RESEARCH ARTICLE

**Editorial Process:** Submission:10/05/2025 Acceptance:03/31/2026 Published:04/07/2026

# Oncological Outcomes and Risk Factors for Local Recurrence and Distant Metastasis After Upfront Surgery in cT3 Rectal Cancer With an Uninvolved Circumferential Resection Margin on Magnetic Resonance Imaging

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## Abstract

**Objective:** To evaluate oncological outcomes and potential risk factors for local recurrence (LR) and distant metastasis (DM) after upfront surgery in patients with magnetic resonance imaging (MRI)–defined cT3 rectal cancer, with an uninvolved circumferential resection margin (mrCRM) and no extramural vascular invasion (EMVI), in a Vietnamese cohort. **Methods:** A single-center, retrospective–prospective cohort of 144 patients who met these criteria and underwent upfront curative surgery between January 2018 and April 2022 was analyzed. The cumulative incidences of LR and DM were estimated. Univariate Cox regression and penalized regression models (Ridge and LASSO least absolute shrinkage and selection operator) were applied to explore potential risk factors. **Results:** With a median follow-up of 56 months, LR occurred in 7 patients (4.9%), with 3-, 5-, and 7-year cumulative rates of 3.6%, 5.3%, and 5.3%, respectively. LR was most consistently associated with mesorectal violation, while anastomotic leakage and involved pathological circumferential resection margin (pCRM) showed less stable associations. DM occurred in 15 patients (10.4%), with cumulative incidences of 8.5%, 11.6%, and 11.6% at 3, 5, and 7 years, respectively. Stage III patients had significantly higher DM rates compared with stage II ($p = 0.009$). Preoperative carcinoembryonic antigen (CEA) ≥ 5 ng/mL and pathological nodal positivity (pN+) were the most consistent predictors of DM, while mesorectal violation and involved pCRM appeared as secondary contributors. **Conclusion:** Upfront surgery yielded favorable outcomes in selected low-risk cT3 rectal cancer patients. Mesorectal violation was most consistently associated with LR, though estimates were limited by the small number of events. DM appeared to be primarily driven by tumor biology (CEA and pN), with mesorectal violation and involved pCRM as possible secondary factors. These findings warrant validation in larger prospective cohorts.

**Keywords:** MRI- mesorectal violation- carcinoembryonic antigen- pathological nodal positivity- involved pCRM

*Asian Pac J Cancer Prev,* **27 (4)**, 1487-1496

## Introduction

LR and DM remain major concerns in rectal cancer management. The adoption of total mesorectal excision (TME), particularly when integrated with neoadjuvant chemoradiotherapy (nCRT), has markedly reduced LR compared with historical data, with contemporary 5-year LR rates of 5–10% reported in the literature [1, 2]. In the TME era, DM has emerged as the primary cause of treatment failure [3] and rectal cancer mortality, with 3–5-year rates ranging from 9% to 14%, including approximately 10% in surgery-only cohorts [4, 5].

The 2025 European Society for Medical Oncology guidelines endorse a risk-adapted approach, in which upfront surgery is considered an appropriate option for carefully selected patients with MRI-defined cT3 tumors, uninvolved circumferential margins (mrCRM), and negative extramural vascular invasion (EMVI) [6]. This strategy may be suitable for patients at low risk of LR or those unfit for nCRT due to toxicities such as hematologic suppression or gastrointestinal dysfunction [7]. Additional concerns include postoperative complications following radiotherapy, particularly anastomotic leakage, which significantly impairs postoperative quality of life [8, 9]. In low- and middle-income countries like Vietnam, limited radiotherapy infrastructure and prolonged waiting times may further justify upfront surgery, as delays risk disease progression or emergency interventions.

Multiple clinicopathologic factors have been associated with LR and DM. For LR, these include involved pathological circumferential margin (pCRM), poor differentiation, anastomotic leakage, low anterior

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resection, and vascular or perineural invasion [10-12]. For DM, risk factors include elevated preoperative CEA, nodal metastasis, number of lymph nodes metastases, EMVI, and tumor diameter [13-15].

While emerging evidence supports the oncologic feasibility of upfront surgery [5, 16]. The prognostic implications of conventional risk factors may differ in the absence of nCRT. In this setting, early risk stratification can help guide treatment decisions, surveillance strategies, and selective use of nCRT. Therefore, we conducted this study to estimate LR and DM rates and explore clinicopathologic predictors in MRI-staged cT3 rectal cancer patients with uninvolved mrCRM and negative EMVI undergoing upfront laparoscopic resection without nCRT.

## Materials and Methods

*Study settings*

This cohort was carried out at the University Medical Center Ho Chi Minh City, a high-volume tertiary hospital with approximately 250–300 rectal cancer surgeries annually in Vietnam, from January 2018 to April 2022.

*Study Design and Participants*

This single-center retrospective-prospective cohort included both retrospective and prospective arms, without a comparison group. Patients treated prior to ethics approval were retrospectively identified, while later cases were prospectively enrolled under a unified protocol. Standardized diagnostic, surgical, and follow-up procedures were applied across all patients.

