# Cancer of the Upper Rectum

*Peter Bondeven*

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**THE THREE ORIGINAL PAPERS ARE**

1. Bondeven P, Hagemann-Madsen RH, Laurberg S, Pedersen BG. Extent and completeness of mesorectal excision by postoperative MRI of the pelvis. *Br J Surg* 2013; 100: 1357-67.
2. Bondeven P, Laurberg S, Hagemann-Madsen RH, Pedersen BG. Suboptimal surgery and omission of neoadjuvant therapy for upper rectal cancer is associated with a high risk of local recurrence. *Colorectal Dis* 2015; 17: 216-24.
3. Bondeven P, Hagemann-Madsen RH, Bro L, Moran BJ, Laurberg S, Pedersen BG. Objective measurement of the distal resection margin by MRI of the fresh and fixed specimen after partial mesorectal excision for rectal cancer: 5 cm is not just 5 cm and depends on when measured. *Acta Radiol* 2016; 57(7): 789-795.

## INTRODUCTION

There have been several key advances in the optimal management of rectal cancer during the past decades, primarily by standardisation and improvement of the surgical procedure.
There is now general agreement that the optimal surgical treatment involves the concept of total mesorectal excision (TME)[1, 2] and that a resection with tumour-free margins is crucial[3, 4]. In addition to the surgical advances, neoadjuvant radiotherapy or chemoradiotherapy, preoperative staging by magnetic resonance imaging (MRI) to assess tumour stage and local tumour extent, and quality assurance by pathological assessment have all contributed to better outcomes in this complex but curable disease[5-12]. These advances are best delivered by multidisciplinary team (MDT)-directed treatment planning involving surgeons, oncologists, radiologists, pathologists, and specialised nurses[13-15]. As a consequence, the survival rate of patients with rectal cancer now surpasses that of colon cancer patients[16].

The characterisation of rectal cancer into high, mid and low is traditionally measured from the anal verge using a rigid proctoscope. Whereas TME or APE is optimal for mid and low rectal cancer, there has been very little focus on the optimal surgical management of upper rectal cancer. Tumours of the upper rectum (>10-15 cm) may not require TME and may be optimally managed by perpendicular transection of the mesorectum at least 5 cm below the lower edge of the tumour. Partial mesorectal excision (PME) is currently advocated for the majority of tumours in the upper rectum, based on the rationale that the less extensive PME, with preservation of a distal part of the rectum and mesorectum, results in better long-term functional outcome and fewer postoperative complications, while being as oncologically safe as TME[17-19].

Indeed, dedicated centres have reported local recurrence rates between 4% and 8% with PME for upper rectal cancer without the use of neoadjuvant treatment, equal or better to the local recurrence rates of TME[18-21]. Based on data from the Stockholm Colorectal Cancer Study Group, Syk *et al.* reported a crude local recurrence rate of 9% in patients who underwent PME for upper rectal cancer, despite the wide use of preoperative short-course radiotherapy. In these patients with local recurrence, residual mesorectum was observed in 86% on postoperative MRI[22, 23].
They suggested that an intentional or inadvertent PME, combined with the omission of radiotherapy, was the cause of recurrence in these patients. Other authors have reported less than favourable outcomes after treatment for cancer of the upper rectum[24, 25].
The benefit of additional neoadjuvant therapy for resectable tumours of the upper rectum is controversial, and preoperative radio(chemo)therapy is not recommended according to Danish guidelines[26].
Differences in local recurrence rates most likely reflect variation in the surgical technique and use of adjuvant therapy in routine daily care.

This thesis aims to discuss aspects of the treatment of rectal cancer with regard to the adequacy of mesorectal excision and oncological outcome with a particular focus on cancer of the upper rectum.

## BACKGROUND

### Rectal cancer

*"Case 45: One having tumours. An ailment with which I will contend",* - from the Edwin Smith Papyrus translated by James Henry Breasted, 1930.

Colorectal cancer is one of the most challenging problems encountered by colorectal surgeons and is currently the second leading cause of cancer deaths in Western countries. According to data collected from Europe, colorectal malignancies are third in overall frequency of cancers, with around 150,000 cancer-related mortalities recorded in 2012[27, 28]. Rectal cancer constitutes one-third of all colorectal cancers, with an estimated incidence in Europe of 20 new cases per 100,000 inhabitants. In Denmark, the incidence of rectal cancer is increasing; in 2012, 1,398 cases were registered. Of these, 38% were located in the upper rectum[29].

Although mortality is generally highly associated with the systemic spread of disease, local recurrence of tumour has mostly been coupled to failure in surgical technique and is responsible for immense morbidity. This problem has been the focus of much attention over the past decades. Local recurrence rates of more than 30% have been seen in some older series[30-33]; however, recent improvements in the management of rectal cancer have resulted in rates of less than 10% being commonly reported together with improved survival[20, 34-39]. Clearly, the advances in surgical technique created by a clearer understanding of the local spread of tumour, the widespread adoption of neoadjuvant therapy and better preoperative staging by magnetic resonance imaging (MRI) have been pivotal in improving local recurrence rates.

The definition of rectal cancer varies, but the most accepted definition in Europe is that of adeno-carcinoma arising within 15 cm of the anal verge as measured by rigid proctoscopy[40]. The rectum is commonly subdivided into thirds: upper (>10-15 cm), mid (>5-10 cm), and low (0-5 cm), since prognosis and surgical management are affected by the location of the tumour. Although the rectum is predominantly a retroperitoneal organ, an appreciable part of the upper rectum anteriorly and laterally is enveloped by peritoneum, and not by mesorectum. The significance of this difference may translate into a different impact of T-stage for upper rectal cancer, because of the likelihood of anterior peritoneal involvement (in up to 27% of patients), which is associated with local recurrence[41-43]. Due to such anatomical considerations, upper rectal cancer may also have disparate characteristics than that of mid or low rectal cancer with regard to the benefit of neoadjuvant therapy[44].

The following sections will review some of the literature with regard to the treatment of rectal cancer and focus on cancer of the upper rectum.

### Anatomy

*"No man should marry until he has studied anatomy and dissected at least one woman",* - Honore de Balzac (1799-1850)

A comprehensive understanding of the topographical anatomy of fasciae and spaces that surround the rectum is of utmost importance and an essential prerequisite for rectal cancer surgery, preoperative staging and pathological evaluation of the specimen.

The rectum is generally considered to begin at level of the sacral promontory. It descends along the curvature of the sacrum and coccyx and ends by passing through the levator ani muscles, at which level it abruptly turns downward and backward due to the contraction of the puborectalis sling to become the anal canal. The anal sphincter complex is composed of the internal anal sphincter, which consists of smooth muscle derived from the rectal wall, and the external anal sphincter composed of striated muscle, which closely fuses with the puborectal muscle. A small inter-sphincteric space separates the external from the internal sphincter.

The enclosures of the rectum are commonly divided into three parts: the upper (10.1-15 cm), middle (>5-10 cm) and lower rectum (0-5 cm). Most of the rectum is extraperitoneal, although the upper third is partly intraperitoneal and covered by peritoneum anteriorly and laterally. The extraperitoneal part of the rectum is covered by the fascia propria recti, a sheath of thin areolar tissue, or in the world of surgical pathology also called the mesorectal fascia. The mesorectal fascia encompasses a separate compartment consisting of perirectal fat and containing vessels and lymphatic tissue, i.e. the mesorectum.
Posterior to the mesorectal fascia is the presacral fascia, which is a part of the parietal pelvic fascia that covers the internal obturator, levator ani, coccygeal, and piriformis muscles together with the periosteal surface of the sacrum and coccyx. The virtual retrorectal space between the mesorectal fascia and presacral fascia constitutes the proper plane for mobilisation of the mesorectum, that when opened has been described to resemble 'angel's hair' due the loose areolar tissue within; the so-called "holy plane"[45].

In its course the rectum is related posteriorly to the sacrum, coccyx, levator ani muscles, median sacral vessels, and roots of the sacral nerve plexus. Anteriorly, in males, the extraperitoneal rectum is related to the prostate, seminal vesicles, vasa deferentia, ureters, and urinary bladder, and the intraperitoneal rectum may be in contact with loops of the small bowel and sigmoid colon. In females, the extraperitoneal rectum lies behind the posterior vaginal wall, and the intraperitoneal rectum may be related to the upper part of vagina, uterus, fallopian tubes, ovaries, small bowel, and sigmoid colon.

**Surgical technique**

*"May I ask you to move a little? You've been standing on my foot for half an hour",* - Dr. William S. Halsted (1852-1922) during one of his lengthy breast resections, sacrificing speed and style for scrupulous care and anatomical integrity.

While a door may be opening to the non-surgical management of a selected group of rectal tumours, surgical resection is still regarded as the cornerstone of curative treatment for rectal cancer. At the beginning of the 20th century, rectal cancer surgery carried both a high mortality and a near 100% recurrence rate, and was largely considered a non-curable disease.

In 1908, Miles published a thorough description of the radical abdominoperineal procedure; introducing the basis for modern rectal cancer surgery[46]. Miles, like Halsted with breast cancer, studied the lymphatic spread of rectal cancer in planning his operation. Abdominoperineal excision, which entails the removal of the pelvic mesocolon compromising "the zone of upward spread", in a combined abdominal and perineal approach with anatomical correct dissection of the rectum and anal canal and the creation of a permanent colostomy, remained the standard of care in rectal cancer throughout the following decades, irrespective of tumour height.

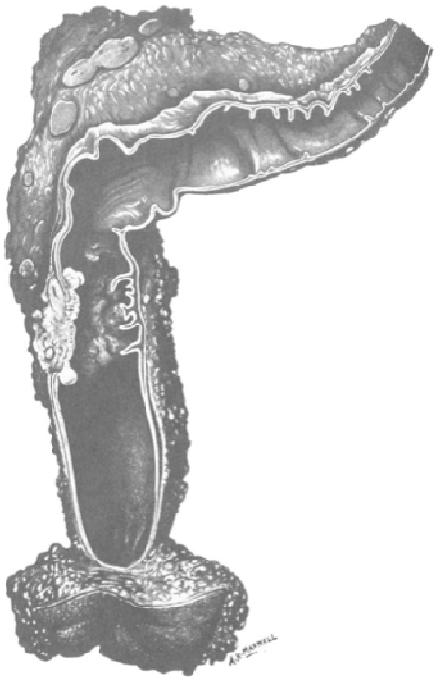
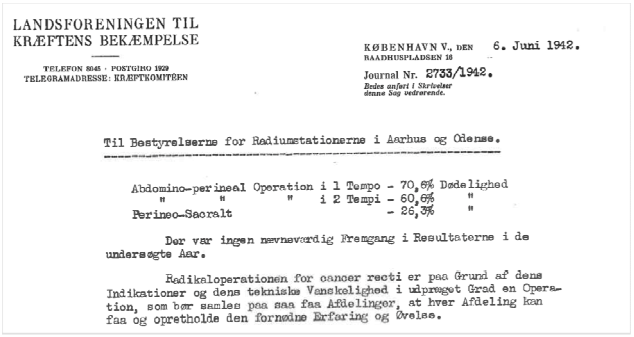


**Figure 1**
Specimen after Miles' abdominoperineal excision. It is notable that this procedure was also performed for a tumour well above the pelvic floor, as in this example.

A report in 1942 on the outcome for patients with rectal cancer in Denmark in the time period from 1931 to 1935 showed that the prognosis was far from favourable. In that time period 1,444 patients were admitted in 121 hospitals. Only 27% of patients had radical surgery, and perioperative mortality was as high as 60% to 70%[47].



LANDSFORENINGEN TIL
KRÆFTENS BEKÆMPELSE

TELEFON 8045 · POSTGIRO 1829
TELEGRAMADRESSE: KRÆFTKOMITÉEN

KØBENHAVN V., DEN 6. Juni 1942.
RAADHUSPLADSEN 16

Journal Nr. 2733/1942.
Bedes anført i Skrivelser denne Sag vedrørende.

Til Bestyrelserne for Radiumstationerne i Aarhus og Odense.

Abdomino-perineal Operation i 1 Tempo - 70,6% Dødelighed
" " " i 2 Tempi - 60,6% "
Perineo-Sacralt - 26,3% "

Der var ingen nævneværdig Fremgang i Resultaterne i de undersøgte Aar.

Radikaloperationen for cancer recti er paa Grund af dens Indikationer og dens tekniske Vanskelighed i udpræget Grad en Operation, som bør samles paa saa faa Afdelinger, at hver Afdeling kan faa og opretholde den fornødne Erfaring og Øvelse.

**Figure 2**
Extract from the Danish report anno 1942 on cancer recti.
"To the boards of the Radiation departments of Aarhus and Odense. Abdominoperineal resection in 1 tempi – 70.6% mortality, -do- in 2 tempi – 60.6% mortality, Perineo-sacral – 26.3%. There was no observable improvement during the study period.
Radical surgery for cancer recti is due to its indication and technical difficulty is ever more so an operation, which should be managed at only some few departments, so that each department may achieve and sustain the necessary experience and training.

Sphincter preservation with re-establishment of intestinal continuity in rectal cancer surgery became a controversial issue in the early 1940s and 50s[48]. It was supposed not to be sufficiently radical and to increase mortality due to anastomotic leakage, and was therefore rejected by many. However, the safety of a restorative procedure for rectal cancer was established by Claude F. Dixon in 1948, when he reported on his series using anterior resection of the rectum for tumours in the mid and upper third of the rectum[49]. Anterior resection became the standard in surgical cure of mid and upper rectal tumours, and new technical developments, such as staplers, made sphincter-preserving surgery possible even in mid or low-lying tumours without compromising oncological outcomes[50-52].

*Total mesorectal excision*

Good surgical technique is integral to optimising oncological outcome and minimising morbidity in rectal cancer surgery. Before the standardisation of surgery with TME, the reported rate of local recurrence after curative resection varied between 4% and 55% with significant differences reported among surgeons with an otherwise similar case mix[31, 53]. Total mesorectal excision was first described by Heald[1, 2] in 1979, suggesting that mesorectal residues of tumour might be the primary cause of local recurrence. The main principle of the procedure was to maintain the integrity of the mesorectal envelope by sharp dissection in the "holy plane" between the fascia propria of the rectum and the presacral fascia with the complete removal of the mesorectum and an intact enveloping fascia[45]. Since the plane which surrounds the mesorectum is created by a separate embryological origin, Heald reasoned that the tumour may initially tend to be confined within the mesorectal fascia; "an almost impenetrable barrier to the spread of carcinoma"[45]. Heald's technique resulted in an unseen at the time local recurrence rate of 4% and improved survival when compared to conventional, non-standardised blunt rectal cancer surgery[20, 30, 33, 36-38, 54-58]. Macfarlane et al. concluded that most carcinomas that recur initially within the pelvis could probably have been cured by better surgery[37].
The technique of TME also proved to be highly teachable despite the initial doubts about whether the excellent results of specialised surgeons could be repeated on a national level[54, 58]. During

the last decades, Heald and colleagues have championed the concept of TME with collaborative surgical workshops worldwide, and TME has been successfully implemented in many countries, with a subsequent dramatic improvement in local recurrence and survival rates[34, 35, 39, 56]. The basic principles of TME surgery remain the same in modern surgical management of rectal cancer, whether the technique is performed as an open, laparoscopic, or robotic procedure.

*Partial mesorectal excision*

A smaller and less extensive variation of TME is partial mesorectal excision (PME), also called tumour-specific mesorectal excision, which is suggested for upper rectal cancer. The idea involves resecting an ample distal margin of mesorectum particular to the location of the tumour. Discontinuous mesorectal deposits from the primary tumour have been investigated by pathological assessment of resected specimens, and estimated to be present in up to 24% of specimens, for which 5 cm in a fixed specimen is the furthest extent reported to date; usually exceeding distal intramural spread[2, 59-65]. Hence, tumours of the upper rectum may not require TME and may be optimally managed by mesorectal transection 5 cm below the lower edge of the tumour as a PME. In contrast, with complete removal of the mesorectum, a distal margin of 1 cm or even less is considered sufficient, as intramural spread seldom exceeds 1 cm.

Based on the literature on the extent of distal spread of tumour in the mesorectum, PME appears to be a valid technique if performed according to the same high standards of TME, i.e. perpendicular transection of the mesorectum to avoid coning and avoidance of defects in the enveloping mesorectal fascia. The presence of defects in the mesorectal tissue or coning indicates mesorectal tissue left behind, which may include residual tumour satelittes[66]. However, the rationale for preserving a distal part of remnant rectum is that it offers a better long-term functional outcome and fewer postoperative complications, while being as oncological safe as TME[17-19]. By not making total mesorectal excision obligatory for upper rectal cancer, Law et al. reported lower anastomotic leak rates and fewer postoperative complications in patients who underwent PME for upper rectal cancer[18]. Furthermore, recent studies suggest that PME, compared to TME, results in significantly less long-term bowel, urinary, and sexual dysfunction[17, 67-69].

*Abdominoperineal excision*

Following the acceptance of TME as the gold standard for rectal cancer surgery, the oncological outcome of abdominoperineal excision (APE) has not improved to the same degree and remains inferior to that of anterior resection[5, 12, 70, 71]. This difference has been attributed to the creation of a waist at the level of the tumour-bearing segment when performing conventional synchronous combined APE. Recent focus on low rectal cancer has suggested that an extralevator approach in the perineal part of APE, which aims at a wider circumferential resection margin (CRM), improves the rates of inadvertent bowel perforation and involved CRM, and, subsequently, reduces the risk of local recurrence in patients with low rectal cancer[72-75]. There is currently enormous debate internationally on whether this is the optimal approach or not.

Based on well-defined anatomic structures identifiable on MRI, the procedure can be performed either as an intersphincteric, extralevator, or ischioanal APE depending on the tumour stage and clinical assessment of the patients.

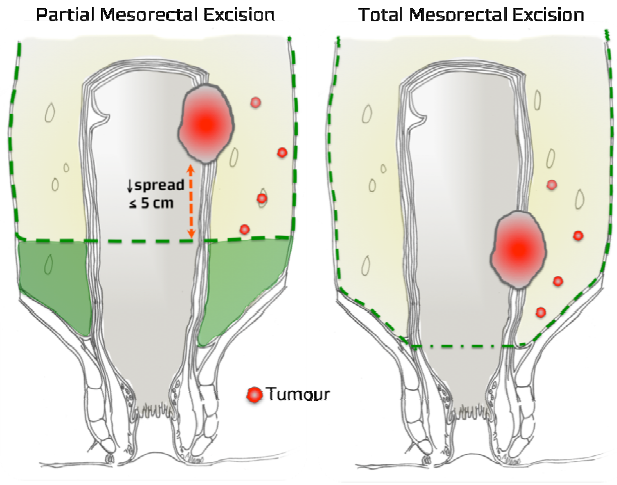



**Figure 3**

Schematic representation of partial and total mesorectal excision for rectal cancer. (Left) Partial mesorectal excision with perpendicular transection of the bowel and mesorectum a minimum of 5 cm below the level of the primary tumour. (Right) Total mesorectal excision with complete removal of the mesorectum.

*Beyond TME*

The management of primary locally advanced rectal cancer growing outside the mesorectal fascia and into adjacent organs in the pelvis is challenging[76-81]. To achieve cure in these patients, multivisceral, exenterative surgery beyond conventional planes is required. A consensus statement on the management of these patients was published recently[82].

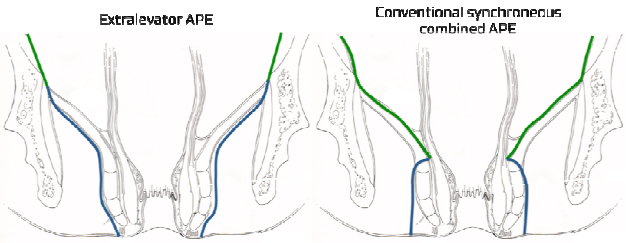



**Figure 3**

Schematic representation of extralevator and conventional abdominoperineal excision. (Left) Extralevator abdominoperineal excision with mobilisation of the rectum and mesorectum down to the top of the levator muscle (green). The perineal dissection proceeds just outside the external sphincter and along the levator up to its origin at the obturator internus muscle (blue). (Right) When performing the conventional abdominoperineal excision, the abdominal dissection is done as in TME down to the top of the anal canal (green), and the perineal part along the external sphincter. The two planes meet at the level of the puborectalis muscle, which creates a waist on the specimen.

