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Pancreatic endocrine tumors with ductules [author's reply]

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Clarification of Criteria for (i +) Nodes Associated With Breast Carcinoma

To the Editor:

The recently published review by Lerwill² incorrectly states that "(i +)" is used to indicate when metastatic deposits ≤ 0.2 cm are detected only on immunohistochemical stains. First, the "(i +)" stands for isolated tumor cells and not immunohistochemistry, as was implied. Second, this designation is used when epithelial deposits are identified measuring ≤ 0.2 mm, not centimeters, as was stated. Third, the method of detection of the isolated tumor cells has no impact on the stage, although as indicated in a note in the *AJCC Cancer Staging Manual* (6th ed),¹ they are usually detected by immunohistochemical staining. This appears to be a common misconception among pathologists, surgeons, and oncologists.

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REFERENCES

- Green FC, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual*, 6th ed. New York: Springer-Verlag, 2002.
- Lerwill MF. Current practical applications of diagnostic immunohistochemistry in breast pathology. *Am J Surg Pathol*. 2004;28:1076–1091.

Clarification of Criteria for (i +) Nodes Associated With Breast Carcinoma

Author's Reply:

In my recent review,² I stated that the special identifier "i+" is used to indicate when metastatic deposits ≤ 0.2 cm are "detected only on immunohistochemical stains." I intended this comment to clarify the nodal classification of metastatic deposits of this size when they

are found *only* by immunohistochemical methods, and I did not mean to imply that this is the *only scenario* in which the "i+" identifier is used. As Drs. Tickman and Wang state in their letter, the "i+" designation is used for metastatic foci ≤ 0.02 cm, regardless of whether the deposits are detected on hematoxylin and eosin or cytokeratin stains (ie, pN0(i+)).⁴ The "i+" identifier is also used for micrometastatic foci (>0.02 cm and ≤ 0.2 cm) that are detected on immunohistochemical stains alone (ie, pN1mi(i+)).^{1,3,4} Furthermore, in Table 1 provided by Singletary and Greene in their discussion of the revised TNM classification, they also use the "i+" identifier for metastatic foci >0.2 cm detected by immunohistochemistry (ie, pN1a(i+)) for a 0.3-cm metastasis.⁴ Although confirmatory hematoxylin and eosin slides are likely to be available with metastases >0.2 cm, resulting in the uncommon use of "i+" in this setting, it appears that metastases of this size are not simply N1 (with secondary designation of a, b, or c) as I stated but may also bear an "i+" identifier.

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REFERENCES

- Green FC, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual*, 6th ed. New York: Springer-Verlag, 2002.
- Lerwill MF. Current practical applications of diagnostic immunohistochemistry in breast pathology. *Am J Surg Pathol*. 2004;28:1076–1091.
- Singletary SE, Allred C, Ashley P, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol*. 2002;20:3628–3636.
- Singletary SE, Greene FL. Revision of breast cancer staging: the 6th edition of the TNM classification. *Semin Surg Oncol*. 2003;21:53–59.

Pancreatic Endocrine Tumors With Ductules

To the Editor:

We would like to compliment van Eeden and colleagues on their meticulous study, which confirms the non-

neoplastic nature of ductules encountered in pancreatic endocrine tumors.³ They have concluded from clonality studies and immunohistochemistry that the ductular component is entrapped rather than a neoplastic process. We have commented previously on the presence of ductules in pancreatic endocrine tumors,¹ and we wish to present some additional observations.

Four cases of so-called ductulo-insular pancreatic endocrine tumors were retrieved from the files of the Departments of Pathology, University Health Network, Toronto, and Wayne State University, Harper University Hospital, Detroit. All 4 cases were clinically symptomatic insulin-producing tumors. It is worth noting that 9 of 16 cases reported by van Eeden et al³ and 6 of 15 cases in the series by Deshpande et al² were insulin-producing endocrine tumors.

Microscopically, all 4 cases showed tubules intimately associated with the endocrine elements. Many of the cytologically benign tubules were centrally located within these tumors. Focal chronic pancreatitis, remote to the tumor mass, was present. In addition, all the tumors were characterized by dense stromal sclerosis in which the ductules were embedded. This latter feature was also commented on by Deshpande et al.²

