borderline tumours and 5 well-differentiated carcinomas. All 2 ADN were associated with pattern A. Three out of 4 lesions showing a pattern B1 were classified as BRD at histological examination. Three out of 4 lesions with a pattern B2 resulted to be WDC at pathology. The remaining nodules were 1 borderline tumour and 1 well differentiated carcinoma, showing pattern A.

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MVD evaluation demonstrated a statistically significant difference among the 3 CT patterns (p<0.0001) showing the lower levels of MVD for lesions with CT pattern B2 (Fig. 2).
Fig.: MVD evaluation demonstrated a statistically significant difference among the 3 CT patterns.

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By comparing CT findings to histological results we demonstrated a high MVD value for ADNs (average level: 463 vessels/mm²), middle level of MVD for BRDs (average level: 373 vessels/mm²) and low level for WDCs (average level: 237 vessels/mm²), with a significant (p=0.0291) difference between ADNs and WDCs, thus confirming previous results of Couvelard study (2005) *(Fig.3).*
Fig.: By comparing CT findings to histological results we demonstrated a significant (p=0.0291) difference between ADNs and WDCs, thus confirming previous results of Couvelard study.

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Grouping together non-malignant lesions (2 ADN and 5 BRD), we obtained a statistically significant difference (p=0.0252) between the 2 groups, while by using the Couvelard system (MVD=number of vessels/surface unit) the difference resulted to be not significant (p=0.1096) (Fig.4-5).
Fig.: Grouping together non-malignant lesions (2ADN and 5BRD), we obtained a statistically significant difference (p=0.0252) between the 2 groups.

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Fig.: By using the Couvelard system (MVD=number of vessels/surface unit) the
difference resulted to be not significant (p=0,1096)

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Regarding malignant lesions, the analysis of pathological findings showed that
other important parameters may be considered. We identified statistically significant
differences between WDC showing pattern A and B2 (p=0,0045). We observed that
B2 lesions showed nodal (N+) and distant (M+) spreading more frequently (80% and
60%, respectively) than tumours having pattern A; they also presented more frequently
tumoral fibrosis (80% of cases) (p<0,01), associated with hemosiderin pigment in the
cases showing higher desmoplasia, that represent morphological findings suggesting a
longer disease time (Fig.6).
Fig.: Regarding malignant lesions, we identified statistically significant differences between WDCs showing pattern A and B2 (p=0.0045). We observed that B2 lesions showed nodal (N+) and distant (M+) spreading more frequently (80% and 60%, respectively) than tumours having pattern A; they also presented more frequently tumoral fibrosis (80% of cases).

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Furthermore, fibrosis may explain the post-contrastographic behaviour of carcinomas, that usually show a delayed wash-out nor wash-out after iodinate contrast medium administration; it is probably due both to the presence of a lower vascularization (low MVD value), both to the existence of fibrous tissue caused by reparation mechanisms consequent from regressive phenomena occurring into malignant lesions.

This is partially supported by the observation that well differentiated carcinomas lacking of fibrosis showed pattern A (1 case) or B1 (1 case), maybe representing younger lesions.
Fig. 0: After surgical resection, pathological analysis demonstrated 2 adenomas, 5 borderline tumours and 5 well-differentiated carcinomas. All 2 ADN were associated with pattern A. Three out of 4 lesions showing a pattern B1 were classified as BRD at histological examination. Three out of 4 lesions with a pattern B2 resulted to be WDC at pathology. The remaining nodules were 1 borderline tumour and 1 well differentiated carcinoma, showing pattern A.

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**Fig. 0:** MVD evaluation demonstrated a statistically significant difference among the 3 CT patterns.

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Fig. 0: By comparing CT findings to histological results we demonstrated a significant (p=0.0291) difference between ADNs and WDCs, thus confirming previous results of Couvelard study.
Fig. 0: Grouping together non-malignant lesions (2ADN and 5BRD), we obtained a statistically significant difference (p=0.0252) between the 2 groups.
Fig. 0: By using the Couvelard system (MVD=number of vessels/surface unit) the difference resulted to be not significant (p=0.1096)
Fig. 0: Regarding malignant lesions, we identified statistically significant differences between WDCs showing pattern A and B2 (p=0.0045). We observed that B2 lesions showed nodal (N+) and distant (M+) spreading more frequently (80% and 60%, respectively) than tumours having pattern A; they also presented more frequently tumoral fibrosis (80% of cases).

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Conclusion

At the state of the art, the best available criteria to formulate a suspicion of benignity/malignancy of a neuroendocrine pancreatic lesion are the presence of a clinical syndrome, the lesion dimension (according to the WHO classification system) and the presence of signs of local or distant invasion at imaging [1]. On the basis of our experience, the lesion post-contrastographic pattern at MDCT may represent a further criterion for suspecting lesion malignancy. In fact, studies [4] have demonstrated an association between MVD and degrees of tumour enhancement.

The introduction of many subsequent post contrastographic acquisitions for the identification and characterization of neuroendocrine pancreatic neoplasms found its reason in the characteristic hypervascularity of such tumors. By considering MVD value, we obtained a significant correlation among lesions post-contrastographic patterns, biological behaviour and levels of MVD, resulting in a higher vascularization for adenomas and lower levels of MVD for carcinomas, as previously reported by other authors [2,3]. Moreover, in neuroendocrine neoplasms, it is possible to find out a different organization of the vascularization; in small benign lesions, the multiple neovessels maintain a regular architecture and distribution, while in malignant nodules, because of a disorganized angiogenesis, neovessels result to be dysmorphic, thus leading to an abnormal lesion in and out flow. This different vascular structure is the main reason of the different post-contrastographic behaviour of malignant neoplasms, as reported in literature. On the basis of these statements, it is then possible to affirm that the persistence of contrast enhancement during a late phase may be considered as a prognostic sign of malignancy, being related to the lack of organization of the vascular structures and to the thrombosis into the perilesional capillaries, that retards the normal lesion wash-out [5,6,7]. Moreover, malignant lesions corresponding to pattern B2, are characterized by higher amount of fibrosis, that further justifies the delayed wash-out.

MDCT perfusion data have been shown to strictly correlate with the intratumoral MVD, that may have prognostic value [8]. However perfusion is usually performed in previously diagnosed PNET, while the added value of our study can be the possibility to characterize lesions both in term of nature and aggressiveness in a single diagnostic MDCT exam.

In conclusion, MDCT may suggest the nature of a neuroendocrine pancreatic neoplasm and particularly, the lesion post-contrastographic pattern may represent a further criterium, significantly related to the MVD, for suspecting lesion malignancy.
References


