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ORIGINAL ARTICLE

Oncological outcome of peripartum colorectal carcinoma—a single-center experience

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Abstract

Objectives This study aimed to analyze disease presentation, management, and oncological outcomes of patients diagnosed with peripartum colorectal cancer (CRC).

Methods Retrospective cohort study of all consecutive women of childbearing age (18–45 years) between 2002 and 2014 diagnosed with CRC adenocarcinoma at a tertiary academic institution. Patients who experienced pregnancy within 12 months of their diagnosis (peripartum period, group 1) were compared to the remaining patients of the cohort (group 2). Overall survival (OS) was compared between the two groups through Kaplan-Meier estimates.

Results Out of 555 consecutive women with a mean age of 37.8 ± 6 years, 31 (5.6%) were diagnosed with CRC in the peripartum period. Of these, all patients were symptomatic during pregnancy due to bleeding, abdominal pain, or constipation; however, only 11 CRC (35.5%) were diagnosed during pregnancy, 1 (3.2%) during C section, and the remaining (61.3%) postpartum. TNM stage at presentation was I in 6 patients (19.4%), II in 4 patients (13.9%), III in 8 patients (25.8%), and IV in 13 patients (41.9%). Surgical resection was performed in 23 patients (74.2%): 2 while pregnant, 2 at the time of C section, and the remainder postpartum. Across all stages, OS was 95% at 1 year and 62% at 5 years and did not differ between the two comparative groups ($p = 0.16$).

Conclusions A suspicious attitude towards cancer-related symptoms during pregnancy is crucial to prevent delayed evaluation for CRC.

Keywords Colorectal carcinoma · Pregnancy · Outcome · Survival

Introduction

Cancer during pregnancy occurs in about one out of 1000 pregnancies [1–3], with hematologic and gynecologic malignancies being the most common forms [4]. Colorectal cancer (CRC) is fortunately a rare condition in childbearing women, with an incidence of about 2.2–7.7 per 100,000 pregnancies [5–7]. Due to the increasing incidence of CRC in young patients and a trend towards delayed childbearing with advanced maternal age, pregnancy-related CRC is likely to rise [8–10].

A major challenge for clinicians and patients may be diagnosing CRC in pregnant women due to masked symptoms such as abdominal pain, anemia, and fatigue that are often attributed to pregnancy [4]. In particular, rectal bleeding as a common symptom during pregnancy due to bleeding hemorrhoids may distract from attributing bleeding to cancer [11].

Reports derived from small retrospective case series, including oncological outcome, are scarce and ambiguous. While some series show encouraging outcomes with similar prognosis despite advanced disease forms [12, 13], others report worse outcomes [14, 15]. In addition to potentially presenting with more advanced disease, the oncologic management of peripartum women with CRS, regardless of stage, poses numerous challenges.

The present study aimed to assess disease presentation and treatment of women diagnosed with peripartum CRC and to compare oncological outcomes to non-pregnant women of childbearing age.

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Methods

We performed a retrospective cohort study of consecutive women of childbearing age (18–45 years) who were diagnosed with colorectal adenocarcinoma (CRC) at Mayo Clinic, Rochester, MN, a tertiary academic institution, between January 1, 2002 and December 31, 2014. This study was approved by the institutional review board and patient-related data was de-identified prior to analysis.

Demographic information included age, race, tumor location (rectum or colon), tumor stage according to the seventh edition of the American Joint Committee on Cancer (AJCC) Staging Manual [16], and underlying genetic disorder (either familial adenomatous polyposis (FAP) or Lynch syndrome). The study cohort was divided in two groups: patients who had a pregnancy within 12 months of the diagnosis of CRC (denominated pregnant group) and women with CRC diagnosed between the ages of 18 and 45 years without a pregnancy within 12 months of diagnosis (non-pregnant group). Addition chart review was undertaken to identify CRC-related symptoms, timing of diagnosis (during pregnancy or after delivery), and treatment strategy (including type and timing of surgery, chemotherapy, and/or radiotherapy) in the pregnant group.

