Pericolonic Tumor Deposits in Patients with T3N+M0 Colon Adenocarcinomas

Markers of Reduced Disease Free Survival and Intra-Abdominal Metastases and Their Implications for TNM Classification

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BACKGROUND. A pericolonic tumor deposit (PTD) is a grossly palpated adenocarcinomas within pericolonic adipose tissue not within a lymph node. The source and prognostic significance of PTDs has not been well defined.

METHODS. The authors studied 418 T3N+M0 colon adenocarcinomas to determine the frequency and significance of PTDs. They also step-sectioned 30 PTDs to determine their origin and assist in their optimum TNM classification.

RESULTS. Seventy-one (18%) of 400 consecutively examined cases had PTDs. The actuarial 1-, 2-, and 5-year disease free survival rates were significantly lower among patients with a PTD. PTDs, regardless of size, significantly impacted disease free survival. Increasing numbers of PTDs was associated with shorter disease free survival. Adenocarcinoma grade, a PTD, increasing numbers of PTDs, and number of lymph node metastases were independently associated with shorter disease free survival. The likelihood of extrahepatic abdominal failure was proportionally greater with increasing numbers of PTDs. Adenocarcinoma was observed in perineural, peri-large vessel, or intravascular locations in step-sectioned PTDs.

CONCLUSIONS. A PTD is a perineural, perivascular, or intravascular tumor extension beyond the muscularis propria. They are distinct from lymph node metastases and should not be considered their prognostic equivalent. The disease free survival impact of even small PTDs was significant, suggesting that PTDs of all sizes should be considered a single entity. TNM classification of PTDs as lymph node metastases or discontinuous tumor extension is probably not accurate. The number and greatest dimension of PTDs should be reported separately from lymph node metastases. ***Cancer* 2000;88:2228–38.** © *2000 American Cancer Society.*

KEYWORDS: colon, adenocarcinoma, lymph node metastases, vascular invasion, perineural invasion, prognosis, pathology, pericolonic tumor deposits.

Pericolonic tumor deposits (PTDs) are found in the pericolonic and mesenteric adipose tissue around colon adenocarcinomas. These lesions are palpable and grossly similar to small lymph nodes. The microscopic features of PTDs are discontinuous adenocarcinoma in fibroadipose and desmoplastic tissues not associated with a lymph node. The prognostic significance of PTDs has not been well defined.[1] One group of authors found them to be an independent predictor of poor outcome in patients with right-sided colon carcinoma.[2]

The source of PTDs is unknown, making their optimum classification unclear. Some authors have suggested that they derive from vascular metastases that grow through the vessel wall and into the surrounding tissue. It is not clear whether they should be classified as vascular invasion, direct extension from the adenocarcinoma, or

lymph node metastases. The 1997 TNM classification recommends that a PTD greater than 0.3 cm be classified as a regional lymph node metastasis and that a PTD 0.3 cm or less be classified as a discontinuous T3 adenocarcinoma.[3] However, this recommendation is not based on patient survival data.

We studied 418 colon adenocarcinomas that had extended beyond the muscularis propria and had lymph node metastases to examine the frequency and clinical significance of PTDs. We also step-sectioned 30 PTDs to resolve the question of their origin.

MATERIALS AND METHODS

Patient Selection

Four hundred consecutive patients with colonic T3N+M0 adenocarcinomas of common glandular histologic type who had follow-up information were identified in the files of the William Beaumont Surgical Pathology Department and Tumor Registry during the time period January 1, 1973, through December 14, 1984, and an additional 18 patients with T3N+M0 adenocarcinomas and PTDs were identified in the anatomic pathology files of Harper Hospital during the time period July 1986 to January 1992, using the definitions set forth in the 1998 fifth editions of the American Joint Committee on Cancer's *AJCC Cancer Staging Manual* and *AJCC Cancer Staging Handbook*.[3,4] Our goal was study the natural course of these patients. Therefore, we chose a time period in which adjuvant chemotherapy was not administered to patients with regionally spread colon carcinoma (William Beaumont Hospital patients) or in which adjuvant therapy was not administered prior to metastasis or recurrence (Harper Hospital patients). Patients who received adjuvant therapy prior to the first tumor metastasis were excluded from the analysis. In addition, patients with rectal or rectosigmoid carcinoma were excluded from the study due to the differing metastasis and local recurrence patterns in these patients and because postoperative radiation therapy was offered to many such patients during these time periods. Finally, patients with mucinous, signet ring cell, and high grade neuroendocrine carcinomas were excluded.

All patients had T3 adenocarcinomas that invaded through the muscularis propria into the subserosa or, in the right colon, into nonperitonealized pericolic tissues without penetration of the serosal surface or direct extension into another organ or loop of bowel.[3] Regional (pericolonic) lymph node metastases were present in all cases, but patients with distant metastases at the time of diagnosis or whose metastasis was identified within 1 month of the initial diagnosis were considered to have metastatic disease at the time of surgery and were excluded.

The following information was extracted from the Tumor Registry data bases for each patient: date of birth; date of surgery; date of last follow-up; date of first recurrence; site of first recurrence, classified as liver, lung, bone, intra-abdominal (extra-hepatic), other, or unknown; and location of the adenocarcinoma, classified as right, transverse, descending, or sigmoid colon.