Patients with rectal adenocarcinoma ≤12 cm from the anal verge were eligible. Tumors were staged as cT3a (<1 mm), cT3b (1–5 mm), or cT3c (5–15 mm) of extramural spread. MRI inclusion required uninvolved mrCRM (>1 mm) and negative EMVI. In accordance with ESMO recommendations [6], cT3c tumors in the low rectum are generally excluded because of their high risk of pCRM involvement. In this study, however, all cT3c tumors (upper, mid, and low rectum) were included within a strictly selected, risk-adapted cohort. Upfront surgery was offered only when the multidisciplinary tumor board (MTB) deemed the prognostic profile favorable. For low-rectal cT3c tumors, eligibility required negative mrCRM, absence of EMVI, and non–poorly differentiated histology. This selection strategy reflects our institutional risk-stratification approach and ensures internal cohort homogeneity despite limitations in radiotherapy capacity.

Patients were excluded if they had DM, suspicious lateral pelvic lymph nodes on imaging (short-axis diameter >7 mm, irregular border, or heterogeneous signal intensity on MRI), inflammatory bowel disease, inherited colorectal cancer syndromes, simultaneous tumors, or had undergone surgery for a different primary tumor. Patients with gastrointestinal stromal tumors (GIST) on final pathology were also excluded. Patients who refused to provide informed consent were also excluded from the study.

*Treatment Protocol*

Rectal MRI was performed using a 3.0-Tesla system with a phased-array coil. High-resolution protocols included axial and coronal T2-weighted sequences (≤3 mm), sagittal T2-weighted (3.5 mm), and T1-weighted (3.5 mm) images, along with diffusion-weighted imaging (DWI) for lesion characterization. Imaging was independently reviewed by two specialized radiologists, with consensus in cases of discordance.

Surgical management involved laparoscopic resection following total or partial mesorectal excision principles, with high vascular ligation. Dissection proceeded medial-to-lateral, then lateral-to-medial. Proximal and distal resection margins were maintained at ≥10 cm and ≥2–4 cm, respectively, depending on tumor location and extent of excision.

Patients with pT3N0 tumors and high-risk features (e.g., low location, poor differentiation, lympho-vascular or perineural invasion, <12 lymph nodes) were recommended pelvic radiotherapy (45 Gy in 28 fractions) with concurrent capecitabine (825 mg/m² twice daily). Those with pT4, pN+, or involved pCRM received adjuvant chemoradiotherapy with 3–4 cycles of XELOX, followed by pelvic irradiation with concurrent capecitabine, then additional XELOX to complete eight cycles, based on institutional protocols informed by ESMO recommendations [6] and MTB discussions. Treatment decisions were made via MTB discussions, incorporating patient preferences and clinical judgment, which may differ from certain international guidelines.

Postoperative surveillance included clinical examination, serum CEA testing, chest X-ray, and abdominal ultrasound every 3 months for 2 years, then biannually until year 5, and annually thereafter. Thoracoabdominal–pelvic CT and pelvic MRI (when indicated) were performed every 6–12 months or sooner if clinically necessary. Colonoscopy was done at 1 year post-surgery and repeated every 3–5 years. There was no loss to follow-up during the study period (Figure 1).

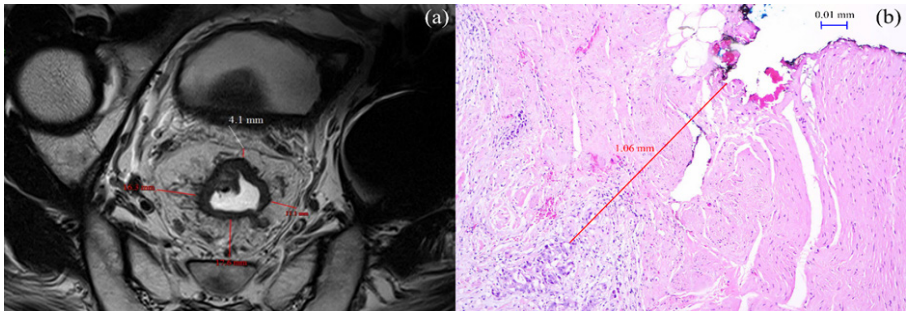


Figure 1. Radiologic and Pathologic Assessment of CRM. (a) MRI shows uninvolved mrCRM (4.1 mm). (b) Pathology indicated uninvolved pCRM (1.06 mm)

*Sample Size and Sampling*

Sample size was estimated using a precision-based formula for a single proportion at 95% confidence (Z = 1.96) and 5% error. Based on anticipated rates of LR (8%) [1, 12] and DM (10%) [4, 5], the minimum required sample sizes were 114 and 139, respectively. To ensure sufficient statistical precision, a total of 144 eligible patients were consecutively included. Specifically, for the retrospective arm, all eligible patients treated between January 2018 and the ethics approval date (November 12, 2020) were identified consecutively from electronic medical records and imaging archives. For the prospective arm, eligible patients presenting after ethics approval were consecutively enrolled until April 2022 under the unified protocol.

*Key Outcome Variables*

LR was defined as pelvic tumor regrowth at the anastomosis, rectal stump, pelvic tissues, perineum, or regional nodes, after curative resection. Diagnosis was based on clinical findings (e.g., symptoms such as pain, bleeding, or palpable masses) supported by imaging (e.g., CT, MRI, or PET-CT), endoscopy, or histopathology when indicated to confirm recurrence and exclude differentials like inflammation or benign strictures.

