Multidisciplinary Management of Rectal Cancer

Questions and Answers

Second Edition

Vincenzo Valentini
Hans-Joachim Schmoll
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Editors
Vincenzo Valentini
Dept. of Radiation Oncology
Università Cattolica S Cuore
Rome
Italy

Cornelis J.H. van de Velde
Department of Surgery
Leiden Univ Med Ctr
Leiden
The Netherlands

Hans-Joachim Schmoll
Head, Div. Clinical Oncology Research
University Clinic Halle (Saale)
Martin-Luther-University Halle-Wittenberg
Halle
Sachsen-Anhalt
Germany

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Foreword

During the past few decades, there have been many advances in the management of rectal cancer. Building on a more comprehensive understanding of anatomy and patterns of local recurrence, new surgical techniques such as total mesorectal resection and sphincter-sparing coloanal anastomosis have become standards. Preoperative adjuvant therapy has been enhanced by more effective chemoradiation programs. The increase in response rates has not only improved local control and sphincter-preserving surgery but led to a growing experience in nonoperative approaches ("watch and wait"). Advances in radiation planning, delivery, and hypofractionation schemes coupled with new cytotoxic and targeted chemotherapeutic agents hold the promise of reduced toxicity and increased tumor response and control rates. Diagnostic modalities such as high-resolution MRI have helped identify which therapeutic approaches and modalities are best suited to an individual tumor allowing a more selective approach. Advances in new cytotoxic and targeted chemotherapeutic agents have improved survival in the adjuvant setting as well as the outcomes of patients with metastatic disease. As patients with metastatic disease live longer, the selective addition of local ablative therapies including radiation, surgery, and interventional radiology has an increasing role. Lastly, a renewed focus on expert pathologic analysis coupled with the evolving field of prognostic and predictive molecular markers has facilitated the development of surrogate endpoints of response.

Although each discipline has made their individual diagnostic and therapeutic contributions, the cornerstone of success has been the unified movement toward multidisciplinary management. It is the collaborative efforts of surgeons, radiation oncologists, medical oncologists, radiologists, and pathologists which have truly had the most significant impact on outcome.

The second edition of this landmark book updates and broadens this multidisciplinary approach to the field of rectal cancer. In contrast to the traditional didactic approach, each of the 76 chapters directly engages the reader with timely questions and answers. Building on the value of multidisciplinary management, Professors Valentini, Schmoll, and Van de Velde have assembled an internationally known group of contributors from centers of excellence. Broad areas of expertise include risk factors, imaging, radiotherapy, chemotherapy, surgery, and pathology. The advances of the past four decades as well as new emerging controversies are discussed.

In this updated and expanded edition, the editors have succeeded in providing us with the foundation, relevant data, and guidance to multidisciplinary management of rectal cancer. This team approach sets the standard for modern cancer management.

Houston, TX, USA Bruce D. Minsky

Preface

In an era where all patients are entitled to access healthcare systems expecting the highest quality of treatment delivered within a safe healthcare environment, the multidisciplinary team is of central importance and a critical requirement in the development of modern oncology.

Joint efforts of different specialists involved in the diagnosis, staging, treatment, and evaluation of outcomes in rectal cancer were devoted throughout Europe in the last years to promote mutual understanding and collaboration by managing multidisciplinary meetings, consensus, and teaching courses. It created the background to the holistic approach in promoting the multidisciplinarity of this book.

The success of the first edition of this book, with more than 16,000 copies sold or downloaded and a full Chinese translation, is largely related to have identified the most common questions that arose in the practice of a multidisciplinary team and to have involved a recognized group of clinicians, mostly involved in the management of the more significant trials published in Europe in the last decade. In this edition, we more than double the questions keeping in place the approach to provide simple and focused answers to support the best choices in a multidisciplinary setting. We are very grateful to their enthusiastic and fully supportive participation to this project of all the distinguished colleagues involved in this project.

With this book, we hope to contribute to improve the overall care of the patient, supporting the multidisciplinary teams in their unique responsibility for patient's ongoing care and well-being.

Rome, Italy — Vincenzo Valentini
Halle, Sachsen-Anhalt, Germany — Hans-Joachim Schmoll
Leiden, The Netherlands — Cornelis J.H. Van de Velde

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M.M. Lange, A.C. Kraima, C.J.H. van de Velde, and M.C. deRuiter

1.1 Epidemiology

Rectal cancer constitutes one-third of all colorectal cancers, representing the cancer with the second highest incidence and the second cause of cancer death in the western society [1, 2]. An estimated 100,000 new cases of rectal cancer are diagnosed each year in Europe. The incidence is increasing, mainly due to earlier detection and increasing age of the population, as the highest incidence of rectal cancer is found in the sixth and seventh decades. High incidence rates are found especially in western world populations, i.e. Western Europe, North America and Australia. This can probably be explained by a combination of factors, including dietary patterns with high amounts of red meat, obesity and smoking [3]. The United States is the only country with significantly decreasing incidence rates in both males and females in the most recent time period, which largely reflects detection and removal of precancerous lesions through colorectal cancer screening [4]. Next to dietary and lifestyle factors, risk factors for rectal cancer include inflammatory bowel disease and primary sclerosing cholangitis. Also genetic predisposition plays a role; however, rectal cancer most commonly occurs sporadically and is inherited in only 5% of the cases. Five-year survival rate of rectal cancer is about 60% and depends to a large extent on disease stage at diagnosis [5].

1.2 The Rectum

The anatomy and physiology of the rectum makes rectal cancer treatment a potential cause of severe, long-term morbidity [6, 7]. In order to comprehend rectal cancer, the principles of treatment and its implications, it is necessary to understand the anatomy and the function of the rectum.

1.2.1 Anatomy

The rectum continues from the sigmoid colon and ends at the upper part of the anal canal. Anatomically, the rectum differs from the sigmoid colon in having no sacculations and appendices epiploicae. Approximately 5 cm above the rectosigmoid junction, the taeniae blend and form two wide muscular bands descending posteriorly and anteriorly in the rectal wall. These muscular bands fuse and form an encircling layer of longitudinal muscle that invests the rectum along its complete length. The rectum has a variable length from about 12 to 15 cm. As a rule, the upper third of the

M.M. Lange • A.C. Kraima • C.J.H. van de Velde (✉)
Leiden University Medical Center (The Netherlands), Department of Surgery, Leiden, The Netherlands
e-mail: C.J.H.van_de_Velde@lumc.nl

M.C. deRuiter
Leiden University Medical Center (The Netherlands), Department of Anatomy and Embryology, Leiden, The Netherlands

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rectum is located intraperitoneally and the lower two-thirds of the rectum extraperitoneally. The anal canal extends from the anorectal junction, which is located in front of and slightly below the tip of the coccyx, until the anal verge. Three epithelial zones can be recognized downwards consisting of simple columnar epithelium, stratified columnar epithelium and stratified squamous epithelium. The dentate line marks the transformation of columnar to squamous epithelium, dividing the anal canal into an upper third and lower two-thirds. The anal verge forms a transitional zone between the squamous epithelium of the anal canal and the perianal skin. The anal sphincter complex surrounds the anal canal and is build up by the internal anal sphincter, longitudinal muscle and external anal sphincter. The longitudinal muscle integrates the internal and external anal sphincters and provides a strong fixation of the anorectum to the perineal body and levator ani muscles (Fig. 1.1).

