European Journal of Surgical Oncology 48 (2022) 1831–1839

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Characteristics and fate of patients with rectal cancer not entering a curative-intent treatment pathway: A complete nationwide registry cohort of 3,304 patients

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ARTICLE INFO

Article history:
Received 25 November 2021
Received in revised form
3 March 2022
Accepted 19 April 2022
Available online 30 April 2022

Keywords:
Rectal cancer
Metastatic disease
Incurable disease
Treatment
palliative care
Surgery
oncological treatment
survival

ABSTRACT

Background: Treatment options for advanced and metastatic rectal cancer have increased during the past decades. However, a considerable proportion of the patients are not eligible for curative treatment, and data on this subset are scarce from a population-based perspective. This study aimed to describe treatment pathways and survival in a national cohort of patients with primary stage IV rectal cancer or stage I-III rectal cancer not eligible for curative treatment.

Methods: A national cohort of all patients reported 2008–2015 to the Norwegian Colorectal Cancer Registry with primary metastatic rectal cancer or who did not undergo curative resections for stage I-III rectal cancer was studied with regard to patient characteristics, treatments, and survival.

Results: Of 8291 patients diagnosed with rectal cancer, 3304 (39.9%) were eligible for analysis. The majority (76.8%) had metastatic disease, and 23.2% did not undergo curative resections for other reasons. We identified four main treatment journeys: no tumour-directed treatment, 25.1%; resection of the primary tumour, 44.6%; oncological treatment, 28.4%; and R0 resection of the primary tumour and metastases, 1.9%; these translated into ten different treatment pathways. Survival differed considerably between a median of 5.3 months for M1 disease with non-tumour-directed treatment to a five-year survival of 67% for M1 with R0 resection.

Conclusion: Almost 40% of all patients with rectal cancer did not enter a curative-intent treatment pathway. The patient journeys and outcomes varied greatly. This large but understudied population warrants further in-depth analyses of treatment efficacy and effects on quality of life.

1. Introduction

Rectal cancer occurs in about one-third of all patients with colorectal cancer (CRC), the second most frequent cancer affecting both sexes. The incidence varies between countries, with the highest incidence observed in countries with a high Human Development Index [1]. Radical surgery (i.e., resection with free microscopic margins, R0), either primarily or after neoadjuvant radiotherapy (RT) or chemoradiotherapy (CRT), offers the best chance for cure, as expressed by a >96% five-year relative survival for stage I-II and >81% for stage III in Norway [2]. However, about 25% of all patients are diagnosed with synchronous metastatic disease, i.e., stage IV rectal cancer [2,3]. Despite many advances in multimodal treatments for advanced and metastatic disease, the five-year relative survival for patients with metastatic rectal cancer remains about 20% [2,4]. Moreover, significant comorbidities or frailty may preclude curative treatment, even in patients with non-

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https://doi.org/10.1016/j.ejso.2022.04.013

metastatic resectable disease. Also, at times the patients' personal preferences are not consistent with embarking on major surgical procedures [5]. Recently, a population-based study showed an increasing trend of non-surgical management in patients with stage I-III rectal cancer and better survival outcomes associated with radio- or chemoradiotherapy [6]. Banghu et al. showed that patients ≥80 years were less likely to undergo curative surgery for colorectal cancer, while surgical resection resulted in better survival than non-surgical treatment [7].

Contemporary treatment alternatives have evolved during the past decades, including improved chemotherapy and targeted therapies, implementation of radiotherapy and minimally invasive surgical techniques. For patients with stage I-III, new treatment options aiming at organ-preservation include the watch & wait approach for patients with clinical complete response after neoadjuvant treatment or local excision combined with neoadjuvant therapy. These options are currently not recommended as standard of care but may be available options for patients with incurable disease [8]. Also, the combined surgical resection of metastatic disease and the primary tumour, sometimes after downsizing the metastatic lesions by chemo- and/or radiotherapy, is increasingly employed to cure patients diagnosed with stage IV. However, an R0 resection with curative intent remains an option only for a select group of these patients [9–11].

In parallel, the concept of palliative care has evolved with a focus not only on symptom-relieving treatments, but also on other essential domains to maintain quality of life in patients with incurable disease [12]. Early integration of palliative care and active tumour-directed treatments needs to be further explored in modern surgical oncology [13].

Since our previous report on a national cohort of patients with incurable rectal cancer was published in 2007 [3], few population-based studies have been published [14].

This study aims to identify treatment pathways in a national cohort of patients with primary metastatic rectal cancer and patients with stage I-III rectal cancer who did not receive curative treatment. Patient characteristics and outcomes in terms of five-year overall survival are described across the different treatment pathways.

2. Patients and methods

All patients reported to the Cancer Registry of Norway (CRN) between January 2008 and December 2015 with primary metastatic rectal cancer or non-metastatic rectal cancer who did not undergo curative resection were included. Clinical and histopathological data and details of radiotherapy, including dose and fractionation, during the first year after the diagnosis were provided by the Norwegian Colorectal Cancer Registry (NCCR), which is part of the Cancer Registry of Norway (CRN). Data on the American Society of Anesthesiologists physical status classification system (ASA) were missing in 68.1% of all patients, mostly among those who did not undergo surgery. ASA status was categorised into ASA 1–2, ASA 3–4 or "not reported". Data on surgical treatments and chemotherapy during the first year after diagnosis were obtained from the Norwegian Patient Registry (NPR). Of note, data on chemotherapy were only reported from the outpatient setting.