DM was defined as tumor spread beyond the pelvis, including the liver, lungs, peritoneum, bones, brain, or nonregional lymph nodes. Diagnosis was based on surveillance imaging (e.g., thoracoabdominal–pelvic CT, chest X-ray, abdominal ultrasound) or symptom-driven evaluation (e.g., clinical symptoms such as pain, weight loss, or organ-specific dysfunction), confirmed by appropriate imaging (e.g., PET-CT for equivocal findings) or histology when indicated to verify metastatic disease and exclude differentials like infection or non-malignant lesions.

For retrospectively included patients, data for both LR and DM were retrieved from electronic medical records and imaging archives, based on standardized follow-up protocols.

*Statistical Methods*

Data were analyzed with R version 4.4.2 (R Core Team, Vienna, Austria). Frequencies and percentages were used for categorical variables, assessed via Chi-square or Fisher's exact tests. Continuous variables were shown as mean ± SD or median (IQR), depending on Shapiro–Wilk normality assessment. Group comparisons used ANOVA or Kruskal–Wallis tests, as appropriate. Kaplan–Meier estimates were used to calculate LR and DM rates at 3, 5, and 7 years, with comparisons between pN0 (stage II) and pN+ (stage III) groups by log-rank test.

To explore predictors of LR and DM, univariate Cox regression was first performed. Variables with $p< 0.10$ were considered for multivariable models, subject to event-per-variable thresholds. Penalized regression was additionally applied without preselection to reduce overfitting. LASSO regression was used for variable selection by shrinking less informative coefficients to zero, whereas Ridge regression was employed to manage potential multicollinearity among covariates.

Histologic grade was dichotomized as well versus moderate–poor, and mesorectal violation grouped near-complete and incomplete excisions, with complete excision as reference. Significance was set at $p< 0.05$.

*Ethical Considerations*

The study was approved by the Ethics Committee of University Medical Center Ho Chi Minh City (Approval No. 50/GCN-HĐĐĐ, November 12, 2020). Informed consent was obtained from all participants, prospectively at enrollment or retrospectively during follow-up.

## Results

*Clinical characteristics*

We enrolled 175 patients with cT3 rectal cancer from January 2018 through April 2022. Preoperative exclusion criteria eliminated 28 patients, primarily due to DM (n=12) and lateral pelvic lymph node involvement (n=8), along with other causes including other primary surgeries (n=4), inflammatory bowel disease (n=3), and synchronous tumors (n=1). Although 147 patients proceeded to surgery, three were later excluded due to GIST findings. The final cohort comprised 144 patients followed for ≥ 36 months, including 95 retrospective and 49 prospective cases. Of these, 49.3% were cT3b, 34.7% cT3c, and 16% cT3a. The study enrolled 67 men (46.5%) and 77 women (53.5%); mean age 62 ± 12 years (Figure 2).

The median preoperative CEA was 3.35 ng/mL [IQR: 1.8–6.5]. Most tumors were located in the mid and low rectum. Tumor size and clinical nodal (cN) status differed significantly across cT3 substages. Median tumor diameter increased with substage: 3 cm in cT3a, 4 cm in cT3b, and 5 cm in cT3c ($p< 0.005$). Lesions ≤4 cm were mostly found in cT3a/b (76.5%), while tumors ≥7 cm occurred only in cT3c. cN+ was lowest in cT3a (11.2%) and higher in cT3b (52%) and cT3c (36.8%) ($p< 0.005$).

All surgeries were completed laparoscopically. Intraoperative complications occurred in 4 patients (2.8%), including hemorrhage, bowel perforation, nerve injury, and iliac vein laceration. Postoperative morbidity was 16.7%, mainly Clavien–Dindo grade I–II. Anastomotic leakage occurred in 3.6% of anastomoses (2.8% overall), with half needing reintervention. No perioperative deaths were reported (Table 1).

*Pathological and adjuvant characteristics*

Complete mesorectal integrity was achieved in 97.2% of cases; incomplete specimens were rare and evenly distributed ($p= 1.0$). Mesorectal quality was evaluated using the Enker grading system [17], which categorizes total mesorectal excision as complete, near-complete, or incomplete. Mesorectal violation was defined as any near-complete or incomplete excision with defects extending into the muscularis propria. Clear proximal and distal margins were obtained in all cases, with median lengths of 10 cm [IQR: 10–15] and 3 cm [IQR: 2–4], respectively. Involved pCRM was uncommon (2.8%), seen only in cT3b/c tumors ($p= 0.82$). Pathological staging revealed 6.3% pT2, 85.4% pT3, and 8.3% pT4a, correlating with substage ($p< 0.005$); pT2 occurred mainly in cT3a, while

