Vincenzo Valentini
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Multidisciplinary Management of Rectal Cancer

Questions and Answers

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ISBN 978-3-642-25004-0 ISBN 978-3-642-25005-7 (eBook)
DOI 10.1007/978-3-642-25005-7
Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2012940207

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

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. The move toward preoperative adjuvant therapy has been facilitated by more effective chemoradiation programs. Advances in radiation planning, delivery, and fractionation techniques coupled with new cytotoxic and targeted chemotherapeutic agents hold the promise of reduced toxicity and increased tumor response and control rates. New 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. 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.

This exciting new book is a unique contribution to the field of rectal cancer. In contrast to the traditional didactic approach, each chapter 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 a number of European centers of excellence. Broad areas of expertise include risk factors, imaging, radiotherapy, chemotherapy, surgery, and pathology. The advances of the past three decades as well as new emerging controversies are discussed.

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.

Chicago, IL, USA — Bruce D. Minsky, M.D.

Preface

In an era where all patients are entitled to access healthcare systems that enable the highest quality of treatment delivered within a safe healthcare environment, and access to appropriate advice, support and long term follow-up, 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 throughout Europe to promote mutual understanding and collaboration by managing multidisciplinary consensus conferences (EURECA-CC1-2) and the publication of their recommendation were undertaken.

This was extended to a multidisciplinary teaching course (5 editions across Europe and 1 in China) and culminated to the endorsement of these activities by European cancer societies like ESTRO, ESSO and ESMO and hence creating the background to the holistic approach in promoting the multidisciplinarity of this book.

The aim of this book is to report the most common questions that arose in the practice of a multidisciplinary team, devoted to address the health request of patients with rectal cancer. A recognised group of clinicians, mostly involved in the management of the more significant trials published in Europe in the last decade, were requested 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.

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 on-going care and wellbeing.

Vincenzo Valentini
Hans-Joachim Schmoll
Cornelius J.H. van de Velde

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Part I

Introduction

What Do We Consider Cancer of the Rectum?

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Marilyne M. Lange and Cornelis J.H. van de Velde

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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].

V. Valentini et al. (eds.), *Multidisciplinary Management of Rectal Cancer*,
DOI 10.1007/978-3-642-25005-7_1,

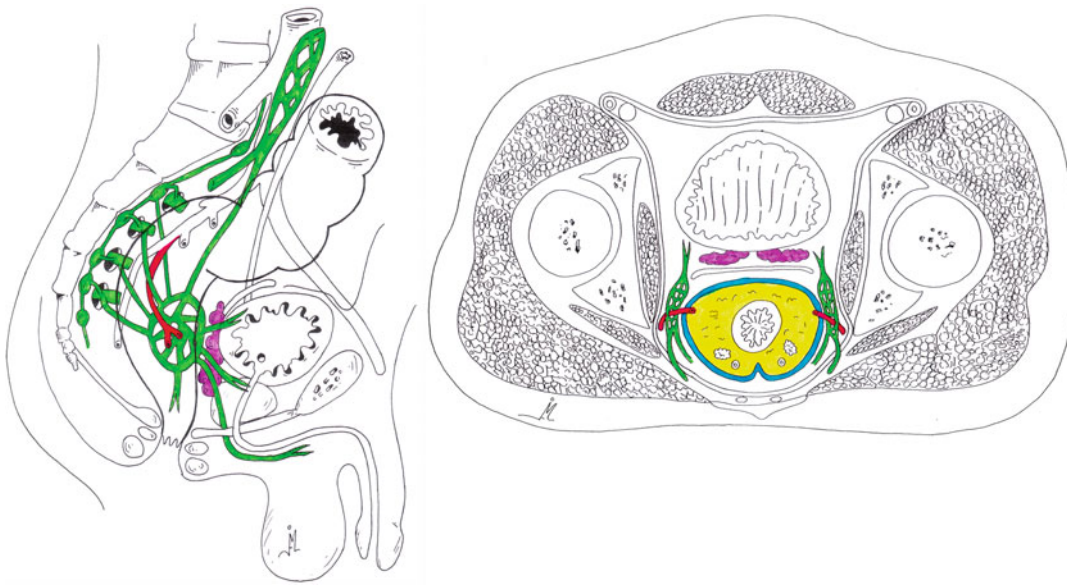

Fig. 1.1 Sagittal and transversal illustration of the male pelvis. Sympathetic and parasympathetic nerves (*green*), mesorectum (*yellow*), mesorectal fascia (*blue*), middle rectal artery (*red*), seminal vesicles (*purple*) (Illustrated by J.F.M. Lange)

1.2 The Rectum

The anatomic relations 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

Anatomically, the rectum extends from the anal verge for about 12–15 cm, where it curves anteriorly and merges into the sigmoid. As a rule, one third of the rectum is located intraperitoneally and two thirds extraperitoneally. 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]. Circumferentially, the rectum is surrounded by fatty and connective tissue, which is known as the mesorectum (Fig. 1.1). 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 rectal (pelvic, proper rectal) fascia, separating it from the parietal endopelvic fascia. In between is a dorsal layer of thin fat, containing autonomic nerves to the pelvic organs, and the more ventral retrorectal space, filled with loose areolar tissue (‘holy plane of Heald’). The midline hindgut (rectum) and the mesorectum, containing

