Debating Deposits
An Interobserver Variability Study of Lymph Nodes and Pericolonic Tumor Deposits in Colonic Adenocarcinoma

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Context.—The American Joint Committee on Cancer’s Cancer Staging Manual 7th edition defines pericolonic tumor deposits (TDs) as discrete tumor foci in pericolonic fat showing no evidence of residual lymph node (LN). This definition relies on subjective features rather than size (5th edition) or shape (6th edition) and introduced the category N1c. Although typically straightforward, metastases are encountered for which the distinction between LNs and TDs is unclear. For data to be meaningful, agreement on distinguishing features between positive LNs and TDs is needed.

Objectives.—To assess agreement among gastrointestinal pathologists evaluating difficult metastases and to report the distinguishing features they found helpful.

Design.—Twenty-five tumor metastases from right-sided colonic adenocarcinomas were selected in which the distinction between positive LNs and TDs was challenging. Virtual slides were reviewed by 7 gastrointestinal pathologists. A list of features potentially helpful in differentiating positive LNs and TDs was ranked for usefulness by each pathologist. Every metastasis was diagnosed as positive LN or TD. For each case diagnosed as positive LN, reviewers were asked to list every feature used in diagnosis.

Results.—Complete agreement was found for 11 of 25 metastases, 5 positive LNs and 6 TDs (statistic, 0.48; 95% confidence interval, 0.28–0.67). Top-ranked features included round shape, peripheral lymphocyte rim, peripheral lymphoid follicles, possible subcapsular sinus, residual LN in surrounding fibroadipose tissue, and thick capsule. The top used features were similar among reviewers.

Conclusions.—Significant agreement on positive LNs and TDs in difficult colonic adenocarcinoma metastases was found among evaluators, but inconsistency remains. Round shape, peripheral lymphocyte rim, peripheral lymphoid follicles, possible subcapsular sinus, residual LN in surrounding fibroadipose tissue, and thick capsule were most often used to aid in diagnosis.

Debating Deposits—Rock et al 637

RESULTS

Interobserver Agreement in Distinguishing Positive LNs From TDs

Of the 25 scanned slides, 7 were called a TD by a majority of the reviewing pathologists. Complete agreement among

MATERIALS AND METHODS

Colon cancer cases during a 5-year period (2005–2009) were identified, and slides were reviewed from all right-sided colorectal adenocarcinomas that had not received neoadjuvant chemotherapy or radiation therapy. These cases were chosen in an attempt to minimize the effects of tumor location and neoadjuvant therapy on tumor metastases. From these cases, 2 pathologists (WR, JR) compiled a collection of 25 tumor metastases taken from pericolonic adipose tissue for which the distinction between a positive LN and a pericolonic TD was challenging to determine using the AJCC 7th edition criteria. The metastases collected were chosen to attempt to cover a wide breadth of potential pitfalls in LN identification such as metastases with dense associated fibrosis, extensive mucin, and associated lymphoid tissue without definite LN structure, among others.

The 25 pericolonic metastases were imaged using the Scan Scope XT (Aperio, Vista, California) and uploaded for review using Imagescope software (Aperio). The virtual slides were sent to 7 pathologists (MW, VA, JG, EM, MR, RY, WF) with a specific interest in gastrointestinal pathology for review. Each pathologist was asked to render an opinion of either TD or LN metastasis for each of the 25 slides.

A list of potential microscopic features that may be useful to aid in the distinction between TD and a positive LN was compiled and sent out for ranking with the virtual slides. Each reviewer was asked to rank these features from the most essential in diagnosing an LN metastasis to the least essential. Factors that the reviewers thought provided no useful information toward this distinction were not ranked. If the reviewer believed that an additional distinct histologic finding was useful, he or she was asked to list this feature separately in the assessment. In addition, for each virtual slide diagnosed as a positive LN, the reviewer was asked to list each feature thought to have been helpful to reach this diagnosis.

The results were gathered, and agreement among the reviewing pathologists was calculated using the $\kappa$ statistic to determine the intraclass correlation coefficient, and a 95% confidence interval (CI) for $\kappa$ was then produced. The results and $\kappa$ statistics were reviewed and discussed face-to-face among the reviewing pathologists. As a result of these discussions, additional deeper sections and elastin stains were performed from the blocks for each case and reviewed independently by 2 pathologists (WF, JR) to assess if the additional slides contributed to the distinction between a TD and positive LN.