Histopathologic Review

All of the slides of each adenocarcinoma and the surgical pathology report were reviewed for the following information: confirmation of T3 status; histologic tumor grade, categorized as Grade 1 (well differentiated), Grade 2 (moderately differentiated), or Grade 3 (poorly differentiated), using the extent of gland formation and microtubular structures as the primary grade criteria;[5,6] presence of small vessel or lymphatic space invasion; presence of extramural large vein invasion; number of lymph nodes recovered and examined as determined from the examined slides (to exclude PTDs, below); number of lymph nodes that contained metastases; and number and maximum dimension of pericolonic tumor deposits (PTDs). The measurement of PTD maximum dimension was measured on the slide. Step sections were not used for PTD maximum dimension measurements. The desmoplastic response around the adenocarcinoma in the PTD was included in the PTD maximum dimension measurement. This was usually only 1 or 2 millimeters of fibrous tissue around the periphery of the adenocarcinoma.

The distance of the tumor from proximal and distal margins was obtained from the surgical pathology report, and slides of the margins were reviewed to verify lack of involvement. The status of the radial margin was not recorded for right colon resection specimens because it was not defined or noted in surgical pathology reports and the specimens were not inked.

Metastatic adenocarcinoma in a lymph node was defined as the presence of residual lymph node tissue or a completely infarcted metastasis with the rounded, smoothly contoured shape of a lymph node. Remnant lymph node capsule was useful in confirming the presence of pre-existing lymph nodes.

A PTD was defined as adenocarcinoma within adipose or fibrous tissue but not associated with a lymph node (Figs. 1 and 2).[1,7] PTDs were grossly palpated lesions and were typically submitted as lymph nodes. Each PTD was a separate tissue fragment. Some PTDs were small; these had a rim of granulation

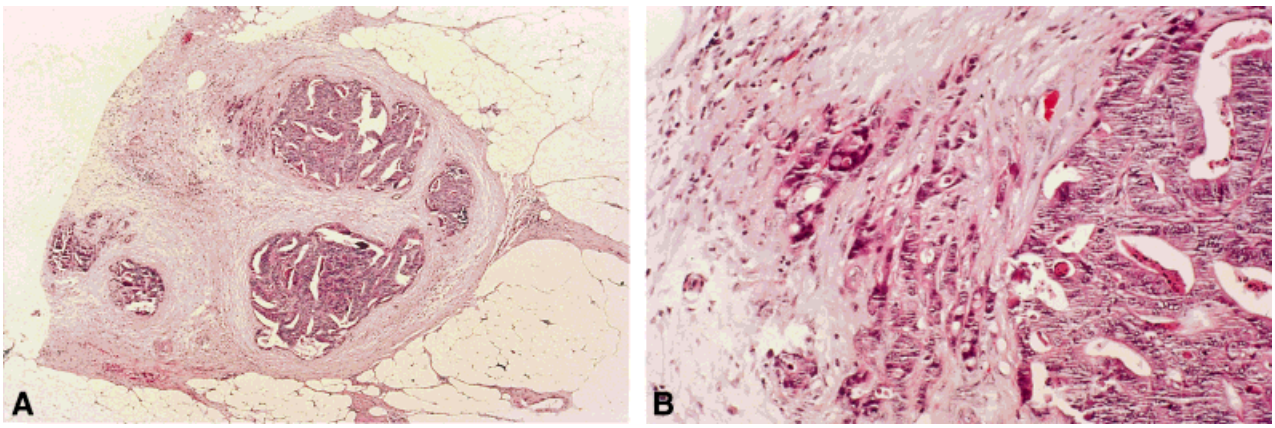

FIGURE 1. (A) Pericolonic tumor deposit. A nodule of adenocarcinoma is present within mesenteric adipose tissue not associated with a lymph node. The nodule is surrounded by desmoplastic stroma that produces a smooth, bosselated outer surface. No lymph node structures are seen (H & E, original magnification ×4). (B) Higher magnification of (A). Invasive adenocarcinoma is present within the desmoplastic stroma (H & E, original magnification ×50).

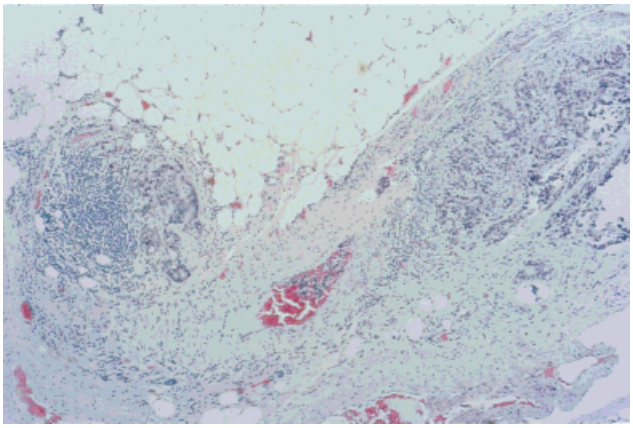

FIGURE 2. Pericolonic tumor deposit. Adenocarcinoma is growing within and around a thick-walled vessel. There is also involvement of the perivessel adipose tissue. No lymph node structures are seen (H & E, original magnification ×4).

tissue around the periphery of the malignant glands. These lesions almost always had an infiltrative appearance and often surrounded a large vessel or nerve, producing the appearance that the adenocarcinoma was extending out from a perineural or perivascular structure or directly out from an intravascular growth. Direct extension of adenocarcinoma into adipose tissue from a lymph node metastasis was not considered a PTD.