Table 1. Clinico-Pathological Characteristics and Oncologic Outcomes of Patients with T3 Rectal Cancer, Uninvolved mrCRM (n = 144)

| Characteristics | cT3a (n = 23; 16%) | cT3b (n = 71; 49.3%) | cT3c (n = 50; 34.7%) | Total n = 144, n (%) | p-values |
|---|---|---|---|---|---|
| Age, n (%) | 60.4 ± 13 | 62.8 ± 11.4 | 61.7 ± 12.5 | 62 ± 12 | 0.83 |
| <50 | 6 (27.3) | 10 (45.4) | 6 (27.3) | 22 (15.3) | 0.31† |
| ≥50 | 17 (13.9) | 61 (50) | 44 (36.1) | 122 (84.7) | |
| Sex, n (%) | | | | | |
| Female | 13 (16.9) | 39 (50.6) | 25 (32.5) | 77 (53.5) | 0.82* |
| Male | 10 (14.9) | 32 (47.8) | 25 (37.3) | 67 (46.5) | |
| Pre-operative CEA level (ng/ml), n (%) | 2.5 [1.5;4.9] | 3.4 [1.8;6.4] | 3.75 [2.5;6.9] | 3.35 [1.8;6.5] | 0.22 |
| <5 | 17 (19.1) | 42 (47.2) | 30 (33.7) | 89 (61.8) | 0.43* |
| ≥5 | 6 (10.9) | 29 (52.7) | 20 (36.4) | 55 (38.2) | |
| Anastomotic leakage , n (%) | | | | | |
| No | 16 (14.8) | 54 (50) | 38 (35.2) | 108 (75) | 0.82† |
| Yes | 0 (0) | 2 (50) | 2 (50) | 4 (2.8) | |
| APR+Hartmann | 7 (21.9) | 15 (46.9) | 10 (31.2) | 32 (22.2) | |
| Post-operative complication, n (%) | | | | | |
| No | 18 (15) | 58 (48.3) | 44 (36.7) | 120 (83.3) | 0.76* |
| Yes | 5 (20.8) | 13 (54.2) | 6 (25) | 24 (16.7) | |
| Mesorectal integrity, n (%) | | | | | |
| Complete | 23 (16.4) | 68 (48.6) | 49 (35) | 140 (97.2) | 1† |
| Nearly-complete | 0 (0) | 2 (66.7) | 1 (33.3) | 3 (2.1) | |
| Incomplete | 0 (0) | 1 (100) | 0 (0) | 1 (0.7) | |
| Histological tumor grade (Pre & post-operative), n (%) | | | | | |
| Well | 1 (33.3) | 1 (33.3) | 1 (33.3) | 3 (2.1) | 0.79† |
| Moderate | 21 (15.4) | 68 (50) | 47 (34.6) | 136 (94.4) | |
| Poor | 1 (20) | 2 (40) | 2 (40) | 5 (3.5) | |
| pT, n (%) | | | | | |
| pT2 | 6 (66.7) | 3 (33.3) | 0 (0) | 9 (6.3) | <0.005† |
| pT3 | 17 (13.8) | 59 (48) | 47 (38.2) | 123 (85.4) | |
| pT4a | 0 (0) | 9 (75) | 3 (25) | 12 (8.3) | |
| pN, n (%) | | | | | |
| pN0 | 19 (18.8) | 50 (49.5) | 32 (31.7) | 101 (70.1) | 0.27* |
| pN+ | 4 (9.3) | 21 (48.8) | 18 (41.9) | 43 (29.9) | |
| Lymph node harvested, n (%) | | | | | |
| <12 | 9 (18.4) | 24 (49) | 16 (32.6) | 49 (34) | 0.84* |
| ≥12 | 14 (14.7) | 47 (49.5) | 34 (35.8) | 95 (66) | |
| pCRM, n (%) | | | | | |
| Uninvolved | 23 (16.4) | 68 (48.6) | 49 (35) | 140 (97.2) | 0.82† |
| Involved | 0 (0) | 3 (75) | 1 (25) | 4 (2.8) | |
| Local recurrence, n (%) | | | | | |
| No | 23 (16.8) | 66 (48.2) | 48 (35) | 137 (95.1) | 0.59† |
| Yes | 0 (0) | 5 (71.4) | 2 (28.6) | 7 (4.9) | |
| Distant metastasis, n (%) | | | | | |
| No | 21 (16.3) | 64 (49.6) | 44 (34.1) | 129 (89.6) | 0.93† |
| Yes | 2 (13.3) | 7 (46.7) | 6 (40) | 15 (10.4) | |

CEA, carcino-embryonic antigen; APR, Abdominoperineal resection; pT, pathological tumor; pN, pathological nodal; pCRM, pathological circumferential resection margin; *, indicates Chi-square test; †, indicates Fisher's exact test