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RESULTS

Interobserver Agreement in Distinguishing Positive LNs From TDs

Of the 25 scanned slides, 7 were called a TD by a majority of the reviewing pathologists. Complete agreement among
all reviewing pathologists was found for 11 of the 25 metastases (44%), of which 5 were deemed a positive LN (Figure 2, A, B, and D) and 6 a pericolonic TD (Figure 3, A through D). In the remaining 14 cases, concurrence rates among the reviewing pathologists were 6 of 7 (strong agreement for 4 cases) (Figure 2, C and E), 5 of 7 (weak agreement for 6 cases), and 4 of 7 (nonagreement for 4 cases) (Figure 4, A through D). In these 14 cases, the majority of pathologists called the metastasis a positive LN in 13 and a pericolonic TD only once (nonagreement for 4 of 7). Among the reviewing pathologists, 10.2 (range, 7–14) metastases on average per pathologist were called pericolonic TDs. The estimated $\kappa$ statistic was 0.48 (95% CI, 0.28–0.67). This $\kappa$ statistic is significantly greater than 0 ($P < .001$), indicating that agreement is significantly greater than what would be expected if agreement was due to chance (Figures 2 through 4).

Microscopic Features Thought Useful in Distinguishing Positive LNs From TDs

The reviewing pathologists returned varying rank order lists when asked to rank microscopic features useful in discriminating LNs from pericolonic TDs. The top-ranked feature by most pathologists was round shape (average rank, 2.6) (Table 1). The following additional 5 features were closely ranked: peripheral lymphocytic rim, peripheral lymphoid follicles, possible subcapsular sinus, residual LN in surrounding fibroadipose tissue, and thick capsule. These characteristics were separated by less than 1 spot in the mean ranking, and each feature was ranked in the top 3 by at least 1 reviewing pathologist. The following 3 factors were listed as noncontributory by at least 1 of the reviewing pathologists: contiguous lymphovascular channels (1 pathologist), admixed lymphocytes (2 pathologists), and size greater than 3 mm (2 pathologists). The following 2 additional features were listed by 1 reviewing pathologist: the presence of a complete thin capsule and the absence of entrapped structures such as nerves.

Microscopic Features Actually Used in Distinguishing LNs From TDs

Using the responses generated from each reviewing pathologist for each case called a positive LN, the features the reviewers actually used in making the distinction between a positive LN and a TD were collected. Round shape was the most used feature, listed as useful in distinguishing an LN in 89% of all reviewed metastases called a positive LN (Table 2). Four additional features (thick capsule, peripheral lymphoid follicles, peripheral lymphocytic rim, and size >3 mm) were listed as useful in at least 60% of metastases called a positive LN.

Efficacy of Deeper Sections and Elastin Staining in Supporting the Diagnosis

Deeper sectioning and special stains for elastin have been reported as helpful ancillary methods to aid in the
distinction of tumor metastases in colorectal cancer, particularly in the distinction between positive LNs and venous invasion.10–12 Deeper sections and elastin staining were performed on sections from each case and then reviewed by 2 pathologists (J.B.R. and W.L.F.). Elastin staining was negative in all 25 metastases, with appropriate staining in adjacent vasculature as an internal control. Therefore, this stain was noncontributory to the distinction between positive LNs and pericolonic TDs; however, it confirmed that none of our cases represented tumor invasion within medium to large vessels.

The ranked list of factors deemed most useful by our reviewing pathologists was used as a basis for determining the utility of deeper sectioning. Any factor identified on deeper sectioning that was not visualized in the initial section was interpreted as a useful deeper section. Using these criteria, deeper sectioning into the block proved useful in distinguishing the metastasis as a likely positive LN in 3 of the slides (numbers 3, 9, and 14 in supplemental digital content available at www.archivesofpathology.org). In number 3, an increased area of peripheral lymphoid follicles and definitive subcapsular sinus was identified in the deepest section, supporting the consensus among our reviewers in diagnosing this metastasis as a positive LN. In number 14, a single peripheral lymphoid follicle was noted in deeper sections not seen on the initial section, helping to support the impression of 6 of 7 reviewers that this metastasis likely represented a positive LN. In one metastasis (number 9) unanimously called a TD by the reviewers, an increase in the peripheral rim of lymphocytes

Figure 3. Tumor metastases lacking a combination of features suggestive of a lymph node were unanimously classified as tumor deposits by 7 of 7 reviewers even if individual features such as round shape (A), peripheral lymphoid follicles (B and C), or peripheral lymphocyte rim (D) were present (hematoxylin-eosin, original magnifications ×100).
Tumor metastases in which features suggestive of lymph nodes were present but less clear-cut resulted in the most disagreement among our evaluators. These metastases were classified as a lymph node (A through C) or tumor deposit (D) by a slim 4 of 7 majority of our evaluators (hematoxylin-eosin, original magnifications ×100).