The definitions of rectum and low rectal cancer are highly variable. Some publications define the rectum as 15 cm from the anal verge as measured by rigid endoscopy, defining low rectal cancer within 5 cm from the anus [8, 9]. Other definitions are related to anatomy rather than endoscopic measurement. These define the rectum as located below the border of the second sacral vertebra and low rectal cancer as a tumour of which the major part is located at or below the peritoneal reflection [10]. In women the peritoneal reflection (4–7 cm from the anal verge) can descend to 4 cm from the anal verge. The rectum forms an acute 90–115° anorectal angle with the dorsally directed anal canal. This angle, widening during defaecation (more than 130°), is caused by the puborectal sling of the levator ani muscles, inserting just cranially to the level of the mucocutaneous line, halfway the anal canal [11]. The rectum is surrounded by fatty and connective tissue, which is known as the mesorectum (Fig. 1.2). Starting at the sacral promontory, the mesorectum being most pronounced at the dorsal site of the rectum diminishes below the rectosacral fascia around the levator ani muscles at the end of the distal third of the rectum. The mesorectum is enveloped by the visceral fascia, which is often referred to as the mesorectal or proper rectal fascia, separating it from the parietal fascia, which is also known as the presacral fascia. Posterolaterally between these fasciae, an avascular space consisting of loose areolar tissue is situated. The pelvic autonomic nerves are located in this so-called holy

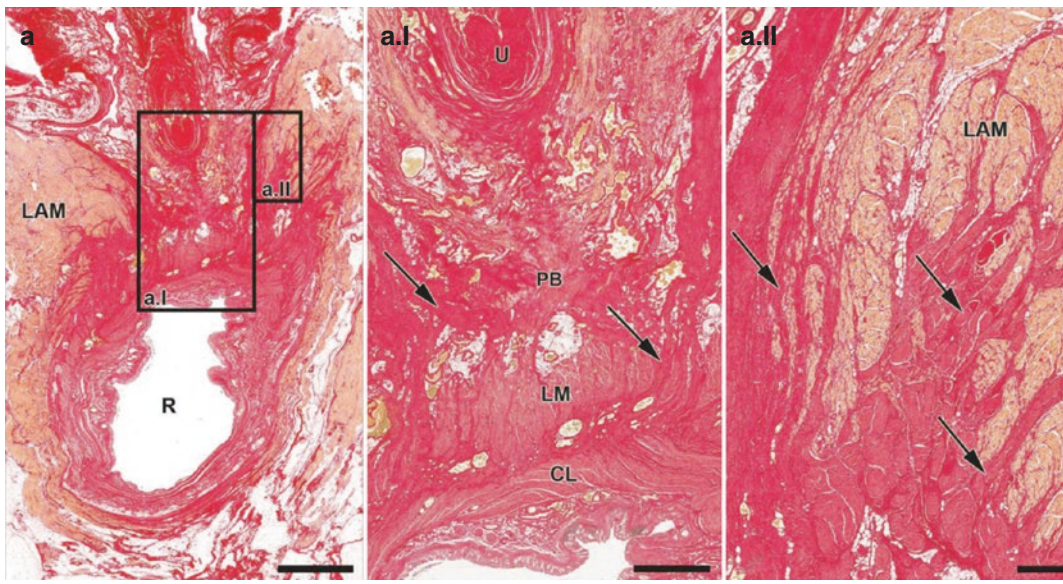

Fig. 1.1 Microscopic section showing the fixation of the anorectum into the perineal body and levator ani muscles. Window (**a**) shows a whole mount microscopic section of a male cadaveric specimen stained with *picrosirius red*, in which striated muscle fibres appear as *yellow* and smooth muscle fibres and collagen appear as *red*. The *arrows* in detail windows (**a.I**) and (**a.II**) point out the role of the longitudinal muscle (*LM*) in providing the fixation of the anorectum to the perineal body and levator ani muscle. *LAM* levator ani muscles, *PB* perineal body, *R* rectum, *CL* circular layer of the rectal muscular wall. Scale bar window **a** 6 mm, window **a.I** 2 mm, window **a.II** 600 µm

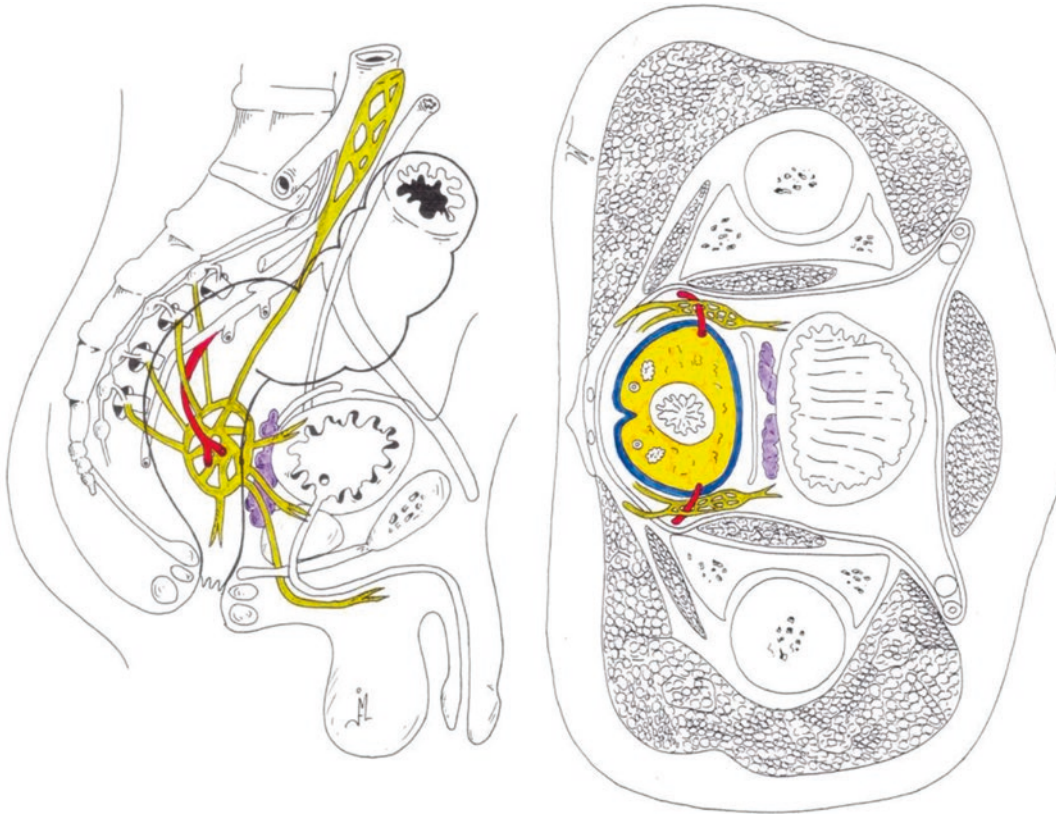

Fig. 1.2 Sagittal and transversal illustration of the male pelvis. Sympathetic and parasympathetic nerves (*green*), mesorectum (*yellow*), mesorectal fascia (*blue*), middle rectal artery (*red*), seminal vesicles (*purple*) (Illustrated by J.F.M. Lange)