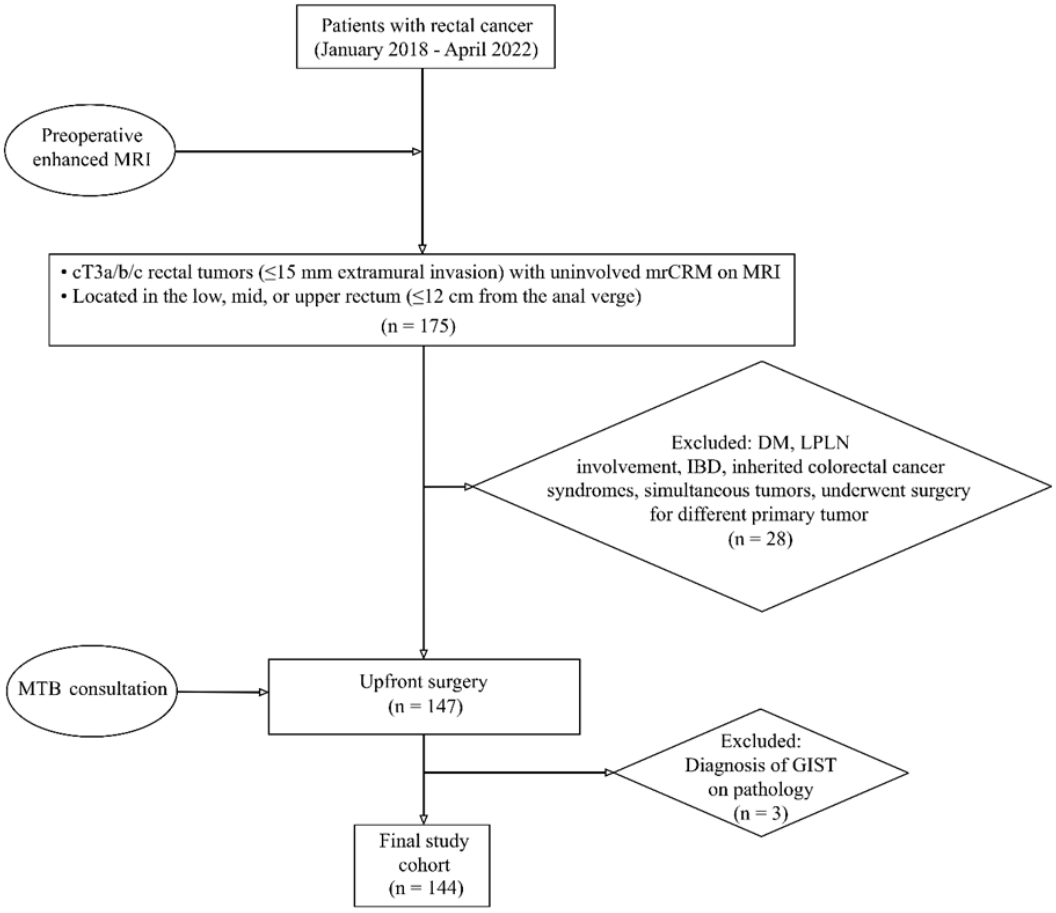


Figure 2. Patient Enrollment and Follow-up Schema. Overview of case selection, treatment pathway, and outcome tracking throughout the study period.

pT4a was exclusive to cT3b/c. pN status showed no significant substage difference (p= 0.27), with 70.1% pN0 and 29.9% pN+. The mean lymph node yield was 12.6 ± 4.9, with ≥12 nodes retrieved in 66% of patients.

Adjuvant therapy was administered in 60.4%, with 25.7% receiving chemotherapy, 2.1% radiotherapy, and 32.6% chemoradiotherapy. Supplementary Table 1 shows all clinico-pathological characteristics and oncologic outcomes.

*Oncologic outcomes*

Over a median follow-up of 56 months [IQR: 42.75–68], LR and DM occurred in 4.9% and 10.4% of patients, respectively. No port- or extraction-site metastases were noted. LR was detected in 7 cases (3 anastomotic, 4 pelvic), while 15 patients developed DM, most frequently in the liver (n=5) and lungs (n=5), with others in bone (n=1), peritoneum (n=1), or multiple sites (n=3). Cumulative incidences of disease events were as follows. The 3-, 5-, and 7-year LR rates were 3.6% (95% CI 1.2–10.6), 5.3% (95% CI 2.2–12.5), and 5.3% (95% CI 2.2–12.5), respectively. The corresponding rates of DM were 8.5% (95% CI 4.6–15.3), 11.6% (95% CI 6.8–19.3), and 11.6% (95% CI 6.8–19.3) (Figure 3).

*Factors associated with local recurrence*

LR was observed only in cT3b (5/71) and cT3c (2/50), with no cases in cT3a (0/23); there was no significant association (p= 0.59, Fisher's exact test).

In univariate Cox regression, mesorectal violation (HR: 245.4, p<0.005), involved pCRM (HR: 19.0, p<0.005), anastomotic leakage (HR: 8.41, p=0.06), and postoperative complications (HR: 6.19, p=0.03) were associated with LR. In multivariable analysis, mesorectal violation (HR: 179.3, p<0.005) and anastomotic leakage (HR: 15.6, p=0.036) remained significant, though wide confidence intervals reflected statistical instability due to limited event counts. To improve robustness, regularized regression was employed: Ridge regression retained both variables with attenuated effects, while LASSO preserved only mesorectal violation (HR: 76.42), shrinking all others to zero. These findings suggest mesorectal violation as the most stable and reproducible predictor of LR in this cohort. However, the high hazard ratios should be interpreted with caution due to the small number of LR events (n=7), which may inflate effect estimates despite penalized adjustment (Table 2).

*Factors associated with distant metastasis*

DM occurred in 15 patients (10.4%), distributed as 2/23 in cT3a, 7/71 in cT3b, and 6/50 in cT3c. Although slightly more frequent in cT3c tumors, the difference among subgroups was not statistically significant (p=0.93).