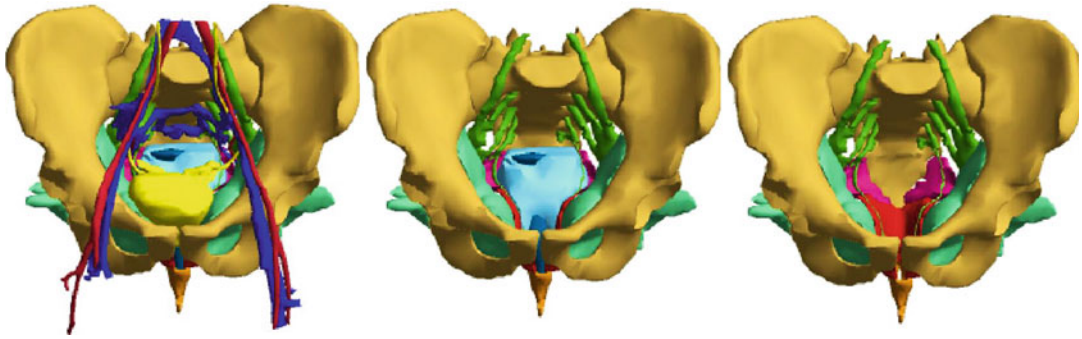

Fig. 1.2 Three-dimensional reconstruction of the male pelvis. The levator ani nerve, running just cranially to the pelvic floor (*green*), is closely related to the mesorectum (*light blue*)

its vessels, fat and most of its lymph glands, are embryologically derived together as a 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 muscles within the embryologically determined, avascular plane outside the mesorectum between the parietal and visceral rectal fascia [12]. This allows for radical resection of the tumour and preservation of the pelvic autonomic nerves which are essential for urogenital and anorectal functions [6, 7].

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 men, containing the middle rectal blood vessels and lymphatics [13]—these adhere close to the sympathetic and parasympathetic inferior hypogastric plexuses—(2) the rectosacral fascia, just cranially to the pelvic floor, at the anorectal junction at level S4; (3) levator ani complex, covered by fat and the parietal rectal fascia.

The arterial supply of the rectum is supported by the superior rectal (haemorrhoidal) artery, representing the inferior mesenteric artery after spring-off of the left colic and sigmoid arteries. The inferior haemorrhoidal arteries from the internal iliac and the middle rectal artery also contribute blood to the rectum. Venous return follows the arteries. 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.

The nerve supply to the pelvic organs, i.e., the rectum, vagina, uterus, vestibular bulbs, clitoris, bladder, urethra, penis, prostate and pelvic floor, are closely related to the rectum. From the superior hypogastric plexus (at level L4-S1, at the level of the promontory) within the aorta bifurcation, the two sympathetic hypogastric nerves 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. 1.1). The levator ani nerve, which is responsible for the innervation of the levator ani muscle, also arises from S3–4 and runs over the surface of the pelvic floor muscles, only covered by the parietal fascia [14] (Fig. 1.2).

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 [15]. 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 sphincters keep the anal canal closed in a resting

state. In addition to the resting anal pressures, the mesenteric 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 [16].

1.3 Pathophysiology

The majority of rectal cancers develop from benign preneoplastic 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), 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 [17, 18]. Familial adenomatous polyposis (FAP) and its attenuated variant (AFAP) represents 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 an 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 nonpolyposis colorectal cancer, HNPCC (Lynch syndrome). It has been observed that MSI is most common in (right-sided) colon cancer and rare in rectal carcinoma [19]. Nevertheless, compared with colon cancer, the number of mutations detected is significantly higher in rectal cancer [20]. Furthermore, cyclooxygenase-2 (COX2) is overexpressed in 90% of rectal tumours but in only 20% of colonic tumours [21]. 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 reorganisation of epithelial cells to make invasion and metastasis possible [22]. 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 [23]. 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 [24]. 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 [25]. 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 metastasise 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 pri-

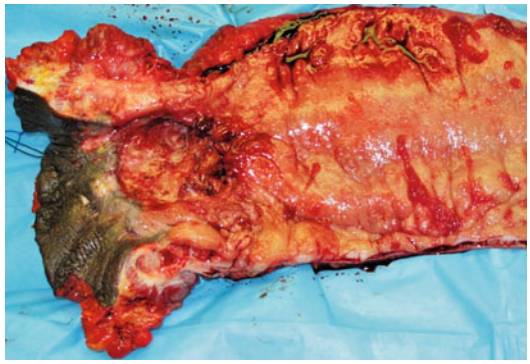

Fig. 1.3 Ulcerative rectal carcinoma. Resection specimen after abdominoperineal resection for ulcerative rectal carcinoma located at the anal verge

mary 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) [26, 27].

1.4 Presentation

Next to polypoidal disease, a rectal carcinoma can appear as an atypical ulcer, with rolled edges and a necrotic base (Fig. 1.3). 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 [27].

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) is used for staging and evaluating locoregional disease and predicting if negative surgical margins can be achieved, which is the case in approximately 75% [28]. 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 optimise oncologic and functional results.

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What Is the Ongoing Recommendation in the Management of Rectal Cancer?

2

Vincenzo Valentini, Hans-Joachim Schmoll, and Cornelis J.H. van de Velde

Contents

During the past 20 years, we have seen major changes in the way patients with rectal cancer are investigated and treated. The key components are the improvements in preoperative staging, in surgical technique and histopathological assessment of the resected specimen, and in combining multimodality treatments to ameliorate the long-term outcome.