plane. Anteriorly, Denonvilliers' fascia (rectogenital septum) is adherent to the mesorectal fascia and prostatic fascia in males or posterior vaginal wall in females. The lateral edges of Denonvilliers' fascia are continuous with the mesorectal fascia and are dangerously closely related to the neurovascular bundles [12]. The midline hindgut (rectum) and the mesorectum, containing its vessels, fat and most of its lymph glands, are embryologically derived as one single unit. The anatomy and embryological origin is respected by the current golden standard for rectal cancer resection total mesorectal excision (TME) as it involves en bloc resection of the rectum and the mesorectal tissue to the level of the levator ani muscles within the embryologically determined, avascular plane outside the mesorectum between the parietal and visceral fascia [13]. This allows for radical resection of the tumour and preservation of the pelvic autonomic nerves which are essential to maintain urogenital and anorectal functions [6, 7].

Surgically, the mesorectum is suspended to the pelvic wall by (1) the 'lateral ligaments' which are strands of condensed tissue, located ventrolaterally to the rectum, at the level of the seminal vesicles in males, containing the middle rectal blood vessels and lymphatics [14]. These adhere close to the inferior hypogastric plexuses; (2) the rectosacral fascia, just cranially to the pelvic floor, at the anorectal junction at level S4; and (3) levator ani complex, covered by fat and the parietal rectal fascia. The lateral ligaments are not seen on radiologic imaging or histology, but appear only as an identifiable structure with surgical traction on the rectum. The rectosacral fascia histologically appears as an increased amount of collagen rather than a true fascia. From an anatomical point of view, these structures probably play a very minor role in supporting the rectum.

The arterial supply of the rectum is supported by the superior rectal artery, representing the inferior mesenteric artery after spring-off of the

left colic and sigmoid arteries. The inferior arteries from the internal iliac and the middle rectal artery also contribute blood to the rectum. The venous return follows the arteries and the lymphatic drainage mirrors its vasculature. The first nodal level is located in the mesorectum, draining mostly to the inferior mesenteric nodes and then the para-aortic nodes. The lower lymph drainage is variable both proximally and laterally along the middle rectal vessels towards nodes at the internal iliac vessels.

Adequate functioning of pelvic organs, i.e. the rectum, vagina, uterus, vestibular bulbs, clitoris, bladder, urethra, penis, prostate and pelvic floor, requires combined action of the sympathetic and parasympathetic nervous systems with input from the somatosensory nervous system. The superior hypogastric plexus (located at the promontory at the level of L4-S1) and hypogastric nerves are commonly considered as being part of the sympathetic nervous system, but recently it has been shown that parasympathetic nerves run in these neural structures as well [15]. The hypogastric nerves, which often form small neural plexuses rather than two single nerve strands, descend dorsally to the mesorectum, parallel to the ureters towards the inferior hypogastric plexuses (plexi pelvini), where they join the parasympathetic pelvic splanchnic nerves (nervi erigentes) coming from S2-4 (Fig. 1.2).

Nerves branching from the inferior hypogastric plexus innervate essentially the pelvic organs. The vesical plexus, which is formed by the nerves innervating the bladder, is located in close relation to the distal part of the ureter and are prone to surgical damage when the ureter is completely mobilized until its insertion in the bladder (Fig. 1.3). The pelvic floor is dually innervated: inferiorly by

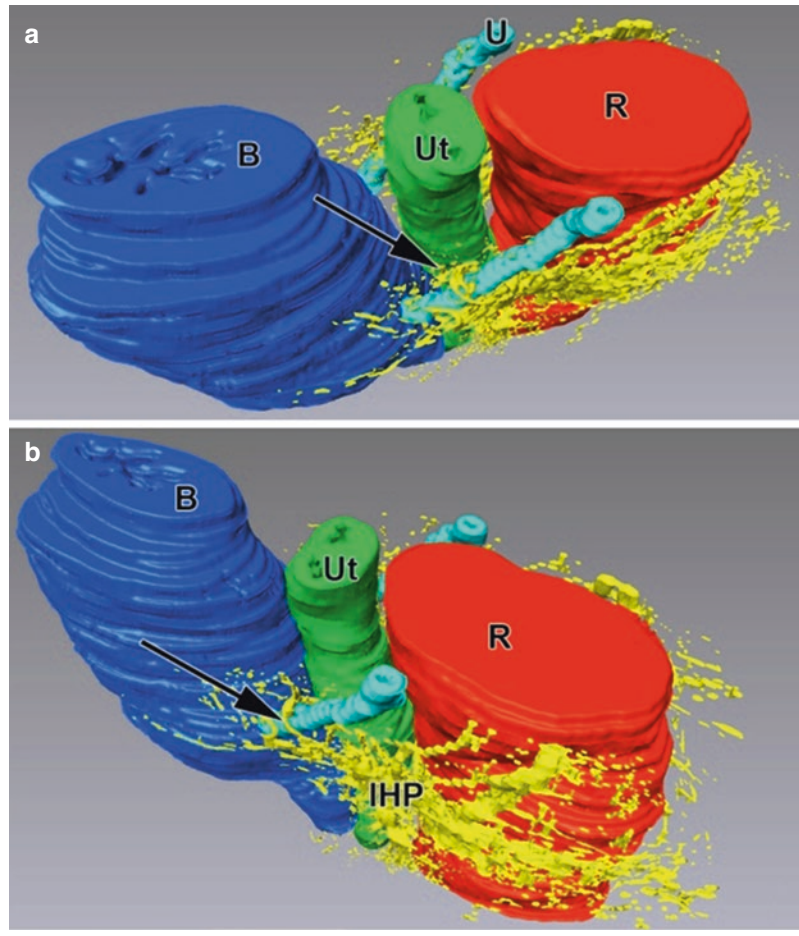

Fig. 1.3 Three-dimensional reconstruction of the pelvic autonomic network. Windows (**a**, **b**) offer superior views on the pelvic autonomic network (*yellow*) of a female fetus. Note the close relation of the big mesh-like inferior hypogastric plexus to the rectum (*red*) and uterus (*green*). The *arrows* indicate the vesical plexus, which surrounds the distal part of the ureter (*light blue*), to innervate the bladder (*dark blue*). *B* bladder, *Ut* uterus, *R* rectum, *IHP* inferior hypogastric plexus

