Long-term benefits, risks and adverse events after intended curative rectal cancer treatment in Denmark

PhD dissertation

Jesper Beck Jørgensen

Health
Aarhus University

Department of Surgery,
Aarhus University Hospital
2020

Supervisors

Professor, Lene Hjerrild Iversen, MD, PhD, DMSc (main supervisor)
Department of Surgery, Aarhus University Hospital
Aarhus, Denmark

Bodil Ginnerup Pedersen, MD, PhD
Department of Radiology, Aarhus University Hospital
Aarhus, Denmark

Professor, Søren Laurberg, MD, DMSc
Department of Surgery, Aarhus University Hospital
Aarhus, Denmark

Collaborators

Rune Erichsen, MD, PhD
Department of Clinical Epidemiology, Aarhus University Hospital
Department of Surgery, Regional Hospital Randers
Aarhus Denmark

Peter Bondeven, MD, PhD
Department of Surgery, Aarhus University Hospital
Department of Surgery, Regional Hospital Randers
Aarhus, Denmark

Evaluation committee

Brendan Moran, MD, MCh, FRCS, FRCSI
Department of Surgery
Basingstoke and North Hampshire Hospital
Basingstoke, England

Professor Torbjörn Holm, MD, PhD
Department of Surgery
Södersjukhuset
Stockholm, Sweden

Professor Kari Tanderup, Cand.scient., PhD (chairman)
Department of Oncology
Aarhus University Hospital
Aarhus, Denmark

Preface

This thesis is based on studies carried out during my employment at Department of Surgery, Aarhus University Hospital and Regional Hospital Randers. The work is funded by the Danish Cancer Society and performed between 2014 and 2020. I wish to express my sincere gratitude to all those who have helped directly or indirectly during this work.

First of all, I wish to express my deepest gratitude to Lene Hjerrild Iversen. I am truly grateful for your commitment and devotion to this project. You have invested heart and soul, and have catalyzed my development and continued learning with a never failing enthusiasm. You own an ability to make the best of things and have shown incredible loyalty and patience in all contexts during this journey. I really appreciate our friendship and confidentiality.

To Bodil Ginnerup Pedersen. I have the utmost respect for your professional and personal dedication. You have shown wise and caring support, and have been bedrock throughout the realization of this work. I thank you for your always-constructive criticism and unquestionable integrity.

To Søren Laurberg. You have provided truly inspiring mentoring sessions and have brought huge dedication in to this project. Throughout the process you have been offering great hospitality and provided constructive criticism delivered in a personal and subtle way. I admire your passion for research and sense of humour.

To my estimated colleagues, Rune Erichsen and Peter Bondeven, who have offered excellent professional and personal guidance throughout the process. I thank you both for your availability and cheerful support.

Finally, I am especially thankful to my best friend and wife, Ann Olivia and our beautiful children Sia, Anton, Sigurd, Alma, and Otto for your patience and loving support. I am infinitely grateful for your strength and wise guidance in all matters of life. You are truly inspiring and the best companion through unprecedented paths in life. I would be lost without you.

Table of contents

List of publications **10**

Introduction **11**

Background **13**

Rectal cancer *13*

Survival and Recurrence *13*

Staging of rectal cancer *16*

Magnetic Resonance Imaging *17*

Multidisciplinary team directed treatment *19*

Neoadjuvant treatment *20*

Surgical treatment *24*

Total mesorectal excision 25

Partial mesorectal excision 25

Abdominoperineal resection 26

Use of diverting stoma 27

Postoperative surveillance *28*

Long-term adverse events following intended curative rectal cancer treatment *30*

Adverse events 30

Non-reversal of diverting stoma 30

Pelvic insufficiency fractures 33

Aims of dissertation **35**

Hypotheses **36**

Methods **37**

Study designs and settings *37*

Data sources *37*

Civil Registration System (CRS) 37

Danish Colorectal Cancer Group (DCCG) Database 37

The Danish National Patient Registry (DNRP) 38

Study cohorts *38*

Oncological and surgical treatment *41*

Histopathology *42*

3-year postoperative pelvic MRI *42*

Recurrent disease ... *45*
Outcomes ... *46*
Overall survival and recurrent disease (Paper I) ... 46
Stoma reversal (Paper II) ... 46
Pelvic insufficiency fractures (Paper III) ... 46
Statistical analysis ... *47*
Characteristics ... 47
Overall survival, cumulative incidence proportion, and competing risk analysis (Paper I and II) ... 47
Cox proportional Hazards (Paper I and II) ... 47
Multiple logistic regression (Paper III) ... 48
Methodological considerations ... *49*
Strengths ... 49
Limitations ... 49
Results ... 51
Survival ... *51*
Recurrence ... *55*
Stoma reversal ... *59*
Pelvic insufficiency fractures ... *62*
Discussion ... 65
Survival ... *65*
Recurrence ... *66*
Stoma reversal ... *68*
Pelvic insufficiency fractures ... *69*
Conclusions ... 72
Perspective ... 73
Summary ... 76
Summary in Danish (Dansk resumé) ... 77
References ... 78
Paper I ... 98
Paper II ... 127
Paper III ... 148

List of tables and figures

Table 1: Cumulative incidence proportions of recurrence and survival 5 years after rectal cancer treatment according to randomised controlled trials (p15)

Table 2: Rectal cancer treatment with curative intent according to Danish guidelines (p23)

Table 3: Previous studies on diverting stoma reversal after restorative rectal cancer resection (p32)

Table 4: Studies on pelvic insufficiency fractures following intended curative rectal cancer treatment (p34)

Table 5: Rates of 3-year overall survival, and cumulative incidence proportions of distant recurrence and local recurrence in stage I-IV rectal cancer patients, Denmark 2011-2012 (particular low survival rates and CIPs are presented only) (p53)

Table 6: Significant predictors of overall survival, distant recurrence and local recurrence for stage I-IV patients undergoing intended curative rectal cancer resection, Denmark 2011-2012 (p54)

Table 7: Characteristics of 6,859 patients undergoing intended restorative rectal resection or Hartmann's operation, Denmark 2001-2012 (p58)

Table 8: One and three-year cumulative incidence proportions of stoma reversal in patients undergoing intended restorative rectal cancer resection with diverting stoma, Denmark 2001-2012 (particular low CIPs are presented only) (p60)

Table 9: Significant hazard ratios (0-3 years), of predictive characteristics associated with delay in stoma reversal for patients with intended restorative rectal cancer resection with diverting stoma, Denmark 2001-2012 (p61)

Table 10: Risk factors significantly associated with PIF (p63)

Figure 1: Flow chart on diagnostics and intended curative treatment of rectal cancer in Denmark during 3 years of follow-up (p29)

Figure 2: Study populations in Paper I and III (p40)

Figure 3: Study population in Paper II (p41)

Figure 4: Sagittal STIR sequence showing bone marrow oedema in Alae Ossis Sacri (p43)

Figure 5: Axial T2 was planned from sagittal T2 (p44)

Figure 6: Axial T2-weighted MRI showing sclerosis and fracture in Alae Ossis Sacri (p44)

Figure 7: Planning of coronal T2 including the anterior edge of sacrum (p45)

Figure 8: Overall survival rates of stage I-IV rectal cancer after intended curative resectional surgery during 3 years of follow-up (p52)

Figure 9: Cumulative incidence proportion of local and/or distant recurrence in stage I-IV rectal cancer patients during 3 years of follow-up (p55)

Figure 10: Cumulative incidence proportion of distant recurrence in stage I-IV rectal cancer patients during 3 years of follow-up (p56)
Figure 11: Cumulative incidence proportion of local recurrence in stage I-IV rectal cancer patients during 3 years of follow-up (p56)
Figure 12: Cumulative incidence proportion of stoma reversal during 3 years of follow up (p59)
Figure 13: Anatomical distribution and frequency of pelvic insufficiency fractures (p64)

Abbreviations

APE	Abdominoperineal excision
AR	Anterior resection
CRC	Colon and rectal cancer
CRM	Circumferential resection margin
CRT	(Chemo) radiotherapy
CT	Computed Tomography
DCCG	Danish Colorectal Cancer Group
DRM	Distal resection margin
DS	Diverting stoma
ELAPE	Extralevator abdominoperineal excision
EMVI	Extramural venous invasion
ENTD	Extra nodal tumour deposits
LR	Local recurrence
MDT	Multidisciplinary team
MRF	Mesorectal fascia
MRI	Magnetic resonance imaging
mrT	Preoperative T-category on MRI
PIF	Pelvic insufficiency fractures
PME	Partial mesorectal excision
pT	Pathological T-category
QoL	Quality of life
STIR	Short T2 inversion recovery sequence
TME	Total mesorectal excision
TNM	Tumor, nodes, metastasis

List of publications

This PhD dissertation is based on the following papers referred to in the text by Roman numerals:

#

I. **Jørgensen JB**, Bondeven P, Laurberg S, MRI Study Group, Pedersen BG and Iversen LH. Comorbidity and UICC stage IV disease are main risk factors for decreased 3-year survival and recurrence after intended curative surgery for rectal cancer – A population-based study. *In preparation for submission, August 2020.*

II. **Jørgensen JB**, Erichsen R, Pedersen BG, Laurberg S, Iversen LH. Stoma reversal after intended restorative rectal cancer resection in Denmark. A nationwide population-based study. *BJS Open 2020: In press.*

III. **Jørgensen JB**, Bondeven P, Iversen LH, Laurberg S, Pedersen BG. Pelvic insufficiency fractures are frequent after preoperative chemo-radiotherapy for rectal cancer – A nationwide MRI study. *Colorectal Disease.* 2018; 20(10): 873-80

#

Introduction

There have been major advances in management of rectal cancer over the past decades. Standardization of rectal cancer surgery, involving the concepts of mesorectal excision surgery and rectal resection with tumour free margins, are the main reasons for these improvements. In addition to surgery, all of pre-operative rectal cancer staging by magnetic resonance imaging (MRI), multidisciplinary team directed treatment planning, neoadjuvant (chemo) radiotherapy (CRT), and quality assurance by pathological assessment, contribute to improved outcome for rectal cancer patients. Consequently, survival rates in rectal cancer are now superior to colon cancer [1].

Despite a thorough optimization in management of rectal cancer in Denmark, with significantly increased survival rates [1-4], we still need more knowledge about the oncological implications of current treatment strategies in the management of rectal cancer, including rates of local (LR) and distant recurrence (DR). Accordingly, we have conducted a population-based cohort study to evaluate overall survival (OS), and particularly LR and DR rates in Denmark.

In rectal cancer surgery, diverting stomas (DS) are created during intended restorative resection for mid and distal rectal cancer (i.e. tumour located 0-10 cm from the anal verge) primarily to reduce the consequences of a possible anastomotic leakage [5-11]. Unfortunately, not all patients have their DS reversed after surgery [12-22], resulting in significant restrictions to activities of everyday life and requiring resources to adapt both physically, socially and mentally [13, 18, 23, 24]. In order to provide detailed and concise information to patients prior to surgery, we have conducted a nationwide study concerning implications of the widespread DS use during restorative rectal cancer surgery.

Over the last three decades, there has been a considerable effort to define the role of radiotherapy. Although neoadjuvant chemo-radiotherapy (CRT) reduces the risk of LR, there is no evidence of improved survival [25-28]. Successful CRT induces downsizing and downstaging of the rectal tumor and increases the chance of clear circumferential resection margin (R0 resection). However, the possible benefits must

be weighed against the risks of both early and late toxicities [28-35]. Pelvic insufficiency fractures (PIF) are a frequent complication to CRT in the treatment of pelvic malignancies, and detection rates between 3% and 11% following rectal cancer treatment have been reported in previous trials [36-39]. In order to provide the best possible conditions for detection and evaluation of PIF, we conducted a study with consequent use of MRI including highly sensitive sequences for this the specific purpose.

Background

Rectal cancer

Colorectal cancer (CRC) is currently the third leading cause of cancer globally with 1.8 million new cases in 2018 [40]. Cancer is the second leading cause of death worldwide and was responsible for estimated 9.6 million deaths in 2018, corresponding to about 1 in 6 deaths globally [40]. However, public access to treatment services and availability of data on cancer treatment is still far from the desired level globally. More than 90% of high-income countries reported available treatment services compared to less than 30% of low-income countries, and only 1 in 5 low- and middle-income countries have the necessary data to drive cancer policy [40]. In Denmark, 4,433 patients had the diagnosis of colon or rectal cancer in 2018, with rectal cancer accounting for about one third of the patients (n=1,369) [41]. European data on CRC from 2014 reveals similar results with rectal cancer incidence of 20 per 100,000 inhabitants annually, constituting about one third of all colorectal cancer cases across Europe [42].

The definition of rectal cancer in Denmark is adenocarcinoma arsing from 0 to 15 cm from the anal verge, as measured by rigid proctoscopy [11]. The rectum is subdivided into thirds: upper (>10-15 cm), mid (>5-10 cm), and lower (0-5 cm), since prognosis and surgical management is affected by location of the tumour.

In March 2014, CRC screening was implemented in Denmark and the incidence of CRC went from 4,138 new cases in 2013 to 5,186 new cases in 2014 [43, 44]. Since 2015 the incidence has been declining and is now almost at a level similar to the pre-screening era [41, 43-49].

Survival and Recurrence

Distant recurrence (DR) and/or local recurrence (LR) of rectal cancer occurs in up to 40% of patients undergoing curatively intended surgery, and 60%-80% of recurrences present within 2 years of surgery and 90% within 5 years of surgery, with liver and lung metastasis as the most frequent locations [50, 51]. This opens for a discussion of when the terms of synchronic or metachronous disease can be used in a temporal context (i.e. at 120 or 180 days, or something else, following completed rectal cancer treatment). DR of disease is generally associated with increased mortality and may represent progression of disease not detected initially, rather than inadequate

treatment. Contrary, LR, which often is responsible for severe morbidity, is increasingly recognized as failure of complete tumour resection, and thus, associated with failure of surgical technique. However, the definition of LR varies. Following the introduction of TME surgery, the risk of LR after rectal resection has decreased below 10% and an additional risk reduction has been achieved by implementation of neoadjuvant CRT [27]. These findings are commonly reported together with improved survival rates [52, 53], but the effect of these initiatives on DR remains unclear. Reported outcome from major rectal cancer trials during the last two decades are presented in Table 1. The advances in surgery evolving from a comprehensive understanding of the local spread of disease, and the adoption of neoadjuvant CRT along with optimized preoperative staging with MRI have all contributed to improved outcome in rectal cancer treatment nationally and internationally [1, 54]. The effect of optimal surgery and neoadjuvant CRT on OS and recurrence will be discussed in specific sections below.

Table 1: Cumulative incidence proportions of recurrence and survival 5 years after rectal cancer treatment according to randomised controlled trials

Trials	Inclusion period	Number of patients	Treatment	5-year CIP of overall recurrence	5-year CIP of distant recurrence	5-year CIP of local recurrence	5-year overall survival
Swedish Rectal Cancer Trial, 1997 [55]	1987-1990	n=1168	Preop. RT/ surgery vs. surgery	28% vs. 38% *(p<0.001)*		11% vs. 27% *(p<0.001)*	58% vs. 48% *(p=0.004)*
German Rectal Cancer Trial, 2004 [26]	1995-2002	n=823 *UICC stage II-III*	Preop. CRT/ TME vs. TME/ postop. CRT		36% vs. 38% *(p=0.840)*	6% vs. 13% *(p=0.006)*	76% vs. 74% *(p=0.800)*
FFCD 9203 Trial, 2006 [56]	1993-2003	n=733 *UICC stage II-III*	Preop. CRT/ surgery vs. Preop. RT/ surgery			8.1% vs. 16.5% *(p=0.004)*	67.9% vs. 67.4% *(p=0.684)*
EORTC Radiotherapy Group Trial, 2006 [57]	1993-2003	n=1011 UICC stage II	1) Preop. RT/ surgery 2) Preop. CRT/ surgery 3) Preop. RT/ surgery/ Postop. CT 4) Preop. CRT/ surgery/ Postop. CT		No difference between groups *(p=0.620)*	1) 17.1% vs. 2) 8.7% 3) 9.6% 4) 7.6% *(p=0.002)*	No diference between groups *(p=0.430)*

Dutch TME Trial, 2007 [58]	1996-1999	n=1861	Preop. RT/ TME vs. TME alone	25.8% vs. 28.3% *(p=0.387)*	5.6% vs. 10.9% *(p<0.001)*	64% vs. 64% *(p=0.902)*
MRC-CR07 Trial, 2009 [25]	1998-2005	n=1350	Preop. RT/ TME vs. TME/ postop. RT	19% vs. 21%*	4.7% vs. 11.5% *(p<0.001)*	70% vs. 68% *(p=0.400)*

*Distant recurrence rates (no CIP / p-value indicated in study)

Staging of rectal cancer

The Union for International Cancer Controls (UICC) 8th edition of the Tumour, Node, Metastasis (TNM) classification from 2017 is an anatomical tumour classification, which is based on the depth of tumour infiltration through the intestinal wall and whether the tumour infiltrates neighbouring organs or structures (T category), involvement of regional lymph nodes (N category) and occurrence of disseminated disease (M category) [59]. The classification includes additional categories on venous invasion (V category), nervous infiltration (Pn category), lymphatic invasion (L category) and incomplete resection with residual tumour (R category). Two classifications are applied for each patient: (1) Clinical TNM (cTNM) is based on clinical examinations, endoscopic and radiological findings before decision and evaluation of treatment. (2) Pathological TNM (pTNM) is based on examination of the excised specimen, including the tumour and associated regional lymph nodes. Determination of the pM category often relies on preoperative staging alone; however, the pathoanatomical findings may supplement or modify preoperative clinical findings.

The UICC stage indicates the anatomical spread of cancer disease and both a clinical and a pathological UICC stage may be registered. The clinical UICC stage, which determines the decision on treatment strategy, might be registered in the medical records at primary multidisciplinary teams (MDT) conference. The pathological UICC stage can be determined when the definitive surgical procedure has been performed and requires the presence of both the pT and pN category.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has an important role in the preoperative multidisciplinary assessment of rectal cancer and is primarily used for local tumour staging (T and N categories), selection of patients for neoadjuvant treatment, and planning of surgical strategy. Given the improved ability to produce high-quality images of the primary tumour, preoperative staging with pelvic MRI has been mandatory in Denmark throughout the last two decades.

MRI with high-resolution T2 weighted sequences and thin sections with slices perpendicular to the axis of the tumour is a mandatory requirement in the efforts to achieve necessary and sufficient image quality [60, 61]. This provides the opportunity to assess both the depth of tumour infiltration (T category), distance to the mesorectal fascia (MRF) (representing the anticipated circumferential resection margin (CRM) in successful surgery) and pelvic floor, lymph node involvement, tumour deposits, and presence of extramural vascular invasion.

MRI has been particularly useful in the ability to evaluate the MRF and predict either involved, threatened or clear margins and thus direct a treatment strategy [60, 62]. Supplemental sagittal and coronal images will add important additional information on tumour height in the rectum and the relation between advanced stage tumours and adjacent pelvic structures. These parameters underlie the potential decision for neoadjuvant treatment and planning of the surgical treatment strategy [63, 64]. Furthermore, MRI is useful in re-assessment of rectal cancer with evaluation of tumour response to neoadjuvant treatment and planning of additional intervention [65, 66].

Tumour infiltration depth has been validated as a significant prognostic factor in rectal cancer [67-70]. In patients with an extramural tumour penetration depth ≤5 mm (T3a) and ≥5 mm (T3b), respectively, a corresponding cancer specific 5-year survival of 85% and 54% has been found regardless of lymph node status [67]. In a British study, 94% weighted agreement between MRI and pathology assessment of T category was demonstrated [60]. Moreover, a European multicentre study comparing the tumour infiltration depth estimated by pathological evaluation and preoperative

MRI, respectively, found a mean difference of 0.05 mm, and thus concluded that extramural depth of infiltration was accurately predicted to within 0.5 mm in 95% of 295 patients who had surgery without neoadjuvant CRT [71]. An additional Danish multicentre study, conducted in the Central and Northern Region of Jutland, demonstrated good inter-observer agreement between radiologists in assessment of the tumour infiltration depth by MRI [72].

The MRF is clearly identified on axial T2 weighted images as a narrow hypo intense line and can be reliably assessed preoperatively [73]. Patients with threatened MRF on MRI should be considered for neoadjuvant CRT (including the majority of very low tumours) to reduce the risk of CRM involvement at subsequent surgery by downstaging of disease or possible downsizing of the tumour [74, 75]. A threatened MRF on preoperative MRI is accurately correlated with pathological evaluation of the resected specimen [60, 62, 76]. The MERCURY study, conducted using state-of-the-art MRI protocols and with histopathological evaluation of the resected specimen as golden standard, found that a free resection margin within a 1 mm limit could be predicted with a high specificity using MRI [64, 77, 78]. When the MRF was predicted free of tumour on MRI and the patient had surgery without neoadjuvant CRT, a histologically clear CRM was achieved in 92% of patients.

Studies on survival has found that a histopathological free resection margin of ≥2 mm is associated with improved survival in relation to a 1 mm cut off value [79], and an exponential increase in LR rate with decreasing distance to CRM [80]. None of these studies were correlated with findings on MRI. However, a retrospective Dutch study from 2001 found that a pathological tumour free margin of ≥1 mm is predictable if the measured distance on MRI is ≥5 mm. Further, a Danish study anticipating the reproducibility of MRI measurements on minimal distance from tumour to the MRF, found a moderate to good inter-observer agreement concerning CRM status at the 1-mm level, but less acceptable at 5 mm distance [72]. Based on these findings, a 0-2 mm distance from tumour to the MRF evaluated by MRI underlies the current Danish recommendations for allocation to preoperative CRT [64, 72].

In a number of countries, the presence of metastatic regional lymph nodes, extra nodal tumour deposits (ENTD), and extramural venous invasion (EMVI), demonstrated by

preoperative MRI, serve as prognostic markers in the allocation of patients to neoadjuvant therapy [81-83]. ENTD serve as an independent prognostic factor [83] and is used as an indication for preoperative treatment with short distance to the MRF [11]. Tumour deposits may be perceived as either lymph node metastasis or focus of EMVI. However, the correlation between MRI and pathology is not unequivocal when it comes to predicting lymph node status, and metastatic lymph nodes, as evaluated by MRI (mrLN), is not recognised as an independent criterion for referral to neoadjuvant treatment nationally, unless the distance of a metastatic lymph node is < 2 mm to the MRF [11, 73, 84-86].

EMVI with direct tumour infiltration of mesorectal vessels leads to significantly impaired prognosis [87] and MRI evaluation of EMVI (mrEMVI) is therefore incorporated in recent recommendations from The European Society of Gastrointestinal and Abdominal Radiology (ESGAR) 2016 [88, 89]. mrEMVI < 2 mm to MRF is implemented as an independent criterion for referral to neoadjuvant treatment nationally, and guidelines from European Society for Medical Oncology (ESMO) recommends re-staging within 3 months to exclude metastatic disease [90].

Tumour response to neoadjuvant CRT may be predicted by MRI performed (weeks) after completed oncologic treatment [78]. It is particularly important to ensure that tumour does not progress on the given treatment urging the previously established surgical strategy to change.

Multidisciplinary team directed treatment

Regular and structured conferences in multidisciplinary teams (MDT) must be established to ensure optimal diagnosis and treatment of rectal cancer patients, in accordance with National and international recommendations [91-93]. Dedicated specialists in oncology, radiology, pathology, and colorectal surgery are reviewing incoming results from preoperative clinical and radiological examinations. The structured discussion of each patient aims at an optimized and individual treatment strategy to improve prognosis [94-96].

MDT conference can be held (1) as decision-making (preoperative) conference on treatment of newly diagnosed rectal cancer patients; (2) to assess optional treatment strategies in newly diagnosed patients with metastatic disease and in re-evaluation of patient response to neoadjuvant treatment; and (3) as post-operative follow-up

conference, advantageously held for auditing and teaching purposes, aiming to strengthen and develop the MDT concept. Post-operative MDT offers the opportunity to assess the quality of radiological staging, effect of neoadjuvant treatment, tumour characteristics, and the quality of surgery, in order to schedule an individualized surveillance program and decide for content and frequency of follow-up.

Neoadjuvant treatment

Neoadjuvant treatment in rectal cancer is characterized by preoperative treatment with either radiotherapy (RT) alone or concomitant chemo and radiotherapy (CRT).

Indications for neoadjuvant treatment are both to reduce the risk of LR and to achieve downstaging of primary non-resectable tumours, in order to facilitate R0 resection.

In randomized controlled trials, use of neoadjuvant CRT in addition to mesorectal excisional surgery has been found to significantly decrease LR rates, but no difference was found in survival (Table 1) [25-28]. Only a meta-analysis from 2001 based on data from 22 studies and completed before the introduction of mesorectal excisional surgery found that preoperative radiotherapy of rectal tumours gave rise to a survival benefit [97]. The Swedish rectal cancer trial of 1168 patients, the largest single study contributor to the meta-analysis, found significant improvements in OS following pre-operative short course radiotherapy (25 Gy / 5 fractions) with increased 5-year survival (58% vs. 48%) [55].

In a German, randomized controlled study of UICC stage II and III rectal cancer patients, a 5-year CIP of LR at 6% was found in patients treated with pre-operative chemo-radiotherapy versus 13% after postoperative chemo-radiotherapy. No difference in the 5-year survival was found (76% versus 74% respectively). The study primarily included patients with mid and lower rectal cancer [26].

In the Dutch TME trial, including 1,861 patients with resectable rectal cancer, patients were randomised to TME surgery either with or without pre-operative radiotherapy (25 Gy / 5 fractions). A significant reduction in the frequency of LR among patients treated with pre-operative radiotherapy was found (5% versus 11%) at 10 years of follow-up. For patients with a negative CRM, the effect of radiotherapy was independent of tumour height [27, 28]

In the English / Canadian MRC CR07 NCIC CO16 study, 1350 patients were randomised to either preoperative short course radiotherapy or selective postoperative CRT. A significant reduction in the LR rate of 6.2% in preoperatively irradiated

patients was found independent of tumour location in the rectum. There was no difference in survival [25].

Apart from improved local control, neoadjuvant CRT provides various potential advantages to rectal cancer patients. It allows for early re-assessment of disease by MDT, and could potentially enable the consideration of organ preservation by allowing for more effective local excision and even non-operative management strategies.

Patients treated with neoadjuvant CRT exhibit a pathologic complete response (pCR) at the time of surgical resection in up to 33% and have improved oncological outcome with reported LR rates of less than 1% and 5-year survival above 90%, leading to question the added benefit of surgery in these patients [98-101]. The rate of pCR is higher after treatment with long-course CRT than short-course radiotherapy (SCRT) at re-evaluation 6-8 weeks after completed oncological treatment [102], and meta-analysis has shown increased pCR rate with increasing interval to surgery [103]. Recent studies, evaluating non-operative management of UICC stage I disease following neoadjuvant CRT, have been conducted in patients undergoing various watchful waiting protocols [104-110]. A meta-analysis from 2017, found that 16% of patients undergoing a watchful waiting strategy had intraluminal recurrence following clinical complete response (cCR) [111]. Further, analysis from an international watchful waiting database reported a DR rate of 8%, a LR rate of 25%, and a 5-year OS of 85% within 2 years, and curative treatment was achieved in 95% of patients who developed LR. Pelvic MRI may play an increasingly important future role in monitoring of treatment effect and presence of local recurrence [104, 106, 109].

Delivering systemic chemotherapy before surgery in patients at risk for distant metastatic disease has the potential to improve survival by addressing micrometastatic disease earlier [112, 113]. The NEOLAR study [113] and the RAPIDO Trial [112] are both ongoing randomised controlled trials from Denmark and The Netherlands, respectively, investigating the effect of preoperative chemotherapy on distant recurrence(s) of rectal cancer. It is anticipated that intense systemic combination chemotherapy reduces the risk of distant recurrence and increases survival by eradication of potential micrometastatic disease. Previous trials studying the effect of postoperative chemotherapy in combination with preoperative radiotherapy did not

result in an improved survival [56, 114]. The hypothesis is that traditional rectal cancer treatment is associated with high complication rates due to primarily preoperative radiotherapy, leading to a substantial proportion of patients unable to receive chemotherapy postoperatively. Further, early surgical and medical complications, the functional outcome, toxicity and quality of life (QoL) may all be improved if radiotherapy can be avoided, adding significant perspectives to future rectal cancer treatment.

National guidelines on rectal cancer rectal treatment with curative intent are summarized in Table 2.

Table 2: Rectal cancer treatment with curative intent according to Danish guidelines*

Distance of primary tumour (lower edge) from anal verge (cm)	Rectal cancer surgery without neoadjuvant CRT	Rectal cancer surgery and neoadjuvant long-course CRT	Post operative chemotherapy**
>10-15	cT1, cT2, cT3 and resectable cT4	Non-resectable cT4	UICC stage III and none neoadjuvant CRT or UICC stage II with at least one risk factor*** and none neoadjuvant CRT
>5-10	cT1, cT2, cT3 with >2 mm* to mesorectal fascia or transmural infiltration 0-5 mm	cT4, cT3 with 0-2 mm* to mesorectal fascia, including mesorectal nodal and extra nodal tumour deposits or transmural infiltration >5 mm	d.o.
0-5	cT1, cT2	cT3, cT4	d.o.

* Guidelines revised October 2018 with a previous limit of 0-5 mm distance from tumour to mesorectal fascia

** Offered to patients aged ≤75 years with WHO performance status ≤2, and without microsatellite instability.

*** Emergency surgery, anastomotic leakage, pT4 category, <12 lymph nodes in the excised specimen as detected at histopathological evaluation.

Surgical treatment

Surgical resection is considered a cornerstone in intended curative treatment of rectal cancer.

However, new approaches to rectal cancer management have developed in recent years with non-surgical management of selected patients and refinement of endoscopic microsurgical techniques. Early in the 20th century, rectal cancer was considered a non-curable disease and patients underwent different perineal procedures with palliative intent to address primarily symptomatic and typically advanced disease. Patients had near 100% recurrence rates and very high perioperative mortality rates.

In The Lancet in 1908, Ernest W. Miles published "A method of performing abdominoperineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon" presenting the successful results of radical treatment of 12 patients with a perioperative mortality rate of 41.6% [115]. This description of a curatively intended two-part procedure introduced a new era in rectal cancer surgery and became the gold standard throughout the following decades.

In a national report from 1942 on 1444 rectal cancer patients undergoing APE in 121 different hospitals in Denmark in the time period from 1931 to 1935, only 27% of patients had radical surgery with perioperative mortality rate of 60% to 70% [116].

In 1940's and 1950's, sphincter-sparing rectal cancer surgery with re-establishment of intestinal continuity became a much-debated issue. Scepticism towards oncological safety of the approach and mortality rates related to anastomotic failure was main the main causes of concern. However, in 1948 restorative rectal cancer resection was introduced by Claude F. Dixon in the surgical treatment of mid and upper rectal cancer, with the concept of anterior resection (AR) of the rectum [117]. His results justified the surgical concept and AR became the standard surgical approach to upper rectal cancer in the following years. During the next decades, technical advances made restorative surgery possible even in patients with low rectal tumours and without compromising oncological results [118-120].

Total mesorectal excision

In the past few decades, there have been remarkable advances in treatment of rectal cancer. This is primarily through standardization of rectal cancer surgery, involving concepts of mesorectal excisional surgery [121, 122] and rectal resection with tumour free margins [123, 124]. The concept of total mesorectal excision (TME) was introduced by Heald et al. in 1979[122], which involved sharp en bloc resection of the tumour and mesorectal tissue to the level of the levator muscles. Heald recognized that the midline hindgut and its mesorectum were derived together [52] and the tissue surrounding the mesorectum derived from a separate embryological origin. Later, Hida supported the rationale for TME by demonstrating that the field of lymphatic spread was primarily contained within the mesorectum[125] and confirmed that rectal cancer is a disease of the supralevatory compartment. The main principles of the TME procedure were to maintain the integrity of the mesorectal fascia by sharp dissection in the avascular retrorectal space (‘holy plane’) between the presacral fascia and the mesorectal fascia, with complete removal of the mesorectum and maintenance of an intact mesorectal fascia. Heald’s principles of surgery resulted in reduced perioperative bleeding, decreased local recurrence rates from 30%-40% [126] to less than 4% [127], and increased disease free survival from 45%-55% [126] to 80% and 78% at 5 and 10 years respectively [127]. Furthermore, identification and preservation of the inferior hypogastric plexus and the pelvic splanchnic nerves resulted in reduced urogenital dysfunction and improved quality of life, which had been an inevitable part of the radical surgery for rectal cancer before the introduction of TME surgery. In the following years in Japan, new dissection techniques with lateral pelvic lymphadenectomy developed [128-130].

Partial mesorectal excision

The extent of resection in rectal cancer surgery is determined by tumour location in the rectum, the involvement and management of direct tumour spread to related organs, and decision of high versus low vascular ligation [131-135]. In upper rectal cancer, the necessity for TME surgery is debateable. The extent of tumour spread in the mesorectum in anal direction of the tumour is the key aspect and mesorectal tumour deposits has been reported in a distance of up to 4 cm below the distal intramural margin of the tumour [121, 136]. Mesorectal transection 5 cm below the anal edge of the tumour carefully performed tangentially to the mesorectum and

muscle tube seems adequate and TME surgery for upper rectal cancer is often considered unnecessary for oncological reasons [137-139].
The concept of partial mesorectal excision (PME) evolved on basis of these findings and the rationale is that this procedure is less extensive, results in a better long-term functional outcome, decreases post-operative complication rates, and is an oncological safe method that reflects outcome after TME surgery [35, 138, 140].

However, in Swedish series of resectional rectal cancer surgery a LR rate of 9% was found in tumours of the upper rectum following PME surgery despite concomitant treatment with neoadjuvant radiotherapy [141]. Interestingly the Swedish study described radiological evidence of residual mesorectum (RM) in 86% of patients with LR [141, 142]. Later, a Danish cohort study reported a 3-year LR rate of 7% following resectional rectal cancer surgery performed between 2007 and 2010 in a specialized colorectal referral centre [143]. The 3-year LR rate after PME surgery, however, was found to be significantly increased compared to TME or APE surgery (14% vs. 3% or 6%). In parallel to the Swedish observations, all patients with LR after PME surgery had evidence of either RM or insufficient distal resection margin (DRM) as evaluated by MRI [143].

Abdominoperineal resection

Abdominoperineal excision (APE) is performed in rectal cancer if sphincter-preserving surgery is not an option, either for oncological or functional reasons, or in frail and elderly patients where potential complications of attempts to restore intestinal continuity are prohibitive [58, 144-146].
It is therefore of great importance preoperatively to determine the precise location of the tumour in relation to the anal verge, the levator ani muscles, and the sphincter complex, both radiologically and clinically [77]. In clinical practice, a distinction is made between intersphincteric APE, conventional APE, extralevatory APE (ELAPE), and ischioanal APE [11]. Intersphincteric APE is used in patients with increased risk of functional problems, severe comorbidity or high age, and in patients with cT1 and cT2 tumours if an anastomosis is not an option. Conventional APE is the traditional method of rectal resection, as described by Miles, and indicated in selected patients with cT1, cT2 or early cT3 tumours if intersphincteric APE is oncologically unsafe. ELAPE can be used if tumour is inseparable from the puborectal/levator muscle(s) or

the internal sphincter. The method is recommended to avoid a waist at the specimen in order to increase the chances for R0-resection [147]. ELAPE was introduced in Denmark in 2007 with systematic implementation of the surgical technique at selected centres and training with assistance from international experts. Ischioanal APE is recommended in tumours involving the ischioanal compartment, either at the levator or sphincter level. Reconstruction of the pelvic floor should be considered in patients undergoing ELAPE and is always required after ischioanal APE.

In recent years, several authors have shown that oncologic outcomes after APE have not improved to the same degree as those seen after implementation of TME surgery. Compared with patients undergoing TME during the same time period, patients undergoing APE have higher rates of local recurrence and poorer survival [146, 148]. The difference in oncologic outcomes may be explained to a substantial degree by the increased risk of tumour-involved margins (CRM) and inadvertent bowel perforations associated with APE, as both of these factors are significantly related to local control and survival [149].

Use of diverting stoma

A diverting stoma (DS) is created during restorative resection to reduce the consequences of a possible anastomotic leakage and is recommended according to Danish guidelines along with TME as part in the surgical treatment of mid and low rectal cancer [11]. A DS is not routinely created during PME surgery for upper rectal cancer [150]. In randomized trials it has been reported that anastomotic leakage rates decline in patients receiving a DS after TME surgery with low anastomosis [5, 151-155] while other trials found no effect of diversion [6, 8, 9, 156, 157]. The value of a DS has been a subject for much debate as several trials are clearly indicating a protective function of a DS as it reduces the consequences of an eventual leakage (faecal peritonitis, lower rates of reoperation, reduced long-term morbidity, decreased permanent stoma rates and reduced mortality rates) [5, 6, 8-10]. On contrary, stoma-related complications are common, not to mention the risk of a permanent stoma. Accordingly, many centres have adopted a highly selective approach to diversion depending on both patient-related risk factors and anastomotic height with promising results [157, 158].

Postoperative surveillance

Postoperative surveillance is indicated for early detection of local and distant recurrence after intended curative colorectal cancer treatment, for early diagnosis of metachronous cancer, for prevention of rectal cancer by removal of adenomas in the rectum, for psychosocial support, in assessment of the quality of treatment, to identify long-term adverse events, and to initiate treatment of these. However, established scientific committees have published guidelines with widely differing recommendations for postoperative surveillance [159-162] and studies of clinical practice in member countries of the European Society of Coloproctology (ESCP) reveal great disparity at international level [162].

The standard surveillance programme according to the Danish Colorectal Cancer Group (DCCG) guidelines is a computed tomography (CT) scan of thorax, abdomen, and pelvis after 12 and 36 months, in addition to outpatient visits with rigid proctoscopy after 6, 12, 18, 24, and 36 months [11]. Pelvic MRI is not a part of the standard surveillance programme in Denmark.

An intensive surveillance program in patients undergoing intended curative colorectal cancer surgery has previously been shown to increase survival by 7-8% [163-165]. However, a recent meta-analysis [166] and a systematic review [162] have questioned these findings, as underlying studies are highly heterogeneous on follow-up regimens [162, 166]. Asymptomatic recurrence of disease is more frequently detected when patients undergo follow-up with short intervals, and may be surgically treated more often than symptomatic LR [167, 168]. However, intensive surveillance programmes has high costs for both patients and society, as it will result in a high degree of mental distress and large economical expenses. Intended curative surgery for local recurrent rectal cancer is achieved in less than 40% of patients as they are often diagnosed with advanced disease [169, 170].