In univariate analysis, elevated preoperative CEA ≥ 5

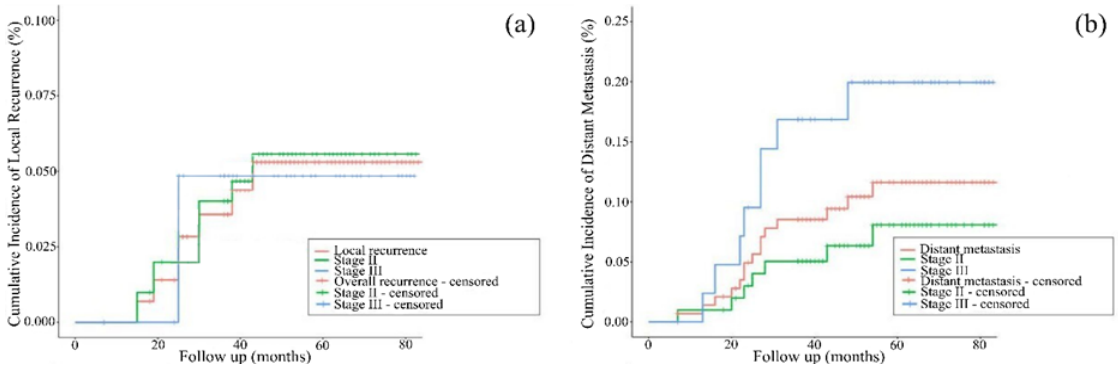


Figure 3. Kaplan–Meier Curves for Local Recurrence (a) and distant metastasis (b). LR rates at 3, 5, and 7 years: 3.6%, 5.3%, and 5.3% (p = 0.97, stage II vs III). DM rates: 8.5%, 11.6%, and 11.6% (p = 0.009, stage II vs III).

Table 2. Risk Factor Analysis for Local Recurrence in cT3 Rectal Cancer with Uninvolved CRM (N = 144): univariate screening, multivariable Cox, and regularized regression (Ridge, LASSO)

| Characteristics | Local recurrence | | | | | |
|---|---|---|---|---|---|---|
| | Univariate | | Multivariate | | Ridge | LASSO |
| | HR (95% CI) | P | HR (95% CI) | P | HR | HR |
| Sex | | | | | | |
| Female | | | | | Ref. | |
| Male | 7.45 (0.9-61.86) | 0.06 | 2.2 (0.2-25.2) | 0.52 | 1.38 | |
| Anastomotic leakage | | | | | | |
| No | | | | | Ref. | |
| Yes | 8.41 (0.94-75.58) | 0.06 | 15.6 (1.2-203.5) | 0.036 | 3.2 | |
| APR+Hartmann | 1.75 (0.32-9.55) | 0.52 | | | 0.85 | |
| Post-operative complication | | | | | | |
| No | | | | | Ref. | |
| Yes | 6.19 (1.2-31.89) | 0.03 | 1.9 (0.3-12.36) | 0.48 | 1.66 | |
| Mesorectal integrity | | | | | | |
| Complete | | | | | Ref. | |
| Mesorectal violation | 245.4 (26.2-2297) | <0.005 | 179.34 (10.36-3106.03) | <0.005 | 39.93 | 76.42 |
| pCRM | | | | | | |
| Uninvolved | | | | | Ref. | |
| Involved | 19 (3.61-100.18) | <0.005 | 1.26 (0.15-10.8) | 0.83 | 2.15 | |

Ref, Reference; LASSO, Least absolute shrinkage and selection operator; APR, Abdominoperineal resection; pCRM, pathological circumferential resection margin.

ng/mL (HR: 5.04, p= 0.006), mesorectal violation (HR: 7.6, p= 0.009), pN+ (HR: 2.86, p= 0.043), and involved pCRM (HR: 5.95, p= 0.02) were associated with a higher risk of DM.

In the multivariable Cox model, preoperative CEA ≥ 5 ng/mL (HR: 4.85, p= 0.008) and pN positivity (HR: 3.12, p= 0.039) remained significant predictors, while mesorectal violation and involved pCRM lost significance, likely due to overlapping effects and wide confidence intervals.

Regularized regression models provided more stable estimates. Ridge regression retained all four variables with reduced coefficients. LASSO regression selected preoperative CEA ≥ 5 ng/mL (HR: 2.48), mesorectal violation (HR: 3.06), pN+ (HR: 1.51), and involved pCRM (HR: 1.72), while excluding other factors (Table 3).

Supplementary Tables 2 and 3 summarize the full results of univariate analyses, multivariable Cox regression, and regularized models (Ridge and LASSO) for all variables evaluated in relation to LR and DM.

## Discussion

This cohort demonstrated an encouraging LR rate of 4.9%, with 3-year, 5-year, and 7-year cumulative rates of 3.6%, 5.3%, and 5.3%, respectively. These figures are in line with previous reports on upfront surgery for selected patients with cT3 rectal cancer, where LR rates typically ranged from 3.3% to 10.3% with median follow-up times of 20–48 months [5, 16, 18-20]. Notably, the 5-year LR rate in our study (5.3%) was comparable to the outcomes observed in the Dutch TME trial for