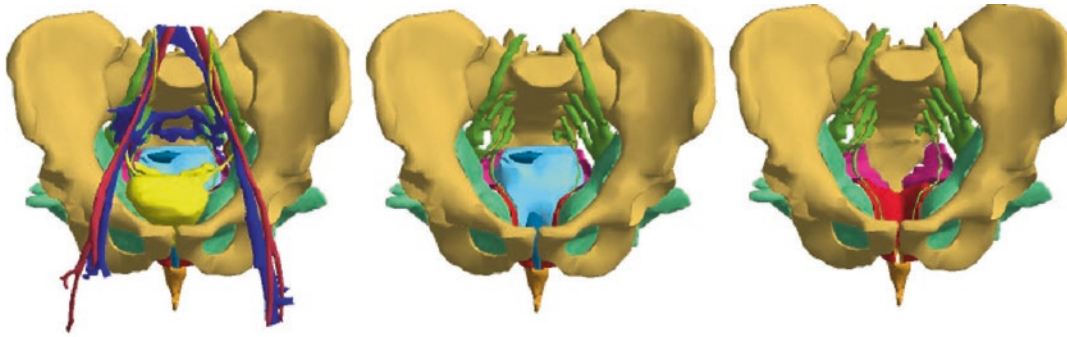

Fig. 1.4 Three-dimensional reconstruction of the male pelvis. The levator ani nerve, running just cranially to the pelvic floor (*green*), is closely related to the mesorectum (*light blue*)

the pudendal nerves and superiorly by the levator ani nerves. The latter arise from S3-4 and run over the surface of the levator ani muscles, covered solely by the parietal fascia [16] (Fig. 1.4).

1.2.2 Function

The anorectum is responsible for maintaining faecal continence and, when socially appropriate, defaecation. This is possible as the rectum has a capacity to store an amount of faeces, acting as a reservoir [17]. Furthermore, the anal canal contains a rich network of nerve endings sensitive to pain, temperature and touch, which is used to differentiate solid or liquid stool from flatus and allows for selective passage of flatus. The anal sphincter complex keeps the anal canal closed in a resting state. In addition to the resting anal pressures, the myenteric plexus of the internal anal sphincter enables the recto-inhibitory reflex, which implies relaxation of the internal anal sphincter in response to increased pressure in the rectum. And finally, the pelvic floor (levator ani muscles) is responsible for the anorectal angle, flattening during defaecation [18].

1.3 Pathophysiology

The majority of rectal cancers develop from benign pre-neoplastic lesions: the adenomatous polyps or adenomas. Polyps are histologically classified as tubular (5% malignant), villous (40% malignant) or mixed (20% malignant) depending on glandular structure. Degree of dysplasia (atypical cells) is graded: chance of malignancy varies from about 5% (low grade) to about 35% (high grade). Risk of malignancy is also collated with size: 90% of adenomas are less than 1 cm (1% risk of malignancy), and 10% are bigger than 1 cm (about 10% malignant). Progression from a benign adenoma to a malignant carcinoma passes through a series of well-defined histological stages, which is referred to as the adenoma-carcinoma sequence. Two major mechanisms of genomic instability lead to colorectal carcinoma development and progression: chromosomal instability (CIN) and microsatellite instability (MSI). The former mechanism is associated with a series of genetic changes that involve the activation of oncogenes (uncontrolled cell growth; k-ras gene) and inactivation of tumour suppressor genes (uninhibited growth; APC gene, p53 gene, DCC/SMAD4 gene) and contributes predominantly to carcinogenesis in the rectum [19, 20]. Familial adenomatous polyposis (FAP) and its attenuated variant (AFAP) represent the (hereditary) syndrome dealing with APC mutation. The MSI pathway, in which mutations in DNA mismatch repair (MMR) genes result in a failure to repair errors that occur during DNA replications in repetitive sequences (microsatellites), results in an accumulation of frameshift mutations. This failure leads to MSI type of tumour, which is more frequently poorly differentiated and with an unusual histologic type (mucinous and marked intra- and peritumoural lymphocytic infiltration).

It is also the hallmark of hereditary non-polyposis colorectal cancer, HNPCC (Lynch syndrome). It has been observed that MSI is most common in (right-sided) colon cancer and rare in rectal carcinoma [21]. Nevertheless, compared with colon cancer, the number of mutations detected is significantly higher in rectal cancer [22]. Furthermore, cyclooxygenase-2 (COX2) is overexpressed in 90% of rectal tumours but in only 20% of colonic tumours [23]. These genetic characteristics confirm that rectal cancer is a different entity in colorectal cancer.

In the progression of rectal cancer, microenvironmental interactions are important. Loss of cell adhesion leads to reorganization of epithelial cells to make invasion and metastasis possible [24]. Angiogenesis is vital for tumour growth and is mediated by multiple molecules, such as vascular endothelial growth factor (VEGF), which are released by tumour cells [25]. For a full understanding of the process of normal cells becoming malignant tumours, all the genetic pathways and mechanisms need to be identified.

Direct spread of rectal cancer occurs intramurally and radially, resulting in invasion of adjacent tissues or organs. Indirect spread through lymph and blood vessels was first described by Harrison Cripps in 1890 [26]. Consequently, his pupil, William Ernest Miles stretched the importance of resecting the rectal tumour *en bloc* with its mesorectum, lymph nodes and blood supply, introducing the first curative resection for rectal cancer [27]. Lymphatic spread occurs in stepwise progression. Skip metastases appear in less than 5%. Haematogenous spread is the most important pattern of spread, most commonly involving the liver. However, rectal cancer may also metastasize initially to the lungs because the inferior rectal vein drains into the inferior vena cava, rather than into the portal venous system. Other infrequent sites are the adrenal glands, kidneys, bones and brain. In addition spread within the peritoneal cavity happens, initially close to the tumour with small nodules arising from cells shed from the primary tumour. Later plaques become more widespread, omentum is involved and ascites is produced. Peritoneal involvement is a poor prognostic factor (median survival less than 6 months) [28, 29].

