



Position Paper

EURECCA colorectal: Multidisciplinary management: European consensus conference colon & rectum [☆]



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Abstract Background: Care for patients with colon and rectal cancer has improved in the last 20 years; however considerable variation still exists in cancer management and outcome between European countries.

Large variation is also apparent between national guidelines and patterns of cancer care in Europe. Therefore, EURECCA, which is the acronym of European Registration of Cancer Care, is aiming at defining core treatment strategies and developing a European audit structure in order to improve the quality of care for all patients with colon and rectal cancer. In December 2012, the first multidisciplinary consensus conference about cancer of the colon and rectum was held. The expert panel consisted of representatives of European scientific organisations involved in cancer care of patients with colon and rectal cancer and representatives of national colorectal registries.

Methods: The expert panel had delegates of the European Society of Surgical Oncology (ESSO), European Society for Radiotherapy & Oncology (ESTRO), European Society of Pathology (ESP), European Society for Medical Oncology (ESMO), European Society of Radiology (ESR), European Society of Coloproctology (ESCP), European CanCer Organisation (ECCO), European Oncology Nursing Society (EONS) and the European Colorectal Cancer Patient Organisation (EuropaColon), as well as delegates from national registries or audits. Consensus was achieved using the Delphi method. For the Delphi process, multidisciplinary experts were invited to comment and vote three web-based online voting rounds and to lecture on the subjects during the meeting (13th–15th December 2012). The sentences in the consensus document were available during the meeting and a televoting round during the conference by all participants was performed. This manuscript covers all sentences of the consensus document with the result of the voting. The consensus document represents sections on diagnostics, pathology, surgery, medical oncology, radiotherapy, and follow-up where applicable for treatment of colon cancer, rectal cancer and metastatic colorectal disease separately. Moreover, evidence based algorithms for diagnostics and treatment were composed which were also submitted to the Delphi process.

Results: The total number of the voted sentences was 465. All chapters were voted on by at least 75% of the experts. Of the 465 sentences, 84% achieved large consensus, 6% achieved moderate consensus, and 7% resulted in minimum consensus. Only 3% was disagreed by more than 50% of the members.

Conclusions: Multidisciplinary consensus on key diagnostic and treatment issues for colon and rectal cancer management using the Delphi method was successful. This consensus document embodies the expertise of professionals from all disciplines involved in the care for patients with colon and rectal cancer. Diagnostic and treatment algorithms were developed to implement the current evidence and to define core treatment guidance for multidisciplinary team management of colon and rectal cancer throughout Europe.

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1. Introduction

This consensus document is the result of the first multidisciplinary consensus conference on colon and rectal cancer care held in December 2012 in Perugia, Italy. It was designed to provide up to date, multidisciplinary support to multidisciplinary teams (MDTs) throughout Europe for decision making for patients having colon or rectal cancer. For this reason we developed diagnostic and treatment algorithms, which can be found online. <http://dx.doi.org/10.1016/j.ejca.2013.06.048>. It is important to acknowledge that this consensus document is based on an expert review of the available literature, along with the evidence from large observational databases. In case of no or poor quality evidence available, recommendations are based on expert opinion and experience. Policies of national scientific societies have been accounted for. In addition, we have taken into account the policies of our national scientific Societies. This consensus document should support doctors attending MDT discussions in their decision making. However, the full responsibility of the final decisions of individual patients is left between the responsible physician and the patient.

Two previous editions of the consensus meeting, which were organised in 2004 and 2008, were on rectal cancer only [1,2]. The reason to encompass colon cancer in this recent edition is based on the following observation. The EURO-CARE data [3] revealed that the survival of colorectal cancer substantially increased over time in all European regions, however the increases were more pronounced for rectal than for colon cancer. In addition, large variation still exists between the European countries in cancer outcomes [3]. EURECCA is the acronym of European Registration of cancer care and EURECCA was founded by leading professionals in cancer care, to reduce variance and improve cancer care in Europe through registry, feedback and definition of core treatment strategies. It supports the development of a European audit structure in order to improve the quality of care for all patients with colon and rectal cancer. To undertake this, the definition of treatment standards in colon and rectal cancer care in Europe is necessary.