The concept of "mesorectal excision," where meticulous dissection of the anatomical plane surrounding the mesorectal fat, is of crucial importance and has been reported to result in significantly lower rates of local recurrence in specialist centers, population-based audit, and within the framework of randomized controlled trials. By far, surgery remains the most important treatment of rectal cancer; nevertheless, the management of this disease has evolved to become multidisciplinary.

Conclusive studies established the ability of MRI to demonstrate the relationship of the macroscopic tumor to the surrounding well-defined anatomical plane of surgical excision. This development is closely linked with the ability of relatively simple histopathological techniques to assess and measure the distance of microscopic tumor to the circumferential resection margin (CRM) of the resected rectal cancer specimen, providing the choice of optimal surgical planes. MRI showed a great reliability in predicting mesorectal fascia (MRF) involvement, and more properly it was recently proposed to report it as MRF +/–.

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V. Valentini et al. (eds.), *Multidisciplinary Management of Rectal Cancer*,
DOI 10.1007/978-3-642-25005-7_2, © Springer-Verlag Berlin Heidelberg 2012

In the last decade, several European phase III trials evaluating the role of radiotherapy and chemotherapy in rectal cancer have been published. From these trials, the efficacy of both short-course preoperative radiotherapy and preoperative concurrent chemoradiotherapy was determined [1–7]. Anyway, although the findings of large randomized trials have addressed important questions, there remain patient care issues that cannot be addressed by subgroup analyses of existing trials and large areas of controversies are still in place.

To support physicians to deliver more tailored choices—as the oncology profession moves into the era of individualized medicine—some European Consensus guidelines were proposed under the collaboration of the major Oncology Society ESTRO (European SocieTy of Radiotherapy and Oncology), ESSO (European Society of Surgical Oncology), and ESMO (European Society of Medical Oncology) [8, 9].

Two papers summarized these efforts: The EURECA project elaborated the Consensus document using the Delphi method [8]. A group of experts delegated by the three Oncology Societies voted sentence by sentence for three times a web-based document customized for the consensus process. A meeting was openly held to debate by attendees the more controversial sentences. The total number of voted sentences was 207. Of the 207, 86% achieved large consensus, 13% achieved moderate consensus, and only 3 (1%) resulted in minimum consensus. The document addresses a wide range of topics relating to the management of rectal cancer and, of equal importance, identifies areas where future research is a priority.

A second document was addressed by ESMO inside their program of organ oriented guidelines. A group of experts invited by ESMO debated in a 2-day meeting the key issues about the management of rectal and colon cancer and a document circulated between them till a final approval [9].

To get more information about the different strategies regarding staging and treatment of rectal cancer, we recommend the reading of these two documents as well as the different answers to the main questions, which arose in a multidisciplinary group in the daily management of rectal cancer patients, reported in this book (Figs. 2.1–2.10 and Tables 2.1–2.3). In this chapter, we tried to