We agree with van Eeden et al³ that the ductules are non-neoplastic; we would like to reiterate that the prevalence of insulin production and stromal fibrosis raises the question whether these two features are involved in the process. It would appear that both insulin and stromal sclerosis are recurring and common threads in this characteristic pancreatic endocrine tumor. It is well recognized that factors, such as insulin-like growth factor and transforming growth factor alpha and beta, are capable of inducing fibrosis. Are the ductules merely resident entrapped ductules or are they proliferating in reaction to the extensive stromal fibrosis and growth factors? In our cases, the ductules were clustered and multiple, and their number, size and distribution suggest a non-neoplastic, proliferative process. It is possible that these ductules are proliferating in response to the "trophic" or "proxicrine" effect of the endocrine

cells. If this is the case, then this phenomenon may introduce a new perspective to endocrine–exocrine interaction in the pancreas, and to the age-old question of whether local endocrine activity has any role in the initiation and progression of ductal neoplasia, and indeed, in influencing the aggressiveness of ductal adenocarcinoma by exerting a “proxicrine” effect, a term coined by Dr. Murray Korc (personal communication, Utah, September 1999). This term has been used to describe the trophic effect of endocrine cells that are in close proximity to ductal cells, as opposed to either autocrine or paracrine activity. These are issues that warrant separate consideration and further scrutiny.

The nature of the ductules may present an intriguing intellectual exercise, but from a practical point of view, it is important to recognize this particular type of endocrine tumor at frozen section

as the ductules embedded within a sclerotic stroma can be mistaken for ductal carcinoma of the pancreas.

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REFERENCES

1. Chetty R, Asa SL. Ductules in pancreatic neuroendocrine tumors. *Am J Surg Pathol.* 2004;28:417.
2. Deshpande V, Selig MK, Nielsen GP, et al. Ductulo-insular pancreatic endocrine neoplasms: clinicopathological analysis of a unique subtype of pancreatic endocrine neoplasms. *Am J Surg Pathol.* 2003;27:461–468.

3. van Eeden S, de Leng WWJ, Offerhaus GHA, et al. Ductuloinsular tumors of the pancreas. *Am J Surg Pathol.* 2004;28:813–820.

Pancreatic Endocrine Tumors With Ductules

Authors' Reply:

The comments by Chetty and colleagues are very much appreciated, and we agree that it is critical to appreciate the nonneoplastic nature of the ductules for proper diagnosis. As far as the mechanisms and the pathogenesis are concerned, a number of questions remain.

Whether or not the phenomenon of entrapped ductules needs to be regarded as quite typical for insulinomas depends on the prevalence of insulinomas in the group of pancreatic endocrine tumors (PETs) with entrapped nonneoplastic