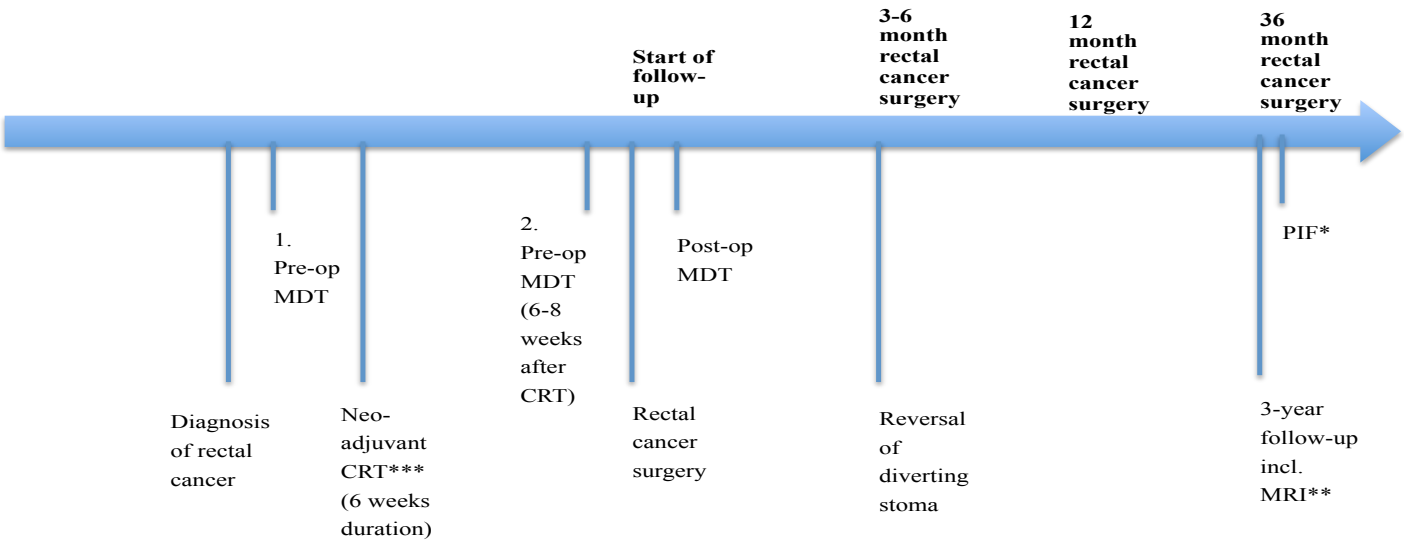
With the existing postoperative surveillance programmes, patients with recurrence of disease have often exceeded possibilities of curative treatment due to delayed diagnostics. The IMPROVE IT2 trial is a National Danish interdisciplinary initiative to facilitate potential early detection of recurrence by cancer DNA testing in blood. Preliminary results are promising, and it is expected that this program will increase

the proportion of patients eligible for intended curative surgery due to early diagnosis [171, 172].

In currently available European guidelines, no consensus has been reached on surveillance regimen after treatment of colorectal cancer (CRC) with curative intent. The evidence for alternating international follow-up programs is limited, as current multimodal follow-up methods has failed to show any impact on survival. Results from current trials, investigating new biomarkers [171] and individualized 'patient-driven' follow-up [173] are awaited and may potentially lead to international consensus between countries being member of the European Society of Coloproctology on a joint CRC surveillance program.

Figure 1 summarizes the timely relation between diagnostics and intended curative treatment of rectal cancer in Denmark during 3-years follow-up.

Figure 1: Flow chart on diagnostics and intended curative treatment of rectal cancer in Denmark during 3 years of follow-up.



* PIF may occur at any point of time during 3-year follow-up.

** Three-year postoperative MRI is not a part of the standard surveillance programme in Denmark.

*** Excluding a) low cT1-cT2, b) mid cT1-cT2 and cT3 with >2 mm to MRF and transmural infiltration 0-5 mm, and c) upper cT1-cT3 and resectable cT4.

Long-term adverse events following intended curative rectal cancer treatment

Adverse events

Understanding the consequences of treatment is important to optimise patient support and minimise impact on daily life. Adverse effects of long-course CRT combined with rectal resection are well documented and include a broad variety of clinical manifestations. Frequent and well-described complications with a substantial impact on QoL are bowel dysfunction, sexual dysfunction, urinary problems, occasional rectal bleeding, impaired wound healing, and mental distress among others [29, 31-35]. Following restorative rectal cancer surgery, the long-term functional outcome is poor in approximately half of the patients with frequent and fragmented stools, urgency, and incontinence described as 'low anterior resection syndrome' (LARS) [35, 174, 175]. A symptom scoring system assessing the severity of LARS (grouped in three categories: no LARS, minor LARS and major LARS) has been developed and validated in Denmark in 2012 [176]. The risk of severe bowel dysfunction is increased in patients undergoing neoadjuvant CRT [35, 145, 177], in patients with low anastomoses [178, 179], in patients undergoing TME vs. PME [35], following anastomotic leakage [180, 181], in patients with more than two than anastomoses [182-184], and the use of a diverting ileostomy is associated with twice the risk of suffering from LARS [185, 186]. Thorough preoperative counselling emphasizing the expected postoperative changes in bowel function and the possible of improvement over time enables the patient to better assist in the choice of surgical method and to better adapt to the situation [174].

Non-reversal of diverting stoma

Although stoma closure is considered a simple surgical procedure, the interval between stoma construction and reversal is often prolonged, and some patients, DS may never be reversed [18]. In recent years, much attention has been given to perioperative management, morbidity, oncological outcome, and QoL analysis in rectal cancer patients. Less attention has been given to long-term risk of permanent stoma. Non-reversal of a DS or secondary construction of a permanent colostomy, are the two main conditions responsible for a permanent stoma after intended restorative rectal cancer resection. The prevalence of non-closure of intended temporary stomas

after rectal resection is reported as 3% to 32% after 1.5 to 7.1 years [12-22], and in multicentre studies on rectal cancer patients only [12, 13, 18, 20], a risk of 17% [12] to 25% [13] of a permanent stoma after intended restorative rectal resection is reported, Table 3. Previously reported risk factors associated with non-reversal of an intended temporary stoma include advanced age [13, 21], anastomotic leak [14, 17, 18], and metastatic disease [14, 20].

Recent studies from The Netherlands found no difference in the short-term postoperative complication rates between patients undergoing rectal cancer resection with DS by routine or if DS only was performed in highly selective patients [157, 158]. It seems that the ability to select patients for stoma construction is the key towards preferable outcomes, not a risk adverse strategy [157].

Table 3: Previous studies on diverting stoma reversal after restorative rectal cancer resection

Studies	Setting	Number of patients	Type of stoma	Median time to reversal, days	Follow-up, years (range)	Permanent stoma rate
Bailey et al. 2003 [19]	*Local* (Reading, England)	n=59	End stoma/ Diverting stoma	-	4.0 (1.5-6.5)	9%
Lordan et al. 2006 [16]	*Local* (Camberley, England)	n=50	Diverting stoma	142	- (-)	32%
den Dulk et al. 2007 [18] *(Prospective design)*	*National* (Netherlands)	n=523	End stoma/ Diverting stoma	123	7.1 (2.5-9.8)	19%
David et al. 2010 [13]	*National* (England)	n=964	Diverting stoma	207	3.0 (-)	25%
Lindgren et al. 2011 [20] *(Prospective design)*	*National* (Sweden)	n=234	End stoma/ Diverting stoma	570	6.0 (3.5-9.0)	19%
Gessler et al. 2012 [14]	*Regional* (Västra Götaland, Sweden)	n=262	Diverting stoma	178	2.8 (0-4.8)	23%
Dinnewitser et al. 2013 [17]	*Local* (Salzburg, Austria)	n=98	Diverting stoma	240	5.1 (1.8-9.4)	
Chiu et al. 2014 [21]	*Local* (Vancouver, Canada)	n=162	End stoma/ Diverting stoma	347	- (-)	15%
Pan et al. 2016 [15]	*Local* (Beijing, China)	n=296	Diverting stoma	192	2.4 (1.8-8.3)	17%
Gustafsson et al. 2018 [12]	*National* (Sweden)	n=3564	Diverting stoma	191	1.5 (-)	17%

Pelvic insufficiency fractures

Neoadjuvant CRT in the treatment of rectal cancer may result in a number of acute and late toxicities [29, 31-35], and the widespread use of RT in rectal cancer patients accentuates the importance of understanding these toxicities. PIF is considered an uncommon late complication to pelvic radiotherapy and is acknowledged as a stress fracture in structurally weakened bone [187, 188]. It can cause significant morbidity [189-195] with reported symptoms in 16% to 58% of patients and chronic pain as the most frequent clinical manifestation [196-198]. Unfortunately, patients with PIF often face missed or delayed diagnosis and may mimic local recurrence of rectal cancer in their presentation. However, PIF present characteristic patterns on modern modalities of MRI, thus obviating the need for biopsies and other diagnostic interventions [36-39].

Although many studies have investigated insufficiency fractures after radiotherapy for gynaecologic cancers with PIF rates from 8% to 45% and other pelvic malignancies (i.e. prostate and anal cancer) with PIF rates between 6% and 14% [191, 196-200], the incidence and clinical course of insufficiency fractures in rectal cancer patients have not been well characterized [190, 201, 202]. In previous small retrospective studies of rectal cancer patients only, PIF rates between 3% and 11% have been reported, Table 4. During the course of the present study, we were increasingly aware of PIF as a common radiological presentation on MRI in patients undergoing preoperative CRT.

Table 4: Studies on pelvic insufficiency fractures following intended curative rectal cancer treatment

Authors	Inclusion period	Patients and treatment	Number of patients	Imaging modality	Incidence of PIF	Time to follow-up (years)	Fracture site	Risk factors
Baxter et al. 2005 [190]	1986-1999	Women ≥65 Surgery +/- neoadjuvant CRT	1,317	-	11%	5	Femur neck (90%) Pelvic ring (10%)	Neoadjuvant CRT
Herman et al. 2009 [202]	1989-2004	Surgery + neoadjuvant CRT	562	CT	3%	3	Sacrum	Female gender
Kim et al. 2012 [201]	1998-2007	Surgery + neoadjuvant CRT	582	CT, MRI	9%	4	Sacrum	Age >60 Female gender Osteoporosis

Aims of dissertation

This dissertation aims to discuss aspects of the outcome of intended curative rectal cancer treatment in Denmark with regard to long-term benefits and with a particular focus on risk factors, but also on two less well-described adverse events.

The specific aims were as follows:

I. To estimate the 3-year overall survival rate and risk of recurrence in a well-defined Danish cohort with a particular focus on risk factors.

II. To examine the use of diverting stoma and the stoma reversal rate 3 years after intended restorative rectal cancer resection in Denmark.

III. To determine the prevalence and localization of pelvic insufficiency fractures detected on 3-year postoperative MRI after mesorectal excision surgery with or without neoadjuvant CRT.

Hypotheses

The specific hypotheses were as follows:

I. Several national initiatives during the last two decades has generally improved rectal cancer outcome, however, recurrence rates following rectal cancer resection with curative intent are underestimated due to inadequate surveillance programmes with anachronistic and insufficient diagnostic methods of follow-up.

II. A substantial part of patients undergoing intended restorative rectal cancer resection with a diverting stoma would eventually end up with a permanent stoma or significant delay in time to reversal and the risk may be extensively underestimated in previous studies mainly due to varying inclusion criteria.

III. State of the art MRI detected pelvic insufficiency fractures are common in a consecutive population undergoing comparable preoperative oncological treatment across Denmark.

Methods

Study designs and settings

The studies I and III were conducted on a well-defined Danish cohort of rectal cancer patients 3 years after intended curative surgery with prospective sampling of data. Study II, a population-based nationwide cohort study, was conducted in the setting of the entire Danish population, a country with 5.8 million citizens [203]. The studies were performed in accordance with the regulations of the National Board of Health (ref.: 3-3013-1272/1/), the Scientific Committee of the Danish Colorectal Cancer Group (DCCG.dk), and approved by the Danish Data Protection Agency (ref.: 2007-58-0010) pursuant to the Danish act on storage and processing of personal data. The National Health Service in Denmark provides universal, tax-supported health care to all citizens [204], guaranteeing free access to general practitioners and public hospitals treating rectal cancer.

The following is a supplement and discussion of some of the applied methods in Papers I to III.

Data sources

Civil Registration System (CRS)

Since April 1968, the Danish CRS has assigned a unique 10-digit personal identification number (Civil Personal Register number) to every resident in Denmark (1) born alive of a mother already registered in the CRS; (2) have their birth or baptism registered in a Danish electronic church register; or (3) reside legally in Denmark for 3 months or more [205]. The registry provides data on date of birth, gender, residence, vital status (updated daily), and death. The CPR number permits data linkage among registries in Denmark and within the healthcare system [206].

Danish Colorectal Cancer Group (DCCG) Database

Since May 2001, perioperative details on Danish colorectal cancer patients have been consecutively reported to the DCCG database, including >60.000 registered patients with approximately one-third rectal cancer and an overrepresentation of men [207]. The purpose of the database is to monitor the compliance and ensure uniform quality in the treatment of colorectal cancer in Denmark with defined quality standards set by

the DCCG to improve the prognosis in this patient group. All surgical departments across the country prospectively report data to the registry on patient performance and comorbidity, diagnostic staging, treatment and postoperative complications (occurring within 30 days after surgery) [207]. Pathological departments provide data on tumour type, number of lymph nodes / metastatic lymph nodes, surgical margin status, and other pathological risk factors. The database does not provide data on recurrences after primary surgery. The estimated completeness in the DCCG Database was 99% in the study period [207]. The DCCG database links to the CRS and variables of patient demographics, tumour location, surgical type, and pathological T category were retrieved from the database along with relevant data from the CRS.

The Danish National Patient Registry (DNRP)

Since 1977, the DNRP has expanded as a key Danish health register, maintaining records on all hospitalizations including information on hospital diagnoses and procedures [208]. Data were originally collected for administrative purposes only, unrelated to research objectives. Since 2003, with the introduction of a private healthcare sector in Denmark, it has additionally served as the basis for tax-funded payment of both public and private hospitals via the Diagnostic Related Group (DRG)-system [209]. Data include the CPR number, dates of admission and discharge and up to 20 discharge diagnoses, among others. Diagnostic coding were performed by physicians according to the 10th revision of the International Classification of Diseases (ICD-10) from 1993 and onwards [209]. Registration of surgical procedures in Denmark has been classified according to the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures since 1996. DCCG and DNRP data were linked to obtain information on surgical events during follow-up.

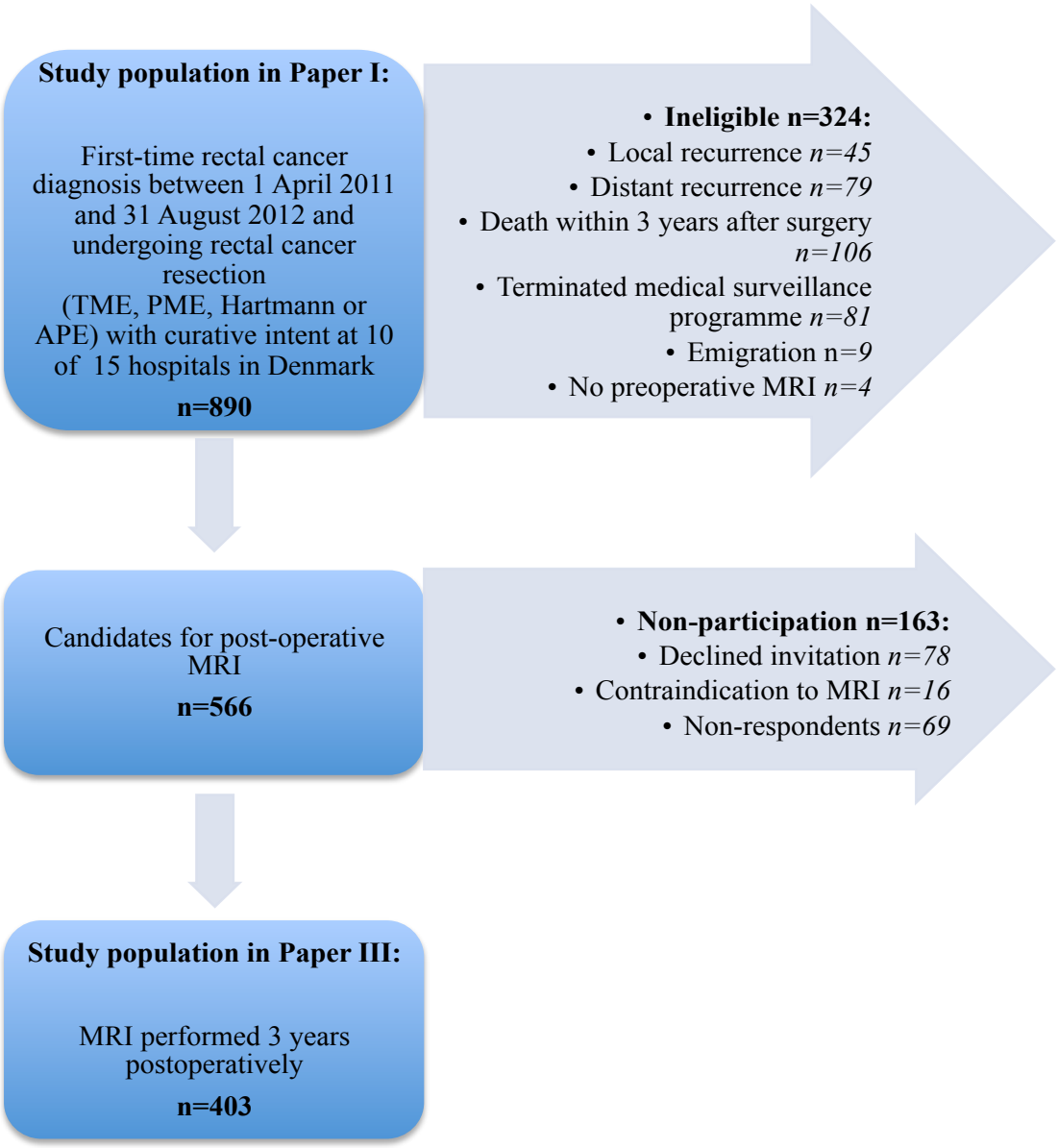
Study cohorts

In the studies I and III, patients registered in the DCCG database with rectal carcinoma (located ≤ 15 cm from the anal verge) and undergoing TME, PME, APE or Hartmann's operation with curative intent from April 2011 through August 2012, were invited to participate in a national MRI study aiming to evaluate rectal cancer outcome and specifically to detect LR 3 years after surgery. Approximately 1100 patients underwent treatment in 15 surgical centres in Denmark during the study period [46]. Ten departments (Aarhus University Hospital, Odense University Hospital, Regional Hospital Randers, Regional Hospital West Jutland, Hvidovre

Hospital, Zealand University Hospital, Slagelse Hospital, Svendborg Hospital, Vejle Hospital, and Esbjerg Hospital), providing for approximately 65% of the entire Danish population, were able to include patients. The remaining 5 departments abstained from participation mainly due to deficient capacity.

Patients were examined for vital status through the DNRP based on CPR number and eligibility was determined from a thorough review of medical records by the author. All data on patient demographics including comorbidity, tumour characteristics, cancer treatment, and follow-up data on recurrence of disease, were obtained from medical records and retrieved for further analysis. Patients with disseminated disease or local recurrence, or who had left the country, or terminated their surveillance programme due to old age and/or advanced comorbidity, were exempt from invitation to further examination. Included patients were offered a pelvic MRI at their 36-month follow-up visit additional to standard examinations with proctoscopy and CT, in order to obtain a more precise estimate of the incidence of recurrence at 3 years rectal cancer surgery. Study populations in Paper I and Paper III are depicted in Figure 2.

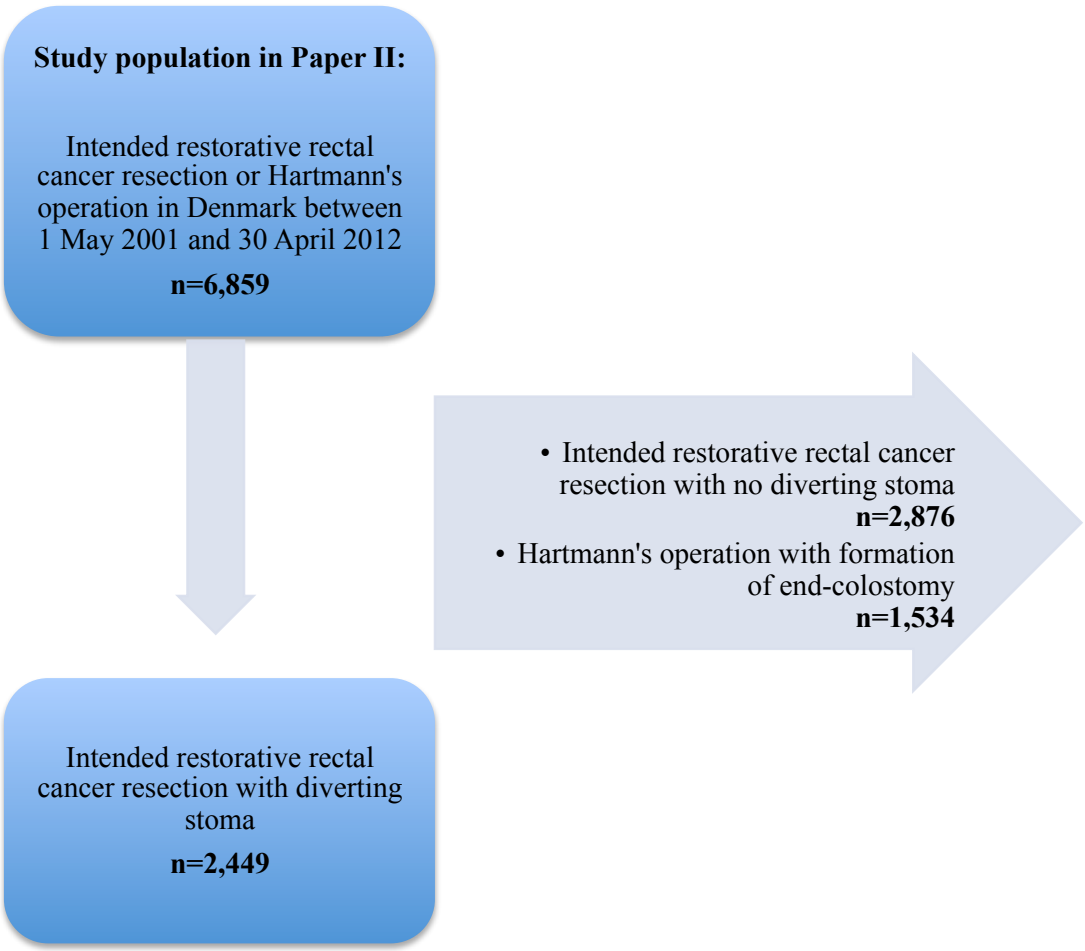
Figure 2: Study populations in Paper I and III



In study II, patients registered in the DCCG database from May 2001 through April 2012 who were diagnosed with rectal carcinoma (located ≤ 15 cm from the anal verge) and undergoing restorative rectal resection (TME, PME) or Hartmann's operation with curative intent (index procedure), were included using existing national registries. Patients undergoing surgical procedures other than the above mentioned or surgery with palliative intent, or had registration of a surgical procedure in the DCCG without confirmation of in the DNRP, were excluded.

Patients with a DS were followed from the date of the index procedure until the date of stoma reversal, death, emigration or end of 3-year follow-up. Data on stoma reversal or non-reversal within 3 years of follow-up among patients undergoing restorative rectal cancer resection, were retrieved from the DNRP records of surgical procedures via the NOMESCO classification system. This information was validated through a systematic review of medical records in 9% of the patients. Study population in Paper II is depicted in Figure 3.

Figure 3: Study population in Paper II.



Oncological and surgical treatment

Oncological and surgical treatment was performed according to recommendations in Danish guidelines as described in sections above (see Table 2 and Figure 1). National guidelines recommend neoadjuvant long-course CRT (50 Gy in 25-28 fractions

combined with 5-Fluorouracil (5-FU)) to patients with locally advanced rectal cancer [11]. Intended restorative rectal resection and Hartmann's operation performed as mesorectal excision were done 8-10 weeks after the completion of CRT. All other patients underwent direct intended restorative rectal resection or Hartmann's operation. Short-course radiotherapy with immediate surgery is not routinely performed in Denmark. Selected UICC stage II rectal cancer patients were offered 6 months of adjuvant chemotherapy. The same applied for UICC stage III rectal cancer patients who had not received neoadjuvant CRT [11].

Histopathology

The quality of the excised specimen was determined by pathologists according to the classification system by Quirke et al. [144, 210]. The pathological examination includes information from a) macroscopic evaluation (extent and dimensions of the specimen, location of the index tumour, diameter of the index tumour, occurrence of tumour perforation, and the plane of surgery), b) combined microscopic / macroscopic evaluation (the depth of infiltration of the index tumour through the intestinal wall including the CRM (involved CRM defined as any tumour, ENTD, or involved lymph nodes ≤1mm from the lateral resection margin), the distal resection margin (DRM), and the microradicality of the resection), and c) microscopic evaluation (histology and degree of differentiation of the index tumour, tumour response after preoperative neoadjuvant oncological treatment, infiltration to free peritoneum, infiltration of neighbouring organs or structures, occurrence of lymphatic invasion, venous invasion, nervous invasion, tumour budding, tumour satellites, number of metastatic and non-metastatic regional lymph nodes). Further, the evaluation includes a description tumour characteristic according to the TNM Classification of Malignant Tumours, 8th (pTNM and UICC stage) [59].

3-year postoperative pelvic MRI

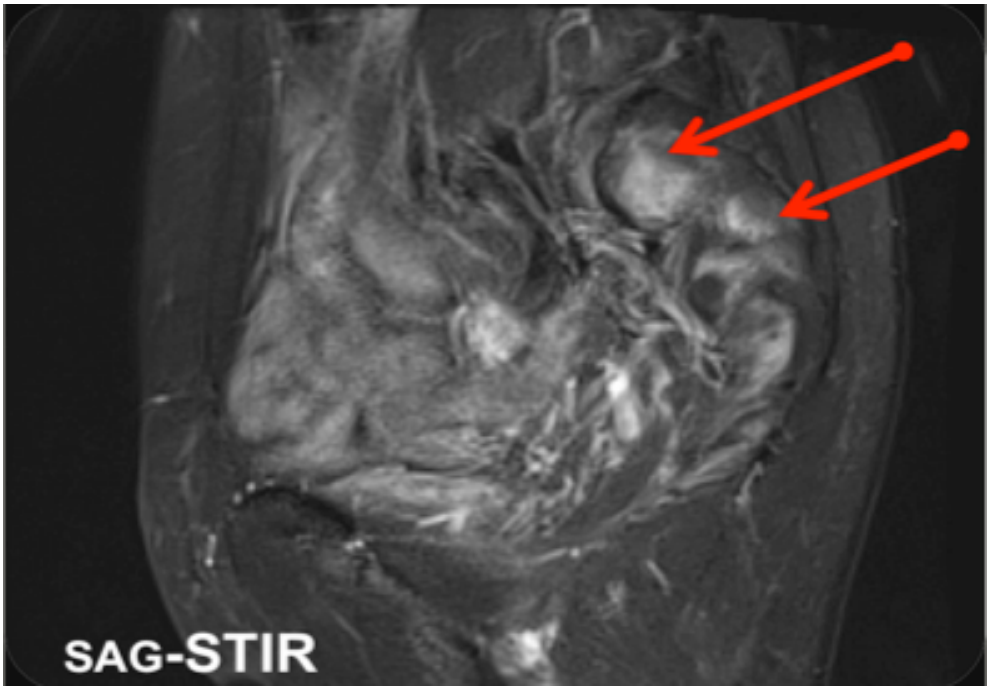
All patients fulfilling the eligibility criteria in study I and III were invited to a 3-year postoperative MRI in addition to the standard 3-year postoperative surveillance programme. Those, who did not respond to the primary request received a supplemental inquiry by telephone.

Postoperative 3-year pelvic MRI examinations were performed using 1.5 Tesla (preferred) or 3 Tesla platforms with a detailed scan-protocol established by the

research group. Sagittal, axial and coronal T2-weighted turbo spin echo images, field of view (FOV) 240 mm, slice thickness 4-5 mm, were obtained.

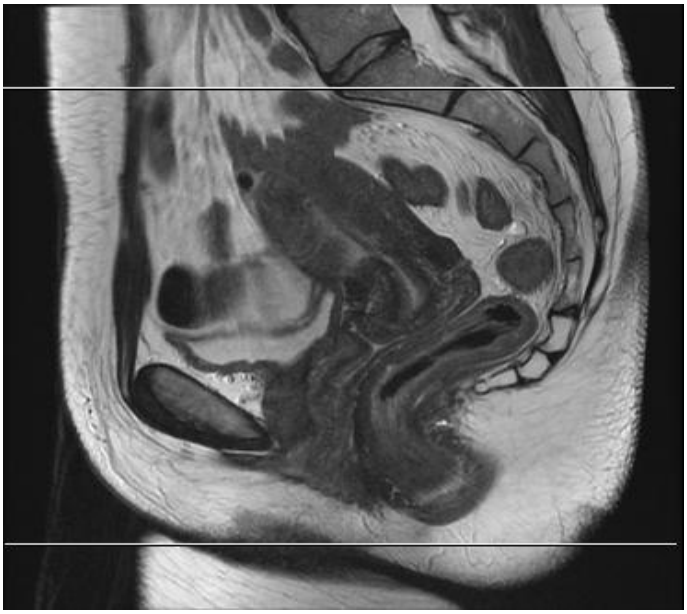
Additionally, sagittal short tau inversion recovery (STIR) sequence of the bony pelvis (Figure 4) and a sagittal T2 3D sequence of the smaller pelvis were obtained. The sagittal sequences covered the pelvis from tuber ischii to tuber ischii with the L5 depicted cranially.

Figure 4: Sagittal STIR sequence showing bone marrow oedema in Alae Ossis Sacri



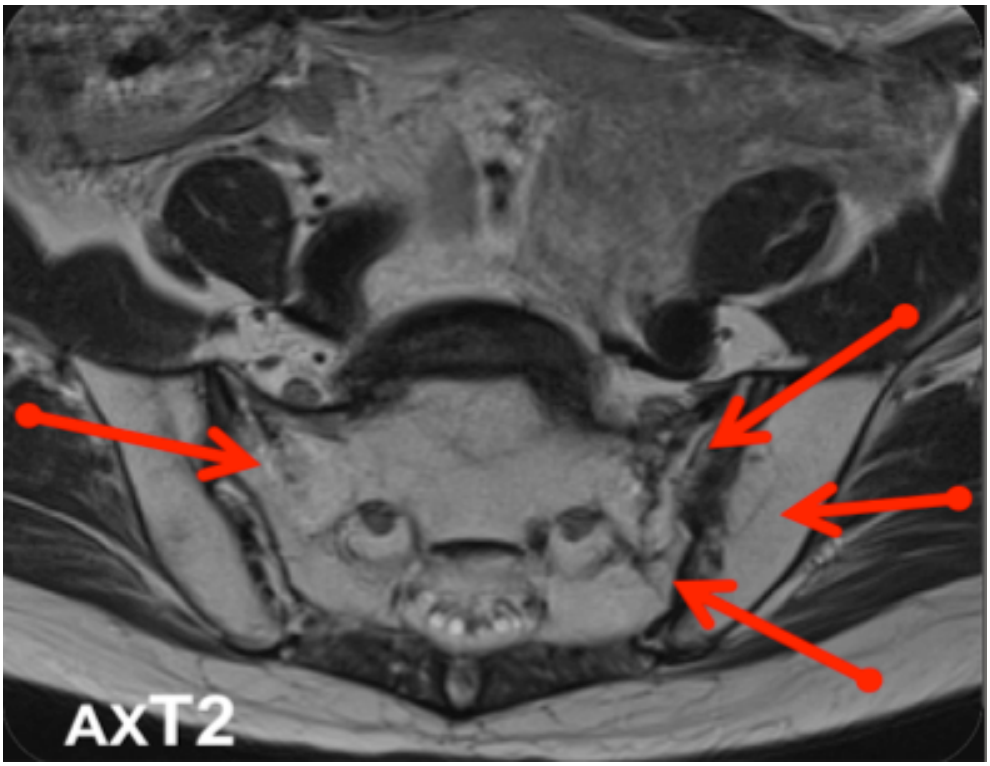
The axial sequence covered the entire pelvis from the lower border of the external sphincter to the promontory, Figure 5. Sequences were performed covering the entire anal canal scanned including the subcutaneous part of the external sphincter, representing the anal verge on MRI.

Figure 5: Axial T2 was planned from sagittal T2



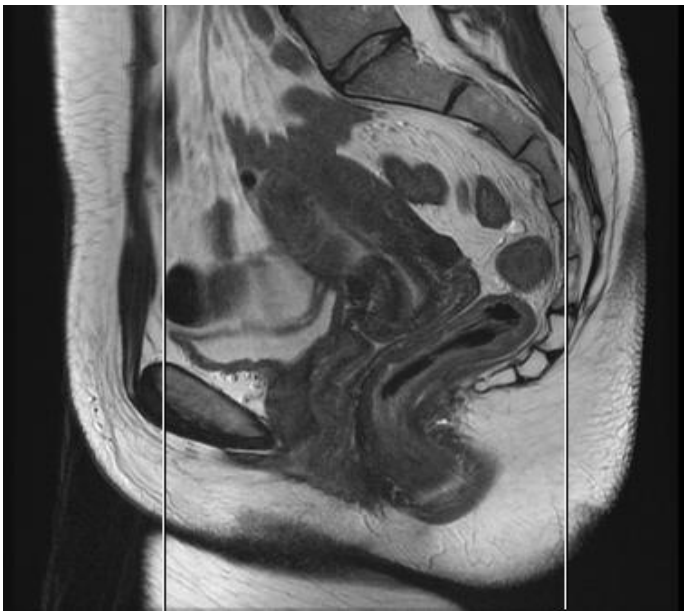
STIR images indicating bone marrow oedema accompanied by subtle linear changes of low signal intensity at T2 weighted images (Figure 6), were regarded as suggestive of PIF.

Figure 6: Axial T2-weighted MRI showing sclerosis and fracture in Alae Ossis Sacri



The coronal sequence covered the pubic bone anteriorly and the sacrum posteriorly, Figure 7. The sag T2 3D sequence covered the smaller pelvis with a slice thickness of 1 mm.

Figure 7: Planning of coronal T2 including the anterior edge of sacrum



In patients undergoing perineal reconstruction with a vertical rectus abdominis musculocutaneous (VRAM) flap or similar, MRI scans included 'open air' caudally and reached the promontory cranially since recurrences in these patients are often located at the edges of the VRAM flap. In patients with perineal herniation the VRAM flap may be quiet declive.

A dedicated multidisciplinary team radiologist at Aarhus University Hospital with 8 years of sub-specialisation in pelvic MRI re-evaluated all examinations and was blinded to all clinical data with the exception of the preoperative MRI examination.

Recurrent disease

Recurrent tumour mass outside the pelvic cavity, documented in the medical record by radiological, clinical or histological examination, was defined as DR.

Recurrent pelvic tumour mass detected by clinical or radiological examination or histologically verified adenocarcinoma as documented in the medical record or by the 3-year postoperative MRI was defined as LR, independent of the presence or absence of concomitant DR. The MDT at Aarhus University Hospital evaluated any pelvic

tumour mass detected at 3-year postoperative MRI and suspicious of LR. Histopathological confirmation was obtained if clinically relevant.

Outcomes

Overall survival and recurrent disease (Paper I)

In study I, outcomes were 3-year OS and cumulative incidence proportion (CIP) (named risk) of DR and/or LR in UICC stage I-IV rectal cancer patients treated with intended curative resectional surgery. Secondary outcome measures were significant predictors of OS, DR, and LR.

Stoma reversal (Paper II)

In study II, outcomes were 1 and 3-year stoma reversal rates in patients undergoing intended restorative rectal resection with a DS. Secondary outcome measures were significant predictors of stoma reversal during 3-years of follow-up.

Pelvic insufficiency fractures (Paper III)

In study III, outcome was the PIF rate as detected by 3-year postoperative MRI in patients following rectal cancer resection with curative intent with or without preoperative CRT. Secondary outcome measures were significant risk factors of PIF and the anatomical distribution of PIF.

Statistical analysis

Characteristics

Characteristics and demographics were presented as categorical variables by counts and percentages in studies I, II, and III.

In study I, characteristics were presented in groups as patient-related, pathology/tumour-related, or treatment-related variables, including rectal resection procedure (PME, TME, Hartmann's procedure, or APE), neoadjuvant treatment, and histopathological examination.

In study II, patients were grouped according to the surgical procedure and characterized pursuant to year of index operation and demographics. Patients with a DS, patients with no stoma, or patients undergoing Hartmann's procedure were presented in separate groups.

In study III, continuous data were categorised and categorical data were compared by Fisher's exact test (univariate analysis).

Overall survival, cumulative incidence proportion, and competing risk analysis (Paper I and II)

The OS rate and CIP of DR and/or LR at 3 years (Paper I) and stoma reversal at 1 and 3 years (Paper II) following rectal cancer surgery were calculated overall and for various patient-, pathology/tumour-, and treatment-related factors treating death as a competing risk. Kaplan-Meier survival curves were constructed. Disease-free survival (DFS) was calculated as the rate of patients who were alive and had no sign of recurrence 3 years after rectal cancer resectional surgery.

Cox proportional Hazards (Paper I and II)

Cox proportional Hazards regression analysis with computed Hazard ratios and corresponding 95% confidence intervals were used to explore potential predictors for OS, DR, and LR (study I) and stoma reversal (study II). Univariate and multivariate analysis were performed. All predictors were entered into a multivariate Cox regression model to adjust for potential confounders and to identify independent risk factors.

In Paper I, potential predictive factors (risk factors) for OS, DR, LR were explored in the following groups: *patient-related* risk factors: gender, age at surgery, Charlson

comorbidity index, ASA classification; *pathology/tumour-related* risk factors: tumour height (low (0-5 cm) vs. mid/high (6-10 cm / 11-15 cm), (y)pT-category (according to T category), UICC stage, and involved CRM (<1mm); and *treatment-related* risk factors: use of pre-operative CRT, surgical approach, type of rectal resection, intraoperative blood loss (0-300 ml vs. >300 ml), anastomotic leakage, and plane of surgery.

In Paper II, potential predictive factors of stoma reversal included in the analysis were: period of surgery, gender, age at surgery, body-mass index (BMI), Charlson comorbidity index (CCI), ASA classification, distance of primary tumour (lower edge) from anal verge (categorised as low (0 - 5 cm) vs. mid/ high (6 - 10 cm / 11 - 15 cm), use of neoadjuvant CRT, surgical approach, intraoperative blood loss, anastomotic leakage, (y)pT category (according to T category), and UICC stage.

Multiple logistic regression (Paper III)

Factors found to have significance less than 0.1 in the univariate model were entered into a multiple logistic regression model to identify independent predictors for PIF Adjusted ORs for PIF were computed using multiple logistic regression to estimate the impact of gender, age at surgery (categorised as <65 years or ≥65 years according to the median age at time of surgery), use of neoadjuvant therapy, tumour height (categorised as low *vs.* mid/high), surgical procedure (categorised as APE *vs.* TME/PME), and pT/ypT-category (according to T-subcategory). A p-value of less than 0.05 was considered significant.

Stata® version 12.0 (StataCorp, College Station, Texas, USA) was used for statistical analysis.

Methodological considerations

Strengths

Studies I and III include a prospective design and well-defined study cohorts of 890 and 403 patients, respectively, undergoing treatment regimens that comply with modern standards and a long follow-up period of 3 years. The data volume was of a considerable size and was retrieved from a reliable register based on prospective national data sampling with high data completeness [207]. The author reviewed medical records from all patients and information from the data extraction were re-evaluated. In study III, the consequent use of MRI with STIR sequences that is highly sensitive in detecting PIF strengthened the estimate significantly, and further, blinding of the multidisciplinary team radiologist to clinical data reduced the risk of information bias.