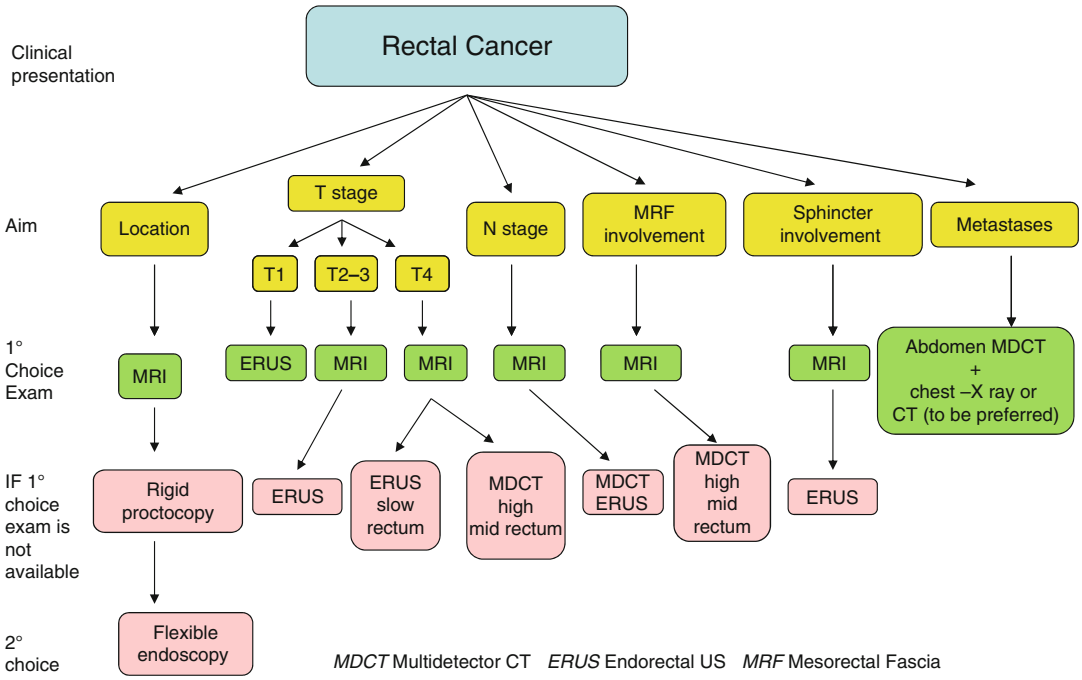

Fig. 2.1 Imaging work-up

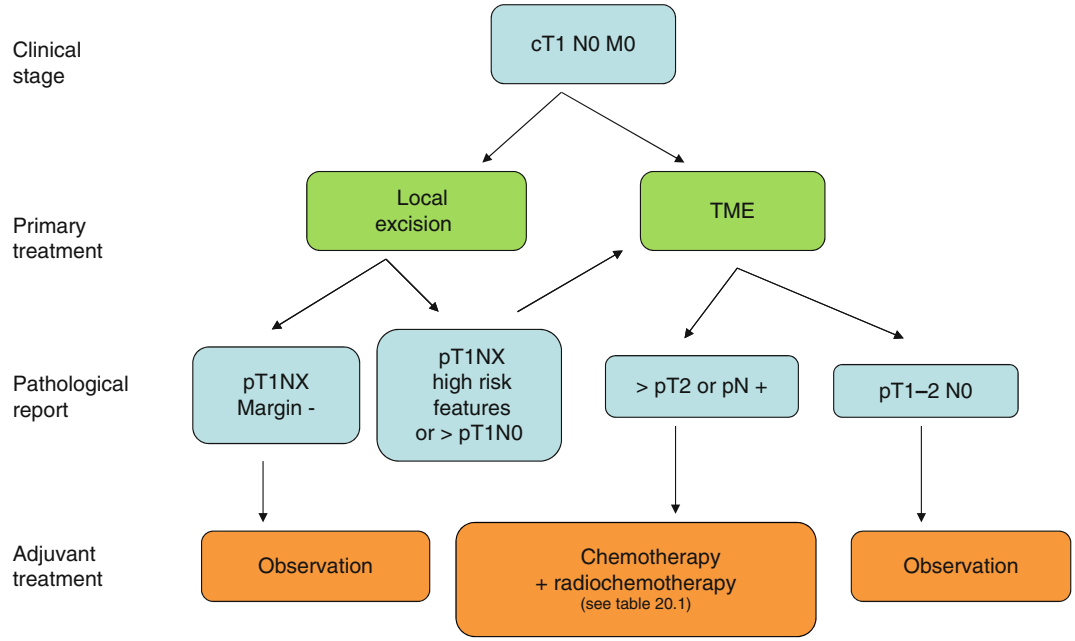

Fig. 2.2 Treatment strategy: cT1 N0 M0

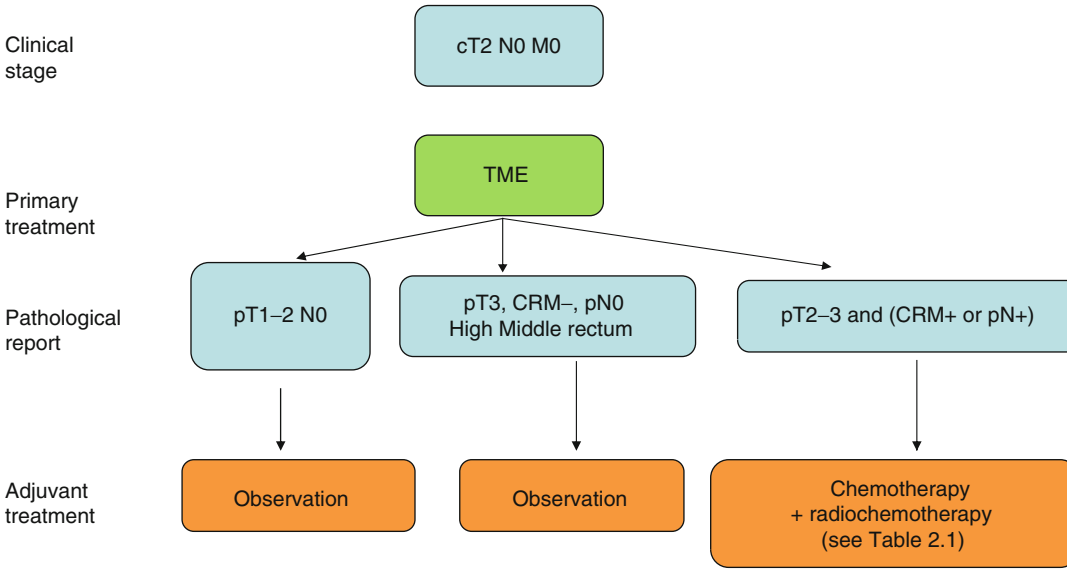

Fig. 2.3 Treatment strategy: cT2 N0 M0

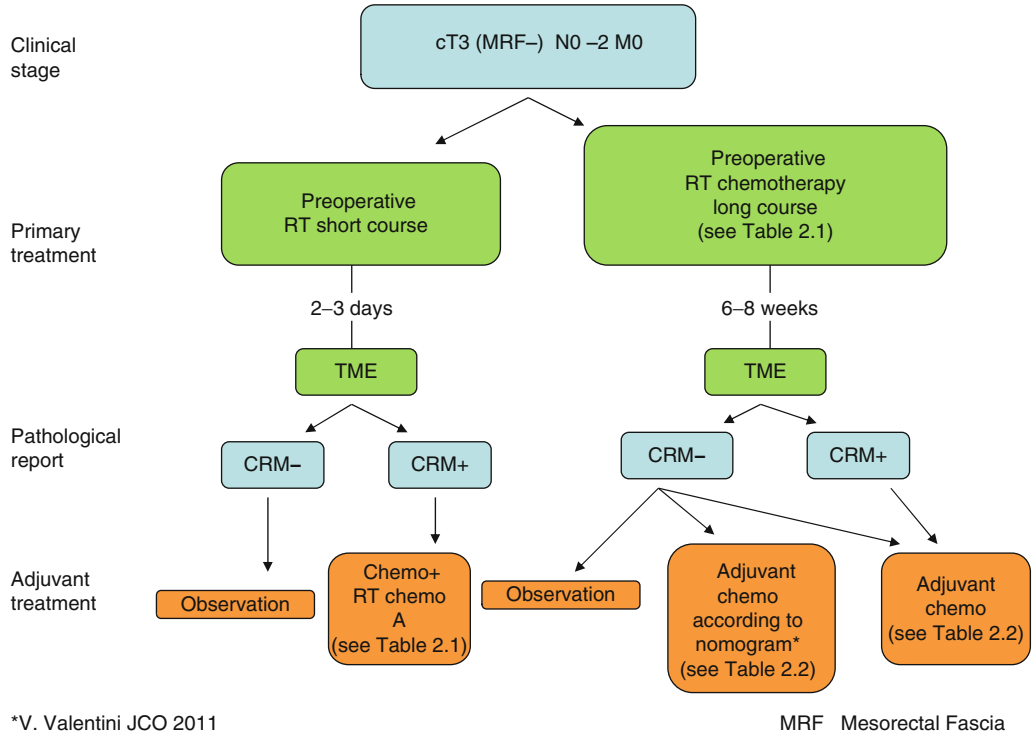