The mission statement is the publication that announces the present document and illustrates our missions [4]. On the topics discussed during the consensus meeting, the experts have been invited to write expert reviews, highlighting the recommendations and providing valuable background information about the results of this consensus document. These reviews will be published as appendices of the *European Journal of Cancer*; *European Journal of Surgical Oncology* *Virchows Archives*, *Radiotherapy & Oncology* and in *Annals of Oncology*.

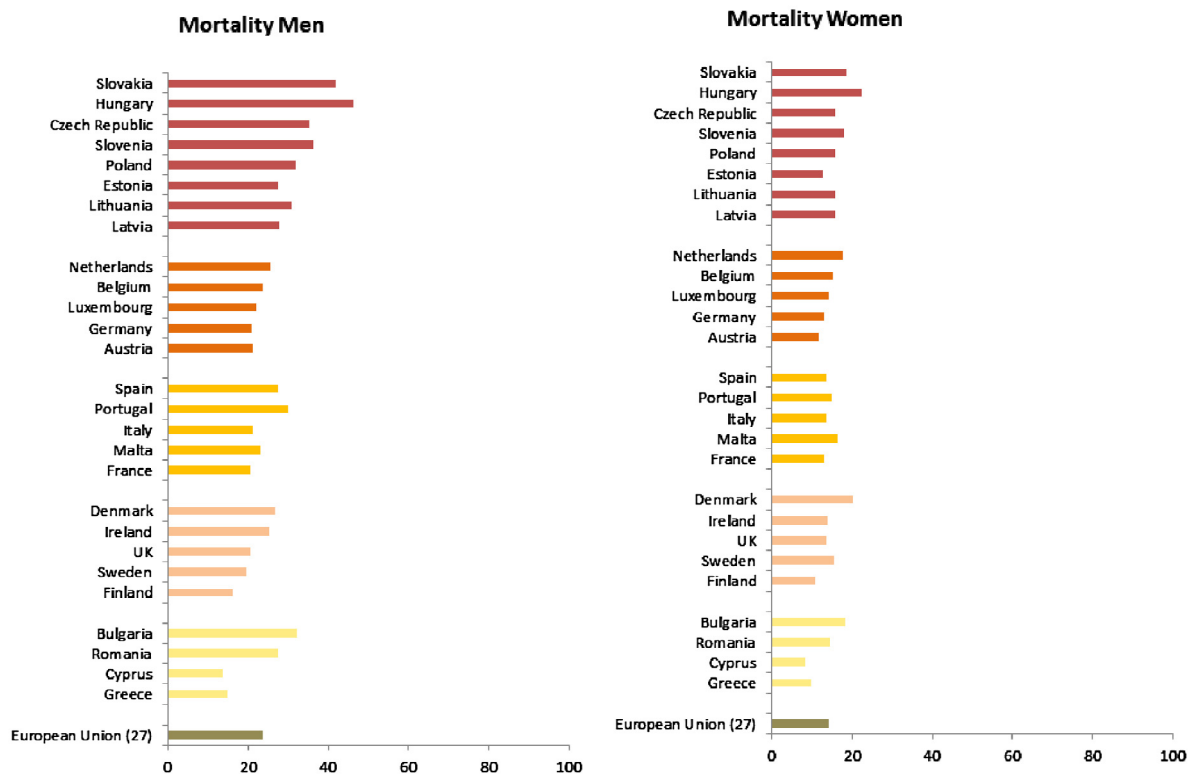
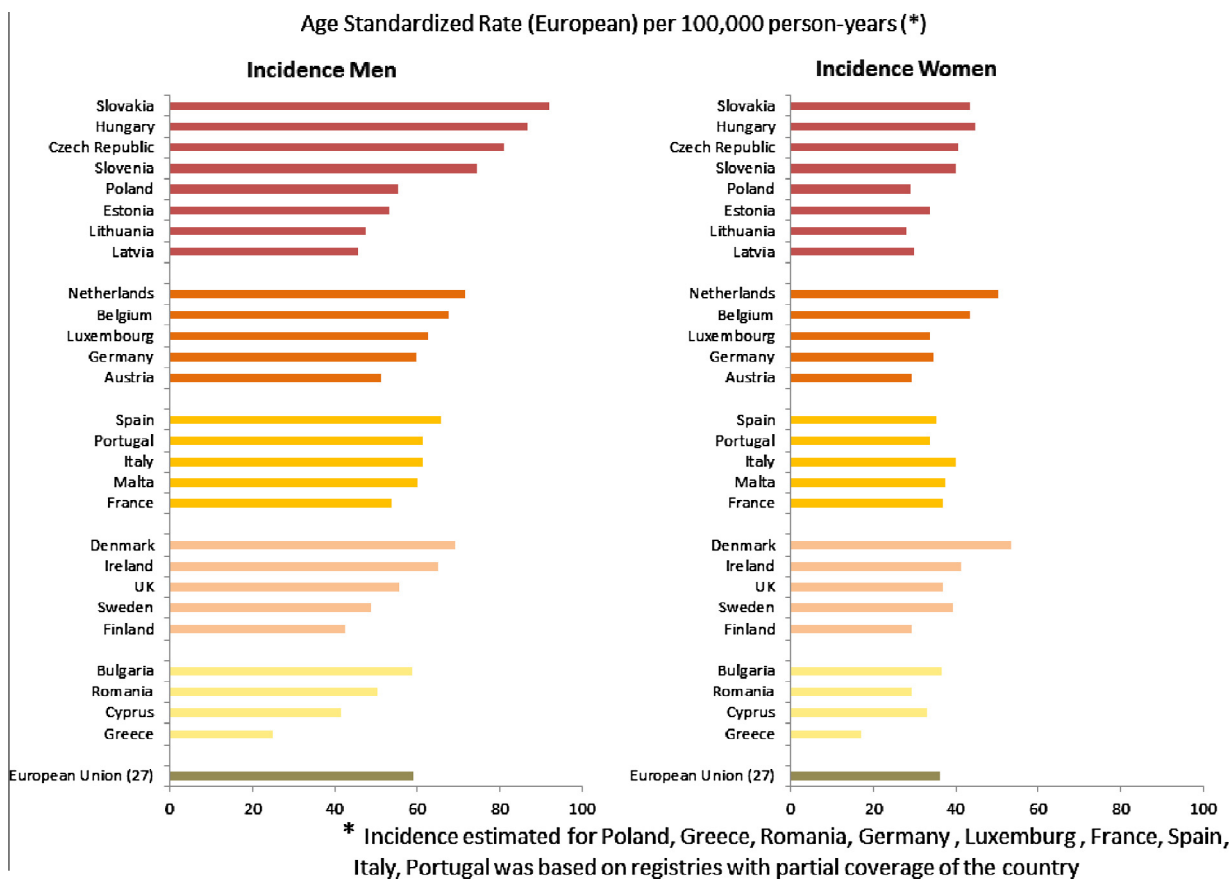
2. Epidemiology of colorectal cancer in Europe