In study II, the nationwide prospective design and the large patient cohort constituted the biggest strengths. Data were retrieved from three highly reliable registries with prospective sampling of data and high data completeness [206-209, 211].

Limitations

Despite data being retrieved from validated databases, incorrect reporting of data from the individual hospitals may occur. In study I, estimates of survival are based on data from the Danish CRS and thereby very reliable. However, recurrence estimates are dependent on methods of follow-up, including variations in quality of the clinical and radiological examinations. Lack of follow-up according to the study algorithm and death between follow-up may tend towards an underestimated rate of recurrence. The same applies for patients with metastatic disease at various locations, whom will only rarely have all foci encoded. However, recurrence of disease is not always histologically verified and an estimate of recurrence on basis of information from medical records only, may, potentially, lead to an overestimation of the actual recurrence rate.

In study II, incorrect reporting of data with coding errors related to operative procedures may occur. However, data from DNPR regarding stoma status at 3-year follow-up were consistent with data from medical records in a sample survey of 9% of patients who had rectal resection with formation of a DS.

In study III, the primary limitation was the lack of information regarding clinical symptoms of PIF (typically pelvic pain). Further, information on the exact radiotherapy regimen and

information on potentially predisposing conditions (osteoporosis, corticosteroid use etc.) for development of PIF were not included.

Even though the DCCG Database has a high patient completeness, missing values are present in some variables, like patient characteristics as height/weight, tobacco use, alcohol consumption, ASA score, among other. Multiple imputation for missing data has not been performed in any of the three studies.

Results

The following section intends to give a summary of the most important findings in Papers I to III.

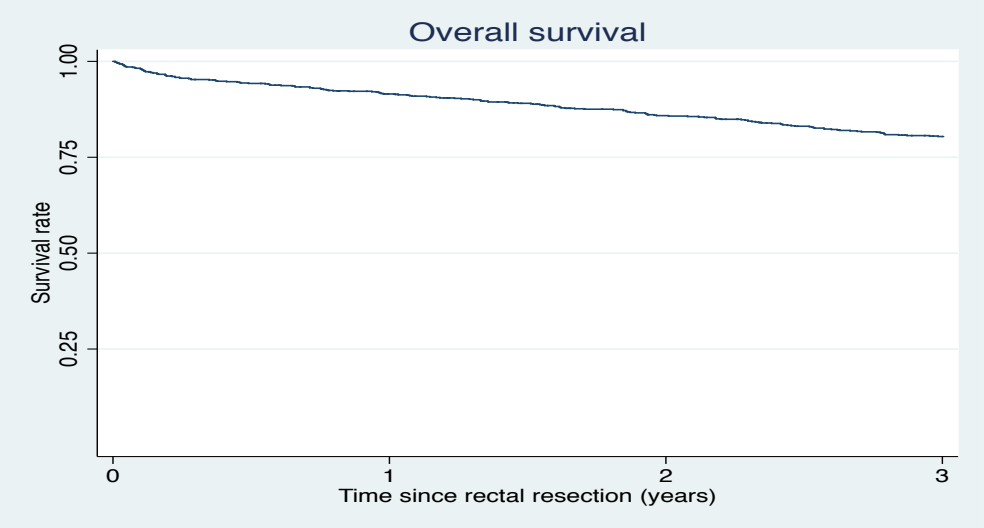
I: Comorbidity and UICC stage IV disease are main risk factors for decreased 3-year survival and recurrence after intended curative surgery for rectal cancer – A population-based study.
Jørgensen JB, Bondeven P, Laurberg S, MRI Study Group, Pedersen BG, Iversen LH.
In preparation for submission to Dis Colon & Rectum, August 2020.

In study I, survival and recurrence after intended curative resectional surgery for rectal cancer was evaluated in a national trial by 3-year postoperative follow-up of 890 patients with pelvic MRI, CT of the thorax and abdomen, and proctoscopy.
In total, 1,976 patients had rectal cancer diagnosed between April 2011 and August 2012. Ninety-four patients undergoing local excision, 124 patients undergoing palliative surgery, and 405 patients not undergoing surgery were excluded from the study. Accordingly, resectional surgery with curative intend was performed on 1,353 patients. In total, 10 of 15 surgical departments treating rectal cancer were able to include patients for pelvic MRI at 3-year postoperative follow-up, excluding an additional 463 patients, Figure 2.
Demographics, tumour characteristics, and treatment regimens of 890 patients included in the study are summarised in Table 1, Paper I.

Survival

In total, 169 patients died during 3 years of follow up after rectal cancer resection. Among the deceased patients, 107 (63.3%) died without recurrence of disease. For UICC stage I-IV patients, the 3-year overall survival rate was 80.6% and the 3-year disease-free survival was 73.0%. Restricted to UICC stage I-III patients, the 3-year overall survival rate and disease-free survival rate was 83.6% and 77.1%, respectively. OS in stage I-IV rectal cancer patients is depicted in Figure 8.

Figure 8: Overall survival rates of stage I-IV rectal cancer after intended curative resectional surgery during 3 years of follow-up



Factors associated with particularly poor 3-year OS are summarized in Table 5. Statistical significant factors predictive of decreased OS in multivariable analysis are presented in Table 6.

Table 5: Rates of 3-year overall survival, and cumulative incidence proportions of distant recurrence and local recurrence in stage I-IV rectal cancer patients, Denmark 2011-2012 (particular low survival rates and CIP's are presented only)

Characteristic		3-year overall survival % (95% CI)	Distant recurrence CIP_3 * % (95% CI)	Local recurrence CIP_3 * % (95% CI)
Total		80.6 (77.9; 83.1)	12.8 (10.6; 15.2)	6.5 (5.0; 8.4)
Age >65 years		75.9 (72.2; 79.4)	-	-
Charlson Comorbidity Index ≥2		61.0 (52.6; 69.6)	-	-
ASA-grade	**II**	80.4 (76.8; 83.8)	-	-
	III-IV	61.2 (52.9; 69.6)		
pT/ypT-category	**T3**	-	14.0 (11.0; 17.4)	-
	T4	65.7 (55.5.; 75.6)	17.9 (9.7; 28.2)	25.0 (16.1; 34.8)
UICC stage	**III**	-	16.8 (12.4; 21.8)	9.4 (6.2; 13.5)
	IV**	58.7 (49.3; 68.5)	46.3 (36.0; 56.1)	12.6 (6.9; 20.1)
Involved CRM (<1 mm)***		63.2 (52.7; 73.8)	34.5 (23.9; 45.2)	19.7 (11.6; 29.3)
Laparotomy as surgical approach******		73.7 (68.4; 78.7)	18.5 (14.1; 23.4)	11.6 (8.1; 15.8)
PME surgery		-	17.6 (13.1; 22.7)	11.0 (7.4; 15.3)
Blood loss >300 ml (intraoperative)		69.8 (63.5; 76.0)	-	13.5 (9.1; 18.9)
Non-mesorectal plane of surgery		75.7 (71.0; 80.2)	-	-

* Three-year cumulative incidence proportion. Calculated treating death as a competing risk.

** UICC stage IV rectal cancer patients had curatively intended treatment of distant metastasis along with rectal resection either during the index procedure or during an independent procedure in close timely relation to the index procedure.

*** Circumferential resection margin

**** Includes intended laparoscopic surgery but converted to open surgery.

Table 6: Significant predictors of overall survival, distant recurrence and local recurrence for stage I-IV patients undergoing intended curative rectal cancer resection, Denmark 2011-2012.

Characteristic	Overall survival	Distant recurrence	Local recurrence
Patient related	Charlson Comorbidity Index ≥2 (HR 2.72) ASA grade III-IV (HR 2.71) Age >65 years (HR 1.86)	Charlson Comorbidity Index ≥2 (HR 2.15)	Charlson Comorbidity Index ≥2 (HR 3.32)
Pathology/tumour related	UICC stage IV (HR 3.27)	UICC stage IV (HR 8.86) Involved CRM (HR 2.27)	UICC stage IV (HR 6.57) Distance of primary tumour (lower edge) from anal verge 0-5 cm (HR 4.60) Involved CRM (HR 2.72)
Treatment related	Plane of surgery Non-mesorectal (HR 1.68)		PME surgery (HR 4.70)

Recurrence

For UICC stage I-IV patients, the overall CIP of rectal cancer recurrence following resectional surgery with or without neoadjuvant treatment was 14.9%. The CIP of DR was 12.8% and the CIP of LR was 6.5%. Synchronous DR was found among 49% of the patients with LR.

The majority of patients with DR were diagnosed between 0 and 12 months after surgery, whereas the majority of patients with LR were diagnosed between 12 and 24 months after surgery.

In 403 patients undergoing 3-year postoperative pelvic MRI, a previously undiagnosed LR was found in 2% of the patients. The risk of LR after 3 years rectal cancer surgery was 5.6% excluding LR detected by pelvic MRI. Accordingly, by including pelvic MRI in the follow-up programme a 16.1% increase in the LR estimate was achieved.

Analysis of UICC stage I-III patients was performed in order to investigate if the outcome of rectal cancer treatment Denmark is comparable with recently reported results from neighbouring countries. Accordingly, an overall recurrence rate of 11.0%, a DR rate of 8.4%, and a LR rate of 5.8% were found among UICC stage I-III patients.

CIPs of DR and/or LR in stage I-IV rectal cancer patients are shown in Figures 9-11.

Figure 9: Cumulative incidence proportion of local and/or distant recurrence in stage I-IV rectal cancer patients during 3 years of follow-up

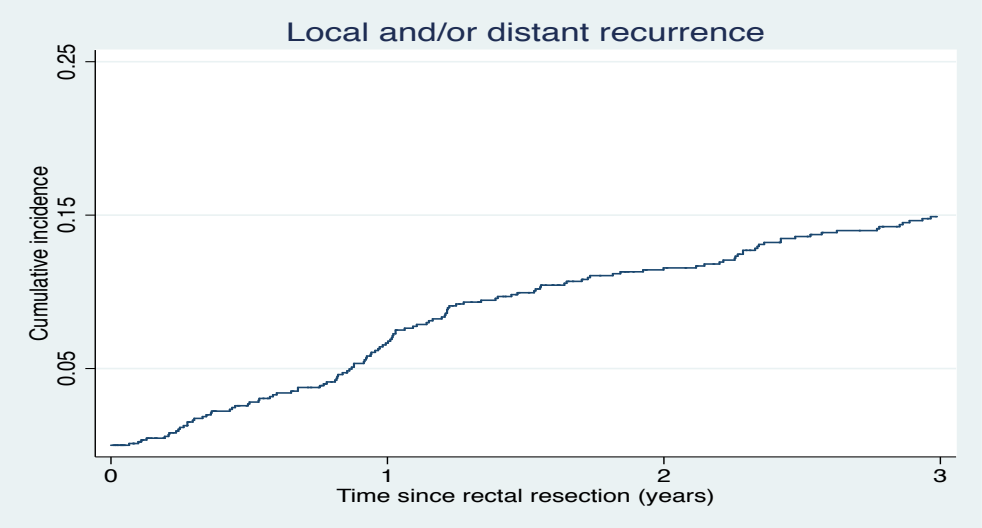


Figure 10: Cumulative incidence proportion of distant recurrence in stage I-IV rectal cancer patients during 3 years of follow-up

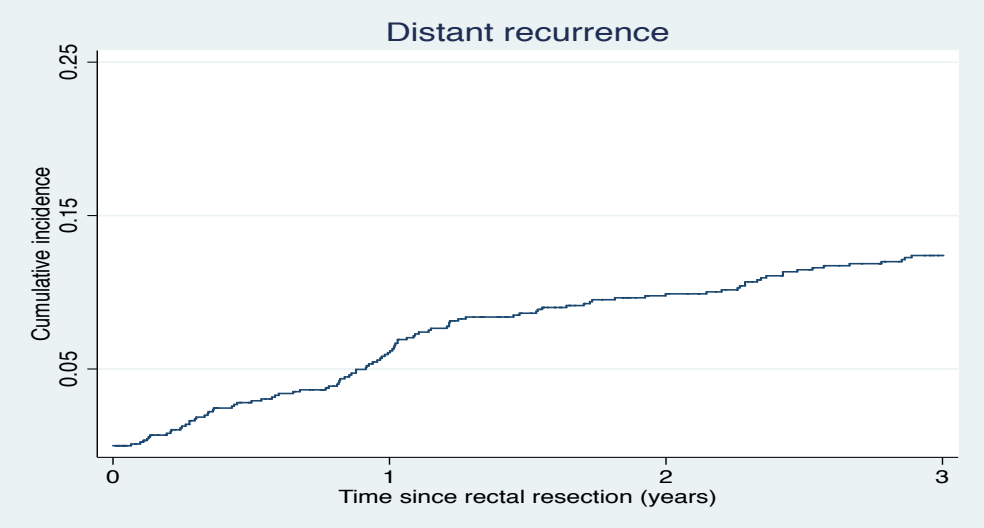
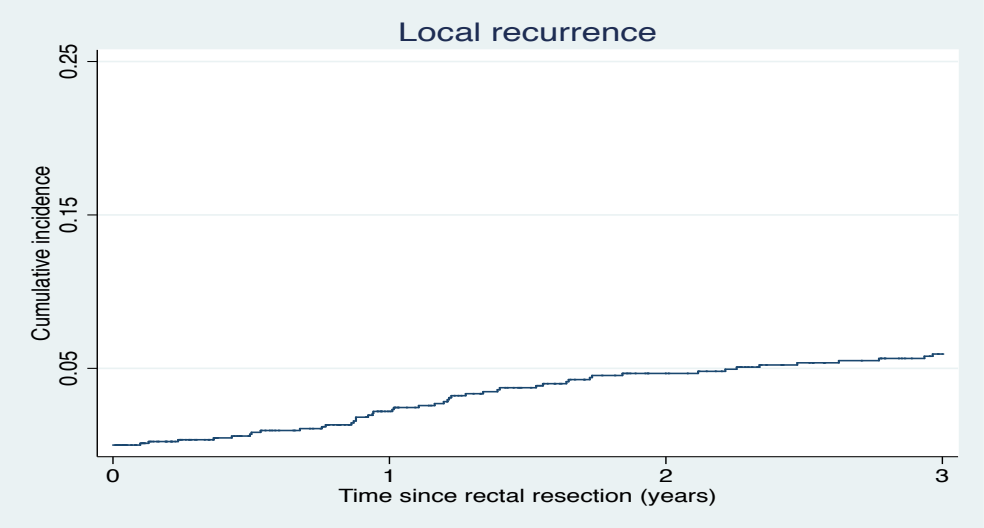


Figure 11: Cumulative incidence proportion of local recurrence in stage I-IV rectal cancer patients during 3 years of follow-up



Factors associated with particularly low CIPs of DR and LR are presented in Table 5 (see above). Statistical significant predictors of DR and LR in multivariable analysis are presented in Table 6 (see above).

II: Stoma reversal after intended restorative rectal cancer resection in Denmark. A nationwide population-based study.

Jørgensen JB, Erichsen R, Pedersen BG, Laurberg S, Iversen LH.

BJS Open 2020: In press.

In total, 6,859 rectal cancer patients underwent intended restorative rectal resection or Hartmann's operation with curative intent in Denmark between May 1 2001 and April 2012 and comprised the study cohort (Figure 3). Excluded patients are shown in Figure 1, Paper II. Interestingly, we found a general tendency towards increasing proportion of patients undergoing restorative rectal resection with DS during the study period from 29.7% (2001 - 2004) to 42.2% (2009-2012). Accordingly, we found a generally declining trend for both restorative rectal resection with no DS and Hartmann's procedure, Table 7.

Comparing patients undergoing restorative rectal resection, the use of a DS was observed more often among patients with low rectal tumours and in patients undergoing neoadjuvant CRT. Demographics, tumour characteristics and treatment regimens are summarized in Table 7.

To ensure valid estimates for stoma reversal at 3-year follow-up, 225 medical records were reviewed in a random audit by the author. Incorrect NOMESCO registration of stoma reversal in medical records during follow-up or incorrect registration of the CPR number, caused discrepancies for 7 patients (3.1%) as compared with the register-based status.

Table 7: Characteristics of 6,859 patients undergoing intended restorative rectal resection or Hartmann's operation, Denmark 2001-2012

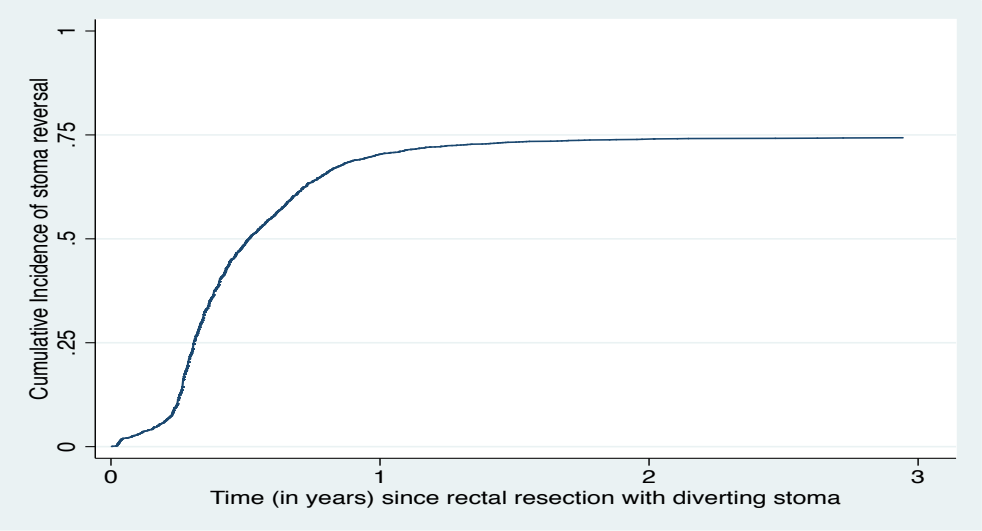
Characteristic		Rectal resection with diverting stoma n (%)	Rectal resection with no stoma n (%)	Hartmann's operation n (%)
Number		2,449 (35.7)	2,876 (41.9)	1,534 (22.4)
Period of surgery	**May 2001– Dec 2004**	677 (29.7)	979 (43.0)	620 (27.2)
	Jan 2005 – Dec 2008	865 (35.4)	1,090 (44.6)	490 (20.0)
	Jan 2009 – Apr 2012	907 (42.4)	807 (37.7)	424 (19.8)
Gender	**Male**	1,551 (63.3)	1,571 (54.6)	943 (61.5)
	Female	898 (36.7)	1,305 (45.4)	591 (38.5)
Age (years), median (range)		65 (20-91)	67 (29-97)	75 (28-94)
Charlson Comorbidity Index	**0**	2,079 (84.9)	2,390 (83.1)	1,082 (70.5)
	1-2	327 (13.4)	424 (14.7)	363 (23.7)
	+3	43 (1.8)	62 (2.2)	89 (5.8)
ASA grade	**I**	745 (30.4)	903 (31.4)	178 (11.6)
	II	1,402 (57.2)	1,567 (54.5)	789 (51.4)
	III	250 (10.2)	332 (11.5)	466 (30.4)
	IV	5 (0.2)	22 (0.8)	52 (3.4)
	Missing	47 (1.9)	52 (1.8)	49 (3.2)
UICC stage	**I**	655 (26.8)	613 (21.3)	283 (18.5)
	II	763 (31.2)	1 013 (35.2)	526 (34.3)
	III	839 (34.3)	943 (32.8)	430 (28.0)
	IV*	175 (7.2)	277 (9.6)	270 (17.6)
	Missing	17 (0.7)	30 (1.0)	25 (1.6)
Death within 3 years after surgery		394 (16.1)	551 (19.2)	661 (43.1)

* UICC stage IV rectal cancer patients had curatively intended treatment of distant metastasis along with intended restorative rectal resection or Hartmann's operation either during the index procedure or during an independent procedure in close timely relation to the index procedure.

Stoma reversal

The cumulative incidence proportion of diverting stoma reversal after 1 and 3 years restorative rectal cancer resection was 70.3% and 74.3%, respectively, (Figure 12) with a median time from the index operation to stoma reversal of 173 days. The highest 3-year CIP of stoma reversal at 80.0% was observed among patients with UICC stage I disease and the lowest CIP at 45% in patients with anastomotic leakage.

Figure 12: Cumulative incidence proportion of stoma reversal during 3 years of follow up*



*Cumulative incidence proportion was calculated treating death as competing risk

Particularly low 1 and 3 year CIPs of stoma reversal in patients undergoing intended restorative rectal cancer resection with a DS are presented in Table 8. Independent predictors of delay in time to stoma reversal in multivariable analysis are shown in Table 9.

Table 8: One and three-year cumulative incidence proportions of stoma reversal in patients undergoing intended restorative rectal cancer resection with diverting stoma, Denmark 2001-2012 (particular low CIP's are presented only)

Characteristic		CIP_1* (95% CI)	CIP_3* (95% CI)
Total		0.70 (0.68;0.72)	0.74 (0.73;0.76)
Age (y)	**>65**	-	0.72 (0.69;0.74)
ASA grade	**III-IV**	0.60 (0.54;0.66)	0.64 (0.58;0.69)
Neoadjuvant (chemo-) radiotherapy		0.64 (0.60;0.67)	0.68 (0.64;0.71)
Blood loss, intraoperative (ml)	**>300**	0.66 (0.63;0.69)	0.70 (0.67;0.73)
Anastomotic leak		0.33 (0.29;0.38)	0.45 (0.39;0.51)
(y)pT-category	**T3**	0.68 (0.65;0.71)	0.73 (0.70;0.75)
	T4	0.61 (0.50;0.70)	0.66 (0.56;0.74)
UICC stage	**III**	0.66 (0.63;0.69)	0.71 (0.68;0.74)
	IV	0.50 (0.42;0.57)	0.57 (0.50;0.64)

Table 9: Significant hazard ratios (0-3 years), of predictive characteristics associated with delay in stoma reversal for patients with intended restorative rectal cancer resection with diverting stoma, Denmark 2001-2012

Characteristic		Crude Hazard-ratio* (95%CI)	Adjusted Hazard-ratio** (95%CI)
Total		-	-
ASA grade	**I**	1.0 (ref)	1.0 (ref)
	II	0.87 (0.79;0.96)	-
	III-IV	0.75 (0.63;0.89)	-
Neoadjuvant (chemo-) radiotherapy	**Yes**	0.76 (0.69;0.85)	0.75 (0.66;0.85)
	No	1.0 (ref)	1.0 (ref)
Blood loss, intraoperative (ml)	**≤300**	1.0 (ref)	1.0 (ref)
	>300	0.80 (0.73;0.88)	0.86 (0.76;0.97)
Anastomotic leakage	**Yes**	0.42 (0.35;0.50)	0.41 (0.33;0.50)
	No	1.0 (ref)	1.0 (ref)
(y)pT-category	**T1**	1.0 (ref)	1.0 (ref)
	T2	0.83 (0.69;0.99)	-
	T3	0.63 (0.53;0.74)	0.63 (0.47;0.83)
	T4	0.51 (0.39;0.69)	0.62 (0.42;0.90)
UICC stage	**I**	1.0 (ref)	1.0 (ref)
	II	0.86 (0.76;0.97)	-
	III	0.65 (0.58;0.73)	-
	IV	0.42 (0.34;0.52)	0.57 (0.41;0.80)

* COX regression analysis. Hazard ratio (HR) <1 describes reduced "risk" of stoma reversal (i.e. the "risk" of early stoma closure is reduced when HR<1).

** Mutually adjusted

III: Pelvic insufficiency fractures are frequent after preoperative chemo-radiotherapy for rectal cancer – A nationwide MRI study

Jørgensen JB, Bondeven P, Iversen LH, Laurberg S, Pedersen BG.

Colorectal Disease. 2018; 20(10):873-80

Between April 1, 2011 and August 31, 2012, 890 patients underwent rectal cancer resection with curative intent at 10 hospitals in Denmark. In total, 403 patients had 3-year postoperative pelvic MRI and comprised the study cohort, Figure 2. Of these, 116 patients underwent neoadjuvant CRT and the frequency (28.8%) of neoadjuvant treatment was comparable to the group of patients not included for postoperative MRI (33.3%). Details regarding the study cohort are described in Results/Study 1 and illustrated in Figure 2. Patient demographics, tumour characteristics, and treatment regimens are summarised in Table 1, Paper III.

Pelvic insufficiency fractures

In total, 49 patients had PIF detected on 3-year postoperative pelvic MRI and the rate of PIF was 12.2% overall. We found a significantly increased PIF rate of 33.6% among patients undergoing preoperative radiotherapy. The rate of PIF in the non-irradiated group of patients was 3.5% (p<0.001). Risk factors significantly associated with PIF in both univariate and multivariate analysis are presented in Table 10.

The localization and anatomical distribution of pelvic insufficiency fractures as detected by 3-year pelvic MRI is shown in Figure 13. The sacrum and the ileum (near the sacroiliac articulations) were found to be the anatomical predilection sites of PIF observed in 95.9% and 91.8% of the patients, respectively.

Table 10: Risk factors significantly associated with PIF.

Characteristic		Patients with PIF n (%)	Unadjusted *p****	Adjusted OR (95% CI)*****
Number		49 (12.2)	.	.
Gender	**Male**	22 (8.7)	0.008	3.52 (1.7; 7.5)
	Female	27 (17.9)		
Age (y)	**<65**	16 (8.4)	0.032	3.20 (1.5; 6.9)
	≥65	33 (15.6)		
Distance of primary tumour from anal verge (cm)*	**0-5**	26 (26.8)	<0.001	1.75 (0.89; 3.42)
	>5-10	22 (12.8)		
	>10-15	1 (0.8)		
Neoadjuvant (chemo-) radiotherapy	**No**	10 (3.5)	<0.001	14.2 (6.1; 33.1)
	Yes	39 (33.6)		
Surgical preocedure	**PME**	5 (4.2)	<0.001	2.17 (0.71; 6.58)
	TME	14 (8.1)		
	APE	30 (26.5)		
pT/ypT-category**	**T0**	8 (50.0)	0.001	0.81 (0.56; 1.17)
	T1	3 (14.3)		
	T2	15 (12.8)		
	T3	20 (9.3)		
	T4	3 (10.3)		

OR = odds ratio, CI = confidence interval.

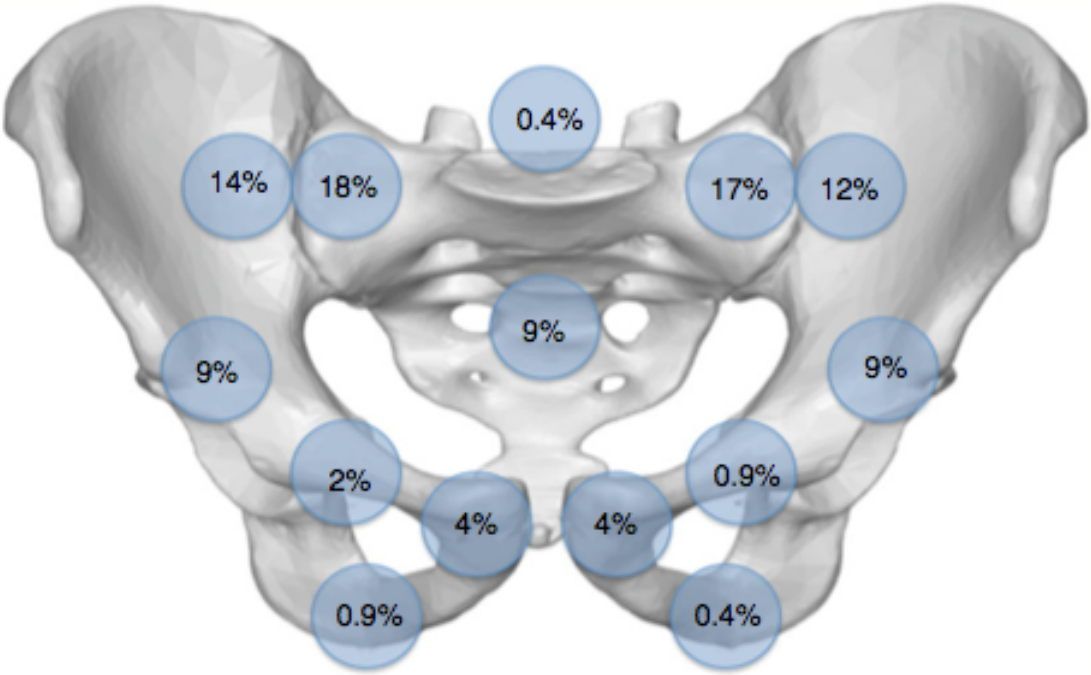
* Measured by rigid proctoscopy at pre-treatment clinical evaluation.

** Based on histopathological evaluation of excised specimen. The pathological tumour category for the 115 patients who had neoadjuvant CRT was: ypT0, 15; ypT1, 9; ypT2, 32; ypT3, 51; ypT4, 8). One patient with T0 did not receive CRT. This patient underwent local excision of the tumour prior to definitive surgery and the T-categorization here was T0.

*** Fisher's exact test.

**** Multiple logistic regression adjusted for gender, age at surgery, tumour height, surgical procedure, neoadjuvant therapy and pT/ypT-category.

Figure 13: Anatomical distribution and frequency of pelvic insufficiency fractures



Discussion

This thesis presents long-term benefits and risks of intended curative rectal cancer treatment in Denmark. Three different studies have been conducted to elucidate some common and critical challenges in the long-term postoperative course after rectal cancer treatment.

Survival

We found a 3-year OS rate of 81% and a DFS rate of 73% in UICC stage I-IV rectal cancer patients treated with intended curative resectional surgery in a well-defined Danish cohort. Excess mortality the first 12 months after diagnosis in Denmark as compared to other countries, has repeatedly been demonstrated in cohorts diagnosed between 1960's until the end of 1990's [212-214]. The present results indicate that survival rates in rectal cancer patients in Denmark are now comparable to rates observed in other Scandinavian countries with similar health systems [54] and more favorable as compared to survival estimates in OECD cancer care 2013 [215]. Present estimates are based on data from the national clinical DCCG database with a patient coverage of at least 99% since 2010 and histological verifications of the great majority of patients.

Standardization and quality assurance of mesorectal excision by training and pathological audit were implemented in previous trials to ensure that optimal surgery was performed [144, 210]. We have demonstrated favorable survival and recurrence rates for Danish patients diagnosed with rectal cancer from 2011 through 2012, after implementation of several initiatives aiming to improve outcome of rectal cancer therapy nationally. During the last two decades, a national strategy has been initiated with centralisation of surgery from 47 to 15 surgical departments involved in rectal cancer treatment in Denmark. Additionally, the implementation of mesorectal excision surgery and national guidelines for rectal cancer treatment, repeated postgraduate multidisciplinary training and teaching programmes, specialization of personnel involved in MDT (colorectal surgeons, oncologists, pathologists, and dedicated radiologists), and establishment of continuous data reporting to a national database, has markedly optimised outcome of rectal cancer [1, 3].

UICC stage IV disease was the most important predictor for decreased overall survival with a three times higher risk of death during follow-up as compared to UICC stage I-III patients

(HR 3.27). Other independent patient-related predictors for decreased 3-year OS were age >65 years (1 in 4 patients dying during follow-up), ASA grade III-IV (1 in 3 patients dying during follow-up), and Charlson comorbidity index ≥2 (1 in 3 patients dying during follow-up), all of which are not surprising findings in the view of their life-threatening character.

Recurrence

The observed 3-year DR rate of 12.8% and LR rate of 6.5% are low rates [25, 54, 58]. With inclusion of a 3-year pelvic MRI, the LR rate was increased by 16% (from 5.6% to 6.5%). Reported LR rates in the modern era of rectal cancer treatment with mesorectal excisional surgery and neoadjuvant CRT are highly variable ranging from 4% to 14% [54, 216, 217].
UICC stage IV disease was the most important predictor for recurrence with a DR rate of 46% and LR rate of 13%. Charlson comorbidity index ≥2 was the only patient-related risk factor predictive of recurrence in multivariate analysis and increased the risk of both DR and LR significantly. The negative impact of comorbidity on recurrence may be due to suboptimal oncological treatment in patients with excessive chronic illness due to either omission or interruption of neoadjuvant CRT, and/or compromised surgery with less central ligation and less extensive mesorectal excision (confounding-by-indication). Alternatively, comorbidity may increase the risk of recurrent disease per se, and comorbidity obviously has negative impact on survival.

Internationally, PME surgery and omission CRT for cancer in the upper rectum have resulted in poor outcomes with LR rates between 9% and 16% [141, 143, 216, 218]. Results from the present study confirm these findings with a significantly increased LR rate of 11.0% in patients undergoing PME surgery. Data from the DCCG reveals a tendency to overestimate tumour height in the rectum by rigid proctoscopy with preoperative MRI as reference [48]. The differentiation between mid or upper rectum has a significant impact on the treatment regimen (see Table 2). Furthermore, radiological evidence of residual or inadvertent mesorectum has been observed in 63% to 74% of patients undergoing PME surgery, indicating suboptimal quality of the surgery performed [63, 141-143]. These findings may partly explain the higher incidence of LR in patients undergoing PME surgery for rectal cancer.

In previous studies, R1 resection with CRM involvement (margin <1mm) is negatively associated with outcome of curatively intended rectal cancer treatment [79, 219-221]. In the present study, a significantly increased DR rate of 35% and a LR rate of 20% were observed after 3 years, including a markedly decreased OS rate of 63%.

Thus, present study suggests that the outcome of rectal cancer is hampered due to particularly two specific determinants: the proportion of patients presenting with UICC stage IV disease and the management of patients with severe comorbidity. Therefore, efforts aiming to decrease their proportions should be addressed. Furthermore, R0 resection is critically important both to reduce recurrence rates and improve survival.

Since implementation of a national colorectal cancer screening programme in March 2014, data from the DCCG indicates a permanent reduction in the proportion of patients with UICC stage IV disease [41, 222]. The proportion of UICC stage IV disease has decreased from 23% in 2012 (study period in Paper I) [46] to 16% in 2018 [41], according to annual DCCG reports. Additionally, reported data in study I, indicates that survival has markedly improved following curatively intended treatment of UICC stage IV disease, with a 3-year OS of 59% (Table 5). An additional gain may be achieved through reduction of patient delay by increased symptom awareness, and equally important, developing an understanding of when to act on these symptoms [223, 224].

The negative impact of comorbidity in an aging population may be addressed by optimization of surgical decision-making, and efforts should be directed against evaluation of the adequateness of pre-, intra-, and postoperative therapy. Traditional approaches have targeted the postoperative period for rehabilitation and lifestyle changes. However, recent evidence shows that the preoperative period might be the optimal moment for intervention with smoking cessation, psychological coping, individualized training programmes, and nutritional support [225, 226]. Multimodal prehabilitation may improve functional capacity and reduce postoperative complication rates in extensively comorbid rectal cancer patients, resulting in improved OS [225].

Surveillance in rectal cancer has repeatedly failed to prove any impact on rectal cancer outcome and has primarily been focused on detection of recurrent disease [227-230]. However, in the present study, nearly two thirds of the patients dying within 3 years of follow-up had no sign of recurrence. The effect of various surveillance programmes may remain limited, as the majority of patients dying within 3 years of rectal cancer treatment will not die from recurrence of disease.

Three-year postoperative pelvic MRI of 403 patients, revealed a previously undetected LR in 8 patients only. Accordingly, number needed to examine was 50 patients to detect 1 extra patient with LR. Further, considering that only 40% of patients diagnosed with LR will be potential candidates for curatively intended surgery, 3-year pelvic MRI may be a poor investment. As the majority of patients with LR were diagnosed between 12 and 24 months after surgery, the best possible timing of pelvic MRI may be approximately 12 months postoperatively in order to detect non-symptomatic LR's. Considering that it may be possible to diagnose LR in an early stage, the rate of possible candidates for curatively intended surgery may increase above 40%.

Stoma reversal

Approximately 45% of patients undergoing intended restorative rectal resection in Denmark between 2001 and 2012 had a DS and only 74% of these patients had their stoma reversed during 3 years of follow-up. In previous multicenter studies investigating stoma reversal rates in rectal cancer patients, the reported permanent stoma rate after intended restorative rectal resection together with a DS is similar to our findings with a risk of 17-25% [12, 13, 18, 20]. However, these studies are few and obvious differences in baseline characteristics of the patient cohorts may lead to non-comparable results [13, 18, 20]. In a recent Swedish retrospective multicenter study 3,564 patients underwent restorative rectal cancer resection with a DS. Stoma reversal was performed in 2,954 (82.9%) patients during 1.5 years of follow-up. However, the follow-up was short and information on stoma use at index surgery was unavailable, and the study included no validation on clinical information from Swedish registries [12]. The total number of patients undergoing restorative rectal cancer resection is unknown and, accordingly, the proportion of patients undergoing restorative rectal resection unspecified.

Accordingly, results from previous studies cannot be extrapolated directly as the inclusion period; baseline characteristics of the cohorts, type and use of diverting stomas at index surgery, and period of follow-up are differing.

Risk factors for stoma non-reversal within 3 years in present study were all of anastomotic leakage, advanced UICC stage IV, T category 4, T category 3, use of neoadjuvant CRT, and perioperative blood loss > 300 ml. Consistently, previous studies have found that increasing age and comorbidity [13, 15, 20, 21, 23], advanced T category and UICC stage [14, 15, 19, 20], any postoperative complications [14, 15, 18, 20] and anastomotic leakage [17, 19, 21] increase the probability of a permanent stoma after rectal cancer resection.

Interestingly, our study, including patients undergoing restorative rectal cancer resection or Hartmann's operation, revealed an increasing proportion of patients with a DS from 2001-2004 to 2009-2012, with a 30% rate in the early period to a 42% rate in the late period. Similarly, the proportions of patients undergoing restorative rectal resection without a DS or Hartmann's operation decreased. Revision of national guidelines in 2009 and methodological alignment between departments are the most obvious explanations for this general change in surgical approach, and suggest that surgeons may be increasingly more cautious for anastomotic leakage following restorative rectal cancer resection and thus, defunction with a DS. However, according to DCCG data, anastomotic leakage rates following rectal cancer resection in Denmark were increasing from 2001 (11.0%) to 2012 (15.6%) [46, 231].

Furthermore, recent studies from the Netherlands of patients undergoing restorative rectal cancer resection with DS found no difference in the short-term postoperative complication rates between routine use and highly selective use of a DS [157, 158]. Findings from present study suggest that selection of specific patient groups for stoma construction may be a key element in optimizing long-term patient outcomes. Thus, the future trend may likely change toward a more selective approach to DS construction during index surgery.

Pelvic insufficiency fractures

Study III reports the 3-year rate of pelvic insufficiency fractures in patients undergoing curatively intended rectal cancer treatment in Denmark. The main finding was an unexpectedly high PIF-rate of 33.6% in patients undergoing neoadjuvant CRT followed by

mesorectal excision surgery. In the group of patients treated with surgery alone, the corresponding PIF rate was 3.5% only, which is equivalent to rates in the background population [232]. Despite technological advances with development of modern intensity modulated radiotherapy, we have demonstrated a risk of PIF following CRT that markedly exceeds the expected level of 3-11% in literature [190, 201, 202]. As MRI constitutes a particularly sensitive tool in detection of PIF, the consequent use of MRI in study III with sequences (STIR) that are specifically suitable in detecting PIF (i.e. bone marrow oedema) may likely explain the difference between detection rates of PIF in previous studies and the present study [37].