Outcomes

The primary outcome was overall survival (OS). In a second step, the independent impact of pregnancy on OS was assessed through multivariable analysis considering available clinico-pathological data potentially predictive of survival.

Statistical analysis

Qualitative data are presented as numbers with percentages, whereas quantitative data as means ± standard deviation. Pathological stages were compared using the Pearson's χ^2 test for categorical variables. Chi-square test was used to compare remaining variables; all tests were two-sided and a level of 0.05 was defined to indicate statistical significance.

Unadjusted OS was estimated through Kaplan-Meier survival analysis and compared through log-rank test. Cox proportional hazard analysis was performed to determine independent predictors of OS in a multivariable model. Statistical analysis was performed using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA).

Results

Demographics

Out of 555 women with a mean age of 37.8 ± 6 years, 31 (5.6%) were diagnosed with CRC in the peripartum period (pregnant group). Table 1 displays demographic characteristics of both groups, which were comparable regarding tumor stage and location. Women in the pregnant group were younger (33 ± 6 vs. 38 ± 6 years) ($p < 0.001$). Within the comparative group of non-pregnant women, tumor stages did not differ significantly between colon and rectal cancers. Overall, 114 patients (49%) with rectal cancer received neoadjuvant treatment, whereas the rate of adjuvant chemotherapy was 58% in patients with colon cancer.

Disease presentation and diagnosis in peripartum patients

Table 2 provides an overview of timing of diagnosis and disease presentation and treatment in peripartum patients. All patients were symptomatic during pregnancy due to rectal bleeding (64.5%), abdominal pain (25.8%), or constipation/altered bowel habits (19.4%). Further, one complete bowel obstruction occurred during pregnancy and one at 5 weeks postpartum. Unfortunately, only 11 peripartum CRC (35.5%) were diagnosed during pregnancy.

Peripartum women with stage IV disease (13, 42%) had the following sites of metastases: liver (8 patients), retroperitoneal (4 patients), liver, and lung (1 patient).

Treatment of peripartum patients

Surgical resection was performed in 23 patients (74.2%): 2 while pregnant in the first and third trimester since surgery could not be deferred (1 low anterior resection (LAR), 1 subtotal colectomy, both for obstructing symptoms), 2 at the time of C section (1 LAR for perforated sigmoidal adenocarcinoma, 1 abdominoperineal resection (APR)), and the remainder postpartum (Table 2). Three patients with rectal cancer had neoadjuvant radiotherapy in the postpartum period, followed by surgery. Chemotherapy was administered in the postpartum period in 10 patients: in 2 patients exclusively without surgical management due to advanced disease. Two patients with rectal cancer had concomitant liver resections for metastatic disease.

Six patients in the colon cancer group underwent either subtotal or total colectomy. Of these, two patients were diagnosed with FAP, two patients with ulcerative colitis (UC), one patient had suspected MYH-associated polyposis (MAP) due to several juvenile polyps throughout the colon, and one patient synchronous right-sided and splenic flexure adenocarcinoma.

Pregnancies resulted in liveborn infants in the majority of patients (87%). Further fetal/neonatal outcome was as follows:

- One woman was diagnosed with rectal cancer during pregnancy and lost the baby in the second trimester

Table 1 Demographics

	All patients ($n = 555$)	Pregnancy ($n = 31$)	No pregnancy ($n = 524$)	P
Age (mean ± SD)	37.8 ± 6	32.7 ± 5.9	38.3 ± 6.2	**< 0.001**
Rectal cancer (%)	232 (41.8)	14 (45.2)	218 (41.6)	0.696
Caucasian race (%)	464 (83.6%)	27 (87.1)	437 (83.3)	0.589
Underlying genetic disorder				
FAP (%)	13 (2.3)	2 (6.5)	11 (2.1)	0.12
Lynch syndrome (%)	40 (7.2)	1 (3.2)	39 (7.4)	0.362
Tumor stage				0.856
I	78 (14.1)	6 (19.4)	72 (13.7)	
II	73 (13.2)	4 (12.9)	69 (13.2)	
III	155 (27.9)	8 (25.8)	147 (28.1)	
IV	249 (44.9)	13 (41.9)	236 (45)	