1.4 Presentation

Next to polypoidal disease, a rectal carcinoma can appear as an atypical ulcer, with rolled edges and a necrotic base (Fig. 1.5). This tends to infiltrate more deeply and is more likely to perforate. Also stenosing or annular lesions have been described. Lastly, rectal cancer can be a diffuse infiltrative disease, appearing as an extensive lesion infiltrating the bowel wall over many centimetres. The macroscopic appearance influences the symptomatology of rectal cancer. Patients present either electively or as an emergency with obstruction or perforation. Obstruction leads to abdominal distension, pain, nausea and vomiting. Elective symptoms include altered bowel habit, rectal bleeding, mucus discharge, abdominal pain, fatigue, weight loss and palpable abdominal mass. Less common symptoms include tenesmus, in case of pelvic floor involvement, and neuropathic pain syndrome due to sciatic or obturator nerve involvement in locally advanced disease. Approximately 20% of patients have distant metastatic disease at the time of presentation [29].

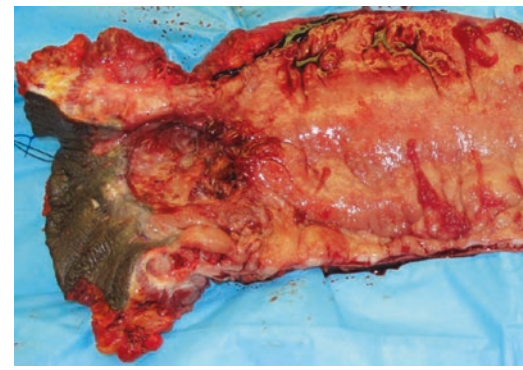

Fig. 1.5 Ulcerative rectal carcinoma. Resection specimen after abdominoperineal resection for ulcerative rectal carcinoma located at the anal verge

1.5 Diagnosis

Rectal cancer can be suspected from the symptoms and signs described above or may be asymptomatic and discovered by routine screening (faecal occult blood testing, colonoscopy). Histological confirmation is sought through colonoscopy and biopsy. In patients in whom colonoscopy is impossible, computed tomography (CT) colonoscopy can provide radiographic diagnosis. The entire large bowel should be examined for the presence of synchronous lesions. Magnetic resonance imaging (MRI) and endorectal ultrasound (EUS; differentiate T1 from T2) are used for staging and evaluating locoregional disease and predicting if negative surgical margins can be achieved, which is the case in approximately 75% [30]. Colonic tomography and/or abdominal ultrasound are used to identify extrapelvic metastases. Furthermore a thorax x-ray is performed to identify lung metastasis. Once the diagnosis is established and the local and distant extent of disease spread is determined, therapy and prognosis are discussed in a multidisciplinary setting. Modern multimodal treatment of rectal cancer attempts to integrate surgery, radiotherapy and chemotherapy and uses the expertise and knowledge of pathology and radiology to optimize oncologic and functional results.

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The Patient's Perspective

2

P.G. Boelens, G. Henning, and Claire Taylor

2.1 What Is Known About the Patient's Endpoints?

Patients facing the diagnosis of rectal cancer first of all desire to be cured. Moreover, patients hope that their treatment does not cause too many long-lasting adverse effects impacting on their daily life after the treatment. Because having rectal cancer is a new experience to them, the information at hand from health-care professionals is very important when making decisions about their treatment [1]. Modern cancer management has become multidisciplinary, and complex decisions are an emergent consequence of the interaction of various health-care professionals deliberating on the best diagnostic and treatment modalities to fit the individual patient. Shared decision making, discussing the benefits and harms of each treatment modality and using option grids or decision aids have shown to aid the patient facing life-changing cancer treatment [2]. Moreover, to move from a one-size-fits-all to tailored treatment, we should be informed about our patients' preferences, values and expectations to know and aid the person it's all about.

Strikingly, only few qualitative studies have tried to unravel what are the relevant endpoints for the patients with rectal cancer. Recently, a four-round Delphi method was performed with two expert panels: (1) the patient survivors of rectal cancer (n = 31) and (2) the radiation oncologists (n = 35) [3]. Benefits and risks of preoperative radiotherapy were evaluated by both groups to be important to be discussed during the consultation in a scale to 'do not mention'. The patient panel and the radiation oncologists had a significant overlap in topics to be explained during this outpatient visit. The second part of the study was designed to compare this list of the Delphi consensus with daily practice; at this point, 81 audiotaped consultations were analysed for congruence. It was already known from previous research that information provision by physicians is worryingly varied [4]. The study of Kunneman et al. showed that on average only half of the 'benefits and harms deemed important' were mentioned during the consultations [3]. Rationally, all patients have the right to be equally well informed about their treatment options with an

P.G. Boelens (✉) • G. Henning • C. Taylor
Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands

EUROPAColon,
Unit 5, Deans Farm, Stratford sub Castle, Salisbury SP1 3YP, UK

Colorectal care, St Mark's Hospital,
Harrow, Middlesex, UK
e-mail: P.G.Boelens@lumc.nl

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objective representation of benefits and harms of the different treatment alternatives. Unfortunately, we are not there yet.

2.2 Variation in Information

Most health-care professionals are aware of individual patient values, patient preferences and perspectives but may not be trained to proficiently implement this information in the medical decision making [5]. Variation in information provision between clinicians and patients might have an impact on the degree of decisional conflict or regret related to patients feeling uninformed and later emotional recovery of the oncological experience.

A recent study explored surgeons' opinions on content of the preoperative information using questionnaires (response rate of 43%, $n = 103$) and evaluated what was actually discussed by audiotaping 32 consultations [6]. Information provided was incomplete, and none of the items was used consistently. Just as an example, anastomotic leakage was discussed in 93%; however, the consequences of a leak such as prolonged hospital stay and death were only mentioned in 6%. End colostomy as an option was given in just 22% of the patients. Although surgeons acknowledge the value of most information in their daily practice, this was not reflected in the consultations [6].

2.3 What Are Relevant Endpoints?

Over the last decade, there has been growing awareness that the traditional outcome measures such as tumour recurrence, mortality and survival are equally important as patient-reported outcome (PRO) measures and adverse effects of the treatments. PROMs encompass patient outcome assessments such as health-related quality of life, survivorship and rehabilitation. Weighing the benefits and harms of rectal cancer treatment is a complex process; it is balancing between reducing risks of local recurrence to chronic bowel, urinary and sexual dysfunction.

The evidence generated by properly designed trials is still very valuable and creates the base of improvements in rectal cancer care. Nevertheless, it should be contemplated that trial results are not per se representative of the overall cancer population. The minority of rectal cancer patients is included in trials. For example, patients above a certain age were often excluded from clinical trials with drugs, whilst this elderly cohort represents the fast majority of rectal patients to treat. Another aspect influencing on trial outcome is that patients participating in trials are different than the average population because they have less comorbid diseases, a higher socioeconomic status and smaller tumours; in patients older than 75 years, this resulted in worse outcomes of cancer treatment in the unselected population in comparison to the trial participants [7]. Extrapolating trial results could lead to over or under treatment with harmful effects for the general rectal cancer population.