Reporting of all patients diagnosed with cancer to the CRN is mandatory by law. The NPR is a national registry of all patient contacts with the public specialist healthcare system, forming the base for reimbursement by the government. Both registries have documented excellent data quality and completeness [15,16]. Data were analysed and reported according to the STROBE guidelines for an observational study [17].

2.1. Definitions

Treatments characterised as *non-tumour-directed,* include treatments intended not to alter the biological course of the disease. The dataset contains information on surgical procedures such as stoma, bypass or self-expanding metal stent, but no further details on other symptom-directed treatments and their effects on symptom relief.

Tumour-directed treatment includes any treatment that may alter the biological course of the disease, i.e., surgery, chemotherapy, radiotherapy, or any combinations of these, aiming at optimal control of the primary tumour and/or metastatic disease, including an *attempt to cure, i.e.,* complete surgical resection of the primary tumour and distant metastases (R0 resection) either in combination with oncological treatment or not.

Oncological treatment includes either palliative chemotherapy or radiotherapy, or a combination of these, given to prolong life and/or alleviate symptoms. No surgery is done.

2.2. Statistics

Categorical variables were analysed by cross-tabulations and compared by Pearson Chi-square statistics. For continuous variables, parametric (i.e., Student's t-test) or non-parametric methods (i.e., Mann-Whitney *U* test) were used for normal or non-normal distributions.

Overall survival (OS) was estimated by the Kaplan-Meier method, and the log-rank test compared survival differences between groups. The independent importance of various treatments for mortality was estimated using Cox regression analysis and expressed by the hazard ratio (HR).

All tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics v. 25, IBM, Armonk, New York, USA.

The various treatment pathways were described by a Sankey diagram according to metastatic or non-metastatic disease by using the SankeyMATIC diagram builder (https://sankeymatic.com). A Sankey diagram illustrates flows of any kind, and the width of the arrows is proportional to the size of the proportion.

2.3. Ethics

The Regional Committee for Medical and Health Research Ethics approved the study (2016/409 REK Sør-Øst B), including the permission to link these data to the Norwegian Patient Registry (NPR).

3. Results

3.1. Patients

Between January 2008 and December 2015, 8291 patients were diagnosed with rectal cancer in Norway. After excluding patients with stage I-III disease who underwent curative resection, patients with unknown disease stage or unknown type of surgical procedures, and those with endoscopic removal of an early invasive tumour, the remaining 3304 patients (39.9%) constituted the study cohort and were eligible for analysis. These patients had primary metastatic rectal cancer (76.8%), or stage I-III disease but did not undergo curative resections for unknown reasons (23.2%), Fig. 1. The study cohort had significantly more males (n = 1948, 59%) than females (1356, 41%; p < 0.000). The median age was 70 years (range, 20–98 years). Clinical and pathological details are shown in Table 1. Most patients with M1 disease (65.7%) had metastases at multiple sites. Significantly more patients ≥80 years did not receive