In previous studies, reported predisposing conditions for development of PIF is primarily osteoporosis and radiotherapy, including a number of medical conditions associated with development of osteoporosis. Thus, elderly postmenopausal women constitute a group of patients particularly vulnerable to PIF [189, 190, 233]. Accordingly, in present study, independent risk factors for PIF were female gender (OR=3.52), age above 65 (OR=3.20), and preoperative CRT (OR=14.20).

Consistent with observations in other studies of PIF, the anatomical predilection sites were found in the sacrum and the medial part of os ileum near the sacroiliac articulations, which are the weight-bearing parts of the pelvic ring. Performing specific MRI sequences with identification of characteristic patterns in specific areas of the pelvic ring will assist in differentiating PIF from LR in rectal cancer patients with pelvic pain. MRI examination in patients who are examined on suspicion of recurrence should include bone-specific sequences, as PIF may be the only (visible) explanation for their pain. Many patients will be able to cope with their symptoms, if they are thoroughly examined for recurrence of disease. Future MRI studies combined with QoL assessment are needed to evaluate pelvic pain in relation to PIF in patients treated for rectal cancer.

New regimens for neoadjuvant therapy may have potential to reduce the risk of PIF. Preoperative 3 arc volumetric arc therapy (intensity modulated radiotherapy) has demonstrated pronounced bone sparing capacity and proton beam therapy have the potential

to further lower doses [234]. However, precise dose planning would lower the exposure of pelvic bones regardless of the applied technique [234].

Conclusions

In summary, this thesis presents favorable three-year outcome of intended curative rectal cancer treatment in Denmark with high OS and low recurrence rates for UICC stage I-IV patients diagnosed from 2011 through 2012. However, less advantageous long-term outcome has been demonstrated in patients undergoing intended restorative rectal cancer treatment with a concerning high permanent stoma rate. Furthermore, neoadjuvant CRT in curatively intended treatment of rectal cancer is associated with a surprisingly high risk of PIF during 3 years of follow-up. Potential risk factors for poor 3-year outcome of rectal cancer treatment in all three studies were specifically related to patient age and comorbidity (low OS, high recurrence rates, and high PIF rates), neoadjuvant CRT (non-reversal of DS and high PIF rates) and UICC stage IV (low OS, high recurrence rates, and non-reversal of DS).

Specific conclusions:

- Intended curative treatment of rectal cancer including UICC stage IV conveys a high 3-year OS and low DR and LR rates. The main risk factors of poor outcome are UICC stage IV and Charlson comorbidity index ≥2.

- One quarter of rectal cancer patients undergoing intended restorative resection had not their diverting stoma reversed within 3 years after surgery. The permanent stoma rate increased more than 100% if patients developed anastomotic leakage postoperatively.

- Neoadjuvant CRT in the treatment of rectal cancer was associated with a 14 times higher risk of PIF after 3 years, whereas female gender and age above 65 years each tripled the risk of PIF detected by MRI.

Perspective

Treatment of rectal cancer is constantly changing with optimized principles of surgery; technical advances in radiotherapy, modified imaging modalities, and improved pathological and immunohistochemical audits of the specimen. These changes are further driven forward by the implementation of colorectal cancer screening in the general population, an increased focus on non-surgical management of rectal caner in patients with pCR after neoadjuvant treatment, increasing use of minimally invasive surgical techniques, investigation of the potential of circulating tumour DNA in diagnosis and surveillance of rectal cancer, and trials examining the role of preoperative chemotherapy as a potential successor to preoperative radiotherapy.

The most optimal strategy to reduce the rectal cancer burden is primary prevention of disease with a lowering of its incidence. The incidences may decline with continuous efforts to improve unfavourable and characteristic lifestyle in the Western populations in addition to the positive effects already seen after implementation of the national CRC screening programme. Therapeutic delay has been reduced by several initiatives from the National Board of Health since the introduction of 'the National Cancer Plan' in 2000, and the two-week waiting time guarantee from diagnosis to treatment and fast track cancer packages introduced by the Government (latest revision in 2012).

In rectal cancer surgery, patient age and comorbidity determines the number and severity of complications and predicts poor oncological outcome as it is closely related to preoperative functional capacity, nutritional state and psychological reserve. Recent studies show that the preoperative period may be the optimal moment for intervention (prehabilitation) in comorbid and elderly patients contrary to traditional approaches targeting the postoperative period for rehabilitation and lifestyle changes. A randomised controlled trial is initiated to explore possible benefits of multimodal prehablitation as determined by effect on complication rates and survival[225, 235], among others.

On-going randomised controlled trials [112, 113] are investigating the effect of neoadjuvant chemotherapy on recurrence of rectal cancer. The main hypothesis is that compared to

neoadjuvant CRT, neoadjuvant chemotherapy reduces the rate of distant recurrence without increasing the rate of local recurrence. Furthermore, surgical and medical complications, the functional outcome, toxicity and QoL may be improved if radiotherapy can be avoided. Avoidance of radiotherapy, potentially leading to reduced complication rates, may additionally increase the number of patients capable of receiving postoperative oncological treatment. However, according to findings in the present study, the effect of chemotherapy may be limited, as the majority of patients dying within 3 years of rectal cancer treatment will not die from recurrence of disease. Further, among those dying within 3 years after surgery the majority die from comorbidity, which will limit these patients from receiving chemotherapy at all.

Moreover, patients undergoing preoperative RT are exposed to a particularly high risk of postoperative complications, increasing both mortality and long-term adverse events. Neoadjuvant preoperative chemotherapy with omission of RT, may potentially reduce postoperative complications in these patients leading to increased survival and reduced rates of long-term adverse events. Yet another concern may be that neoadjuvant CRT is a greater burden for patients with advanced comorbidity, resulting in a higher mortality. Data are biased by confounding by indication, restraining possibilities of interpretation of causal relationships.

In selected groups of UICC stage I patients unable to undergo surgery (i.e. due to high age or advanced comorbidity), however, neoadjuvant CRT provides various potential advantages. It allows for early re-assessment of disease by MDT, and may potentially enable the consideration of organ preservation by allowing for more effective local excision and non-operative management strategies. In light of various watchful waiting protocols evaluating deferral of surgery after radiation therapy of early rectal cancers, pelvic MRI may in future not only be a useful tool to monitor the effect of treatment or the presence of local recurrence, but may also be a useful tool for the evaluation of more gentle ways to irradiate rectal tumours.

There is an urgent need in future studies to explore new methods of surveillance in rectal cancer patients, as previous studies evaluating various surveillance programmes, has found no impact on colorectal cancer outcome [227, 229, 230]. The COLOFOL trial[236], investigating

the impact of frequent CT scans in addition to the normal surveillance programme, found no significant effect on DR. In the present study, we found that additional pelvic MRI had only limited effect on detection of LR. The on-going FURCA trial [230], investigates the effect of patient-led follow-up based on patient education and self-referral, with recurrence as primary outcome. The IMPROVE-IT2 trial [171, 172] investigating circulating tumour DNA guided post-operative surveillance, may result in earlier detection of recurrent disease and identify more patients eligible for curative treatment. This method of surveillance may potentially provide information about radicality of the primary resection, response to adjuvant therapy, incipient recurrence and response to treatment performed in relation to diagnosis of recurrence. However, the findings in the present study suggest that high attention should primarily be paid to reduce comorbidity, as the majority of patients dying within 3 years have no sign of recurrence.

Patients undergoing preoperative RT with the current modalities of intensity-modulated radiotherapy are prone to develop PIF with multiple fracture sites, as detected by pelvic MRI at 3-year postoperative follow-up. A more selective use of CRT, precise dose planning, and new technologies, including proton beam therapy, have potential to increase the bone sparing capacity with further lowering of doses. We await results to be validated in larger and preferably prospective cohorts [234].

Summary

This dissertation is based on three original articles, two of which have been accepted and/or published in international scientific journals and a third is in preparation for submission. The papers have not previously been included in a dissertation. The work was funded by the Danish Cancer Society and performed between 2014 and 2020 while the author was employed at Department of Surgery, Aarhus University Hospital / Regional Hospital Randers.

This thesis presents long-term benefits, risks and adverse events 3 years after intended curative rectal cancer treatment in Denmark. The papers I-III contain an evaluation of 3-year survival and recurrence, and attempts to illuminate important adverse events related to rectal cancer treatment, affecting the overall outcome.

Rectal cancer constitutes one third of colorectal cancers, and the incidence in Denmark have been declining since the implementation of a national screening programme in 2014. We have demonstrated favorable survival and recurrence rates for Danish patients diagnosed with rectal cancer from 2011 through 2012, after implementation of several initiatives aiming to improve outcome of rectal cancer therapy nationally. In study I, we found a high 3-year OS of 81% and a low risk of DR (12.8%) and/or LR (6.5%) in UICC stage I-IV rectal cancer patients treated with intended curative resectional surgery in a well-defined Danish cohort.

In study II, we found that only 74% of UICC stage I-IV patients undergoing intended restorative rectal cancer resection in Denmark between 2001 and 2012 had their stoma reversed during 3 years of follow-up.

In study III, an unexpectedly high PIF-rate of 33.6% was detected by 3-year postoperative MRI, in patients undergoing neoadjuvant CRT followed by curatively intended mesorectal excision surgery, in a well-defined Danish cohort, between April 2011 and August 2012.

Summary in Danish (Dansk resumé)

Denne afhandling er baseret på tre originalarbejder, hvoraf to er blevet accepteret og / eller publiceret i internationale videnskabelige tidsskrifter og en tredje klar til submission. Arbejderne er ikke tidligere inkluderet i en afhandling. Arbejdet er finansieret af Kræftens Bekæmpelse og udført mellem 2014 og 2020, mens forfatteren var ansat på Kirurgisk Afdeling, Aarhus Universitetshospital / Regionshospitalet Randers.

Afhandlingen præsenterer langsigtede fordele, risici og bivirkninger 3 år efter intenderet kurativ behandling af endetarmskræft i Danmark. Arbejderne I-III indeholder en evaluering af 3-års overlevelse og recidiv, og belyser desuden bivirkninger relateret til behandling af endetarmskræft som har stor betydning for patienters livskvalitet og dermed afgørende betydning for det samlede resultat af behandlingen.

Endetarmskræft udgør en tredjedel af det samlede antal tilfælde af tyk- og endetarmskræft, og forekomsten i Danmark har været faldende siden implementeringen af et nationalt screeningsprogram i 2014. Vi har påvist gunstige overlevelse- og recidiv rater for danske patienter, der er diagnosticeret med endetarmskræft i 2011 og 2012, efter implementering af flere initiativer, der sigter mod at forbedre resultaterne af endetarmskræft behandling nationalt.

Studie I viser en høj 3-års overlevelse på 81% og en lav risiko for fjern recidiv (12,8%) og / eller lokal recidiv (6,5%) i UICC stadie I-IV endetarmskræftpatienter behandlet med intenderet kurativ resektion i en veldefineret dansk kohorte.

Studie II viser, at kun 74% af UICC stadie I-IV patienter, der gennemgår intenderet restorativ resektion for endetarmskræft i Danmark mellem 2001 og 2012, fik deres stomi lagt tilbage i løbet af 3 års opfølgning.

Studie III beskriver en uventet høj insufficiensfraktur rate på 33,6% påvist ved 3 års postoperativ MR skanning af bækkenet hos patienter, der gennemgik neoadjuverende kemo-stråleterapi efterfulgt af kurativt intenderet mesorektal excision, i en veldefineret dansk kohorte, mellem april 2011 og august 2012.

References

1. Iversen, L.H., et al., *Improved survival of colorectal cancer in Denmark during 2001-2012 - The efforts of several national initiatives.* Acta Oncol, 2016. **55 Suppl 2**: p. 10-23.
2. Bulow, S., et al., *Improved survival after rectal cancer in Denmark.* Colorectal Dis, 2010. **12**(7 Online): p. e37-42.
3. Iversen, L.H., *Aspects of survival from colorectal cancer in Denmark.* Dan Med J 2012. **59**: p. B4428.
4. Poulsen, L.O., et al., *Local recurrence rate in a national Danish patient cohort after curative treatment for rectal cancer.* Acta Oncol, 2018. **57**(12): p. 1639-1645.
5. Matthiessen, P., et al., *Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial.* Ann Surg, 2007. **246**(2): p. 207-14.
6. Gastinger, I., et al., *Protective defunctioning stoma in low anterior resection for rectal carcinoma.* Br J Surg, 2005. **92**(9): p. 1137-42.
7. Karanjia, N.D., et al., *Risk of peritonitis and fatal septicaemia and the need to defunction the low anastomosis.* Br. J. Surg., 1991. **78**: p. 196-1 98.
8. Marusch, F., et al., *Value of a Protective Stoma in Low Anterior Resections for Rectal Cancer.* Dis Colon Rectum, 2002. **45**: p. 1164-1171.
9. Dehni, N., et al., *Influence of a defunctioning stoma on leakage rates after low colorectal anastomosis and colonic J pouch–anal anastomosis.* British Journal of Surgery, 1998. **85**: p. 1114–1117.
10. Chow, A., et al., *The morbidity surrounding reversal of defunctioning ileostomies: a systematic review of 48 studies including 6,107 cases.* Int J Colorectal Dis, 2009. **24**(6): p. 711-23.
11. (DCCG), D.C.C.G. *Guidelines for the diagnosis and the management of colorectal cancer (in Danish)* 2009; 4:[Available from: https://dccg.dk/wp-content/uploads/2017/08/Retningslinier2009revOKT2010.pdf.
12. Gustafsson, C.P., et al., *Loop-ileostomy reversal-patient-related characteristics influencing time to closure.* Int J Colorectal Dis, 2018. **33**(5): p. 593-600.

13. David, G.G., et al., *Loop ileostomy following anterior resection: is it really temporary?* Colorectal Dis, 2010. **12**(5): p. 428-32.
14. Gessler, B., E. Haglind, and E. Angenete, *Loop ileostomies in colorectal cancer patients--morbidity and risk factors for nonreversal.* J Surg Res, 2012. **178**(2): p. 708-14.
15. Pan, H.D., et al., *Risk Factors for Nonclosure of a Temporary Defunctioning Ileostomy Following Anterior Resection of Rectal Cancer.* Dis Colon Rectum, 2016. **59**: p. 94–100.
16. Lordan, J.T., et al., *Following anterior resection for rectal cancer, defunctioning ileostomy closure may be significantly delayed by adjuvant chemotherapy: a retrospective study.* Colorectal Dis, 2007. **9**(5): p. 420-2.
17. Dinnewitzer, A., et al., *Cumulative Incidence of Permanent Stoma After Sphincter Preserving Low Anterior Resection of Mid and Low Rectal Cancer.* Dis Colon Rectum, 2013. **56**: p. 1134–1142.
18. den Dulk, M., et al., *A multivariate analysis of limiting factors for stoma reversal in patients with rectal cancer entered into the total mesorectal excision (TME) trial: a retrospective study.* The Lancet Oncology, 2007. **8**(4): p. 297-303.
19. Bailey, C.M.H., et al., *The incidence and causes of permanent stoma after anterior resection.* Colorectal Disease, 2003. **5**: p. 331–334.
20. Lindgren, R., et al., *What is the risk for a permanent stoma after low anterior resection of the rectum for cancer? A six-year follow-up of a multicenter trial.* Dis Colon Rectum, 2011. **54**(1): p. 41-7.
21. Chiu, A., et al., *Failing to reverse a diverting stoma after lower anterior resection of rectal cancer.* Am J Surg, 2014. **207**(5): p. 708-11; discussion 711.
22. Maggiori, L., et al., *Conservative management is associated with a decreased risk of definitive stoma after anastomotic leakage complicating sphincter-saving resection for rectal cancer.* Colorectal Dis, 2011. **13**(6): p. 632-7.
23. Kairaluoma, M., et al., *Outcome of Temporary Stomas.* Dig Surg, 2002. **19**: p. 45–51.
24. O'Leary, D.P., et al., *Quality of life after low anterior resection with total mesorectal excision and temporary loop ileostomy for rectal carcinoma.* British Journal of Surgery, 2001. **88**: p. 1216-1220.

25. Sebag-Montefiore, D., et al., *Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial.* Lancet, 2009. **373**: p. 811–20.
26. Sauer, R., et al., *Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer.* N Engl J Med, 2004. **351**(17): p. 1731-40.
27. Kapiteijn, E., C.A.M. Marijnen, and I.D. Nagtegaal, *Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer.* N Engl J Med, 2001. **345**: p. 638-46.
28. van Gijn, W., et al., *Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial.* The Lancet Oncology, 2011. **12**(6): p. 575-582.
29. Marijnen, C.A., et al., *Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial.* J Clin Oncol, 2005. **23**(9): p. 1847-58.
30. Birgisson, H., et al., *Late adverse effects of radiation therapy for rectal cancer - a systematic overview.* Acta Oncol, 2007. **46**(4): p. 504-16.
31. Pollack, J., et al., *Late adverse effects of short-course preoperative radiotherapy in rectal cancer.* Br J Surg, 2006. **93**(12): p. 1519-25.
32. Dahlberg, M., et al., *Preoperative Irradiation Affects Functional Results After Surgery for Rectal Cancer.* Dis Colon Rectum, 1998. **41**(5): p. 543-49.
33. Peeters, K.C., et al., *Risk factors for anastomotic failure after total mesorectal excision of rectal cancer.* Br J Surg, 2005. **92**(2): p. 211-6.
34. Marijnen, C.A.M., et al., *Acute Side Effects and Complications After Short-Term Preoperative Radiotherapy Combined With Total Mesorectal Excision in Primary Rectal Cancer: Report of a Multicenter Randomized Trial.* Journal of Clinical Oncology, 2002. **20**(3): p. 817-25.
35. Bregendahl, S., et al., *Bowel dysfunction after low anterior resection with and without neoadjuvant therapy for rectal cancer: a population-based cross-sectional study.* Colorectal Dis, 2013. **15**(9): p. 1130-9.
36. Mammone, J.E. and M.E. Schweitzer, *MRI of occult sacral insufficiency fractures following radiotherapy.* Skeletal Radiol, 1995. **24**: p. 101-104.

37. Blomlie, V., et al., *Incidence of Radiation-Induced Insufficiency Fractures of the Female Pelvis: Evaluation with MR Imaging.* Am Journal of Radiology, 1996. **167**: p. 1205–10.
38. Brahme, S.K., et al., *Magnetic resonance appearance of sacral insufficiency fractures.* Skeletal Radiol, 1990. **19**: p. 489-493.
39. Cabarrus, M.C., et al., *MRI and CT of insufficiency fractures of the pelvis and the proximal femur.* AJR Am J Roentgenol, 2008. **191**(4): p. 995-1001.
40. Cancer, I.A.f.R.o. *Cancer today*. World Health Organisation (WHO) 2018; Available from: https://gco.iarc.fr/today/fact-sheets-cancers.
41. (DCCG), D.C.C.G. *Annual report (in Danish)*. 2018; Available from: https://dccg.dk/wp-content/uploads/2019/09/DCCG-%C3%85rsrapport-2018.pdf.
42. van de Velde, C.J., et al., *EURECCA colorectal: multidisciplinary management: European consensus conference colon & rectum.* Eur J Cancer, 2014. **50**(1): p. 1 e1-1 e34.
43. (DCCG), D.C.C.G., *Annual report (in Danish)*. 2013.
44. (DCCG), D.C.C.G. *Annual report (in Danish)*. 2014; Available from: https://dccg.dk/wp-content/uploads/2017/10/Aarsrapport_2014.pdf.
45. (DCCG), D.C.C.G. *Annual report (in Danish)*. 2011; Available from: https://dccg.dk/wp-content/uploads/2017/10/Aarsrapport_2011.pdf.
46. (DCCG), D.C.C.G. *Annual report (in Danish)*. 2012; Available from: https://dccg.dk/wp-content/uploads/2017/10/Aarsrapport_2012.pdf.
47. (DCCG), D.C.C.G. *Annual report (in Danish)*. 2015; Available from: https://dccg.dk/wp-content/uploads/2017/10/Aarsrapport_2015.pdf.
48. (DCCG), D.C.C.G. *Annual report (in Danish)*. 2016; Available from: https://dccg.dk/wp-content/uploads/2017/10/Aarsrapport_2016.pdf.
49. (DCCG), D.C.C.G. *Annual report (in Danish)*. 2017; Available from: https://dccg.dk/wp-content/uploads/2019/03/DCCG-%C3%85rsrapport-2017v2.pdf.
50. Galandiuk, S., et al., *Patterns of recurrence after curative resection of carcinoma of the colon and rectum.* Surg Gyn & Obstetrics
, 1992. **174**: p. 27-32.
51. Anthony, T., et al., *Practice parameters for the surveillance and follow-up of patients with colon and rectal cancer.* Dis Colon Rectum 2004. **47**(6): p. 807-17.

52. Wibe, A., et al., *A National Strategic Change in Treatment Policy for Rectal Cancer—Implementation of Total Mesorectal Excision as Routine Treatment in Norway. A National Audit.* Dis Colon Rectum, 2002. **45**(7): p. 857-66.
53. Martling, A., et al., *Impact of a surgical training programme on rectal cancer outcomes in Stockholm.* Br J Surg, 2005. **45**(7): p. 225-229.
54. Glimelius, B., et al., *Two countries – Two treatment strategies for rectal cancer.* Radiotherapy and Oncology, 2016. **121**(3): p. 357-363.
55. Cedermark, B., et al., *Improved survival with preoperative radiotherapy in resectable rectal cancer: Swedish rectal cancer trial.* N Engl J Med, 1997. **336**(14): p. 980-87.
56. Gerard, J.P., et al., *Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203.* J Clin Oncol, 2006. **24**(28): p. 4620-5.
57. Bosset, J.F., et al., *Chemotherapy with Preoperative Radiotherapy in Rectal Cancer.* N Engl J Med, 2006. **355**: p. 1114-23.
58. Peeters, K.C., et al., *The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma.* Ann Surg, 2007. **246**(5): p. 693-701.
59. Brierley, J., M.K. Gospodarowicz, and C. Wittekind, *TNM classification of malignant tumours. Eighth edition. ed.* Chichester, West Sussex, UK ; Hoboken, NJ: John Wiley & Sons, Inc., 2017.
60. Brown, G., et al., *Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging.* Br J Surg 2003. **90**(3): p. 355–64.
61. Brown, G., et al., *High-resolution MRI of the anatomy important in total mesorectal excision of the rectum.* AJR Am J Roentgenol 2004. **182**(2): p. 431-439.
62. Beets-Tan, R.G., *MRI in rectal cancer: the T stage and circumferential resection margin.* Colorectal Dis, 2003. **5**(5): p. 392–5.
63. Bondeven, P., et al., *Impact of a multidisciplinary training programme on outcome of upper rectal cancer by critical appraisal of the extent of mesorectal excision with postoperative MRI.* BJS Open, 2019.
64. Battersby, N.J., et al., *Prospective Validation of a Low Rectal Cancer Magnetic Resonance Imaging Staging System and Development of a Local Recurrence Risk Stratification Model: The MERCURY II Study.* Ann. Surg. , 2016. **263**: p. 751–760.

65. Patel, U.B., et al., *MRI after treatment of locally advanced rectal cancer: how to report tumour response - the MERCURY experience.* AJR Am J Roentgenol, 2012. **199**(4): p. 486-495.
66. Battersby, N.J., et al., *MR imaging for rectal cancer: The role in staging the primary reponse to neoadjuvant therapy.* Expert Rev Gastroenterol Hepatol, 2014. **8**(6): p. 703-719.
67. Merkel, S., et al., *The prognostic inhomogeneity in pT3 rectal carcinomas.* Int J Colorectal Dis 2001. **16**(5): p. 298-304.
68. Willett, C.G., et al., *Prognostic factors in stage T3N0 rectal cancer: do all patients require postoperative pelvic irradiation and chemotherapy?* . Dis Colon Rectum, 1999. **42**(2): p. 167-173.
69. Steel, M.C., et al., *Extent of mesorectal invasion is a prognostic indicator in T3 rectal carcinoma.* ANZ J Surg, 2002. **72**(7): p. 483-487.
70. Miyoshi, M., et al., *Extent of mesorectal tumor invasion as a prognostic factor after curative surgery for T3 rectal cancer patients.* Ann Surg, 2006 **243**(4): p. 492-498.
71. MERCURY, S.G., *Extramural depth of tumor invasion at thin-section MR in patients with rectal cancer: results of the MERCURY study.* Radiology 2007. **243**(1): p. 132-139.
72. Pedersen, B.G., et al., *Reproducibility of depth of extramural tumor spread and distance to circumferential resection margin at rectal MRI: enhancement of clinical guidelines for neoadjuvant therapy.* AJR Am J Roentgenol, 2011. **197**(6): p. 1360-6.
73. Lahaye, M.J., et al., *Imaging for Predicting the Risk Factors—the Circumferential Resection Margin and Nodal Disease—of Local Recurrence in Rectal Cancer: A Meta-Analysis.* Seminars in Ultrasound, CT and MRI, 2005. **26**(4): p. 259-268.
74. Frykholm, G.J., L. Påhlman, and B. Glimelius, *Combined chemo- and radiotherapy vs. radiotherapy alone in the treatment of primary, nonresectable adenocarci- noma of the rectum.* Int J Radiat Oncol Biol Phys 2001. **50**(2): p. 427–34.
75. Fernandez-Acenero, M.J., et al., *Prognostic influence of histopathological regression patterns in rectal adenocarcinoma receiving neoadjuvant therapy.* J Gastrointest Oncol 2017. **8**(1): p. 49-54.

76. Blomqvist, L., et al., *Rectal tumours – MR imaging with endorectal and/or phased-array coils, and histopathological staging on giant sections. A comparative study.* . Acta Radiol 1997. **38**(3): p. 437–44.
77. group, M.s., *Diagnostic accuracy of preoperative magnetic resonance imagination in predicting curative resection of rectal cancer: prospective observational study.* BMJ 2006. **333**: p. 770-84
78. Patel, U.B., et al., *Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience.* J Clin Oncol, 2011. **29**(28): p. 3753-3760.
79. Nagtegaal, I.D., et al., *Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit.* . Am J Surg Path 2002. **26**(3): p. 350–7.
80. Wibe, A., et al., *Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer.* Br J Surg, 2002. **89**: p. 327-34.
81. Smith, N. and G. Brown, *Preoperative staging of rectal cancer.* Acta Oncol, 2008. **47**(1): p. 20-31.
82. Blomqvist, L. and B. Glimelius, *The 'good', the 'bad', and the 'ugly' rectal cancers.* Acta Oncol 2008. **47**(1): p. 5-8.
83. Lord, A.C., et al., *Significance of extranodal tumour deposits in colorectal cancer: A systematic review and meta-analysis.* Eur. J. Cancer 2017. **82**: p. 92–102.
84. Klerkx, W.M., et al., *Detection of lymph node metastases by gadolinium-enhanced magnetic resonance imaging: systematic review and meta-analysis.* J Natl Cancer Inst 2010. **102**(4): p. 244-253.
85. Bipat, S., et al., *Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a metaanalysis.* Radiology 2004. **232**(3): p. 773-783.
86. Al Sukhni, E., et al., *Diagnostic Accuracy of MRI for Assessment of T Category, Lymph Node Metastases, and Circumferential Resection Margin Involvement in Patients with Rectal Cancer: A Systematic Review and Metaanalysis.* Ann Surg Oncol 2012. **19**(7): p. 2212-23.
87. Harrison, J.C., et al., *From dukes through jass: Pathological prognostic indicators in rectal cancer.* Hum. Pathol. , 1994. **25**: p. 498-505.

88. Chand, M., et al., *The prognostic significance of postchemoradiotherapy high-resolution MRI and histopathology detected extramural venous invasion in rectal cancer.* Ann. Surg. , 2015. **261**: p. 473–479.
89. Taylor, F.G.M., et al., *Preoperative Magnetic Resonance Imaging Assessment of Circumferential Resection Margin Predicts Disease-Free Survival and Local Recurrence: 5-Year Follow-Up Results of the MERCURY Study.* J. Clin. Oncol. , 2014. **32**: p. 34–43.
90. Glynne-Jones, R., L. Wyrwicz, and E.e.a. Tiret, *Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up.* Ann Oncol. , 2017. **28**: p. 72–83.
91. Wille-Jorgensen, P. and S. Bulow, *The multidisciplinary team conference in rectal cancer - a step forward.* Colorectal Dis, 2009. **11**(3): p. 231-232.
92. Brown, G., *Specialist multidisciplinary team working in the treatment of cancer* BMJ, 2012. **344**: p. e2780.
93. Augestad, K.M., et al., *International preoperative rectal cancer management: staging, neoadjuvant treatment, and impact of multidiscplinary teams.* World J Surg 2010. **34**(11): p. 2689-2700.
94. Burton, S., G. Brown, and I.R. Daniels, *MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins?* British Journal of Cancer, 2006. **94**: p. 351 – 357.
95. Palmer, G., et al., *Preoperative tumour staging with multidisciplinary team assessment improves the outcome in locally advanced primary rectal cancer.* Colorectal Dis, 2011. **13**(12): p. 1361-9.
96. Engelen, S.M., et al., *Modern multidisciplinary treatment of rectal cancer based on staging with magnetic resonance imaging leads to excellent local control, but distant control remains a challenge.* Eur J Cancer, 2013. **49**(10): p. 2311-20.
97. Group, C.C.C., *Adjuvant radiotherapy for rectal cancer: a systematic overview of 8507 patients from 22 randomised trials.* The Lancet, 2001. **358**(9290): p. 1291-1304.
98. Francois, Y., C.J. Nemoz, and B. J., *Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial.* J Clin Oncol., 1999. **17**: p. 2396

99. Park, I.J., Y.N. You, and A. Agarwal, *Neoadjuvant treatment response as an early response indicator for patients with rectal cancer.* . J Clin Oncol., 2012. **30**: p. 1770–6.
100. Martin, S.T., H.M. Heneghan, and D.C. Winter, *Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer.* Br J Surg. , 2012. **99**: p. 918–28.
101. Zorcolo, L., A.S. Rosman, and A. Restivo, *Complete pathologic response after combined modality treatment for rectal cancer and long-term survival: a meta-analysis.* Ann Surg Oncol., 2012. **19**(9): p. 2822–32.
102. Glynne-Jones, R., M. Harrison, and R. Hughes, *Challenges in the neoadjuvant treatment of rectal cancer: balancing the risk of recurrence and quality of life.* Cancer Radiother. , 2013. **17**(7): p. 675-85.
103. Petrelli, F., et al., *Increasing the interval between neoadjuvant chemoradiation and surgery in rectal cancer. A metaanalysis of published studies.* Ann Surg, 2016 **263**(3): p. 458-64.
104. Habr-Gama, A., et al., *Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control.* Int J Radiat Oncol Biol Phys, 2014. **88**(4): p. 822-8.
105. Habr-Gama, A., G.P. Sao Juliao, and R.O. Perez, *Nonoperative management of rectal cancer: identifying the ideal patients.* Hematol Oncol Clin North Am, 2015. **29**(1): p. 135-51.
106. Appelt, A.L., et al., *High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study.* The Lancet Oncology, 2015. **16**(8): p. 919-927.
107. Beets, G.L., et al., *A new paradigm for rectal cancer: Organ preservation: Introducing the International Watch & Wait Database (IWWD).* Eur J Surg Oncol, 2015. **41**(12): p. 1562-4.
108. Smith, J.D., et al., *Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy.* Ann Surg, 2012. **256**(6): p. 965-72.
109. Smith, R.K., et al., *Surveillance after neoadjuvant therapy in advanced rectal cancer with complete clinical response can have comparable outcomes to total mesorectal excision.* Int J Colorectal Dis, 2015. **30**(6): p. 769-74.

110. Maas, M., et al., *Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer.* J Clin Oncol, 2011. **29**(35): p. 4633-40.
111. Dossa, F., et al., *A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis.* Lancet Gastroenterol Hepatol., 2017. **2**(7): p. 501-513.
112. van Etten, **B.** *Rectal Cancer And Pre-operative Induction Therapy Followed by Dedicated Operation. The RAPIDO Trial (RAPIDO)*. 2011; Available from: https://clinicaltrials.gov/ct2/show/NCT01558921.
113. Gögenur, I. *NEOadjuvant Chemotherapy Only Compared With Standard Treatment for Locally Advanced Rectal Cancer: a Randomized Phase II Trial (NEOLAR)*. 2017; Available from: https://clinicaltrials.gov/ct2/show/study/NCT03280407.
114. Bosset, J.F., et al., *Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results--EORTC 22921.* J Clin Oncol, 2005. **23**(24): p. 5620-7.
115. Miles, W.E., *A method of performing abdomino-perineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon.* Lancet 1908. **2** p. 1812-1813.
116. Bekæmpelse, L.t.K., *Skrivelse vedr. cancer recti.* København, 1942.
117. Dixon, C.F., *Anterior resection for malignant lesions of the upper part of the rectum and lower part of the sigmoid.* Ann Surg, 1948. **128**(3): p. 425-442.
118. Pollett, W.G. and R.J. Nicholls, *The relationship between the extent of distal clearance and survival and local recurrence rates after curative anterior resection for carcinoma of the rectum.* . Annals of Surgery, 1983. **198**(2): p. 159–63.
119. Parks, A.G., *Transanal technique in low rectal anastomosis.* Proc R Soc Med, 1972. **65**(11): p. 975-976.
120. Parks, A.J. and J.P. Percy, *Resection and sutured colo-anal anastomosis for rectal carcinoma.* Br J Surg, 1982. **69**(6): p. 301-304.
121. Heald, R.J., E.M. Husband, and R.D.H. Ryall, *The mesorectum in rectal cancer surgery-the clue to pelvic recurrence?* Br J Surg, 1982. **69**: p. 613-616.
122. Heald, R.J., *A new approach to rectal cancer.* Br J Hosp Med, 1979. **22**(3): p. 277-281.

123. Quirke, P., et al., *Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread an surgical excision.* Lancet, 1986. **2**(8514): p. 996-999.
124. Adam, I.J., et al., *Role of circumferential margin involvement in the local recurrence of rectal cancer.* Lancet, 1994. **344**(8924): p. 707-711.
125. Hida, J., et al., *Lymphnode metastaes detected in the mesorectum distal to carcinoma of the rectum by the clearing method: justification of total mesorectal excision.* J Am Coll Surg, 1997. **184**: p. 584-588.
126. Enker, W.E., *The natural history of rectal cancer 1908-2008: the evolving treatment of rectal cancer into the twenty-first century.* Semin Colon Rectal Surg, 2010. **21**: p. 56-74.
127. Heald, R.J., et al., *Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997.* Arch Surg, 1998. **133**: p. 894-9.
128. Moriya, Y., et al., *Nerve-sparing surgery with lateral node dissection for advanced lower rectal cancer.* Eur J Cancer 1995. **31A**(7–8): p. 1229-32.
129. Sugihara, K., et al., *Pelvic auto- nomic nerve preservation for patients with rectal carcinoma. Oncologic and functional outcome.* Cancer 1996. **78**(9): p. 1871-80.
130. Mori, T., K. Takahashi, and M. Yasuno, *Radical resection with autonomic nerve preservation and lymph node dissection techniques in lower rectal cancer surgery and its results: the impact of lateral lymph node dis- section.* Langenbecks Arch Surg 1998. **383**(6): p. 409-15.
131. Enker, W.E., S. Philipshen, and M.L. Heilwell, *En bloc pelvic lymphadenectomy and sphincter preservation in the surgical management of rectal cancer* Ann Surg 1986. **293**: p. 426–33.
132. Moriya, Y., K. Hojo, and T. Sawada, *Significance of lateral node dissection for advanced rectal car- cinoma at or below the peritoneal reflection.* Dis Colon Rectum 1989. **32**: p. 307–15.
133. Yano, H. and B.J. Moran, *The incidence of lateral pelvic sidewall nodal involvement in low rectal cancer may be sim- ilar in Japan and the West.* Br J Surg 2008. **95**(1): p. 33–49.
134. Surtees, P., J. Ritchie, and R.K.S. Phillips, *High versus low ligation of the inferior mesenteric artery in rectal cancer.* Br J Surg 1990. **77**: p. 618–21.

135. Corder, A.P., N.D. Karanjia, and J.D. Williams, *Flush aortic tie versus selective preservation of the ascend- ing left colic artery in low anterior resection for rec- tal carcinoma.* Br J Surg 1992. **79**: p. 680–2.
136. Morikawa, E., et al., *Distribution of metastatic lymph nodes in colorectal cancer by the modified clearing method.* Dis Colon Rectum, 1994. **37**(3): p. 219–23.
137. Bokey, E.L., et al., *Local recurrence after curative excision of the rectum for cancer without adjuvant therapy: role of total anatomical dissection.* British Journal of Surgery, 1999. **86**: p. 1164-70.
138. Lopez-Kostner, F., et al., *Total mesorectal excision is not necessary for cancers of the upper rectum.* Surgery, 1998. **124**(4): p. 612-18.
139. Nesbakken, A., et al., *Local recurrence after mesorectal excision for rectal cancer.* Eur J Surg Oncol, 2002. **28**(2): p. 126-34.
140. Law, W.L. and K.W. Chu, *Anterior Resection for Rectal Cancer With Mesorectal Excision.* Annals of Surgery, 2004. **240**(2): p. 260-268.
141. Syk, E., et al., *Local recurrence in rectal cancer: anatomic localization and effect on radiation target.* Int J Radiat Oncol Biol Phys, 2008. **72**(3): p. 658-64.
142. Syk, E., et al., *Radiological findings do not support lateral residual tumour as a major cause of local recurrence of rectal cancer.* Br J Surg, 2006. **93**(1): p. 113-9.
143. Bondeven, P., et al., *Suboptimal surgery and omission of neoadjuvant therapy for upper rectal cancer is associated with a high risk of local recurrence.* Colorectal Dis, 2015. **17**(3): p. 216-24.
144. Sebag-Montefiore, D., et al., *Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial.* Lancet, 2009. **373**: p. 821–28.
145. Pahlman, L., et al., *The Swedish rectal cancer registry.* Br J Surg, 2007. **94**(10): p. 1285-92.
146. Marr, R., et al., *The modern abdominoperineal excision: the next challenge after total mesorectal excision.* Ann Surg, 2005. **242**(1): p. 74-82.
147. Holm, T., et al., *Extended abdominoperineal resection with gluteus maximus flap reconstruction of the pelvic floor for rectal cancer.* Br J Surg, 2007. **94**(2): p. 232-8.