Table 1. Microscopic Features Thought Useful in Distinguishing Positive LNs From TDs

<table>
<thead>
<tr>
<th>Factor</th>
<th>Overall Rank</th>
<th>Average</th>
<th>Mode (No.)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Round shape</td>
<td>1</td>
<td>2.6</td>
<td>1 (3)</td>
<td>1–6</td>
</tr>
<tr>
<td>Peripheral lymphocyte rim</td>
<td>2</td>
<td>3.9</td>
<td>4 (3)</td>
<td>1–7</td>
</tr>
<tr>
<td>Peripheral lymphoid follicles</td>
<td>3</td>
<td>4.0</td>
<td>2 (2)</td>
<td>2–8</td>
</tr>
<tr>
<td>Possible subcapsular sinus</td>
<td>4</td>
<td>4.1</td>
<td>1 (2)</td>
<td>1–7</td>
</tr>
<tr>
<td>Residual LN in surrounding fibroadipose tissue</td>
<td>4</td>
<td>4.1</td>
<td>2 (2)</td>
<td>1–8</td>
</tr>
<tr>
<td>Thick capsule</td>
<td>6</td>
<td>4.4</td>
<td>3 (4)</td>
<td>3–7</td>
</tr>
<tr>
<td>Tumor in nearby lymphovascular channels</td>
<td>7</td>
<td>7.0</td>
<td>6 (2)</td>
<td>4–9</td>
</tr>
<tr>
<td>Contiguous lymphovascular channels</td>
<td>7</td>
<td>7.0</td>
<td>5 (2)</td>
<td>5–9</td>
</tr>
<tr>
<td>Admixed lymphocytes</td>
<td>7</td>
<td>7.0</td>
<td>7 (2)</td>
<td>3–9</td>
</tr>
<tr>
<td>Size &gt;3 mm</td>
<td>10</td>
<td>10.0</td>
<td>10 (5)</td>
<td>10–10</td>
</tr>
</tbody>
</table>

Abbreviations: LNs, lymph nodes; TDs, tumor deposits.
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is noted on deeper sectioning. This finding may have suggested an LN to some reviewers had it been present on the scanned sections.

**COMMENT**

The current AJCC definition for TDs was designed to better characterize an entity that did not clearly fit within any of the 3 traditional pillars of the TNM system to guide future editions about their significance. Tumor deposits have been theorized to represent lymphovascular invasion, discontinuous direct tumor extension, or metastatic LNs with extensive extranodal extension, among others. Previous editions of the TNM staging system relied on arbitrary cutoffs of size and shape to characterize pericolonic tumor metastases and attempted to integrate those characterized as TDs into the T category. However, these deposits were often treated in clinical practice as equivalents to LN metastases. As a result of these treatment practices, TDs were reclassified into the N category, and a new designation (N1c) was created in an attempt to better identify patients with otherwise node-negative disease whose prognosis differed from those with true node-negative disease regardless of vascular invasion.13,14 The N1c subclassification will allow for future data collection on TDs in node-negative patients to better understand their prognostic significance. Pericolonic TDs have been shown to negatively affect prognosis in patients with concurrent positive LNs, with studies15–18 showing reduced disease-free and overall survival for all cases regardless of the T or N classification. The implications of these findings highlight the necessity to document pericolonic TDs for all patients with colorectal adenocarcinomas.

Several studies and opinion papers have been published challenging the AJCC 7th edition definition of a TD and assessing its usefulness.19 The concern centers on the subjectivity among observers allowed by the current definition, particularly for cases with thick capsule, irregular shape, or a Crohn-like tumor response.20–23 This subjectivity has led some to question whether we should revert back to entirely objective measurement criteria used in the AJCC 5th edition.24–26 It is clear that the frequency of changes to the definition of a TD has caused confusion among pathologists and clinicians; however, the size criterion of the AJCC 5th edition was arbitrary and had its own share of pitfalls. These included possible failure to recognize positive LNs spanning less than 3 mm27 and overcalling positive lymph nodes in mucinous tumors with disseminated spread, among others.

