



Tumor deposits in colorectal cancer: the need for a new “pN” category

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Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Comment on: Liu F, Zhao J, Li C, *et al.* The unique prognostic characteristics of tumor deposits in colorectal cancer patients. *Ann Transl Med* 2019;7:769.

Submitted Feb 25, 2020. Accepted for publication Mar 12, 2020.

doi: 10.21037/atm.2020.03.175

View this article at: <http://dx.doi.org/10.21037/atm.2020.03.175>

Background

Tumor deposits (TD) are foci of carcinoma separated from the main lesion and identified in pericolonic or perirectal fat or the adjacent mesentery (mesocolonic fat) within the lymphatic drainage area, away from the invasive front of the tumor (however, there is not an established standardized distance) and in the absence of identifiable lymph node tissue. It is postulated that they are produced either by discontinuous dissemination of the tumor or by vascular/perineural dissemination. Its identification can be macroscopic or microscopic, and the size and shape are variable. It has been identified in 10.2–22% of colorectal carcinomas and it has been postulated that they may represent either a lymph node, a vascular structure, or a nerve completely replaced by carcinoma (1,2).

Due to a possible prognostic impact—not well demonstrated at that time—they were incorporated into the staging of the Tumor-Node-Metastasis (TNM) system in its 5th edition in 1997, but its definition and concept were changing as they began to be studied in a standardized manner. In the 5th Edition the “3 mm rule” was introduced, where the classification was based exclusively on its size, regardless of histology. Thus, any tumor collection in perivisceral fat was considered as an extension of the primary tumor if it was 3 mm or less in diameter (it would be included in the pT category) and if it was larger than 3 mm it was considered as lymph node metastasis (LNM)

and would be placed in the pN category. This subdivision had no scientific support, so it was abandoned in the 6th edition (2002), where size was disregarded as a classification criterion and replaced by one based on the “shape and contour rule”. This rule is based on morphological criteria, but neither did it have a scientific or biological basis. It was considered that if the tumor nodule had no histological evidence of residual lymphatic tissue (tumor-replaced lymph node) but the nodule had the shape and smooth contour of a lymph node, it was considered as a tumor-replaced lymph node. If the tumor nodule had irregular contours and there was no evidence of residual lymphatic tissue, it was considered a TD. Most of these cases were examples of lymphovascular invasion or, more rarely, perineural invasion. In the 7th Edition (2009) “the pathologists discretion’s rule” was incorporated, where the pathologist would decide whether the group of neoplastic cells could represent a lymph node replaced by tumor or could represent a tumor deposit; in addition, a new category (pN1c) was created that included all tumor deposits in stages I and II with the absence of LNM to locate them in Stage III. The pN1c category then represents the presence of TD, but apparently only in stages I and II, since it is not specified how the presence of TD in stage III would be classified. The existence of TD does not change the T stage, but the N stage does. Again, there is no evidence to support this change or the creation of the pN1c category. Finally, the

presence of interobserver discrepancies has been reported when it is necessary to decide how to consider a smooth contour and it is difficult to determine whether or not a rounded nodule is a completely replaced lymph node (3).

In the current TNM classification (8th edition, 2017), TD are defined as tumor nodules separated from the primary carcinoma, without identifying nodal, vascular or neural residual tissue and within the lymphatic drainage area (4). Neither the shape, contour, size or judgment of the pathologist is considered for this designation. For this edition, the pN1c stage is maintained and care is emphasized when applying the term TD in tumor foci that can be observed in post-neoadjuvant surgical specimens, since isolated cells or groups away from the main tumor can represent remnant viable tumor cells discontinuous with each other and their significance is in relation to the tumor response against this therapy.

Clinical relevance of tumor deposits

Since the TD was described, studies on its biological behavior have been published. In a systematic review with a meta-analysis of 10,106 patients were identified in 22% of colorectal carcinomas and it was found that TD were associated with LNM and extramural vascular invasion. TD were invariably associated with worse prognosis, especially with increasing the rate of distant metastases, multivariable disease-free survival analysis (n=1,536) confirmed decreased survival in the presence of TD [hazard ratio (HR) 2.0; 95% confidence interval (95% CI): 1.4 to 2.8] but it has substantial heterogeneity between the studies ($I^2=66\%$). Multivariable disease specific survival analysis (n=1,185) confirmed decreased disease specific survival in the presence of TD (HR 1.7; 95% CI: 1.4 to 2.1, $I^2=0\%$). For overall survival (OS), it was decreased in the presence of TDs (multivariable HR 2.2; 95% CI: 1.7 to 2.8, $I^2=0\%$). Survival outcomes worsens when TD occurs concomitantly with LNM (2). Other studies have also investigated their association with survival.