Ideally, population-based data coming from national audits and cancer registries could present the real outcome of treatment. Unfortunately these can be less complete, and in most countries, accurate treatment details are not collected. At this moment, cancer registries in Europe are very diversely structured and most registries do not have data collections on type of treatment to provide information of compliance to cancer guidelines [8]. Functional outcome and PROMs are not collected by most countries.

This chapter will discuss what is recently studied on topics as quality of life, functional outcomes and PROMs after rectal cancer surgery. Some overlap is anticipated with the chapters on side effects of surgery, radiation oncology, medical oncology and quality of life.

The aim of this chapter is to create awareness of the inconsistent and insufficient information that professionals in rectal cancer care provide to their patients [3, 4, 6]. It is imperative to gain knowledge of the patient's preferences and expectations, before commencement of treatment that may overshadow survivorship. Discussing the endpoints of rectal cancer treatment should be a dialogue between patients and clinicians on existing treatment options, using standardized

decision aids incorporating values coming from the individual patient and results from clinical studies ultimately to reduce the variation in information and incorporate the patient's perspective.

2.4 Does Type of Surgery Influence Functional Outcome in Rectal Cancer?

Yes, so this needs to be addressed in a structured way. A qualitative study was performed on the patients' expectations of functional outcome after rectal surgery. Twenty-six patients facing sphincter-saving rectal cancer surgery were enrolled and submitted to semi-structured interviews. One of the interpretations was that the information received by the patients is pivotal in the process of forming expectations of postoperative outcome [1]. Expectations of bowel function after treatment influence satisfaction and postoperative quality of life [9].

Of note is that functional outcome after rectal cancer can be very diverse depending on the extent of surgery performed to achieve a complete removal of the tumour. Extent of tissue and concomitant organs resected will result in loss of function especially if anatomical planes cannot be followed in advanced and recurrent diseases [10]. Awareness and adequate training in sharp dissection of anatomical planes where possible spares the pelvic nerves situated in close proximity of the mesorectal fascia and improves functional outcome [11]. Important, since functional outcome and quality of life are entwined.

Minimal invasive techniques have clear advantages in functional outcome. In certain favourable Tis and T1 rectal cancers, endoscopic treatments, such as conventional endoscopic resection or endoscopic submucosal dissection (ESD), can be offered, preserving most of the gastrointestinal and urogenital function [12]. Local recurrences after endoscopic resection may be higher than after TME surgery and may impact on long-term outcome [12]. Patients undergoing the endoscopic resection should be adequately informed about the possibility of tumour removal without surgery, the changes of piecemeal resection and thus operation anyway (so-called salvage or completion TME surgery), local regrowth or recurrence rates and the benefits of functional outcomes. No information is available of the patient's perspective of these techniques.

Transanal endoscopic microsurgery (TEM) is also a new kid on the block. It is the recommended local excision technique for medium-sized rectal cancers (Tis and T1 favourable characteristics only) performed by a transanal single port. It can be organ preserving, sparing the pelvic nerves and may result in normal long-term function [13]. However, patients undergoing completion surgery after TEM might have worse oncologic outcomes than when primary TME would have been performed [14]. Local recurrences have been significantly higher in patients undergoing TEM with clear resection margins in comparison to TME populations; there are clear benefits in postoperative mortality, hospital stay, morbidity and stoma formation [14, 15]. The benefits in long-term function [13] should be adequately discussed in light of the negative drawbacks of having a higher stage tumour or in case an incomplete TEM resection is performed. Quality of life and anorectal function of patients the first year after TEM is reported as a temporary dysfunction [16].

If quality of life of patients undergoing TEM pT1 was compared to patients undergoing TME surgery laparoscopically, no difference was measured at 12 months with regard to preoperative conditions [17].

Total mesorectal excision (TME) surgery is the gold standard for rectal cancer surgery, following the anatomical 'holy' planes, leaving the mesorectal fascia intact and the pelvic nerves intact. Survivors of rectal cancer treatment of the Eindhoven Cancer Registry were identified as treated by surgery alone or with preoperative radiotherapy; the latter group reported significant worse outcomes with respect to body image, gastrointestinal function and male sexual function still 10 years after treatment [18].

Importantly, the two mainstay surgical procedures that follow the mesorectal planes are (1) low anterior resection (LAR) with formation of a colo-anal or colorectal anastomosis and (2) the

abdominoperineal resection (APR) with formation of a permanent stoma. The choice of either one is usually determined by patient characteristics such as preoperative sphincter function, comorbidities, preference of the surgeon and perioperative estimation of a complete resection. Patients have been very passive in these decisions in the past; 65% of the patients would leave the decision to the surgeon [19]. Nevertheless equal oncological outcome can be achieved by either of these two procedures in most patients, and significant quality of life trade-offs exist; patients could play an active role in choosing their procedure [20]. Each procedure has its own specific benefits and harms to consider. LAR can be complicated with a high rate of incontinence, chronic use of protective pads, risk of other bowel dysfunctions and a risk of anastomotic leakage resulting in reoperations, abscess, prolonged hospital stay and even death [21]. Because of the risk of anastomotic leakage, many patients will receive a protective stoma that will be removed in second operation [21]. The latter has also well-known complications such as diarrhoea, leakage, reoperation and several more [22].

APR has a high risk of stoma-related complications (prolapse, dermatitis due to leakage under the plastic pouching system, ileus, parastomal hernia, stoma stenosis and reoperation). Body image with a stoma is changed for life [23].

Recently, a decision aid was developed for patients undergoing rectal cancer surgery decisions for LAR vs APR [24]. Implementation and evaluation of decisional conflict are unfortunately not yet published. In another study describing the decisional needs of patients with rectal cancer when deciding on surgical treatment and identifying gaps in information provision, it was reported that none of the patients perceived that they were offered an option between APR and LAR; nearly half of the patients could recall discussing postoperative bowel function, half of the patients were not aware of sexual dysfunction, and the majority were not aware of problems with urinary function [25]. There is a problem with paternalistic and inconsistent information provision by several health-care professionals such as surgeons and radiotherapists; patients are not retaining all information in a way which offers them a viable choice of alternative treatments [3, 4, 6, 25].

For locally advanced and locally recurrent rectal cancers, chemoradiation and surgery both are very harmful for functional outcome [10]. Quality of life after exenteration and 1-year survivorship usually is comparable to who did not have the exenteration [26]. To underline, the previous information from a patient's perspective, it will take most patients 9 months to recover from this extensive surgery and to adapt to the changes [27, 28]. Patients with a more severe threat of life are usually satisfied with less quality than patients with better prognosis.

2.5 Is Bowel Function After Sphincter-Saving Surgery a Relevant Endpoint for Patients?

Yes, bowel function after rectal surgery is a very important aspect impacting on long-term quality of life [29]. Only few will have a normal bowel function after radical rectal surgery. In the 14-year follow-up evaluation of the Dutch TME study, comparing radiotherapy plus TME surgery versus surgery alone, it was found that radiotherapy with surgery was associated with more bowel dysfunction in patients without a stoma, in comparison to surgery alone [29]. Local recurrence and faecal incontinence are regarded as the worst outcomes reported by patients and clinicians similarly [30].

