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Identification of an Objective Cut-Off Point to Define the Clinical Stage T4a in Colon Cancer

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Abstract: Introduction: The current state of pathology practice and the variability in diagnosing pT4a colon cancer have been underexplored in existing studies. Our objective was to establish a specific cutoff point to distinguish between the pathological stages of pT3 and pT4a in colon cancer. Methods: We conducted a cross-sectional study involving pT3 and pT4 (pN0-2, cM0) colon cancers, measuring the distance to the serosa. Patients were categorized and analyzed based on this distance and the peritoneal reaction, with the aim being to ascertain their prognostic implications. Results: A total of 384 patients were analyzed. Patients with a distance between the invading front of cancer and the serosa $\geq$ 1 mm without a peritoneal reaction exhibited a median survival of 118 months, contrasting the amount of 70 months for those with <1 mm plus peritoneal reaction. Only lengths <1 mm with peritoneal reaction showed a significant correlation with mortality ($p < 0.001$). Conclusion: Our study revealed that patients in whom neoplastic cells were less than 1 mm from the serosal surface, accompanied by a peritoneal reaction (hemorrhage, inflammation, neovascularization, fibrin), had significantly lower survival rates compared to those with more than 1 mm distance and without peritoneal response (70 vs. 118 months, $p < 0.001$). Hence, such cases should be considered within the pT4a stage.

Keywords: colon cancer; clinical staging; mortality; risk factors; serous invasion

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1. Introduction

With an annual incidence exceeding one million cases and over half a million associated deaths, colorectal cancer poses a significant global health threat [1]. Its prevalence varies globally, ranking as the fourth most common cancer worldwide. In the United States, it stands as the second leading cause of cancer-related deaths, with an estimated 49,960 deaths occurring in 2020 [2].

In Mexico, colorectal cancer has emerged as the second most prevalent digestive tract cancer, following gastric carcinoma, with a noticeable uptick having occurred since the late 1970s. Out of 102,657 recorded malignant tumors in Mexico, 2433 were located in the colon, predominantly of the adenocarcinoma type [3].

A substantial portion of colon cancer cases present with pT4 tumors, denoting the highest level of local invasion and an elevated risk of peritoneal metastases. The pTNM staging system, encompassing pathologic tumor, nodal, and the metastasis status, plays a pivotal role in cancer reporting by pathologists [4–6]. Within the pT4 stage, two subcategories exist—pT4a and pT4b—that signify distinct degrees of invasion. Varied treatment approaches, such as adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) and revision laparoscopy, are currently under investigation in regard to pT4 colon cancer patients. Additionally, contemporary clinical guidelines advocate for adjuvant chemotherapy

in stage II colon cancer patients exhibiting a pT4 presence. Recent studies also leverage pT4 status to determine the duration of adjuvant chemotherapy in stage III colon cancer [7].

The recognition of a pT4 status is increasingly crucial for effective patient management. Notably, a tumor need not necessarily breach the serous surface to qualify as pT4a. Tumors in close proximity to the serosa, or those inducing a peritoneal reaction, are observed to exhibit behavior akin to those penetrating the serosa [8–11].

Improving survival rates in colon carcinoma necessitates identifying patients who benefit from adjuvant treatments and intensive management. Achieving this requires a comprehensive evaluation of prognostic and predictive factors. Pathologists encounter challenges with the pT4 category, particularly in discerning pT4a specimens, as the TNM definition mandates complete penetration of tumor cells through the peritoneum [12]. National histopathology reporting guidelines may offer more lenient criteria. To prevent underdiagnosis, specific features are considered indicative of pT4a. Furthermore, the precise microscopic detection of pT4 relies on meticulous specimen evaluation and sampling during resection [13–16].

Given the growing clinical importance of pT4a, establishing a clear criterion for diagnosing and defining it is crucial. Presently, there exists a gap in understanding how far neoplastic cells must be from the serosa to qualify, which would aid in distinguishing between pT4a and pT3 stages [17–19]. Our objective was to identify an objective measurement in millimeters to differentiate between the pT3 and pT4a stages of colon cancer and assess the association with survival rates.