**Multidisciplinary team-directed treatment planning**

*"None of us is as smart as all of us"* - Japanese proverb

The multidisciplinary team (MDT) conference is an important step towards achieving an optimal treatment strategy for cancer and is recommended in many countries and across specialities[83-85]. The results of the preoperative investigations and the clinical information about the patient are reviewed in the presence of dedicated specialists in surgery, oncology, radiology, pathology, and patient care. The structured discussion of each patient aims at individualising and hence optimising the treatment and improving prognosis[13-15, 86].

Based on the pathology report postoperatively, a MDT conference offers the opportunity to assess tumour characteristics, effect of neoadjuvant therapy and quality of the radiological staging and the surgery to decide whether any adjuvant therapy is required or whether close follow-up is advisable. Follow-up conferences are also valuable for teaching and multidisciplinary team development.

*Tumour location*

The characterisation of rectal cancer into upper, mid, and lower has traditionally been measured by using a combination of digital rectal examination and rigid proctoscopy, and is recommended in the Danish guidelines. The distance from the anal verge to the location of the tumour is used to decide on the appropriate type of surgery, and whether restorative surgery is feasible.

*Staging*

Preoperative staging is an essential part of modern rectal cancer management, and radiological assessment is central to this process. Ideally, imaging modalities should be combined to enable detailed information on both the specific tumour characteristics and the extent of disease spread to reliably guide decision-making and individualise treatment. In the last decade, enormous progress in preoperative staging has been made. The two common modalities used for local staging of rectal cancer are magnetic resonance imaging (MRI) and endoluminal ultrasound. Although both are considered to have specific advantages, MRI provides more detailed information about the locoregional anatomy of the pelvis and can accurately identify the specific features that are considered important determinants in treatment planning. Local tumour extension, location with respect to the sphincter, levator ani and the peritoneal reflection, N-stage, potential CRM/mesorectal fascia involvement, and extramural venous invasion need to be addressed. Endoluminal ultrasound is recommended for assessing early rectal tumours, and has been shown to be of high accuracy in selecting early-stage T1 tumours suitable for local excision[87]. For the assessment of distant metastases, computed tomography (CT) of the liver and thorax is generally used.

In the future, functional imaging may further help in selection of patients most likely to benefit from neoadjuvant therapy and in determining a complete pathological response to this treatment, thus selecting patients in whom surgery may be avoided.

*Magnetic resonance imaging*

Magnetic resonance imaging has emerged as the preferred imaging tool for the pre-treatment assessment of rectal cancer, and pioneered by a few dedicated radiologists.

Routine use of MRI in the context of a multidisciplinary assessment of rectal cancer assists in staging of the tumour, in identifying patients who may benefit from stage-appropriate neoadjuvant therapy, and in planning of optimal surgery. Preoperative staging by MRI has been mandatory for patients with newly diagnosed rectal cancer in Denmark since 2002.

The success of the technique depends on obtaining good-quality, high-resolution T2-weighted images of the primary tumour, the mesorectal fascia, peritoneal reflection, and the pelvic organs in relation to the rectum. Although axial T2-weigthed images are the cornerstone for the staging of primary rectal cancer, sagittal and coronal images provide additional value, i.e. with regard to tumour height in the rectum and in assessing the relationship between advanced stage tumours and adjacent pelvic structures.

Preoperative MRI of primary rectal tumours can be used to identify prognostic factors in terms of tumour stage, relationship to the mesorectal fascia and pelvic floor, extramural depth of invasion, lymph node involvement, and presence of extramural vascular invasion (EMVI). MRI is also considered useful in re-assessing rectal cancer with regard to tumour response and planning intervention after long course chemoradiotherapy[88, 89].

Tumour staging of rectal cancer with MRI is largely based on an observable difference in T2 signal intensity between the tumour, submucosa, muscular layer, and the mesorectum. While T1 tumours are confined to the mucosa and submucosa, T2 tumours invade the muscularis propria and T3 lesions extend beyond the muscularis propria. One limitation in T-staging on MRI includes difficulty in differentiating fibrosis from tumour infiltration, typically leading to an incorrect differentiation between T2 and early T3 tumours[10]. However, subdivision of T3 tumours based on the depth of tumour invasion outside the muscularis propria showed that an extramural depth exceeding 5 mm resulted in significantly poorer survival[90, 91]. This suggests that T2 tumours and early stage T3 tumours (<5 mm invasion) may be grouped together, separate from advanced T3 tumours based on prognosis. In light of this, it has been shown that MRI can accurately measure the depth of extramural tumour spread, and results from the MERCURY study show that MRI correlated within 0.5 mm of that measured at histopathological examination[92]. This prediction can be reliably reproduced among radiologists[93, 94].

The mesorectal fascia is easily identifiable on axial T2-weigthed images as a thin hypointense line. The relationship of the tumour to the mesorectal fascia can be reliably assessed at MRI with high specificity and is critical for surgical planning by predicting an involved CRM[9, 10, 95-97]. There is some disagreement among histopathologists as to when the CRM should be considered involved. In most cases, the CRM is considered to be involved when the distance from the tumour to the margin is less than 1 mm; however a 2-mm or 3-mm cut-off point has also been considered based on the risk of local recurrence[3, 4, 98-102]. In 2001, Beets-Tan et al. found that a tumour-free margin of at least 1 mm can be predicted with a high degree of certainty when the measured distance on MRI is at least 5 mm[10]. The Danish guidelines for allocation to neoadjuvant therapy are to some extent based on the study by Beets-Tan, and a study on survival and CRM by Wibe *et al.*[99]. Nonetheless, the optimal distance between the tumour and the mesorectal fascia for the prediction of an involved margin on MRI seems to be 1 mm. A 5-mm cut-off on MRI does not increase the accuracy of MRI with regard to prediction of CRM involvement or poor outcome[96, 103]. Furthermore, the measurement of a 5-mm distance, compared to 1-mm distance, may be difficult to interpret and reproduce among radiologists, and this may lead to the risk of overtreatment[93].

Careful assessment of the peritoneal reflection must be performed in upper rectal tumours. The peritoneal reflection can be seen on sagittal T2-weighted images as a hypointense linear structure, and on axial images, it has a V shape and attaches onto the anterior aspect of the rectum[104]. The relationship to the peritoneal reflection is important in staging, since rectal tumours with invasion through the peritoneal reflection are categorised as stage T4a lesions, which has a significant impact on prognosis[41, 43]. Burton et al. showed that these tumours may readily be identified using preoperative MRI and may benefit from preoperative chemoradiotherapy[105, 106].

In cases of low-lying rectal tumours, preoperative MRI must define the location of the tumour relative to the sphincter complex and levator ani to determine whether sphincter-preserving surgery is feasible, or if APE is needed to secure oncological safety[107]. The prospect of clear resection margins can be significantly improved by using MRI for surgical road mapping, enabling precise preoperative planning and adjustment of the conventional surgical approach of low rectal tumours[74, 107].

Assessment of lymph node involvement by MRI, for the most part, involves the evaluation of nodes in the mesorectum as the predominant field of spread with regard to signs of malignancy (size, irregularity, spiculation, and heterogeneous signal intensity) and the relationship of clearly malignant nodes to the mesorectal fascia. However, despite promising initial results, studies have not been able to reproduce the very high accuracy rates for the diagnosis of malignant lymph nodes[103]. Information of a suspected malignant node or tumour deposit less than 1 mm from the mesorectal fascia is important to the surgeon, who must stay well clear of the tumour at that margin. Malignant nodes within the confines of the mesorectal fascia will be resected as part of a good-quality TME[108]. Potentially involved extra-mesorectal lymph nodes can be targeted with a widened field of preoperative radiotherapy and extended surgical resection.

Extramural vascular invasion is defined histologically as the presence of tumour cells within a vascular structure that has smooth muscle in the wall beyond the muscularis propria. Although vascular invasion does not affect pre-treatment decision-making and is assessed at pathological examination, it has prognostic significance and should, if possible, be evaluated at imaging[109, 110].

Magnetic resonance imaging is the preferred primary imaging method for evaluation of local recurrence from rectal cancer[111], although the diagnosis of local recurrence should be confirmed by biopsy or supplemented by PET-CT. Interestingly, although MRI is the first-choice staging modality for primary rectal cancer, there is little in the literature on the use of MRI for predicting local recurrence and the extent of recurrent tumour invasion[112, 113]. An early local recurrence may be difficult to distinguish from postoperative fibrosis. In these cases, repeated evaluations with MRI may be necessary to establish recurrence[114].

**Adjuvant therapy**

*"In God we trust. All others must have data."* - Dr. Bernard Fisher (1918– )

In rectal cancer treatment, the use of long-course neoadjuvant chemoradiotherapy for potentially resectable but locally advanced cancers has been thoroughly established and is now common practice[7, 28, 115]. In contrast, the use of neoadjuvant radio- and/or chemotherapy, short course (5 x 5 Gy), or long course (~52 Gy) for primarily resectable cancer is controversial and still a subject of discussion in many countries.

Several large randomised trials have shown that combinations of radiotherapy and chemotherapy markedly reduced the risk of local recurrence for resectable rectal cancer, although not having any major influence on survival[5, 6, 8, 116-119]. To date, only the Swedish Rectal Cancer Trial published in 1997 has reported a pronounced effect of preoperative radiotherapy on survival, but this was in the pre-TME era with conventional blunt surgery and an unacceptably high risk of local recurrence in the group of patients treated with surgery alone[120]. When proper surgical technique with TME is used, the significance of adding preoperative radiotherapy on survival becomes considerably less. There is very strong data based upon randomised trials that suggest that radiotherapy is best given preoperatively[6, 117, 118, 121], and that preoperative radio(chemo)therapy produces the same proportional reduction in the rate of local recurrence following the widespread application of TME-based surgery as that seen in previous studies undertaken before such excision[5, 6, 8, 116-119]. Furthermore, there seems to be no significant difference in the effect on local control between short-course radiotherapy and long-course chemoirradiation for resectable rectal cancer, although more tumour downstaging is achieved with chemoirradiation[122, 123]. Still, many details regarding how neoadjuvant therapy should be administered are open to discussion, and practice varies between countries[40, 124-127].

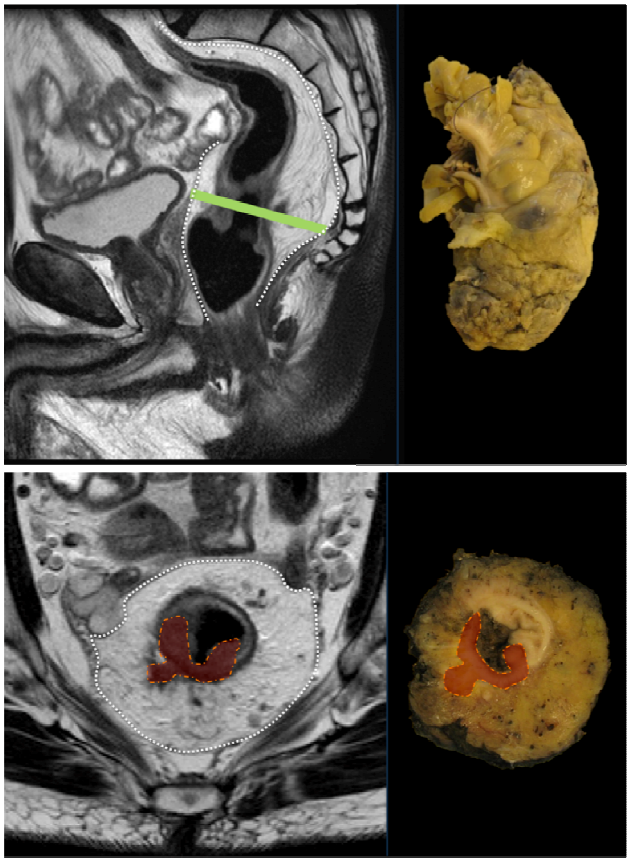


**Figure 4**
Sagittal and axial T2-weighted MRI of a T3 tumour of the mid-rectum and the corresponding pathology specimen. Green line marks the angulation of the axial MRI below.

Danish guidelines[26] recommend a selective approach in application of long-course chemo-radiotherapy for rectal cancer according to the stage and location of the tumour discussed at an MDT conference (*table 1*). All patients with resectable cancer of the upper rectum and patients with cancer in the mid or low rectum considered to be cT1-T2 at preoperative evaluation undergo surgery directly, without neoadjuvant treatment. Patients with a cT3 tumour of the mid-rectum are allocated to long-course preoperative radiochemotherapy (LCPRCT) if the distance from the

tumour to the mesorectal fascia is less than 5 mm on preoperative MRI. cT3-T4 tumours of the low rectum are all considered candidates for LCPRCT. In 2012, 28% of all rectal cancer patients in Denmark received neoadjuvant therapy prior to surgery[29].

The role of neoadjuvant therapy in the treatment of upper rectal cancer remains controversial. None of the major randomised trials that have evaluated neoadjuvant radiotherapy with regard to tumour location has observed any significant benefit for upper rectal cancer regarding local control or survival (*table 2*)[5, 6, 116, 118-120, 128]. In the Swedish Rectal Cancer Trial, 27% of the patients had a tumour of the upper rectum (>11 cm). A significant improvement in local control and overall survival for patients with mid and low rectal tumours receiving short-course radiotherapy and surgery was demonstrated, but no significant difference for tumours of the upper rectum was observed[128]. In the Dutch TME Trial, a significant association between local recurrence rates and the use of short-course radiotherapy was also found. However, in subgroup analysis, the 30% of patients with upper rectal cancer (10.1-15 cm) had no improvement in local recurrence rates compared to the surgery-alone cohort[5, 116, 119]. A few years later, the MRC CR07 study once again confirmed the efficacy in reducing the risk of local recurrence with the use of preoperative short-course radiotherapy, as compared to surgery-alone (selective postoperative radiotherapy in cases of close CRM; 11%)[6]. Only 15% of the patients in this study had a tumour of the upper rectum (>10-15 cm), and this may suggest some selection of patients randomised in the trial. Although the risk of local recurrence was 1.2% at 3 years in patients with preoperative radiotherapy and surgery compared to 6.2% in the surgery-alone group, this reduction was not significant (*P*=0.07).

The prevention of local recurrence, with the severe morbidity this may have, must ultimately be weighed against the morbidity caused by neoadjuvant radio(chemo)therapy that all treated patients are at risk of developing. Radiotherapy is associated with serious side effects such as impaired healing, anorectal and genitourinary dysfunction, and secondary malignancies[129]. Furthermore, because radio- and chemotherapy are cost and resource demanding it is of vital importance to identify patients in whom the benefits of neoadjuvant treatment exceed the risks. Preoperative MRI was not used in the standard preoperative evaluation for rectal cancer in any of the major randomised trials, which would have enabled a better selection of patients most likely to benefit from neoadjuvant therapy.

Another idea might be to use preoperative chemotherapy alone for the downsizing of tumours and to avoid radiotherapy. This is currently being tested in the ongoing randomised trial FOxTROT for colon cancer (including upper rectum), but long-term data are not yet available[130].

For several years, adjuvant 5-fluorouracil (5-FU) has been standard in the management of high-risk colon cancer. By contrast, no randomised trials have shown a benefit of adding adjuvant chemotherapy following surgery for rectal cancer, and debate continues as to whether adjuvant chemotherapy should be used for rectal cancer or not. Still, the majority of countries include chemotherapy regimens in their guidelines similar to what is recommended for patients with colon cancer. A population-based study from Sweden found that overall survival improved significantly in stage III rectal cancer patients who received adjuvant chemotherapy[131]. In Denmark, selected high-risk patients have been offered postoperative chemotherapy with 5-FU +/- oxaliplatin since 2009[26].

**Audit and quality of surgery**

*"Beauty is only skin deep, but ugly goes clean to the bone."* – Dorothy Parker (1893-1967)

Paralleling the standardisation of rectal cancer surgery with TME was the evolution of quality assurance in the discipline of surgical pathology with major support of the precise excision of the mesorectum. In 1986, Quirke et al. reported tumour involvement of the lateral margin (circumferential resection margin) in 27% of rectal specimens resected by conventional blunt techniques performed by most surgeons at the time[3]. Eighty-six per cent of the patients with an involved margin developed local recurrence, suggesting that the CRM was a major predictor of local recurrence[3, 4]. Quirke et al. explained that the origin of most pelvic recurrences occurring was due to inadequate resection of the mesorectum with conventional surgery, characterised mainly by a violated CRM[132]. By adopting a standardised approach to the rectal cancer specimen, with thin serial transverse sections, the possibility of real quality assurance in rectal cancer surgery was overt. This became even more practical with the introduction of TME, as it produces an intact, anatomically reproducible specimen containing rectal cancer surrounded by an un-violated mesorectum, with identifiable landmarks and ample lateral and distal margins. In the case of best-quality TME, the surface of the resection is smooth and does not show incisions or tearing into the mesorectum[11, 12]. Defects on the surface may suggest mesorectal tissue left behind which may include tumour satellites that would give rise to local recurrence[66].
With supporting photo-documentation of specimens, it is recommended that all rectal cancer specimens be graded by specifically trained pathologists for macroscopic quality of the mesorectal excision according to the plane of surgery achieved, as initially demonstrated by Nagtegaal and Quirke (*table 3*)[11, 12].

Slicing of the specimen allows for a good assessment of the adequacy of excision and the regularity of the CRM. The achieved plane of surgery and an involved circumferential resection margin have been shown to be strongly associated with the risk of local recurrence and disease-free surgival[4, 11, 12, 133, 134]. Hence, high-quality surgery indicated by a complete TME in the mesorectal plane results in a large reduction of local recurrence and increase in survival[12, 135].

Apart from margin involvement and plane of surgery, pathological stage is the most important prognostic factor in rectal cancer. The TNM (currently 7$^{th}$ edition) is the most commonly used system and is based on the depth of local tumour invasion (T-stage), extent of regional lymph node involvement (N-stage), and presence of distant metastases (M-stage)[136].