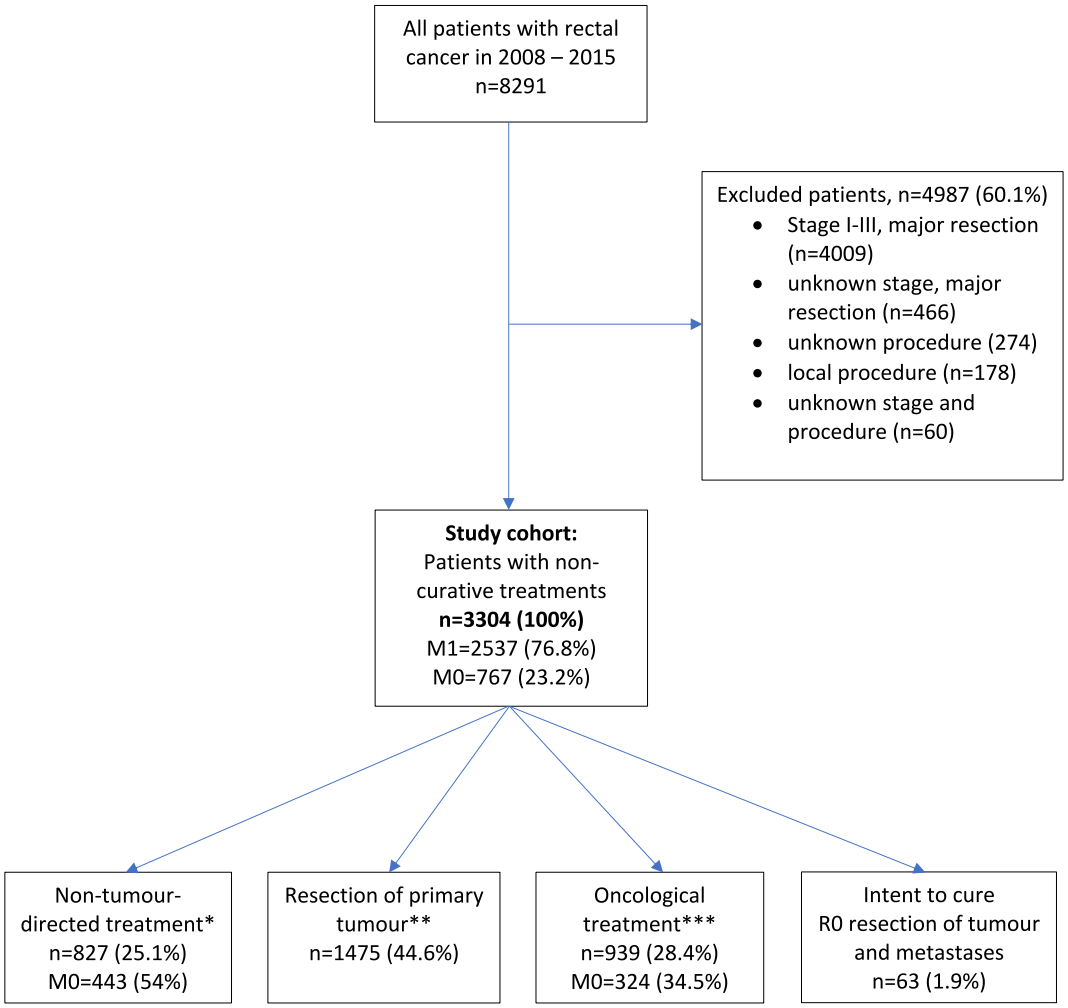

Fig. 1. National cohort 2008–2015 of patients with primary metastatic rectal cancer and non-metastatic rectal cancer who did not undergo curative resections, and the primary treatment journeys that were applied.

tumour-directed treatment ($p < 0.001$). Table 2 shows the clinical and pathological characteristics of the patients with M0 disease ($n = 767$) and M1 patients ($n = 2537$). Significantly more patients (44.7%) were ≥80 years as compared to 17.9% in the M1 group, $p = 0.000$, and ASA status was not reported in nearly all of them. Further details on the reasons for non-operative treatment for M0 disease, such as comorbidities, frailty, or personal preferences, were not available.

3.2. Treatments

Four treatment journeys and ten treatment pathways were identified (Figs. 1 and 2). Non-tumour-directed treatments were employed in 25% of the patients, including surgical procedures for symptom relief in 15.8% of the patients (Table 1). The Sankey diagram (Fig. 3) depicts ten treatment pathways concerning M1 or M0 disease. For unknown reasons, 767 patients (23.2%) with non-metastatic rectal cancer (M0 disease) did not undergo surgical resection of the primary tumour; 324 from this group (44.5%) received tumour-directed oncological treatment with radiotherapy for local tumour control. None of them received chemo-radiotherapy, as this treatment was only recommended in the neo-adjuvant setting during the study period. Of 2537 patients with metastatic disease, the primary tumour was removed in 1475 patients (58.1%), either alone or in combination with preoperative radio- or chemoradiotherapy (Table 1, Fig. 3). Some 939 patients (28.4%) received oncological treatment; most of them (78.2%) were younger than 80 years (Table 1). Of those, 239 (Fig. 3) received oncological treatment alone, mostly chemoradiotherapy ($n = 120$; 50.2%), systemic chemotherapy ($n = 98$; 41%) or radiotherapy ($n = 21$; 8.8%), including 21 patients who underwent resection of metastases without removing the primary tumour.

Radiotherapy was given with a median dose of 39 Gy during a median of 13 fractions (range, 1 to 40). A potentially curative R0 resection was achieved among 4.1% of those with M1 disease who underwent resection of the primary tumour ($n = 63$). Most of them ($n = 52$; 82.5%) were treated in a multimodal setting with either radio-, chemo- or chemoradiotherapy.

3.3. Survival

The median overall survival (OS) of patients treated non-curatively for rectal cancer was 27.6 months (95% confidence interval (CI), 26.1 to 29). It varied significantly between the four treatment journeys and M-status, from a median of 5.3 months for M1 disease with no tumour-directed treatment to a five-year survival of 67% with R0 resection of the primary tumour and metastases, Table 3 and Fig. 4a and b.

Table 1
Demographics and clinico-pathological characteristics of patients with primary metastatic rectal cancer, or other stages treated non-curatively for other reasons.