148. den Dulk, M., et al., *The abdominoperineal resection itself is associated with an adverse outcome: the European experience based on a pooled analysis of five European randomised clinical trials on rectal cancer.* Eur J Cancer, 2009. **45**(7): p. 1175–83.
149. Bülow, S., et al., *Intra-operative perforation is an important predictor of local recurrence and impaired survival after abdominoperineal resection for rectal cancer.* Colorectal Dis, 2011. **13**(11): p. 1256-64.
150. Danish Society of Surgery, D.C.C.G., *Guidelines for the diagnosis and the management of colorectal cancer (in Danish).* 2009(4).
151. Huser, N., et al., *Systematic review and meta-analysis of the role of defunctioning stoma in low rectal cancer surgery.* Ann Surg 2008. **248**(1): p. 52–60.
152. den Dulk, M., et al., *Multicentre analysis of oncological and survival outcomes following anastomotic leakage after rectal cancer surgery.* Br J Surg 2009. **96**(9): p. 1066–75.
153. Tan, W.S., et al., *Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer.* Br J Surg, 2009. **96**(5): p. 462-72.
154. Gu, W.L. and S.W. Wu, *Meta-analysis of defunctioning stoma in low anterior resection with total mesorectal excision for rectal cancer: evidence based on thirteen studies.* World J Surg Oncol, 2015. **13**(1): p. 9.
155. Matthiessen, P., et al., *Population-based study of risk factors for postoperative death after anterior resection of the rectum.* Br J Surg, 2006. **93**(4): p. 498-503.
156. Pakkastie, T.E., et al., *A randomised study of colostomies in low colorectal anastomoses.* Eur J Surg, 1997 **163**(12): p. 929-33.
157. Snijders, H.S., et al., *Optimal Treatment Strategy in Rectal Cancer Surgery: Should We Be Cowboys or Chickens?* Ann Surg Oncol, 2015. **22**(11): p. 3582-9.
158. Blok, R.D., et al., *Impact of an institutional change from routine to highly selective diversion of a low anastomosis after TME for rectal cancer.* Eur J Surg Oncol, 2018. **44**(8): p. 1220-1225.
159. Figueredo, A., et al., *Follow-up of patients with curatively resected colorectal cancer: a practice guideline.* BMC Cancer 2003 **3**(1): p. 26.
160. Desch, C.E., et al., *Recommended colorectal cancer surveillance guidelines by the American Society of Clinical Oncology.* J Clin Oncol 1999. **17**(4): p. 1312.

161. Anthony, T., et al., *Postoperative colorectal cancer surveillance.* J Am Coll Surg, 2000 **190**(6): p. 737-49.
162. Bastiaenen, V.P., et al., *Consensus and controversies regarding follow-up after treatment with curative intent of nonmetastatic colorectal cancer: a synopsis of guidelines used in countries represented in the European Society of Coloproctology.* Colorectal Dis, 2019. **21**(4): p. 392-416.
163. Tjandra, J.J. and M.K. Chan, *Follow-up after curative resection of colorectal cancer: a meta-analysis.* Dis Colon Rectum 2007 **50**(11): p. 1783-99.
164. Jeffery, M., B.E. Hickey, and P.N. Hider, *Follow-up strategies for patients treated for non-metastatic colorectal cancer* Cochrane Database Syst Rev 2007. **1**: p. CD002200.
165. Renehan, A.G., et al., *Impact on survival of intensive follow-up after curative resection for colorectal cancer: systematic review and meta- analysis of randomised trials.* Br Med J 2002. **324**: p. 813.
166. Baca, B., R.W. Beart, and D.A. Etzioni, *Surveillance after colorectal cancer resection: a systematic review.* Dis Colon Rectum 2011. **54**(8): p. 1036-48.
167. Kjeldsen, B.J., et al., *A prospective randomized study of follow-up after radical surgery for colorectal cancer.* Br J Surg 1997 **84**(5): p. 666-9.
168. Bruinvels, D.J., et al., *Follow-up of patients with colorectal cancer. A meta-analysis.* Ann Surg 1994 **219**(2): p. 174-82.
169. Barillari , P., et al., *Surveillance of colorectal cancer: effectiveness of early detection of intraluminal recurrences on prognosis and survival of patients treated for cure.* Dis Colon Rectum 1996 **39**(4): p. 388-93.
170. Nielsen, M.B., S. Laurberg, and T. Holm, *Current management of locally recurrent rectal cancer.* . Colorectal Dis, 2011 **13**(7): p. 732-42.
171. Sunesen, K.G., et al. *IMPROVE-IT2*. 2020; Available from: https://clinicaltrials.gov/ct2/show/NCT04084249.
172. Nors, J., et al., *IMPROVE-IT2: implementing noninvasive circulating tumor DNA analysis to optimize the operative and postoperative treatment for patients with colorectal cancer–intervention trial 2. Study protocol.* Acta Oncologica, 2020. **59**(3): p. 336-341.

173. Jakobsen, I.H., et al., *Follow-up After Rectal Cancer: Developing and Testing a Novel Patient-Led Follow-Up Program. Study Protocol.* Acta Oncol, 2017 **56**(2): p. 307-313.
174. Engel, J., et al., *Quality of life in rectal cancer patients: a four-year prospective study.* Ann Surg, 2003 **238**(2): p. 203-13.
175. Bryant, C.L., et al., *Anterior resection syndrome.* Lancet Oncol 2012 **13**(9): p. 403-408.
176. Emmertsen, K.J. and S. Laurberg, *Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer.* Ann Surg 2012. **255**(5): p. 922-8.
177. Peeters, K.C., et al., *Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients - a Dutch colorectal cancer group study.* J Clin Oncol 2005. **23**(25): p. 6199-206.
178. Lee, T.G., et al., *Risk factors for persistent anal incontinence after restorative proctectomy in rectal cancer patients with anal incontinence: prospective cohort study.* World J Surg 2011. **35**(8): p. 1918-24.
179. Mulsow, J. and D.C. Winter, *Sphincter preservation for distal rectal cancer--a goal worth achieving at all costs?* . World J Gastroenterol, 2011. **17**(7): p. 855-61.
180. Hallbook, O. and R. Sjodahl, *Anastomotic leakage and functional outcome after anterior resection of the rectum.* Br J Surg 1996 **83**(1): p. 60-62.
181. Nesbakken, A., K. Nygaard, and O.C. Lunde, *Outcome and late functional results after anastomotic leakage following mesorectal excision for rectal cancer.* Br J Surg, 2001. **88**(3): p. 400-404.
182. Fazio, V.W., et al., *A randomized multicenter trial to compare long-term functional outcome, quality of life, and complications of surgical procedures for low rectal cancers.* Ann Surg, 2007. **246**(3): p. 481-488.
183. Heriot, A.G., et al., *Meta-analysis of colonic reservoirs versus straight coloanal anastomosis after anterior resection.* Br J Surg, 2006. **93**(1): p. 19-32.
184. Brown, C.J., D.S. Fenech, and R.S. McLeod, *Reconstructive techniques after rectal resection for rectal cancer.* Cochrane Database Syst Rev 2008. **2**: p. CD006040.

185. Keane, C., et al., *Impact of temporary ileostomy on long‐term quality of life and bowel function: a systematic review and meta‐analysis.* ANZ Journal of Surgery, 2020. **90**: p. 687-692.
186. Gadan, S., et al., *Does a Defunctioning Stoma Impair Anorectal Function After Low Anterior Resection of the Rectum for Cancer? A 12-Year Follow-up of a Randomized Multicenter Trial.* Dis Colon Rectum, 2017. **60**(8): p. 800-806.
187. Pentecoast, R.L., R.A. Murray, and H.H. Brindley, *Fatigue, insufficiency, and pathologic fractures.* JAMA, 1964: p. 1001-4.
188. Lourie, H., *Spntaneous osteoporotic fracture of the sacrum.* Spine, 1982. **248**: p. 715-17.
189. Ogino, I., et al., *Pelvic insufficiency fractures in postmenopausal woman with advanced cervical cancer treated by radiotherapy.* Radiotherapy and Oncology, 2003. **68**(1): p. 61-67.
190. Baxter, N.N., et al., *Risk of Pelvic Fractures in Older Women Following Pelvic Irradiation.* JAMA, 2005. **294**(2): p. 2587-93.
191. Oh, D. and S.J. Huh, *Insufficiency fracture after radiation therapy.* Radiat Oncol J, 2014. **32**(4): p. 213-20.
192. Ikushima, H., et al., *Pelvic bone complications following radiation therapy of gynecologic malignancies: clinical evaluation of radiation-induced pelvic insufficiency fractures.* Gynecol Oncol, 2006. **103**(3): p. 1100-4.
193. Saraux, A., I. Valls, and C. Guedes, *Insufficiency fractures of the sacrum in elderly subjects.* Rev Rhum Engl Ed, 1995. **62**: p. 582-86.
194. Gotis-Graham, I., L. McGuigan, and T. Diamond, *Sacral insufficiency fractures in the elderly.* J Bone Joint Surg Br, 1994. **76**: p. 882-886.
195. Rawlings, C.E., R.H. Wilkins, and S. Martinez, *Osteoporotic sacral fractures: A clinical study.* Neurosurgery, 1988. **22**: p. 72-76.
196. Oh, D., et al., *Pelvic insufficiency fracture after pelvic radiotherapy for cervical cancer: analysis of risk factors.* Int J Radiat Oncol Biol Phys, 2008. **70**(4): p. 1183-8.
197. Kwon, J.W., et al., *Pelvic bone complications after radiation therapy of uterine cervical cancer: evaluation with MRI.* AJR Am J Roentgenol, 2008. **191**(4): p. 987-94.

198. Tokumaru, S., et al., *Insufficiency fractures after pelvic radiation therapy for uterine cervical cancer: an analysis of subjects in a prospective multi-institutional trial, and cooperative study of the Japan Radiation Oncology Group (JAROG) and Japanese Radiation Oncology Study Group (JROSG).* Int J Radiat Oncol Biol Phys, 2012. **84**(2): p. e195-200.
199. Igdem, S., et al., *Insufficiency fractures after pelvic radiotherapy in patients with prostate cancer.* Int J Radiat Oncol Biol Phys, 2010. **77**(3): p. 818-23.
200. Ramlov, A., et al., *Risk Factors for Pelvic Insufficiency Fractures in Locally Advanced Cervical Cancer Following Intensity Modulated Radiation Therapy.* Int J Radiat Oncol Biol Phys, 2017. **97**(5): p. 1032-1039.
201. Kim, H.J., et al., *Fractures of the sacrum after chemoradiation for rectal carcinoma: incidence, risk factors, and radiographic evaluation.* Int J Radiat Oncol Biol Phys, 2012. **84**(3): p. 694-9.
202. Herman, M.P., et al., *Sacral insufficiency fractures after preoperative chemoradiation for rectal cancer: incidence, risk factors, and clinical course.* Int J Radiat Oncol Biol Phys, 2009. **74**(3): p. 818-23.
203. Frank, L., *When an Entire Country Is a Cohort.* Science, 2000. **287**: p. 2398-99.
204. *Statistics Denmark – StatBank Denmark – Population at the first day of the quater by municipality, sex, age, marital status, ancestry, country of origin and citizenship* Data and statistics available from : http://www.statistikbanken.dk/statbank5a/SelectVarVal/Define.asp, 2013.
205. *The CPR law (in Danish: CPR-loven)*. 2013, The Ministry of Economic Affairs and the Interior.
206. Schmidt, M., L. Pedersen, and H.T. Sorensen, *The Danish Civil Registration System as a tool in epidemiology.* Eur J Epidemiol, 2014. **29**(8): p. 541-9.
207. Ingeholm, P., I. Gogenur, and L.H. Iversen, *Danish Colorectal Cancer Group Database.* Clin Epidemiol, 2016. **8**: p. 465-468.
208. Schmidt, M., et al., *The Danish National Patient Registry: a review of content, data quality, and research potential.* Clin Epidemiol, 2015. **7**: p. 449-90.
209. Lynge, E., J.L. Sandegaard, and M. Rebolj, *The Danish National Patient Register.* Scand J Public Health, 2011. **39**(7 Suppl): p. 30-3.

210. Nagtegaal, I.D., et al., *Macroscopic evaluation of rectal cancer resection specimen: Clinical significance of the pathologist in quality control.* Journal of Clinical Oncology, 2002. **20**(7): p. 1729-1734.
211. Schmidt, M., et al., *The Danish health care system and epidemiological research: from health care contacts to database records.* Clin Epidemiol, 2019. **11**: p. 563-591.
212. Klint, A., et al., *Trends in survival of patients diagnosed with cancer of the digestive organs in the Nordic countries 1964-2003 followed up to the end of 2006.* Acta Oncol 2010. **49**: p. 578–607.
213. Engholm, G., et al., *Colorectal cancer survival in the Nordic countries and the United Kingdom: excess mortality risk analysis of 5 year relative period survival in the period 1999 to 2000.* Int J Cancer, 2007. **121**: p. 1115–22.
214. Engeland, A., et al., *Relative survival of cancer patients-a comparison between Denmark and the other Nordic countries.* Acta Oncol 1998. **37**: p. 49–59.
215. Publishing, O., *Cancer Care: Assuring Quality to Improve Survival.* OECD Health Policy Studies, 2013.
216. Kodeda, K., et al., *Regional differences in local recurrence rates after rectal cancer surgery.* Colorectal Dis, 2010. **12**(10 Online): p. e206-15.
217. Guren, M.G., et al., *Nationwide improvement of rectal cancer treatment outcomes in Norway, 1993-2010.* Acta Oncol, 2015. **54**(10): p. 1714-22.
218. Rosenberg, R., et al., *Does a rectal cancer of the upper third behave more like a colon or a rectal cancer?* Dis Colon Rectum, 2010. **53**(5): p. 761-70.
219. Wibe, A., et al., *Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer.* Br J Surg, 2002. **89**: p. 327-34.
220. Quirke, P. and M. Dixon, *The prediction of local recurrence in rectal adenocarcinoma by histopathological examination.* . International Journal of Colorectal Disease, 1988: p. 127–131.
221. Tilly, C., et al., *R1 rectal resection: look up and don't look down.* Ann Surg, 2014 **260**(5): p. 794-800.
222. Larsen, M.B., et al., *Potential for prevention: a cohort study of colonoscopies and removal of adenomas in a FIT-based colorectal cancer screening programme.* Scandinavian Journal of Gastroenterology, 2019. **54**(8): p. 1008-1014.

223. Austoker, J., et al., *Interventions to promote cancer awareness and early presentation: systematic review* Br J Cancer, 2009. **101**: p. 31-39.
224. Neal, R.D., *Do diagnostic delays in cancer matter?* Br J Cancer, 2009. **101**: p. 9-12.
225. van Rooijen, S., et al., *Multimodal Prehabilitation in Colorectal Cancer Patients to Improve Functional Capacity and Reduce Postoperative Complications: The First International Randomized Controlled Trial for Multimodal Prehabilitation.* BMC Cancer, 2019 **19**(1): p. 98.
226. Gillis, C., et al., *Effects of Nutritional Prehabilitation, With and Without Exercise, on Outcomes of Patients Who Undergo Colorectal Surgery: A Systematic Review and Meta-analysis.* Gastroenterology, 2018. **155**(2): p. 391-410.
227. Wille-Jørgensen, P., et al., *Effect of more vs less frequent follow-up testing on overall and colorectal cancer-specific mortality in patients with Stage II or III colorectal cancer: The COLOFOL randomized clinical trial.* JAMA, 2018. **319**(20): p. 2095-2103.
228. Rosati, G., et al., *randomized trial of intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma.* Ann Oncol. , 2016. **27**(2): p. 274-280.
229. Snyder, R., et al., *Association between intensity of post-treatment surveillance testing and detection of recurrence in patients with colorectal cancer.* JAMA, 2018. **319**(20): p. 2104-2115.
230. Jakobsen, I.H. *Individual Follow-up After Rectal Cancer (FURCA)*. 2018; Available from: https://clinicaltrials.gov/ct2/show/study/NCT03622437?cond=follow+up+after+rectal+cancer&draw=2&rank=2.
231. (DCCG), D.C.C.G. *Annual report (in Danish)*. 2001; Available from: https://dccg.dk/wp-content/uploads/2017/10/Aarsrapport_20012002.pdf.
232. Melton, r.L.J., et al., *Epidemiologic features of pelvic fractures.* Clinical orthopaedics and related research, 1981(155): p. 43-47.
233. Cooper, K.L., J.W. Beabout, and R.G. Swee, *Pelvic insufficiency fractures of the sacrum.* Radiology, 1985. **156**: p. 15-20.

234. Kronborg, C.J.S., et al., *Pelvic insufficiency fractures, dose volume parameters and plan optimization after radiotherapy for rectal cancer.* Clin Transl Radiat Oncol. , 2019 **19**: p. 72–76.

235. *Fit for Surgery. Clinical Randomized Trial of Multimodal Prehabilitation Strategy in Patients With Colorectal Cancer.* 2019; Available from: https://clinicaltrials.gov/ct2/show/study/NCT04167436?term=Multimodal+prehabilitation+in+colorectal+cancer&draw=2&rank=1.

236. Andersson, P.H., et al., *The COLOFOL trial: study design and comparison of the study population with the source cancer population.* Clin Epidemiol, 2016. **8**: p. 15–21.

Paper I

Comorbidity and UICC stage IV disease are main risk factors for decreased 3-year survival and recurrence after intended curative surgery for rectal cancer – A population-based study

J. B. Jørgensen[1, 2], P. Bondeven[1, 3], S. Laurberg[1], MRI Study Group[4] B. G. Pedersen[3], and L. H. Iversen[1]

[1] Aarhus University Hospital, Department of Surgery
[2] Regional Hospital Randers, Department of Surgery
[3] Aarhus University Hospital, Department of Radiology
[4] MRI Study Group:
Niels Qvist and Jon Thor Asmussen, Odense University Hospital. Safaa Al-Ubaidi and Frédérique Johnsen, Regional Hospital West Jutland. Steffen Jais Rosenstock and Annette Bøjer Jensen, Hvidovre Hospital. Ole Roikjær and Karina Vinum, Zealand University Hospital. Sharaf Karim Perdawood and Odai Adnan Jalel, Slagelse Hospital. Thomas Kolbro and Jacob Christian Bang, Svendborg Hospital. Lars Bundgaard and Søren Rafaelsen, Vejle Hospital. Pernille Øhlenschlager Larsen, Esbjerg Hospital.

Corresponding author
Jesper Beck Jørgensen, M.D.
Aarhus University Hospital, Department of Surgery
Palle Juul-Jensens Boulevard 99
8200 Aarhus N
Denmark
E-mail: jesjoe@rm.dk

Conflict of interest statement
None declared

Word count

Abstract

Background

In the last two decades, there have been marked improvements in the treatment of rectal cancer due to optimization of both the surgical and oncological treatment. The aim of this study was to evaluate 3-year overall survival (OS), and rates of distant recurrence (DR) and local recurrence (LR), in a well-defined Danish cohort undergoing intended curative rectal cancer resection.

Method

Patients registered with primary rectal cancer in the Danish Colorectal Cancer Group database, who underwent rectal cancer resection with curative intent from April 2011 through August 2012 were included and followed 3 years after surgery. Patients being disease-free up to the 3-year follow-up visit were offered a pelvic MRI in addition to routine computed tomography of the lungs and abdomen. The 3-year OS, and 3-year cumulative incidence proportions (CIP) of DR and LR were calculated treating death as competing risk. Predictive factors of OS, DR, and LR were explored using multiple Cox regression analysis.

Results

In total, 890 patients from 10 of 15 centres in Denmark treating rectal cancer were included. Among these, 403 patients had a 3-year follow-up MRI. Three-year OS, and 3-year CIP of DR and LR was 80.6% (95% CI 77.9-83.1), 12.8% (95% CI 8.2-12.5), and 6.5% (95% CI 5.0-8.4) respectively.

Conclusion

The 3-year OS after mesorectal excisional surgery in a well-defined cohort of patients in Denmark was high and 3-year rates of DR and LR were low. Main risk factors of both inferior survival and recurrence were UICC stage IV disease and advanced patient comorbidity.

Introduction

In the past few decades, there have been remarkable advances in treatment of rectal cancer. This is primarily through standardization of rectal cancer surgery, involving concepts of mesorectal excisional surgery [1, 2] and resection with tumour free margins [3, 4]. Furthermore, the management of rectal cancer has been fundamentally revised with organized treatment planning directed by a multidisciplinary team (MDT), following pre-operative staging by magnetic resonance imaging (MRI), use of neoadjuvant (chemo) radiotherapy (CRT), and quality assurance by pathological assessment of the excised specimen [5-7]. All these elements combined have resulted in improved outcome for rectal cancer patients [8-14] and survival rates exceeding those of colon cancer [15, 16].

Despite a thorough optimization in management of rectal cancer over the last 10 to 20 years in Denmark, with significantly increased survival rates [15-18], we still need more knowledge about the oncological implications of current treatment strategies in the management of rectal cancer[18-20].

Following results from the Swedish rectal cancer trial [21] implying that neoadjuvant CRT could reduce the frequency of local recurrence (LR) with 50%, the approach to rectal cancer treatment has changed. In general, the introduction of preoperative CRT and an intensified focus on the quality of surgery performed have led to a decreased LR rates internationally and nationally[18]. However, data on DR rates is limited internationally, although this is the most frequent form of rectal cancer recurrence [19, 22].

Standardized surveillance programmes for detection of recurrent disease in rectal cancer with, for instance, computed tomography (CT) [23] and clinical examination with rigid proctoscopy at regular intervals [23] most often fail to detect recurrence[23]. Therefore, we hypothesized that pelvic MRI 3 years after rectal cancer resection might be valuable in detecting LR assuming this modality has the potential to detect yet asymptomatic LR. Accordingly, we conducted a prospective population-based study in which rectal cancer patients were offered a pelvic MRI 3 years after rectal resection, besides the standard CT, to achieve a more comprehensive estimate of the combined rate of LR and DR.

Thus, the aim of this study was to evaluate OS, the rates of DR and LR, including the combined rate, in rectal cancer patients 3 years following mesorectal excisional surgery in a well-defined cohort of patients in Denmark. Further, we aimed to evaluate predictive factors of OS, DR, and LR.

Materials and methods

Study design and setting

A prospective population-based study was conducted on a well-defined Danish cohort of rectal cancer patients 3 years after intended curative surgery.

The National Health Service in Denmark provides universal, tax-supported health care to all citizens [24], guaranteeing free access to general practitioners and public hospitals treating rectal cancer.

During the study period, patients undergoing surgery for rectal cancer were treated in 15 departments in Denmark. Screening for colorectal cancer was not implemented at time of surgery. The standard surveillance programme according to the Danish Colorectal Cancer Group (DCCG) guidelines was rigid proctoscopy after 6, 12, 18, 24, and 36 months, and a computed tomography (CT) scan of thorax, abdomen, and pelvis after 12 and 36 months. To obtain a better estimate of the local recurrence risk within 3 years after surgery, the participating departments were asked to offer a pelvic MRI at 36-month follow-up visit in patients without confirmed and without symptoms of distant and local recurrence. Ten out of 15 departments, serving approximately 65% of the Danish population, were able to include patients for MRI.

The study was approved by the National Board of Health (ref.: 3-3013-1272/1/), the Scientific Committee of the Danish Colorectal Cancer Group (DCCG.dk), and the Danish Data Protection Agency (ref.: 2007-58-0010). The Central Denmark Region Committees on Health Research Ethics considered the study as a quality assurance study.

Data sources

There has been a consecutive national reporting on patients with colorectal cancer to the DCCG Database since May 2001 [25]. Data on diagnostic staging, treatment and postoperative complications are prospectively provided to the registry. The DCCG database obtain data from the Danish National Patient Registry (indsæt reference) to summarize the Charlson comorbidity index (Indsæt reference J Chronic Dis 1987, 40:373-383). The estimated completeness in the DCCG Database was in the study period 99% [25].

Data is linked between registries by the Danish Civil Registration System number, a unique 10-digit personal identification number assigned to every citizen in Denmark

since 1968 allowing for data linkage and ensuring complete follow-up of patients. The registry maintains information on date of birth and death, gender, residence and vital status[26].

Cohort

Patients with rectal adenocarcinoma (located ≤ 15 cm from the anal verge) who underwent rectal resection (partial mesorectal excision (PME), total mesorectal excision (TME), Hartmann's operation, or abdominoperineal excision (APE)), i.e. the index operation, with curative intent from April 2011 to August 2012 were identified through the DCCG Database. Patients, who according to medical records were disease-free up to the planned 3-year follow-up visit, were offered a pelvic MRI scan unless they had left the country, or terminated their surveillance programme due to very old age or comorbidity. Medical records from all patients were reviewed by the first author (surgical trainee), and information regarding cancer treatment, comorbidity, and recurrence of disease was extracted.

Oncological and surgical treatment

Rectal cancer treatment was performed according to national guidelines [23]. Preoperative staging included CT scan of thorax, abdomen, and pelvis and pelvic MRI. Treatment planning was discussed at MDT conference. Most patients underwent mesorectal excision upfront without neoadjuvant treatment. Patients with locally advanced rectal cancer (low cT3 and cT4 tumours, mid cT4 tumours, and mid cT3 tumours with <5mm distance to mesorectal fascia at MRI) were offered neoadjuvant long-course CRT. Short-course radiotherapy could be used in selected cases. Restorative rectal resection, Hartmann's operation, or abdominoperineal resection, performed as mesorectal excision, was performed 8-10 weeks after completion of neoadjuvant treatment.

UICC stage IV patients undergoing intended curative treatment for distant metastases (resection or local treatment with radiofrequency ablation, microwave ablation, or stereotactic radiotherapy) in the perioperative course of the rectal cancer resection either during the index procedure or during an independent procedure in close timely relation to the index procedure were eligible.

Postoperative chemotherapy was offered to patients aged ≤75 years with WHO performance status ≤2, and without microsatellite instability if either UICC stage II

with at least one risk factor (emergency surgery, anastomotic leakage, pT4 category, <12 lymph nodes in the excised specimen as detected at histopathological evaluation) or UICC stage III and none neoadjuvant CRT [23].

Histopathology

The histopathological examination was performed in accordance to the principles described in DCCG [23]. An involved circumferential resection margin (CRM) was defined as residual tumour within 1 mm of the resection margin and classified as R1 resection. The quality of the specimen was evaluated and classified as mesorectal (mesorectal defects ≤5 mm), intramesorectal (mesorectal defects >5 mm), or muscularis plane of surgery (visible muscularis propria or perforation of the rectal wall).

3-year postoperative pelvic MRI

All patients fulfilling the eligibility criteria were invited to a 3-year postoperative MRI in addition to the standard 3-year postoperative surveillance programme. Those who did not respond to the primary request received a supplemental inquiry by telephone.

MRI examinations were performed on 1.5T or 3T platforms with a detailed scan-protocol established by the research group. Sagittal, axial and coronal T2-weighted turbo spin echo images, field of view (FOV) 240 mm, slice thickness 4-5 mm, were obtained. Based on the sagittal T2 weighted sequence, the axial T2 and the coronal T2 weighted sequences were planned. The axial sequence covered the entire pelvis from the lower border of the subcutaneous part of the external sphincter to the promontory. The sag T2 3D sequence covered the smaller pelvis with a slab of 88 slices, slice thickness 1 mm.

All MRI examinations were re-evaluated by a dedicated MDT radiologist at Aarhus University Hospital with 8 years of sub-specialisation in pelvic MRI. This radiologist was blinded to all data with the exception of the preoperative MRI examination.

Recurrent disease

DR was defined as radiological, clinical or histological evidence of a recurrent tumour outside the pelvic cavity as documented in the medical record.

LR was defined as clinical or radiological evident tumour mass, or histologically

verified adenocarcinoma in the pelvis, regardless of the presence or absence of simultaneous distant metastases as documented in the medical record or by the 3-year post-operative MRI. The multidisciplinary team at Aarhus University Hospital evaluated any radiological evident pelvic mass suspicious of LR. Histopathological verification was only achieved if clinical relevant.

Outcome measures

The primary outcome was OS and the cumulative incidence (risk) proportion (CIP) of DR, LR, and DR and/or LR 3 years after rectal cancer surgery. Secondary outcome measures were significant predictors of OS, DR, and LR.

Statistical analysis

Patient characteristics, demographics, rectal resection procedure (PME, TME (including Hartmann's procedure), APE), neoadjuvant treatment, histopathological examination are presented as categorical variables by counts and percentages.
We calculated the 3-year OS rate and constructed Kaplan-Meier survival curves.
Patients with UICC stages I-III were analysed separately

We estimated the CIP (risk) of DR and/or LR as well as DR and LR separately at 3 years following rectal cancer surgery and adjusted for various *patient-related* risk factors (gender, age at surgery, Charlson comorbidity index, ASA classification), *pathology/tumour-related* risk factors (tumour height (low (0-5 cm) vs. mid/high (6-10 cm / 11-15 cm), (y)pT-category (according to T category), UICC stage, and involved CRM (<1mm)), and *treatment-related* risk factors (use of pre-operative CRT, surgical approach, type of rectal resection, intraoperative blood loss (0-300 ml vs. >300 ml), anastomotic leakage, and plane of surgery) treating death as a competing risk. Potential predictors for recurrence and survival were explored in a Cox regression model. Stata® version 12.0 (StataCorp, College Station, Texas, USA) was used for statistical analysis.

Results

In total, 1,353 rectal cancer patients with UICC stage I-IV had resectional surgery (PME, TME or APE) with curative intent in Denmark from April 2011 through August 2012 (excluding patients undergoing local excision (n=94), patients undergoing palliative surgery (n=124), and patients not undergoing surgery (n=405)). Of these, 890 patients (65.8% of the total national cohort) underwent surgery at one of the 10 participating hospitals and comprised the study cohort, Figure 1. Demographics, tumour characteristics, and treatment regimens are summarised in Table 1.

Overall survival and disease-free survival at 3 years (Figure 2 and Table 2)

The 3-year OS rate was 80.6% (95% CI 77.9-83.1) and for UICC stage I-III patients it was 83.6% (95% CI 80.9-86.2). The 3-year disease-free survival (DFS) was 73.0% (95% CI 70.0-75.9) and restricted to UICC stage I-III patients it was 77.1% (95% CI 74.1-80.0). Among the 169 deceased patients (UICC stage I-IV), 62 patients (36.7%; 29.3-44.0) died with recurrent disease (LR and/or DR). OS stratified for *Patient-related*, *Pathology/tumour-related*, and *Treatment-related* factors are presented in Table 2.

Factors predictive of decreased OS in multivariable analysis (Table 3)

Statistical significant *patient-related* risk factors predictive of decreased OS rate were Charlson comorbidity index ≥2, ASA grades III-IV, and age >65 years. UICC stage IV was the only significant *pathology/tumour-related* risk factor and non-mesorectal plane of surgery was the only significant *treatment-related* risk factor.

Recurrence of rectal cancer within 3 years (Figures 3-5)

The risk of DR and/or LR following rectal cancer resection was 14.9% (95% CI 12.6-17.3) and for UICC stage I-III patients it was 11.0% (95% CI 8.9-13.3).

The risk of DR was 12.8% (95% CI 10.6-15.2) and for UICC stage I-III patients it was 8.4% (95% CI 6.5-10.5). The majority of patients with DR were diagnosed between 0 and 12 months after surgery with a CIP of 6.1% (95% CI 4.6-7.9).

The risk of LR was 6.5% (95% CI 5.0-8.4) and for UICC stage I-III patients it was 5.8% (95% CI 4.2-7.7). The majority of patients with LR were diagnosed between 12 and 24 months after surgery with a CIP of 2.5% (95% CI 2.0–2.9) from 12 to 24

months. The 3-year post-operative MRI revealed an undiagnosed LR in 8 of 403 (2.0%; 95% CI 0.6-3.4) patients. The risk of LR at 3-year excluding MRI detected LR was 5.6% (95% CI 4.1-7.3). Among 53 patients with LR, 26 (49.1%; 95% CI 35.1-63.0) had synchronous DR.
LR and DR stratified for *Patient-related*, *Pathology/tumour-related*, and *Treatment-related* risk factors are presented in Table 2.

Factors predictive of distant recurrence in multivariable analysis (Table 3).
The only significant *patient-related* risk factor of DR was Charlson comorbidity index ≥2. Significant *pathology/tumour-related* risk factors were UICC stage category IV and involved CRM, while no *treatment-related* risk factors were found.

Factors predictive of local recurrence in multivariable analysis (Table 3)
The only significant *patient-related* risk factor of LR was Charlson comorbidity index ≥2. Significant *pathology/tumour-related* risk factors were UICC stage IV, tumour height 0-5 cm from anal verge, and involved CRM. PME surgery was the only significant *treatment-related* risk factor.

Discussion

This prospective study reports favourable 3-year outcome of UICC stage I-IV rectal cancer patients treated with intended curative resectional surgery in a well-defined Danish cohort. Advanced disease (UICC stage IV) and severe comorbidity (Charlson comorbidity index ≥2) were the main risk factors for poor outcome. Other risk factors had only minor impact on both survival and risk of recurrence. Nearly two thirds of the patients died without sign of recurrence.

A very high 3-year OS rate of 81% and a relatively high 3-year DFS of 73% were found in the present study [11, 27, 28]. Recent studies have reported less favourable outcome after rectal cancer treatment, but direct comparison should be made with caution, as patient inclusion, treatment strategies, and follow-up regimens differ[18, 19]. As expected UICC stage IV disease was the most important predictor for decreased overall survival after intended curative treatment of rectal cancer with a 3-year OS rate of 59% opposed to 84% among UICC stage I-III patients (HR 3.27). Patient-related risk factors, including age >65 years, ASA grade III-IV, and Charlson comorbidity index ≥2, were important predictors for decreased OS rate. The majority of patients dying within 3 years had no sign of recurrence, which may underlie our finding of a high DFS rate. Non-mesorectal plane of surgery was another independent risk factor, which has not been found in previous studies [9, 30]

The observed DR rate of 13% was very low in relation to findings in previous studies[8, 31]. UICC stage IV disease was the most important predictor for DR with a very high 3-year DR rate of 46% opposed to 8% among UICC stages I-III patients (HR 8.86). Among the analysed variables, Charlson comorbidity index ≥2 was the only significant patient-related risk factor predictive of DR in multivariate analysis.

Present study found a low 3-year risk of LR at 6.5%[8, 31]. Reported LR rates in the modern era of rectal cancer treatment with mesorectal excisional surgery and neoadjuvant CRT are highly variable ranging from 4% to 14% [19, 22, 32]. This relatively low risk of LR was found despite the added pelvic MRI at 3 years to obtain a more accurate estimate. With inclusion of pelvic MRI, a relative increase in the LR rate of 16% was achieved. However, as the LR rate was relatively low, only a very

modestly increased CIP from 5.6% to 6.5% was observed. UICC stage IV was the most important predictor for development of LR (HR 6.57) with a significantly increased LR rate of 13% opposed to 6% in UICC stage I-III patients. Among the analysed variables, Charlson comorbidity index ≥2 was the only significant patient-related risk factor predictive of LR.

PME surgery was an independent predictor for LR (HR 4.7) with TME surgery as reference. Poor outcomes with LR rates between 9% and 15% have been reported following PME surgery and no CRT for cancer in the upper rectum nationally and internationally [32-35]. This is likely due to suboptimal PME surgery [34], since optimizing surgery for upper rectal cancer with a more selective use of PME surgery has led to substantially decreased LR rates [36].

CRM involvement (margin <1mm) significantly increased the risk of both DR (35% at 3 years) and LR (20% at 3 years). However, CRM involvement did not affect OS unlike findings in previous studies [37, 38]

Interestingly, increased Charlson comorbidity index ≥2 both have a negative impact on OS and risk of DR and LR. We may speculate that the negative impact of comorbidity on both DR and LR may be due to suboptimal oncological treatment or that comorbidity per se increases the risk of recurrence.

In this population-based study, we found a very high OS and a low DR and LR rate compared to a recent study from neighbouring Scandinavian countries [19]. This is in contrast to data from the 1980's, showing that the outcome of rectal cancer treatment in Denmark was clearly inferior to results from both Norway and Sweden[39]. The achievements documented here is most likely due to a national strategy to improve outcome of rectal cancer by implementation of national guidelines, continuous data reporting to a national database, centralisation of rectal cancer surgery from 47 to 15 surgical departments, specialization of surgeons (colorectal surgeons), Så sandelig også radiologer (i hvert fald 'dedicated'), patologer og onkooger
and effectuation of postgraduate multidisciplinary training and teaching programmes [16, 17].

This study suggests that we can improve outcome of rectal cancer by (1) reducing the proportion of patients presenting with UICC stage IV disease and (2) improving the management of patients with comorbidity. In March 2014, colorectal cancer screening was implemented nationally and the national database has shown a substantial reduction in patients with stage IV patients since the initiation of this programme [40, 41].
Generally, increased resources must be deployed into primary (preventive) health care to reduce comorbidity and improve the general health status in an aging population. Specifically, multimodal prehabilitation with smoking cessation, psychological coping, individualized training programmes, and nutritional support may improve functional capacity and reduce postoperative complication rates in extensively comorbid rectal cancer patients, resulting in improved OS [42, 43].

Until now, surveillance has primarily been focused on detection of recurrence. However, the majority of patients dying within 3 years have no sign of recurrence. Furthermore, previous studies on the impact of various surveillance programmes, has found no impact on colorectal cancer outcome [44-47]. In the present study, nearly two thirds of the patients dying within 3 years had no sign of recurrence. Therefore, there is an urgent need for studies to explore if specific symptom awareness
Symptomer på recidiv – eller anden sygdom (komorbidtiy) - specificer
and improved collaboration between general practitioners and internists, will improve survival. Skal uddybes – fremstår lidt 'out of context' for ikke -danskere

The NEOLAR study[48] and the RAPIDO Trial[49] are on-going randomised controlled trials investigating the effect of preoperative chemotherapy on recurrence of locally advanced rectal cancer. Chemotherapy may contribute to improved outcome of rectal cancer treatment, however, the effect may be limited as the majority of patients dying within 3 years of rectal cancer treatment will not die from recurrence of disease.

The strength of present study includes the prospective design, a large and well-defined patient cohort comprising 890 patients, and a long follow-up period of 3 years. Data were retrieved from a highly reliable registry with prospective data sampling and high data completeness[15]. Further, one surgical trainee systematically

reviewed medical records from all 890 included patients. Unlike most previous studies; present study is based on data from current time period, and the treatment regimens comply with modern standards.

The study has some limitations, as recurrence estimates may depend on the method of follow-up, including the frequency and quality of radiological and clinical patient examinations. In a society with highly reliable registries, the OS rate will be an accurate estimate, as opposed to estimates of DR and LR. Accordingly, some patients died in the intervals between follow-up, and not all patients received follow-up according to the study algorithm, both of which may underestimate the DR and LR rates. Further, patients with disseminated disease will rarely have all recurrent foci encoded. This may result in an underestimation of both DR and LR. On the other hand, from review of medical records it is obvious that recurrence is not always histologically verified, which potentially may lead to an overestimation of the recurrence rate.

Intended curative treatment of rectal cancer including stage IV carries a high 3-year OS and low DR and LR rates. The main risk factors are UICC stage IV and Charlson comorbidity index ≥2.

Acknowledgements

The present study was funded by the Danish Cancer Society.
The Study Group of the project *"Mesorectal Excision for Rectal Cancer: Aspects of Recurrence and Survival"* is acknowledged for their contribution in patient recruitment and MRI examinations.

References

1. Heald, R.J., E.M. Husband, and R.D.H. Ryall, *The mesorectum in rectal cancer surgery-the clue to pelvic recurrence?* Br J Surg, 1982. **69**: p. 613-616.
2. Heald, R.J., *A new approach to rectal cancer.* Br J Hosp Med, 1979. **22**(3): p. 277-281.
3. Quirke, P., et al., *Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread an surgical excision.* Lancet, 1986. **2**(8514): p. 996-999.
4. Adam, I.J., et al., *Role of circumferential margin involvement in the local recurrence of rectal cancer.* Lancet, 1994. **344**(8924): p. 707-711.
5. Burton, S., G. Brown, and I.R. Daniels, *MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins?* British Journal of Cancer, 2006. **94**: p. 351 – 357.
6. Engelen, S.M., et al., *Modern multidisciplinary treatment of rectal cancer based on staging with magnetic resonance imaging leads to excellent local control, but distant control remains a challenge.* Eur J Cancer, 2013. **49**(10): p. 2311-20.
7. Palmer, G., et al., *Preoperative tumour staging with multidisciplinary team assessment improves the outcome in locally advanced primary rectal cancer.* Colorectal Dis, 2011. **13**(12): p. 1361-9.
8. Peeters, K.C., et al., *The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma.* Ann Surg, 2007. **246**(5): p. 693-701.
9. Sebag-Montefiore, D., et al., *Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial.* Lancet, 2009. **373**: p. 821–28.
10. Braendengen, M. and B. Glimelius, *Preoperative radiotherapy or chemoradiotherapy in rectal cancer - Is survival improved? An update of the "Nordic" LARC study in non-resectable cancers.* Radiother Oncol, 2018. **127**(3): p. 392-395.
11. Bosset, J.F., et al., *Chemotherapy with Preoperative Radiotherapy in Rectal Cancer.* N Engl J Med, 2006. **355**: p. 1114-23.