**Table 1**

| Table 1: Danish guidelines for allocation to neoadjuvant therapy. | | |
|---|---|---|
| Tumour height measured by rigid proctoscopy | Surgery alone | Combined CRT and surgery |
| Low (<5 cm) | T1, T2 | T3, T4 |
| Mid (5.1-10 cm) | T1, T2<br>T3; ≥ 5mm to MRF | T3; <5 mm to MRF<br>T4 |
| High (10.1-15 cm) | Resectable T1-T4 | Non-resectable T4 |

**Table 2**

| Table 2: Local recurrence in randomised trials of neoadjuvant therapy according to tumour location in the upper rectum | | | | |
|---|---|---|---|---|
| RCT Trial | Inclusion time | Number of patients with upper rectal tumour (%) | Treatment | Local recurrence outcome |
| Swedish Rectal Cancer Trial (1997) | 1987-90 | >11 cm:<br>*n*=243 (27) | Preoperative short-course RT *vs.* surgery alone | 8% vs. 12%<br>(P=0.3) |
| Dutch TME Trial (2007) | 1996-99 | 10.1-15 cm:<br>*n*= 551 (31) | Preoperative short-course RT *vs.* surgery alone | 4% vs. 6%<br>(P=0.122) |
| MRC-CR07 (2009) | 1998-05 | >10-15 cm:<br>*n*= 207 (15) | Preoperative short course RT *vs.* selective postop CRT. | 1.2% vs. 6%<br>(P=0.07) |

**Table 3**

| Table 3: Macroscopic grading of the resection specimen[11, 12]. | | |
|---|---|---|
| Grade | Plane | Criteria |
| Complete | Mesorectal | Intact mesorectum with only minor irregularities of a smooth, mesorectal surface; no defect deeper than 5 mm; no coning; and smooth circumferential margin on slicing. |
| Nearly complete | Intramesorectal | Moderate bulk to mesorectum, with irregularities of the mesorectal surface; moderate distal coning; muscularis propria not visible with the exception of levator insertion; and moderate irregularities of circumferential resection margin. |
| Incomplete | Muscularis propria | Little bulk to mesorectum with defects down onto muscularis propria; very irregular circumferential resection margin; or both. |

**Table 4: Review of processing variability of the resected specimen**

| *Authors* | *Year* | *Cases (n)* | *Processing of the specimen* | *Tissue variability mean (range)* |
|---|---|---|---|---|
| Williams *et al.*[138] | 1983 | 10 | Pinned, fixed | 99% (88-106) |
| Ono *et al.*[144] | 2002 | 40 | Pinned, fixed | 60% (15-133) |
| Zhao *et al.*[147] | 2005 | 45 | Pinned, fixed | 85% (72-98) |
| Weese *et al.*[139] | 1986 | 10 | Unpinned, fixed | 80% (59-100) |
| - | | | Pinned, fixed | 150% (85-210) |
| Søndenaa *et al.*[140] | 1990 | 20 | Unpinned, fixed | 79% (58-93) |
| - | | | Pinned, fixed | 120% (60-270) |
| Kwok *et al.*[141] | 1996 | 55 | Unpinned, fixed | 79% (NA) |
| Goldstein *et al.*[142] | 1999 | 26 | Unpinned, fixed | 72% (NA) |

**Table 5: Review of length of distal spread in the mesorectum in patients with rectal cancer.**

| *Authors* | *Year* | *Cases* | *Processing of the specimen* | *Prevalence of distal spread (n)* | *Maximum length of distal spread* | *Recommended distal margin in mesorectum* |
|---|---|---|---|---|---|---|
| Heald *et al.*[2] | 1982 | 100 | Pinned, fixed | 5% (5) | 4 cm | 5 cm, or TME |
| Morikawa *et al.*[65] | 1994 | 133 | Pinned, fixed | 24% (32) | 4 cm | . |
| Scott *et al.*[59] | 1995 | 20 | Pinned, fixed | 25% (5) | 3 cm | 4-5 cm, or TME |
| Shirouzu *et al.*[61] | 1995 | 610 | Pinned, fixed | 10% (61) | >2 cm | 1 cm |
| Reynolds *et al.*[60] | 1996 | 44 | Pinned, fixed | 27% (12) | 5 cm | TME |
| Hida *et al.*[62] | 1997 | 158 | Unpinned, fixed | 23% (36) | 4 cm | 5 cm or TME if T3/T4 tumour |
| Tocchi *et al.*[143] | 2001 | 53 | Pinned, fixed | 17% (9) | NA | TME |
| Ono *et al.*[144] | 2002 | 40 | Pinned, fixed | 15% (6) | 2 cm | 3 cm |
| Zhao *et al.*[147] | 2005 | 45 | Pinned, fixed | 22% (10) | 3.6 cm | 4 cm |
| Wang *et al.*[145] | 2005 | 31 | Pinned, fixed | 13% (4) | 3.5 cm | 4 cm |
| Shimada *et al.*[146] | 2011 | 381 | Pinned, fixed | 15% (56) | 3.8 cm | 4-5 cm |
| Komori *et al.*[64] | 2012 | 629 | Fixed | 12% (73) | 3.6 cm | 4 cm |
| Hayden *et al.*[63] | 2012 | 75 | Fixed | 16% (12)* | 3 cm | . |

Please notice the substantial variation in prevalence of spread, length of spread and recommended margin among the studies.
*All patients received preoperative radiotherapy.

One technical aspect that is not mentioned in some of the studies describing macroscopic assessment of the specimen is the important differentiation between a TME and PME. By TME the mesorectum is completely excised downwards to the pelvic floor. In contrast, when performing PME the mesorectum should be transected perpendicular to the rectal wall with a healthy length of mesorectum beyond the gross distal margin of the tumour; circumferentially the excision is performed in the same way as in TME, i.e., it includes the mesorectal fascia[66]. If the surgeon "cones" down the dissection distally, then too much of a distal mesorectal tail will be left, which may compromise local control of the cancer[137]. Similarly, the extent of the distal resection of mesorectum is of interest when transecting the mesorectum during PME, as an insufficient dissection of the mesorectum in close proximity to the tumour may leave mesorectal tumour deposits behind. The histological rationale shows us that the adequate margin when performing PME is at least 5 cm in the mesorectum (*table 5*), as we have discussed earlier. For distal margin examination, it is important to recognise fixation-induced shrinkage of the specimen (*table 4*). Most studies have directly established the *in vivo* optimal clearance margin from the histologically observed extent of distal spread, neglecting the tissue variability that occurs after resection and during fixation of the rectal specimen, and methods of examination vary considerably[59-62, 64, 138-147].

**Local recurrence**

*"The emperor of all maladies – the king of terrors",* - quote by a 19th-century surgeon

A major problem after surgery for rectal cancer is the advent of local recurrence of tumour in the pelvis. The clinical manifestation of a local recurrence depends on its site and involvement of adjacent organs. Less than 35% of patients with local recurrence are diagnosed at routine follow-up[32, 78, 148]. In the remaining, symptoms (pain, rectal bleeding, discharge, and/or change in bowel habit) often precede the diagnosis of local recurrence and are the cause of major morbidity with poor quality of life[149, 150]. In 40-60% of the patients, local recurrence is the only manifestation of recurrent disease.

Treatment of local recurrences shares similarities with the treatment of primary advanced rectal cancer. Most careful mapping of the tumour by MRI is necessary. Long-term chemoradiotherapy before surgery for local recurrence is recommended if not been given previously. The surgical approach depends on the location, but often a wide resection of the tumour with APE or pelvic exenteration, including adjacent organ in the pelvis, is performed. Radical, curative resection of local recurrence is the only treatment that offers any significant improvement in prognosis[78, 79, 151].

Time to the diagnosis of local recurrence is variable; however, most local recurrences will occur within 2-3 years, and only rarely after 5 years[70, 76, 78, 116, 152, 153].

**AIMS OF THE THESIS**

This dissertation aims to discuss aspects of the treatment of rectal cancer with regard to the adequacy of mesorectal excision and oncological outcome, with a particular focus on cancer of the upper rectum.

The *specific* aims were:

I. To determine the prevalence and localisation of inadvertent residual mesorectum detected on postoperative MRI after mesorectal excision surgery.

II. To estimate the risk of local recurrence in an audited cohort of patients, with a particular focus on patients with upper rectal cancer who underwent PME without neoadjuvant therapy.

III. To objectively measure the length of the distal resection margin in the fresh and fixed specimen after PME using MRI to document the amount of tissue shrinkage that occurs after surgical removal and fixation. The tissue shrinkage ratio was used to calculate an equivalent 5-cm distal resection margin in the fixed specimen at histopathological examination.

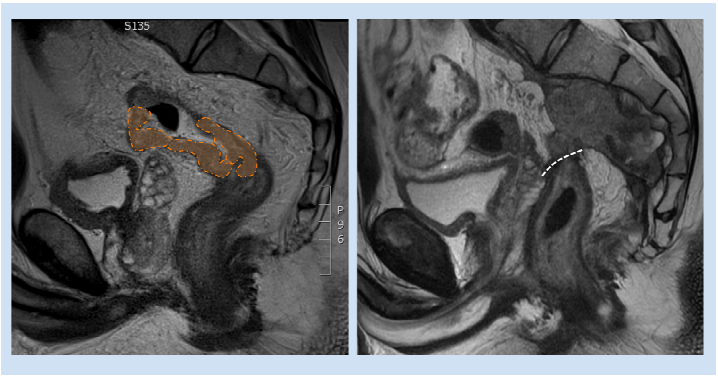



**Figure 6**

Local recurrence after surgery for rectal cancer. (Left) Preoperative MRI of a 52-year-old man with an mrT4a tumour of the upper rectum (orange). The patient underwent partial mesorectal excision without neoadjuvant therapy; pT4N1M0V2, R1. (Right) Postoperative MRI: Seven months later he was diagnosed with a local recurrence. The white line marks the level of the anastomosis.

**METHODOLOGICAL CONSIDERATIONS**

The following is a supplement and a discussion of some of the applied methods in Papers I to III. The studies were all performed in accordance with the regulations of the Local Danish Ethics Committee and approved by the Danish Data Protection Agency pursuant to the Danish act on storage and processing of personal data.

**Study populations**

During the study period the Department of Surgery P at Aarhus University Hospital had a primary catchment population of 400,000 inhabitants, and approximately 120 patients with rectal cancer were surgically treated each year. The department serves as a secondary referral centre for low rectal cancers in the region and is a tertiary referral centre in Denmark for very advanced and locally recurrent rectal cancers that often necessitate extensive resection beyond regular TME planes (population of 1.25 million and 5.5 million, respectively).

All patients with adenocarcinoma of the rectum were assessed at a multidisciplinary team conference based on preoperative MRI of the pelvis, computed tomography (CT) of the thorax and abdomen, and clinical examination with rigid proctoscopy. Rectal resection in patients without signs of distant metastasis and with

tumours considered to be resectable with a clear margin at preoperative evaluation and after neoadjuvant therapy was classified as treatment with curative intent, irrespective of pCRM involvement at definitive pathological examination.
Patients with primary rectal adenocarcinoma (15 cm or less from the anal verge) who underwent PME, TME, or APE from mid 2007 to 2010 were included in Papers I and II. All patients with surgery for rectal cancer were registered in a prospective database at the Department of Pathology. Patients from tertiary referral with locally advanced cancer often needing extensive surgery, or had a surgical procedure other than TME, PME, or APE (i.e., local excision of tumour or pelvic exenteration) were excluded from analysis, as were patients who underwent planned palliative surgery. Furthermore, patients with disseminated disease, previous diagnosis of local recurrence or macroscopic non-radical resection (R2), contraindication to having MRI, or who were deceased at inclusion were exempt from invitation to postoperative MRI in paper I. Additionally, we excluded patients without follow-up, unable to give informed consent, or with insufficient histopathological data. A flow chart of the study populations in Papers I and II is shown in *figure 8*.
In Paper III, we prospectively included 10 patients with upper rectal cancer in whom a PME was planned at preoperative MDT conference between January 2012 and August 2013. In the time period, a total of 41 resections with PME was performed. Undoubtedly, we would have preferred to include more of these patients to strengthen the study; however, in most cases it was not possible to time completion of surgery with the availability of the MRI scanner, which was in clinical use during the daytime.
All data on patient demographics, tumour characteristics, type of operation and treatment, and follow-up were obtained from clinical records that included imaging data and surgical and pathology reports.

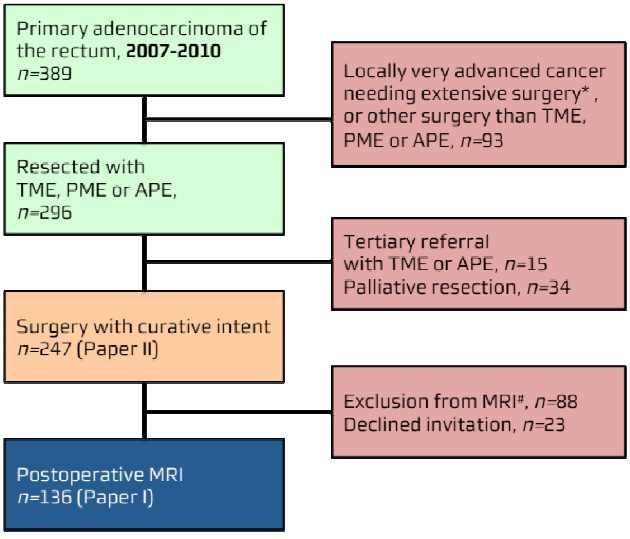



**Figure 6**
Study populations in Paper I and II. *i.e. pelvic exenteration ± brachy-therapy primarily from tertiary referral. #Further exclusion criteria described in the text and Paper I.

***Postoperative magnetic resonance imaging***
Postoperative pelvic MRI was performed using a Magnetom Avanto 1.5 Tesla MRI-scanner (Siemens AG, Erlangen, Germany) a minimum of 6 months following surgery to avoid confusion with postoperative changes. Sagittal, axial, and coronal T2-weighted turbo spin echo images were obtained in addition to a sagittal short T1 inversion recovery (STIR) image of the bony pelvis and a sagittal T2 3D sequence of the smaller pelvis.
The parameters were as follows: sagittal T2 BLADE: slice thickness 5 mm, spacing 0.5 mm, 27 slices, field of view (FOV) 240 x 240 mm, matrix 320 x 320, BLADE coverage 125.9%, TR 5830 ms, TE 104 ms. Axial T2 BLADE: no angulation, slice thickness 4 mm, spacing 0.4 mm, 25 slices, FOV 240 x 240, matrix 320 x 320, BLADE coverage 126.1%, TR 2930 ms, TE 109 ms. Coronal T2 BLADE: no angulation, slice thickness 4 mm, spacing 0.4 mm, 20 slices, FOV 240 x 240, matrix 320 x 320, BLADE coverage 125.0%, TR 3520 ms, TE 70 ms. Sagittal T2 3D space: slice thickness 1 mm, 1 slab, 88 slices per slab, FOV 256 x 256 mm, phase resolution 100%, slice resolution 79%, TR 2000 ms, TE 123 ms. Sagittal STIR: slice thickness 5 mm, spacing 0.5 mm, 25 slices, FOV 300 x 300 mm, matrix 320 x 256, TR 3500 ms, TE 22 ms, TI 160 ms. Image analysis was performed at a dedicated PACS-workstation (HP xw6000 workstation, Hewlett Packard, North America) with IMPAX-software (IMPAX 6, Agfa Healthcare N.V., Mortsel, Belgium) using computed calliper measurements.
Radiological assessment was blinded to the pathological evaluation and all clinical data, with the exception of preoperative MRI findings and type of surgery.
The evaluation of the postoperative MRI included assessment for the presence and localisation of residual mesorectum, level of the anastomosis, and detection of local recurrence. All radiological examinations were evaluated by the same radiologist (BGP) together with PB for consensus.

***Inadvertent residual mesorectum***
On postoperative MRI, mesorectal fatty tissue with a discernible tissue interface of fibrosis, which separates the mesorectum from the mesocolon, was considered a sign of residual mesorectum. Tissue fibrosis was differentiated from the mesorectal fascia as fibrosis typically has a lower signal on T2-weighted images, often seems more continuous, and may appear thicker than the mesorectal fascia.
Inadvertent residual mesorectum was defined as any residual mesorectum detectable after TME or APE. Only mesorectum above the level of the anastomosis perpendicular to the bowel was regarded as inadvertent residual mesorectum following PME. The localisation of residual mesorectum was categorised in relation to height in the pelvis and position to the level of resection in a standardised manner and dependent on the type of surgery, as:

(1) Cranially located mesorectum independent of the distal level of resection.
(2) Perianastomotic residual mesorectum was defined as residual mesorectum located directly above the level of the anastomosis. This applies in patients with TME or PME.
(3) Distal residual mesorectum below the level of resection after TME.

In patients who underwent APE, the extent of the resection of the levator ani and sphincters was noted as well, and will be addressed in future studies.

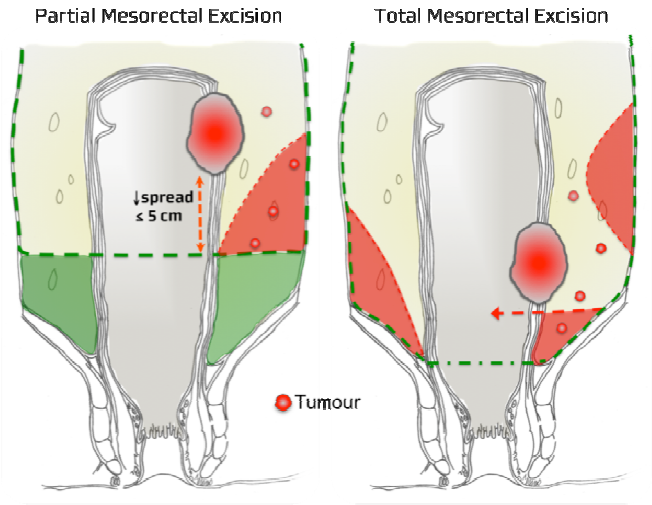



**Figure 7**
Schematic representation of inadvertent residual mesorectum according to localisation and type of surgery. **(Left) I**nadvertent residual mesorectum according to localisation following partial mesorectal excision. Green dashed line indicates optimal dissection and perpendicular transection. Red area shows perianastomotic residual mesorectum directly above the level of the anastomosis. The distal resection margin (DRM) is marked from the distal border of the luminal tumour to the level of resection.
**(Right)** Residual mesorectum according to localisation following total mesorectal excision. Green dashed line indicates complete removal of the mesorectum. Red area (top) shows cranially located mesorectum independent of the distal level of resection. Red area (left) shows perianastomotic residual mesorectum in direct relation to the anastomosis. Red area (bottom right) shows residual mesorectal tissue below the distal level of resection (red dashed line).

***Histopathological assessment***

The quality of the excised specimen was determined prospectively by the pathologist according to the grading system classified by Quirke and colleagues[11, 12] (mesorectal, intramesorectal and muscularis propria plane). Pathology reports were analysed with regard to the plane of surgery achieved, the CRM (positive CRM was defined as any tumour or involved lymph node 1 mm or less from the lateral margin), distal resection margin (DRM), and tumour characteristics according to the tumour node metastasis (TNM) classification[154]. During the study period, all rectal cancer specimens were primarily evaluated by one pathologist who had been personally trained by P. Quirke.
Based on standardised photographic documentation, a trained multidisciplinary pathologist, blinded to the clinical data and MRI findings, evaluated the specimens retrospectively for possible volume defects in the mesorectum according to the adequacy of the excision, smoothness of the specimen, and infiltration of ink beneath the mesorectal fascia (*figure 10*).

During the study period, some shortcomings in the grading of specimens according the plane of surgery achieved were identified. A misconception when grading PME specimens has been that the distal 1 to 2 cm of the specimen was typically left out of the evaluation of the plane of surgery achieved because the mesorectum is intentionally violated at transection. A non-perpendicular transection with coning of the distal part of the mesorectum in PME would in this way not necessarily result in a poor grading. Further, grading of APE specimens was somewhat ill-defined during the study period, and confusion in the grading of the mesorectal and perineal portions of the specimen could have resulted in substantially more being reported to be in the muscularis propria plane. Currently, more requisite and precise guidelines for grading of specimens are being used together with a greater understanding of the procedures.

***Correlation between MRI and pathology***

The direct correlation of MRI and histopathological assessment can be difficult, as these observational methods grade according to the tissue left behind and the tissue removed at surgery, respectively. For example, in patients in whom we observe distal residual mesorectum after TME, the pathologist can only grade according to the specimen removed at surgery and not on the basis of any residual mesorectum.

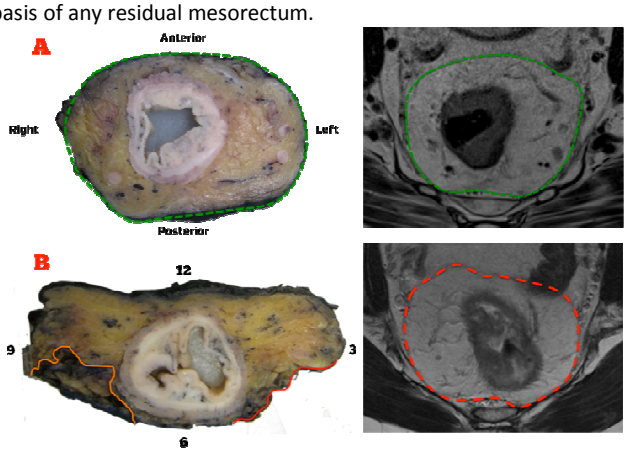



**Figure 8**
Evaluation of mesorectal volume defects at retrospective review of specimens based on standardised photo-documentation. On the right, the preoperative MRI corresponding to the height of the slice is shown
A) Complete mesorectal plane and no volume defect in the mesorectum. B) Volume defect in the mesorectum (3 to 5 o'clock; red line) and infiltration of ink beneath a defect in the mesorectal fascia (7 to 9 o'clock; orange line).