Variable	Non-tumour directed treatments N (%)	Resection of primary tumour N (%)	Oncological treatmentN (%)	R0 resection of primary + metastases N (%)	Total N (%)	P-value
All patients[a]	827(25)	1475(44.6)	939(28.4)	63(1.9)	3304(100)	
Sex						
Females	374(45.2)	540(36.6)	414(44.1)	28(44.4)	1356(41)	0.001
Males	453(54.8)	935(63.4)	525(55.9)	35(55.6)	1948(59)	
Age, years						
<66	204(24.7)	697(47.3)	306(32.6)	24(38.1)	1231(37.3)	0.001
66-79	288(34.8)	606(41.1)	356(37.9)	27(42.9)	1277(38.7)	
80+	335(40.5)	172(11.7)	277(29.5)	12(19)	796(24.1)	
ASA-status[b]						
I - II	9(1.1)	625(42.4)	37(3.9)	26(41.3)	697(21.1)	0.001
III - IV	36(4.4)	257(17.4)	44(4.7)	19(30.2)	356(10.8)	
Unknown	782(94.6)	593(40.2)	858(91.4)	18(28.6)	2251(68.1)	
Histology						
Adenocarcinoma	805(97.3)	1348(91.4)	908(96.7)	62(98.4)	3123(94.5)	0.001
Mucinous type	21(2.5)	121(8.2)	27(2.9)	1(1.6)	170(5.1)	
Other types	1(0)	6(0.4)	4(0.4)	0(0)	11(0.3)	
pT Stage						
unknown	827(100)	109(7.4)	915(97.4)	7(56.2)	1857(56.2)	0.001
pT1-2	0(0)	242(16.4)	2(0.2)	27(42.9)	272(8.2)	
pT3-4	0(0)	1124(76.2)	22(2.4)	29(46)	1175(35.6)	
pN Stage						
unknown	827(100)	105(7.1)	915(97.4)	6(9.5)	1852(56.1)	0.001
pN0	0(0)	557(37.8)	11(1.2)	37(58.7)	606(18.3)	
pN+	0(0)	813(55.1)	13(1.4)	20(31.7)	846(25.6)	
Primary metastases						
M0	443(53.6)	0(0)	324(44.5)	0(0)	767(23.2)	0.001
M1	384(100)	1475(100)	615(100)	63(100)	2537(76.8)	
liver[c]	130(33.9)	490(33.2)	130(21.1)	51(81)	801(24)	
lung[c]	19(5)	272(18.4)	43(7)	5(7.9)	339(10.3)	
multiple sites[c]	235(61.1)	713(48.4)	442(71.9)	7(11.1)	1397(65.7)	

Values are the numbers (%) of patients in the indicated columns, unless otherwise indicated. ASA: American Society of Anaesthesiologists.
[a] Percentage of total number of patients (n = 3304).
[b] 68.1% of ASA data was missing.
[c] Percentages of the total number of patients in the M1 group shown in each column.

Table 2
Characteristics of patients treated non-curatively for non-metastatic (M0) or metastatic (M1) rectal cancer.

Characteristic	M0 N (%[a])	M1 N (%[a])	P-value
All patients	**767 (23.2)**	**2537 (76.8)**	
Sex			0.000
Females	357 (53.5)	999 (60.6)	
Males	410 (46.5)	1538 (39.5)	
Age, years			0.000
<66	173 (22.6)	1058 (41.7)	
66-79	251 (32.7)	1026 (40.4)	
80+	343 (44.7)	453 (17.9)	
ASA			0.000
1-2	8 (1)	689 (27.2)	
3-4	25 (3.3)	331 (13)	
Unknown	734 (95.7)	1517 (59.8)	
Histology			0.000
Adenocarcinoma	747 (97.4)	2376 (93.7)	
Mucinous type	16 (2.1)	154 (6.1)	
Other types	4 (0.5)	7 (0.2)	
pT stage			0.000
Unknown	766 (99.9)	1091 (43)	
pT1-2	1 (0.1)	271 (10.)	
pT3-4	–	1175 (46.3)	
pN stage			0.000
Unknown	765 (99.7)	1933 (76.2)	
pN0	2 (0.3)	604 (23.8)	
pN+	–	–	

[a] Percentage within column.

Fig. 5a–c displays overall survival for the various non-curative treatment pathways stratified by treatment journey. Of patients who did not undergo tumour-directed treatment, patients with metastatic disease had the shortest survival compared to patients with M0 disease, median 5.3 months versus 18 months (Fig. 5a). Median survival in patients undergoing tumour resection was 50.5 months, and higher when combined with oncological treatment (Table 3, Fig. 5b; p = 0.030). All patients who, for unknown reasons, underwent resection of metastases without the primary rectal tumour had deceased within 36 months (Fig. 5c).

4. Discussion

This national cohort study revealed that 39.1% of all patients diagnosed with rectal cancer did not undergo treatment with the potential to cure, either because of advanced rectal cancer and systemic disease, or for other reasons, most likely including high age and comorbidity. Although most had metastatic disease, 23% had M0 disease. Four main treatment journeys and ten treatment pathways were identified.

