ANTICANCER RESEARCH *40*: 5853-5860 (2020)
doi:10.21873/anticanres.14604

Upfront Radiotherapy in Patients With Asymptomatic Incurable Rectal Cancer: A Retrospective Cohort Study

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Abstract. *Background/Aim: The optimal treatment sequencing for asymptomatic de novo metastatic rectal cancer is unclear. The aim of this study was to investigate the role of upfront radiotherapy, with or without chemotherapy on risk for local complications, in patients with asymptomatic advanced metastatic rectal cancer treated with palliative intention. Patients and Methods: All patients with de novo metastatic rectal cancer diagnosed between January 2008 and December 2017 in two healthcare regions in Sweden (Örebro län, Sörmland) were identified and data were extracted from electronic medical records. Patients were divided into 3 groups based on treatment sequence: upfront radiotherapy, upfront chemotherapy, and only palliative surgery. Results: In total, 102 patients were included in the study cohort, 30 patients in upfront radiotherapy group, 54 in upfront chemotherapy, and 18 in only palliative surgery group. Patients with only upfront CT [odds ratio (OR)= 5.10; 95% confidence interval (CI)=1.24-20.91, p=0.024] had a higher risk to suffer from a local complication compared to those who received upfront radiotherapy. Cause-specific Cox regression analysis among patients who received oncological therapy revealed that female patients [cause-specific hazard ratio (csHR)=3.61; 95% confidence interval (CI)=1.67-7.81] and upfront chemotherapy [csHR=1.85; 95% CI=1.11-3.77] were associated with increased cumulative incidence of local complication over time, whereas primary surgery with ostomy or stent with lower risk [csHR=0.45; 95% CI=0.21-0.99]. Conclusion: Patients who received upfront radiotherapy, with or without chemotherapy, had fewer local complications due to primary tumor compared to patients who only received chemotherapy. This could indicate that radiotherapy to the primary tumor could be discussed with the patients as a first treatment option for asymptomatic metastatic rectal cancer to prevent local complications later during the disease.*

Approximately 20% of patients with rectal cancer are presented with *de novo* metastatic disease and receive treatment with palliative intention (1). These patients are at increased risk for intestinal complications including bowel obstruction, rectal bleeding, pelvic pain, fistula formation, and perforation that can impair quality of life of the patients (1).

In patients with symptomatic advanced rectal cancer, the treatment strategy includes an upfront local therapeutic approach with either surgery or radiotherapy to relief local symptoms. Considering the negative effect of colostomy following surgery in quality of life (2), alternative local treatment strategies have been tested to avoid surgery. In fact, several prospective phase II studies have found that upfront radiotherapy, with or without chemotherapy, offers a symptom control rate of >85% which is often long-lasting (3-5).

The treatment approach in patients with asymptomatic advanced rectal cancer is, however, more controversial. Traditionally, prophylactic tumor resection has been considered as the first step on the cancer management to avoid local complications (6). Nevertheless, recent data suggest that upfront chemotherapy with modern chemotherapeutic agents in combination decreases the risk for intestinal complications and need for surgery due to complications (7-10). Most of these studies mainly included patients with colon cancer; as a result, the generalizability of these results in patients with rectal cancer is questionable. A third treatment approach that has not been directly studied in patients with asymptomatic advanced rectal cancer is the use of upfront radiotherapy instead of surgery. A recent phase II study in patients with symptomatic rectal cancer showed that

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Key Words: Stage IV rectal cancer, radiotherapy, chemotherapy, local complication.

upfront short-course radiotherapy followed by chemotherapy is a valid option offering a high and sustained symptom control rate (3). Whether this approach is beneficial in patients with asymptomatic advanced rectal cancer remains unanswered.

The aim of the present study was to investigate the role of upfront radiotherapy, with or without chemotherapy in patients with asymptomatic advanced rectal cancer treated with palliative intention.