12. MECURY, S.G., *Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study.* BMJ, 2006. **333**(7572): p. 779.
13. Beets-Tan, R.G.H., et al., *Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery.* Lancet, 2001. **357**: p. 497–504.
14. Nagtegaal, I.D., et al., *Macroscopic evaluation of rectal cancer resection specimen: Clinical significance of the pathologist in quality control.* Journal of Clinical Oncology, 2002. **20**(7): p. 1729-1734.
15. Bulow, S., et al., *Improved survival after rectal cancer in Denmark.* Colorectal Dis, 2010. **12**(7 Online): p. e37-42.
16. Iversen, L.H., *Aspects of survival from colorectal cancer in Denmark.* Dan Med J 2012. **59**: p. B4428.
17. Iversen, L.H., et al., *Improved survival of colorectal cancer in Denmark during 2001-2012 - The efforts of several national initiatives.* Acta Oncol, 2016. **55 Suppl 2**: p. 10-23.
18. Poulsen, L.O., et al., *Local recurrence rate in a national Danish patient cohort after curative treatment for rectal cancer.* Acta Oncol, 2018. **57**(12): p. 1639-1645.
19. Glimelius, B., et al., *Two countries – Two treatment strategies for rectal cancer.* Radiotherapy and Oncology, 2016. **121**(3): p. 357-363.
20. Bernstein, T.E., et al., *What is a safe distal resection margin in rectal cancer patients treated by low anterior resection without preoperative radiotherapy?* Colorectal Disease, 2012 **14**(2): p. 48–55.
21. Cedermark, B., et al., *Improved survival with preoperative radiotherapy in resectable rectal cancer: Swedish rectal cancer trial.* N Engl J Med, 1997. **336**(14): p. 980-87.
22. Guren, M.G., et al., *Nationwide improvement of rectal cancer treatment outcomes in Norway, 1993-2010.* Acta Oncol, 2015. **54**(10): p. 1714-22.
23. (DCCG), D.C.C.G. *Guidelines for the diagnosis and the management of colorectal cancer (in Danish)* 2009; 4:[Available from: https://dccg.dk/wp-content/uploads/2017/08/Retningslinier2009revOKT2010.pdf.
24. *Statistics Denmark – StatBank Denmark – Population at the first day of the quater by municipality, sex, age, marital status, ancestry, country of origin*

and citizenship Data and statistics available from : http://www.statistikbanken.dk/statbank5a/SelectVarVal/Define.asp, 2013.

25. Ingeholm, P., I. Gogenur, and L.H. Iversen, *Danish Colorectal Cancer Group Database.* Clin Epidemiol, 2016. **8**: p. 465-468.
26. Schmidt, M., L. Pedersen, and H.T. Sorensen, *The Danish Civil Registration System as a tool in epidemiology.* Eur J Epidemiol, 2014. **29**(8): p. 541-9.
27. Sauer, R., et al., *Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer.* N Engl J Med, 2004. **351**(17): p. 1731-40.
28. Gerard, J.P., et al., *Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203.* J Clin Oncol, 2006. **24**(28): p. 4620-5.
29. Brouwer, N., et al., *An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients.* . International journal of cancer 2018. **143**(11): p. 2758–2766.
30. Kitz, J., et al., *Association of Plane of Total Mesorectal Excision With Prognosis of Rectal Cancer: Secondary Analysis of the CAO/ARO/AIO-04 Phase 3 Randomized Clinical Trial.* JAMA Surg, 2018. **153**(8): p. e181607.
31. Sebag-Montefiore, D., et al., *Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial.* Lancet, 2009. **373**: p. 811–20.
32. Kodeda, K., et al., *Regional differences in local recurrence rates after rectal cancer surgery.* Colorectal Dis, 2010. **12**(10 Online): p. e206-15.
33. Syk, E., et al., *Local recurrence in rectal cancer: anatomic localization and effect on radiation target.* Int J Radiat Oncol Biol Phys, 2008. **72**(3): p. 658-64.
34. Bondeven, P., et al., *Suboptimal surgery and omission of neoadjuvant therapy for upper rectal cancer is associated with a high risk of local recurrence.* Colorectal Dis, 2015. **17**(3): p. 216-24.
35. Rosenberg, R., et al., *Does a rectal cancer of the upper third behave more like a colon or a rectal cancer?* Dis Colon Rectum, 2010. **53**(5): p. 761-70.
36. Bondeven, P., et al., *Impact of a multidisciplinary training programme on outcome of upper rectal cancer by critical appraisal of the extent of mesorectal excision with postoperative MRI.* BJS Open, 2019.

37. Nagtegaal, I.D., et al., *Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit.* . Am J Surg Path 2002. **26**(3): p. 350–7.
38. Wibe, A., et al., *Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer.* Br J Surg, 2002. **89**: p. 327-34.
39. Engeland, A., et al., *Relative survival of cancer patients-a comparison between Denmark and the other Nordic countries.* Acta Oncol 1998. **37**: p. 49–59.
40. (DCCG), D.C.C.G. *Annual report (in Danish)*. 2018; Available from: https://dccg.dk/wp-content/uploads/2019/09/DCCG-%C3%85rsrapport-2018.pdf.
41. Larsen, M.B., et al., *Potential for prevention: a cohort study of colonoscopies and removal of adenomas in a FIT-based colorectal cancer screening programme.* Scandinavian Journal of Gastroenterology, 2019. **54**(8): p. 1008-1014.
42. van Rooijen, S., et al., *Multimodal Prehabilitation in Colorectal Cancer Patients to Improve Functional Capacity and Reduce Postoperative Complications: The First International Randomized Controlled Trial for Multimodal Prehabilitation.* BMC Cancer, 2019 **19**(1): p. 98.
43. Gillis, C., et al., *Effects of Nutritional Prehabilitation, With and Without Exercise, on Outcomes of Patients Who Undergo Colorectal Surgery: A Systematic Review and Meta-analysis.* Gastroenterology , 2018. **155**(2): p. 391-410.
44. Wille-Jørgensen, P., et al., *Effect of more vs less frequent follow-up testing on overall and colorectal cancer-specific mortality in patients with Stage II or III colorectal cancer: The COLOFOL randomized clinical trial.* JAMA, 2018. **319**(20): p. 2095-2103.
45. Rosati, G., et al., *randomized trial of intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma.* Ann Oncol. , 2016. **27**(2): p. 274-280.

46. Snyder, R., et al., *Association between intensity of post-treatment surveillance testing and detection of recurrence in patients with colorectal cancer.* JAMA, 2018. **319**(20): p. 2104-2115.
47. Jakobsen, I.H. *Individual Follow-up After Rectal Cancer (FURCA)*. 2018; Available from: https://clinicaltrials.gov/ct2/show/study/NCT03622437?cond=follow+up+after+rectal+cancer&draw=2&rank=2.
48. Gögenur, I. *NEOadjuvant Chemotherapy Only Compared With Standard Treatment for Locally Advanced Rectal Cancer: a Randomized Phase II Trial (NEOLAR)*. 2017; Available from: https://clinicaltrials.gov/ct2/show/study/NCT03280407.
49. van Etten, **B.** *Rectal Cancer And Pre-operative Induction Therapy Followed by Dedicated Operation. The RAPIDO Trial (RAPIDO)*. 2011; Available from: https://clinicaltrials.gov/ct2/show/NCT01558921.

Table 1: Characteristics of 890 patients undergoing rectal cancer resection with curative intent, Denmark 2011-2012		
		No. of patients n (%)
Number		890
Patient-related		
Gender	Male	557 (62.6)
	Female	333 (37.4)
Age (years)	≤65	331 (37.2)
	>65	559 (62.8)
Charlson comorbidity	0	633 (71.1)
index	1	130 (14.6)
	≥ 2	127 (14.3)
ASA grade	I	224 (25.2)
	II	532 (59.8)
	III-IV	129 (14.5)
	Missing	5 (0.6)
Pathology/tumour-related		
Distance of primary tumour (lower edge)	0-5	218 (24.5)
from anal verge (cm)*	>5-10	367 (41.2)
	>10-15	265 (29.8)
	Missing	40 (4.5)
pT/ypT category	T0-T2	296 (33.3)
	T3	490 (55.1)
	T4	89 (10.0)
	Missing	15 (1.7)
UICC stage	I	229 (25.7)
	II	283 (31.8)
	III	270 (30.3)
	IV**	103 (11.6)
	Missing	5 (0.6)
Involved CRM	No	768 (86.3)
(<1 mm)***	Yes	83 (9.3)
	Missing	39 (4.4)

Treatment-related		
Neoadjuvant (chemo-) radiotherapy	No	610 (68.5)
	Yes	280 (31.5)
Surgical approach	Open****	301 (33.8)
	Laparoscopy	589 (66.2)
Surgery	TME	355 (39.9)
	PME	258 (29.0)
	APE	277 (31.1)
Blood loss,	0-300	674 (75.7)
intraoperative (ml)	>300	211 (23.7)
	Missing	5 (0.6)
Anastomotic leakage	Yes	92 (10.3)
	No	798 (89.7)
Plane of surgery	Mesorectal	511 (57.4)
	Non-mesorectal	343 (38.5)
	Missing	36 (4.0)

* Measured by rigid proctoscopy
** UICC stage IV rectal cancer patients had curatively intended treatment of distant metastasis along with rectal resection either during the index procedure or during an independent procedure in close timely relation to the index procedure.
*** Circumferential resection margin
**** Includes intended laparoscopic surgery but converted to open surgery.

Table 2: Three-year cumulative incidence proportions of 3-year overall survival, distant recurrence and local recurrence, Denmark 2011-2012

Characteristic		**3-year overall survival % (95% CI)**	**Distant recurrence CIP_3 * % (95% CI)**	**Local recurrence CIP_3 * % (95% CI)**
Total		80.6 (77.9; 83.1)	12.8 (10.6; 15.2)	6.5 (5.0; 8.4)
Patient-related				
Gender	Male	79.2 (75.7; 82.5)	13.0 (9.6; 17.0)	6.7 (4.7; 9.1)
	Female	83.0 (78.7; 86.9)	12.7 (10.0; 15.8)	6.3 (4.0; 9.4)
Age (years)	≤65	88.3 (84.5; 91.5)	12.9 (9.5; 16.9)	6.4 (4.0; 9.4)
	>65	**75.9** (72.2; 79.4)	12.7 (10.0; 15.8)	6.6 (4.7; 9.0)
Charlson Comorbidity Index	0	84.6 (81.6; 87.3)	12.1 (9.7; 14.9)	6.2 (4.4; 8.3)
	1	80.2 (72.8; 86.6)	11.9 (6.9; 18.5)	6.9 (3.2; 12.5)
	≥2	**61.0** (52.6; 69.6)	18.2 (11.3; 26.4)	8.2 (3.8; 14.7)
ASA-grade	I	91.8 (87.7; 94.9)	12.3 (8.4; 17.0)	6.8 (4.0; 10.7)
	II	**80.4** (76.8; 83.8)	12.2 (9.5; 15.3)	6.6 (4.6; 9.0)
	III-IV	**61.2** (52.9; 69.6)	17.3 (10.7; 25.3)	5.9 (2.4; 11.6)
Pathology/tumour-related				
Distance of primary tumour (lower edge) from anal verge (cm)**	0-5	79.1 (73.4; 84.2)	10.4 (6.7; 15.1)	6.0 (3.3; 10.0)
	>5-10	81.1 (76.9; 85.0)	11.9 (8.7; 15.6)	5.7 (3.6; 8.5)
	>10-15	82.0 (77.1; 86.4)	15.7 (11.4; 20.5)	7.5 (4.6; 11.3)
pT/ypT-category	T0-T2	86.7 (82.6; 90.3)	5.1 (2.9; 8.2)	2.9 (1.4; 5.5)
	T3	79.5 (75.7; 83.0)	**14.0** (11.0; 17.4)	5.5 (3.6; 7.9)
	T4	**65.7** (55.5.; 75.6)	**17.9** (9.7; 28.2)	**25.0** (16.1; 34.8)
UICC stage	I	88.2 (83.6; 92.0)	3.8 (1.8; 7.0)	1.9 (0.6; 4.4)
	II	83.8 (79.2; 87.8)	4.1 (2.2; 7.0)	5.5 (3.2; 8.8)
	III	79.5 (74.3; 84.2)	**16.8** (12.4; 21.8)	**9.4** (6.2; 13.5)
	IV***	**58.7** (49.3; 68.5)	**46.3** (36.0; 56.1)	**12.6** (6.9; 20.1)
Involved CRM (<1 mm)****	No	82.8 (80.1; 0.85)	9.8 (7.7; 12.1)	5.0 (3.6; 6.8)
	Yes	**63.2** (52.7; 73.8)	**34.5** (23.9; 45.2)	**19.7** (11.6; 29.3)
Treatment-related				
Neoadjuvant (chemo) radiotherapy	No	81.6 (78.4; 84.7)	11.1 (8.8; 14.0)	6.7 (4.8; 8.9)
	Yes	78.4 (73.4; 83.0)	16.4 (12.1; 21.7)	6.3 (3.7; 9.7)

Surgical approach	Laparoscopy	84.0 (80.9; 86.8)	10.0 (7.7; 12.7)	4.0 (2.6; 5.9)
	Open*****	**73.7** (68.4; 78.7)	**18.5** (14.1; 23.4)	**11.6** (8.1; 15.8)
Type of surgery	TME	84.6 (80.6; 88.1)	9.5 (6.6; 12.9)	3.1 (1.6; 5.4)
	PME	79.0 (73.7; 83.9)	**17.6** (13.1; 22.7)	**11.0** (7.4; 15.3)
	APE	76.9 (71.8; 81.7)	9.8 (6.4; 14.1)	6.9 (4.2; 10.5)
Blood loss, intraoperative (ml)	0-300	84.0 (81.1; 86.7)	11.0 (8.7; 13.6)	4.5 (3.1; 6.3)
	>300	**69.8** (63.5; 76.0)	18.5 (13.3; 24.4)	**13.5** (9.1; 18.9)
Anastomotic leak	No	80.9 (78.1; 83.6)	12.3 (10.0; 14.7)	6.4 (4.8; 8.4)
	Yes	77.8 (68.8; 85.7)	17.8 (10.3; 27.0)	7.6 (3.1; 14.7)
Plane of surgery	Mesorectal	83.9 (80.6; 87.0)	11.6 (8.9; 14.7)	5.6 (3.7; 7.9)
	Non-mesorectal	**75.7** (71.0; 80.2)	14.3 (10.7; 18.4)	8.0 (5.4; 11.4)

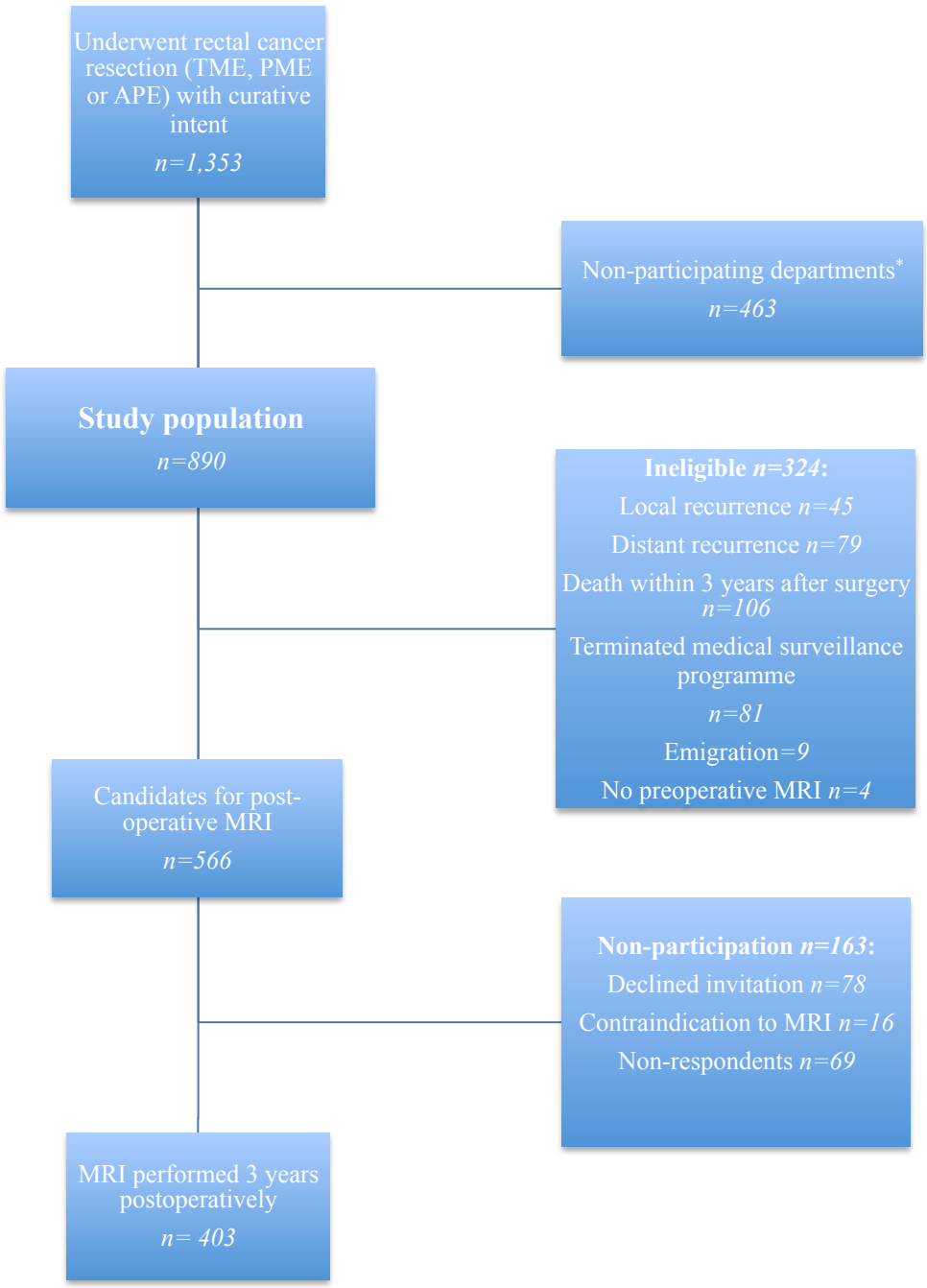
* Three-year cumulative incidence proportion. Calculated treating death as a competing risk.
** Measured by rigid proctoscopy
*** UICC stage IV rectal cancer patients had curatively intended treatment of distant metastasis along with rectal resection either during the index procedure or during an independent procedure in close timely relation to the index procedure.
**** Circumferential resection margin
***** Includes intended laparoscopic surgery but converted to open surgery.

Table 3: Adjusted Hazard Ratios (0-3 years) associating different characteristics with overall survival, distant recurrence and local recurrence after intended curative rectal cancer resection				
Characteristic		**Adjusted Hazard ratio Overall survival* (95%CI)**	**Adjusted Hazard ratio Distant recurrence* (95%CI)**	**Adjusted Hazard ratio Local recurrence* (95%CI)**
Total		-	-	-
Patient-related				
Gender	Male	1.05 (0.72; 1.52)	0.84 (0.52; 1.36)	0.97 (0.50; 1.90)
	Female	1.0 (ref)	1.0 (ref)	1.0 (ref)
Age (years)	≤65	1.0 (ref)	1.0 (ref)	1.0 (ref)
	>65	**1.86** (1.19; 2.91)	1.19 (0.73; 1.94)	1.18 (0.58; 2.42)
Charlson Comorbidity Index	0	1.0 (ref)	1.0 (ref)	1.0 (ref)
	1	1.11 (0.67; 1.84)	1.11 (0.53; 2.32)	1.27 (0.50; 3.24)
	≥2	**2.72** (1.77; 4.16)	**2.15** (1.08; 4.29)	**3.32** (1.37; 8.06)
ASA grade	I	1.0 (ref)	1.0 (ref)	1.0 (ref)
	II	1.70 (0.97; 2.98)	0.67 (0.39; 1.16)	0.95 (0.43; 2.07)
	III-IV	**2.71** (1.41; 5.21)	0.84 (0.37; 1.89)	0.54 (0.17; 1.75)
Pathology/tumour-related				
Distance of primary tumour (lower edge) from anal verge (cm)**	>10-15	1.0 (ref)	1.0 (ref)	1.0 (ref)
	>5-10	1.06 (0.64; 1.79)	0.77 (0.39; 1.52)	2.55 (0.99; 6.55)
	0-5	1.06 (0.54; 2.07)	0.73 (0.31; 1.70)	**4.60** (1.28; 16.46)
pT/ypT category	T0-T2	1.0 (ref)	1.0 (ref)	1.0 (ref)
	T3	1.24 (0.62; 2.46)	2.45 (0.94; 6.39)	0.56 (0.17; 1.85)
	T4	1.34 (0.58; 3.10)	2.06 (0.68; 6.24)	2.31 (0.65; 8.18)
UICC stage	I	1.0 (ref)	1.0 (ref)	1.0 (ref)
	II	0.82 (0.36; 1.90)	0.58 (0.14; 2.37)	1.76 (0.36; 8.73)
	III	1.34 (0.64; 2.85)	2.52 (0.70; 9.07)	3.56 (0.84; 15.13)
	IV***	**3.27** (1.50; 7.11)	**8.86** (2.48; 31.74)	**6.57** (1.43; 30.16)
Involved CRM (<1 mm)****	Yes	1.60 (0.95; 2.68)	**2.27** (1.26; 4.09)	**2.72** (1.18; 6.26)
	No	1.0 (ref)	1.0 (ref)	1.0 (ref)
Treatment-related				
Neoadjuvant CRT	Yes	1.17 (0.77; 1.76)	1.53 (0.91; 2.59)	0.98 (0.42; 2.29)

	No	1.0 (ref)	1.0 (ref)	1.0 (ref)
Surgical approach	Laparoscopy	0.73 (0.49; 1.10)	0.64 (0.38; 1.09)	0.68 (0.31; 1.46)
	Open*****	1.0 (ref)	1.0 (ref)	1.0 (ref)
Type of surgery	TME	1.0 (ref)	1.0 (ref)	1.0 (ref)
	PME	1.53 (0.89; 2.63)	1.25 (0.62; 2.57)	**4.70** (1.70; 13.03)
	APE	1.37 (0.85; 2.19)	1.09 (0.57; 2.08)	0.80 (0.30; 2.10)
Blood loss,	0-300	1.0 (ref)	1.0 (ref)	1.0 (ref)
intraoperative (ml)	>300	1.46 (0.96; 2.23)	1.28 (0.73; 2.24)	1.98 (0.94; 4.16)
Anastomotic leakage	Yes	1.46 (0.87; 2.47)	1.16 (0.60; 2.28)	0.97 (0.37; 2.56)
	No	1.0 (ref)	1.0 (ref)	1.0 (ref)
Plane of surgery	Mesorectal	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Non-mesorectal	**1.68** (1.17; 2.38)	1.29 (0.81; 2.07)	1.24 (0.64; 2.41)

* COX regression analysis. Mutually adjusted. Hazard ratio (HR) >1 describes increased risk of local recurrence or distant recurrence, or reduced survival.
** Measured by rigid proctoscopy
*** UICC stage IV rectal cancer patients had curatively intended treatment of distant metastasis along with rectal resection either during the index procedure or during an independent procedure in close timely relation to the index procedure.
**** Circumferential resection margin
***** Includes intended laparoscopic surgery but converted to open surgery.

Figure 1 Flow-chart of 1,353 patients with first-time rectal cancer diagnosis between 1 April 2011 and 31 August 2012 and treated at 10 hospitals in Denmark



*Bispebjerg, *n=78*, Herlev, *n=97*, Hillerød, *n=92*, Aalborg, *n=131*, Sønderjylland, *n=62*, Horsens, *n=1*, Viborg, *n=2*

Figure 2 Overall survival of rectal cancer during 3 years of follow-up

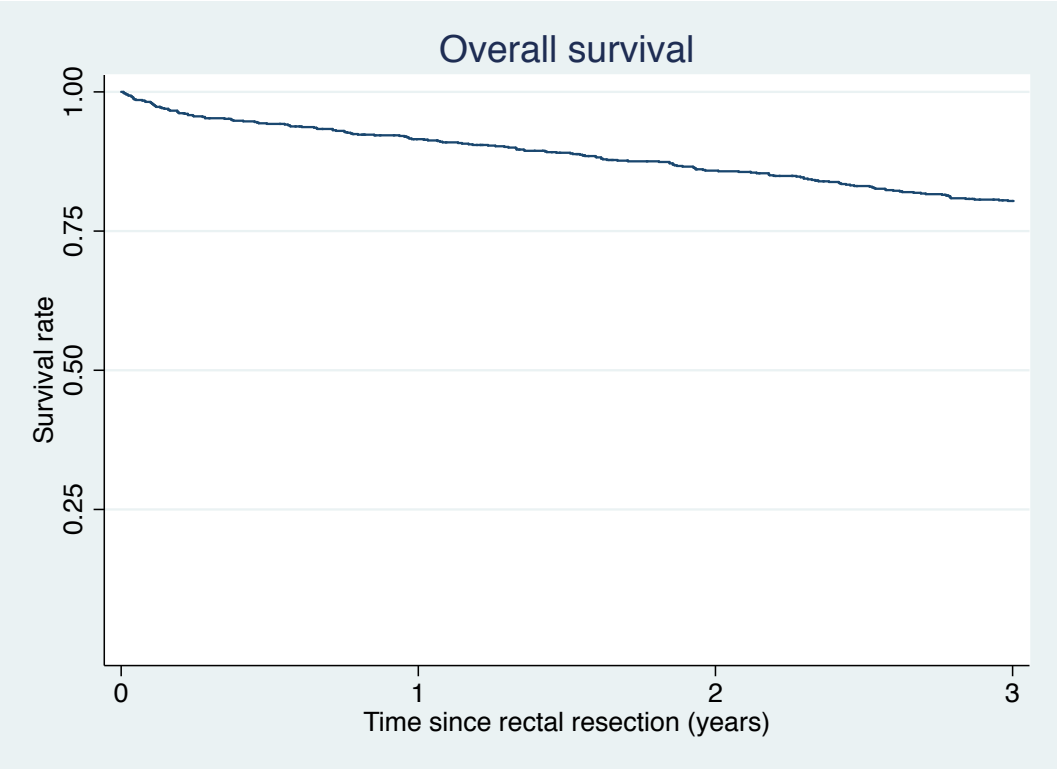


Figure 3 Cumulative incidence proportion of local and/or distant recurrence during 3 years of follow-up

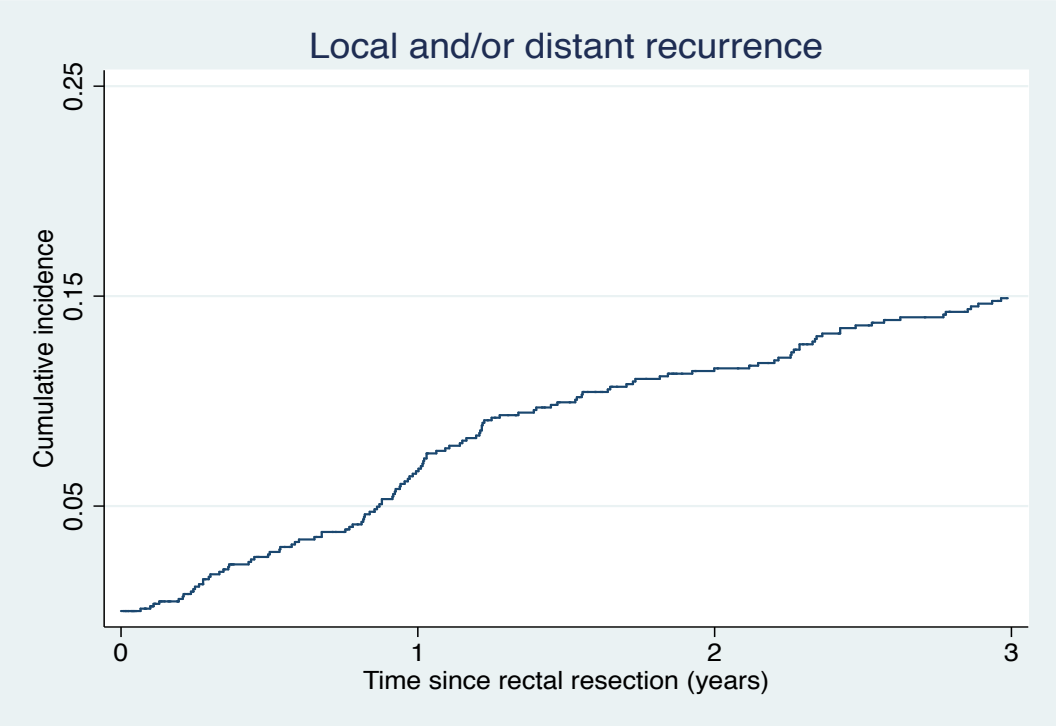


Figure 4 Cumulative incidence proportion of distant recurrence during 3 years of follow-up

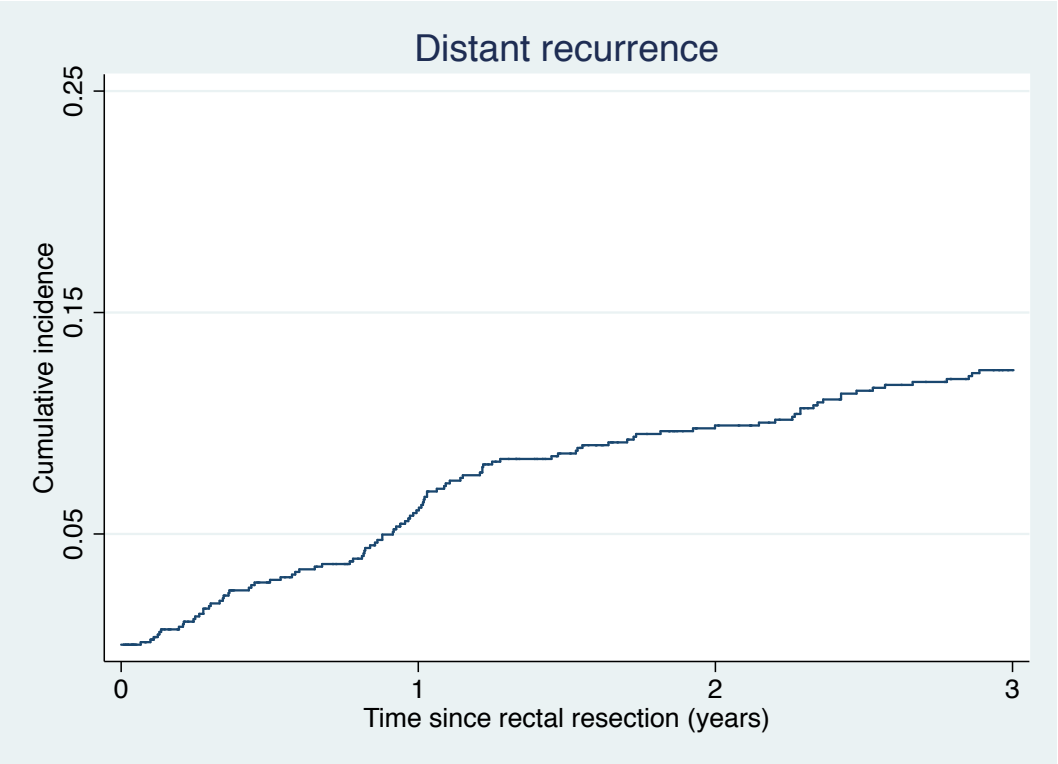
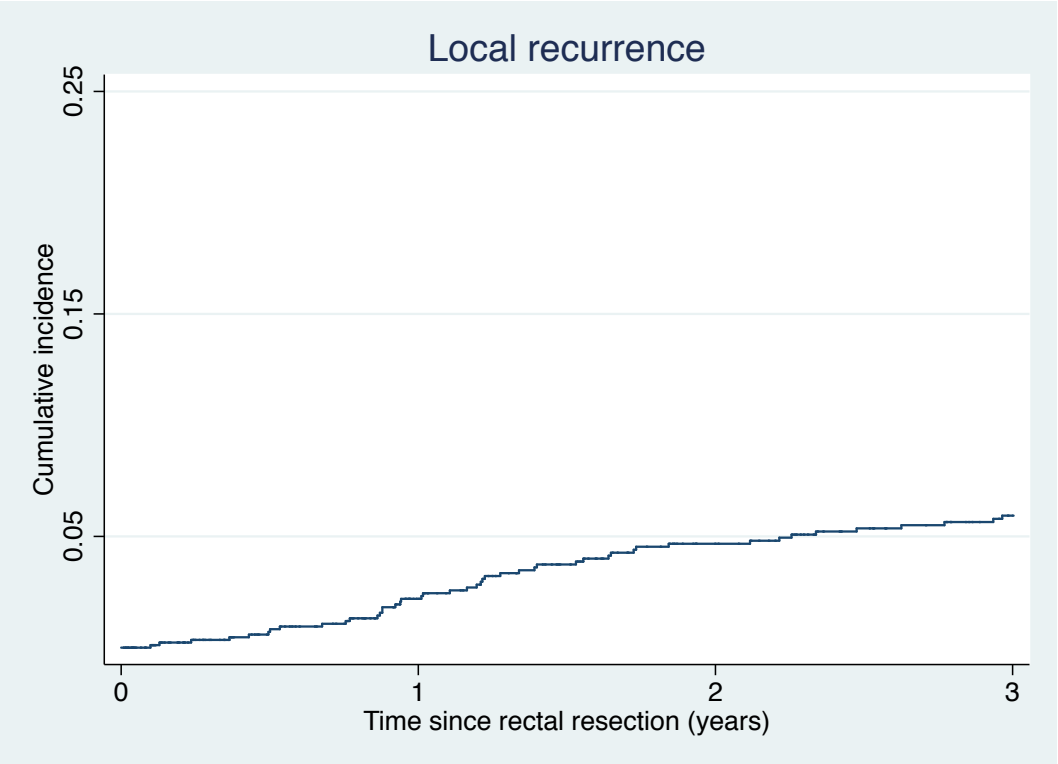


Figure 5 Cumulative incidence proportion of local recurrence during 3 years of follow-up



Paper II

Stoma reversal after intended restorative rectal cancer resection in Denmark. A nationwide population-based study.

J. B. Jørgensen[1,2], R. Erichsen[2,3], B. G. Pedersen[4], S. Laurberg[1], and L. H. Iversen[1,5]

[1] Aarhus University Hospital, Department of Surgery, Denmark

[2] Randers Regional Hospital, Department of Surgery, Denmark

[3] Aarhus University Hospital, Department of Clinical Epidemiology, Denmark

[4] Aarhus University Hospital, Department of Radiology, Denmark

[5] Danish Colorectal Cancer Group, Copenhagen, Denmark

Corresponding author

Jesper Beck Jørgensen, M.D.

Aarhus University Hospital, Department of Surgery

Palle Juul-Jensens Boulevard 99

8250 Aarhus N

Denmark

E-mail: jesjoe@rm.dk

Abstract

Background

Data on stoma reversal (SR) following restorative rectal resection (RRR) with a diverting stoma (DS) are conflicting. This study investigated a Danish population-based cohort of patients undergoing RRR to evaluate factors predictive of SR during 3 years of follow-up.

Method

Patients from National Registries with rectal cancer undergoing RRR or Hartmann's operation (HO) with curative intent from May 2001 through April 2012 were included.

RRR patients with a DS were followed from the time of primary rectal cancer resection until date of SR, death, emigration or end of 3 years follow-up. The cumulative incidence proportion (CIP) of SR at 1 and 3 years was calculated treating death as a competing risk. Predictive factors of SR were explored using multiple Cox regression.

Results

Out of the 6 859 patients included, 35.7%, 41.9% and 22.4% had RRR with DS, RRR without a stoma, and HO with an end-colostomy respectively. In patients with a DS, CIP of SR was 70.3% (95% CI 68.4-72.1) after 1 year, and 74.3% (95% CI 72.5-76.0) after 3 years. Neoadjuvant treatment (HR 0.75; 95% CI 0.66-0.85), blood loss > 300 ml (HR 0.86; 95% CI 0.76-0.97), anastomotic leakage (HR 0.41; 95% CI 0.33-0.50), T category 3 (HR 0.63; 95% CI 0.47-0.83), T category 4 (HR 0.62; 95% CI 0.42-0.90) and UICC stage IV (HR 0.57; 95% CI 0.41-0.80) were possible predictors for delayed SR.

Conclusion

One quarter of the patients had not had their diverting stoma reversed three years after the intended restorative rectal cancer resection.

Introduction

In rectal cancer surgery, diverting stomas (DS) are created primarily to reduce the consequences of a possible anastomotic leakage [1-6]. Danish guidelines recommend a DS along with total mesorectal excision (TME) in the surgical treatment of mid-and distal rectal cancer (i.e., tumour located 0 - 10 cm from the anal verge). A DS, however, is not routinely created as part of partial mesorectal excision (PME) for upper rectal cancer [7].

DSs are usually reversed after 3 months and possibly even earlier in selected cases with uneventful postoperative courses [8]. For patients in the need of postoperative oncological treatment however, stoma reversal can be postponed [8].

Unfortunately, not all patients undergo reversion of the stoma after surgery. The risk of a non-reversal after rectal resection with an intended temporary DS varies between 3 and 32% after 1.5 to 7.1 years [9-19]. Current literature suggests a median time to reversal between 1.5 and 5.1 years [9-19]. Consequences of non-reversal may be grave. Stoma-related complications ranging from minor inconvenience (e.g. leakage from the appliance and skin rash) to major disabilities (e.g. dehydration and electrolyte imbalance due to a high stoma output, parastomal hernia and stoma prolapse) are common [6], and may be associated with restriction in social activities and reduced quality of life [10, 15, 20, 21].

Many studies have been conducted in a regional setting, [11-18]; therefore, a nationwide registry-based cohort study of rectal cancer patients that are managed according to modern treatment regimens can be important to have a clear picture of the current clinical practice.

The primary aim of this study was to estimate the DS reversal rate among patients undergoing rectal resection. Secondary aims included characteristics of patients undergoing RRR and Hartmann's operation, estimation of the proportion of patients receiving a stoma, along with the exploration of predictors of DS reversal.

Material and methods

Study design and setting. This population-based nationwide cohort study was approved by the National Board of Health (ref.: 3-3013-1272/1/), the Scientific Committee of the Danish Colorectal Cancer Group (DCCG.dk), and the Danish Data Protection Agency (ref.: 2007-58-0010). The study was conducted in the setting of the entire Danish population [22]. The National Health Service in Denmark provides universal, tax-supported health care to all citizens, guaranteeing free access to general practitioners and public hospitals[23].