Colorectal cancer (CRC) accounting for 13% of all cancers, is the third most frequent cancer in the 27

countries of the European Union, after breast and prostate, and after lung cancer it the second most frequent cause of death [5]. New cancer cases diagnosed in 2012 in Europe were estimated to be 342,137 (almost 1000 patients per day), comprising 191,620 males (56%) and 150,514 females (44%). The proportion of rectal cancer cases is variable depending on the cancer registry and classification of recto-sigmoid tumours, ranging from 27% to 58% [3]. The estimated number of deaths caused by CRC was 149,984, comprising 53% males and 47% females [5]. There is considerable variability among different EU countries as shown in Fig. 1. The highest incidence of CRC amongst males is observed in central European countries, such as Slovakia, Hungary or the Czech Republic in contrast to very low rates in Greece and Cyprus. Among females, Denmark and The Netherlands have the highest incidence of CRC followed by Hungary and Slovakia, Greece and Finland have a low incidence. The variability in mortality among countries is lower than variability in incidence, probably related to differences in stage of presentation and treatment between countries.

Using population based analysis of relative survival (i.e. corrected for the average mortality at any age and sex [3]), in the countries analysed in the EURO-CARE project, survival has markedly improved since the 1980s. From 1980 until 2000–2002, five-year survival for all patients increased from 51% to 60% in northern Europe; from 52% to 62% in western European registries and from 45% to 58% in southern European registries. Among females relative survival was 2% better than in males across all registries. In general, improvements in survival were lower among patients aged 75 or older. By stage at diagnosis, survival improved markedly among patients diagnosed in local or regional disease while almost no progress was observed among patients with metastatic cancer [3]. The major differences in survival observed among (and often also within) EU countries has a multifactorial origin. Problems in access to screening or endoscopic diagnosis might be one of the explanations, suggested by the higher percentage of advanced stages in some cancer registries, but also by differences in quality of cancer care [6–8]. An interesting observation made by the EURO-CARE analysis was that the more noticeable improvements in survival for rectal than for colon cancer patients during the 1990's, with the exception of Eastern European countries demonstrating equal five year survival rates for patients with colon and rectal cancer. See Fig. 1 for Estimated Colorectal Incidence and Mortality in Europe.

With the improvements in survival, the risk of developing a second malignant tumour has increased in relevance. Using data from all patients diagnosed with CRC stage I–III in the Netherlands from 1989 to 2008, a higher risk of detecting a second CRC has been observed among patients with tumours at all subsites [9]: 1.5% of patients appeared to develop a metachronous tumour with a median of 3 years after diagnosis of the



Source: European Cancer Observatory, 2012

Fig. 1. Incidence and mortality of colorectal cancer in Europe.

first tumour, mostly – and increasing over time – in the proximal colon. Alongside, the improvements in survival, the quality of life of long-term survivors is a matter of concern due to side-effects of CRC treatment and should be assessed and carefully considered in the treatment decision-making process [10,11].

Co-morbidity can change clinical decision-making, especially in older colorectal cancer patients and also has a major impact on the outcome [12]. This factor will become increasingly relevant in the coming years since the average age at diagnosis of colorectal cancer patients is around 70 years and the general ageing of most European societies. For example in the south of the Netherlands the prevalence of co-morbidity among colorectal cancer has increased from 1995 to 2010 from 47% to 62% and multi-morbidity from 20% to 37%. Older age and low socioeconomic level was associated with higher risk of co-morbidity [13]. This potential for worsening of the clinical condition of the colorectal cancer patients will increase the requirement identifying cancers at an early stage through screening, for subsequent multidisciplinary clinical decision-making and also careful organisation of care.

3. Modifiable risk factors for colorectal cancer

The data presented in Fig. 1, suggest that the risk for colorectal cancer can be modified, especially in males. The major debate on risk factors for CRC has always been focused on the role of dietary components with convincing evidence that increased consumption of red and processed meat, alcoholic drinks (especially among males), body and abdominal fatness all increase the risk for colorectal cancer, especially in taller people [14]. There is also convincing evidence that foods containing dietary fibre reduce the risk of CRC, that regular physical activity reduces the risk of colon cancer. Thus lifestyle recommendations for CRC prevention include increasing dietary fibre and reducing red and processed meat consumption and alcoholic drinks as well as regular physical exercise for colon cancer prevention.

Smoking has also been associated with an increased risk of CRC with long latency times [15]. Some drugs have been related to CRC risk such as statins, although no consistent evidence was found in a meta-analysis [16]. Oral contraceptive was found protective regarding CRC risk [17]. Aspirin might also be a chemo-preventive agent, especially among patients with Lynch syndrome, albeit without consensus about the dose and the long-term balance between risk and benefit and thus demanding further research [18].