Seventy-one PTDs were found from the specimens accessioned into the William Beaumont Hospital anatomic pathology department. Thirty consecutive PTDs from this group were selected for the serial sectioning component of the study. Each PTD-containing block was cut through using hematoxylin and eosin–stained 5-micron step sections. The mean and median number of step sections examined per case were 11.5 and 10.0, respectively (range, 10–18; standard deviation, 2.2). Elastic stains were obtained on level 5.

The presence of perineural, peri-large vessel, and intravascular adenocarcinoma was categorized as present or absent within each set of PTD step sections. We attempted to identify and photograph contiguous growth of the invasive-appearing adenocarcinoma at the edge of the PTD and the centrally located perineural, peri-large vascular, or intravascular adenocarcinoma.

Statistical Analysis

Metastatic disease was defined as either an intra-abdominal recurrence or distant metastasis. The disease free survival period was defined as the interval from surgery until the metastatic disease was diagnosed. Associations were analyzed using the Fisher exact test (two-tailed) for categoric variables and logistic regression for continuous variables. Actuarial results for metastatic disease and disease free survival were calculated by the Kaplan–Meier method. The statistical significance of differences between actuarial curves was calculated with the log rank test. Multivariate analysis was performed using the Cox proportional hazards model and stepwise logistic regression. A P value of $\leqq 0.05$ was considered a statistically significant association. Statistical analysis was performed with SAS software, version 6.12 (SAS Inc., Cary, NC).

RESULTS

Two hundred patients (47.8%) had sigmoid adenocarcinomas, 68 (16%) patients had descending colon adenocarcinomas, 31 (7.4%) had transverse colon ade-

TABLE 1
Distribution of Pericolonic Tumor Deposits

No. of PTDs	No. of cases	% of cases with PTDs
1	31	35%
2	15	17%
3	9	10%
4	11	12%
5	4	5%
6	10	11%
7	5	6%
8	2	2%
9	1	1%
10	1	1%
Total	89	100%

PTDs: pericolonic tumor deposits.

nocarcinomas, and 119 (28.5%) had right colon adenocarcinomas. Two hundred eighty-four patients (68%) developed metastatic disease. Initial metastasis occurred in the liver in 127 patients (44%), in the abdomen (extrahepatic) in 59 patients (21%), in unknown locations in 33 patients (12%), in the lungs in 30 patients (11%), and in other sites in 8 patients (3%). The median age of patients at diagnosis was 68 years (range, 23–93 years; standard deviation, 12 years). The overall mean and median follow-up periods were 4 and 2.5 years, respectively (range, 2 days–24 years; standard deviation, 5 years). The patients with short follow-up periods died of surgical complications but were disease free at death. The mean and median follow-up periods for those patients who did not develop metastases were 9 and 7 years, respectively (range, 2 days–24 years; standard deviation, 7 years). The mean and median time periods until the metastatic disease became clinically apparent were 2.4 and 2.1 years, respectively (range, 30 days–11.7 years; standard deviation, 1.7 years).

Forty-six adenocarcinomas (11%) were histologic Grade 1, 190 (45.5%) were Grade 2, and 182 (43.5%) were Grade 3. Extramural venous invasion was present in 65 cases (15.6%). Lymphatic invasion was present in 58 cases (14%). The mean and median number of lymph nodes recovered per case was 10 (range, 3–27 lymph nodes; standard deviation, 3.4 lymph nodes). The mean and median number of lymph nodes metastases were 4 and 3, respectively (range, 1–20; standard deviation, 2.3).

Of the 400 consecutively examined adenocarcinomas, PTDs were identified in 71 cases (18%). An additional 18 patients with PTDs were identified separately, for a total of 89 cases with PTDs. The number of PTDs identified in each case is listed in Table 1. The mean and median size of the largest PTD per case was 4.0 and 3.8 mm, respectively (range, 1.0–10.2 mm; standard deviation, 2.0 mm).

TABLE 2
Univariate Analysis of Features Associated with Metastatic Disease

Feature	Metastatic disease: No	Metastatic disease: Yes	*P* value[a]	Odds ratio
No. of PTDs			< 0.01[b]	2.13
Any PTDs	12 (14%)	77 (87%)	< 0.01	
Adenocarcinoma				
Grade 1	22 (48%)	24 (52%)		
Grade 2	73 (38%)	117 (62%)	< 0.01	
Grade 3	39 (21%)	143 (79%)		
No. of LN metastases			< 0.01[b]	1.37
PTD size			0.034[b]	194
Extramural venous invasion	17 (26%)	48 (74%)	0.042	
Lymphatic space invasion	18 (31%)	40 (69%)	1.00	
Tumor site			0.81	
Lymph nodes recovered			0.92[b]	

PTDs: pericolonic tumor deposits; LN: lymph nodes.
[a] Chi-square test (general association).
[b] Logistic regression.

TABLE 3
Relation of PTDs and Number of Lymph Node Metastases to Metastatic Disease

No. of lymph node metastases	% with metastatic disease: No PTDs	% with metastatic disease: PTDs present	*P* value
1	37%	47%	
2	50%	61%	
3	58%	100%	
4	75%	95%	< 0.01[a]
5	67%	100%	
6	77%	83%	
7	89%	89%	
≥ 8	67%	100%	

PTDs: pericolonic tumor deposits.
[a] *P* value reflects the overall association of the entire table.