Low anterior resection syndrome (LARS) is the term used to describe the alteration in bowel function after anterior resection surgery [31]. The syndrome affects at least 50–90% of those treated with sphincter-saving resection surgery for rectal cancer. It covers several bowel symptoms, including frequency, urgency, incontinence of flatus and/or faeces and fragmentation of stools, often experienced together to varying degrees [31]. The most severe impact of the altered bowel function is that it affects patients' body image and ideal body and jeopardizes body control. To illustrate this with patients' expressions, bowel

activities after rectal surgery are described as forceful, irregular and unpredictable and can occur during the day as the night [31]. Rectal cancer specialists do not really grasp the impact of gastrointestinal function as it is perceived by the patients undergoing LAR; this was investigated in a study submitting clinicians to exercises based on the LARS score. The clinicians clearly underestimated the impact of clustering of bowel motions and urgency of defecation [32].

The LARS score is a validated practical list of the bowel symptoms that fit to the experiences after rectal cancer treatment; patients were involved in testing, piloting and optimizing the questionnaire [33]. This validation study had an exceptional high response rate of 92.8%, reflecting the importance of the subject from the patients' perspective. Validity of the LARS score was tested and proven reliable in different European countries [34].

Bowel symptoms after rectal cancer treatment have a major impact on social life [33]. Incontinent patients were less satisfied with bowel function and were more restricted in daily and social activities [35]. To underline, gastrointestinal dysfunction has an enormous impact on the patient's daily life; sexuality; ability to work, engage in physical activity and go on holidays; and more [36].

More incontinence is observed in patients undergoing surgery and radiotherapy [29]. Significantly more patients undergoing preoperative radiotherapy and TME surgery need to wear protective pads even 14 years after treatment (58% vs 34.4% in the surgery only arm) [29]. This was also reported in a study of Knowles et al. aimed at defining the long-term prevalence of pelvic dysfunction following curative rectal cancer care. It should be stated that wearing incontinence pads is embarrassing for most patients, besides it is inconvenient and expensive [37]. To study patients' preferences towards sphincter-saving surgery with formation of an anastomosis or abdominoperineal resection with permanent stoma, patients were asked to weigh the certainty of a stoma against the risk of incontinence [20]. The majority of patients would choose for a LAR above APR with acceptance of the risk of incontinence.

We would like to state that clearly informing patients with rectal cancer about postoperative bowel function and its impact on daily life is integral in clinical decision making.

2.6 Is Having a Stoma a Relevant Endpoint for Patients?

When facing the diagnosis of rectal cancer, most patients fear an ostomy and 'Will I need a bag?' is one of the questions to be answered. Initial reactions are rarely positive, but over time, adjusting and coping of the changed body image with an ostomy improves for most. There are gender differences in adjusting to an ostomy, and it is described that younger women (<age 75 years) scored consistently lower with quality of life in a control-matched cross-sectional study of rectal cancer survivors with and without ostomy [38]. These gender differences were also found in focus group discussions of long-term colorectal survivors reporting on the challenges of living with an ostomy [39]. In both groups, males and females, having an ostomy impacted on sexuality, intimacy and physical and social well-being. Nevertheless, quality of life of elderly rectal cancer patients with a stoma was similar to those without a stoma [40].

The 2012 update of the Cochrane review, studying quality of life after rectal resection for cancer, with or without permanent colostomy, concluded that on the basis of the available evidence, 35 non-randomized studies, no firm conclusions can be made about superiority of the choice for an abdominoperineal resection (APR) with a permanent stoma or the anterior resection (AR) with an anastomosis and frequently a temporary ostomy [41]. Based on quality of life questionnaires, this emphasizes the results of the earlier meta-analysis of Cornish et al., that these procedures produce comparable general quality of life [42].

Since oncological safety is comparable between both procedures, with advances of medical stapling device formation of an anastomosis, sphincter-saving rectal cancer surgery is chosen by a majority of the surgeons. However, low and

ultra-low resections might compromise safety with regard to higher anastomotic leakage, besides a poor gastrointestinal outcome and quality of life. There are important trade-offs to discuss with each individual patient [20].

Most patients with permanent stomas can enjoy an equally good quality of life. For some this is achieved by gaining a degree of control over their bowel function by the use of simple techniques such as colostomy irrigation. Of course, there is a huge variation in how individuals experience living with a stoma, partly influenced by their experience of stoma-related difficulties such as prolapse, parastomal hernia and skin irritation [43, 44] but also other factors such as age and professional and social support [45]. In sum, there is no doubt that having an ostomy is a big adjustment for most people, and the defining endpoint for those with a permanent stoma may be adaptation to and acceptance of 'self-with-a-stoma'.

Patients undergoing stoma reversal after some time have an equal quality of life with those who never had a stoma, although for a half of patients there will be a significant change and lasting change in bowel function and body image [46].

2.7 Is Sexual Function a Relevant Endpoint for Patients?

Yes, and a change in sexual function (whether this be a change in sexual desire, ability to orgasm or difficulty at any other stage in the sexual response cycle) can happen to most of our patients after rectal cancer treatments. TME surgery and extended surgery for locally advanced disease dramatically impact on sexual activity, regardless of the procedure performed [47]. Between these two groups of patients undergoing different procedures, the quality of life was not scored differently.

In the 14-year follow-up of the Dutch TME trial, patients undergoing preoperative radiotherapy in combination with TME surgery reported more erection difficulties than patients after surgery alone [29]. In 2005, Marijnen already described a decline in sexual activity between the two study arms, being larger in the preoperative radiotherapy group in comparison to surgery alone [48]. In males, erection and ejaculation problems were increased, whilst in females, sexual functioning was deteriorated by vaginal dryness and pain during intercourse (dyspareunia) [48]. Quality of life between the groups was not different. Moreover, quality of life between APR and LAR was also not affected [48]. In the 14-year follow-up and compared to the Dutch population, both treatment arms reported a small decrease in quality of life [29].

It is conceivable that the importance afforded to changes in sexual function is dependent on the patients' individual priorities, which can alter at phases in their life. In advanced stages, patients bargain for much less to have a change to survive for a few years. There is enormous decrease in sexual activity and well-being after TME surgery, which is lower after a combination with neoadjuvant treatments. Patients should be adequately informed about sexual dysfunction after TME surgery with or without neoadjuvant therapies. Despite the high prevalence of sexual dysfunction in survivors of colorectal cancer, studies have shown that patients and providers rarely discuss how these symptoms may be influencing overall quality of life [49]. Despite the high prevalence of sexual problems of rectal cancer survivors, clinicians rarely discuss these symptoms and their implications on quality of life [49].