4. Screening

CRC screening has been shown to be effective in reducing mortality of the population aged 55–74 years

and possibly incidence as well. A Cochrane review showed a relative reduction of 16% in the risk of CRC death using faecal occult blood tests (FOBT) every 2 years [19]. Immunochemical FOBT have now become the choice of population based screening programmes in Europe according to the recent European guidelines for quality assurance for CRC screening [20]. Over the last few years, convincing evidence from randomised trials has been published showing the efficacy of flexible sigmoidoscopy in reducing the incidence and mortality from CRC [21,22]. CRC population based screening is recommended at EU level and it has been progressively implemented in more than 12 countries, mostly using the immunochemical test [20], although participation levels in some of these screening programmes is still matter of concern. The quality of all components, the access to endoscopic services and the evaluation of its expected impact should be considered before planning a screening programme. From this perspective, the recently published guidelines for quality assurance of this screening will offer a framework for assessing the necessary requirements for a high quality programme, which will minimise the risks of adverse effects and maximise the effectiveness of this screening [19]. Taking into account the impact of CRC on the EU population, with the associated use of expensive adjuvant and palliative therapies, organising mass CRC screening is a priority which will contribute to reduce incidence, improve prognosis and decrease treatment related morbidity because of stage migration. A population-based cancer registry is a necessity to monitor investments and quality measure, either by implementing primary prevention, population based screening or by improved diagnosis and clinical care for CRC patients [23].

5. Methodology consensus on colon and rectal cancer care

This consensus document is divided into several sections about colonic cancer, rectal cancer and metastatic colorectal cancer describing evidence based sentences and algorithms on diagnostics, pathology, surgery, medical oncology, radiotherapy and follow-up. The procedure to form the body of this text was a consensus process using the Delphi method. In order to undertake the Delphi Method, a multidisciplinary expert panel was formed, consisting of delegates of the European Society of Surgical Oncology (ESSO), European Society for Radiotherapy & Oncology (ESTRO), European Society of Pathology (ESP), European Society for Medical Oncology (ESMO), European Society of Radiology (ESR), European Society of Coloproctology (ESCP), European Cancer Organisation (ECCO), European Oncology Nursing Society (EONS) and the European Colorectal Cancer Patient Organisation (EuropaColon), as well as delegates from national registries or audits on colon and rectal cancer care. A multidisciplinary panel

was composed of prominent researchers and leaders of epidemiology, surgery, pathology, radiology, radiation oncology, medical oncology, oncology nursing and representatives of the patient organisation, supported by a scientific team, local organisers and congress bureau. An online web programme was available for the executive committee and the experts to express agreement or disagreement and to comment on the sentences created. Experts commented and voted on two web-based online voting rounds before the meeting (between 4th and 25th October and between the 20th November and 3rd December 2012) as well as one online round after the meeting (4th–20th March 2013) and were invited to lecture on the subjects during the meeting (13th–15th December 2012). The sentences of the consensus document were available to the experts during the online rounds and voting at the meeting by all participants. More information is available at the EURECCA website www.canceraudit.eu. The Executive Committee scored percentage consensus in two categories depending on the presence of disagreement: (1) If no members disagreed and the percentage of agreement was greater than 80%, ‘large consensus’ was achieved, if the percentage of agreement was 71–80% ‘moderate consensus’ was achieved and if the percentage of agreement was 51–70%, ‘minimum consensus’ was achieved (2). If one member or more members disagreed and the percentage of agreement was greater than 95%, ‘large consensus’ was achieved, if the percentage of agreement was 75–94% ‘moderate consensus’ was achieved, and if the percentage of agreement was 51–74% ‘minimum consensus’ was achieved. If less than 50% agreement was reached, this is indicated as no consensus in the text. Most experts commented during the voting process on sentences with less than 50% consensus that either this topic is not studied enough to make the stated conclusions or that the phrasing was not clear, or for example that two statements were together in one sentence, and one of those was not agreed.