An intramesorectal or muscularis propria plane of surgery may be determined due to even relatively small defects/cuts into the muscular part of the bowel but may not highlight larger volume defects in the mesorectum and may not be visible on MRI. These differences may in part explain discrepancies between MRI and pathological assessments, and will be addressed in the following. A correlation between the area of volume defect in the mesorectum at pathological examination and inadvertent residual mesorectum on MRI would, however, strengthen the validity of residual mesorectum observed on MRI. But it may be difficult to compare these areas with accuracy, as the specimen may rotate during fixation and slicing, resulting in a difference between the evaluation performed by the pathologist and on MRI. The points of reference are more easily recognised by virtual rotation on MRI. Without adjusting for rotation inaccuracies, overlap of the areas was present in 70% of the excisions in which MRI and pathology agreed upon a defect and either perianastomotic residual mesorectum or cranially located residual mesorectum.

***Tumour height***
Tumour height was prospectively measured by both rigid proctoscopy at preoperative evaluation and on preoperative MRI. The height measured by rigid proctoscopy was set as the method of reference, as this is currently recommended by Danish guidelines. On MRI, tumour height was measured as the distance between the lower border of the subcutaneous part of the external sphincter, reflecting the anal verge, and the most distal part of the luminal tumour.
A subset of the patients with postoperative MRI was investigated in another study focusing on the length of remnant rectum and risk of having low anterior resection syndrome. In this study, the measurement of tumour height and level of anastomosis on MRI were validated, and the correlation between the two observers was found to be good (κ >0.75).

***Distal resection margin***
The length of the distal resection margin (DRM) was prospectively measured in all rectal cancer specimens at histopathological examination. The length of the DRM was measured on the fixed specimen after being sectioned in 5-mm slices, as the distance between the luminal lower border of the tumour and the distal cut edge (*figure 12)*.
The DRM on MRI was calculated as the difference between the height of the lower luminal border of tumour on preoperative MRI and the height of the anastomosis on postoperative MRI in patients with restorative surgery. We acknowledge that this may be an approximation of the actual distal clearance, but argue that it reflects the extent of the mesorectal excision performed.

In Paper III, we assessed the length of the DRM in the fresh and fixed specimen to calculate the degree of tissue shrinkage that occurs after surgical removal and fixation of a rectal cancer specimen. To assess this, we also measured the total length of both the fresh and fixed specimen as the distance between the proximal and distal cut edges. Similarly, the shortest distance from the peritoneal reflection to the distal cut edge was noted anteriorly on the fresh and fixed specimens. The specimen was not opened, stretched nor pinned prior to fixation.
Unfortunately, we did not have a measure of the length of the DRM *in situ* before extraction of the specimen, and as the specimen was not opened, a DRM on the fresh specimen was not obtainable. However, the fresh specimen was measured and photographed immediately after extraction (<5 min) to ensure minimal tissue shrinkage between surgical removal and examination of the fresh specimen.

***Magnetic resonance imaging of the resected specimen***
All MRI examinations were performed on a 1 Tesla extremity scanner using a 10-cm coil. The fresh and fixed specimens were examined without further preparation and placed in an MRI-compatible wooden berth. After an initial localisation scan, T2-weighted imaging was performed parallel to the long axis of the specimen (sagittal) and perpendicular to the long axis of the specimen (axial).
The length of the distal resection margin was measured as the distance between the lower border of the primary tumour and the distal part of the specimen. If the distal cut edge was oblique or if either intramural or mesorectal margins differed, the shortest and longest margins were noted as well (*figure 13*). All measurements were made by one radiologist (BGP) without knowledge of histo-pathological findings.

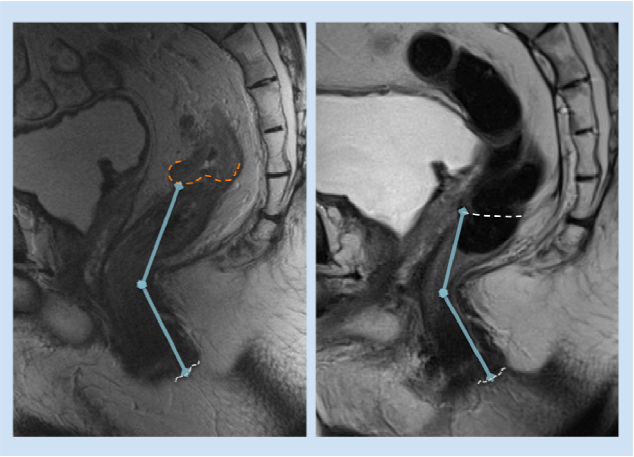


**Figure 9**
The distal resection margin on MRI was calculated as the difference between the height of the lower border of tumour on preoperative MRI and the height of the anastomosis on postoperative MRI.
**(Left)** Preoperative sagittal T2-weighted MRI shows a tumour located 9.8 cm from the anal verge. The distal luminal border of the tumour is marked by the orange line. **(Right)** Postoperative MRI shows the anastomosis located 8.5 cm from the anal verge. The white line marks the level of the anastomosis. The grey line marks the level of the lower border of the subcutaneous part of the external sphincter reflecting the anal verge.

**Figure 11**
The length of the distal resection margin was measured on the fixed specimen after being sectioned in 5 mm slices, as the distance between the luminal border of the tumour and the distal cut edge.

In short, the parameters were as follows: slice thickness 3 mm, spacing 0.3 mm. TR 3000 ms, TE 85 ms, FOV 16, matrix 512x512. Image analysis was performed at a dedicated PACS-workstation (HP xw6000 workstation, Hewlett Packard, North America) with IMPAX-software (IMPAX 6, Agfa Healthcare N.V., Mortsel, Belgium) using computed calliper measurements.

***Assessment for local recurrence and follow-up***
Local recurrence is a commonly used parameter for assessing the effectiveness and quality of treatment for rectal cancer. In this regard, it is important to consider that the local recurrence rate will depend on a number of factors, such as patient case-mix, inclusion and exclusion criteria (i.e. exclusion of R1-R2 resections in some studies), use of preoperative (chemo)radiotherapy and intensity of follow-up. In study II, we studied a population-based cohort of patients with primary rectal cancer, and only excluded non-curative cases based on the preoperative assessment and had a robust follow-up with more than half of the patients also receiving postoperative MRI of the pelvis.

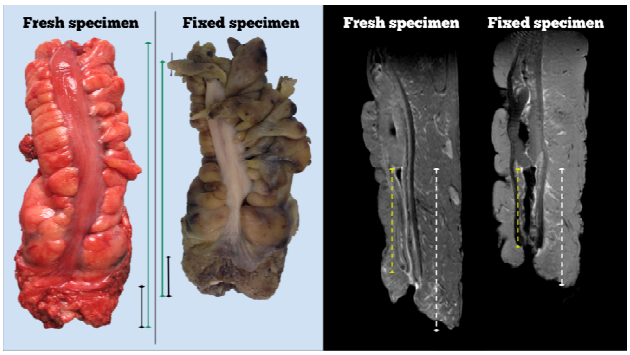



**Figure 10**
Methods of measurement in paper III. (Left) Histopathological specimen fresh and after fixation. Green line measures the total specimen length, while the black line measures the distance between the level of the anterior peritoneal reflection and distal cut edge of the mesorectum. (Right) Magnetic resonance imaging of the fresh and fixed specimen with markings of the shortest (yellow) and longest (white) distal margin.

Local recurrence was defined as a clinical, symptomatic, radiologically evident tumour or biopsy-proven adenocarcinoma located in the pelvis, regardless of the presence of simultaneous distant metastases. Histological verification was not achieved in all patients and was not a prerequisite for final diagnosis of local recurrence.

In study II, the clinical records of all patients were reviewed for development of local recurrence, distant metastasis and death status a minimum of 3 years following primary surgery in December 2013. Potential bias might exist regarding what was recorded in the medical records and how these were interpreted by the study examiner.

There is no general agreement on a follow-up programme for rectal cancer patients. At the Department of Surgery in Aarhus patients were generally included in a follow-up regimen with outpatient visits at 3, 6, 12, 18, 24, and 36 months after surgery. At each visit, a clinical examination and rigid proctoscopy (if applicable) or palpation of the perineum were performed. CT of the thorax and abdomen was performed according to the protocol for the COLOFOL trial, with frequent and nonfrequent arms.
Hence, the standard range of follow up in Aarhus was 3 years, albeit a full colonoscopy is offered 5 years following primary surgery for metachroneous cancer, often at another hospital.
It is generally considered that local recurrence rates should be reported as 5-year rates; however, most local recurrences will occur within 2-3 years[70, 76, 78, 116, 152, 153]. If the patients are not followed up at a surgical or oncological clinic, recurrences may be missed and unreported. It may not be that uncommon to omit follow-up for local failure if a patient is found to have disseminated disease. This may result in underestimation of the incidence of local recurrence.

Radiological images from each patient were examined to assess the localisation of local tumour recurrence. The most accurate radiological examination for the diagnosis is MRI, but an early and very tiny local recurrence may be difficult to distinguish from postoperative fibrosis. Repeated evaluations with MRI may be necessary to establish the recurrence. PET-CT can give additional valuable information. If possible, a biopsy will confirm the diagnosis. Before extensive surgery, it is of the utmost importance also to rule out disseminated disease with lymph node involvement above the pelvic region or distant metastases. PET-CT has a high sensitivity for this.
Regarding MRI examinations, the following parameters were recorded: the localisation of local recurrence and its height in the pelvis, evidence of residual mesorectum, the height of the primary tumour, and the height of the anastomosis (if applicable).

The classification system described by the Memorial Sloan-Kettering Cancer Centre was used to categorise local recurrence[155]. If the tumour recurrence extended to more than one compartment, the compartment with the greatest tumour load was noted. Distant recurrence was defined as radiological, clinical, or histological evidence of a recurrent tumour in any other region.

***Statistical analyses***
All statistical analyses were performed using the statistical software package Stata® version 11 (StataCorp LP, College Station, Texas, USA). $\chi^2$ test or Fisher's exact test was used for comparison of proportions. P values of <0.05 were considered significant.
In paper I, inter-method agreement with regard to findings of residual mesorectum and measurement of the length of distal resection margin was calculated. Percentage of agreement was calculated as the exact agreement between the observations. Correlation was calculated with κ statistics and interpreted as follows: <0.2 = poor, 0.21 to 0.4 = fair, 0.41-0.6 = moderate, 0.61-0.8 = good, and 0.81-1.00 = very good[156].
In paper II, local recurrence and overall survival rates were estimated using Kaplan-Meier actuarial methods. Comparison between groups was performed using the log rank test. The time to local recurrence was measured from the date of primary surgery to the date of diagnosis of local recurrence. Patients without local recurrence were censored on the date of their last outpatient visit or upon death. Patients who died within 1 month of surgery were excluded from the analysis of local recurrence.
In paper III, tissue shrinkage ratios were calculated based on the method of measurement as the measurement in the fixed specimen divided by the measurement in the fresh specimen.

**RESULTS**

The following section intends to give a short summary and discussion of the most important findings in Papers I to III and to present any supplementary results not included in the published papers.

**I: Extent and completeness of mesorectal excision evaluated by postoperative magnetic resonance imaging.**
Bondeven P, Hagemann-Madsen RH, Laurberg S, Pedersen BG. *Br J Surg.* 2013; 100: 1357-1367

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In study I, the extent and completeness of mesorectal excision was evaluated by postoperative MRI as a quality assessment of the surgery performed.

***Inadvertent residual mesorectum***
Inadvertent residual mesorectum was identified in 54 (39.7%) of the 136 patients with postoperative MRI. The plane of surgery achieved, tumour stage, involved CRM, adjuvant treatment, and gender did not correlate with evidence of inadvertent residual

mesorectum (*table 6*). Patients with macroscopic non-radical (R2) and those disseminated disease or local recurrence at time of inclusion were excluded from invitation to have a postoperative MRI. Because of this, we may have excluded the patients more likely to have inadvertent residual mesorectum. Thus, the data in Paper I may have underestimated the prevalence on inadvertent residual mesorectum in the entire cohort.

In patients who underwent PME, inadvertent residual mesorectum was detected in 63%; all of these were categorised as perianastomotic residual mesorectum above the level of the anastomosis. Perianastomotic residual mesorectum may indicate coning of the mesorectum down to the level of the anastomosis, which may suggest that there is some difficulty in performing a perpendicular transection of the bowel and mesorectum.

Following TME, 36% of the patients demonstrated residual mesorectum in 30 different locations; 8 cranial, 10 perianastomotic, and 12 distal. By definition, TME involves the complete removal of the mesorectum down to the pelvic floor. However, in the compromise between oncological and functional outcome, a distal part of the mesorectum may have been left behind. The primary tumour height was median 9 cm (range, 6 to 11 cm) in the 20% of patients who underwent TME and had evidence of residual mesorectum distal to the level of the anastomosis on MRI.
In patients who underwent APE, cranially located residual mesorectum was observed in 13% of the patients. Cranially located residual mesorectum most likely results from "losing the plane" during mesorectal dissection. When performing ELAPE, the mobilisation of the rectum and mesorectum is not undertaken all the way down to the puborectalis as in the regular TME, but rather stopped at the top of the levators. In this way, the levator muscles are excised *en bloc* with the mesorectum to protect the most distal part of the rectum. None of the patients with ELAPE (20 of 32) had evidence of residual mesorectum.

***Distal resection margin***
As described earlier, the DRM was estimated by MRI in patients with restorative surgery and measured at prospective histopathological examination of the fixed specimen. A Bland-Altman plot of the differences between the DRM measured by MRI and on the pathological specimen plotted against the mean, demonstrated that the individual difference was a mean of -0.25 mm (IQR: -8 to +9 mm), with good correlation between MRI and pathology (κ=0.62). The findings that the DRM measured by MRI correlates well with that measured on the fixed histo-pathological specimen indicate that some stretch or alignment of the preserved rectal stump may occur when anastomosed to the proximal part of the colon.
Based on the results from Paper III, we propose that a sufficient cut-off value for DRM should be 3.5 cm in the mesorectum when PME has been performed measured by either MRI or at histopathological examination. Accordingly, 65% (30 of 46) had a DRM of less than 3.5 on MRI, and 56% (26 of 46) on histopathological specimen.
The length of the DRM was also registered in patients who underwent TME, and was reported to be less than 1 cm in 10% and less than 2 cm in 46%, as measured by either MRI or pathology.

***Primary tumour height in patients with partial mesorectal excision***
Danish guidelines recommend rigid proctoscopy to establish the location and height of the tumour. Accordingly, all patients who underwent PME had a tumour located more than 10 cm from the anal verge as measured by rigid proctoscopy. However, when measured by MRI, 26% of the patients underwent PME for tumours located in the mid-rectum (5.1-10 cm). In relation to these findings, the 2012 annual report from the Danish Colorectal Cancer Group (DCCG) showed large a discrepancy in subdivision of tumour height between measurements by rigid proctoscopy and MRI. Data from our unit suggest that the difference between the two measurement methods increases with higher tumour height *(*n= 357; *correlation coefficient: 0-5 cm, κ= 0.6; 5-10 cm, κ =0.6; 10-15 cm, κ =0.4).* Differences in measurements on MRI and by rigid proctoscopy may have clinical implications with regard to type of surgery and allocation to neoadjuvant therapy depending on tumour stage.

***Macroscopic assessment of histopathology***
Discernible volume defects in the mesorectum, when re-evaluated by the pathologist on standardised photographic documentation, were present in 54% of the 136 specimens. When these observations were correlated with the prospective macroscopic assessment of the specimen with regard to the plane of surgery achieved, 42% had observable volume defects in the mesorectum despite being initially graded to be in the complete mesorectal plane.
Correlation between the findings of inadvertent residual mesorectum on MRI and mesorectal volume defect of the specimens was only fair (κ =0.32). However, overlap of the areas was present in 70% of the excisions in which MRI and pathology agreed upon a defect in the mesorectum.
The findings of inadvertent residual mesorectum on MRI did not correlate with an inferior plane of surgery reported, and the correlation was especially poor in patients who underwent PME and APE. The possible reasons for this have been discussed in the methodology section.

***Local recurrence***
Postoperative MRI was performed a median of 17 months after surgery. A previously un-diagnosed local recurrence was suspected in seven of the patients with postoperative MRI. An early local recurrence may be difficult to distinguish from postoperative fibrosis, and in two of these patients further examinations dismissed local recurrence. In the remaining five, local recurrence was confirmed by PET-CT and biopsy. More details on the individual patients with local recurrence are presented in Paper II.

| Table 6: Magnetic resonance imaging-detected inadvertent residual mesorectum | | | | |
|---|---|---|---|---|
| | | No. of patients (% of total) | Residual meso-rectum (% rate) | *P-value* |
| Operation | PME | 46 (34%) | 29 (63%) | <0.001 |
| | TME | 58 (43%) | 21 (36%) | |
| | APE | 32 (23%) | 4 (13%) | |
| Tumour height measured by rigid proctoscopy | Low (0-5 cm) | 36 (26%) | 7 (19%) | <0.001 |
| | Mid (>5-10 cm) | 51 (38%) | 17 (33%) | |
| | High (>10-15 cm) | 49 (36%) | 30 (61%) | |
| Pathological tumour stage | pT0-T2 | 54 (39%) | 22 (16%) | 0.795 |
| | pT3 | 65 (48%) | 26 (40%) | |
| | pT4 | 17 (13%) | 6 (35%) | |
| Involved CRM (<1 mm) | No | 124 (91%) | 50 (40%) | 0.763 |
| | Yes | 12 (9%) | 4 (33%) | |
| Plane of surgery achieved | Mesorectal | 55 (40%) | 24 (44%) | 0.328 |
| | Intramesorectal | 48 (35%) | 15 (31%) | |
| | Musc. propria | 33 (24%) | 15 (45%) | |

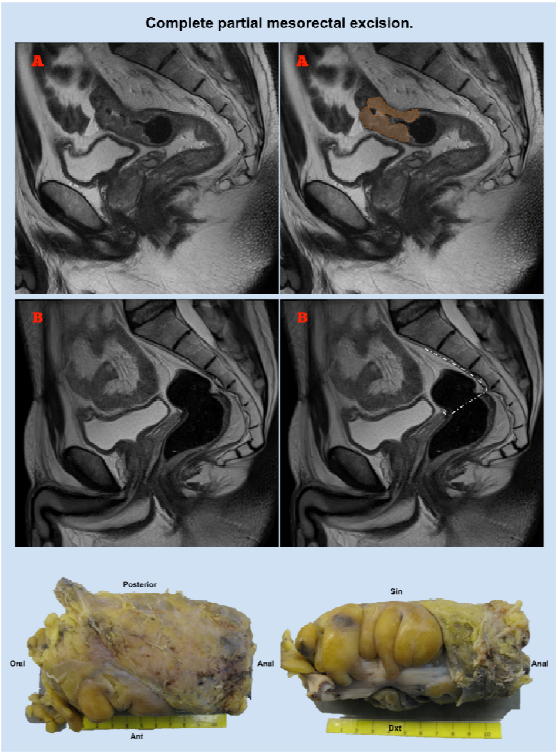


**Figure 13:** Partial mesorectal excision with perpendicular transection of the mesorectum and sufficient distal margin (>3.5 cm). **(A)** Preoperative sagittal MRI shows a T3 tumour of the upper rectum (orange). **(B)** Postoperative sagittal MRI shows the plane of dissection and level of anastomosis (white line). Only mesorectum below the level of the anastomosis can be observed. **(Bottom)** Macroscopic assessment of the specimen shows no coning of the distal mesorectum and sharp perpendicular transection of the mesorectum. (left: posterior view, right: anterior view