Baseline demographic and surgical parameters of pregnant patients within 12 months of diagnosis ($n = 31$) and non-pregnant patients ($n = 524$)

FAP familial adenomatous polyposis syndrome

Bold characters indicate significant values ($p < 0.05$)

- One woman had an unplanned, premature birth at 29 weeks of gestation and underwent extensive surgery (APR) thereafter
- One woman diagnosed with cancer voluntarily interrupted pregnancy shortly thereafter at 9–10 weeks of gestation
- One woman had a stillborn infant with trisomy 18 and was subsequently diagnosed with colon cancer.

Overall survival

Figure 1 illustrates Kaplan-Meier estimates for overall survival of pregnant and non-pregnant patients, which did not differ significantly (0 = 0.16). Across all stages, OS was 95% at 1 year and 62% at 5 years, with a median survival of the entire cohort of 67 months (95% CI 56.4–82.8 months). Mean follow-up time was 3.2 ± 3 years.

Pregnancy had no significant impact on overall survival after multivariable analysis (Table 3). Tumor stage III and IV were associated with increased mortality, while Caucasian race was associated with better survival.

Discussion

In this single-center experience, overall survival was similar in 31 patients diagnosed with CRC within 12 months of pregnancy and a large comparative group of young non-pregnant women with CRC. Only one third of cancers were diagnosed during pregnancy despite cancer-related symptoms being present in all patients. Hence, this study emphasizes the importance of a high degree of suspicion in pregnant symptomatic women to prevent any delay in diagnosis and subsequent oncological treatments. Of note, a former institutional series of young-onset colorectal cancer in patients without genetic predisposition revealed similar patterns of trivialized symptoms, delayed diagnosis, and advanced stage disease presentation [17].

Prior studies have suggested that women diagnosed with CRC during or shortly after pregnancy commonly present with advanced disease [18, 19]. A recent European study with data from an international cancer network revealed advanced disease in 73% of patients [13], similar to the present study

Table 2 Details on peripartum patients

	Colon ($n = 17$)	Rectum ($n = 14$)
Diagnosis (%)		
During pregnancy	7 (41)	4 (29)
During C section	1 (6)	0 (7)
Postpartum (within 12 months)	9 (53)	10 (71)
Symptoms (%)		
Bleeding	9 (53)	11 (79)
Pain	5 (29)	3 (21)
Constipation/obstruction	5 (29)	1 (7)
Treatment		
Surgery (%)	12 (71)	11 (79)
Type of surgery	3 LH, 3 RH, 6 S/TC	4 APR, 6 LAR, 1 LE
Chemotherapy (%)	6 (35), 4 adj., 2 excl.	4 (29), 2 neoadj., 2 adj.
Radiotherapy	0	3 (21) neoadj.

Timing of diagnosis, disease presentation, and treatment modalities of pregnant patients within 12 months of diagnosis ($n = 31$)

APR abdominoperineal resection, LAR low anterior resection, LE local excision, LH left colectomy, RH right colectomy, S/TC sub/total colectomy, adj. adjuvant, neoadj. neoadjuvant, excl. exclusive