Univariate Analysis

The features that were associated with metastatic disease in univariate analysis were the presence of any PTDs, increasing numbers of PTDs, increasing PTD maximum dimension, increasing numbers of lymph node metastases, increasing tumor grade, and extramural venous invasion (Table 2).

Tables 3 and 4 show the relation of PTDs, numbers of lymph node metastases and PTDs, and adenocarcinoma grade to metastatic disease. The trends of increasing distant metastasis rates with increasing numbers of lymph node metastases or adenocarci-

TABLE 4
Relation of PTDs and Adenocarcinoma Grade on Metastatic Disease

Adenocarcinoma grade	% with metastatic disease		*P* value[a]
	No PTDs	PTDs present	
1	51%	100%	
2	59%	74%	< 0.01
3	72%	92%	

PTDs: pericolonic tumor deposits.
[a] *P* value reflects the overall association of the entire table.

TABLE 5
Actuarial Disease Free Survival Rates

Feature	Survival			*P* value
	1-yr	2-yr	5-yr	
Any PTDs	76%	46%	13%	< 0.01
0 PTDs	88%	71%	35%	
1 PTDs	86%	56%	28%	
2 PTDs	72%	44%	14%	
3 PTDs	55%	33%	0	< 0.01
4 PTDs	63%	27%	0	
5 PTDs	50%	0	0	
≥ 6 PTDs	45%	10%	0	
1 positive lymph node	90%	77%	50%	
2 or 3 positive lymph nodes	87%	70%	38%	< 0.01
4 or 5 positive lymph nodes	83%	62%	21%	
≥ 6 positive lymph nodes	76%	48%	11%	

PTDs: pericolonic tumor deposits.

noma grade were significantly greater if PTDs were present.

Actuarial Survival

The actuarial 1-, 2-, and 5-year disease free survival rates were significantly decreased in those patients with a PTD, increasing numbers of PTDs, and increasing numbers of lymph node metastases (Table 5). The presence of a PTD was associated decreased disease free survival among patients with two or more lymph node metastases (Table 6). Figure 3 shows the actuarial survival of patients with no PTDs, 1 or 2 PTDs, or 3 or more PTDs. The 5-year actuarial survival was 35%, 24%, and 2%, respectively ($P < 0.01$).

Multivariate Analysis

Three analyses were performed using the Cox proportional hazards model and modeling for metastatic disease over time (Table 7). The first analysis entered the variables of any PTDs, adenocarcinoma grade, number of lymph node metastases, tumor site, patient age, extramural venous invasion, and lymphatic invasion into the model. Adenocarcinoma grade, the presence of any PTDs, and the number of lymph node metastases were each independently associated with metastatic disease.

The variables used in the second analysis were identical to those in the first analysis except that the number of PTDs was substituted for the presence of PTDs. In this model, adenocarcinoma grade, number of PTDs, and number of lymph node metastases were each independently associated with disease free survival.

The third analysis was limited to patients with PTDs and used the following variables: maximum dimension of the PTD, adenocarcinoma grade, number

TABLE 6
Actuarial Survival Values for Numbers Lymph Nodes Metastases with and without Pericolonic Tumor Deposits

Feature	Survival			*P* value
	1-yr	2-yr	5-yr	
1 positive lymph node:				
No PTDs	87%	87%	62%	0.23
PTDs present	88%	73%	44%	
2 or 3 positive lymph nodes:				
No PTDs	89%	76%	41%	< 0.01
PTDs present	68%	31%	16%	
4 or 5 positive lymph nodes:				
No PTDs	85%	64%	25%	0.012
PTDs present	76%	51%	8%	
≥ 6 positive lymph nodes:				
No PTDs	80%	62%	16%	0.017
PTDs present	71%	29%	3%	

PTDs: pericolonic tumor deposits.

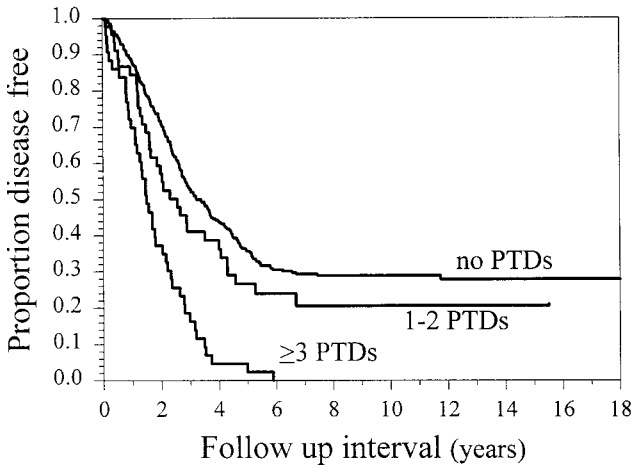

FIGURE 3. Actuarial survival graph stratified by the number of pericolonic tumor deposits (PTDs). The differences between the curves at 5 years of follow-up was statistically significant ($P < 0.01$).