6. Results

The total number of the voted sentences was 465. All chapters were voted on by at least 75% of the experts. Of the 465 sentences, 84% achieved large consensus, 6% achieved moderate consensus and 7% resulted in minimum consensus. Only 3% was disagreed by more than 50% of the members. Eleven algorithms on diagnostic

and treatment modalities were created and these were also voted on. An overview of the consensus is depicted in Table 1.

7. Consensus document

7.1. Hereditary colorectal cancer

About 3–5% of CRC are of hereditary origin. If there is a clinical suspicion of polyposis or Lynch Syndrome/ Hereditary non-polyposis colorectal cancer (HNPCC), the patient should be referred to a specialist in human genetics for genetic testing. Clinical suspicion is based on clinical criteria or on an abnormal molecular screen in the context of a suggestive personal or family history.

HNPCC is the most common hereditary CRC syndrome and is estimated to account for 3–5% of all CRC cases. HNPCC is caused by mutations in DNA mismatch repair (MMR) genes which are inherited in an autosomal dominant pattern and are associated with accelerated development of cancers. Lifetime risk for colorectal and endometrial cancers approaches 70–80% and 40–60%, respectively. At risk family members who undergo screening colonoscopy have a reduced risk of developing HNPCC-related CRC cancers and lower mortality [24]. Colonoscopies with polypectomies and endometrial biopsies with transvaginal ultrasonography, repeated frequently in HNPCC are recommended. With surveillance intervals of 1–2 years, members of families with HNPCC have a lower risk of developing CRC than with surveillance intervals of 2–3 years [25–27].

Familial adenomatous polyposis (FAP), caused by mutations in the adenomatous polyposis coli (APC) gene, is characterised by the development of multiple adenomas in the rectum and colon during the second decade of life. Individuals with FAP carry a 100% risk of CRC. Cancer prevention and maintaining a good quality of life are the main goals of management with regular and systematic follow-up and supportive care should be offered to all patients [28]. Important topics in hereditary CRC syndromes that are still open for discussion are the role of aspirin in prevention, optimal type and time of surveillance modalities, ideal patient tailored timing for surgery and extent of surgery. In FAP patients, prophylactic surgery to prevent CRC is advocated by the late teens or early twenties. Total proctocolectomy, either with or without anal mucosectomy,

Table 1

The achieved consensus of sentences of the consensus document per chapter (*n* in number and percentage %) of the last round.

	Colon cancer (<i>N</i>)	<i>n</i> /115 (%)	Rectal cancer (<i>n</i>)	<i>n</i> /258 (%)	CRC metastases (<i>n</i>)	<i>n</i> /92 (%)	Total (<i>n</i>)	<i>n</i> /465 (%)
‘Large consensus’	102	89	205	79	83	90	390	84
‘Moderate consensus’	5	4	18	7	5	5	28	6
‘Minimum consensus’	6	5	23	9	3	3	32	7
‘No consensus’	2	2	12–2 ^a	4	0	0	14	3

^a 2 sentences/votes discarded which were no treatment option in the algorithm.

with ileo-pouch anal anastomosis (IPAA) is recommended for FAP. Subtotal colectomy with ileorectal anastomosis (IRA), may be considered in highly selected FAP patients [29]. Desmoid tumours are rare non-metastasising fibromatoses that might occur in association with FAP. Desmoids have a prevalence of 10–26% in FAP and are usually a major source of morbidity and one of the most common causes of death in these patients. An interaction between female gender and early (<18 years) colectomy in patients developing desmoids has been published (HR 2.5) [30].

7.2. Colon cancer care

7.2.1. Diagnostics

The next sentences were voted on during the consensus process, if less than 80% of agreement was achieved this is indicated clearly at the end of each paragraph or in the legends of the tables or algorithms.