2.8 Is Bladder Function a Relevant Endpoint for Patients?

Yes. TME surgery and radiotherapy or chemoradiation can cause damage to the urogenital nerves. Symptoms of voiding, urge incontinence, urine retention or symptoms of a hypotonic bladder are described in several reports [50, 51]. APR results in more urinary dysfunction when compared to AR, some selection bias should be contemplated [50]. Micturition problems are less common than bowel and sexual dysfunction and improve in time in most patients [50–52].

Most studies lack information on urinary tract function at all. Most clinicians do not mention the possibility of these problems to their patients, and patients are often equally reluctant to report even if they do experience urinary problems, particularly incontinence.

2.9 Is Emotional Function a Relevant Endpoint for Patients?

Patients undergoing rectal cancer treatment are in a vulnerable period of their lives [53]. Feelings such as helplessness, depression, shock, fear of the unknown are common following a cancer diagnosis. Whilst the intensity of these acute emotions tends to subside, a range of emotions will still be palpable months after treatment. Distress may extend to uncertainty about the future, fear of dependence, disappointment over outcomes and with time from treatment a sense of abandonment.

Psychological distress can understandably stem from experiencing physical symptoms after treatment including pain and/ or bowel, urinary or sexual effects, which may remain a problem for some, long after achieving remission of their rectal cancer. Rectal cancer and its treatment also cause people to perceive their body differently, and when this image is more disturbed, the risk of anxiety and depression increases [54]. A significant relationship between depression and level of social function in patients after colorectal cancer may exist as the low mood may become socially debilitating leading to isolation, furthering the depression [55]. Anxiety associated with the disease may also be perceived as interfering with their family life and social activities. A survey conducted by the UK charity Macmillan of 606 patients highlights the challenge on how to live with cancer every day, which is often an emotional one, with over half (56%) patients reporting fears about their cancer recurrence [56].

Presence of anxiety and depression can be a major predictor of a patient's quality of life [57]. Most factors associated with possible or probable depression may be modified with appropriate intervention [58]. A good endpoint is being able to forget about the cancer by ignoring intrusive thoughts which can prevent people doing what matters most to them. It is thus vital that people know where to go for good information, advice and support [56].

2.10 Is Pain a Relevant Endpoint for Patients?

Yes. If pain is studied, many rectal cancer survivors have chronic pain. Pain is in the top five major concerns of patients facing rectal cancer treatment. In a population-based, cross-sectional study of chronic pain and quality of life in patients treated for rectal cancer in Denmark, a brief pain questionnaire was mailed to 1713 patients, of which 80% responded. Thirty-one percent reported chronic pain in the pelvic area and lower extremities and 41% had daily pain. Being female, receiving chemoradiation and type of surgery was associated to experiencing pain [59].Moreover, whilst curative surgery offers prolonged survival, it also can cause significant chronic pain among long-term survivors of locally recurrent rectal cancer [60].

Certain patients with specific polymorphisms of the nucleotides have higher toxicity (Grade 3 acute toxicity of 23.8%) to neoadjuvant therapies for locally advanced radiotherapy [61].

Peripheral neuropathy is one of the major survivorship issues for many of those who have had chemotherapy with oxaliplatin impacting on quality of life [62]. This condition manifests as pain, numbness and/or tingling in both hands and feet. It can cause severe pain and can affect patients' ability to do things like walking, writing, buttoning their shirt or picking up coins. In a prospective study, FOLFOX and XELOX caused similar high incidence (80%) and severity of acute neurotoxicity [63]. Chemotherapy-induced peripheral neuropathy (CIPN) can result in chemotherapy dose reduction or discontinuation, which often causes patients' concern about the consequent future implications. CIPN can also have long-term effects on quality of life with the course of the symptoms being unpredictable: as

whilst they may resolve after chemotherapy is discontinued, they can also continue for years.

Chronic pain is prevalent in far more than 10% of the patients and should therefore be discussed in consultations about rectal cancer treatment.

2.11 Is Tiredness a Relevant Endpoint for Patients?

Yes. Tiredness or fatigue is a frequently occurring sign after cancer treatment that is not easily discussed or treated, and it influences recovery and rehabilitation to have a full life enormously. Fatigue related to cancer and its treatment can make even simple tasks feel exhausting. At its worst, fatigue can leave people incapacitated. As many as 75% of people living with cancer feel fatigued at some point [64, 65]. In a national survey of people living with breast, colorectal or prostate cancer or non-Hodgkin lymphoma, 43% of those diagnosed up to 5 years previously reported always feeling tired [66].

Fatigue is a common symptom affecting postoperative recovery negatively which may provide a more global assessment of recovery than other more commonly used measures such as length of postoperative hospital stay. This is because fatigue can interfere with performance of daily activities and ability to concentrate, causing feelings of frustration and depression [67].

Cancer-related fatigue is often multifactorial and more complex to resolve since it is often not experienced in isolation, with clusters of symptoms often described. Fatigue, QOL, anxiety/depression and cognitive symptoms have been associated as interrelating factors affecting recovery of cancer treatment [68].

2.12 Is Radiotherapy's Effect a Relevant Endpoint for the Patients?

Yes. Evidence suggests that pelvic radiotherapy leads to a number of common adverse effects including diarrhoea, dermatological problems, micturition problems, fatigue, sexual dysfunction and pain. Some can lead to a decline in quality of life during treatment and cause prolonged surgical recovery times, but there appears to be no long-term deterioration in quality of life [69].

Rectal cancer patients undergoing neoadjuvant CRT may experience a reduction in global QOL along with significant gastrointestinal and genitourinary symptoms during treatment. Moreover, provider-rated toxicity scales may not fully capture this decrease in patient-reported QOL. Although most symptoms are transient, impairment in gastrointestinal and sexual function may persist after the completion of therapy and merits further investigation [70].

2.13 Future Perspectives

Patients need to be partners in studies evaluating endpoints of rectal cancer care. Quality of care and symptom assessment should be incorporated into a wider appraisal of holistic care needs [71]. The Southampton CREW study (a prospective cohort study on the recovery of health and well-being following colorectal cancer) captures patient-reported data before surgery and at regular points during and after treatment as well as medical data. This study indicates that there are four distinct recovery trajectories for CRC patients over the first 2 years of recovery after treatment, determined by age, social support, anxiety and depression and self-efficacy and not by disease stage or treatment received. On the basis of such studies, we may, in the future, be able to more accurately predict and prepare patients and also be more aware in monitoring those patients who potentially have a worse recovery with poorer functional outcomes following rectal cancer treatments.

To conclude, in the treatment of rectal cancer, all endpoints are relevant when changing a life forever. Patients need to be completely informed about pros and cons of different alternative treatments. Consistent and complete information provision and pursuing patients' preferences are still underdeveloped skills in the consultations of clinicians. More attention is

necessary to address choices of treatment together with the patients in shared decision making.

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