2. Methods

All pathology reports related to pT3 and pT4 (pN0-2, cM0) colon cancers from the years 2010 to 2015 were obtained. According to the original reports, tumors were classified into pT3 (colon cancers infiltrating the muscularis propria towards the pericolic fat), pT4a (those penetrating the serosa), and pT4b (invading adjacent tissues or organs) in accordance with the eighth edition of the Tumor Node Metastasis system (TNM 8) [7].

Clinical information was extracted from clinical records and histopathology reports. Among all specimens, only those categorized as pT3 and pT4a were selected. For pT3 specimens, the distance to the serosa in millimeters was determined. Two pathologists specializing in gastrointestinal pathology identified the histological section where neoplastic cells were closest to the peritoneal surface. The measurement was performed using a thin, adhesive ruler calibrated for histological preparations. This ruler, almost as thin as adhesive tape, was visible under any microscope, and its accuracy was confirmed through calibration and verification in a physics laboratory; additionally, the ruler featured divisions every 0.05 mm. The distance assessment involved four independent observers with varying levels of experience, resulting in an excellent intraclass correlation of 0.92.

After establishing the distance, a specific threshold between the tumor and the serosa was sought using the ROC curve to determine its correlation with survival rates. Following the determination of these critical points, patients were categorized as pT3 if the threshold showed no significant association with the outcomes of interest. Conversely, patients were labeled as pT4 if they exhibited a distance smaller than that encountered in the ROC curve. Additionally, patients with disruption of the mesothelial surface were noted, including: (1) mesothelial inflammatory and hyperplastic responses with a tumor near, but not on, the serosal surface; (2) tumor on the serosal surface with inflammatory reaction or mesothelial hyperplasia (Figure 1); (3) tumor cells that penetrate the serosal surface.

These findings were then analyzed using the Kaplan–Meier method before also being compared with confirmed pT4a patients (specimens with undoubted ruptures or in contact with the serosa). Normality (Kolmogorov) tests were conducted to determine the parametric nature of numerical variables. Parametric variables were presented as mean and standard deviation, while non-parametric variables were summarized as median and interquartile range. Between-group comparisons for categorical variables were assessed using chi-square

tests, while a Student's *t*-test was applied for normally distributed numerical data and a Mann–Whitney's U-test was utilized for non-parametric numerical data.

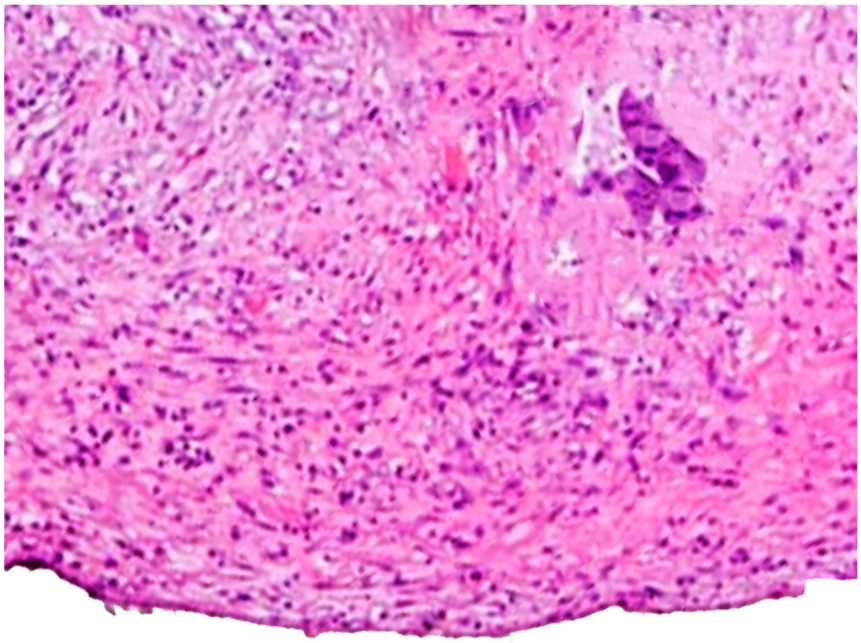

Figure 1. A peritoneal reaction consists of fibrosis, hemorrhage, and vascular changes (neovascularization, dilated vessels) and inflammation.