Physical examination, family history for colon or rectal cancer, polyps, other cancers and a CEA should be obtained if colon cancer is suspected [31,32]. Although a preoperative CEA lacks sensitivity, and for that reason CEA cannot be used for diagnosis, it can assist in staging and evaluation of prognosis [33]. It is recommended to obtain a colonoscopy as a first choice exam because it has the advantage over all other imaging modalities of biopsy, polypectomy and tattooing the colonic wall to facilitate perioperative localisation of small colon cancers or suspected malignant polyps (especially important for laparoscopy). Colonoscopy is recommended over sigmoidoscopy because of the advantage of also detecting proximal lesions, which makes sigmoidoscopy a lesser choice diagnostic tool. Histological confirmation is preferred although there are cases with a high suspicion of invasive growth based on the macroscopic features during endoscopy whose biopsies fail to show invasion of the submucosa. These patients are recommended to proceed to surgery.

In case of incomplete preoperative visualisation of the colon: intraoperative colonoscopy can be performed in selected cases if sufficient expertise is available. In case of incomplete preoperative visualisation of the colon: colonoscopy is recommended to be performed within 3 months after surgery. A computed tomography (CT) colonography (virtual colonoscopy) could be considered as second choice diagnostic test for patients with incomplete colonoscopy [34].

Conventional colonoscopy screening results in similar detection rate for advanced neoplasia as primary CT colonography screening, however colonoscopy with biopsy remains the first choice examination [35]. Sensitivity of colonoscopy for detection of colorectal cancer was 94.7%. Given a prevalence of CRC of 3.6%, sensitivity of CT colonography with bowel preparation has a range of 95.9–96.1% for detection of colorectal cancer.

When polyps of all sizes were included, studies were too heterogeneous in sensitivity (range, 45–97%) and specificity (range, 26–97%) to allow meaningful meta-analysis [36].

With moderate consensus, it was agreed that a barium enema is indicated as the third choice diagnostic test for patients (without obstruction) when colonoscopy is not possible or contraindicated and CT colonography is not available [34].

7.2.2. Staging colon cancer

Colon cancer is classified according to the AJCC TNM classification (5th–7th edition). TNM version should be stated in the pathology report. Staging before surgical treatment is focused on locoregional extent, synchronous lesions and on the presence of distant metastasis. For locoregional staging, a CT-abdomen is recommended as preoperative imaging. This will deliver information about tumour invasion of adjacent organs, presence of lymphadenopathy, presence of ascites, abundant peritoneal carcinomatosis or distant metastasis (liver). CT-abdomen is limited for defining T1-3 stage, N-stage or small liver metastasis and early appearances of peritoneal carcinomatosis. Colonoscopy cannot be used for staging colon cancer. Colonoscopy does not deliver information about T stage, nodal status, invasion of adjacent structures or distant metastasis and is known to be unreliable for estimating exact tumour location. Colon cancers are most accurately staged after surgical exploration of the abdomen and pathologic examination of the surgical specimen. There is insufficient evidence to support the routine use of fluor-18-deoxyglucose (FDG) positron emission tomography in combination with computed tomography (PET/CT) in preoperative staging of primary colorectal cancer [37].

No consensus was achieved on the following; after an abdominal CT, a CT colonography could be considered for better identification of colonic masses (diameter > 3 cm), completion of colonic evaluation in case of incomplete colonoscopy and segmental localisation of tumour [38].

7.2.3. T-stage colon cancer

It is recommended to perform an abdominal CT for patients with colon cancer, taking into account that the accuracy of an abdominal CT for TN-staging of colon cancer is only reasonable, accuracy for T-staging of 67%, and N staging of 69%. The real value of CT is its high accuracy to detect distant metastases (95%) [39–41].

7.2.4. N-stage colon cancer

Size is not a good predictor for malignancy and should not be used for defining whether lymph nodes are involved or not [42]. Multidetector CT cannot

accurately identify node status preoperatively in colon cancer [40].

7.2.5. M-stage

Contrast-enhanced CT of the abdomen is recommended to estimate the abdominal M-stage of all patients diagnosed with colon cancer [43]. CT-chest as routine work-up for colorectal cancer is recommended; although there is evidence that a chest X-ray may be used for routine work up [44,45]. Target ultrasound, magnetic resonance imaging (MRI) or PET-CT may be used as a second line diagnostic tool when CT is not clear in diagnosing liver metastases [46].

Please see Fig. 2 for Elective imaging workup for colon cancer.