TABLE 7
Multivariate (Cox Proportional Hazards Model) Analyses

Analysis	Significant features	*P* value	Risk ratio	95% confidence limits
1	No. of lymph node metastases	0.0002	1.12	1.05–1.17
	Adenocarcinoma grade	0.0039	1.34	1.10–1.65
	Any PTDs	0.0050	1.50	1.13–2.00
2	Increasing no. of PTDs	0.0428	1.08	1.02–1.15
	No. of lymph node metastases	0.0068	1.09	1.02–1.17
	Adenocarcinoma grade	0.0014	1.39	1.13–1.69
3	Adenocarcinoma grade	0.0121	1.30	1.06–1.60
	No. of lymph node metastases	0.0058	1.47	1.12–1.93
	PTD maximum dimension	0.0001	1.95	1.40–2.70

PTDs: pericolonic tumor deposits.

of lymph node metastases, tumor site, patient age, extramural venous invasion, and lymphatic invasion. Adenocarcinoma grade, number of lymph node metastases, and maximum dimension of the PTD were independently associated with metastatic disease. Notably, extramural venous invasion and lymphatic invasion were not independent prognostic factors when PTDs were present.

Metastases Location

The presence of any PTDs ($P < 0.01$), increasing numbers of PTDs ($P < 0.01$), and increasing maximum dimension of PTDs ($P < 0.01$) were associated with the site of initial metastasis. A disproportionate number of patients who had PTDs developed intra-abdominal metastases compared with the overall patient group in which the liver was the most common site of metastasis. The likelihood of developing intra-abdominal metastases compared with other sites of metastases was proportionally greater with increasing numbers of PTDs ($P < 0.01$) (Table 8). Of the 207 patients who developed metastatic disease and did not have PTDs, 12% initially had nonhepatic intra-abdominal metastases, compared with 59% of the patients who had PTDs. In contrast, 47% of the 207 patients who did not have PTDs initially developed hepatic metastases, compared with 24% of the patients with PTDs.

Multivariate analysis, modeling for features associated only with intra-abdominal metastases identified only increasing numbers of PTDs ($P < 0.001$; odds ratio, 5.3; confidence limits, 1.39–20.2) as having a significant association. The number of PTDs was independently associated with intra-abdominal metastases compared with failures in other locations and nonfailures ($P < 0.01$; odds ratio, 1.59; confidence limits, 1.3–1.85).

TABLE 8
Relation between Increasing Number of Pericolonic Tumor Deposits and Extrahepatic Intra-abdominal Metastases

No. of PTDs	No. of patients with intra-abdominal metastases	% of patients with intra-abdominal metastases	Overall no. of patients who developed distant metastases
0	24	12%	207
1	6	28%	21
2	3	23%	13
3	3	33%	9
4	8	72%	11
5	2	50%	4
6	6	60%	10
≥ 7	7	63%	11

PTDs: pericolonic tumor deposits.

TABLE 9
Components of Pericolonic Tumor Deposits

Feature of PTD	No. (%)
Perineural alone	2 (7%)
Perivascular alone	1 (3%)
Intravascular alone	0
Perineural and perivascular	3 (10%)
Perineural and intravascular	6 (20%)
Perivascular and intravascular	7 (23%)
Perineural, perivascular, and intravascular	11 (37%)
Component of perineural growth	23 (77%)
Component of perivascular growth	22 (73%)
Component of intravascular growth	25 (83%)

PTD: pericolonic tumor deposit.

Tumor site ($P = 0.37$), number of lymph nodes recovered ($P = 0.49$), and number of lymph nodes metastases ($P = 0.58$) were not associated with the initial site of metastases.

Factors Associated with Pericolonic Tumor Deposits

The features that were independently associated with the presence of a PTD were number of lymph node metastases ($P < 0.01$; odds ratio, 1.28; confidence limits, 1.14–1.45), increasing adenocarcinoma grade ($P < 0.01$, odds ratio, 2.52; confidence limits, 1.58–4.02), and extramural venous invasion ($P < 0.01$; odds ratio, 2.31; confidence limits, 1.26–4.3).

The Source of PTDs

Table 9 shows the distribution of adenocarcinoma located within the three different locations. Adenocarcinoma was most commonly observed (37%) in all 3 locations, perineural, peri-large vessel, and intravascular (Figs. 2, 4–6). The second most common locations involved were peri-large vessel and intravascular