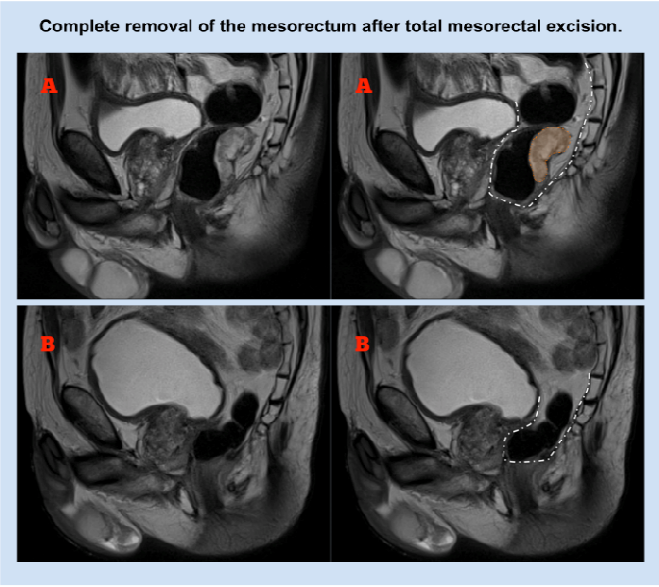


**Figure 14:** Total mesorectal excision with complete removal of the mesorectum. **(A)** Preoperative sagittal MRI shows a T2 tumour located in the mid-rectum (orange). The white line suggests the optimal dissection plane if total mesorectal excision. **(B)** Postoperative sagittal MRI following total mesorectal excision with complete removal of the mesorectum. Plane of dissection and level of the anastomosis is represented by the white line

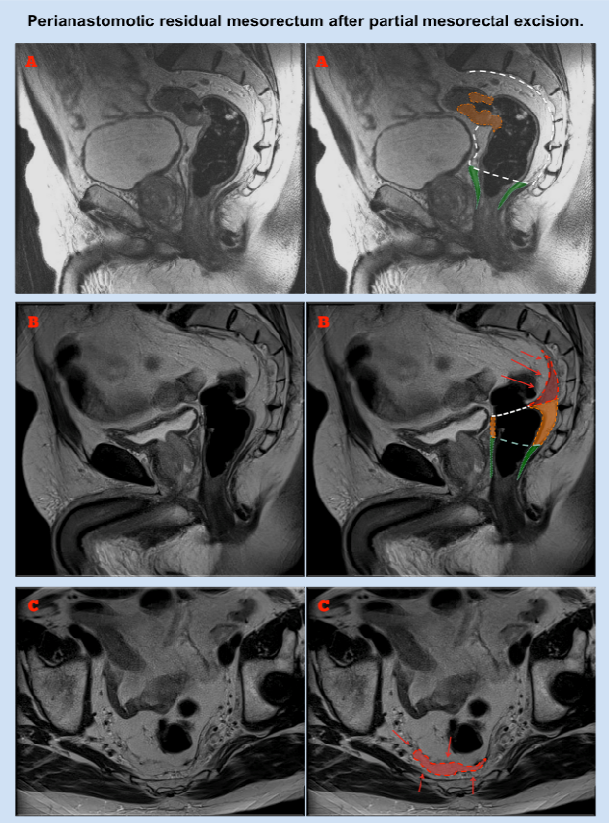


**Figure 15**: Perianastomotic residual mesorectum after partial mesorectal excision. **(A)** Preoperative sagittal MRI shows a T3 tumour of the upper rectum (orange). The white lines suggests optimal dissection if partial mesorectal excision with preservation of distal remnant mesorectum (green). **(B)** Postoperative sagittal MRI after partial mesorectal excision shows perianastomotic residual mesorectum (red) above the level of the anastomosis (white line). The orange marks the area of mesorectum within 5 cm below the primary tumour, as the anastomosis was 2 cm below the level of the primary tumour. **(C)** Axial images showing the localisation of the inadvertent residual mesorectum from 5 to 9 o'clock.

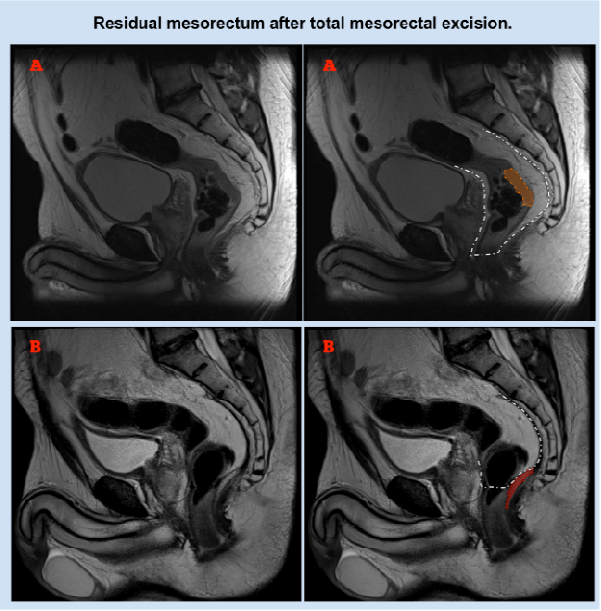


**Figure 16:** Residual mesorectum after total mesorectal excision. **(A)** Preoperative sagittal MRI shows a T3 tumour located in the mid-rectum (orange). The white line suggests the optimal dissection plane if total mesorectal excision. **(B)** Postoperative sagittal MRI after total mesorectal excision shows residual mesorectum within 1 cm of the primary tumour in relation to the anastomosis and distal to it (red). Plane of dissection and level of the anastomosis is represented by the white line.

**II: Suboptimal surgery and omission of neoadjuvant therapy for upper rectal cancer**
**is associated with a high risk of local recurrence.**
Bondeven P, Laurberg S, Hagemann-Madsen RH, Pedersen BG. *Colorectal Disease,* 17: 216-224.

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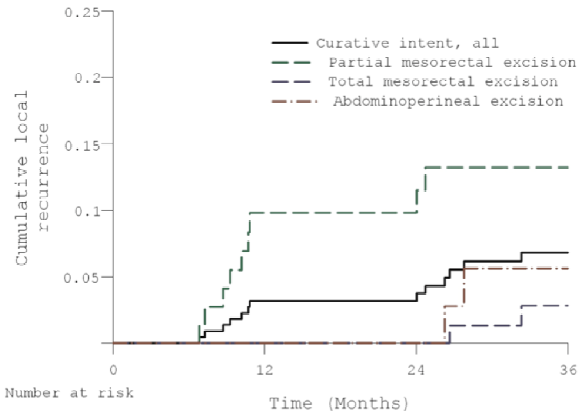
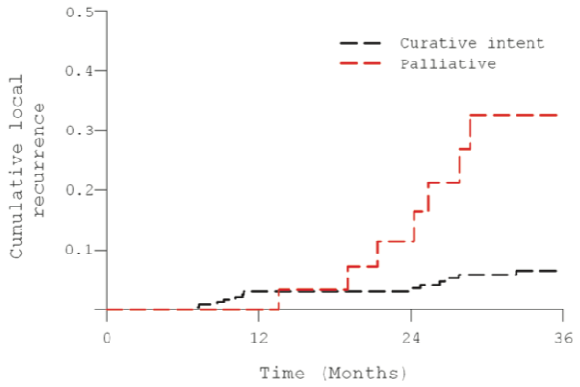
A total of 247 patients underwent surgery with curative intent for primary rectal adenocarcinoma during the study period. After a median follow-up of 36 months (range 0-74 mo.), 17 patients developed local recurrence. The actuarial local recurrence rate was 3.0% (95% CI: 1.5-6.3) and 7.0% (95% CI: 4.0-11.8) after 1 and 3 years, respectively. For comparison, the local recurrence rate in the 34 patients who underwent palliative surgery was 33% at 3 years (*figure 18*).
In our study, the most important predictors of local recurrence were advanced tumours stage (P=0.015) and an involved CRM (P=0.007).

***Risk of local recurrence according to type of surgery***
The 3-year actuarial local recurrence rate was significantly higher in patients who underwent PME (13.5%) compared to TME (2.9%) or APE (5.7%) (P=0.032). In *table 8,* tumour and treatment characteristics are shown according to the type of surgery performed. Long-course preoperative chemoradiotherapy was administered in 33% of patients with TME and in 81% of patients with APE. Neoadjuvant therapy was not applied for cancers of the upper rectum, as recommended by Danish guidelines.

**Figure 17**






Actuarial local recurrence rates for patients treated with curative intent and palliative surgery, and according to type of surgery.

A subanalysis of prognostic factors for local recurrence in the patients who underwent PME is shown in *table 7*. Following PME, local recurrence was predominantly found in relation to the anastomosis (8 of 9). Inadvertent residual mesorectum was identified in five of these patients. Total mesorectal excision was performed in 15% of tumours of the upper rectum. None of these developed local recurrence.

***Distal resection margin after partial mesorectal excision***

The DRM was reported in the pathology report to be less than 3 cm in 54% (44 of 82) of the patients who underwent PME. In these, the risk of local recurrence was 20.1% as compared to 6.8% in patients with PME who had a DRM of more than 3 cm (*P*=0.173). If we adjust the cut-off DRM to 3.5 cm based on our results from Paper III, 66% (54 of 82) of the patients had a DRM of less than 3.5 cm measured by the pathologist on the fixed specimen. None of the patients with more than 3.5 cm of DRM developed local recurrence, as compared to 20.3% with a DRM of less than 3.5 cm (*P*=0.043).

***Tumour stage (mrT and pT)***

Based on the preoperative tumour stage (mrT), T4 disease was overrepresented in both the PME and APE groups. All pT4 tumours of the upper rectum were due to local peritoneal involvement (pT4a). According to Danish guidelines, this had no impact on treatment allocation to patients with tumours of the upper rectum. However, substantial down-staging was achieved in the APE group, with 81% of the patients receiving neoadjuvant therapy. If this had not been the case, the patients in the APE group would presumably have received more extensive surgery, and therefore have been excluded from this analysis.

***Involved circumferential resection margin***

An involved CRM occurred in 13% of the patients treated with curative intent, and in 8%, 9%, and 24% after PME, TME, and APE, respectively (*P*=0.014). An involved CRM was particularly frequent for advanced pT4 tumours (*P*<0.001) and in resections in the muscularis propria plane (*P*=0.012).

A total of five patients (7.4% crude) developed local recurrence following APE and long-course chemoradiotherapy for low mrT3-4 rectal tumours, despite an involved CRM being present in 24% of the patients. Comparably, a prospective study on the use of ELAPE for advanced tumours of the lower rectum (pT4 in 20%) from Karolinska University Hospital in Sweden, found a crude local recurrence rate of 6%, despite reporting an involved margin in 20% of the patients[75]. These figures are also in accordance with the findings of the multicentre study by West *et al.,* in which an involved CRM was reported in 20.3% of ELAPE, even with only 6% having pT4 tumours[72]. Previous reports have suggested that the risk of local recurrence following resection with an involved margin is 14-30%[5, 23, 157, 158].

The CRM positivity rate is dependent on several factors, including the quality of surgery, presence of advanced disease, location of the tumour, and involvement of dedicated pathologists. All rectal cancer specimens at our unit were primarily evaluated by one pathologist, who had a dedicated focus on involvement of the CRM. A root-cause analysis of the patients with an involved CRM after APE is currently being performed to elucidate whether an involved margin was seen more frequently in particular groups of patients (e.g. with anterior location of tumour).

***Plane of surgery achieved***

A mesorectal plane of surgery was reported in 33%, intramesorectal in 33%, and musc. propria in 31%. The plane of surgery achieved according to type of surgery is shown in *table 8*. The plane of surgery achieved was not associated with the risk of local recurrence (*P*=0.44).

***Diagnosis of local recurrence***

Time from date of surgery to development of local recurrence ranged between 7 and 56 months (median 24 months), and was more than 3 years in three patients (1 TME, 2 APE). Time to local recurrence was significantly shorter for patients without neoadjuvant therapy (median 19 mo.) compared to patients with neoadjuvant therapy (median 42 mo.) (*P*=0.025), and in patients who underwent PME (median 11 mo.) as compared to TME (median 27 mo.) or APE (median 28 mo.).

Symptomatic disease was present in 47% (8 of 17) of patients at the time of diagnosis. Seventy-six per cent of the patients had an abnormal finding on clinical examination, including palpable mass or visible tumour. Histological confirmation was achieved in 65% (11 of 17) of patients. In the majority of patients, several diagnostic modalities were used to diagnose local recurrence of tumour. Imaging, in the form of MRI, CT or PET-CT, was available in all patients.

***Treatment of local recurrence***

Six patients had evidence of synchronous local and distant recurrence when local recurrence was detected and were referred for oncological adjuvant treatment. In five patients, a re-resection of tumour with curative intent was performed. Three of these had prior surgery with PME and two had TME. All patients with local recurrence for curative re-resection received preoperative chemoradiotherapy. A negative margin (R0) at re-resection was achieved in four.

**Table 7**

| Table 7: Subanalysis of risk factors for local recurrence in patients treated with PME for upper rectal cancer. | | | |
|---|---|---|---|
| Characteristic | | Number (%) | Actuarial 3-year local recurrence rate |
| Preoperative tumour stage | mrT0-T2 | 21 (26) | 0% |
| | mrT3 | 38 (46) | 20.2% |
| | mrT4 | 14 (17) | 23.1% |
| Distal resection margin* | < 3.5 cm | 54 (66) | 20.3% |
| | > 3.5 cm | 22 (27) | 0% |
| | Missing | 6 (7) | . |
| Pathological tumour stage | pT0-T2 | 18 (22) | 0% |
| | pT3 | 47 (57) | 15.6% |
| | pT4 | 16 (20) | 21.1% |
| Involved CRM (<1 mm) | No | 74 (90) | 12.0% |
| | Yes | 7 (9) | 30.8% |
| Type of surgery for tumours of the upper rectum (>10-15 cm) | TME | 15 (15) | 0% |
| | PME | 82 (85) | 13.6% |

| Table 8: Tumour and treatment characteristics according to type of surgery in the 247 patients treated with curative intent. | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | TME | | PME | | APE* | | *Total* | |
| Preoperative tumour stage | mrT0-T2 | 23 | (24%) | 21 | (26%) | 7 | (10%) | 51 | (21%) |
| | mrT3 | 66 | (68%) | 38 | (46%) | 38 | (56%) | 142 | (57%) |
| | mrT4 | 7 | (7%) | 14 | (17%) | 22 | (32%) | 43 | (17%) |
| | Missing | 1 | (1%) | 9 | (11%) | . | . | 10 | (4%) |
| Radiotherapy | No | 65 | (67%) | 82 | (100%) | 13 | (19%) | 160 | (65%) |
| | Yes | 32 | (33%) | . | . | 55 | (81%) | 87 | (35%) |
| Tumour height measured by rigid proctoscopy | Low (<5 cm) | 5 | (5%) | . | . | 60 | (88%) | 65 | (26%) |
| | Mid (5-10 cm) | 77 | (79%) | . | . | 8 | (12%) | 85 | (34%) |
| | High (10-15 cm) | 15 | (15%) | 82 | (100%) | . | . | 97 | (39%) |
| Pathological tumour stage | pT0-T2 | 40 | (41%) | 18 | (22%) | 31 | (46%) | 89 | (36%) |
| | pT3 | 46 | (47%) | 47 | (57%) | 29 | (43%) | 122 | (49%) |
| | pT4 | 9 | (9%) | 16 | (20%) | 8 | (12%) | 33 | (13%) |
| | Missing | 2 | (2%) | 1 | (1%) | . | . | 3 | (1%) |
| Involved CRM (<1 mm) | No | 86 | (89%) | 74 | (90%) | 51 | (75%) | 211 | (85%) |
| | Yes | 9 | (9%) | 7 | (9%) | 16 | (24%) | 32 | (13%) |
| | Missing | 2 | (2%) | 1 | (1%) | 1 | (1%) | 4 | (2%) |
| Plane of surgery achieved | Mesorectal | 31 | (32%) | 40 | (49%) | 10 | (15%) | 81 | (33%) |
| | Intramesorectal | 36 | (37%) | 17 | (21%) | 28 | (41%) | 81 | (33%) |
| | Musc. propria | 27 | (28%) | 20 | (24%) | 29 | (43%) | 76 | (31%) |
| | Missing | 3 | (3%) | 5 | (6%) | 1 | (1%) | 9 | (3%) |
| Actuarial 3-year local recurrence rate | | 2.9% | | 13.5% | | 5.7% | | 7.0% | |
| Distant metastasis | | 13% | | 16% | | 19% | | 16% | |
| Overall 3-year survival | | 88% | | 84% | | 79% | | 85% | |

**III: Objective measurement of the distal resection margin by MRI of the fresh and fixed specimen after partial mesorectal excision for rectal cancer: 5 cm is not just 5 cm and depends on when measured.**
Bondeven P, Hagemann-Madsen RH, Bro L, Moran BJ, Laurberg S, Pedersen BG.
*Acta Radiol* 2015 Sep 15 [Epub ahead of print].

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Ten patients with upper rectal cancer who underwent curative resection were prospectively included. Partial mesorectal excision was planned in all patients at preoperative MDT conference. However, in one patient the procedure was performed as a TME.

Immediately following surgical resection and specimen removal, the fresh specimen was measured and photographed by a specialist nurse and PB before being positioned in the MRI scanner. After completion of MRI, the fresh specimen was placed directly in formaldehyde, followed by a GEWF solution, and fixed for approximately 48 hours. The fixed specimen underwent MRI on the day of histopathological examination before pathological sectioning.

Measured by MRI, the mean length of the DRM in the fresh specimens was 4.6 cm (range; 0.6 to 10.2 cm) and 3.2 cm (range; 0.5 to 6.2 cm) in the fixed specimen. Comparably, the mean length of DRM measured at histopathological examination of the fixed specimen was 3.3 cm (range: 1 to 6 cm). Five of the ten patients had a DRM of less than 5 cm on the fresh specimen measured by MRI. After fixation of the specimen, 9 of 10 patients had a DRM of less than 5 cm, and four less than 3 cm measured both on MRI and at histopathological examination.

The mean difference between the length of the DRM measured by MRI (fresh and fixed) and histopathological examination is shown in *figure 19*. A collective tissue shrinkage ratio of 70% (95% CI: 67-73%) was calculated based on the different histopathological and MRI measurements of the fresh and fixed specimens (*table 9*). All measurements significantly decreased in length after fixation.

A 5-cm distal margin is generally advocated when performing PME surgery for upper rectal cancer. If a 5-cm DRM of mesorectum below the luminal level of the primary tumour on the fresh specimen is the standard for advanced cancer of the upper rectum treated with PME, an acceptable DRM should be at least 3.5 cm at histopathological examination of the fixed specimen.

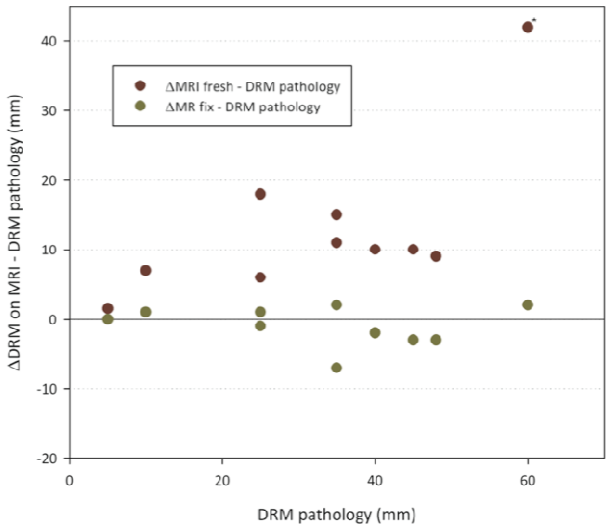


**Figure 18**
Difference in measurements of the distal resection margin between MRI of the fresh (red) and fixed (yellow) specimen and histopathological examination of the fixed specimen. DRM, distal resection margin. *DRM on MRI fresh 10.2 cm; MRI fixed 6.2 cm; DRM pathology 6.0 cm; TSR 61%.