These findings indicate a highly differentiated approach to individually tailoring the optimal treatment of patients with incurable rectal cancer, using effective contemporary treatment options within the context of a multidisciplinary team in line with the evolution of modern oncological modalities with improved systemic treatment and palliative radiotherapy [18,19]. The present analysis indicates that treatment of the primary tumour with radiotherapy was a far more preferred option as compared to a previous Norwegian cohort study on non-curatively treated patients with rectal cancer from 1997 to 2001, when the primary treatment pathway was surgical resection in 69.9% of the patients, and oncological treatment was used to a far lesser extent [3]. Age 80

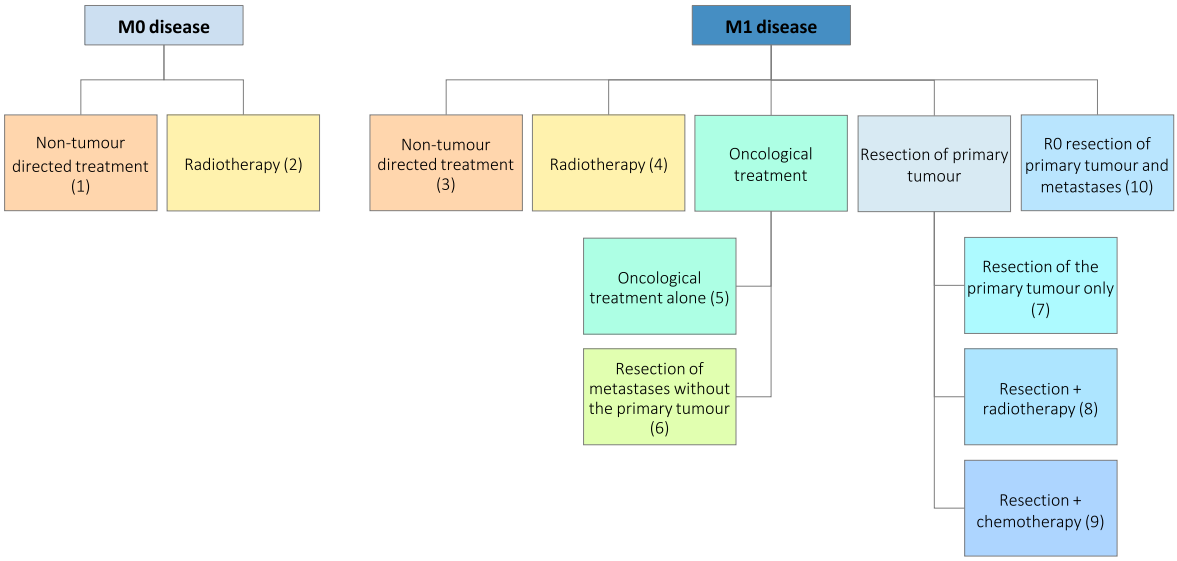

Fig. 2. Ten treatment pathways in a national cohort of patients with primary metastatic rectal cancer and patients with non-metastatic rectal cancer who did not undergo curative resections.

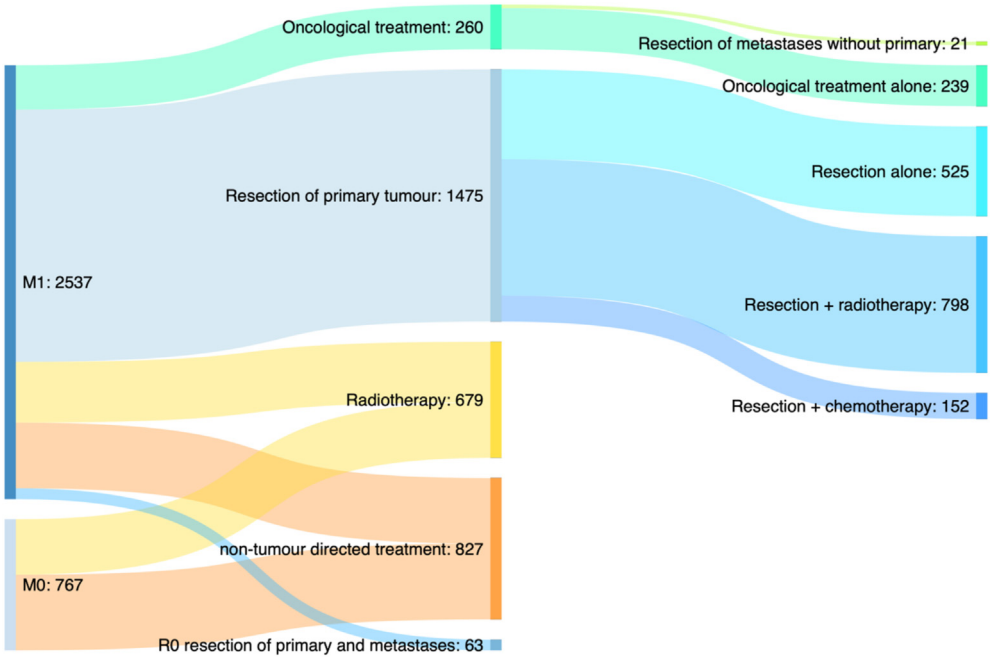

Fig. 3. Sankey diagram of a national cohort of patients with primary metastatic rectal cancer and non-metastatic rectal cancer who did not undergo curative resections (https://sankeymatic.com). The graph displays the size of the various subgroups according to treatment pathways with regard to M0 or M1 disease and treatments chosen.

years or higher was associated with non-surgical treatment. Half of these patients (324 out of 767) received radiotherapy for local tumour control with an estimated 5-year survival of 30%. Indeed, rectal resection may inflict the risk of loss of independence for old patients, or even cause perioperative death in older and frail patients [20,21]. Unfortunately, the registry does not provide other variables describing comorbidities or performance status for the study period. Organ-preserving alternatives to radical surgery are currently being explored, such as the Watch & Wait approach for patients with a clinical complete response after radio- or chemoradiotherapy, or local excision of the persisting tumour after neoadjuvant treatment [22]. Hopefully, these options may contribute to better tumour control and improved quality of life when radical surgery is not indicated or declined. However, these options, which may be less effective in locally advanced disease, are currently not part of standard recommendations and should be offered within clinical trials. The concept of total neoadjuvant treatment, e.g., the RAPIDO regimen [23], may result in an increased proportion of patients with reduced treatment-related failure or possibly a complete response and might thus open for

Table 3
Median overall survival and the risk of mortality for patients with rectal cancer in the four treatment journeys. Non-tumour-directed treatment was set as reference.