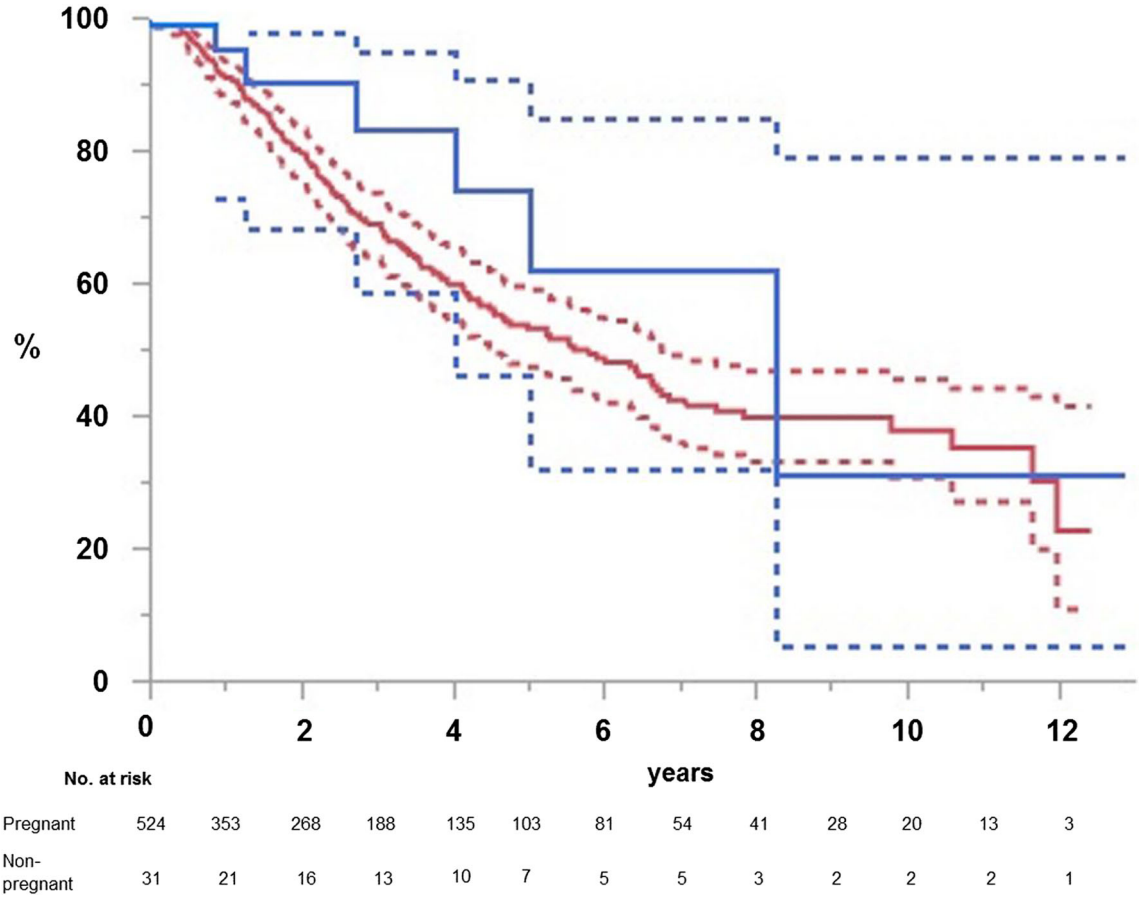

Fig. 1 Kaplan-Meier survival estimates. Survival (months) of pregnant patients within 12 months of diagnosis ($n = 31$, red line) and non-pregnant patients ($n = 524$, blue line, $p = 0.16$). Dashed lines represent 95% confidence intervals

(stage III and IV in 68%). However, in their study, Kocian et al. reported solely on CRC that were diagnosed *during* pregnancy, with over half of patients receiving surgery before delivery [13]. In contrast, our analysis focused on the peripartum period to address the rate of missed diagnoses despite cancer-related symptoms during pregnancy. Indeed, the present study revealed that symptoms such as change in bowel habits and rectal bleeding were attributed to pregnancy in the majority of cases, which delayed evaluation for CRC. This is not surprising though given the patients' young age and symptoms are very similar to those seen with normal pregnancy. However, even in patients diagnosed during pregnancy, surgical and oncological treatment was consistently postponed; all patients but two (emergency indication due to obstruction) were operated on after delivery. Indeed, safety of oncological treatments during pregnancy is still matter of debate, and clear guidelines for treatment decisions are lacking [8].