Fig. 2.4 Treatment modalities: cT3 (MRF–) N0–2 M0

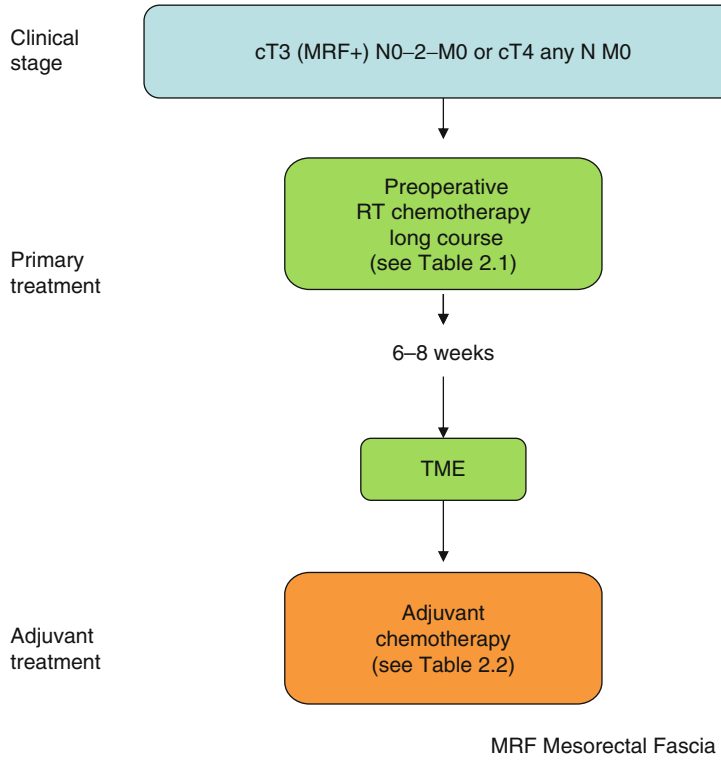

Fig. 2.5 Treatment modalities: cT3 (MRF+) N0–2–M0 or cT4 any N M0

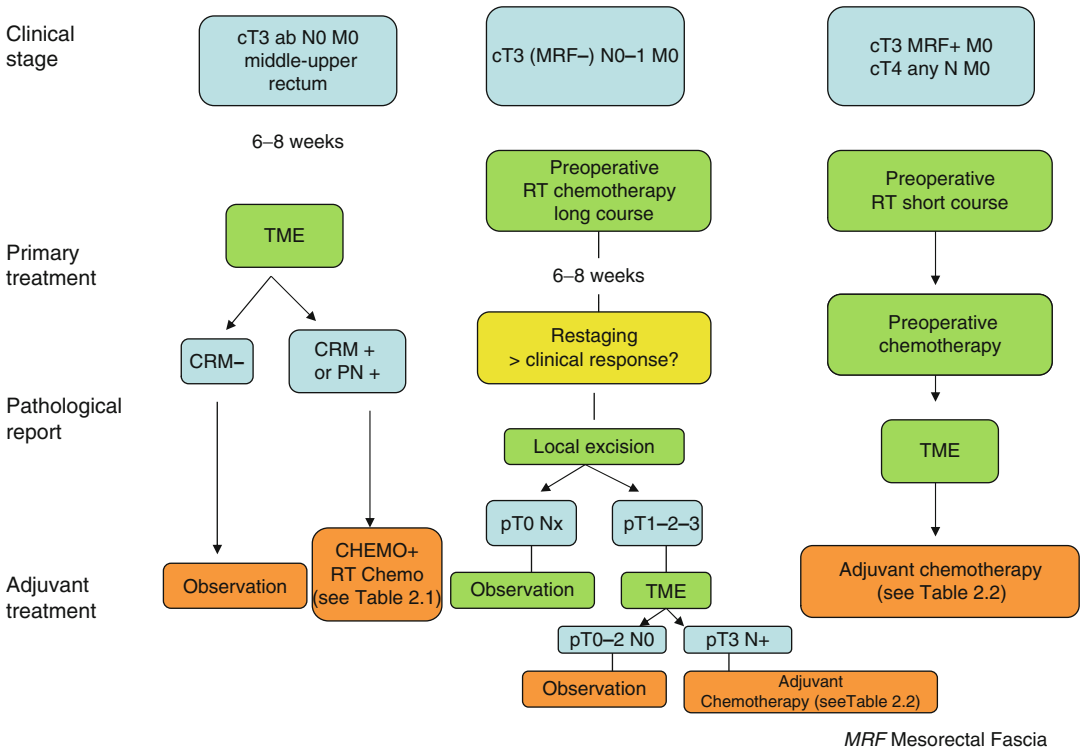

Fig. 2.6 Treatment modalities under clinical evaluation