Treatment category	Median survival (months)	95% CI	HR of death	95% CI	P-value
All patients	27.6	26.1–29	–	–	–
Non-tumour-directed treatment	9.9	8-4 – 11.4	1	–	<0.001
M0	18	13.7–22.3	–		
M1	5.3	4.1–6.2	–		
Resection of primary tumour	50.5	47.7–53.4	0.31	0.28–0.99	<0.001
Surgery only	44	39–48.9	–		
Surgery + oncological treatment	55.4	45.1–65.6	–		
Surgery + radiotherapy	52.6	49.1–56.1	–		
Oncological treatment	16.4	15.2–17.7	0.9	0.81–0.99	0.049
M0, radiotherapy	18.4	15.5–21.3	–		
Oncology only	14.5	12.4–16.6	–		
Resection of metastases without primary	20.3	6.5–34.2	–		
M1, radiotherapy	16.4	14.6–18.1	–		
R0 resection of primary tumour and metastases	n.a.[a]	n.a.	0.14	0.08–0.23	<0.001

HR: hazard ratio; CI: confidence interval.
[a] Median was not reached during the 5-year follow-up.

organ-preserving treatment in patients who are fit for intensive chemotherapy.

The proportion of patients with an R0 resection of the primary tumour and synchronous metastases was 4.1% of all patients who underwent tumour resection, and most of them had liver metastases. This finding is in line with a recent Norwegian population-based study reporting a frequency of 5.7% resection of synchronous liver metastases, and resection rates of early metachronous (≤1 year) and late metachronous (>1 year) metastases of 21.4% and 24.0%, respectively [24]. The low resection rate of synchronous liver metastases is related to the large proportion of patients with multiple synchronous liver metastases not suitable for liver resection. Consequently, the higher resection rates of metachronous liver metastases are based on a smaller denominator defined by a different patient group initially treated for primary stage I-III disease.

Survival differed considerably between the treatment pathways. The prognosis for patients with metastatic disease without tumour-directed treatment is still dismal and relatively unchanged compared to the Norwegian cohort 1997–2001 [3]. While these patients are often old or frail, this group also comprises younger patients, who often need comprehensive symptom-directed care with particular attention to the needs of the patient's family [25,26]. Quality measures of palliative surgical interventions beyond the technical aspects of procedures or survival are notoriously lacking [27], and data on palliative care are so far not adequately addressed in public registries. Consequently, little is known about the burden of disease, resource allocations, and specific needs during the patients' remaining lifetime. The medical community has an intense focus on cancer cure in contrast to cancer care, leading to a neglect of patients in whom "there is nothing more to be done". However, national cancer registries responsible for all cancer patients should be encouraged to collect relevant data for treatment aspects beyond curative intention. Modern palliative care provides a broad spectrum of options to improve and maintain quality of life or optimise end-of-life care [28]. Hopefully, the increased focus on patient-reported outcomes (PROM) will enable cancer registries to provide data to evaluate treatments from the patient perspective [29]. Currently, the CRN is implementing a PROM module that will provide clinicians with important information on the effects of cancer treatment on quality of life and relevant details on the trajectories of advanced malignant disease.

Patients who underwent resection of the primary tumour had significantly better survival than those who received oncological treatment alone. This is in line with the literature and is most likely explained by a selection bias of patients for surgery [30,31]. Not surprisingly, patients who received oncological treatment in addition to surgery had better survival than those with surgery alone. At present, the literature on the survival benefit of resection of the primary tumour in stage IV colorectal cancer is solely based on uncontrolled cohort studies. A randomised controlled trial comparing surgical resection of the primary tumour with upfront oncological treatment for oligo- and asymptomatic rectal cancer was started but failed to recruit patients [32]. A recent instrumental variable analysis comparing surgery for asymptomatic patients with incurable rectal cancer in the Netherlands and Norway concluded that surgery did not translate into a higher one-year survival [33]. Palliative radiotherapy has been shown to be effective symptomatic treatment for rectal cancer patients [18].

Several methodological challenges are encountered when it comes to providing high-quality evidence from palliative surgical procedures or other interventions to alleviate symptoms. This is primarily due to the retrospective design of these often small, observational studies, the inherent selection bias, and the inconsistent definitions of palliative surgery, usually describing non-curative treatments without addressing the effects on symptom relief [34]. The palliative surgical outcome score (PSOS) was introduced to evaluate the impact of palliative surgical interventions and was recently assessed as a helpful instrument [35,36]. Recently, a more general model based on the time at home was proposed to measure the functional outcome after the resection of cancer [37]. Hopefully, these tools will be adopted as essential measures for treatment benefit beyond survival.