Patients and Methods

Study design. We performed a retrospective two-center cohort study with data extraction from electronic medical records (EMRs).

Study population. All patients with *de novo* metastatic rectal cancer that have been diagnosed and treated at the Department of Oncology, Örebro or the Department of Oncology, Eskilstuna between 2008 and 2017 were identified through the National Quality Register for Colorectal Cancer.

Inclusion criteria were: i) untreated patients with advanced rectal cancer with asymptomatic disease at diagnosis and palliative treatment intention; ii) treatment for metastatic rectal cancer given at the Departments that were included in the study; and iii) pathologic examination with manifestation of rectal cancer.

Exclusion criteria were patients with curative intention (rectal cancer stage I-III or stage IV that underwent curative treatment), patients who had symptomatic incurable rectal cancer at diagnosis (defined as patients with manifest obstruction or perforation that needed an intervention, bleeding that required blood transfusion or hospitalization due to pain), patients who have had the tumor resected and patients that were not eligible for any treatment (surgical or oncological) due to impaired performance status.

Data collection. The following data were extracted from EMRs: age at diagnosis, comorbidities, date at diagnosis, performance status at diagnosis; site of metastases, number of metastases at each site, TNM classification; treatment strategy (surgery, radiotherapy, chemotherapy), sequencing of treatment strategy, type of surgery, type of radiotherapy, type of chemotherapy; local complications that needed intervention (obstruction, bleeding, pain, fistula formation, perforation), date for local complication, management of local complications, outcome of local complications; need for rescue local therapies (radiotherapy, surgery); date for disease progression; type of subsequent treatments; death, date of death, and cause of death. Data extraction was performed by two trained investigator by using a pre-specified form.

Definitions and outcomes. Based on the treatment approach, the eligible patients were divided into three study groups: Group A with upfront radiotherapy (upfront RT), with or without chemotherapy irrespectively of any prior prophylactic surgical procedure (ostomy or stent); group B with upfront chemotherapy (upfront CT) irrespectively of any prior prophylactic surgical procedure (ostomy or stent) but without radiotherapy; group C (control) with upfront prophylactic surgical procedure (ostomy or stent) only without any upfront oncological treatment.

The primary outcome was the rate of local complication between the groups, using group C as the control group. A local complication was defined as the presence of bowel obstruction, rectal bleeding, pain that needed intervention (hospitalization or an invasive procedure), fistula formation or perforation. Secondary outcomes were time from diagnosis of rectal cancer to local complication and overall survival (defined as time from diagnosis of rectal cancer until death due to any cause).

Statistical analysis. Categorical variables were summarized by the number and percentage of patients in each category whereas continuous variables were summarized by median and range. The comparison of primary outcome among patients´ groups were performed with chi-square test. For overall survival, the Kaplan-Meier method was used with log-rank test for comparison between the groups.

We used the cumulative incidence function (CIF) to assess the probability of local complication classifying death as a competing event. Gray's test was conducted to test the difference in CIF between upfront RT and upfront CT.

To identify potential predictive factors for local complications, we perform a logistic regression analysis including treatment groups (upfront RT *vs*. upfront CT), age at diagnosis, gender, Charlson comorbidity index, T staging, and primary surgery as covariates.

Cause-specific Cox regression analysis (censored in case of death) was performed to investigate the cumulative incidence of local complication over time between upfront RT and upfront CT after adjustment for age at diagnosis, gender, Charlson comorbidity index, T staging, and primary surgery. Cox regression analysis was also performed for overall survival using the following covariates: treatment group (upfront RT *vs*. upfront CT), age at diagnosis, gender, Charlson comorbidity index, T staging, primary surgery, presence of liver metastasis, and chemotherapy use.

All reported *p*-values of statistical tests are two-tailed and $p<0.05$ were considered statistically significant. All analyses were performed using the SPSS version 20 (IBM, Armonk, NY, USA) except from the estimation of CIF that was performed with R version 3.6.1 (https://www.r-project.org/).