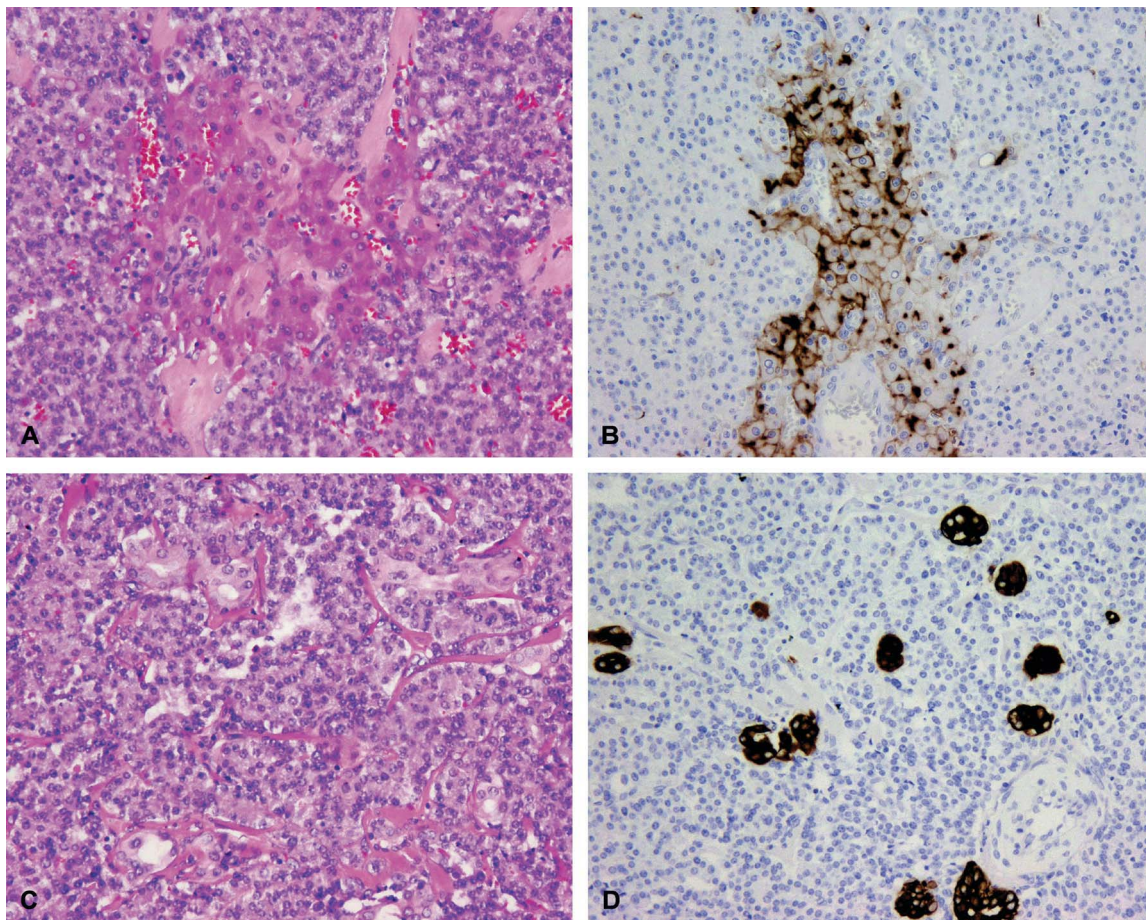


FIGURE 1. Liver metastasis of a previously reported PET with entrapped nonneoplastic ductules. The metastasis contains both entrapped hepatocytes (A), as confirmed in the CD10 immunostaining for bile canaliculi (B), and ductules (C), as confirmed in the cyokeratin 7 immunostaining (D). Data from van Eeden et al.³

ductules compared with the number of insulinomas in the group of conventional PETs. Up to 60% of the conventional PETs have been reported to be insulinomas.⁴ In this respect, the findings of 6 insulinomas in the group of 15 PETs with entrapped nonneoplastic ductules (40%) reported by Deshpande et al² and 9 in 16 cases (56%) in our own study³ are not unexpected. That ductules were found in the majority of 40 PETs reviewed at the Toronto institution as reported in a previous letter¹ also suggests that this phenomenon is not specific for insulinomas.

Based on the observation that the ductules are multiple and clustered, Chetty and colleagues propose that they result from a nonneoplastic proliferative process. However, in our experience, the ductules do not contain mitotic figures and show a very low proliferative rate based on Ki-67 immunohistochemical staining. Therefore, if proliferation plays a role, it has to be an extremely slow process. In our opinion, ductular transformation is another possible pathogenetic mechanism. Our results are not consistent with ductular transformation of the neoplastic endocrine cells, as suggested by Deshpande et al,² but ductular transformation of entrapped acinar cells from the surrounding pancreas, a phenomenon frequently observed in chronic pancreatitis, is possible. Alternatively, the ductules could represent residual entrapped pre-existing small intralobular ductules that remain within the growing endocrine tumor following atrophy of the acinar elements. A similar juxtaposition of

ductules and islets is seen in areas of chronic pancreatitis where there is extensive acinar atrophy (“ductuloinsular complexes”). Indeed, chronic pancreatitis was observed in 11 of our 16 cases.

Moreover, as we have shown, ductules are not the only structures entrapped by PETs. In some of our cases, normal pancreatic islets were also found within the tumors.³ Interestingly, after submission of our manuscript, one of the patients included in our study (case no. 3) underwent resection of liver metastases. He also had developed symptoms of hypergastrinemia. Histologically, the tumor nodules in the liver showed the features of a metastatic PET, and in one of these nodules not only ductules, but also clusters of hepatocytes were found (Fig. 1). While the ductules within the metastatic tumor may be either entrapped bile ducts or transformed hepatocytes, the presence of pancreatic islets in primary PETs and hepatocytes in a liver metastasis indicates that entrapment of nonneoplastic elements certainly occurs, perhaps accompanied by transformation or proliferation.

These observations do not exclude, as suggested by Chetty et al, that PETs produce trophic factors that exert their influence on the surrounding tissue and induce the fibrosis observed in the tumors. But taking into account that not all PETs with entrapped structures are insulinomas, it is most likely that any such trophic factors can be produced by different types of PETs.

We agree with Chetty and colleagues that this is an intriguing issue

and that more research is needed before the pathogenesis of PETs with entrapped nonneoplastic ductules will be fully understood.

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REFERENCES

1. Chetty R, Asa SL. Ductules in pancreatic neuroendocrine tumors. *Am J Surg Pathol*. 2004; 28:417.
2. Deshpande V, Selig MK, Nielsen GP, et al. Ductulo-insular pancreatic endocrine neoplasms: clinicopathological analysis of a unique subtype of pancreatic endocrine neoplasms. *Am J Surg Pathol*. 2003;27:461–468.
3. van Eeden S, de Leng WWJ, Offerhaus GJA, et al. Ductuloinsular tumors of the pancreas: endocrine tumors with entrapped nonneoplastic ductules. *Am J Surg Pathol*. 2004;28: 813–820.
4. <http://www.uptodate.com/>.