**Table 9: Tissue shrinkage based on specimen MRI and measurements by pathology.**

| | Mean (cm) | Range (cm) | Tissue shrinkage ratio (IQR) |
|---|---|---|---|
| **Specimen MRI** | | | |
| *Fresh DRM long* | 5.7 | 2.3 – 11.4 | 71% (62-79) |
| *Fix DRM long* | 4.1 | 1.4 – 6.2 | |
| *Fresh DRM short* | 4.6 | 0.7 – 10.2 | 69% (61-77) |
| *Fix DRM short* | 3.1 | 0.5 – 6.2 | |
| **Histopathological examination** | | | |
| *Fresh specimen length* | 21.9 | 15 - 29 | 69% (61-78) |
| *Fixed specimen length* | 15.3 | 9.5 - 24 | |
| *Fresh PR distance** | 2.4 | 0 – 5.7 | 69% (64-71) |
| *Fixed PR distance** | 1.5 | 0 – 3.5 | |

*PR; distance from the level of the peritoneal reflection to the distal cut edge of the specimen. IQR; interquartile range. Tissue shrinkage ratio was calculated as the fixed measurement divided by the fresh.

## GENERAL DISCUSSION

This thesis presents some disappointing findings with regard to the large group (>30%) of patients with cancer of the upper rectum having PME surgery and in whom evidence of suboptimal surgery was advent. Partial mesorectal excision for tumours of the upper rectum may have been regarded as an *easy case*, while focus has – reasonably – been on improving the outcome for mid/low rectal cancer with TME, and more recently in the current debate with regard to the establishing the optimal treatment of low rectal cancer using an extralevator approach in APE.
Local recurrence is a particular problem after rectal cancer surgery, although generally now only seen in a minority of cases. It results in severe morbidity, and markedly impairs quality of life. Palliative treatment has limited success and leads to death in most cases, although a percentage of cases are cured with locally aggressive surgery[79, 153, 159].
Standardisation and quality assurance of mesorectal excision by training and pathological audit were implemented in the major trials to ensure that optimal surgery was performed[11, 12, 39]. However, it is important that, outside the setting of clinical trials, standardisation and assurance of best-quality surgery are also sustained in routine clinical practice. By using postoperative MRI, we were able to assess the extent and completeness of mesorectal excision after surgery for rectal cancer by indicating inadvertent residual mesorectum, and established that postoperative MRI may serve as a method for quality assessment of both surgery and the pathological assessment of the specimen.
With careful planning and a multidisciplinary approach in the modern treatment of rectal cancer, equivalent oncological outcomes should be achievable for patients with rectal cancer who undergo curative surgery regardless of differences in tumour characteristics and location. We believe that one of the great hallmarks of multidisciplinary team collaboration is assurance and internal audit of the quality of the treatment offered.

Cancer of the upper rectum has historically been associated with a significantly better oncological outcome than that of cancer of the lower or mid rectum – in some series comparable to sigmoid colon cancer, which is considered less perilous[31, 128, 160]. The major problem for patients with rectal cancer was traditionally the high rate of local recurrence, whereas for patients with a primary tumour of the colon, it was the high incidence of distant metastasis. With the introduction of TME-based surgery with meticulous dissection of the avascular "holy plane" between the mesorectum and parieties completed under direct vision, the local recurrence rates for tumours of the upper rectum also improved proportionally. Thus, local recurrence rates have been reported in the major trials to be between only 1 and 6% after surgery for upper rectal cancer with or without neoadjuvant therapy, respectively[5, 6].
In our audited cohort of patients, the risk of local recurrence was 11.3% for tumours of the upper rectum. Similarly, studies from Germany and Sweden have reported local recurrence rates in patients with tumours of the upper rectum to be as high as 10 to 16%[24, 25, 118, 161]. These do not fulfil the present day accepted requirement of local recurrence rates less than 10%, when standardised optimal TME-based surgery is performed, especially for tumours of the upper rectum. These differences most likely reflect variations in the preoperative assessment, surgical technique, or the use of neoadjuvant therapy.

### *Preoperative assessment of upper rectal cancer*

The definition of and differentiations between the colon and the rectum vary widely in the literature. According to guidelines in Scandinavia and the UK, a tumour is generally considered rectal if the lower margin lies within 15 cm of the anal verge[40].
Although measurement of tumour height by rigid proctoscopy is mandatory, it may vary depending on the surgeon performing the examination, the patient, and the method[162]. Care is necessary: any instrument can push a mobile tumour upwards, and flexible instruments often give falsely high measurements. Whereas, it may be easy to define the location of very low tumours, because of their accessibility to the examining finger and easier measurement of distance from the anal verge on imaging, it becomes increasingly difficult to determine the position of tumours higher in the rectum. Indeed, the assumption behind asking the question of which type of surgery that should be performed or whether neoadjuvant therapy is beneficial is that these patients can be accurately identified preoperatively.
It may be worth documenting the height at MRI; indeed, after much debate, the English National Low Rectal Cancer Development Programme (LOREC) suggest a new definition of low rectal cancer as a tumour with its distal margin at or below the level of origin of the levators on the pelvic side-wall[107]. In the same way, tumours of the upper rectum may in the future be defined by anatomical landmarks appreciable on the preoperative MRI such as the level of the peritoneal reflection or distance in mesorectum to the levator, because the division of the rectum by strict centimetre criteria seems unrealistic on an individual basis[104, 163-165]. As measured by MRI, 26% of the patients had PME for tumours of the mid rectum in paper I. Similar findings were reported by Chang *et al.* in a study using MRI to identify high-risk patients with upper rectal cancer[166].
Confident localisation of a rectal tumour is tremendously important, especially in relation to the Danish guidelines, as the differentiation between mid or upper rectum has a significant impact on the decision to allocate for neoadjuvant therapy or not. In our opinion, the level of the tumour is reliably assessable on preoperative MRI and can be used to determine whether PME or TME is preferable. By Delphi method, the European Registration of Cancer Care (EURECCA) recently recommended MRI as the method of choice for assessing tumour height and location in the rectum[28].

### *Surgical technique*

For cancer of the upper rectum it remains unsettled as to whether TME is necessary for upper rectal cancer or whether a PME is adequate. Unfortunately, the major studies have not specifically distinguished between whether TME or PME was performed for upper rectal cancer, and this hinders comparison. However, it is clear that the less extensive PME with preservation of a distal part of remnant rectum offers a better functional outcome and lower risk of anastomotic leakage[17, 18, 167].
Dedicated single-centre trials have shown that it is possible to achieve low rates of local recurrence with PME by skilful surgery, equal to or better than the local recurrence rates achieved with TME, also without the use of neoadjuvant therapy[18-21, 168].
In the results presented here, a high rate of local recurrence was observed following surgery in which a PME was performed for tumours of the upper rectum. Based on data from the Stockholm Colorectal Cancer Study Group, Syk *et al.* reported a relatively high rate of local recurrence of 9% following PME for upper rectal cancer compared to 5% in patients who underwent TME, despite the wide use of short-course preoperative radiotherapy[23].

Rosenberg et al. performed PME for all tumours of the upper rectum and observed a 5-year local recurrence rate of 15.5%, not significantly different from that for mid rectal tumours, but worse than for cancer of the sigmoid[24]. Similarly, Kodeda et al. reported a crude 5-year local recurrence rate of 14.4% for tumours of the upper rectum without routine preoperative radiotherapy in their regional cohort of tumours of the upper rectum, compared to 5.5% based on national data from the Swedish Rectal Cancer Registry[25].

Another important message is that upper rectal cancer, like mid and low rectal cancer, needs best-quality surgery. The studies in this thesis clearly show that surgery was not optimal with evidence of inadvertent residual mesorectum in 63% of patients with postoperative MRI, and a distal margin of less than 3 cm in more than two-thirds of patients who underwent PME. Furthermore, inadvertent residual mesorectum and/or an insufficient distal margin of less than 3 cm was evident in all cases of upper rectal cancers having a local recurrence.
Our findings correspond to the results by Syk *et al.*, in which CT and MRI from 99 patients with local recurrence were analysed[23]. In the study by Syk *et al.*, residual mesorectum was observed in 86% of the patients with local recurrence following PME for upper rectal cancer. The exact definition of residual mesorectal tissue used by Syk et al. was not completely instructive in our opinion, particularly regarding the evaluation of PME, and may differ from the definition in the present study. Still, Syk *et al.* concluded that an intentional or inadvertent partial mesorectal excision, combined with the absence of radiotherapy, may play a role in the recurrence of these tumours[22].
An effort to detect suboptimal surgery with postoperative imaging was even attempted in 1991 before the advent of modern MR imaging. By using postoperative angiography of the mesenteric artery, Hohenberger *et al.* observed that the inferior mesenteric artery and superior rectal artery, together with the attached fatty mesorectal tissue, remained after coning of the mesorectum, which since proved to the source of local recurrence[137, 169].
Kusters *et al.* analysed the patients in the Dutch TME Trial with local recurrence and noted that the analysis of patients with sphincter-preserving surgery was complicated, as it was unclear what proportion of the patients that had received a PME instead of a TME[170]. Most of the local recurrences were located in relation to the anastomosis, especially in the group without the otherwise largest risk factors (T4 tumour, N2 disease, involved CRM). Local recurrence localised in relation to the anastomosis is generally considered to be caused by inadequate or suboptimal surgery, with failure of complete surgical removal of the primary tumour or its initial field of spread in the mesorectum[153, 155, 170-172]. The fact that the most prevalent location of local recurrence in our cohort, in the previous studies described[22, 23, 25, 152] and in the report by Kusters *et al.* from the Dutch TME trial[170] (which was further scrutinised by Heald and Hermanek[127]) suggests that surgery was not optimal.
An association between the finding of inadvertent residual mesorectum on postoperative MRI and risk of local recurrence will likely require a larger prospective study than the present, and also including the patients most likely to have residual mesorectum (R2, disseminated disease etc.). We included all rectal cancer patients treated with surgery, hereby also auditing a group of patients with T0-T2 tumours where spread to the mesorectum is infrequent and with a low risk of local recurrence, even despite possibly having inadvertent residual mesorectum. The key message from our findings indicating suboptimal surgery in the group of patients with upper rectal cancer should thus rather be, as one of the reviewers of Paper II wrote, "to think long and hard about my own practice" to achieve the best results possible.

The plane of surgery achieved by the surgeon has been reported by pathologists for a little more than a decade now and used to assess the quality of surgery. Numerous studies have shown that the integrity of the mesorectum correlates with the rate of local recurrence[11, 12, 133, 134].
Nevertheless, grading of the plane of surgery is still inconsistent, and in a recent national improvement project from Belgium, more than 57% were not graded according to the plane of surgery achieved, and agreement between the local pathologists and a central review committee on the plane of surgery achieved was relatively poor[173, 174].
In paper I, we demonstrated a discrepancy in the assessments made by pathological examination and MRI. Furthermore, based on the retrospective evaluation of the standardised photographic documentation, volume defects were described in 42% of the specimens initially judged by the pathologist to have been performed in the mesorectal plane of surgery. Overestimation of volume defects due to anatomical variations may be a problem for pathologists, as the morphology of the mesorectum differs between patients[175]. Moreover, the value of pathological grading of residual mesorectal tissue is limited by the fact that the pathologist can grade the specimen only according to the tissue removed at surgery. This is particularly obvious with regard to PME. In paper II, plane of surgery did not correlate with the risk of local recurrence, probably as most of the PME resections were graded to have a complete plane of surgery, and developed local recurrence despite this.

We argue that pathology should not blindly be considered the gold standard in the quality assessment of rectal cancer surgery as pathologists fail to report reliably on key diagnostic features and may have significant interobserver variation. Postoperative MRI of the pelvis may provide a useful method for auditing of both pathology and mesorectal excision surgery for rectal cancer.

It has generally been proposed that a minimum of 5 cm of distal mesorectum should always be excised in rectal cancer and thus that the height of the tumour will determine whether a TME is needed or if a PME is adequate. Nonetheless, we observed that the DRM was less than 3 cm in around 50% of PME resections, suggesting a discrepancy between guidelines and the surgery performed.
The length of the distal margin depends on *when* it is measured, with major variation in the length when measured *in situ* before surgical removal compared with the measurement obtained on the fresh specimen or after fixation. Moreover, the *in situ* margin is variable and dependent on tissue stretching under tension and contraction after division of the rectum[140]. National guidelines have not defined when the distal resection margin is best measured.
Direct extrapolation of the length of distal spread in a histopathologically examined specimen to an *in situ* margin measured at operation is difficult, and although the length of the distal margin is widely cited as important, it is usually not specified how this was measured. Previous studies have tried to identify how to determine the optimal *in* situ distal margin in rectal cancer based on histopathological examination of the specimen. However, depending on the method used, the length may vary from 15% to 150% compared between the *in situ* or fresh specimen measure-

ment and after fixation. An early studious description of this phenomenon was made by Ewing in 1952: "The height of the tumour is measured, now in centimetres and now in inches; now in the living subject and now in the resected specimen, where it may be either shrunken and twisted into a miserable shadow of its former self or grown big as it lies"[176].
By correcting for tissue shrinkage, Ono *et al.* concluded that the adjusted maximum extent of distal spread *in situ* was 24 mm, hereby endorsing a distal margin in the mesorectum of 3 cm as sufficient[144].This adjusted estimate of distal spread was based on the measurement of a mean tissue shrinkage ratio of 60% after fixation. This ratio however varied between 15% and 133% in their study of 40 patients – indicating substantial variation in either measurements *in situ* and after fixation, or in the processing of the specimen.
In a recent educational tutorial by Heald *et al.*, it is stated that when mobilising the rectum during partial mesorectal excision surgery, the rectum and mesorectum should be mobilised at least 8 cm below the level of the tumour to achieve an adequate margin in the fresh specimen of at least 5 cm[177]. Based on our results, this margin may further shrink approximately 30% in an unpinned, fixed specimen. We therefore conclude that if a 5-cm distal margin below the luminal level of the primary tumour on the fresh specimen is the objective for advanced cancer of the upper rectum treated with PME surgery, a margin of at least 3.5 cm of mesorectum on the fixed specimen should be attained for the pathologist to accurately establish distal radicality.
The fact that none of the patients who underwent PME with more than 3.5 cm of distal margin developed local recurrence, as compared to 20% with less than 3.5 cm, further supports this conclusion. In 2012, Jullumstrø *et al.* analysed 394 patients in a Norwegian cohort with regard to violation of treatment guidelines[178]. The risk of local recurrence was 11% after curative resection with a distal clearance of less than 2 cm compared to only 3% when the distal clearance was more than 2 cm.

Thirty years ago, Bill Heald reminded surgeons of the importance of best-quality surgery with complete excision of the primary tumour and adequate tumour-free margins. It is evident that this rationale of best-quality surgery remains true also for surgery in the upper rectum with PME performed without, as it has been proved for TME and APE in mid and low rectal cancer.

***Omission of neoadjuvant therapy for upper rectal cancer***
There is ongoing controversy as to whether all, or selected, patients with rectal cancer will benefit from neoadjuvant therapy. In Denmark, only un-resectable cancer of the upper rectum is considered for neoadjuvant therapy. Large population-based studies from Sweden have reported that more than 60% of patients with rectal cancer received neoadjuvant therapy, including 43-58% of tumours of the upper rectum, and more than 40% of patients with T1-T2 tumours[125, 161].
As mentioned previously, none of the largest randomised trials found any significant effect of systematic preoperative radiotherapy for upper rectal cancer. Based on the Stockholm II Trial, Holm et al. showed that preoperative radiotherapy decreased the risk of local recurrence, irrespective of tumour height, when conventional blunt surgery was used[179]. In 2011, Tiefenthal *et al.* showed an effect of preoperative short-course radiotherapy for tumours of the upper rectum in a national population-based study[161]. In total, 43% of patients with upper rectal tumours received short-course radiotherapy, which reduced the local recurrence rate from 10% in patients with surgery alone to 4% (P < 0.001).
National guidelines on the application of neoadjuvant therapy are very different, despite the fact that they all have access to the same literature[40, 124]. There is a difference with regard to the approach depending on stage of disease and with regard the use of neoadjuvant therapy for cancer of the upper rectum. Furthermore, adherence to international guidelines may not be consistent and lead to treatment failure[25, 125, 178, 180].

We observed an overrepresentation of T4 disease in tumours of the upper rectum compared to mid rectal tumours treated with curative intent. All of these were due to involvement of the peritoneal reflection (pT4a), and would thus not have influenced treatment decision based on the current Danish guidelines. A major difference between upper rectal cancer and mid/low tumours located below the level of the peritoneal reflection is that advanced cancers of the upper rectum are prone to involve the peritoneal surface, resulting in an increased risk of local recurrence[41, 43]. In comparison, T4 tumours of the mid or lower rectum will have direct invasion into other structures, such as the prostate or vagina (T4b), and therefore probably have received more extensive surgery and therefore been excluded from our study cohort.
It is reasonable to think that these advanced tumours of the upper rectum may also benefit from neoadjuvant therapy, which is also currently recommended by the European Society of Medical Oncology (ESMO)[115]. In the ESMO guidelines, height is by itself not a contraindication for preoperative neoadjuvant therapy. Furthermore, it has been shown that advanced tumours of the upper rectum can be accurately staged using MRI and could be successfully downstaged by neoadjuvant radiochemotherapy[105, 106].

Some authors have suggested that neoadjuvant therapy should not be used to compensate for poor quality surgery; rather intense efforts should be made to improve the quality of surgery so that fewer patients will need radio(chemo)therapy. It seems clear that if the surgeon expects to be able to perform a curative resection, i.e. to achieve a surgical specimen with intact and adequate mesorectum and clear margins, neoadjuvant may be omitted[181-186]. The accuracy of modern MRI-based local staging permits precise selection for appropriate neoadjuvant treatment[185.]

**CONCLUSIONS**

In summary, this thesis presents a disconcertingly high local recurrence rate in the large group (>30%) of patients with cancer of the upper rectum. In these, suboptimal surgery was evident in the form of coning of the mesorectum and an insufficient distal resection margin. Thirty years ago, Bill Heald reminded surgeons of the importance of best-quality surgery with complete excision of the primary tumour and adequate tumour-free margins. It is evident that this rationale of best-quality surgery remains true also for surgery in the upper rectum with PME, as it has been proved for TME and APE in mid and low rectal cancer.

*Specific conclusions:*

- The extent and completeness of mesorectal excision can be evaluated by postoperative MRI as a quality assessment measure of the surgery performed and of the pathological evaluation based on inadvertent residual mesorectum.

- For tumours of the upper rectum, PME was associated with an unacceptably high risk of local recurrence. This may be attributed to specific problems with the surgical technique or the omission of neoadjuvant therapy for advanced tumours of the upper rectum.

- The length of the distal resection margin is reduced by 30% after surgical removal and fixation of the specimen. If a 5-cm distal margin below the luminal level of the primary tumour on the fresh specimen is the objective for advanced cancer of the upper rectum treated with PME surgery, a margin of at least 3.5 cm of mesorectum on the fixed specimen should be attained for the pathologist to accurately establish distal radicality.