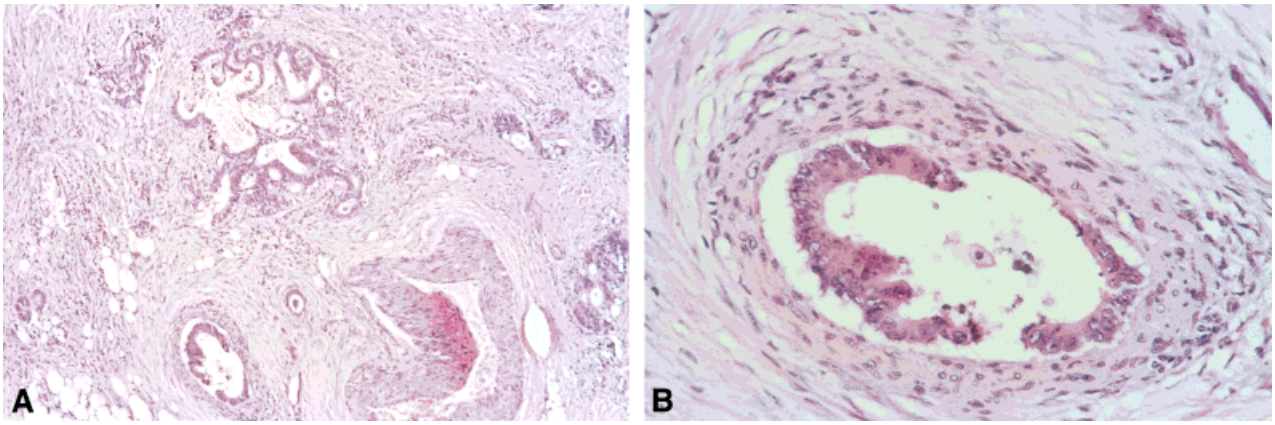

FIGURE 4. (A) Pericolonic tumor deposit, level 1. Adenocarcinoma is present around a large vessel. There is the appearance of extension into the adjacent adipose tissue from the centrally located large vessel (H & E, original magnification ×4). (B) Pericolonic tumor deposit, level 1. Higher magnification shows adenocarcinoma within a medium-sized vessel that is located in the lower left corner of the photograph of (A) (H & E, original magnification ×96).

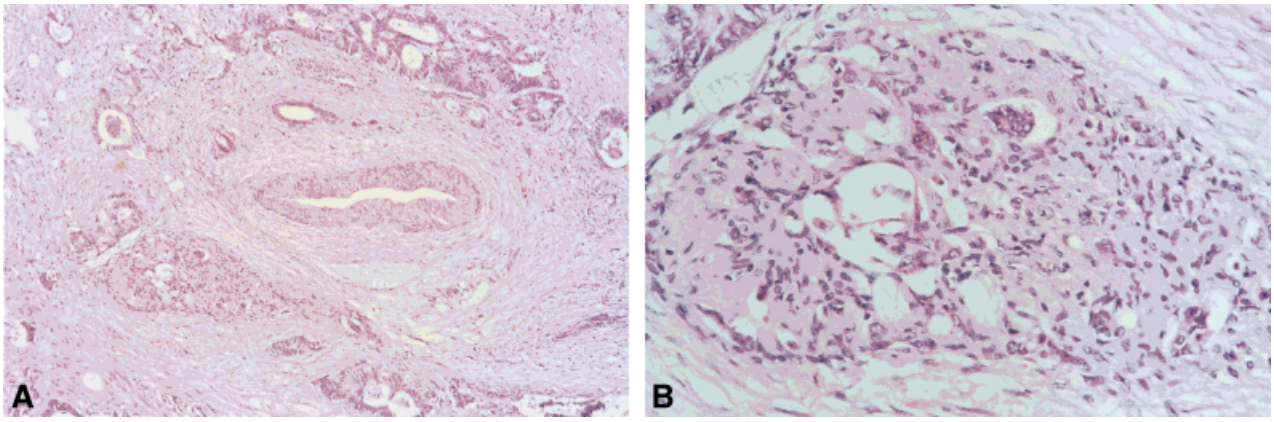

FIGURE 5. (A) Pericolonic tumor deposit, level 4. Circumferential growth of the adenocarcinoma around the centrally located large vessel, and the medium-sized vessel in the lower left corner (H & E, original magnification ×4). (B) Pericolonic tumor deposit, level 4. Higher magnification of the medium-sized vessel from the lower left corner of (A) shows adenocarcinoma within its media (H & E, original magnification ×96).

(23%). Adenocarcinoma was observed in 1 of the 3 locations in all 30 specimens. A single section occasionally displayed adenocarcinoma in more than two locations. Step-sectioning was required to identify adenocarcinoma in the various locations. Frequently, deeper step-sections revealed adenocarcinoma within a perineural or peri-large vessel location. As a component, 83% of PTDs had at least 1 location of intravascular growth, 77% had at least 1 focus of perineural growth, and 73% had at least 1 focus of peri-large vessel growth. No PTDs were determined to represent lymph node metastases upon step-sectioning. Elastic stains occasionally showed a fragment of vessel wall that was destroyed by adenocarcinoma. However, the elastic stain was not generally useful because the involved veins typically contained little elastic tissue in their walls.

DISCUSSION

PTDs have been recognized as an entity since at least 1935, when Gabriel et al. noted their existence and concluded that they were the result of vascular tumor dissemination.[8] Although easily mistaken for lymph nodes on gross dissection, microscopic evaluation shows PTDs to be discontinuous adenocarcinoma unassociated with a lymph node. While one report found PTDs to be an independent predictor of poor outcome in patients with right-sided colon carcinoma,[7] the clinical significance of PTDs is poorly defined, and they have not uniformly been incorporated into staging definitions.[1,3] We found that PTDs were independently associated with metastatic disease and decreased disease free survival, along with adenocarcinoma grade and the number of lymph node metastases. The latter factors have been extensively stud-