Ethical approval. The study was approved by the Swedish Ethical Review Authority (reference no. 2019-02290).

Results

Study cohort. In total, 304 patients were identified using the National Quality Register for Colorectal Cancer, 102 of them matched our inclusion criteria (Figure 1). The baseline characteristics of patients in either group are summarized in Table I. Median age at diagnosis in the whole cohort was 69 years (range=38-88). The majority of patients had a Charlson Comorbidity Index (CCI) of at least 3. Sixteen patients (55%) in the upfront RT group received chemotherapy directly after the upfront RT.

Local complications. A local complication occurred in 10 (33%) patients in upfront RT compared to 28 (52%) patients in group B ($p=0.102$), whereas 6 (33%) patients in the control group suffered from a local complication. The most frequent complication was obstruction in upfront RT and upfront CT groups (Table II).

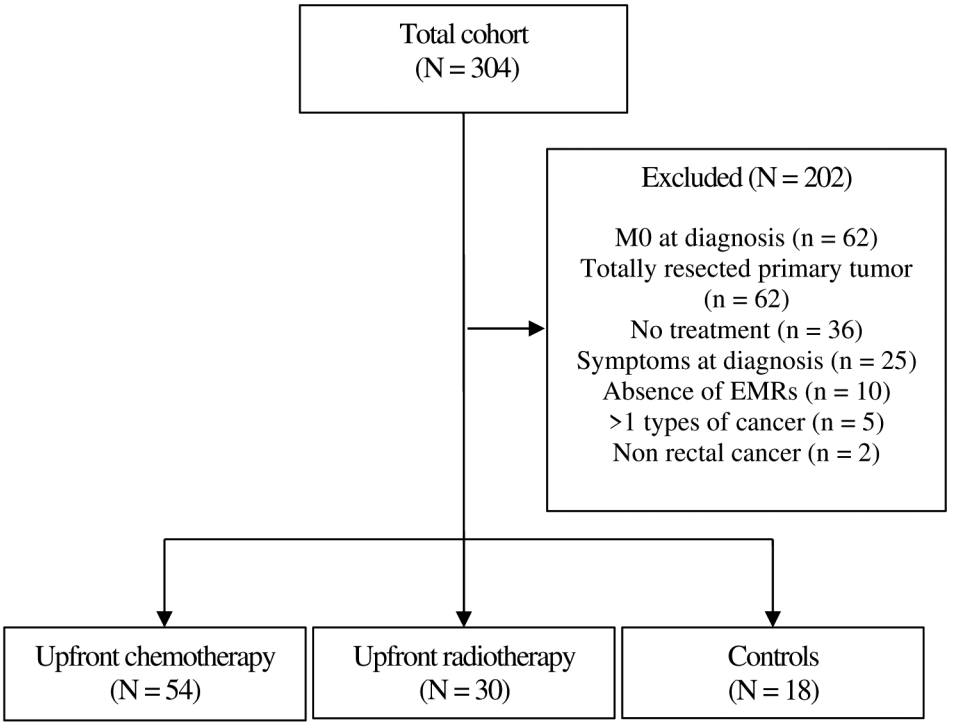

Figure 1. *Flowchart diagram of study cohort. EMRs, Electronic medical records.*

Logistic regression analysis showed that patients with only upfront CT [odds ratio (OR)=5.10; 95% confidence interval (CI)=1.24-20.91, p=0.024] and female gender (OR=4.48; 95% CI=1.39-14.41, p=0.012) had a higher risk to suffer from a local complication.

Local complication in competing risk analysis. Comparison of cumulative incidence of local complication between the groups with active treatment (upfront RT *vs*. upfront CT), using death as a competing event, is shown in Figure 2. Upfront RT group had fewer local complications over time than upfront CT group, when death was considered as a competing event for local complication (p=0.090 according to Gray's test).