Data retrieved included, clinical, demographic data, co-morbidities, ASA score, tumour characteristics (distance from the anal verge), neoadjuvant treatment, pathologic stage, and surgical procedures and approach, blood loss, post-operative anastomotic leakage and death within 3 years from the surgical index procedure.

Data sources. Data were obtained from 3 registries: the Danish Colorectal Cancer Group (DCCG.dk) Database (DCCG), Civil Registration System (CRS) and the Danish National Patient Registry (DNRP).

Since May 2001, DCCG database has been recording information on all patients with colorectal cancer with a completeness of 96–99% [24]. The purpose of the database is to ensure uniform quality in diagnostics and treatment of colorectal cancer in Denmark. All surgical departments across Denmark report on diagnostic staging, treatment and postoperative complications (occurring within 30 days after surgery) prospectively [24]. For this study, the DCCG database was used to identify the study cohort, as described below.

The Danish CRS has assigned a unique 10-digit personal identification number (CPR number) to every resident in Denmark and it is used since 1968. The registry maintains information on date of birth, death, sex, residence and vital status. The civil registration number permits linkage within the healthcare system and among registries in Denmark [25].

Finally, the DNRP has maintained records on all non-psychiatric hospitalisations in Denmark since 1977. These include information on hospital diagnoses and procedures [26]. Data are collected for administrative purposes unrelated to research objectives. For instance, these data include the CPR number, dates of admission and discharge and up to 20 discharge diagnoses, coded by physicians according to the 10th revision of the International Classification of Diseases (ICD-10) from 1993 and onwards [27]. Since January 1, 1996, registration of surgical procedures in Denmark has been classified according to the Nordic Medico- Statistical Committee Classification of Surgical Procedures (NOMESCO). DCCG and

DNRP data were linked to obtain information on surgical events during follow-up (i.e., stoma reversal).

Study cohort. Patients diagnosed with rectal adenocarcinoma (located 15 cm or less from the anal verge) in the DCCG database between May 1, 2001 and April 30, 2012, who underwent intended restorative rectal resection (TME, PME) or Hartmann's procedure with curative intent, were identified. Patients were excluded if they had surgical procedures other than intended restorative rectal resection or Hartmann's operation, those who emigrated before start of follow-up, had palliative surgery or had no registration of any surgical procedure in the DNRP despite registration in the DCCG database (Figure 1).
National guidelines recommend neoadjuvant long-course (chemo)- radiotherapy (CRT) (50 Gy in 25-28 fractions combined with 5-Fluorouracil (5-FU)) to patients with locally advanced rectal cancer [28]. Alternatively, short-course radiotherapy can be offered in some situations. Intended restorative rectal resection and Hartmann's operation performed as mesorectal excision were done 8-10 weeks after the completion of CRT. Short-course radiotherapy with immediate surgery is not routinely performed in Denmark. All other patients underwent direct intended restorative rectal resection or Hartmann's operation. Selected UICC stage II rectal cancer patients were offered 6 months of adjuvant chemotherapy. The same applied for UICC stage III rectal cancer patients who had not received neoadjuvant CRT [28].

Stoma reversal. Patients who underwent intended restorative rectal resection with a DS were followed from the time of primary rectal cancer resection (= index operation) until the date of stoma reversal (study endpoint), death, emigration, or end of follow-up after 3 years. Information on stoma status (i.e., reversal or non-reversal of DS) during 3 years of follow-up was obtained through the DNRP, retrieving surgical procedure codes indicating stoma reversal according to the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures.
Medical records from 9% of patients receiving a DS at the index operation were systemically reviewed in order to validate the stoma status as retrieved from the DNRP. Deviations from stoma status as retrieved from DNRP were registered.

Statistical analysis. Patients were characterized according to rectal resection procedure (DS, no stoma, and Hartmann's procedure), year of index operation and demographics.

The cumulative incidence proportion (CIP) of stoma reversal at 1 and 3 years following rectal cancer surgery were calculated overall, and for various patient- and disease-related factors treating death as a competing risk.

Potential predictive factors for stoma reversal (period of surgery, gender, age at surgery, body-mass index (BMI), Charlson comorbidity index (CCI), ASA classification, distance of primary tumour (lower edge) from anal verge (categorised as low (0 - 5 cm) vs. mid/ high (6 - 10 cm / 11 - 15 cm), use of neoadjuvant CRT, surgical approach, intraoperative blood loss, anastomotic leakage, (y)pT category (according to T category), and UICC stage) were explored in a Cox proportional hazards regression model. Both univariable and multivariable analysis was performed. Multivariable analysis included all potential predictors for stoma reversal.

Stata® version 12.0 (StataCorp, College Station, Texas, USA) was used for statistical analysis.

Results

Between May 1, 2001 and April 30, 2012, 15 303 patients with first-time rectal cancer were treated at 21 hospitals in Denmark. Among these, 6 859 patients underwent intended restorative rectal resection or Hartmann's operation with curative intent and comprised the study cohort. Details regarding selection of the study cohort are described in Figure 1.

The proportion of patients undergoing intended restorative rectal resection with a DS generally increased over the study period from 29.7 to 42.4% between 2001 - 2004 and 2009 - 2012 (Table 1). In comparison, the proportion of patients who had either restorative rectal resection with no DS or Hartmann's procedure, gradually diminished over the study period.

Patients undergoing restorative rectal resection with formation of a DS, and patients without a stoma were comparable with respect to age, BMI, comorbidity, T category, UICC stage, surgical approach, and anastomotic leakage rate (Table 1). However, male gender, tumour location in the lower or mid rectum, use of neoadjuvant CRT, and higher blood loss were more common among patients with a DS compared to those without a DS. Demographics, tumour characteristics and treatment regimens are summarised in Table 1.

In total, 225 medical records were reviewed to validate stoma status at 3-year follow-up. Discrepancies were found for seven patients (3.1%; 95% CI 0.8-5.4) as compared to the register-based status. Discrepancies were caused by incorrect NOMESCO registration of stoma reversal during follow-up (both missing registration of reversal and registration of reversal never mentioned in medical records) or incorrect registration of the CPR number.

Cumulative incidence proportion of stoma reversal. The CIP of DS reversal was 70.3% (95% CI 68.4–72.1) after 1 year, and 74.3% (95% CI 72.5-76.0) after 3 years, as shown in Figure 2 and Table 2. Median time to stoma reversal was 173.0 days (range: 1-1075).

Patients with ASA score > II, neoadjuvant CRT, blood loss > 300 ml, anastomotic leakage, T category > 2, and UICC stage > II had particularly low CIP of stoma reversal at 1 year after the index operation (Table 2). Similarly, at 3 years after the index operation, patients aged > 65 years (CIP 0.72; 95% CI 0.69-0.74), with ASA grade > II (CIP 0.64; 95% CI 0.58-0.69), neoadjuvant CRT (CIP 0.68; 95% CI 0.64-0.71), blood loss > 300 ml (CIP 0.70; 95% CI 0.67-0.73), anastomotic leakage (CIP 0.45; 95% CI 0.39-0.51), T category 3 (CIP 0.73; 95% CI 0.70-0.75) and 4 (CIP 0.66; 95% CI 0.56-0.74), UICC stage III (CIP 0.71; 95% CI 0.68-0.74) and IV (CIP 0.57; 95% CI 0.50-0.64), had particularly low CIP's (Table 2).

Patients with UICC stage I disease had the highest CIP of stoma reversal at 3 years after the index operation (80.0%). Patients with anastomotic leakage had the lowest CIP of stoma reversal at 3 years after the index operation (45.0%).

Factors predictive of delay in stoma reversal in multivariable analysis. Higher ASA grade (ASA II and ASA III-IV), neoadjuvant CRT, blood loss > 300 ml, anastomotic leakage, advanced T category (T category 2, T category 3 and T category 4), and more advanced UICC stage (UICC II, UICC III, and UICC IV) were associated with a risk of delay in time to stoma reversal in univariable analysis.

In multivariable analysis, neoadjuvant CRT (HR 0.75; 95% CI 0.66-0.85), blood loss > 300 ml (HR 0.86; 95% CI 0.76-0.97), anastomotic leakage (HR 0.41; 95% CI 0.33-0.50), T category 3 (HR 0.63; 95% CI 0.47-0.83), T category 4 (HR 0.62; 95% CI 0.42-0.90), and UICC stage IV (HR 0.57; 95% CI 0.41-0.80) were found to be independent predictors of delay in time to stoma reversal (Table 3).

Discussion

The main finding of this nationwide, population-based cohort study was the fact that an unexpectedly low rate of only 74% of rectal cancer patients with an intended temporary DS had their stoma reversed during 3 years of follow-up. Since more than one third of patients undergoing intended restorative rectal resection had a DS, a substantial number of patients end up with a permanent stoma.

Previous studies investigating stoma reversal rates following anterior resection show a great variation in permanent stoma rates [13, 19]. Majority of these studies are based on smaller patient cohorts (ranging from 50 to 523 included patients [11-14, 16, 18]) and originate from single centres or from a local region.

Multicentre studies on rectal cancer patients only [9, 10, 15, 17] report a 17-25% [9] [10] risk of a permanent stoma after intended rectal resection together with a DS, similar to what was herein documented.

In this study, the independent predictive factors for stoma non-reversal within 3 years were anastomotic leakage, advanced UICC stage IV, T category 4, T category 3, use of neoadjuvant CRT, and perioperative blood loss > 300 ml. These results are in line with previous studies, which all show that increasing age, comorbidity [10, 12, 17, 18, 20], locally advanced or metastatic disease [11, 12, 16, 17], any postoperative complications [11, 12, 15, 17] and anastomotic leakage[14, 16, 18] increased the probability of a permanent stoma after anterior resection.

A retrospective, multicentre English study (2001-2003) including 6 582 patients (964 patients with a DS), examined the use of loop-ileostomy following low anterior resection. The study showed that increasing age and comorbidity increased the probability of a permanent stoma. However, only a relatively low proportion of patients (14.6%) had a DS at time of primary surgery and none of the patients had neoadjuvant CRT [10]. In present cohort, neoadjuvant CRT was a significant predictor of stoma non-reversal. The differences in baseline characteristics of the patient cohorts in the two studies may lead to non-comparable results.

A Swedish retrospective multicentre study including 3 564 patients undergoing rectal cancer surgery observed that higher level of education increased the probability of early stoma reversal. Postoperative complications, adjuvant chemotherapy, advanced UICC stage, and advanced ASA grade were associated with delay in time to stoma reversal. This study differs from present study, as it provides no information on the proportion of patients who receive

a stoma at index surgery. Further, follow-up was short (total of 1.5 years) and included no validation on clinical information from Swedish registries [9].

Two prospective multicentre studies examined risk factors of a permanent stoma following TME with formation of either a diverting colostomy (37% and 3% respectively) or ileostomy (63% and 97% respectively). Comorbidity, metastatic disease, anastomotic leakage, deteriorated ano-rectal function, postoperative complications of any kind and secondary constructed stomas were significant risk factors [15, 17]. However, results from these studies cannot be extrapolated directly, as the risk of a permanent stoma following construction of diverting colostomy may be different from a diverting ileostomy.

Interestingly, present study shows that an increasing proportion of patients underwent restorative rectal cancer resection as time passed. Whereas 30% of patients underwent restorative surgery from 2001 to 2004, a whole of 42% did the same from 2009 to 2012. This general change in surgical approach may partly be a result of revision of national guidelines in 2009 and methodological alignment between departments.

Changes in surgical approach over time with extended use of DS have not been found in other studies, and suggest that surgeons may be increasingly more cautious following restorative rectal cancer resection. However, recent studies from The Netherlands found no difference in the short-term postoperative complication rates between patients undergoing rectal cancer resection with DS by routine or if DS only was performed in highly selective patients [29, 30]. Equally, findings from present study suggest that long-term complications might be another important issue that requires attention in the pre-operative setting. Selecting specific patient groups for stoma construction is found to be a key element in optimising patient outcomes. These findings may change the tendency towards a more selective approach to DS construction in future.

The biggest strengths of this study are the nationwide prospective design, the large patient cohort and a long follow-up period of 3 years. Data were retrieved from three highly reliable registries with prospective sampling of data and high data completeness [25, 26, 31]. Unlike most previous studies, this study is based on data from current time period, where treatment regimens comply with modern standards.

Although data were retrieved from validated registries, the validity and methods of data reporting might differ between hospitals. This is one of the limitations, since coding errors related to operative procedures may occur. However, discrepancies between medical records and databases regarding stoma status at 3-year follow-up were low in the sample survey of 9% of patients who had rectal resection with formation of a DS.

The present study shows that a quarter of the patients had not undergone stoma reversal three years after restorative rectal cancer resection in Denmark. This number was doubled, where the postoperative management was complicated by an anastomotic leak.

Acknowledgements

The present study was funded by the Danish Cancer Society.

The scientific committee under the DCCG is acknowledged for their contribution in consultancy services in linkage based on registries and clinical databases.

References

1. Matthiessen, P., et al., *Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial.* Ann Surg, 2007. **246**(2): p. 207-14.
2. Gastinger, I., et al., *Protective defunctioning stoma in low anterior resection for rectal carcinoma.* Br J Surg, 2005. **92**(9): p. 1137-42.
3. Karanjia, N.D., et al., *Risk of peritonitis and fatal septicaemia and the need to defunction the low anastomosis.* Br. J. Surg., 1991. **78**: p. 196-1 98.
4. Marusch, F., et al., *Value of a Protective Stoma in Low Anterior Resections for Rectal Cancer.* Dis Colon Rectum, 2002. **45**: p. 1164-1171.
5. Dehni, N., et al., *Influence of a defunctioning stoma on leakage rates after low colorectal anastomosis and colonic J pouch–anal anastomosis.* British Journal of Surgery, 1998. **85**: p. 1114–1117.
6. Chow, A., et al., *The morbidity surrounding reversal of defunctioning ileostomies: a systematic review of 48 studies including 6,107 cases.* Int J Colorectal Dis, 2009. **24**(6): p. 711-23.
7. Danish Society of Surgery, D.C.C.G., *Guidelines for the diagnosis and the management of colorectal cancer (in Danish).* 2009(4).
8. Alves, A., et al., *Randomized clinical trial of early versus delayed temporary stoma closure after proctectomy.* Br J Surg, 2008. **95**(6): p. 693-8.
9. Gustafsson, C.P., et al., *Loop-ileostomy reversal-patient-related characteristics influencing time to closure.* Int J Colorectal Dis, 2018. **33**(5): p. 593-600.
10. David, G.G., et al., *Loop ileostomy following anterior resection: is it really temporary?* Colorectal Dis, 2010. **12**(5): p. 428-32.
11. Gessler, B., E. Haglind, and E. Angenete, *Loop ileostomies in colorectal cancer patients--morbidity and risk factors for nonreversal.* J Surg Res, 2012. **178**(2): p. 708-14.
12. Pan, H.D., et al., *Risk Factors for Nonclosure of a Temporary Defunctioning Ileostomy Following Anterior Resection of Rectal Cancer.* Dis Colon Rectum, 2016. **59**: p. 94–100.
13. Lordan, J.T., et al., *Following anterior resection for rectal cancer, defunctioning ileostomy closure may be significantly delayed by adjuvant chemotherapy: a retrospective study.* Colorectal Dis, 2007. **9**(5): p. 420-2.
14. Dinnewitzer, A., et al., *Cumulative Incidence of Permanent Stoma After Sphincter Preserving Low Anterior Resection of Mid and Low Rectal Cancer.* Dis Colon Rectum, 2013. **56**: p. 1134–1142.
15. den Dulk, M., et al., *A multivariate analysis of limiting factors for stoma reversal in patients with rectal cancer entered into the total mesorectal excision (TME) trial: a retrospective study.* The Lancet Oncology, 2007. **8**(4): p. 297-303.
16. Bailey, C.M.H., et al., *The incidence and causes of permanent stoma after anterior resection.* Colorectal Disease, 2003. **5**: p. 331–334.
17. Lindgren, R., et al., *What is the risk for a permanent stoma after low anterior resection of the rectum for cancer? A six-year follow-up of a multicenter trial.* Dis Colon Rectum, 2011. **54**(1): p. 41-7.
18. Chiu, A., et al., *Failing to reverse a diverting stoma after lower anterior resection of rectal cancer.* Am J Surg, 2014. **207**(5): p. 708-11; discussion 711.
19. Maggiori, L., et al., *Conservative management is associated with a decreased risk of definitive stoma after anastomotic leakage complicating sphincter-saving resection for rectal cancer.* Colorectal Dis, 2011. **13**(6): p. 632-7.

20. Kairaluoma, M., et al., *Outcome of Temporary Stomas.* Dig Surg, 2002. **19**: p. 45–51.
21. O'Leary, D.P., et al., *Quality of life after low anterior resection with total mesorectal excision and temporary loop ileostomy for rectal carcinoma.* British Journal of Surgery, 2001. **88**: p. 1216-1220.
22. Frank, L., *When an Entire Country Is a Cohort.* Science, 2000. **287**: p. 2398-99.
23. Schmidt, M., et al., *The Danish health care system and epidemiological research: from health care contacts to database records.* Clin Epidemiol, 2019. **11**: p. 563-591.
24. Ingeholm, P., I. Gogenur, and L.H. Iversen, *Danish Colorectal Cancer Group Database.* Clin Epidemiol, 2016. **8**: p. 465-468.
25. Schmidt, M., L. Pedersen, and H.T. Sorensen, *The Danish Civil Registration System as a tool in epidemiology.* Eur J Epidemiol, 2014. **29**(8): p. 541-9.
26. Schmidt, M., et al., *The Danish National Patient Registry: a review of content, data quality, and research potential.* Clin Epidemiol, 2015. **7**: p. 449-90.
27. Lynge, E., J.L. Sandegaard, and M. Rebolj, *The Danish National Patient Register.* Scand J Public Health, 2011. **39**(7 Suppl): p. 30-3.
28. (DCCG), D.C.C.G. *Guidelines for the diagnosis and the management of colorectal cancer (in Danish)* 2009; 4:[Available from: https://dccg.dk/wp-content/uploads/2017/08/Retningslinier2009revOKT2010.pdf.
29. Snijders, H.S., et al., *Optimal Treatment Strategy in Rectal Cancer Surgery: Should We Be Cowboys or Chickens?* Ann Surg Oncol, 2015. **22**(11): p. 3582-9.
30. Blok, R.D., et al., *Impact of an institutional change from routine to highly selective diversion of a low anastomosis after TME for rectal cancer.* Eur J Surg Oncol, 2018. **44**(8): p. 1220-1225.
31. Bulow, S., et al., *Improved survival after rectal cancer in Denmark.* Colorectal Dis, 2010. **12**(7 Online): p. e37-42.

Table 1: Characteristics of 6 859 patients undergoing intended restorative rectal resection or Hartmann's operation, Denmark 2001-2012

Surgical procedure		Rectal resection with diverting stoma n (%)	Rectal resection with no stoma n (%)	Hartmann's operation n (%)
Number		2 449 (35.7)	2 876 (41.9)	1 534 (22.4)
Period of surgery	May 2001 - Dec 2004	677 (29.7)	979 (43.0)	620 (27.2)
	Jan 2005 - Dec 2008	865 (35.4)	1,090 (44.6)	490 (20.0)
	Jan 2009 - Apr 2012	907 (42.4)	807 (37.7)	424 (19.8)
Gender	Male	1 551 (63.3)	1 571 (54.6)	943 (61.5)
	Female	898 (36.7)	1 305 (45.4)	591 (38.5)
Age (years), median (range)		65 (20-91)	67 (29-97)	75 (28-94)
BMI (kg/m^2)	0-19	101 (4.1)	155 (5.4)	109 (7.1)
	20-24	853 (34.8)	1 017 (35.4)	447 (29.4)
	25-29	781 (31.9)	878 (30.5)	339 (22.1)
	+30	277 (11.3)	296 (10.3)	157 (10.2)
	Missing	437 (17.8)	530 (18.4)	482 (31.4)
Charlson Comorbidity Index	0	2 079 (84.9)	2 390 (83.1)	1 082 (70.5)
	1-2	327 (13.4)	424 (14.7)	363 (23.7)
	+3	43 (1.8)	62 (2.2)	89 (5.8)
ASA grade	I	745 (30.4)	903 (31.4)	178 (11.6)
	II	1 402 (57.2)	1 567 (54.5)	789 (51.4)
	III	250 (10.2)	332 (11.5)	466 (30.4)
	IV	5 (0.2)	22 (0.8)	52 (3.4)
	Missing	47 (1.9)	52 (1.8)	49 (3.2)
Distance of primary tumour (lower edge) from anal verge (cm)	0-5	207 (8.5)	87 (3.0)	173 (11.3)
	6-10	1 515 (61.9)	824 (28.7)	823 (53.7)
	11-15	704 (28.8)	1 924 (66.9)	495 (32.3)
	Missing	23 (0.9)	9 (0.3)	4 (0.3)
Neoadjuvant (chemo) radiotherapy		719 (29.4)	274 (9.5)	373 (24.3)
Surgical approach	Laparotomy*	1 887 (77.1)	2 133 (74.2)	1 277 (83.3)
	Laparoscopy	562 (23.0)	743 (25.8)	256 (16.7)
	Missing	0 (0.0)	0 (0.0)	1 (0.0)
Blood loss,	0-300	1 006 (41.1)	1 364 (47.4)	536 (34.9)

intraoperative (ml)	>300	1 413 (57.7)	1 443 (50.2)	943 (61.5)
	Missing	30 (1.2)	69 (2.4)	55 (3.6)
Anastomotic leakage		286 (11.7)	373 (13.0)	NA
(y)pT-category	T1	176 (7.2)	187 (6.5)	46 (3.0)
	T2	528 (21.6)	467 (16.2)	259 (16.9)
	T3	1 316 (53.7)	1 571 (54.6)	734 (47.9)
	T4	97 (4.0)	193 (6.7)	208 (13.6)
	Missing	332 (13.6)	458 (15.9)	287 (18.7)
UICC stage	I	655 (26.8)	613 (21.3)	283 (18.5)
	II	763 (31.2)	1 013 (35.2)	526 (34.3)
	III	839 (34.3)	943 (32.8)	430 (28.0)
	IV†	175 (7.2)	277 (9.6)	270 (17.6)
	Missing	17 (0.7)	30 (1.0)	25 (1.6)
Death within 3 years after surgery		394 (16.1)	551 (19.2)	661 (43.1)

*Includes intended laparoscopic surgery but converted to open surgery.
†UICC stage IV rectal cancer patients had curatively intended treatment of distant metastasis along with intended restorative rectal resection or Hartmann's operation either during the index procedure or during an independent procedure in close timely relation to the index procedure.

Table 2: One and three-year cumulative incidence proportions of stoma reversal in patients undergoing intended restorative rectal cancer resection with diverting stoma, Denmark 2001-2012				
		Patients with rectal resection and DS n (%)	CIP_1* (95% CI)	CIP_3* (95% CI)
Total		2 449	0.70 (0.68;0.72)	0.74 (0.73;0.76)
Period of surgery	May 2001 - Dec 2004	677 (27.6)	0.68 (0.65;0.72)	0.71 (0.67;0.74)
	Jan 2005 - Dec 2008	865 (35.3)	0.69 (0.66;0.72)	0.74 (0.70;0.76)
	Jan 2009 - Apr 2012	907 (37.0)	0.73 (0.70;0.76)	0.78 (0.75;0.80)
Gender	Male	1 551 (63.3)	0.72 (0.69;0.75)	0.75 (0.72;0.78)
	Female	898 (36.7)	0.69 (0.67;0.72)	0.74 (0.71;0.76)
Age (y)	≤65	1 240 (50.6)	0.73 (0.70;0.75)	0.77 (0.74;0.79)
	>65	1 209 (49.4)	0.68 (0.65;0.71)	0.72 (0.69;0.74)
BMI	0-19	101 (4.1)	0.64 (0.54;0.73)	0.65 (0.55;0.74)
	20-24	853 (34.8)	0.72 (0.68;0.75)	0.75 (0.72;0.78)
	25-29	781 (31.9)	0.74 (0.71;0.77)	0.78 (0.75;0.81)
	+30	277 (11.3)	0.70 (0.64;0.75)	0.73 (0.68;0.78)
	Missing	437 (17.8)	-	-
Charlson Comorbidity Index	0	2 079 (84.9)	0.71 (0.69;0.73)	0.75 (0.73;0.77)
	1-2	327 (13.4)	0.66 (0.61;0.71)	0.70 (0.64;0.73)
	+3	43 (1.8)	0.58 (0.42;0.71)	0.60 (0.44;0.73)
ASA grade	I	745 (30.4)	0.75 (0.71;0.77)	0.78 (0.75;0.81)
	II	1 402 (57.3)	0.70 (0.67;0.72)	0.74 (0.71;0.76)
	III-IV	255 (10.4)	0.60 (0.54;0.66)	0.64 (0.58;0.69)
	Missing	47 (1.9)	-	-
Distance of primary tumour (lower edge) from anal verge (cm)†	0-5	207 (8.5)	0.63 (0.56;0.69)	0.68 (0.61;0.74)
	>5-10	1 515 (61.9)	0.70 (0.68;0.73)	0.74 (0.72;0.76)
	>10-15	704 (28.8)	0.72 (0.69;0.75)	0.76 (0.73;0.79)
	Missing	23 (0.9)	-	-
Neoadjuvant (chemo-) radiotherapy	No	1 730 (70.6)	0.73 (0.71;0.75)	0.77 (0.75;0.79)
	Yes	719 (29.4)	0.64 (0.60;0.67)	0.68 (0.64;0.71)
Surgical approach	Laparotomy	1 887 (77.1)	0.71 (0.67;0.73)	0.76 (0.72;0.79)
	Laparoscopy	562 (23.0)	0.70 (0.68;0.72)	0.74 (0.72;0.76)
Blood loss, intraoperative (ml)	0-300	1 006 (41.1)	0.75 (0.72;0.77)	0.79 (0.76;0.81)
	>300	1 413 (57.7)	0.66 (0.63;0.69)	0.70 (0.67;0.73)
	Missing	30 (1.2)	-	-
Anastomotic leak	No	2 162 (88.3)	0.75 (0.73;0.77)	0.78 (0.76;0.80)

	Yes	286 (11.7)	0.33 (0.29;0.38)	0.45 (0.39;0.51)
	Missing	1 (0.0)	-	-
(y)pT-category	T1	203 (8.3)	0.80 (0.74;0.85)	0.83 (0.77;0.88)
	T2	528 (21.6)	0.75 (0.71;0.78)	0.79 (0.75;0.82)
	T3	1 326 (53.7)	0.68 (0.65;0.71)	0.73 (0.70;0.75)
	T4	97 (4.0)	0.61 (0.50;0.70)	0.66 (0.56;0.74)
	Missing	305 (12.5)	-	-
UICC stage	I	655 (26.8)	0.77 (0.74;0.80)	0.80 (0.77;0.83)
	II	763 (31.2)	0.74 (0.71;0.77)	0.77 (0.73;0.79)
	III	839 (34.3)	0.66 (0.63;0.69)	0.71 (0.68;0.74)
	IV	175 (7.2)	0.50 (0.42;0.57)	0.57 (0.50;0.64)
	Missing	17 (0.7)	-	-

*One and three-year cumulative incidence proportion. Calculated treating death as a competing risk.
†Measured by rigid proctoscopy

Table 3: Crude and adjusted hazard ratios (0-3 years), associating different characteristics with delay in stoma reversal for patients with intended restorative rectal cancer resection with diverting stoma, Denmark 2001-2012

Characteristic		No of subjects n (%)	Crude Hazard-ratio* (95%CI)	Adjusted Hazard-ratio† (95%CI)
Total		2 449	-	-
Period of surgery	May 2001 - Dec 2004	677 (27.6)	1.0 (ref)	1.0 (ref)
	Jan 2005 - Dec 2008	865 (35.3)	0.96 (0.85;1.08)	1.08 (0.91;1.28)
	Jan 2009 - Apr 2012	907 (37.0)	1.01 (0.90;1.13)	1.07 (0.90;1.28)
Gender	Male	1 551 (63.3)	0.98 (0.89;1.08)	1.05 (0.94;1.19)
	Female	898 (36.7)	1.0 (ref)	1.0 (ref)
Age (y)	≤65	1,240	1.0 (ref)	1.0 (ref)
	>65	1,209	0.95 (0.87;1.04)	0.92 (0.82;1.03)
BMI	0-19	101 (4.1)	1.0 (ref)	1.0 (ref)
	20-24	853 (34.8)	1.13 (0.87;1.45)	1.12 (0.84;1.49)
	25-29	781 (31.9)	1.17 (0.91;1.51)	1.17 (0.87;1.56)
	+30	277 (11.3)	1.06 (0.80;1.39)	1.08 (0.79;1.48)
	Missing	437 (17.8)	-	-
Charlson Comorbidity Index	0	2 079 (84.9)	1.0 (ref)	1.0 (ref)
	1-2	327 (13.4)	0.93 (0.81;1.07)	0.99 (0.84;1.17)
	+3	43 (1.8)	0.82 (0.56;1.21)	0.77 (0.49;1.20)
ASA grade	I	745 (30.4)	1.0 (ref)	1.0 (ref)
	II	1 402 (57.3)	0.87 (0.79;0.96)	0.91 (0.80;1.03)
	III-IV	255 (10.4)	0.75 (0.63;0.89)	0.82 (0.65;1.02)
	Missing	47 (1.9)	-	-
Distance of primary tumour (lower edge) from anal verge (cm)	0-5	207 (8.5)	0.84 (0.69;1.01)	0.84 (0.66;1.06)
	>5-10	1 515 (61.9)	1.03 (0.93;1.14)	1.11 (0.97;1.26)
	>10-15	704 (28.8)	1.0 (ref)	1.0 (ref)
	Missing	23 (0.9)	-	-
Neoadjuvant (chemo-) radiotherapy	Yes	719 (29.4)	0.76 (0.69;0.85)	0.75 (0.66;0.85)
	No	1 730 (70.6)	1.0 (ref)	1.0 (ref)
Surgical approach	Laparoscopy	562 (23.0)	1.0 (ref)	1.0 (ref)

	Laparotomy	1 887 (77.1)	0.96 (0.86;1.07)	1.00 (0.87;1.16)
Blood loss, intraoperative (ml)	≤300	1 212 (49.5)	1.0 (ref)	1.0 (ref)
	>300	1 207 (49.3)	0.80 (0.73;0.88)	0.86 (0.76;0.97)
	Missing	30 (1.2)	-	-
Anastomotic leakage	Yes	286 (11.7)	0.42 (0.35;0.50)	0.41 (0.33;0.50)
	No	2 162 (88.3)	1.0 (ref)	1.0 (ref)
	Missing	1 (0.0)	-	-
(y)pT-category	T1	203 (8.3)	1.0 (ref)	1.0 (ref)
	T2	528 (21.6)	0.83 (0.69;0.99)	0.86 (0.70;1.05)
	T3	1 316 (53.7)	0.63 (0.53;0.74)	0.63 (0.47;0.83)
	T4	97 (4.0)	0.51 (0.39;0.69)	0.62 (0.42;0.90)
	Missing	305 (12.5)	-	-
UICC stage	I	655 (26.8)	1.0 (ref)	1.0 (ref)
	II	763 (31.2)	0.86 (0.76;0.97)	1.23 (0.94;1.63)
	III	839 (34.3)	0.65 (0.58;0.73)	0.83 (0.65;1.05)
	IV	175 (7.2)	0.42 (0.34;0.52)	0.57 (0.41;0.80)
	Missing	17 (0.70)	-	-

*COX regression analysis. Hazard ratio (HR) <1 describes reduced "risk" of stoma reversal (i.e. the "risk" of early stoma closure is reduced when HR<1).
†Mutually adjusted

Figure 1 Flow chart of 15,303 patients with first-time rectal cancer diagnosis between 1 May 2001 and 30 April 2012 and treated at 21 hospitals in Denmark.

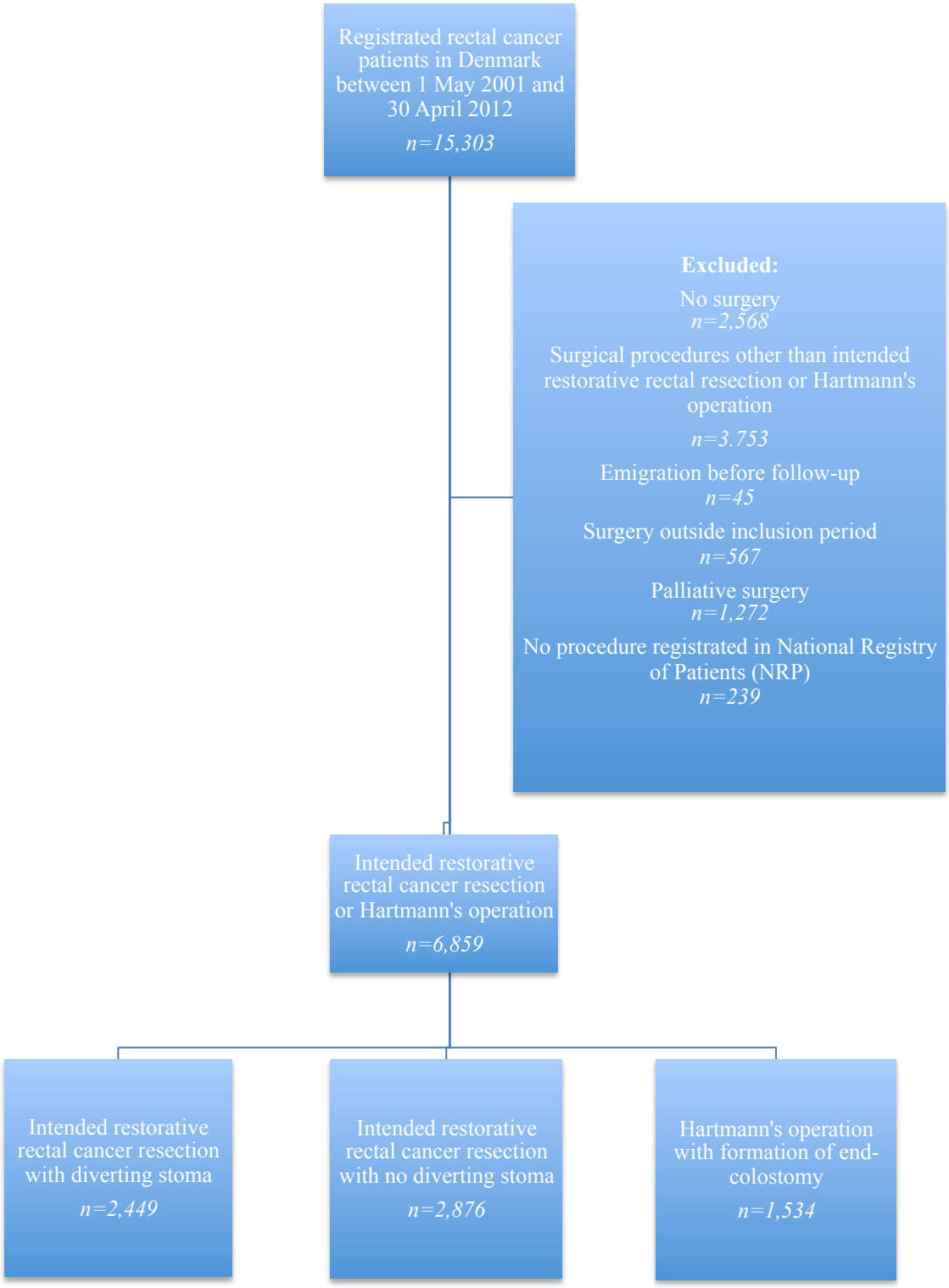
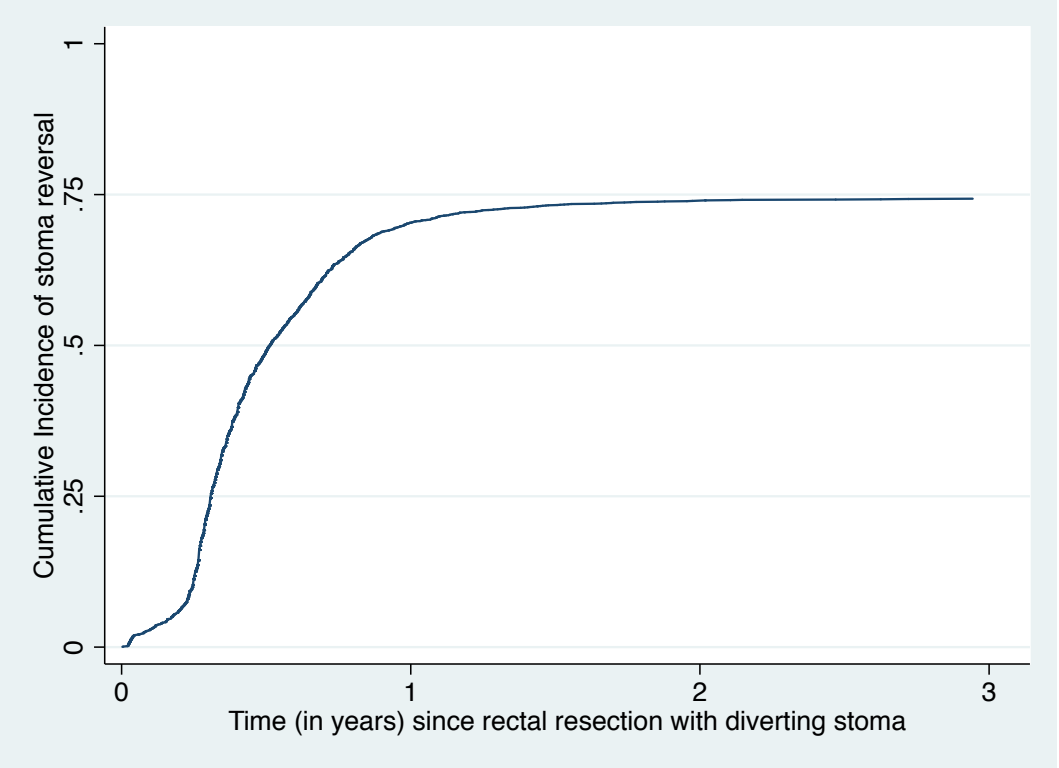


Figure 2 Cumulative incidence of stoma reversal during 3 years of follow up*



*Cumulative incidence proportion was calculated treating death as competing risk

Paper III

Original article

doi:10.1111/codi.14224

Pelvic insufficiency fractures frequently occur following preoperative chemo-radiotherapy for rectal cancer – a nationwide MRI study

J. B. Jørgensen*, P. Bondeven*, L. H. Iversen*, S. Laurberg* and B. G. Pedersen†

*Department of Surgery, Aarhus University Hospital, Aarhus, Denmark, and †Department of Radiology, Aarhus University Hospital, Aarhus, Denmark

Received 5 December 2017; accepted 19 March 2018; Accepted Article Online 19 April 2018

Abstract

Aim The aim of this prospective case–control study was to evaluate the rate of pelvic insufficiency fractures (PIFs) in Denmark using MRI at the 3-year follow-up. All patients had rectal cancer and had undergone surgery with or without preoperative chemo-radiotherapy (CRT).

Method Patients registered with primary rectal cancer in the Danish Colorectal Cancer Group database, who underwent rectal cancer resection from April 2011 through August 2012, were invited to participate in a national MRI study aiming to detect local recurrence and evaluate quality of the surgical treatment. Pelvic MRI including bone-specific sequences 3 years after treatment was obtained. The primary outcome was the rate of PIFs; secondary outcome was risk factors of PIFs evaluated in multivariate analysis.