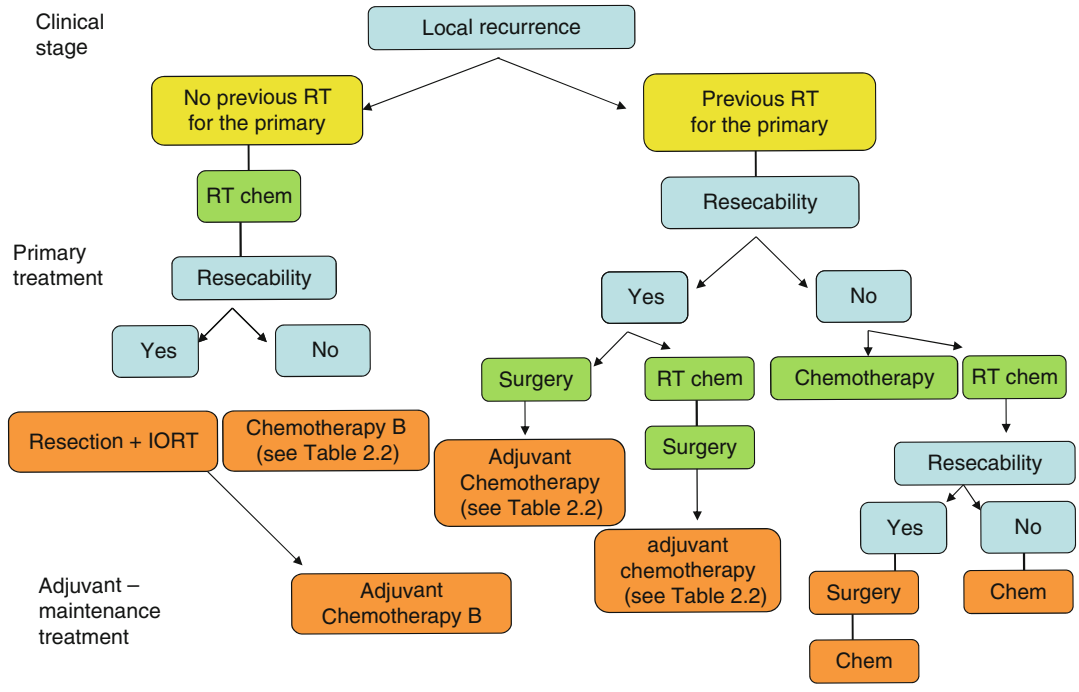

Fig. 2.7 Treatment modalities local recurrence, cM0

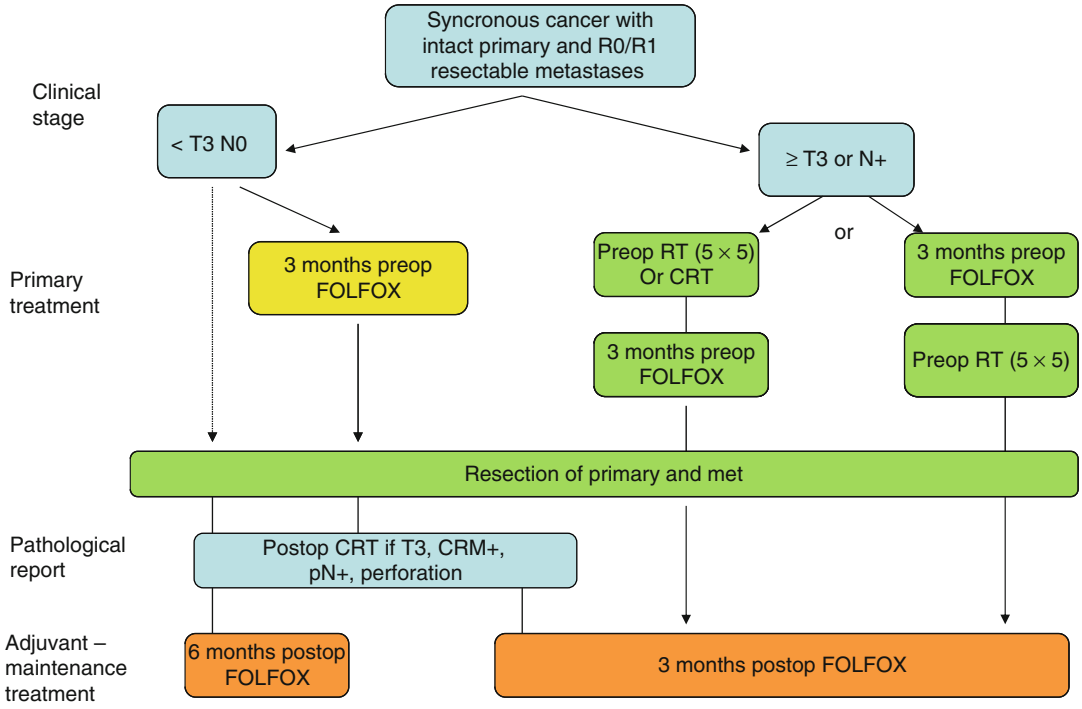

Fig. 2.8 Treatment modalities, cM1, resectable synchronous metastases

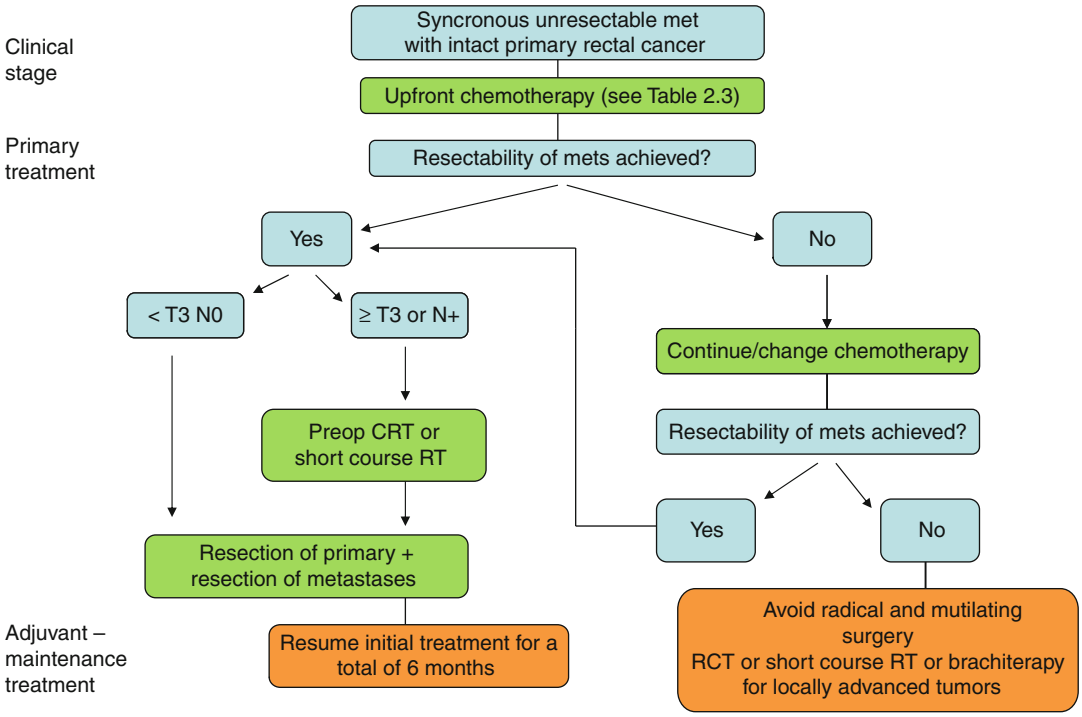