Cause-specific Cox regression analysis among patients who received oncological therapy revealed that female patients [cause-specific hazard ratio (csHR)=3.61; 95% CI=1.67-7.81] and upfront CT (csHR=1.85; 95% CI=1.11-3.77) was associated with increased cumulative incidence of local complication over time, whereas primary surgery with ostomy or stent with lower risk (csHR=0.45; 95% CI=0.21-0.99).

Overall survival. Kaplan-Meier curves for overall survival are shown in Figure 3. The median survival was 13 months in upfront RT group, 17 months in upfront CT group, and 4 months in the control group.

In Cox regression analysis restricted to patients who received an active therapy, treatment group (upfront RT *vs*. CT) was not associated with overall survival after adjustment for age, gender, comorbidity index, T stage, primary surgery, chemotherapy use, and presence of liver metastases. The analysis could not reveal any predictive factor for overall survival in the study cohort.

Discussion

In our cohort of patients with *de novo* metastatic rectal cancer without symptoms from the primary tumor, upfront RT with or without subsequent CT significantly decreased the risk for local complications compared to upfront CT alone without jeopardizing survival. These findings could provide a valuable guidance for clinicians when deciding the optimal sequence of treatment for patients with *de novo* metastatic rectal cancer.

Palliative RT is a well-established treatment strategy in patients with symptomatic advanced rectal cancer with a high symptom control rate (11). Besides, neoadjuvant RT seems to offer a significant clinical benefit in terms of local recurrence in patients with potentially curable advanced rectal cancer (12). However, a direct comparison between upfront RT and upfront CT in asymptomatic patients with incurable rectal cancer, especially in the era of modern CT,

Table I. *Baseline characteristics of study cohort.*

	Upfront RT (N=30)	Upfront CT (N=54)	Control (N=18)	*p*-Value (upfront RT *vs.* CT)
Age*, years	71.5 (54-88)	67.5 (38-78)	75.5 (57-92)	0.004
Gender, n (%)				
Male	14 (47)	32 (59)	5 (28)	0.267
Female	16 (53)	22 (41)	13 (72)	
Charlson comorbidity index, n (%)				
0	0 (0)	5 (9)	0 (0)	0.144
1	2 (7)	7 (13)	1 (5)	
2	7 (23)	16 (30)	3 (17)	
3+	21 (70)	26 (48)	14 (78)	
Site of metastatic disease, n (%)				
Liver	16 (53)	44 (81)	17 (94)	0.006
Lung	17 (57)	26 (48)	7 (39)	0.535
Non-regional lymph nodes	7 (23)	16 (30)	1 (6)	0.454
Peritoneum	0 (0)	2 (4)	1 (6)	0.286
Other	2 (7)	7 (13)	1 (6)	0.371
cT, n (%)				
2	0 (0)	4 (8)	2 (12)	0.214
3	12 (43)	23 (48)	4 (24)	
4	16 (57)	21 (44)	11 (65)	
cN, n (%)				
0	5 (18)	4 (7)	4 (22)	0.607
1	9 (32)	14 (26)	7 (39)	
2	14 (50)	26 (48)	4 (22)	
Primary surgery (ostomy or stent), n (%)	14 (47)	21 (39)	18 (100)	0.488
Upfront RT, n (%)				
Any radiotherapy	30 (36)	0 (0)	0 (0)	NC
5 Gy × 5	25 (30)			
Other hypofractionated scheme	4 (5)			
Other hyperfractionated scheme	1 (1)			
Upfront CT, n (%)				
Any chemotherapy	16 (55)	54 (100)	0 (0)	<0.001
Flourouracil/capecitabine	9 (30)	23 (33)		
Oxaliplatin-based	5 (17)	21 (35)		
Irinotecan-based	2 (7)	10 (19)		

RT, Radiotherapy; CT, chemotherapy. *Data presented as median (range).

is lacking. To compare our results with prior studies on palliative radio- and/or chemotherapy in advanced rectal cancer, one should consider the definition each study used for asymptomatic local disease. We defined asymptomatic disease as the lack of local symptoms requiring emergent treatment, which is a clinically relevant approach considering the fact that the vast majority of patients with colorectal cancer are diagnosed due to symptoms (13). Two prior single-arm studies investigating the role of upfront chemotherapy in colorectal cancer with unresectable primary tumor have found a lower rate of local complication (up to 12%) than we did (7, 9). However, the differences in inclusion criteria among the studies, specifically the inclusion of only rectal cancer patients in our study cohort can partially explain the higher complication rate.