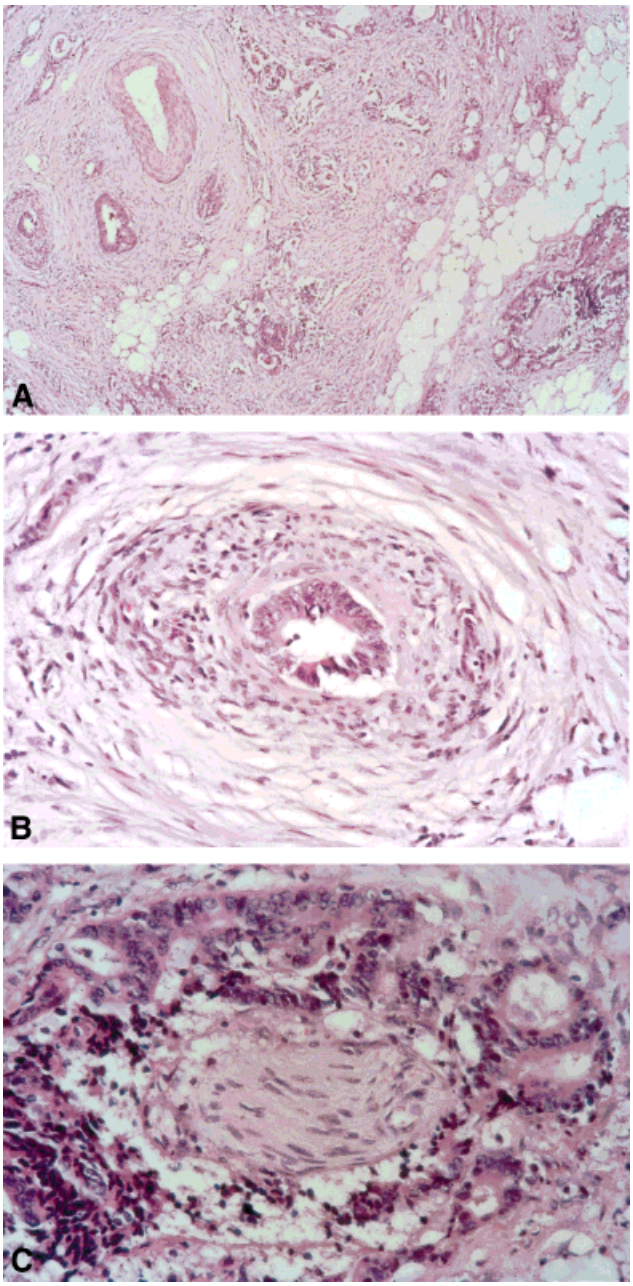

FIGURE 6. (A) Pericolonic tumor deposit, level 10. Invasive adenocarcinoma extends into the pericolonic adipose tissue associated with a desmoplastic response. There is also intravascular (lower left) and perineural (lower right) adenocarcinoma (H & E, original magnification ×4). (B) Pericolonic tumor deposit, level 10. Higher magnification of the medium sized vessel from the left side of (A) shows adenocarcinoma within its luminae. The in-between levels (5–9) also had adenocarcinoma within this vessel, suggesting that the intravascular growth is large (H & E, original magnification ×96). (C) Pericolonic tumor deposit, level 10. Higher magnification of the nerve from the lower right corner of (A) shows circumferential adenocarcinoma in the perineural space (H & E, original magnification ×384).

ied.[2,5,6,9–30] Aside from recognizing that our data is consistent with prior authors' results and therefore probably consists of data on similar patients with similar neoplasms, it is not our intention to discuss these other well-studied prognostic features.

Our results substantiate some of the findings of Harrison et al. These authors found PTDs to be an independent predictor of length of survival among patients with cecal and ascending colon adenocarcinomas.[7] Unlike our study, theirs did not identify a trend of decreasing survival with increasing numbers of PTDs. We do not have an explanation for this difference, but it should be noted that our study was limited to cases with lymph node metastases, whereas Harrison et al. studied patients with all tumor stages. In addition, the endpoint of our study was the initial clinically apparent metastasis (disease free survival), whereas Harrison et al. evaluated overall survival.

The survival impact of even small PTDs was significant. Although we found that increasing PTD size was associated with decreased survival, PTDs of any size, including those less than 3 mm in maximum dimension, clearly portended a significantly worse survival relative to the absence of PTDs. Their presence produces disease free survival curves that overlap with the survival curves of patients who have distant metastases at the time of surgery.[10–14,16,30] The results call the TNM recommendations on how to classify PTDs into question. The 1997 *TNM Cancer Staging Handbook* recommends that, for classification, *multiple* PTDs seen microscopically only in pericolic adipose tissue be considered metastasis in a single lymph node. A PTD greater than 0.3 cm also should be classified as a regional lymph node metastasis. However, a *single* PTD 0.3 cm or less should be classified as discontinuous T3 adenocarcinoma.[4] Our finding that most PTDs contain adenocarcinoma in perineural and peri-large vessel spaces, in addition to intravascular growth within the center of PTDs, makes their optimum TNM classification unclear. PTDs had significantly worse prognostic significance than lymph node metastases, suggesting that they be considered a separate entity unrelated to maximum dimension. Thus, a minimum size criterion for PTDs is not useful as long as they are grossly palpable.

The TNM classification contains an optional venous invasion descriptor, which for the time being might be the most appropriate existing code for these lesions: VX, venous invasion cannot be assessed; V0, no venous invasion; V1, microscopic venous invasion; V2, macroscopic venous invasion.[4] V2 or V1 could be selected based on whether the lesion was evident grossly or represented a microscopic finding. The V classification would thus replace the existing TNM

rule that separates these lesions by size into those representing discontinuous pericolonic spread and positive regional lymph nodes (Leslie Sobin, M.D., personal communication).