Fig. 2.9 Treatment modalities, cM1, unresectable synchronous metastases

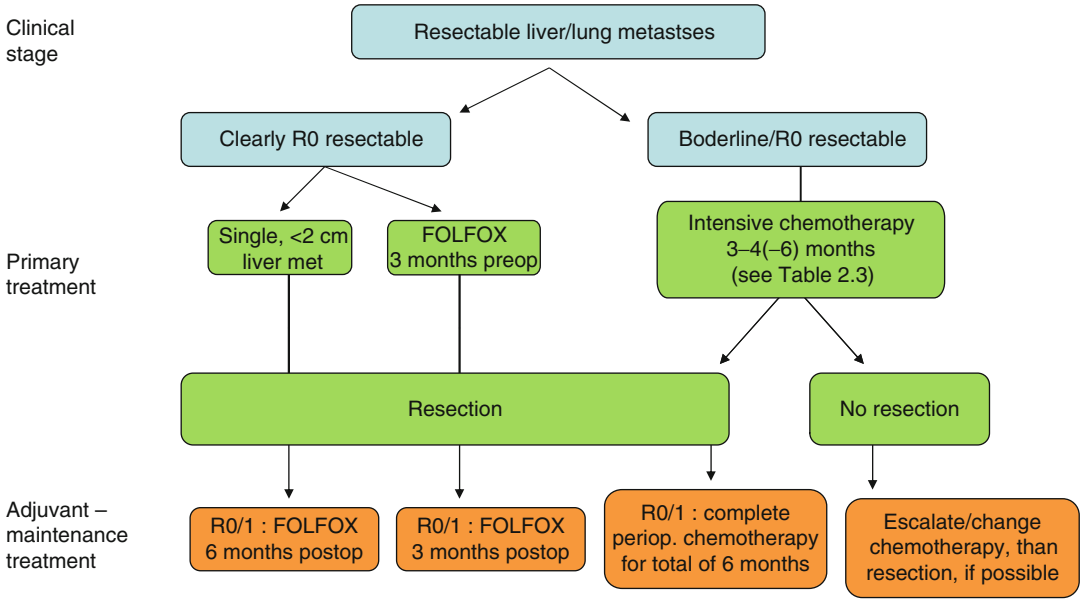

Fig. 2.10 Treatment modalities CM1, non-synchronous

Table 2.1 Chemotherapy-options and doses for concomitant chemotherapy during radiation