The rate of local complications in the patients who received upfront RT in our study cohort is similar to that observed in a previous prospective study on RT in combination with CT in stage IV rectal cancer (3). Although Tyc-Szcepaiak *et al.* allowed only symptomatic patients in the study, most of the patients that we defined as asymptomatic would be classified as symptomatic according to their definition, thereby making the comparison of the results possible. However, Tyc-Szcepaiak *et al.* performed a single-arm prospective study with no information about the potential role of upfront radiotherapy in patients.

Recently, two retrospective cohort studies with propensity score matching approach showed a potential survival benefit for patients with stage IV rectal cancer treated with RT compared to no RT (14, 15). Although these studies did not

Table II. *Type of local complication and outcome in study cohort.*

	Total n (%) (N=102)	Upfront RT n (%) (N=30)	Upfront CT n (%) (N=54)	Control n (%) (N=18)	*p*-Value (upfront RT *vs.* CT)
Local complication					
Any local complication	44 (43)	10 (33)	28 (52)	6 (33)	0.102
Type of local complication					
Obstruction	18 (18)	6 (20)	11 (20)	1 (6)	0.368
Bleeding (need for transfusion)	14 (14)	1 (3)	8 (15)	5 (28)	
Pain (need for hospitalization)	5 (5)	2 (7)	3 (6)	0 (0)	
Fistula	2 (2)	1 (3)	1 (2)	0 (0)	
Perforation	5 (5)	0 (0)	5 (9)	0 (0)	
Treatment of local complication					
Surgery	17 (39)	5 (50)	12 (43)	0 (0)	0.047
Conservative	16 (36)	2 (20)	8 (29)	6 (100)	
Radiotherapy	7 (16)	0 (0)	7 (100)	0 (0)	
Minimally invasive	4 (9)	3 (30)	1 (4)	0 (0)	
Outcome of local complication					
Resolved without sequelae	14 (32)	5 (50)	8 (29)	1 (17)	0.354
Resolved with sequelae	12 (27)	1 (10)	11 (39)	0 (0)	
No improvement	4 (9)	1 (10)	2 (7)	1 (17)	
Worsening	7 (16)	1 (10)	4 (14)	2 (33)	
Death	5 (11)	0 (0)	3 (11)	2 (33)	

RT, Radiotherapy; CT, chemotherapy.

present data on local complications or on the timing of RT in relation to the course of the disease, their findings supported the potential role of upfront RT in patients with *de novo* metastatic rectal cancer not only regarding the risk of local complications but also as a strategy for improved survival.

An interesting but unexpected finding in our study was that female gender was associated with higher risk for local complications than male. The potential presence of gender-differences in colorectal cancer patients in terms of tumor biology, treatment approach, postoperative morbidity and prognosis has been previously studied (16-18). In fact, a recent meta-analysis found that female colorectal cancer patients had significant better cancer-specific and overall survival compared to men, irrespective of tumor stage (16). On the other hand, male gender seems to increase the risk for postoperative morbidities including anastomotic leak, an observation that could partially be explained by the anatomical differences between men and women where the narrower pelvis in males can make the surgical procedure technically more challenging (17, 18). A potential explanation for the increased risk for local complication in women may be the anatomical differences between males and females regarding the organs in the near vicinity of the rectum. Large-scale studies on the role of gender on the risk for local complication due to rectal cancer are necessary to further investigate this potential gender difference.