**FUTURE PERSPECTIVES**

The treatment of rectal cancer is rapidly changing with advances in surgical technique, radiotherapy, imaging and pathology together with the implementation of bowel cancer screening in the general population, focus on non-surgical management of rectal cancer after complete response following neoadjuvant therapy and increasing use of minimally invasive surgical techniques. A 'one size-fits-all' approach in the treatment of rectal cancer is clearly outdated.
The treatment for tumours of the upper rectum needs to be improved. Based on our findings, a more selective use of PME for advanced cancer is being advocated. A local workshop on the current difficulties in treating cancer of the upper rectum was held in the spring of 2011. The workshop involved presentation of cases with TME and PME with corresponding postoperative MRI and pathological photo-documentation. Possible measures to improve the quality of the treatment were discussed in plenum, and attention has especially been directed towards a more standardised approach for tumours of the upper rectum with more weight on the tumour relations available on MRI and on surgical technique.
We have continued with prospective quality assessment of surgery and pathology with postoperative MRI, and a national audit of the quality of surgery and rate of local recurrence is currently being conducted. Furthermore, a training programme with a specific focus on surgery for upper rectal and sigmoid cancer is being planned.

In light of the current debate regarding the optimal approach when performing APE for low rectal cancer, we are currently looking into the possibility of assessing the extent of dissection of the levators on postoperative MRI in patients with an involved CRM.

**SUMMARY**

Rectal cancer constitutes one-third of all colorectal cancers, and the incidence in Denmark increasing. In 2012, 1.400 cases were registered, and of these 38% were located in the upper rectum. There have been several key advances in the optimal management of rectal cancer during the past decades, primarily by standardisation and improvement of the surgical procedure. There is now general agreement that the optimal surgical treatment involves the concept of total mesorectal excision and that a resection with tumour-free margins is crucial.

Controversy exists as to whether total mesorectal excision (TME) is necessary for upper rectal cancers or if a partial mesorectal excision (PME) with mesorectal transection 5 cm below the tumour is adequate. Furthermore, there is no agreement as to whether surgery alone is sufficient or whether neoadjuvant radio- and/or chemotherapy should be administered for tumours of the upper rectum. This thesis aims to discuss aspects of the treatment of rectal cancer with regard to the adequacy of mesorectal excision and oncological outcome with a particular focus on cancer of the upper rectum.

In study I, the extent and completeness of mesorectal excision was estimated by postoperative magnetic resonance imaging of the pelvis in patients with primary surgery for rectal cancer. In the 136 patients with postoperative MRI, inadvertent residual mesorectal tissue was evident in 40%, especially following PME, suggesting suboptimal surgery performed. Additionally in patients who had PME, the distal margin was found to be less than 3 cm in more than 50% of patients, suggesting a discrepancy between guidelines and the actual surgery performed.

In study II, we estimated the risk of local recurrence in the previously audited cohort of patients, with a particular focus on patients with upper rectal cancer treated by PME and without neoadjuvant therapy as standard. Using Kaplan-Meier analysis, the total three-year local recurrence rate was 7% with tumour stage and an involved circumferential margin as the most important predictors of local recurrence. The local recurrence rate after PME was significantly higher than for TME (14% *vs.* 3%; p=0.032), and were diagnosed earlier (p=0.001). In all cases with local recurrence following PME there was evidence of either inadvertent residual mesorectum and/or an insufficient distal resection margin.

In study III, we investigated the length of the distal resection margin and degree of tissue shrinkage after surgical removal and fixation by using MRI of the fresh and fixed specimen. We found that the length of the specimen and the distal margin was reduced by 30% after surgical removal and fixation. If a 5-cm distal margin below the luminal level of the primary tumour on the fresh specimen is the objective for advanced cancer of the upper rectum treated with PME surgery, a margin of at least 3.5 cm of mesorectum on the fixed specimen should be attained for the pathologist to accurately establish distal radicality.

**REFERENCES**

1. Heald RJ. A new approach to rectal cancer. *Br J Hosp Med* 1979;**22**(3): 277-281.

2. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? *Br J Surg* 1982;**69**(10): 613-616.

3. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986;**2**(8514): 996-999.

4. Adam IJ, Mohamdee MO, Martin IG, Scott N, Finan PJ, Johnston D, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 1994;**344**(8924): 707-711.

5. Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, 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): 693-701.

6. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, 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**(9666): 811-820.

7. Braendengen M, Tveit KM, Berglund A, Birkemeyer E, Frykholm G, Pahlman L, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. *J Clin Oncol* 2008;**26**(22): 3687-3694.

8. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006;**355**(11): 1114-1123.

9. Mercury Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ* 2006;**333**(7572): 779.

10. Beets-Tan RG, Beets GL, Vliegen RF, Kessels AG, Van Boven H, De Bruine A, et al. Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery. *Lancet* 2001;**357**(9255): 497-504.

11. Nagtegaal ID, van de Velde CJ, van der Worp E, Kapiteijn E, Quirke P, van Krieken JH, et al. Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol* 2002;**20**(7): 1729-1734.

12. Quirke P, Steele R, Monson J, Grieve R, Khanna S, Couture J, 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. *The Lancet* 2009;**373**(9666): 821-828.

13. Burton S, Brown G, Daniels IR, Norman AR, Mason B, Cunningham D, et al. MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins? *Br J Cancer* 2006;**94**(3): 351-357.

14. Palmer G, Martling A, Cedermark B, Holm T. Preoperative tumour staging with multidisciplinary team assessment improves the outcome in locally advanced primary rectal cancer. *Colorectal Dis* 2011;**13**(12): 1361-1369.

15. Engelen SM, Maas M, Lahaye MJ, Leijtens JW, van Berlo CL, Jansen RL, 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): 2311-2320.

16. Bulow S, Harling H, Iversen LH, Ladelund S, Danish Colorectal Cancer G. Improved survival after rectal cancer in Denmark. *Colorectal Dis* 2010;**12**(7 Online): e37-42.

17. 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**(9): 1130-1139.

18. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. *Ann Surg* 2004;**240**(2): 260-268.

19. Lopez-Kostner F, Lavery IC, Hool GR, Rybicki LA, Fazio VW. Total mesorectal excision is not necessary for cancers of the upper rectum. *Surgery* 1998;**124**(4): 612-618.

20. Nesbakken A, Nygaard K, Westerheim O, Mala T, Lunde OC. Local recurrence after mesorectal excision for rectal cancer. *Eur J Surg Oncol* 2002;**28**(2): 126-134.

21. Bokey EL, Ojerskog B, Chapuis PH, Dent OF, Newland RC, Sinclair G. Local recurrence after curative excision of the rectum for cancer without adjuvant therapy: role of total anatomical dissection. *Br J Surg* 1999;**86**(9): 1164-1170.

22. Syk E, Torkzad MR, Blomqvist L, Ljungqvist O, Glimelius B. Radiological findings do not support lateral residual tumour as a major cause of local recurrence of rectal cancer. *Br J Surg* 2006;**93**(1): 113-119.

23. Syk E, Torkzad MR, Blomqvist L, Nilsson PJ, Glimelius B. Local recurrence in rectal cancer: anatomic localization and effect on radiation target. *Int J Radiat Oncol Biol Phys* 2008;**72**(3): 658-664.

24. Rosenberg R, Maak M, Schuster T, Becker K, Friess H, Gertler R. Does a rectal cancer of the upper third behave more like a colon or a rectal cancer? *Dis Colon Rectum* 2010;**53**(5): 761-770.

25. Kodeda K, Holmberg E, Steineck G, Nordgren S. Regional differences in local recurrence rates after rectal cancer surgery. *Colorectal Dis* 2010;**12**(10 Online): e206-215.

26. Danish Colorectal Cancer Group. Guidelines for the diagnosis and the management of Colorectal Cancer (in Danish). rev. 2009.

27. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013;**49**(6): 1374-1403.

28. van de Velde CJ, Boelens PG, Borras JM, Coebergh JW, Cervantes A, Blomqvist L, et al. EURECCA colorectal: multidisciplinary management: European consensus conference colon & rectum. *Eur J Cancer* 2014;**50**(1): 1 e1-1 e34.

29. Danish Colorectal Cancer Group. National årsrapport 2012; 2013.

30. Pahlman L, Glimelius B. Local recurrences after surgical treatment for rectal carcinoma. *Acta Chir Scand* 1984;**150**(4): 331-335.

31. Hermanek P, Wiebelt H, Staimmer D, Riedl S. Prognostic factors of rectum carcinoma--experience of the German Multicentre Study SGCRC. German Study Group Colo-Rectal Carcinoma. *Tumori* 1995;**81**(3 Suppl): 60-64.

32. Holm T, Cedermark B, Rutqvist LE. Local recurrence of rectal

adenocarcinoma after 'curative' surgery with and without preoperative radiotherapy. *Br J Surg* 1994;**81**(3): 452-455.

33. McCall JL, Cox MR, Wattchow DA. Analysis of local recurrence rates after surgery alone for rectal cancer. *Int J Colorectal Dis* 1995;**10**(3): 126-132.

34. Martling A, Holm T, Rutqvist LE, Johansson H, Moran BJ, Heald RJ, et al. Impact of a surgical training programme on rectal cancer outcomes in Stockholm. *Br J Surg* 2005;**92**(2): 225-229.

35. Wibe A, Møller B, Norstein J, Carlsen E, Wiig JN, Heald RJ, 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): 857-866.

36. Arbman G, Nilsson E, Hallbook O, Sjodahl R. Local recurrence following total mesorectal excision for rectal cancer. *Br J Surg* 1996;**83**(3): 375-379.

37. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993;**341**(8843): 457-460.

38. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. *Arch Surg* 1998;**133**(8): 894-899.

39. Kapiteijn E, Putter H, van de Velde CJ, Cooperative investigators of the Dutch ColoRectal Cancer G. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. *Br J Surg* 2002;**89**(9): 1142-1149.

40. Nielsen LB, Wille-Jorgensen P. National and international guidelines for rectal cancer. *Colorectal Dis* 2014;**16**(11): 854-865.

41. Mitchard JR, Love SB, Baxter KJ, Shepherd NA. How important is peritoneal involvement in rectal cancer? A prospective study of 331 cases. *Histopathology* 2010;**57**(5): 671-679.

42. Shepherd NA, Baxter KJ, Love SB. Influence of local peritoneal involvement on pelvic recurrence and prognosis in rectal cancer. *J Clin Pathol* 1995;**48**(9): 849-855.

43. Keshava A, Chapuis PH, Chan C, Lin BP, Bokey EL, Dent OF. The significance of involvement of a free serosal surface for recurrence and survival following resection of clinicopathological stage B and C rectal cancer. *Colorectal Dis* 2007;**9**(7): 609-618.

44. Popek S, Tsikitis VL, Hazard L, Cohen AM. Preoperative radiation therapy for upper rectal cancer T3,T4/Nx: selectivity essential. *Clin Colorectal Cancer* 2012;**11**(2): 88-92.

45. Heald RJ. The 'Holy Plane' of rectal surgery. *J R Soc Med* 1988;**81**(9): 503-508.

46. Miles WE. A method of performing abdomino-perineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon. *Lancet* 1908;**2**: 1812-1813.

47. Landsforeningen til Kræftens Bekæmpelse: Skrivelse vedr. cancer recti. København; 1942.

48. Heald RJ. Rectal cancer: the surgical options. *Eur J Cancer* 1995;**31A**(7-8): 1189-1192.

49. Dixon CF. Anterior Resection for Malignant Lesions of the Upper Part of the Rectum and Lower Part of the Sigmoid. *Ann Surg* 1948;**128**(3): 425-442.

50. Pollett WG, Nicholls RJ, Chir M. 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): 159-163.

51. Parks AG. Transanal technique in low rectal anastomosis. *Proc R Soc Med* 1972;**65**(11): 975-976.

52. Parks AG, Percy JP. Resection and sutured colo-anal anastomosis for rectal carcinoma. *Br J Surg* 1982;**69**(6): 301-304.

53. Holm T, Johansson H, Cedermark B, Ekelund G, Rutqvist LE. Influence of hospital- and surgeon-related factors on outcome after treatment of rectal cancer with or without preoperative radiotherapy. *The British journal of surgery* 1997;**84**(5): 657-663.

54. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986;**1**(8496): 1479-1482.

55. Bulow S, Christensen IJ, Harling H, Kronborg O, Fenger C, Nielsen HJ, et al. Recurrence and survival after mesorectal excision for rectal cancer. *Br J Surg* 2003;**90**(8): 974-980.

56. Wibe A, Carlsen E, Dahl O, Tveit KM, Weedon-Fekjaer H, Hestvik UE, et al. Nationwide quality assurance of rectal cancer treatment. *Colorectal Dis* 2006;**8**(3): 224-229.

57. Martling AL, Holm T, Rutqvist LE, Moran BJ, Heald RJ, Cedemark B. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. *Lancet* 2000;**356**(9224): 93-96.

58. Enker WE, Merchant N, Cohen AM, Lanouette NM, Swallow C, Guillem J, et al. Safety and efficacy of low anterior resection for rectal cancer: 681 consecutive cases from a specialty service. *Ann Surg* 1999;**230**(4): 544-552; discussion 552-544.

59. Scott N, Jackson P, al-Jaberi T, Dixon MF, Quirke P, Finan PJ. Total mesorectal excision and local recurrence: a study of tumour spread in the mesorectum distal to rectal cancer. *Br J Surg* 1995;**82**(8): 1031-1033.

60. Reynolds JV, Joyce WP, Dolan J, Sheahan K, Hyland JM. Pathological evidence in support of total mesorectal excision in the management of rectal cancer. *Br J Surg* 1996;**83**(8): 1112-1115.

61. Shirouzu K, Isomoto H, Kakegawa T. Distal spread of rectal cancer and optimal distal margin of resection for sphincter-preserving surgery. *Cancer* 1995;**76**(3): 388-392.

62. Hida J, Yasutomi M, Maruyama T, Fujimoto K, Uchida T, Okuno K. Lymph node metastases 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**(6): 584-588.

63. Hayden DM, Jakate S, Pinzon MC, Giusto D, Francescatti AB, Brand MI, et al. Tumor scatter after neoadjuvant therapy for rectal cancer: are we dealing with an invisible margin? *Dis Colon Rectum* 2012;**55**(12): 1206-1212.

64. Komori K, Kanemitsu Y, Ishiguro S, Shimizu Y, Sano T, Ito S, et al. Adequate length of the surgical distal resection margin in rectal cancer: from the viewpoint of pathological findings. *Am J Surg* 2012;**204**(4): 474-480.

65. Morikawa E, Yasutomi M, Shindou K, Matsuda T, Mori N, Hida J, et al. Distribution of metastatic lymph nodes in colorectal cancer by the modified clearing method. *Dis Colon Rectum* 1994;**37**(3): 219-223.

66. Hermanek P, Hohenberger W, Klimpfinger M, Köckerling F, Papadopoulos T. The pathological assessment of mesorectal excision: implications for further treatment and quality management. *Int J Colorectal Dis* 2003;**18**(4): 335-341.

67. Emmertsen KJ, Laurberg S, Rectal Cancer Function Study G. Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. *Br J Surg* 2013;**100**(10): 1377-1387.

68. Nesbakken A, Nygaard K, Bull-Njaa T, Carlsen E, Eri LM. Bladder and sexual dysfunction after mesorectal excision for rectal cancer. *Br J Surg* 2000;**87**(2): 206-210.

69. Guren MG, Eriksen MT, Wiig JN, Carlsen E, Nesbakken A, Sigurdsson HK, et al. Quality of life and functional outcome following anterior or abdominoperineal resection for rectal cancer. *Eur J Surg Oncol* 2005;**31**(7): 735-742.

70. Påhlman L, Bohe M, Cedermark B, Dahlberg M, Lindmark G, Sjödahl R, et al. The Swedish rectal cancer registry. *Br J Surg* 2007;**94**(10): 1285-1292.

71. Marr R, Birbeck K, Garvican J, Macklin CP, Tiffin NJ, Parsons WJ, et al. The modern abdominoperineal excision: the next challenge after total mesorectal excision. *Ann Surg* 2005;**242**(1): 74-82.

72. West NP, Anderin C, Smith KJ, Holm T, Quirke P, European Extralevator Abdominoperineal Excision Study G. Multicentre experience with extralevator abdominoperineal excision for low rectal cancer. *Br J Surg* 2010;**97**(4): 588-599.

73. Holm T. Controversies in abdominoperineal excision. *Surg Oncol Clin N Am* 2014;**23**(1): 93-111.

74. Holm T, Ljung A, Haggmark T, Jurell G, Lagergren J. Extended abdominoperineal resection with gluteus maximus flap reconstruction of the pelvic floor for rectal cancer. *Br J Surg* 2007;**94**(2): 232-238.

75. Palmer G, Anderin C, Martling A, Holm T. Local control and survival after extralevator abdominoperineal excision for locally advanced or low rectal cancer. *Colorectal Dis* 2014;**16**(7): 527-532.

76. Palmer G, Martling A, Blomqvist L, Cedermark B, Holm T. Outcome after the introduction of a multimodality treatment program for locally advanced rectal cancer. *Eur J Surg Oncol* 2005;**31**(7): 727-734.

77. Nielsen MB, Rasmussen PC, Lindegaard JC, Laurberg S. A 10-year experience of total pelvic exenteration for primary advanced and locally recurrent rectal cancer based on a prospective database. *Colorectal Dis* 2012;**14**(9): 1076-1083.

78. Palmer G, Martling A, Cedermark B, Holm T. A population-based study on the management and outcome in patients with locally recurrent rectal cancer. *Ann Surg Oncol* 2007;**14**(2): 447-454.

79. Nielsen M, Rasmussen P, Pedersen B, Hagemann-Madsen R, Lindegaard J, Laurberg S. Early and Late Outcomes of Surgery for Locally Recurrent Rectal Cancer: A Prospective 10-Year Study in the Total Mesorectal Excision Era. *Ann Surg Oncol* 2015.

80. Palmer G. Locally Advanced Rectal Cancer; Thesis, 2009.

81. Georgiou PA, Bhangu A, Brown G, Rasheed S, Nicholls RJ, Tekkis PP. Learning curve for the management of recurrent and locally advanced primary rectal cancer: a single team's experience. *Colorectal Dis* 2015;**17**(1): 57-65.

82. Beyond T. M. E. Collaborative. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. *Br J Surg* 2013;**100**(8): 1009-1014.

83. Wille-Jørgensen P, Bülow S. The multidisciplinary team conference in rectal cancer--a step forward. *Colorectal Dis* 2009;**11**(3): 231-232.

84. Augestad KM, Lindsetmo RO, Stulberg J, Reynolds H, Senagore A, Champagne B, et al. International preoperative rectal cancer management: staging, neoadjuvant treatment, and impact of multidisciplinary teams. *World J Surg* 2010;**34**(11): 2689-2700.

85. Brown G. Specialist multidisciplinary team working in the treatment of cancer. *BMJ* 2012;**344**: e2780.

86. Segelman J, Singnomklao T, Hellborg H, Martling A. Differences in multidisciplinary team assessment and treatment between patients with stage IV colon and rectal cancer. *Colorectal Dis* 2009;**11**(7): 768-774.

87. Mackay SG, Pager CK, Joseph D, Stewart PJ, Solomon MJ. Assessment of the accuracy of transrectal ultrasonography in anorectal neoplasia. *Br J Surg* 2003;**90**(3): 346-350.

88. Battersby NJ, Moran B, Yu S, Tekkis P, Brown G. MR imaging for rectal cancer: the role in staging the primary and response to neoadjuvant therapy. *Expert Rev Gastroenterol Hepatol* 2014;**8**(6): 703-719.

89. Patel UB, Blomqvist LK, Taylor F, George C, Guthrie A, Bees N, et al. MRI after treatment of locally advanced rectal cancer: how to report tumor response--the MERCURY experience. *AJR Am J Roentgenol* 2012;**199**(4): W486-495.