3. Results

From a database of 667 consecutive patients who underwent colectomy at our institution between 2010 and 2015, 384 (57.6%) were identified with pathological stages pT3 and pT4a. These patients were reclassified according to the 8th edition of the TNM classification, with a mean age of 57.48 (range 19–89 years) and a similar male-to-female ratio (51.8% women and 48.2% men). Most patients were in clinical stages II and III (75%), and 320 (83.3%) were still alive at an average follow-up of 43 months. Among the 384 patients, 262 (68.2%) were classified as pathological stage pT3, while 122 (31.8%) were classified as pT4. The clinical and pathological characteristics of the 384 patients according to the pathological stage are summarized in Table 1.

The pT3 group had 52.7% women, a median age of 56 years (range 48–68), and a tumor diameter of 60 mm (range 40–80). In contrast, the pT4 group had an equal male-to-female ratio (50%), a median age of 61 years (range 49–68), and a tumor diameter of 68 mm (range 40–80).

The degree of differentiation, clinical stage, and nodal status were higher in the pT4 group ($p < 0.001$), as were the frequency of lymphatic invasion (32.6% vs. 59.8%, $p = 0.001$), venous (12.6% vs. 36.1%, $p = 0.001$), and perineural (33.3% vs. 42.6%, $p = 0.001$). Regarding surgical margins, 99.2% of the pT3 group were completely resected (R0) compared to 95.1% in the pT4 group ($p < 0.001$).

Survival analysis was performed for each group, revealing a median 5-year survival of 87.2% for the pT3 group, with a mean of 125.4 months, while, for stage pT4a, it was 79.1%, with a mean of 110.4 months ($p < 0.001$).

The 262 patients in the pT3 stage were dichotomized, based on the results of the ROC curve, into those with a distance of less than 1 mm plus a peritoneal reaction (referred to as the risk group) and those with a distance greater than or equal to 1 mm without a peritoneal reaction (referred to as the group without risk) (Figure 2). Patients with a distance between the invading front of the tumor and the serosal surface greater than or equal to 1 mm without a peritoneal reaction had a median survival of 118 months, while those with less than 1 mm plus a peritoneal reaction had 70 months (Figure 3), indicating

inferior survival in comparison to pT4a cases. Table 2 summarizes the clinicopathological characteristics concerning the risk group, where no statistically significant association was observed with age, tumor diameter, histological grade, clinical stage, and lymph vascular or perineural invasion, while only the distance less than 1 mm with a peritoneal reaction was significantly correlated with mortality ($p < 0.001$).

Table 1. Clinicopathological characteristics of 384 patients with colon cancer according to category T.

Variable	pT3 n = 262	pT4a n = 122	*p*-Value *
Sex, n (%)			
Female	138 (52.7)	61 (50)	0.626
Male	124 (47.3)	61 (50)	
Age (years)–Median (IQR)	56 (48–68)	61 (49–68)	0.387
Location—n (%)			
Right	185 (70.6)	85 (69.7)	0.851
Left	77 (29.4)	37 (30.3)	
Tumoral diameter (mm), Median (IQR)	60 (40–80)	68 (40–80)	0.524
Resected lymph nodes, Median (IQR)	24 (18–33)	23 (16–32)	0.281
Metastatic lymph nodes, Median (IQR)	0 (0–3)	1 (0–5)	0.005
Histologic grade, n (%)			
1	52 (19.8)	10 (8.2)	<0.001
2	140 (53.4%)	50 (41)	
3	70 (26.7)	62 (50.8)	
Lymph node status, n (%)			
pN0	135 (51.5)	39 (32)	<0.001
pN1	58 (22.1)	46 (37.7)	
pN2	69 (26.3)	37 (30.3)	
Clinical stage, n (%)			
Stage II	120 (45.8)	30 (24.6)	<0.001
Stage III	91 (34.7)	47 (38.5)	
Stage IV	51 (19.5)	45 (36.9)	
Lymphovascular invasion, n (%)			
No	176 (67.4)	49 (40.2)	<0.001
Yes	85 (32.6)	73 (59.8)	
Venous invasion, n (%)			
No	229 (87.4)	78 (63.9)	<0.001
Yes	33 (12.6)	44 (36.1)	
Perineural invasion, n (%)			
No	217 (82.8)	70 (57.4)	<0.001
Yes	45 (17.2)	52 (42.6)	
Márgenes quirúrgicos, n (%)			
Negative	260 (99.2)	116 (95.1)	0.008
Positive	2 (0.8)	6 (4.9)	
Outcome, n (%)			
Alive	222 (84.7)	98 (80.3)	0.281
Dead	40 (15.3)	24 (19.7)	

* Chi square test for categorical variables, *t*-Student test for numerical variables, IQR = interquartile range.