Table 3 Multivariable survival analysis

	Hazard ratio	95% CI	*P*
Pregnancy	0.544	0.235–1.26	0.156
Race (Caucasian)	0.565	0.385–0.829	**0.003**
Age at diagnosis	1.011	0.984–1.038	0.422
Tumor stage			
II	0.81	0.301–2.183	0.677
III	2.448	1.184–5.063	**0.016**
IV	6.215	3.13–12.341	**< 0.001**
FAP	0.88	0.309–2.51	0.812
Lynch syndrome	0.546	0.252–1.186	0.126

Multivariable Cox proportional hazard model of factors influencing overall survival in patients of childbearing age. Reference groups were non-pregnant patients, non-Caucasian race, tumor stage I, and no genetic disorder, respectively

FAP familial adenomatous polyposis syndrome

Bold characters indicate significant values ($p < 0.05$)

A recent multi-national cohort study demonstrated an increase of antenatal treatments in recent years, especially chemotherapy [20]. Exposed babies were more likely to develop complications, in particular small for gestational age and neonatal intensive care unit admissions. During the first trimester, chemotherapeutic agents may adversely affect embryogenesis, while exposure later on increases the risk of stillbirth and intrauterine growth restriction [9]. A recent systematic review

on CRC diagnosed during pregnancy revealed metastatic disease at the time of diagnosis in 48% of patients [21]. However, chemotherapy was initiated in only 10% of patients before delivery. The authors emphasized the importance of an individualized, multi-disciplinary approach rather than rigid guidelines. During the entire 13-year observation period of our series, medical or radio-oncological treatments were not administered during pregnancy, which we believe had contributed to good neonatal outcomes.

Despite a potential delay in diagnosis, respectively, postponed treatment in pregnant patients, survival was comparable in pregnant and non-pregnant patients in the present cohort. Aggressive treatment in this young and, besides cancer diagnosis, supposedly healthy population may have led to this encouraging outcome despite advanced disease forms. However, former studies demonstrated similar survival rates . In 41 pregnant CRC patients, survival was comparable to the general population in the study of Kocian et al. [13]. Dahling et al. observed similar patterns [12]: women with pregnancy-associated CRC had excellent maternal and neonatal outcomes, and pregnancy was not found to have a significant effect on survival, as in our series. Contrary to these former studies, our institutional series did not compare pregnant patients to the general population, but to an unselected consecutive cohort of women of childbearing age. Both groups were comparable regarding tumor location and stages, whereas age was not retained as significant predictor after multivariable analysis. The similarity of Kaplan-Meier estimates in both groups may thus support the presently applied strategy of aggressive surgical and oncological treatment *after* delivery. It is however important to bear in mind loss to follow-up as an inherent issue in a center with nation-wide patient accrual when interpreting survival estimates, considering the rather short mean follow-up time of 3.2 years. Thus, the presented data has to be interpreted with caution and impedes an uncritical conclusion of equal survival in both groups.

The present study has further limitations beyond its retrospective design that need to be addressed. First, due to the rare event rate (patients with CRC and pregnancy), further subgroup analysis (i.e., colon vs. rectum) was not performed. Further, the study period is long, with changes in oncological and surgical strategies for management of CRC over time. Neoadjuvant therapy was established as standard of care in more recent years, considering the "historical" early study years. Despite changes occurring in both groups in this single institution experience, the small peripartum group is much more vulnerable to treatment bias, which may have influenced the outcomes. Second, intraoperative or surgical short-term outcomes were not available, as they were not the purpose of this study. However, they may have influenced oncological outcomes. Histopathologic and genetic specifics (i.e., mismatch repair status), which would be of particular interest in this young study population, were inconsistently assessed in this institutional dataset, especially in the early study period. Furthermore, the unequally sized comparative groups would impede reliable comparative analyses. Finally, due to the uniqueness of each pregnant patient, treatments were likely to be individualized according to the circumstances. Hence, comparisons are difficult, and results need to be interpreted with caution.

In conclusion, even though the present study seems to suggest similar overall survival after CRC diagnosis in peripartum women and a comparative group of non-childbearing women, these results have to be interpreted with caution given the above discussed limitations and inequality of both groups. Given the rising incidence of CRC in young patient, our findings should promote increased awareness and an aggressive pursuit of symptoms in this otherwise low-risk group, as these symptoms may represent an underlying colorectal malignancy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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