90. Merkel S, Mansmann U, Siassi M, Papadopoulos T, Hohenberger W, Hermanek P. The prognostic inhomogeneity in pT3 rectal carcinomas. *Int J Colorectal Dis* 2001;**16**(5): 298-304.

91. Merkel S, Weber K, Schellerer V, Gohl J, Fietkau R, Agaimy A, et al. Prognostic subdivision of ypT3 rectal tumours according to extension beyond the muscularis propria. *Br J Surg* 2014;**101**(5): 566-572.

92. Mercury Study Group. Extramural depth of tumor invasion at thin-section MR in patients with rectal cancer: results of the MERCURY study. *Radiology* 2007;**243**(1): 132-139.

93. Pedersen BG, Moran B, Brown G, Blomqvist L, Fenger-Gron M, Laurberg S. 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): 1360-1366.

94. Pedersen BG, Blomqvist L, Brown G, Fenger-Gron M, Moran B, Laurberg S. Postgraduate multidisciplinary development program: impact on the interpretation of pelvic MRI in patients with rectal cancer: a clinical audit in West Denmark. *Dis Colon Rectum* 2011;**54**(3): 328-334.

95. Brown G, Radcliffe AG, Newcombe RG, Dallimore NS, Bourne MW, Williams GT. Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. *Br J Surg* 2003;**90**(3): 355-364.

96. Taylor FG, Quirke P, Heald RJ, Moran B, Blomqvist L, Swift I, et al. One millimetre is the safe cut-off for magnetic resonance imaging prediction of surgical margin status in rectal cancer. *Br J Surg* 2011;**98**(6): 872-879.

97. Taylor FG, Quirke P, Heald RJ, Moran BJ, Blomqvist L, Swift IR, 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**(1): 34-43.

98. Nagtegaal ID, Marijnen CAM, Kranenbarg EK, van de Velde CJH, van Krieken JHJM. Circumferential Margin Involvement Is Still an Important Predictor of Local Recurrence in Rectal Carcinoma. *The American Journal of Surgical Pathology* 2002;**26**(3): 350-357.

99. Wibe A, Rendedal PR, Svensson E, Norstein J, Eide TJ, Myrvold HE, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *Br J Surg* 2002;**89**(3): 327-334.

100. Birbeck KF, Macklin CP, Tiffin NJ, Parsons W, Dixon MF, Mapstone NP, et al. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Annals of Surgery* 2002;**235**(4): 449-457.

101. Norsk Gastrointestinal Cancer Gruppe. Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølgning av kreft i tykktarm og endetarm. 2012.

102. Bernstein TE, Endreseth BH, Romundstad P, Wibe A, Norwegian Colorectal Cancer G. Circumferential resection margin as a prognostic factor in rectal cancer. *Br J Surg* 2009;**96**(11): 1348-1357.

103. Ptok H, Ruppert R, Stassburg J, Maurer CA, Oberholzer K, Junginger T, et al. Pretherapeutic MRI for decision-making regarding selective neoadjuvant radiochemotherapy for rectal carcinoma: interim analysis of a multicentric prospective observational study. *J Magn Reson Imaging* 2013;**37**(5): 1122-1128.

104. Gollub MJ, Maas M, Weiser M, Beets GL, Goodman K, Berkers L, et al. Recognition of the anterior peritoneal reflection at rectal MRI. *AJR Am J Roentgenol* 2013;**200**(1): 97-101.

105. Burton S, Brown G, Daniels I, Norman A, Swift I, Abulafi M, et al. MRI identified prognostic features of tumors in distal sigmoid, rectosigmoid, and upper rectum: treatment with radiotherapy and chemotherapy. *Int J Radiat Oncol Biol Phys* 2006;**65**(2): 445-451.

106. O'Neill B, Brown G, Wotherspoon A, Burton S, Norman A, Tait D. Successful downstaging of high rectal and recto-sigmoid cancer by neo-adjuvant chemo-radiotherapy. *Clin Med Oncol* 2008;**2**: 135-144.

107. Moran BJ, Holm T, Brannagan G, Chave H, Quirke P, West N, et al. The English national low rectal cancer development programme: key messages and future perspectives. *Colorectal Dis* 2014;**16**(3): 173-178.

108. Chand M, Heald RJ, Brown G. The importance of not overstaging mesorectal lymph nodes seen on MRI. *Colorectal Dis* 2013;**15**(10): 1201-1204.

109. Chand M, Bhangu A, Wotherspoon A, Stamp GW, Swift RI, Chau I, et al. EMVI-positive stage II rectal cancer has similar clinical outcomes as stage III disease following pre-operative chemoradiotherapy. *Ann Oncol* 2014;**25**(4): 858-863.

110. Bugg WG, Andreou AK, Biswas D, Toms AP, Williams SM. The prognostic significance of MRI-detected extramural venous invasion in rectal carcinoma. *Clin Radiol* 2014;**69**(6): 619-623.

111. Chew MH, Brown WE, Masya L, Harrison JD, Myers E, Solomon MJ. Clinical, MRI, and PET-CT criteria used by surgeons to determine suitability for pelvic exenteration surgery for recurrent rectal cancers: a Delphi study. *Dis Colon Rectum* 2013;**56**(6): 717-725.

112. Messiou C, Chalmers AG, Boyle K, Wilson D, Sagar P. Pre-operative MR assessment of recurrent rectal cancer. *Br J Radiol* 2008;**81**(966): 468-473.

113. Blomqvist L, Holm T, Göranson H, Jacobsson H, Ohlsén H, Larsson SA. MR imaging, CT and CEA scintigraphy in the diagnosis of local recurrence of rectal carcinoma. *Acta Radiol* 1996;**37**(5): 779-784.

114. Dresen RC, Kusters M, Daniels-Gooszen AW, Cappendijk VC, Nieuwenhuijzen GA, Kessels AG, et al. Absence of tumor invasion into pelvic structures in locally recurrent rectal cancer: prediction with preoperative MR imaging. *Radiology* 2010;**256**(1): 143-150.

115. Glimelius B, Tiret E, Cervantes A, Arnold D, Group EGW.

Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;**24 Suppl 6**: vi81-88.

116. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011;**12**(6): 575-582.
117. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;**351**(17): 1731-1740.

118. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012;**30**(16): 1926-1933.

119. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;**345**(9): 638-646.

120. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997;**336**(14): 980-987.

121. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8507 patients from 22 randomised trials. *The Lancet* 2001;**358**(9290): 1291-1304.

122. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006;**93**(10): 1215-1223.

123. Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol* 2012;**30**(31): 3827-3833.

124. van den Broek CB, van Gijn W, Bastiaannet E, Moller B, Johansson R, Elferink MA, et al. Differences in pre-operative treatment for rectal cancer between Norway, Sweden, Denmark, Belgium and the Netherlands. *Eur J Surg Oncol* 2014;**40**(12): 1789-1796.

125. Elliot AH, Martling A, Glimelius B, Nordenvall C, Johansson H, Nilsson PJ. Preoperative treatment selection in rectal cancer: a population-based cohort study. *Eur J Surg Oncol* 2014;**40**(12): 1782-1788.

126. Glimelius B. Neo-adjuvant radiotherapy in rectal cancer. *World J Gastroenterol* 2013;**19**(46): 8489-8501.

127. Hermanek P, Heald RJ. Pre-operative radiotherapy for rectal carcinoma? Has the case really been made for short course pre-operative radiotherapy if surgical standards for rectal carcinoma are optimal? *Colorectal Dis* 2004;**6**(1): 10-14.

128. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol* 2005;**23**(24): 5644-5650.
129. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Late adverse effects of radiation therapy for rectal cancer - a systematic overview. *Acta Oncol* 2007;**46**(4): 504-516.

130. Foxtrot Collaborative Group. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial. *Lancet Oncol* 2012;**13**(11): 1152-1160.

131. Tiselius C, Gunnarsson U, Smedh K, Glimelius B, Pahlman L. Patients with rectal cancer receiving adjuvant chemotherapy have an increased survival: a population-based longitudinal study. *Ann Oncol* 2013;**24**(1): 160-165.

132. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? *J Clin Oncol* 2008;**26**(2): 303-312.

133. Maslekar S, Sharma A, Macdonald A, Gunn J, Monson JR, Hartley JE. Mesorectal grades predict recurrences after curative resection for rectal cancer. *Dis Colon Rectum* 2007;**50**(2): 168-175.

134. Garcia-Granero E, Faiz O, Munoz E, Flor B, Navarro S, Faus C, et al. Macroscopic assessment of mesorectal excision in rectal cancer: a useful tool for improving quality control in a multidisciplinary team. *Cancer* 2009;**115**(15): 3400-3411.

135. Quirke P. Training and quality assurance for rectal cancer: 20 years of data is enough. *Lancet* 2003;**4**(11): 695-702.

136. LH Sobin CW. *International Union Against Cancer (UICC). TNM Classification of Malignant Tumours (5th edn.)*. John Wiley & Sons: New York, 1997.

137. Hohenberger W, Schick CH, Gohl J. Mesorectal lymph node dissection: is it beneficial? *Langenbecks Arch Surg* 1998;**383**(6): 402-408.

138. Williams NS, Dixon MF, Johnston D. Reappraisal of the 5 centimetre rule of distal excision for carcinoma of the rectum: a study of distal intramural spread and of patients' survival. *Br J Surg* 1983;**70**(3): 150-154.

139. Weese JL, O'Grady MG, Ottery FD. How long is the five centimeter margin? *Surgery, gynecology & obstetrics* 1986;**163**(2): 101-103.

140. Søndenaa K, Kjellevold KH. A prospective study of the length of the distal margin after low anterior resection for rectal cancer. *Int J Colorectal Dis* 1990;**5**(2): 103-105.

141. Kwok SP, Lau WY, Leung KL, Liew CT, Li AK. Prospective analysis of the distal margin of clearance in anterior resection for rectal carcinoma. *Br J Surg* 1996;**83**(7): 969-972.

142. Goldstein NS, Soman A, Sacksner J. Disparate surgical margin lengths of colorectal resection specimens between in vivo and in vitro measurements - The effects of surgical resection and formalin fixation on organ shrinkage. *Am J Clin Pathol* 1999;**111**(3): 349-351.

143. Tocchi A, Mazzoni G, Lepre L, Liotta G, Costa G, Agostini N, et al. Total mesorectal excision and low rectal anastomosis for the treatment of rectal cancer and prevention of pelvic recurrences. *Arch Surg* 2001;**136**(2): 216-220.

144. Ono C, Yoshinaga K, Enomoto M, Sugihara K. Discontinuous rectal cancer spread in the mesorectum and the optimal distal clearance margin in situ. *Dis Colon Rectum* 2002;**45**(6): 744-749; discussion 742-743.

145. Wang C, Zhou Z, Wang Z, Zheng Y, Zhao G, Yu Y, et al. Patterns of neoplastic foci and lymph node micrometastasis within the mesorectum. *Langenbecks Arch Surg* 2005;**390**(4): 312-318.

146. Shimada Y, Takii Y, Maruyama S, Ohta T. Intramural and mesorectal distal spread detected by whole-mount sections in the determination of optimal distal resection margin in patients undergoing surgery for rectosigmoid or rectal cancer without preoperative therapy. *Dis Colon Rectum* 2011;**54**(12): 1510-1520.

147. Zhao GP, Zhou ZG, Lei WZ, Yu YY, Wang C, Wang Z, et al. Pathological study of distal mesorectal cancer spread to determine a proper distal resection margin. *World J Gastroenterol* 2005;**11**(3): 319-322.

148. Nielsen MB, Laurberg S, Holm T. Current management of locally recurrent rectal cancer. *Colorectal Dis* 2011;**13**(7): 732-742.

149. Camilleri-Brennan J, Steele RJ. The impact of recurrent rectal cancer on quality of life. *Eur J Surg Oncol* 2001;**27**(4): 349-353.

150. Thaysen HV, Jess P, Laurberg S. Health-related quality of life after surgery for primary advanced rectal cancer and recurrent rectal cancer: a review. *Colorectal Dis* 2012;**14**(7): 797-803.

151. Rahbari NN, Ulrich AB, Bruckner T, Munter M, Nickles A, Contin P, et al. Surgery for locally recurrent rectal cancer in the era of total mesorectal excision: is there still a chance for cure? *Ann Surg* 2011;**253**(3): 522-533.

152. Kodeda K, Derwinger K, Gustavsson B, Nordgren S. Local recurrence of rectal cancer: a population-based cohort study of diagnosis, treatment and outcome. *Colorectal Dis* 2012;**14**(5): 230-237.

153. Sagar PM, Pemberton JH. Surgical management of locally recurrent rectal cancer. *Br J Surg* 1996;**83**(3): 293-304.

154. Sobin LH, Gospodarowicz MK, Wittekind C. *Internation Union against Cancer (UICC) TNM classification of malignant tumours 7th edition*. Wiley-Blackwell: Hoboken, NJ, 2009.

155. Guillem JG, Ruo, L. Strategies in Operative Therapy for Locally Recurrent Rectal Cancer. *Seminars in Colon and Rectal Surgery* 1998;**9**(4 (December)): 259-268.

156. Altman DG. *Practical Statistics for Medical Research* (1st Edition edn). Chapman & Hall: London, UK, 1991.

157. Kennelly RP, Rogers AC, Winter DC, Abdominoperineal Excision Study G. Multicentre study of circumferential margin positivity and outcomes following abdominoperineal excision for rectal cancer. *Br J Surg* 2013;**100**(1): 160-166.

158. Nagtegaal ID, van De Velde CJH, Marijnen CAM, van Krieken JHJM, Quirke P. Low rectal cancer: a call for a change of approach in abdominoperineal resection. *J Clin Oncol* 2005;**23**(36): 9257-9264.

159. Bhangu A, Ali SM, Cunningham D, Brown G, Tekkis P. Comparison of long-term survival outcome of operative vs nonoperative management of recurrent rectal cancer. *Colorectal Dis* 2013;**15**(2): 156-163.

160. Pilipshen SJ, Heilweil M, Quan SH, Sternberg SS, Enker WE. Patterns of pelvic recurrence following definitive resections of rectal cancer. *Cancer* 1984;**53**(6): 1354-1362.

161. Tiefenthal M, Nilsson PJ, Johansson R, Glimelius B, Pahlman L. The effects of short-course preoperative irradiation on local recurrence rate and survival in rectal cancer: a population-based nationwide study. *Dis Colon Rectum* 2011;**54**(6): 672-680.

162. Moran BJ, Heald RJ. *Manual of Total Mesorectal Excision*. CRC Press: London, 2013.

163. Keller DS, Paspulati R, Kjellmo A, Rokseth KM, Bankwitz B, Wibe A, et al. MRI-defined height of rectal tumours. *Br J Surg* 2014;**101**(2): 127-132.

164. Paparo F, Puppo C, Montale A, Bacigalupo L, Pascariello A, Clavarezza M, et al. Comparison between magnetic resonance imaging and rigid rectoscopy in the preoperative identification of intra- and extraperitoneal rectal cancer. *Colorectal Dis* 2014;**16**(11): O379-385.

165. Jung EJ, Ryu CG, Kim G, Kim SR, Nam SE, Park HS, et al. Is rectal MRI beneficial for determining the location of rectal cancer with respect to the peritoneal reflection? *Radiol Oncol* 2012;**46**(4): 296-301.

166. Chang JS, Lee Y, Lim JS, Kim NK, Baik SH, Min BS, et al. The magnetic resonance imaging-based approach for identification of high-risk patients with upper rectal cancer. *Ann Surg* 2014;**260**(2): 293-298.

167. Emmertsen KJLS. The impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. A prospective multicentre study. *DKS* 2013.

168. Pacelli F, Sanchez AM, Covino M, Tortorelli AP, Bossola M, Valentini V, et al. Improved outcomes for rectal cancer in the era of preoperative chemoradiation and tailored mesorectal excision: a series of 338 consecutive cases. *Am Surg* 2013;**79**(2): 151-161.

169. Hohenberger P, Schlag P, Kretzschmar U, Herfarth C. Regional mesenteric recurrence of colorectal cancer after anterior resection or left hemicolectomy: inadequate primary resection

demonstrated by angiography of the remaining arterial supply. *Int J Colorectal Dis* 1991;**6**(1): 17-23.

170. Kusters M, Marijnen CA, van de Velde CJ, Rutten HJ, Lahaye MJ, Kim JH, et al. Patterns of local recurrence in rectal cancer; a study of the Dutch TME trial. *Eur J Surg Oncol* 2010;**36**(5): 470-476.

171. Daniels IR, Fisher SE, Heald RJ, Moran BJ. Accurate staging, selective preoperative therapy and optimal surgery improves outcome in rectal cancer: a review of the recent evidence. *Colorectal Dis* 2007;**9**(4): 290-301.

172. Keighley MR, Hall C. Anastomotic recurrence of colorectal cancer--a biological phenomenon or an avoidable calamity? *Gut* 1987;**28**(7): 786-791.

173. Leonard D, Penninckx F, Fieuws S, Jouret-Mourin A, Sempoux C, Jehaes C, et al. Factors predicting the quality of total mesorectal excision for rectal cancer. *Ann Surg* 2010;**252**(6): 982-988.

174. Demetter P, Vandendael T, Sempoux C, Ectors N, Cuvelier CA, Nagy N, et al. Need for objective and reproducible criteria in histopathological assessment of total mesorectal excision specimens: lessons from a national improvement project. *Colorectal Dis* 2013;**15**(11): 1351-1358.

175. Torkzad MR, Blomqvist L. The mesorectum: morphometric assessment with magnetic resonance imaging. *Eur Radiol* 2005;**15**(6): 1184-1191.

176. Ewing MR. The significance of the level of the peritoneal reflection in the surgery of rectal cancer. *Br J Surg* 1952;**39**(158): 495-500.

177. Kuzu A, Heald RJ, Brown G, Quirke P, Holm T, Park Y. Comprehensive step by step training package on rectal cancer surgery [DVD]; 2013.

178. Jullumstro E, Wibe A, Lydersen S, Edna TH. Violation of treatment guidelines -- hazard for rectal cancer patients. *Int J Colorectal Dis* 2012;**27**(1): 103-109.

179. Holm T, Johansson H, Rutqvist LE, Cedermark B. Tumour location and the effects of preoperative radiotherapy in the treatment of rectal cancer. *Br J Surg* 2001;**88**(6): 839-843.

180. Monson JR, Probst CP, Wexner SD, Remzi FH, Fleshman JW, Garcia-Aguilar J, et al. Failure of evidence-based cancer care in the United States: the association between rectal cancer treatment, cancer center volume, and geography. *Ann Surg* 2014;**260**(4): 625-631; discussion 631-622.

181. Glynne-Jones R, Harrison M, Hughes R. Challenges in the neoadjuvant treatment of rectal cancer: balancing the risk of recurrence and quality of life. *Cancer Radiother* 2013;**17**(7): 675-685.

182. Williamson JS, Jones HG, Davies M, Evans MD, Hatcher O, Beynon J, et al. Outcomes in locally advanced rectal cancer with highly selective preoperative chemoradiotherapy. *Br J Surg* 2014;**101**(10): 1290-1298.

183. Mathis KL, Larson DW, Dozois EJ, Cima RR, Huebner M, Haddock MG, et al. Outcomes following surgery without radiotherapy for rectal cancer. *Br J Surg* 2012;**99**(1): 137-143.

184. Senapati A, O'Leary DP, Flashman KG, Parvaiz A, Thompson MR. Low rates of local recurrence after surgical resection of rectal cancer suggest a selective policy for preoperative radiotherapy. *Colorectal Dis* 2012;**14**(7): 838-843.

185. Taylor FG, Quirke P, Heald RJ, Moran B, Blomqvist L, Swift I, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. *Ann Surg* 2011;**253**(4): 711-719.

186. Simunovic M, Sexton R, Rempel E, Moran BJ, Heald RJ. Optimal preoperative assessment and surgery for rectal cancer may greatly limit the need for radiotherapy. *Br J Surg* 2003;**90**(8): 999-1003.