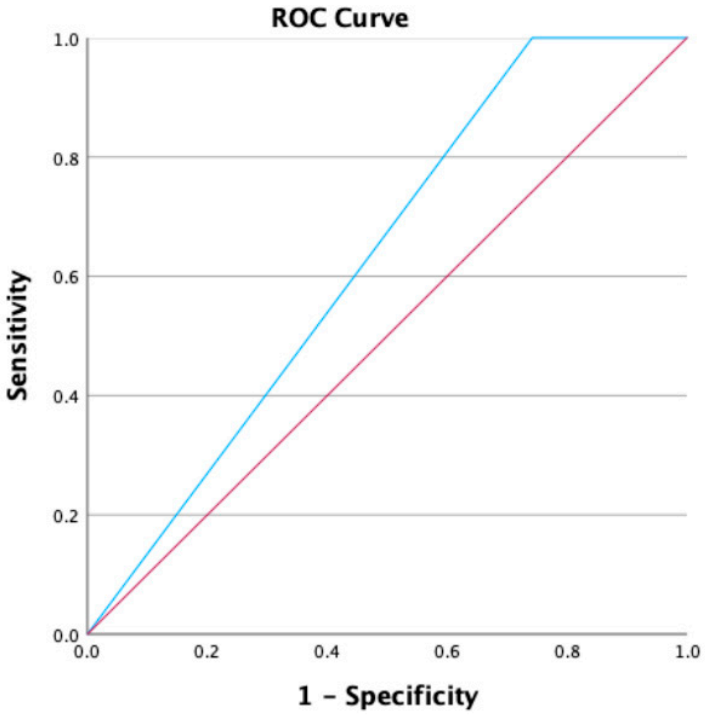

Figure 2. Receptor operating curve (ROC) of distance in millimeters of the tumor regarding serous surface. The best cut-off point was 1 mm. The red line represents the neutrality of the diagnostic test in the ROC curve and the blue line represent our test (distance to the serosal surface).