Furthermore, many of the published studies on TDs are limited by several shortcomings, including varied sampling methods, small sample size, and inclusion of metastatic lesions clearly representing lymphovascular invasion.24,25 As greater prognostic significance is placed not only on the number of positive LNs but also on their location and ratio to negative LNs, increased importance will be put on ensuring an accurate and reproducible definition of a positive metastatic LN.

For the majority of pericolonic metastases, the distinction between a metastatic LN and pericolonic TD can be made with relative ease regardless of which AJCC edition criteria are used in making the distinction because of the presence of obvious residual LN. We focused our analysis on metastases for which the distinction between a positive LN and TD was challenging to better understand how the AJCC 7th edition criteria are being interpreted by pathologists with a focus in gastrointestinal pathology. In the interpretation of 25 difficult metastases, we found a statistically significant degree of agreement among our evaluators. This included complete agreement for 11 of 25 cases (44%) compared with nonagreement for only 4 of 25 cases (16%), for which no consensus was clear. Overall, we found significant agreement in the interpretation of the AJCC 7th edition criteria; however, the κ statistic of 0.48, correlating with a moderate degree of agreement, highlights that some degree of inconsistency among our evaluators was present. Minimizing this degree is important because any inconsistencies could lead to problems in future studies.

We found a disproportionate distribution of cases in which a consensus could be reached. A majority of the reviewing pathologists reported a metastasis as a TD in 7 of 25 cases. Of these 7 cases, 6 were unanimously called a TD, in contrast to the even distribution seen in cases that a majority deemed a positive LN (complete agreement for 5 cases, strong agreement for 4 cases, weak agreement for 6 cases, and 4 nonagreement for 4 cases). The concordance noted when calling a metastasis a TD may suggest a tendency among our evaluators to err on the side of considering a challenging metastasis a positive LN, unless overwhelmingly compelling features of a TD are present to bring them into agreement.

The rank lists of features our reviewing pathologists thought were most useful in distinguishing a positive LN from a pericolonic TD provided some insights into how metastatic lesions are evaluated. Among all our reviewers, a strong carryover from the AJCC 6th edition was noted. Round shape was ranked the most important characteristic, with 5 of 7 evaluators ranking it their top feature, and it had the highest ranking (average rank, 2.6) by all evaluators. Our reviewers clearly favored the following 6 features: round shape, peripheral lymphocyte rim, peripheral lymphoid follicles, possible subcapsular sinus, residual LN in surrounding fibroadipose tissue, and thick capsule. When examining the features that our reviewers actually used when determining that a metastasis represented a positive LN, we again encountered many of these same features.

Our results show some notable trends that highlight important points in the evaluation of pericolonic metastases. It was clear from our data that no single feature or pair of features was uniformly used by all our evaluators to identify a given case as a positive LN or TD. Although round shape was generally thought to be the most helpful feature, the presence of any residual LN characteristics (peripheral...
lymphoid follicles, possible subcapsular sinus or residual LN in the surrounding fibroadipose tissue, and peripheral lymphocyte rim), particularly in combination, often led to the diagnosis of a metastatic LN. Two features listed by our evaluators, the presence of peripheral lymphoid follicles and peripheral lymphocyte rim, are of particular interest because these features are commonly seen in association with colonic adenocarcinomas having microsatellite instability and could be misleading.

Based on this study and other publications, it is apparent that the current definition of a TD in the AJCC 7th edition allows for a level of subjectivity even among pathologists with a specific interest in gastrointestinal pathology. Given that the metastases we selected were specifically chosen for their ability to be debated, we ultimately cannot confirm whether these metastases are nodal or nonnodal in nature, nor can we surmise their prognostic significance. Because studies investigating the prognostic significance of TDs are ongoing, we believe that further efforts are warranted at this time to study the concordance rates among diagnosticians in various practice settings and attempt to standardize diagnostic criteria. We suggest the features of round shape, peripheral lymphocyte rim, peripheral lymphoid follicles, possible subcapsular sinus, residual LN in surrounding fibroadipose tissue, and thick capsule as the most useful in making this distinction.

Among our reviewing pathologists, tumor metastases displaying several of these features were generally categorized as a positive LN rather than a TD. In rare instances, performing deeper sections may assist in making this distinction. By presenting the features our evaluators thought were most useful, we anticipate that others may be able to improve their interobserver agreement and make the distinction between residual LN and TDs more reproducible, to allow for meaningful future study into the effect of TDs.

All the pericolonic metastases sent to our evaluators for assessment are presented for review as supplemental digital content in the May 2014 table of contents.

References