Pericolonic tumor deposits appear to be grossly palpable invasive tumor nodules derived from adenocarcinoma that grows along nerves or large vessels or within vascular structures. Our results support the observations and conclusions of an abstract by Stiles et al.[31] They reported that 60% of cases showed either direct invasion of thick-walled veins or close apposition to venous channels. Twelve percent were unassociated with a structure, but the overwhelming majority of these were caused by mucinous adenocarcinomas. Seven percent were lymph node metastases, and 3% were predominantly perineural invasion. Unlike these authors, we did not uncover lymph node metastases, possibly because we considered pericolonic lesions that had a rounded, lymph node appearance to not represent PTDs. We also excluded patients with mucinous or signet ring histology.

The universal finding that PTDs had a component of peri-large vessel, perineural, or intravascular adenocarcinoma probably explains the strong and independent association of PTDs with decreased survival and intra-abdominal failure. There was a proportionally greater likelihood of intra-abdominal (extrahepatic) metastases with increasing numbers of PTDs. The presence of extramural venous and perineural invasion have each been shown to be associated with failure.[2,10,12–14,16–20,22–26,29,32–37] PTDs are grossly identifiable and, therefore, represent extensive manifestations of extramural venous and perineural invasion. They are similar to the grossly identifiable venous invasion described by Dukes that was associated with extremely poor prognosis.[14] Abundant amounts of tumor in these locations may facilitate intra-abdominal spread. Support of this theory comes from a study of rectal adenocarcinomas in which it was found that positive radial margins greatly increased the risk of local recurrence.[38] Thirty percent of the cases with positive radial margins were secondary to discontinuous tumor spread. If our results are corroborated by prospective studies, it may be appropriate to consider radiation therapy for those patients with PTDs and an adenocarcinoma that has arisen in a fixed portion of the colon.

Pericolonic tumor deposits are not a recently described entity. Careful review of prior authors' works finds a variety of classifications. Some authors have classified them as tumor spread outside the bowel wall. Other authors have considered them foci of vascular space invasion, lymph node metastases, or perineural invasion. Gabriel et al. noted in their 1935 study, ". . .we have found deposits of carcinoma cells at a distance from the primary growth although the lymphatic glands themselves have been free. Most of these non-lymphatic metastases are the result of vascular spread. Whenever the lymphatic glands have been free we have grouped the operation specimens as B cases." However, photographs in the studies by Dukes from the 1940s suggest that he classified some PTDs as extramural venous invasion.[13,14] Some photographs in the 1936 lymph node mapping study by Gilchrist and David are nearly identical to PTDs in our study, suggesting that these authors classified PTDs as lymph nodes.[39] Grinnell, in 1942, also provided photographs of lesions termed large venous invasion that were interchangeable with some PTDs in our study. Sunderland also noted the frequent overgrowth and destruction of medium-sized vessels after invasion took place,[24] and Seefeld and Bargen provided photographs of extensive perineural invasion that were indistinguishable from some of the PTDs in our study.[40] In the 1946 study by Glover and Waugh on lymphatic drainage patterns of rectal carcinomas, these authors noted one case in which a nodule, thought to be a lymph node, was located 1–2 cm below the carcinoma.[41] However, on microscopic examination it was found to be a small blood vessel with a small location of invasive carcinoma cells situated immediately adjacent to the vessel. The photograph of this lesion is identical to what we have classified as a PTD. They pondered whether this lesion was a tiny lymph node that was completely replaced by tumor or a rare demonstration of perivascular spread. Later in their discussion, the authors inferred that they considered this focus equivalent to a lymph node metastasis.

We are unable to explain how pathologists could dissect small PTDs that were 1 or 2 mm in diameter out of pericolonic adipose tissue. Nonetheless, we know the pathologist palpated the PTD because they were present as individual tissue fragments within the blocks submitted as pericolonic lymph nodes. These small PTDs were not serendipitously found in the adipose tissue adjacent to lymph node metastases. Possibly, small PTDs elicit a desmoplastic response that is larger than the adenocarcinoma focus.

Occasionally, microscopic foci of discontinuous pericolonic adenocarcinoma will be incidentally identified in tissue sections, often in sections that are procured from the deep, leading edge of the tumor. We believe that these microscopic lesions should not be classified as "PTDs" as defined in this study. We limited our study to only grossly identifiable lesions that were submitted as lymph nodes within the lymph node tissue blocks of the case. Incidentally identified,

microscopic, discontinuous, pericolonic tumor foci are probably the result of similar growth processes that lead to palpable, larger PTDs. Therefore, we recommend that they be reported as extracolonic perineural, perivascular, or intravascular growth, depending on their histologic features.

One limitation of this study is that sensitive radiographic instruments were not available at the time of metastases for most of these patients. Thus, we were unable to report the specific site of intra-abdominal failure, i.e., mesenteric mass or surface spread. Additional studies are also needed to illuminate the relation between PTDs and site of intra-abdominal metastases. They will also be needed to evaluate the effect of adjuvant chemotherapy on the natural biology of patients with lymph node metastases and PTDs.

In summary, PTDs are invasive adenocarcinoma nodules within pericolonic adipose tissue that appear to represent adenocarcinoma extending along nerves, large vessels, or directly out from intravascular growth. PTDs probably are gross and extreme manifestations of these processes, which may explain the dismal outcomes of patients who have them. Their presence is an independent poor prognostic factor that is separate from lymph node metastases, regardless of the number and size of metastases. Increasing numbers of PTDs and increasing maximum dimension of the PTDs are independently associated with decreased disease free survival. The optimum TNM classification for PTDs remains to be defined. Until then, we recommend that the number and maximum dimension of PTDs be reported separately from lymph node metastases.

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