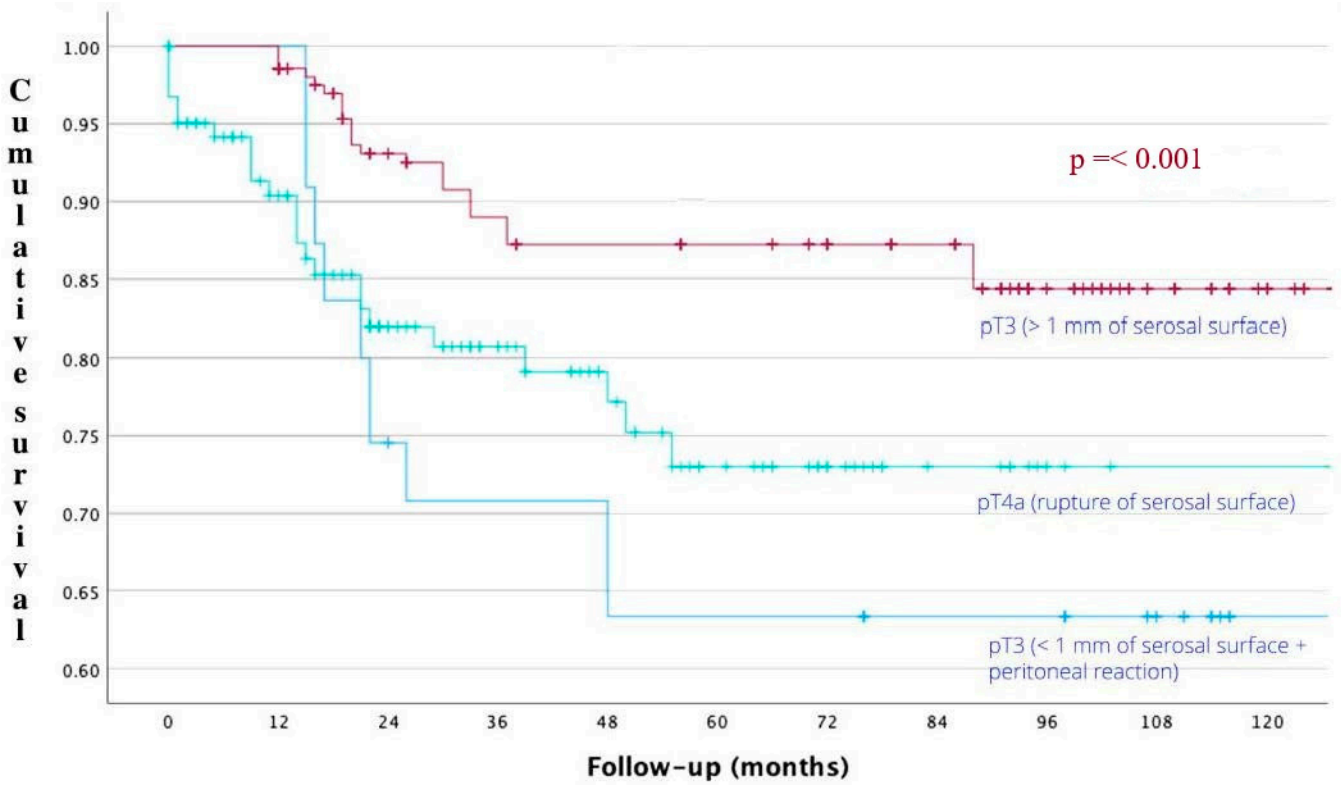

Figure 3. Survival curve for the 384 patients with colon cancer according to the risk of death.

Table 2. Clinicopathological characteristics of 262 patients of colon cancer according to the risk of death (<1 mm + peritoneal reaction).

Variable	Non-Risk n = 207	Risk n = 55	*p*-Value *
Sex, n (%)			
Female	105 (51)	27 (49)	
Male	102 (49)	28 (51)	0.829
Age (years)–Median (IQR)	55 (47–66)	56 (50–62)	0.676
Location—n (%)			
Right	112 (54)	27 (49)	
Left	95 (46)	28 (51)	0.507
Tumoral diameter (mm), Median (IQR)	56 (40–81)	63 (40–78)	0.879
Resected lymph nodes, Median (IQR)	28 (21–34)	26 (18–39)	0.887
Metastatic lymph nodes, Median (IQR)	1 (0–3)	1 (0–5)	0.384
Histologic grade, n (%)			
1	82 (39.6)	17 (31)	
2	100 (48.3)	30 (54.5)	
3	25 (12.1)	8 (14.5)	0.491
Lymph node status, n (%)			
pN0	105 (51)	12 (21.8)	
pN1	51 (24.5)	26 (47.3)	
pN2	51 (24.5)	17 (30.9)	<0.001
Lymphovascular invasion, n (%)			
No	145 (70)	35 (63.6)	
Yes	62 (30)	20 (36.4)	0.362
Perineural invasion, n (%)			
No	189 (91.3)	50 (90.1)	
Yes	18 (8.7)	5 (9.9)	0.926
Surgical margins, n (%)			
Negative	175 (84.5)	48 (87.3)	
Positive	32 (15.5)	7 (12.7)	0.612
Outcome, n (%)			
Alive	188 (90.8)	30 (54.5)	
Dead	19 (9.2)	25 (45.5)	<0.001

* Chi square test for categorical variables, *t*-Student test for numerical variables, IQR = interquartile range.

4. Discussion

Our study, conducted on 384 patients diagnosed with colon adenocarcinoma initially classified as pT3, demonstrated that patients with neoplastic cells located less than 1 mm from the serosal surface, accompanied by a peritoneal reaction (hemorrhage, inflammation, neovascularization, fibrin), had significantly lower survival rates compared to those with a distance greater than 1 mm and without a peritoneal reaction (70 vs. 118 months, $p \leq 0.001$).