The findings of this study should be interpreted in the light of several limitations. First, the retrospective study design has inherent weaknesses with high risk for bias. Second, the number of patients in the study cohort as well as the number of events was relatively low with a direct impact on the statistical power of the study. In addition, nearly 40% of the patients underwent a prophylactic surgical procedure before oncologic treatment despite the lack of emergent local symptoms. The baseline risk of obstruction in this patient subgroup should be considered lower than in patients without prophylactic surgery. Although the inclusion of these patients could influence the number of events in terms of local complications, the comparison between upfront RT and upfront CT should still be considered valid because of the comparable number of patients with prophylactic surgery in the 2 groups. In fact, the study groups where well balanced regarding to our predefined variables, with significant difference found in only 2, namely age (older patients in the upfront RT group) and the presence of liver metastasis (favoring upfront CT). The former could be explained by the notion that older patients are more susceptible to the negative effects of CT, thereby making clinicians opt for the upfront RT approach. The fact that the patients with liver metastases received more often upfront CT could be due to concerns regarding disease progression during RT and the fact that some of these patients could be considered possible candidates for liver resection in the unlikely event of exceptional treatment response, necessitating upfront CT.

Despite the above-mentioned limitations, the study also has some strengths as the inclusion of consecutive patients

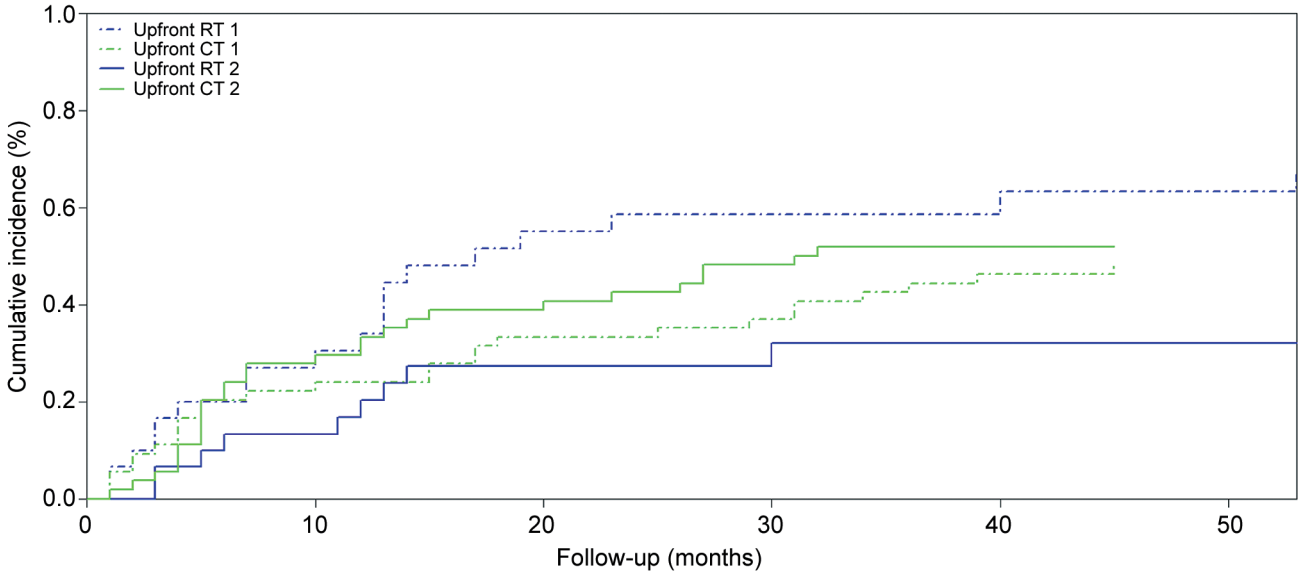

Figure 2. *Cumulative incidence for local complication in upfront radiotherapy (RT) compared to upfront chemotherapy (CT) using death as competing event (Gray's test for local complication; p=0.090). Dashed lines represent the overall mortality and solid lines the local complication.*