Results During the study period, 890 patients underwent rectal cancer surgery. Of these, 403 patients were included in the MRI study and had a 3-year follow-up MRI. PIFs were detected in 49 (12.2%; 95% CI 9.0–15.4) patients by MRI. PIFs were detected in 39 patients (33.6%; 95% CI 24.9–42.3) treated with preoperative CRT compared to 10 (3.5%; 95% CI 1.3–5.6) non-irradiated patients ($P < 0.001$). In a multivariate analysis female gender (OR = 3.52; 95% CI 1.7–7.5), age above 65 years (OR = 3.20; 95% CI 1.5–6.9) and preoperative CRT (OR = 14.20; 95% CI 6.1–33.1) were significant risk factors for PIFs.

Conclusion Preoperative CRT in the treatment of rectal cancer was associated with a 14-fold higher risk of PIFs after 3 years, whereas female gender and age above 65 years each tripled the risk of PIFs.

Keywords Rectal cancer, chemo-radiotherapy, pelvic insufficiency fractures

What does this paper add to the existing literature?

This paper demonstrates a risk of pelvic insufficiency fractures following chemo-radiotherapy in the treatment of rectal cancer that significantly exceeds the expected levels from the international literature. It contributes to a broader awareness of the potential adverse effects of radiation therapy seen in the treatment of locally advanced rectal cancer.

Introduction

Neoadjuvant chemo-radiotherapy (CRT) is indicated for patients with locally advanced rectal cancer in order to reduce the risk of local recurrence. Adverse effects of short-course radiotherapy as well as long-course CRT, combined with rectal resection, are well documented and include a broad variety of clinical manifestations. Frequent and well-described complications, with a substantial impact on quality of life, include bowel dysfunction, sexual dysfunction, urinary problems, occasional rectal bleeding and impaired wound healing among others [1–6].

Pelvic insufficiency fracture (PIF) is another known, although not well described, complication of CRT in the treatment of rectal cancer. PIF occurs as a stress fracture in structurally weakened bone exposed to normal physiological stress [7,8]. Decreased mineralization and deficient elastic resistance are the underlying causes of bone atrophy. Development of radiation-induced osteopenia arises partly from local ischaemia caused by damage to the micro-vascular (Haversian) system in bone [9]. Another part of the pathological pathway is probably direct impairment of regeneration and resorption [10,11].

Correspondence to: Jesper Beck Jørgensen MD, Aarhus University Hospital, THG, Department of Surgery, Tage-Hansens Gade 2, 8000 Aarhus C, Denmark.
E-mail: jesjoe@rm.dk

The most common clinical manifestation of PIF is chronic pelvic pain [12–14]. Between 16% and 58% of patients have been reported to be symptomatic in previous studies [10,15,16].

In the international literature, detection rates of PIF between 3% and 11% are suggested following CRT and resection for rectal cancer. Only a few small, retrospective, non-blinded studies have been conducted until now [17–19]. PIF rates between 8% and 45% are reported in patients with cervical cancer, and rates from 6% to 14% are reported in other pelvic malignancies (i.e. prostate and anal cancer) [10,15,16,20–22]. The imaging modalities underlying these studies include CT, MRI and bone scintigraphy in different combinations. PIF occurs in characteristic locations, and patterns within the bony pelvis are best detected and evaluated using MRI [23–26].

The aim of this study was to evaluate the rate of PIF at 3 years postoperatively among Danish patients treated with curative intent for rectal cancer with mesorectal excisional surgery with or without preoperative CRT.

Methods

The prospective national study *Mesorectal Excision for Rectal Cancer: Aspects of Recurrence and Survival* was approved by the National Board of Health (ref.: 3-3013-1272/1/), the Central Denmark Region Committees on Health Research Ethics, the Scientific Committee of the Danish Colorectal Cancer Group (DCCG.dk) and the Danish Data Protection Agency (ref.: 2007−58−0010). The present study is a supplemental study to the MRI study.

Data sources

In Denmark there has been consecutive national reporting on patients with colorectal cancer to the DCCG database since 1 May 2001 [27]. The purpose of the database is to monitor the compliance and treatment of colorectal cancer with defined quality standards set by the DCCG.dk. Patients were identified in the DCCG database and variables of patient demographics, tumour location, surgical type and pathological T category were retrieved from the database.

Setting

Between 2011 and 2012 approximately 1100 rectal cancer patients were treated surgically in 15 different surgical departments in Denmark [28]. Ten surgical departments (Aarhus University Hospital, Odense University Hospital, Regional Hospital Randers, Regional Hospital West Jutland, Hvidovre Hospital, Zealand University Hospital, Slagelse Hospital, Svendborg Hospital, Vejle Hospital and Esbjerg Hospital) agreed to participate in the MRI study, covering 65% of the patients treated for rectal cancer nationwide in 2011–2012. Reasons for non-participation of the remaining five departments were mainly based on lack of staff capacity.

Patients

Patients with rectal adenocarcinoma (located 15 cm or less from the anal verge) who underwent partial mesorectal excision (PME), total mesorectal excision (TME) or abdominoperineal excision (APE) with curative intent from April 2011 to August 2012 were identified through the DCCG database. Patients were examined for eligibility and vital status by obtaining information from the National Registry of Patients based on Central Person Registry number. Patients who developed disseminated disease or local recurrence of rectal cancer within 3 years of follow-up were not invited to participate. The same applied to patients who had left the country, terminated their medical surveillance programme due to very old age or comorbid disease, or who were deceased.

Consecutive patients fulfilling eligibility criteria were invited for 3-year postoperative MRI of the pelvis. Information on neoadjuvant oncological treatment was retrieved from the medical records.

Oncological and surgical treatment

Patients were treated according to national guidelines [29]. Neoadjuvant long-course CRT [50 Gy in 25–28 fractions in combination with fluorouracil (5-FU)] was offered to patients with locally advanced rectal cancer (low T3 and T4 tumours, mid T4 tumours and mid T3 with < 5 mm to the mesorectal fascia at MRI). Short-course radiotherapy, with delay, could be chosen in those rare situations where long-course therapy seemed to be difficult to complete. Short-course radiotherapy with immediate surgery is not practised in Denmark. Targeted radiation treatment with 3D-conformal and intensity modulated radiation therapy was standard in the participating units. Mesorectal excision was performed 8–10 weeks after completion of CRT regardless of whether it was long-course CRT or short-course radiotherapy. All other patients underwent direct mesorectal excision, without preoperative oncological treatment.

Patients who completed radical surgery for Union for International Cancer Control (UICC) Stage II (with at least one risk factor) or III rectal cancer and had not received neoadjuvant CRT were offered 6 months of

adjuvant chemotherapy with 5-FU [29]. According to national guidelines postoperative radiation therapy is not provided in Denmark.

Magnetic resonance imaging

Patients underwent pelvic MRI as part of a national study aiming to detect local recurrence. All MRI examinations were performed on 1.5 T or 3 T platforms with a detailed scan protocol established by the research group. Sagittal, axial and coronal T2-weighted turbo spin echo images, field of view (FOV) 240 mm, slice thickness 4–5 mm, were obtained in addition to a sagittal short tau inversion recovery (STIR) sequence of the bony pelvis and a sagittal T2 3D sequence of the smaller pelvis. The sagittal sequences depicted the L5 cranially and the buttocks caudally covering the pelvis between the ischial tuberosities. Based on the sagittal T2-weighted sequence, axial T2-weighted and coronal T2-weighted sequences were planned. The axial sequence covered the entire pelvis from the lower border of the subcutaneous part of the external sphincter to the promontory. The coronal sequence covered anteriorly the posterior part of the pubic bone and posteriorly the sacrum. The sagittal T2 3D sequence covered the smaller pelvis with a slab of 88 slices and with a slice thickness of 1 mm.

The MR examinations were all evaluated by a dedicated multidisciplinary team radiologist at Aarhus University Hospital with 8 years of sub-specialization in pelvic MRI. The multidisciplinary team radiologist was blinded to all clinical data with the exception of the preoperative MRI examination.

Detection of pelvic insufficiency fractures by MRI

All MRI examinations were prospectively evaluated for the presence of changes compatible with PIFs. High signal intensity changes in the bone marrow on STIR images (Fig. 1), indicative of bone marrow oedema, accompanied by subtle linear changes of low signal intensity on T2-weighted images were regarded as suggestive of PIFs (Fig. 2). STIR is the most sensitive current method to detect bone marrow oedema while T2 images are primarily used for anatomical mapping and identification of low signal intensity changes [30]. Locations of the areas of abnormal bone marrow signal were reviewed.

Outcome measures

The primary outcome was the rate of PIFs as detected by 3-year postoperative MRI examinations.

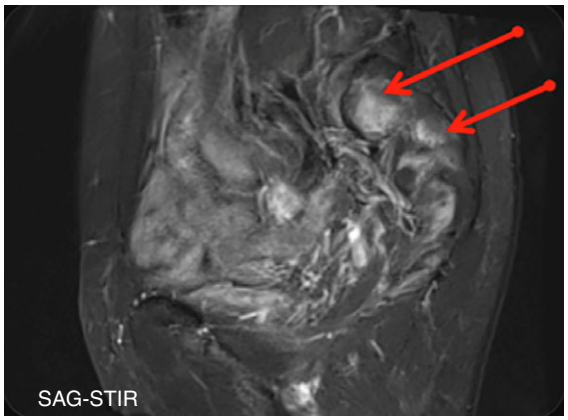


Figure 1 Sagittal STIR sequence showing bone marrow oedema in the alar of the sacrum.

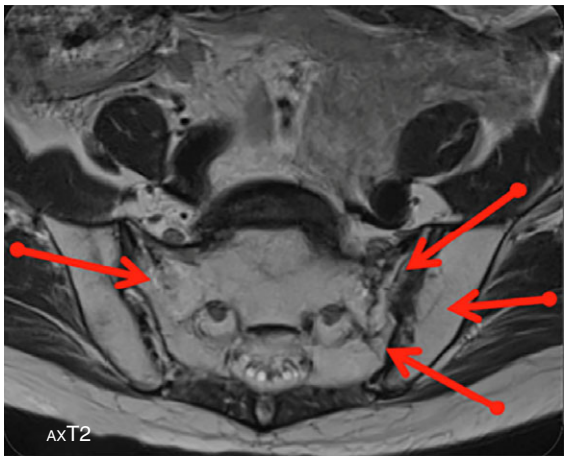


Figure 2 Axial T2-weighted MRI showing sclerosis and fracture in the alar of the sacrum.

Secondary outcomes were the anatomical distribution of PIFs and risk factors of PIF evaluated in multivariate analysis, including sub-analysis of patients who had APE.

Statistical analysis

The PIF rate was calculated and stratified for neoadjuvant CRT. Other potential risk factors for PIF were investigated. Continuous data were categorized. Demographics and categorical data were compared by Fisher's exact test (univariate analysis). Factors found to have a significance less than 0.1 in the univariate model were entered into a multiple logistic regression model to identify independent predictors for PIF. Adjusted ORs for PIF were computed using multiple logistic regression to estimate the impact of gender, age at surgery (categorized as < 65 years or ≥ 65 years according to

the median age at time of surgery), use of neoadjuvant therapy, tumour height (categorized as low *vs* mid/high), surgical procedure (categorized as APE *vs* TME/PME) and pT/ypT category (according to T subcategory). A *P* value of less than 0.05 was considered significant.

Stata® version 12.0 (StataCorp, College Station, Texas, USA) was used for statistical analysis.

Results

In total 890 patients underwent rectal cancer surgery with curative intent at the 10 participating hospitals during April 2011 through August 2012. Of these, 320 patients did not fulfil the eligibility criteria, leaving 570 potentially eligible patients (Fig. 3). In total, 403 patients were included in the MRI study and had a 3-year follow-up MRI. Among these, 116 (28.8%; 95% CI 24.3–33.2) patients had been treated with neoadjuvant CRT. Reasons for non-participation were contraindications to MRI, non-respondents, decline of invitation or missing preoperative MRI (Fig. 3).

The frequency of neoadjuvant CRT in the group of patients not included for MRI ($n = 487$) was 33.3% (95% CI 29.1–37.5). No significant difference in CRT rates between the included and non-included group of patients was observed ($P = 0.167$). Patient demographics, tumour characteristics and treatment regimens are summarized in Table 1.

Pelvic insufficiency fractures

During follow-up at 36 months, 49 (12.2%; 95% CI 9.0–15.4) patients had PIFs detected on MRI. PIFs were detected in 39 of 116 (33.6%; 95% CI 24.9–42.3) patients treated with preoperative CRT. The rate of PIFs in the non-irradiated group was 3.5% (95% CI 1.3–5.6) ($P < 0.001$).

In univariate analysis of risk factors, age above 65 years ($P = 0.032$), female gender ($P = 0.008$), tumour in the lower part (0–5 cm) of the rectum ($P < 0.001$), preoperative CRT ($P < 0.001$), lower tumour category ($P < 0.001$) and APE as surgical procedure ($P < 0.001$) were associated with a higher risk of PIF (Table 1).

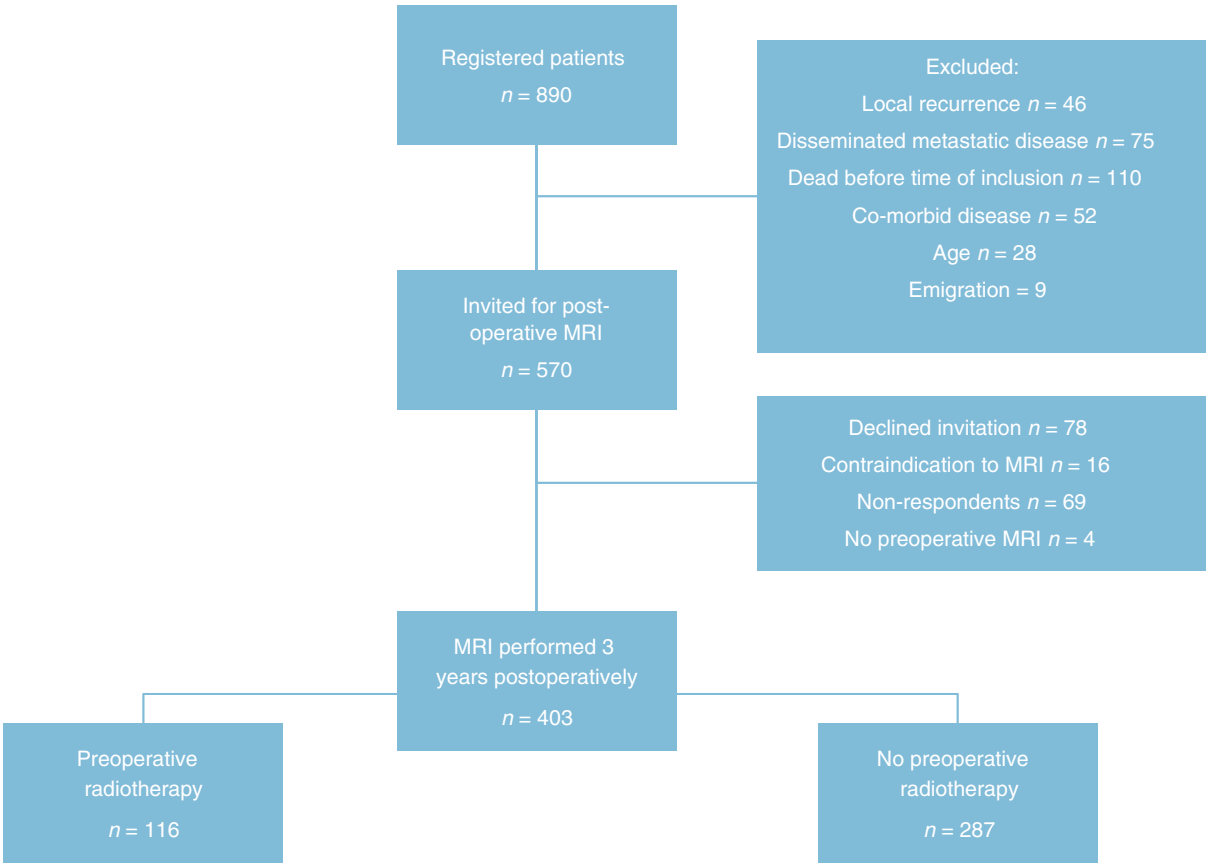


Figure 3 Flowchart.

Table 1 Patient demographics, treatment characteristics and risk factors associated with PIF.

Characteristic		All patients *n* (%)	Patients with PIF *n* (%)	Unadjusted *P**	Adjusted OR (95% CI)	Adjusted *P*†
Number		403	49 (12.2)			
Gender	Male	252 (62.5)	22 (8.7)	0.008	3.52 (1.7;7.5)	0.001
	Female	151 (37.5)	27 (17.9)			
Age (years)	< 65	191 (47.4)	16 (8.4)	0.032	3.20 (1.5;6.9)	0.004
	≥ 65	212 (52.6)	33 (15.6)			
Body mass index (kg/m^2)	< 25	183 (46.3)	25 (13.7)	0.354		
	≥ 25	212 (53.7)	24 (11.3)			
Smoker	Yes	69 (17.2)	7 (10.1)	0.764		
	Former‡	162 (40.3)	23 (14.2)			
	Never	132 (32.8)	14 (10.6)			
	Missing	40 (9.8)	5 (12.8)			
ASA score	I	134 (33.3)	14 (10.5)	0.227		
	II	236 (58.7)	28 (11.9)			
	III	29 (7.2)	7 (24.1)			
	Missing	3 (0.8)	0 (0.0)			
Distance of primary tumour from anal verge (cm)§	0–5	97 (24.1)	26 (26.8)	< 0.001	1.75 (0.89;3.42)	0.118
	> 5–10	172 (42.7)	22 (12.8)			
	> 10–15	120 (29.8)	1 (0.8)			
	Missing	14 (3.5)	0 (0.0)			
Neoadjuvant (chemo-) radiotherapy	No	287 (71.2)	10 (3.5)	< 0.001	14.2 (6.1;33.1)	<0.001
	Yes	116 (28.8)	39 (33.6)			
Surgical approach	Laparotomy	133 (33.1)	18 (13.5)	0.627		
	Laparoscopy	269 (66.9)	31 (11.5)			
Surgical preocedure	PME	118 (29.3)	5 (4.2)	< 0.001	2.17 (0.71;6.58)	0.172
	TME	172 (42.7)	14 (8.1)			
	APE	113 (28.0)	30 (26.5)			
pT/ypT category¶	T0	16 (4.0)	8 (50.0)	0.001	0.81 (0.56;1.17)	0.259
	T1	21 (5.2)	3 (14.3)			
	T2	117 (29.0)	15 (12.8)			
	T3	216 (53.6)	20 (9.3)			
	T4	29 (7.2)	3 (10.3)			
	Missing	4 (1.0)	0 (0.0)			

*Fisher's exact test.

†Multiple logistic regression adjusted for gender, age at surgery, tumour height, surgical procedure, neoadjuvant therapy and pT/ypT category.

‡No smoking within 8 weeks.

§Measured by rigid proctoscopy at pretreatment clinical evaluation.

¶Based on histopathological evaluation of excised specimen. The pathological tumour category for the 115 patients who had neoadjuvant CRT was ypT0, 15; ypT1, 9; ypT2, 32; ypT3, 51; ypT4, 8. One patient with T0 did not receive CRT. This patient underwent local excision of the tumour prior to definitive surgery and the T categorization here was T0.

Multivariate analysis of the risk factors associated with PIF found that age above 65 years ($P = 0.004$), female gender ($P = 0.001$) and preoperative CRT ($P < 0.001$) were independent risk factors for PIF (Table 1).

In patients who underwent APE, excision of the coccyx was associated with a higher risk of PIF (31.5% *vs* 11.9%, $P < 0.001$) but was not an independent risk factor in multivariate analysis (data not shown). Female gender, age above 65 years and preoperative radiotherapy, however, remained significant risk factors of PIF in patients who underwent APE as in the entire cohort (data not shown).

Localization and anatomical distribution of pelvic insufficiency fractures

A fracture was observed in the sacrum in 47 of 49 (95.9%; 95% CI 86.0–99.5) patients with PIFs. Lesions near the sacroiliac joints were observed in 45 (91.8%;

95% CI 83.9–99.8) patients, and 39 (79.6%; 95% CI 67.9–91.3) had bilateral lesions detected. In patients with PIF in the sacrum 38 (80.9%; 95% CI 69.2–92.5) had additional fractures at another site in the pelvis, the right posterior-medial part of ilium (close to the sacral joint) being the most frequent, 68.1% (95% CI 54.3–81.9). The anatomical predilection sites of PIFs are shown in Fig. 4.

Discussion and conclusions

This prospective, population-based, case–control study reports the rate of PIF 3 years after rectal cancer treatment with curative intent in the national setting of Denmark.

The main finding was a surprisingly high PIF rate of 33.6% in patients who underwent neoadjuvant CRT in combination with mesorectal excision surgery compared to only 3.5% in the group of patients treated with surgery alone. This 3-year rate is probably an underestimate as some fractures may heal or partly heal within 3 years.

The lifetime risk of all pelvic fractures at the age of 85 years in the USA has been estimated at 2% for white women and 0.5% for white men, which corresponds well to our findings of 3.5% in the control group [31].

Well known predisposing conditions for development of PIFs are osteoporosis and radiation therapy. PIFs primarily occur in postmenopausal, elderly women. Other conditions associated with PIFs are rheumatoid arthritis, prolonged corticosteroid therapy, renal failure and hip surgery [18,32,33].

In the present study independent risk factors for PIFs were female gender (OR = 3.52), age above 65 (OR = 3.20) and preoperative CRT (OR = 14.20).

In recent years there have been major technological advances in the administration of radiation therapy. Modern intensity modulated radiation therapy is specifically targeted to the malignant tissue. This is supposed to decrease both acute and late-onset toxicity. Despite these technological advances, we have demonstrated a risk of PIF following CRT that greatly exceeds the expected level of 3%–11% reported in the literature.

The difference between our findings and those reported in previous studies may be due to our consistent use of a highly sensitive imaging modality. MRI is superior in this field of interest compared to conventional imaging modalities [23]. In addition, we used MRI sequences (STIR) that are specifically suitable for detecting PIFs (i.e. bone marrow oedema). The use of MRI, with disease-specific sequences, is not seen in previous studies of PIFs in rectal cancer.

Internationally, three different strategies in the neoadjuvant treatment of rectal cancer exist: short-course radiotherapy (25 Gy in five fractions) followed by immediate surgery or delayed surgery, or long-course CRT (50 Gy in 25–28 fractions in combination with a cytostatic agent) and tumour resection 8–10 weeks after completion. Radiation induced damage to bone is highly dependent on exposure.

Recent studies of non-operative management of low rectal cancer following neoadjuvant CRT have been conducted in selected patients with UICC Stage I disease [34–40]. However, none of these trials is assessing the risk of PIF. In the light of various 'watch and wait' protocols evaluating deferral of surgery after radiation therapy of early rectal cancers, pelvic MRI may in future not only be a useful tool to monitor the effect of treatment or the presence of local recurrence, but also be a

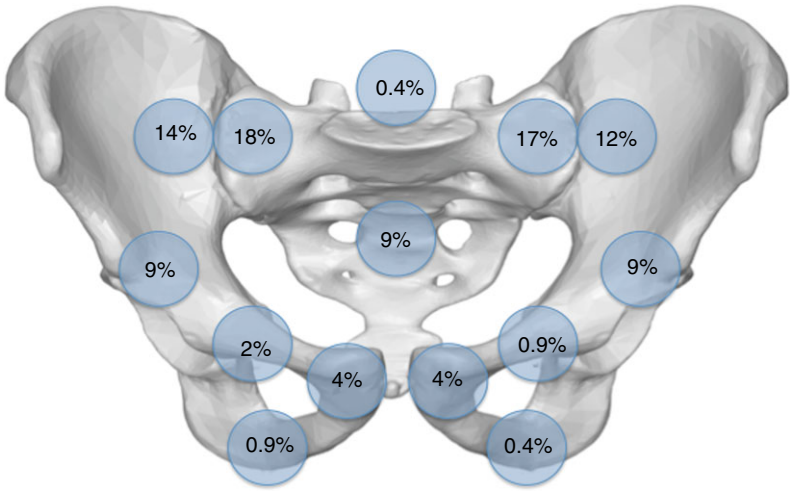


Figure 4 Frequency and anatomical distribution of PIF.

useful tool for the evaluation of more gentle ways to irradiate rectal tumours.

A sub-analysis of risk factors associated with PIFs in patients who had an APE performed was completed to verify if excision of the coccyx adds a further weakening or an additional trauma to the pelvic ring. In the multivariate model excision of the coccyx was not a predictor of PIFs. This is not surprising, since the coccyx is not a weight-bearing part of the pelvic ring.

The anatomical predilection sites of PIFs were found to be the sacrum and the medial part of the os ilium close to the sacroiliac joints. This is the weight-bearing part of the pelvic ring and the high occurrence of PIFs in this area is consistent with observations in other studies.

In a clinical setting, PIFs must be considered a differential diagnosis in patients complaining of pelvic pain following neoadjuvant CRT in the treatment of rectal cancer. In the first instance it is critically important to exclude local recurrence. Performing specific MRI sequences with identification of characteristic patterns of PIFs makes it possible to avoid further unnecessary clinical examination. Assessing the prevalence of pain was not an aim in this study and future MRI studies combined with quality of life assessment are needed to evaluate pelvic pain in relation to PIFs in patients treated for rectal cancer.

The strength of the present study includes the nationwide, prospective design and the consequent use of MRI with STIR sequences which are highly sensitive in detecting PIFs. In addition, blinding of the multidisciplinary team radiologist to all clinical data of the patients reduced the risk of information bias.

The study was initiated with the intent to detect local recurrence of rectal cancer and visualize inadvertent residual mesorectal fat. Regarding the detection of PIFs, it is a limitation that our cohort was not examined with bone sequences (STIR and T1) covering the entire pelvis in at least two planes including the femoral head and the proximal part of the femoral shaft. The latter could potentially harbour insufficiency fractures, especially in patients treated with CRT for low rectal cancer. Our protocol did not include contrast-enhanced sequences either. However, these limitations may tend to underestimate the true prevalence of PIFs in this group of patients.

Other limitations of the study are lack of information on the clinical consequences of PIFs and the presence of chronic pain. Furthermore, we did not have information on the exact radiotherapy regimen as well as the specific dose–volume relationships since the aim of the present explorative study was to evaluate the PIF rate only. In addition we had no information about osteoporosis or corticosteroid use, both of which are associated with increased risk of PIFs.

In conclusion, neoadjuvant CRT in the treatment of rectal cancer is associated with a substantial risk of PIF. One-third of patients who underwent mesorectal excision surgery for rectal cancer in combination with preoperative CRT had PIFs 3 years after surgery detected by MRI.

Acknowledgements

The present study was funded by the Danish Cancer Society. The Study Group of the project *Mesorectal Excision for Rectal Cancer: Aspects of Recurrence and Survival* is acknowledged for their contribution in patient recruitment and MRI examinations. The Study Group consists of Niels Qvist and Jon Thor Asmussen, Odense University Hospital; Safaa Al-Ubaidi and Frédérique Johnsen, Regional Hospital West Jutland; Steffen Jais Rosenstock and Annette Bøjer Jensen, Hvidovre Hospital; Ole Roikjær and Karina Vinum, Zealand University Hospital; Sharaf Karim Perdawood and Odai Adnan Jalel, Slagelse Hospital; Thomas Kolbro and Jacob Christian Bang, Svendborg Hospital; Lars Bundgaard and Søren Rafaelsen, Vejle Hospital; Pernille Øhlenschlager Larsen, Esbjerg Hospital.

Conflict of interest

None declared.

References

1 Pollack J, Holm T, Cedermark B *et al.* Late adverse effects of short-course preoperative radiotherapy in rectal cancer. *Br J Surg* 2006; **93:** 1519–25.
2 Dahlberg M, Glimelius B, Graf W, Påhlman L. Preoperative irradiation affects functional results after surgery for rectal cancer. *Dis Colon Rectum* 1998; **41:** 543–9.
3 Marijnen CA, van de Velde CJ, Putter H *et al.* Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol* 2005; **23:** 1847–58.
4 Peeters KC, Tollenaar RA, Marijnen CA *et al.* Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. *Br J Surg* 2005; **92:** 211–6.
5 Marijnen CAM, Kapiteijn E, van de Velde CJ *et al.* Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol* 2002; **20:** 817–25.
6 Bregendahl S, Emmertsen KJ, Lous J, Laurberg S. Bowel dysfunction after low anterior resection with and without

neoadjuvant therapy for rectal cancer: a population-based cross-sectional study. *Colorectal Dis* 2013; **15:** 1130–9.
7 Pentecoast RL, Murray RA, Brindley HH. Fatigue, insufficiency, and pathologic fractures. *JAMA* 1964; **187:** 1001–4.
8 Lourie H. Spontaneous osteoporotic fracture of the sacrum. *Spine* 1982; **248:** 715–7.
9 Hopewell JW. Radiation-therapy effects on bone density. *Med Pediatr Oncol* 2003; **41:** 208–11.
10 Kwon JW, Huh SJ, Yoon YC *et al.* Pelvic bone complications after radiation therapy of uterine cervical cancer: evaluation with MRI. *AJR Am J Roentgenol* 2008; **191:** 987–94.
11 Howland WJ, Loeffler RK, Starchman DE, Johnson RG. Postirradiation atrophic changes of bone and related complications. *Radiology* 1975; **117:** 677–85.
12 Saraux A, Valls I, Guedes C. Insufficiency fractures of the sacrum in elderly subjects. *Rev Rhum Engl Ed* 1995; **62:** 582–6.
13 Gotis-Graham I, McGuigan L, Diamond T. Sacral insufficiency fractures in the elderly. *J Bone Joint Surg Br* 1994; **76:** 882–6.
14 Rawlings CE, Wilkins RH, Martinez S. Osteoporotic sacral fractures: a clinical study. *Neurosurgery* 1988; **22:** 72–6.
15 Oh D, Huh SJ, Nam H *et al.* Pelvic insufficiency fracture after pelvic radiotherapy for cervical cancer: analysis of risk factors. *Int J Radiat Oncol Biol Phys* 2008; **70:** 1183–8.
16 Tokumaru S, Toita T, Oguchi M *et al.* Insufficiency fractures after pelvic radiation therapy for uterine cervical cancer: an analysis of subjects in a prospective multi-institutional trial, and cooperative study of the Japan Radiation Oncology Group (JAROG) and Japanese Radiation Oncology Study Group (JROSG). *Int J Radiat Oncol Biol Phys* 2012; **84:** e195–200.
17 Kim HJ, Boland PJ, Meredith DS *et al.* Fractures of the sacrum after chemoradiation for rectal carcinoma: incidence, risk factors, and radiographic evaluation. *Int J Radiat Oncol Biol Phys* 2012; **84:** 694–9.
18 Baxter NN, Habermann EB, Tepper JE, Durham SB, Virnig BA. Risk of pelvic fractures in older women following pelvic irradiation. *JAMA* 2005; **294:** 2587–93.
19 Herman MP, Kopetz S, Bhosale PR *et al.* Sacral insufficiency fractures after preoperative chemoradiation for rectal cancer: incidence, risk factors, and clinical course. *Int J Radiat Oncol Biol Phys* 2009; **74:** 818–23.
20 Oh D, Huh SJ. Insufficiency fracture after radiation therapy. *Radiat Oncol J* 2014; **32:** 213–20.
21 Igdem S, Alço G, Ercan T *et al.* Insufficiency fractures after pelvic radiotherapy in patients with prostate cancer. *Int J Radiat Oncol Biol Phys* 2010; **77:** 818–23.
22 Ramlov A, Pedersen EM, Røhl L *et al.* Risk factors for pelvic insufficiency fractures in locally advanced cervical cancer following intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2017; **97:** 1032–9.
23 Blomlie V, Rofstad EK, Talle K, Sundfør K, Winderen M, Lien HH. Incidence of radiation-induced insufficiency fractures of the female pelvis: evaluation with MR imaging. *Am J Radiol* 1996; **167:** 1205–10.
24 Mammone JE, Schweitzer ME. MRI of occult sacral insufficiency fractures following radiotherapy. *Skeletal Radiol* 1995; **24:** 101–4.
25 Brahme SK, Cervilla V, Vint V, Cooper K, Kortman K, Resnick D. Magnetic resonance appearance of sacral insufficiency fractures. *Skeletal Radiol* 1990; **19:** 489–93.
26 Cabarrus MC, Ambekar A, Lu Y, Link TM. MRI and CT of insufficiency fractures of the pelvis and the proximal femur. *AJR Am J Roentgenol* 2008; **191:** 995–1001.
27 Ingeholm P, Gogenur I, Iversen LH. Danish colorectal cancer group database. *Clin Epidemiol* 2016; **8:** 465–8.
28 Danish Colorectal Cancer Group. *D.C.C.G. Annual Report* (in Danish). 2012.
29 Danish Colorectal Cancer Group. *D.C.C.G. Guidelines for the Diagnosis and the Management of Colorectal Cancer* (in Danish). 2009.
30 Matcuk GR, Mahanty SR, Skalski MR, Patel DB, White EA, Gottsegen CJ. Stress fractures: pathophysiology, clinical presentation, imaging features, and treatment options. *Emerg Radiol* 2016; **23:** 365–75.
31 Melton RLJ, Sampson JM, Morrey BF, Ilstrup DM. Epidemiologic features of pelvic fractures. *Clin Orthop Relat Res* 1981; **155:** 43–7.
32 Cooper KL, Beabout JW, Swee RG. Pelvic insufficiency fractures of the sacrum. *Radiology* 1985; **156:** 15–20.
33 Ogino I, Okamoto N, Ono Y, Kitamura T, Nakayama H. Pelvic insufficiency fractures in postmenopausal woman with advanced cervical cancer treated by radiotherapy. *Radiother Oncol* 2003; **68:** 61–7.
34 Habr-Gama A, Gama-Rodrigues J, São Julião GP *et al.* Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. *Int J Radiat Oncol Biol Phys* 2014; **88:** 822–8.
35 Habr-Gama A, Sao Juliao GP, Perez RO. Nonoperative management of rectal cancer: identifying the ideal patients. *Hematol Oncol Clin North Am* 2015; **29:** 135–51.
36 Appelt AL, Pløen J, Harling H *et al.* High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. *Lancet Oncol* 2015; **16:** 919–27.
37 Beets GL, Figueiredo NL, Habr-Gama A, van de Velde CJ. A new paradigm for rectal cancer: organ preservation: introducing the International Watch & Wait Database (IWWD). *Eur J Surg Oncol* 2015; **41:** 1562–4.
38 Smith JD, Ruby JA, Goodman KA *et al.* Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. *Ann Surg* 2012; **256:** 965–72.
39 Smith RK, Fry RD, Mahmoud NN, Paulson EC. Surveillance after neoadjuvant therapy in advanced rectal cancer with complete clinical response can have comparable outcomes to total mesorectal excision. *Int J Colorectal Dis* 2015; **30:** 769–74.
40 Maas M, Beets-Tan RG, Lambregts DM *et al.* Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J Clin Oncol* 2011; **29:** 4633–40.

AARHUS UNIVERSITY

Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Jesper Beck Jørgensen

This declaration concerns the following article/manuscript:

Title:	Comorbidity and UICC stage IV disease are main risk factors for decreased 3-year survival and recurrence after intended curative surgery for rectal cancer – A population-based study
Authors:	J. B. Jørgensen1, P. Bondeven, S. Laurberg, MRI Study Group, B. G. Pedersen, and L. H. Iversen

The article/manuscript is: Published ☐ Accepted ☐ Submitted ☐ In preperation ☒

If published, state full reference:

If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.

A. Has essentially done all the work (>90%)
B. Has done most of the work (67-90 %)
C. Has contributed considerably (34-66 %)
D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** PhD student has been much involved in conception and study design together with supervisiors	
The acquisition, analysis, or interpretation of data:	A
Free text description of PhD student's contribution ***(mandatory)*** PhD student has been managing the datapreparation and calculations with assistance from supervisors	
Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** PhD student has written the manuscript with revisions from the supervisors	
Submission process including revisions:	

AARHUS UNIVERSITY

Free text description of PhD student's contribution ***(mandatory)***
Paper is in preparation for submission

Signatures of first- and last author, and main supervisor

Date	Name	Signature
24.08.2020	Jesper Beck Jørgensen	
24.08.2020	Lene Hjerrild Iversen	

Date:

28.08.20

Signature of the PhD student

AARHUS UNIVERSITY

Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Jesper Beck Jørgensen

This declaration concerns the following article/manuscript:

Title:	Stoma reversal after intended restorative rectal cancer resection in Denmark. A nationwide population-based study.
Authors:	J. B. Jørgensen, R. Erichsen, B. G. Pedersen, S. Laurberg, and L. H. Iversen

The article/manuscript is: Published ☐ Accepted ☒ Submitted ☐ In preperation ☐

If published, state full reference:

If accepted or submitted, state journal: British Jornal of Surgery Open

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.

A. Has essentially done all the work (>90%)
B. Has done most of the work (67-90 %)
C. Has contributed considerably (34-66 %)
D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** PhD student has been much involved in conception and study design together with supervisiors	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** PhD student has been managing the datapreparation and calculations with assistance from supervisors	
Drafting the manuscript:	B
Free text description of PhD student's contribution ***(mandatory)*** PhD student has written the manuscript with revisions from the supervisors	
Submission process including revisions:	A

AARHUS
UNIVERSITY

Free text description of PhD student's contribution ***(mandatory)***
Submission process was essentially managed by the PhD student

Signatures of first- and last author, and main supervisor

Date	Name	Signature
24.08.2020	Jesper Beck Jørgensen	
24.08.2020	Lene Hjerrild Iversen	

Date:

28.08.20

Signature of the PhD student

AARHUS UNIVERSITY

Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Jesper Beck Jørgensen

This declaration concerns the following article/manuscript:

Title:	Pelvic insufficiency fractures are frequent after preoperative chemo-radiotherapy for rectal cancer – A nationwide MRI study
Authors:	J. B. Jørgensen, P. Bondeven, L. H. Iversen, S. Laurberg and B. G. Pedersen

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preperation ☐

If published, state full reference: Jørgensen JB, Bondeven P, Iversen LH, Laurberg S, Pedersen BG. Pelvic insufficiency fractures frequently occur following preoperative chemo-radiotherapy for rectal cancer – a nationwide MRI study. Colorectal Disease. 2018;20(10):873-80.

If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.

A. Has essentially done all the work (>90%)
B. Has done most of the work (67-90 %)
C. Has contributed considerably (34-66 %)
D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	B
Free text description of PhD student's contribution ***(mandatory)*** PhD student has been much involved in conception and study design together with supervisiors	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** PhD student has been managing the datapreparation and calculations with assistance from supervisors	
Drafting the manuscript:	B
Free text description of PhD student's contribution ***(mandatory)*** PhD student has written the manuscript with revisions from the supervisors	
Submission process including revisions:	A

AARHUS
UNIVERSITY

Free text description of PhD student's contribution ***(mandatory)***
PhD student has done the revisions and has submitted the paper with contribution from supervisors

Signatures of first- and last author, and main supervisor

Date	Name	Signature
24.08.2020	Jesper Beck Jørgesen	
24.08.2020	Bodil Ginnerup Pedersen	
24.08.2020	Lene Hjerrild Iversen	

Date: 28.08.20

Signature of the PhD student