Our study has several limitations related to the nature of a cohort study from a national population-based registry. Detailed clinical information for patients reported to the CRN is sparse, particularly for non-surgically treated patients. Moreover, detailed data on chemotherapy were not available for the study period. Our analysis of a registry-based cohort is limited to showing associations but no causal relationship between single factors and outcomes. Further, this analysis is limited to the treatments recorded during the first year after the diagnosis of advanced rectal cancer. Thus, we cannot account for treatments given beyond the first year after diagnosis, such as delayed resections of metastases following extended chemotherapy or eventual resection of the primary tumour during the later course of patients with M0 disease. Consequently, this national cohort study depicts overall trends and outcomes.

On the other hand, the data recorded in our national registries have a high degree of completeness [15,16]. Also, our study depicts

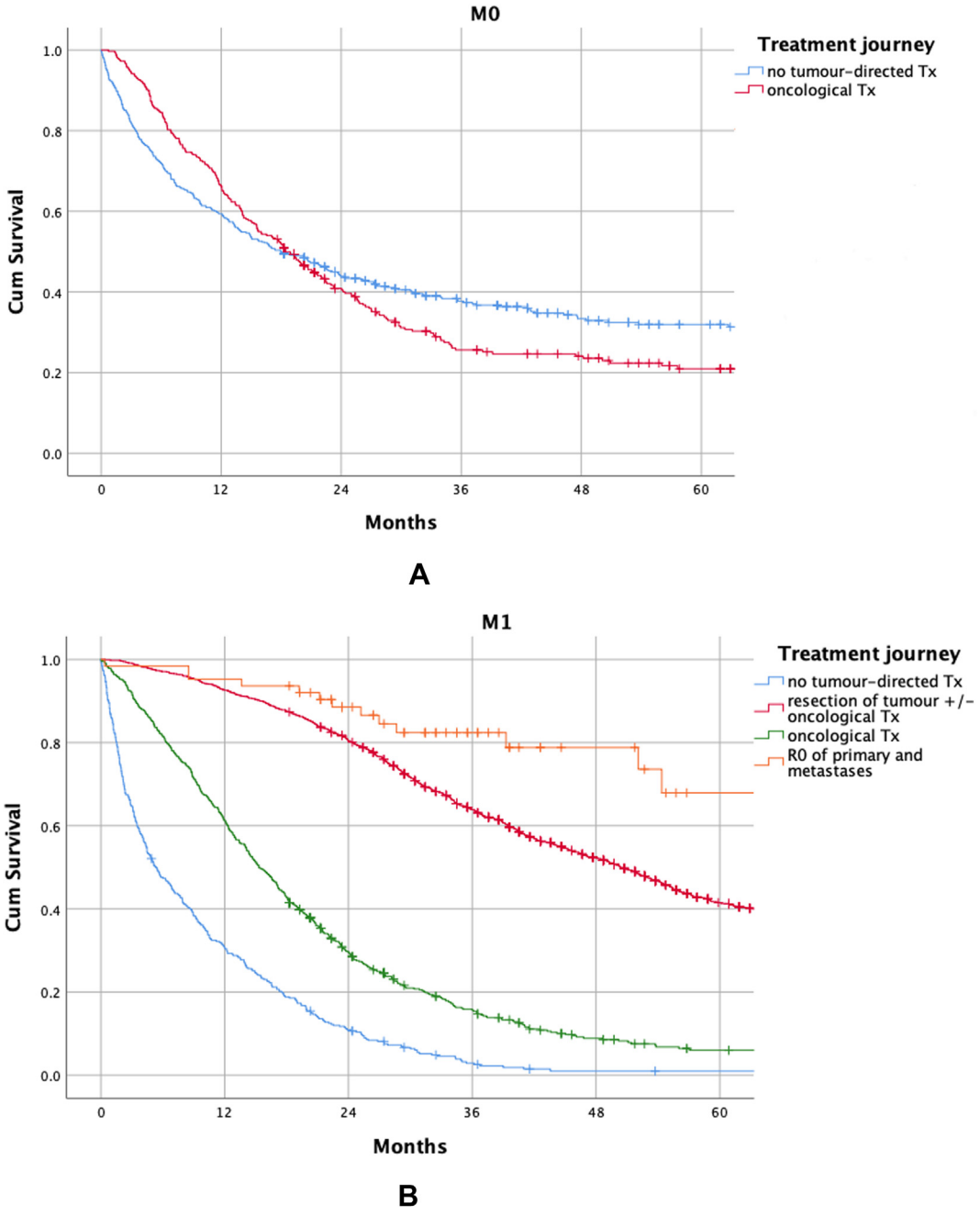

Fig. 4. 5-year overall survival of patients with rectal cancer undergoing non-curative treatment or attempt to cure within four different treatment journeys; **a,** for patients with M0 disease, i.e., no tumour-directed treatment (blue line) and radiotherapy (red line); **b,** for patients with M1 disease, i.e. non-tumour-directed treatment (blue line), resection of the primary tumour with or without oncological treatment (red line), oncological treatment alone (green line), or R0 resection of primary tumour and metastases (orange line).

a complete picture of currently applied care for patients with advanced rectal cancer. Compared to the earlier Norwegian cohort study, non-curative treatment for advanced rectal cancer has changed considerably in parallel with improved and novel oncological treatments. For selected patients, indications for surgical treatment have expanded due to better peri- and postoperative care and the introduction of novel surgical approaches such as minimally invasive surgery and contemporary liver resection techniques.