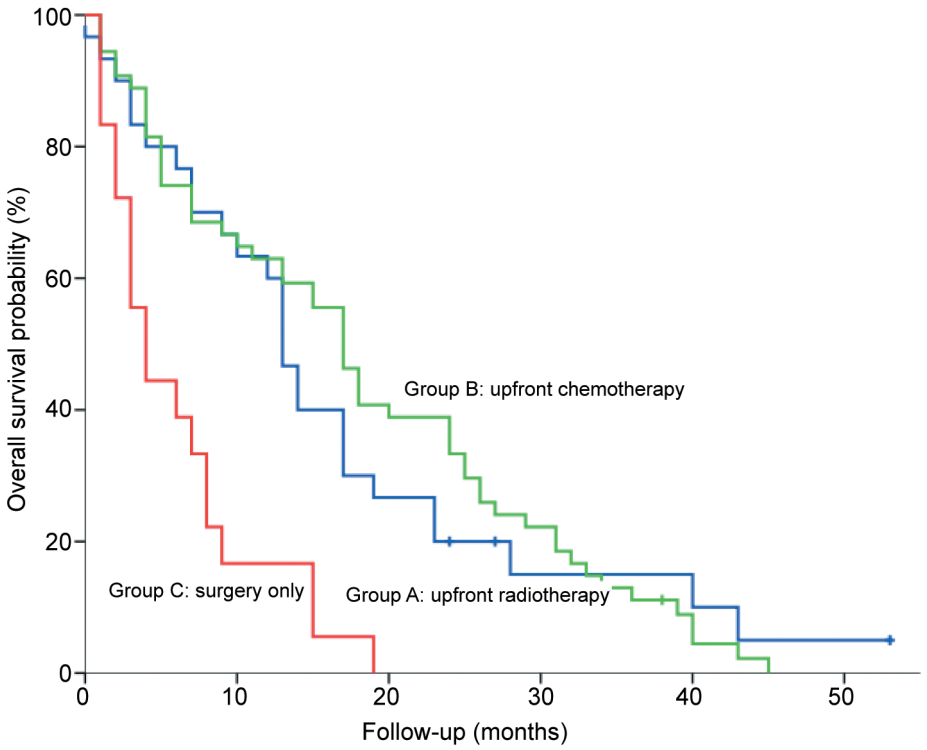

Figure 3. *Kaplan-Meier for overall survival among treatment groups. Upfront radiotherapy (RT) vs. chemotherapy (CT): p=0.133; upfront RT vs. control: p<0.001; upfront CT vs. control: p<0.001.*

with only *de novo* metastatic rectal cancer from two different Departments, thereby reducing the risk of bias due to local treatment traditions, the use of a clinically relevant definition for asymptomatic local disease that makes the results easier to implement in the real-world clinical practice setting, and the use of competing risk analysis to take into account the death as a competing event for local complication.

In conclusion, our study results suggest that in patients with *de novo* metastatic rectal cancer without local symptoms, upfront RT (with or without CT) might offer a clinical benefit in terms of reducing risk for local complications due to primary tumor compared to upfront CT alone. Prospective studies investigating this treatment approach in patients with *de novo* metastatic rectal cancer are essential to provide more convincing evidence. A potential higher risk for local complications in female patients is also suggested by our findings but additional studies with larger sample size are necessary to confirm this observation that could have an important clinical implication on deciding the treatment sequence in *de novo* metastatic rectal cancer patients.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Conceptualization: GJ, LP, KV, AV; Data curation: GJ, LP; Formal analysis: AV; Supervision: KV, AV; Validation: KV, AV; Visualization: GJ, LP, AV; Roles/Writing - original draft: GJ, LP, AV; Writing - review & editing: GJ, LP, KV, AV.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Received June 7, 2020
Revised August 13, 2020
Accepted August 23, 2020