Table 3. Risk Factor Analysis for Distant Metastasis in cT3 Rectal Cancer with Uninvolved CRM (n = 144): univariate screening, multivariable Cox, and regularized regression (Ridge, LASSO)

| Characteristics | Distant metastasis | | | | | |
|---|---|---|---|---|---|---|
| | Univariate | | Multivariate | | Ridge | LASSO |
| | HR (95% CI) | P | HR (95% CI) | P | HR | HR |
| Pre-operative CEA level (ng/ml) | | | | | | |
| <5 | | | | | Ref. | |
| ≥5 | 5.04 (1.6-15.85) | 0.006 | 4.85 (1.5-15.5) | 0.008 | 1.34 | 2.48 |
| Circumferential tumor location | | | | | | |
| Anterior | | | | | Ref. | |
| Posterior | 0.3 (0.08-1.09) | 0.068 | 0.4 (0.1-1.5) | 0.164 | 0.86 | |
| Circumferentially | 0.4 (0.09-1.81) | 0.234 | | | 0.9 | |
| Surgical procedure | | | | | | |
| AR | | | | | Ref. | |
| LAR | 1.86 (0.39-8.93) | 0.441 | | | 1.02 | |
| ISR | NE. | 0.998 | | | 0.81 | |
| APR | 4.1 (0.82-20.1) | 0.087 | NE. | 0.998 | 1.13 | |
| Hartmann | NE. | 0.999 | | | 0.75 | |
| Anastomotic leakage | | | | | | |
| No | | | | | Ref. | |
| Yes | 3.7 (0.46-29.25) | 0.222 | | | 1.28 | |
| APR+Hartmann | 2.73 (0.95-7.88) | 0.063 | | | 1.1 | |
| Mesorectal integrity | | | | | | |
| Complete | | | | | Ref. | |
| Mesorectal violation | 7.6 (1.7-34.8) | 0.009 | 4.85 (0.2-113.2) | 0.326 | 1.86 | 3.06 |
| pN | | | | | | |
| pN0 | | | | | Ref. | |
| pN+ | 2.86 (1.04-7.88) | 0.043 | 3.12 (1.06-9.15) | 0.039 | 1.25 | 1.51 |
| pCRM | | | | | | |
| Uninvolved | | | | | Ref. | |
| Involved | 5.95 (1.33-26.6) | 0.02 | 2.13 (0.1-47.9) | 0.633 | 1.76 | 1.72 |

NE., Not estimable; Ref., Reference; LASSO, Least absolute shrinkage and selection operator; CEA, carcinoembryonic antigen; AR, Anterior resection; LAR, Low anterior resection; ISR, Intersphincteric resection; APR, Abdominoperineal resection; pN, pathological nodal; pCRM, pathological circumferential resection margin.

patients receiving preoperative radiotherapy (5.6%) and markedly lower than that of the surgery-only group (10.9%) [21]. These findings suggest that, in selected cT3 patients with uninvolved CRM and negative EMVI, upfront surgery can achieve acceptable local control when complete mesorectal integrity is ensured. Nevertheless, these comparisons should be interpreted with caution due to population differences, as the Dutch TME trial predominantly involved Western patients with higher BMI and varied tumor levels, while the present single-center Vietnamese cohort consisted mainly of mid-to-lower rectal cancers treated by specialized colorectal surgeons.

In this exploratory analysis, mesorectal violation emerged as the most consistent factor associated with LR. All affected patients developed LR, and this variable remained consistently selected in both univariate and regularized regression models, despite instability in conventional multivariable estimates due to limited event counts. The exceptionally high hazard ratios likely reflect model overfitting rather than true effect magnitude, although regularized methods confirmed its relevance with attenuated coefficients. This finding aligns with García Granero et al., who reported a fourfold increase in LR risk with noncomplete mesorectal integrity [22]. Beyond a statistical correlation, there are clear biological mechanisms that explain its critical prognostic importance. The mesorectal fascia serves as a natural barrier containing the tumor. A surgical violation of this plane can lead to direct spillage and implantation of tumor cells onto pelvic surfaces, resulting in LR. Furthermore, a breach often indicates deviation from the correct surgical plane, which increases the risk of a microscopically involved circumferential resection margin, a powerful predictor of LR [10, 24] and a factor shown to be collinear with mesorectal violation in our analysis. Finally, disruption of the mesorectum may expose previously contained lymphatic and vascular channels, potentially facilitating systemic tumor dissemination and contributing to DM, for which it was identified as a secondary predictor in our models.

Other variables showed less consistent associations with LR. Anastomotic leakage was significant in the multivariable Cox and Ridge models but not retained by LASSO, reflecting uncertainty about its independent contribution. While some studies, like the COLOR II trial [11], reported an association, others found no significant link [18, 23]. This inconsistency, along with only four observed cases, suggests the observed effect may reflect technical challenges or downstream effects on adjuvant therapy rather than a direct causal role. Involved pCRM showed a strong univariate association, consistent with previous findings [10, 24] but lost significance in adjusted and LASSO models, likely due to collinearity with mesorectal violation. Other clinicopathologic features, including tumor location and nodal status, were not predictive in this cohort, despite reported associations in more advanced disease settings [10, 12, 18].

The cumulative incidence of DM in our cohort was 8.5% at 3 years, 11.6% at 5 years, and remained stable at 7 years, yielding an overall rate of 10.4%. These outcomes are favorable and compare well with prior studies. For instance, the OCUM cohort reported 3- and 5-year DM rates of 8.9% and 14.4%, while the MERCURY trial noted a 19% rate among cT3 tumors [4, 25]. Higher incidences were observed in less selectively defined series, including 28.9% in Ptok et al. and 23.8% in Saklani et al., whereas Kulu et al. documented a similar rate of 10% [5, 16, 20]. Such discrepancies may reflect variations in tumor staging, inclusion of cT4 lesions, or differences in CRM assessment. In our series, the liver was the most common metastatic site, followed by the lungs, consistent with rectal venous drainage patterns. Notably, DM was significantly more frequent in stage III than stage II disease ($p= 0.009$), highlighting the central role of pN+ in systemic dissemination.