The first studies to draw attention to the association of TD with survival were published in Asia. One study demonstrated an independent association of TD with decreased disease-specific survival in rectal cancer (5), another demonstrated its independent association with lower overall survival in colorectal cancer (HR 2.42; 95% CI: 1.04–4.90; $P=0.04$, n=344) (1), one more demonstrated lower overall 5-year survival in a series of 4,121 patients (57.7% vs. 78.9%, $P<0.0001$) (6) and, finally, in a series of 313 patients demonstrated a significant and independent decrease in disease-free survival in patients with TD (7).

Subsequently, similar results were replicated in other populations. In the US, a study of 6,424 patients showed that patients with TD without LNM and patients with LNM without TD were independently associated with better survival (HR 0.56, $P=0.001$, HR 0.64, $P<0.001$, respectively) compared to patients with TD with LNM (8). Despite these reports, in a study conducted only in patients with colon cancer of 392 patients, no independent association of tumor deposits with survival was demonstrated; however, if the TD (affected by stage N) were considered as a separated stage, these behave in an intermediate fashion between stage III and stage IV (9). It should also be noted that most of these works defined the TD with TNM criteria of the 7th edition, which is very similar to the 8th edition, a very convenient since it makes these studies more comparable.

Given these heterogeneous and contradictory data, which although point to an association of the TD (especially when they occur simultaneously with LNM) with worse survival and a worse behavior than the nodal stage N2b, the work of Liu *et al.* (10) published in this issue of the Journal, it clarifies in this regard by analyzing two large databases, one American (n=8,480) and one Asian (n=463), where an association of the presence of TDs (regardless of their number is demonstrated) in both cohorts with the OS. In addition, if accompanied by LNM, the OS is even shorter (HR 2.69, 95% CI: 2.597–2.778, $P<0.001$). This work also reinforces the fact that the importance of TD seems to be linked to cases in which LNM is identified, demonstrating that they behave worse than the pN2b category. It is clear then that the TD have negative prognostic value but are not sufficiently categorized in the current TNM staging, since, according to the 8th TNM edition, a tumor with 1 to 3 LNM has the same N category that one without LNM but with TD (that is, both are N1) and, moreover, a carcinoma with TD and with 1 LNM would be classified into the nodal stage pN1a, the lowest sub-stage within category N, an unfortunate fact, since the evidence indicates that its prognosis could be worse than the one assigned to a nodal stage pN2b (the upper limit of the N category). Also, the low conceptual clarity of this subclassification has been criticized, because interobserver variability can cause a ganglion supposedly replaced by the tumor to be interpreted as DT and in reality, the replacement is not total (11,12). With the evidence expressed in this work, added to the existing one, it seems clear that the number and/or presence of the TD should be added to the number of LNM to define the final N stage. The survival curves of published studies that have combined TD with LNM are more similar to a stage IV or at least, are in an intermediate

point between stage III and IV, so we propose to create a specific category for TD with LNM which could be called category N2c or N3.

Perspective

Finally, the fact that approximately 25% of patients with early colorectal cancer will have distant metastases (13) has led to the hypothesis that cancer development and progression may depend in part on changes in various histological features with those with whom we were not familiar, but which are characterized (at least histologically) by being formed by cells or groups of cells separated from the main tumor, all of them associated with a higher rate of LNM, distant metastases, and even survival. These characteristics include tumor budding (TB), poorly differentiated groups or clusters (PDC), TD, and even extracapsular/extranodal tumor extension in LNM. A recent review that delves into these factors is available (12). This fact makes us meditate if what we are doing is calling in different ways the same phenomenon which is characterized by the capacity of cellular response, the greater capacity for migration/dissemination and even the epithelial-mesenchymal transition. In our opinion, we should propose future studies following this line of research to better establish the role of these histological features in the prognosis of these patients and determine if they are actually different entities or they simply represent the same phenomenon at different steps or with different names.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm.2020.03.175>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Lino-Silva LS, Xinaxtle DL, Salcedo-Hernández RA. Tumor deposits in colorectal cancer: the need for a new “pN” category. *Ann Transl Med* 2020;8(12):733. doi: 10.21037/atm.2020.03.175