We identified ten different pathways of care within four main treatment journeys. However, information to bridge the gap between enhanced treatments and perceived quality of life is still mostly lacking. Translating the improved treatment options into improved quality of life, spending the remaining, often limited lifetime according to the patient's individual goals and expectations remains a challenge in the care of patients with incurable rectal cancer.

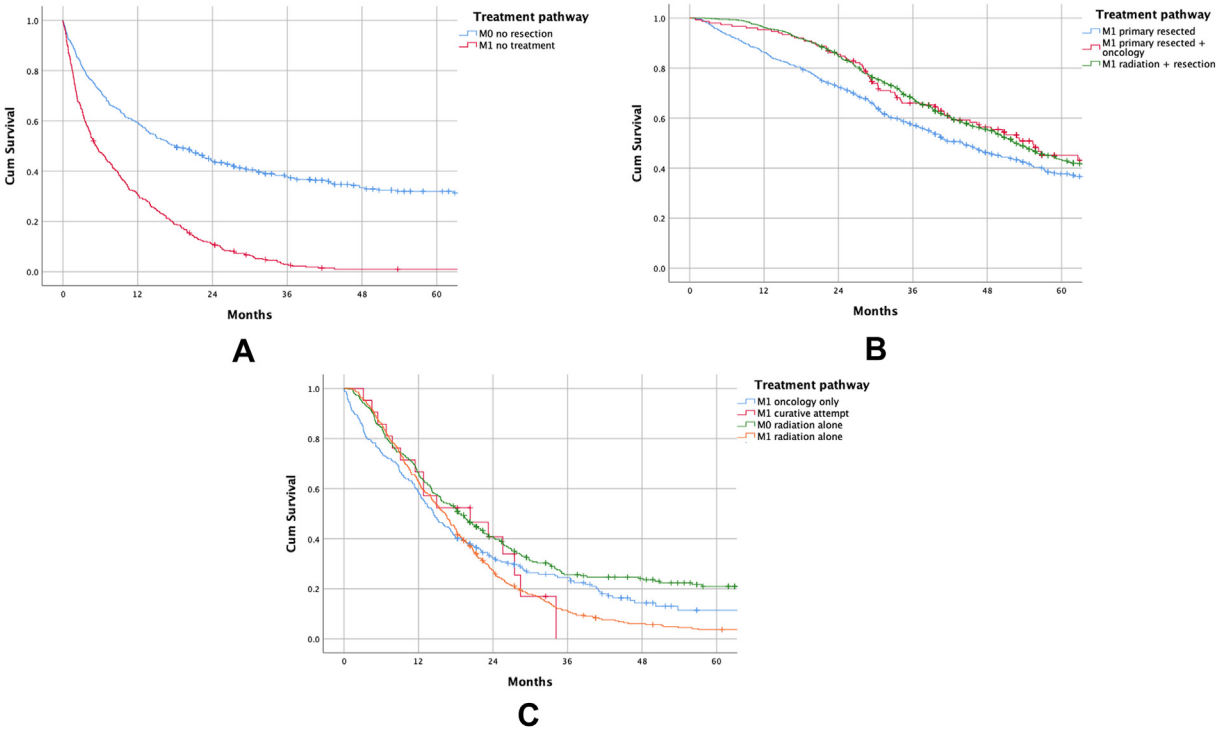

Fig. 5. 5-year overall survival of patients with metastatic rectal cancer according to the various treatment pathways within different non-curative treatment journeys: **a,** no tumour-directed treatment for metastatic (red line) or non-metastatic disease; (blue line) **b,** primary resection of the primary tumour alone (blue line), combined with systemic chemotherapy (red line) or preoperative radio- or chemoradiotherapy (green line); **c,** oncological treatment alone (blue line), resection of metastases without resection of the primary tumour (R2; red line), or radiotherapy for the primary tumour without resection, M1 (orange line) and M0 (green line).

Funding

The study was funded by the Folke Hermansen Fund for Cancer Research at Stavanger University Hospital, grant #424515. The funding source did not influence the acquisition, processing, analysis, or interpretation of data.

Disclaimer

Information from the Norwegian Patient Registry has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred.

Information from the Cancer Registry of Norway has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

CRediT authorship contribution statement

Hartwig Kørner: Conceptualization, Funding acquisition, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Marianne G. Guren:** Conceptualization, Writing – review & editing. **Inger Kristin Larsen:** Writing – review & editing, Visualization. **Dagny Faksvåg Haugen:** Writing – review & editing. **Kjetil Søreide:** Writing – review & editing, Visualization. **Leif Roland Kørner:** Writing – review & editing. **Jon Arne Søreide:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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