Surgery is the central aspect of colon cancer treatment, and, post-resection, various factors affecting staging need evaluation by pathologists. Despite ongoing updates to parameters, there remains considerable variability and subjectivity in classifying and distinguishing between pathological stages pT3 and pT4a. Clear and objective criteria for defining these stages are lacking, and existing recommendations are subjective and non-measurable or reproducible [11–14].

Our study reflected differential clinical and biological behavior between pathological stages pT3 and pT4a, indicating a higher 5-year survival rate for the pT3 group (81.4%). The pT4a group exhibited a higher clinical stage, degree of differentiation, nodal status, and increased frequency of lymph vascular and perineural invasion. Numerous studies

consider the pT4 category to be a significant risk factor for peritoneal metastases, with it being associated with a poorer prognosis [20–22].

To enhance concordance in identifying and histologically distinguishing between the pT3 and pT4a stages, millimeter cut-off points have been previously established for the distance between the tumor and the serosa, along with specific histological characteristics, yielding varying results. Our study identified that patients with a space between the invading tumor front and the serosa of <1 mm, associated with peritoneal reactions, presented a lower survival rate. Similar findings were reported in a study [21] that indicated lower survival rates for patients with tumors < 1 mm from the serosal surface (separated by reactive fibrosis or inflammation) or with tumor cells on the serosal surface compared to those > 1 mm from the serous surface. Other studies support the association of tumors located at <1 mm with fibroinflammatory tissue reaction in the serosa with greater peritoneal recurrence and a high risk of peritoneal metastasis at five years [14,23].

Recent investigations, such as one study [24] that analyzed the distance from the tumor to the peritoneal surface in 189 patients, found higher rates of peritoneal metastases in tumors with shorter distances to the peritoneal surface. Serosal penetration by adenocarcinoma emerges as a crucial predictor of disease recurrence and prognosis. For instance, a study evaluating 579 colorectal cancer resection specimens with regional lymph node metastases found that only 16% of patients with serosal penetration survived after five years [25]. Another group studying 467 colon cancer patients with node-negative disease found that serosal tumor spread was independently associated with reduced 5-year survival [26].

Adenocarcinoma in the intestinal wall induces inflammatory changes in the peritoneum, alerting to the possibility of serosal penetration. Peritumoral abscesses communicating with the serosa represent an underrecognized manifestation of serosal penetration. The peritoneal changes may indicate tissue repair or the desmoplastic/inflammatory response to tumor invasion. Our data support the notion that tumors with viable cells at less than 1 mm, and with a peritoneal reaction, exhibit more aggressive behavior.

Efforts to detect serosal spread have included various techniques beyond conventional hematoxylin and eosin evaluation. For example, elastin staining has been used to identify tumors that can destroy the subserous elastic lamina, correlating with higher postoperative recurrence rates and lower 5-year survival rates [27]. Immunohistochemical stains, however, have shown limited utility in detecting serous spreading of colon cancer [28,29].

The study's limitations include sample size and challenges in assessing the complete tumor lesion, potentially leading to underestimation. Subjectivity and variability in measuring and interpreting peritoneal reactions were addressed through intraclass correlation between participating pathologists, indicating excellent agreement.

5. Conclusions

In conclusion, our study suggests that peritoneal reactions and the distance between the invading tumor front and the serosa are crucial pathological characteristics that have prognostic significance in patients with colon cancer in pathological stages pT3 and pT4a. Patients with pT3 colon adenocarcinomas where neoplastic cells were less than 1 mm from the serosal surface, accompanied by a peritoneal reaction, had significantly lower survival rates than those with a distance greater than 1 mm and without a peritoneal reaction.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board and Ethics Committee of Instituto Nacional de Cancerología (INCan) (protocol code 2022/117 and approved on 22 September 2022).

Informed Consent Statement: Patient consent was waived due to their retrospective nature and because the clinical data of the patients and their identification data were blinded. The subjects of study in our work are not patients, but rather tissues with associated clinical and pathological information. The anonymity of their data is ensured, and the patients were not interviewed nor subjected to any intervention.

Data Availability Statement: The data from our research is accessible to anyone upon reasonable request through the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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