Risk factor analysis supported this interpretation. Preoperative CEA $\geq$ 5 ng/mL and pN+ were the most reliable predictors, maintaining statistical significance in multivariable Cox regression and consistently retained by Ridge and LASSO models. Elevated preoperative CEA has long been recognized as a marker of tumor burden. Restivo et al. reported that high CEA levels predicted early DM in advanced rectal cancer [13], and our findings reinforce its value as both a prognostic indicator and a practical, cost-effective tool for postoperative surveillance. Similarly, the prognostic relevance of pN+ is well established, as malignant cells spread via lymphatic pathways and subsequently gain access to the systemic circulation [14, 15].

Mesorectal violation and involved pCRM also showed associations with DM, although less consistently. Both were significant in univariate analyses and retained by penalized regression, but did not remain independent predictors in the conventional multivariable Cox model, which requires cautious interpretation given the small event number. Prior evidence provides a plausible explanation: involved pCRM has been reported to independently increase the risk of both LR and DM (OR $\approx$ 3.1, $p= 0.004$), whereas mesorectal violation was not directly associated with DM, it showed a strong correlation with involved pCRM ($p= 0.031$) [22]. This supports the notion that involved pCRM may contribute directly to systemic failure, while mesorectal quality may influence outcomes indirectly through its impact on resection margins.

These prognostic dynamics offer a refined perspective compared to our initial report on a smaller cohort of 109 patients (median follow-up: 42.5 months) [26]. While that foundational study comprehensively established the short-term oncological safety and baseline survival rates of this surgical approach, its preliminary risk analysis, which utilized Cox and Ridge regression models, identified involved pCRM, violated mesorectum, and anastomotic leakage as significant predictors for LR, while involved pCRM and violated mesorectum predicted DM. However, with an expanded sample size of 144 patients, a longer median follow-up of 56 months, and the additional application of LASSO regression for strict variable selection in the current study, the risk profiles have become more nuanced. For LR, mesorectal violation emerged as the dominant independent factor, whereas the effect of involved pCRM was attenuated, likely due to collinearity. For DM, while local operative factors (pCRM and mesorectal violation) were prominent in the earlier cohort, systemic and tumor burden markers, specifically elevated preoperative CEA and pN(+), proved to be the most reliable independent predictors in this expanded analysis. This evolution underscores the importance of prolonged follow-up and the integration of advanced variable selection models, such as LASSO, in accurately stratifying risk.

This study has several limitations. The small number of LR and DM events limited statistical power and may have led to unstable hazard ratio estimates, even with penalized regression methods. As a single-center study with a partially retrospective design, external generalizability may be constrained, although standardized protocols and strict eligibility criteria ensured consistency and minimized heterogeneity. Variability in adjuvant therapy may also have influenced outcomes. Competing risks were not accounted for in survival analyses, which could slightly affect cumulative incidence estimates. The absence of a comparator group limits causal interpretation, though the study's primary aim was to explore prognostic factors within an upfront surgery cohort. Finally, molecular profiling (e.g., MSI or RAS mutation status) was unavailable, which may restrict the generalizability of the results in the context of precision oncology.

The narrow eligibility was intentional to ensure a homogeneous cohort aligned with guideline-based upfront surgery criteria. Despite these limitations, the findings offer meaningful clinical insights. Notably, some variables such as anastomotic leakage and involved pCRM are postoperative events and should not guide preoperative decision-making. Their associations with recurrence likely reflect surgical quality or complications rather than intrinsic tumor risk. Ensuring complete mesorectal integrity remains essential for reducing LR, while preoperative CEA $\geq$ 5 ng/mL and pN+ serve as practical, reproducible markers for DM risk stratification. These results underscore the importance of surgical quality

control and biomarker-informed surveillance in carefully selected patients undergoing upfront surgery. In resource-limited settings, these biomarkers can facilitate cost-effective risk stratification without relying on advanced imaging.

In conclusion, this study suggests that upfront surgery may yield acceptable oncological outcomes in carefully selected cT3 rectal cancer patients with clear mrCRM and negative EMVI. LR was most consistently associated with mesorectal violation, while DM appeared primarily driven by elevated preoperative CEA (≥5 ng/mL) and pN+, with mesorectal violation and involved pCRM as potential secondary factors. Given limited number of events, these findings should be interpreted as hypothesis-generating and considered with caution due to potential unmeasured confounding. Nonetheless, they underscore the dual importance of surgical quality and tumor biology in shaping long-term outcomes. Larger, multicenter prospective studies are needed to confirm these associations.

## Author Contribution Statement

All authors contributed equally in this study.

## Acknowledgements

*General*

We are grateful to the patients and families for their participation, the hospital administration for logistical assistance, and Dr. Phat Minh Tran for his support in data analysis.

*Conflict of Interest*

None.

*Ethical Declaration*

The study was performed in accordance with the Declaration of Helsinki for Biomedical Research.

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