Regimen	References
5FU 325–350 mg/m² + LV 20 mg/m² iv bolus, d1–5, week 1 and 5	[3, 10]
5FU 400 mg/m² + LV 100 mg iv bolus, d1, 2, 11, 12, 21, 22	[7]
5FU 225 mg/m² iv continuous infusion, 5 days per week, together with radiotherapy	[11, 12]
5FU 1,000 mg/m² iv continuous infusion, d1–5, week 1 and 5	[1]
Capecitabine 800–825 mg/m² bid po continuously, 5–7 days per week, together with radiotherapy	[11, 13, 14]
UFT (300–350 mg/m²/day) and LV (22.5–90 mg/day) po continuously, 5–7 days per week, together with radiotherapy	[15–18]
5FU 250 mg/m² iv continuous infusion on days 1–14 and 22–35 and oxaliplatin 50 mg/m² iv d1, 8, 22, 29, only preoperatively	[19]

Table 2.2 Standard adjuvant chemotherapy regimens in rectal cancer (number of cycles without chemoradiation are given in brackets)

Regimen	Cycles	References
5FU 350–370 mg/m², +LV 20–25 mg/m² iv bolus, d1–5, q 4 weeks	4 (–6)	[3, 20]
5FU 500 mg/m² iv, continuous infusion, d1–5, q 4 weeks	4	[1]
5FU 500 mg/m² + LV 100 mg, iv Bolus, d1, 2, q 2 weeks	8	[7]
Capecitabine 2,000–2,500 mg/m², po, d1–14, q 3 weeks	5–6 (–8)	[13, 21]

Table 2.3 Choice of first line treatment

2.3 a

Group	Clinical presentation	Treatment aim	Treatment intensity
1	liver and/or lung metastases only		
	which • might become resectable after induction chemotherapy • ±limited/localized metastases to other sites, e.g. locoregional lymphnodes • physically able to undergo major surgery (biological age, heart/lung condition)	• maximum tumour shrinkage	upfront most active combination regimen

Group	KRAS wildtype	Recommend[a]	KRAS mutant	Recommend[a]
1	• FOLFIRI+Cet • FOLFOX+Pan/Cet • FOLFOX/XELOX+Bev • FOLFOXIRI • FOLFIRI/XELIRI+Bev • FOLFOX/XELOX • FOLFIRI/XELIRI • IRIS	+++ +++ ++(+) ++(+)[b] ++(+) [c] + + +	• FOLFOX/XELOX+Bev • FOLFOXIRI • FOLFIRI/XELIRI+Bev • FOLFOX/XELOX • FOLFIRI/XELIRI • IRIS	+++ ++(+) [b] ++(+) [c] + + +

2.3 b

Group	Clinical presentation	Treatment aim	Treatment intensity
2	multiple metastases/sites, with		
	• rapid progression and/or • tumour-related symptoms/risk of rapid deterioration • co-morbidity allows intensive treatment	• clinically relevant tumour shrinkage as soon as possible • at least achieve control of progressive disease	upfront active combination: at least doublet

Group	KRAS wildtype	Recommend[a]	KRAS mutant	Recommend[a]
2	• FOLFIRI+Cet • FOLFOX+Pan • FOLFOX/XELOX+Bev • FOLFIRI/XELIRI+Bev • FOLFOXIRI • FOLFOX+Cet • FOLFOX/XELOX • FOLFIRI/XELIRI • IRIS	+++ +++ +++ ++(+)[c] +(+) [b] +(+) + + +	• FOLFOX/XELOX+Bev • FOLFIRI/XELIRI+Bev • FOLFOX/XELOX • FOLFIRI/XELIRI • FOLFOXIRI • IRIS	+++ ++(+)[c] ++ ++ ++[b] +

2.3 c

Group	Clinical presentation	Treatment aim	Treatment intensity
3	multiple metastases/sites, with		
	• never option for resection • and/or no major symptoms or risk of rapid deterioration • and/or severe comorbidity (excluding from later surgery and/or intensive systemic treatment, as for groups 1+2)	• abrogation of further progression • tumour shrinkage less relevant • low toxicity most relevant	treatment selection according to disease characteristics and patients preference re toxicity and efficacy: • "watchful waiting" • sequential approach: start with – single agent, or – doublet with low toxicity • exceptional triplets

Group	KRAS wildtype	Recommend[a]	KRAS mutant	Recommend[a]
3	• FUFOL/Cape (mono) • FUFOL/Cape+Bev • XELOX/FOLFOX • FOLFIRI/XELIRI • IRIS • Cet/Pan (mono) • watchful waiting triplets (+/-Bev or Cet/Pan)	+++ +++ ++ ++ + (+) + selected pts[d] + option for spec. situations[e]	• FUFOL/Cape (mono) • FUFOL/Cape+Bev • XELOX/FOLFOX • FOLFIRI/XELIRI • IRIS • watchful waiting • triplets (+/-Bev)	+++ +++ ++ ++ + + selected pts.[d] + option for spec. situations [e]

[a]Rec: consented recommendation, however decision might be modified based on individual objective and subjective parameters
[b]FOLFOXIRI: only 2 (small) phase III trials with contradictory results
[c]no randomized data for FOL(XEL)IRI + Bev
[d]option in case of low tumor burden, asymptomatic, indolent disease: close control until definitive progression (not until symptoms!)
[e]Patients who are group 3 but deserve (and tolerate) more intensive treatment due to specific reasons

summarize by charts the contents of those two documents, which largely represent the view of the experts of the three major European Oncology Societies (ESTRO, ESMO, and ESSO), to facilitate the understanding of the approach to management of rectal cancer.

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