7.3. Pathology report

Guidelines are important and there should be national or preferably international guidelines for the dissection and reporting of colon cancer. The Guidelines of the Royal College of Pathologists in the United Kingdom have gained widespread acceptance as the minimum standard for reporting this disease. These are available at <http://www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/G/G049-ColorectalDataset-Sep07.pdf>.

7.3.1. Pathological assessment

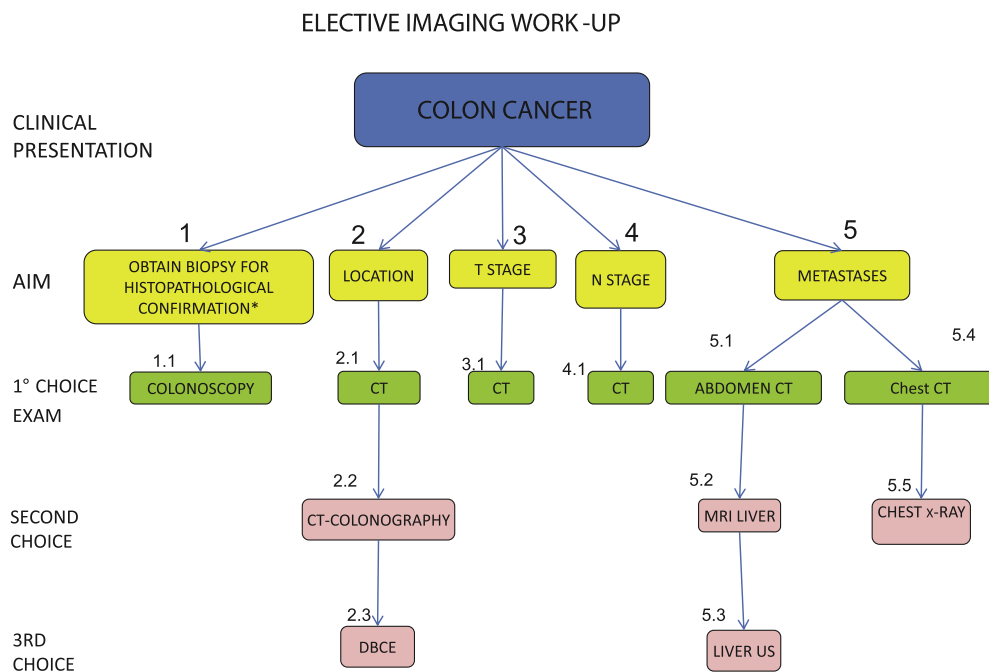
In the report of the pathologic examination of the surgical specimen should include the criteria listed in

Table 2. The macroscopic examination of the specimen is critical and of prognostic significance. Surgeons identify margins that can be involved by tumour spread at a variety of sites. The most well-known are the proximal and distal margins of a resection. An additional margin is the ‘mesocolic or mesenteric’ margin. In colon cancer, the radial surgical margin represents the incised non-peritonealised surface created by the surgeon to remove the bowel and the measurement should be from the tumour to the nearest surgically created radial margin. The serosal (peritoneal) surface does not constitute a surgical margin. The radial margin should be assessed in all colonic segments with non-peritonealised surfaces. In segments of the colon that are completely encased by peritoneum, such as the transverse colon, the mesenteric resection margin is the only relevant radial margin.

With minimal consensus, it was found that all forms of perforation, when identified at gross examination, should be considered as pT4. Perforation is very relevant with regards to prognosis, and should be reported in the operation report and the pathology report.

7.3.2. Complete resection

Reporting margins of excision is mandatory in all pathology reports, the R-classification should only be reported in conjunction with clinical information. Curative resection of colon carcinoma requires a high-quality surgical technique with adequate resection of involved bowel, corresponding mesocolon, and adjacent structures



* In obstructive colon cancer/emergency cases, biopsy could be omitted but CT abdomen is a minimal staging

Fig. 2. Elective imaging work up for colon cancer. All steps in the algorithm achieved large consensus.

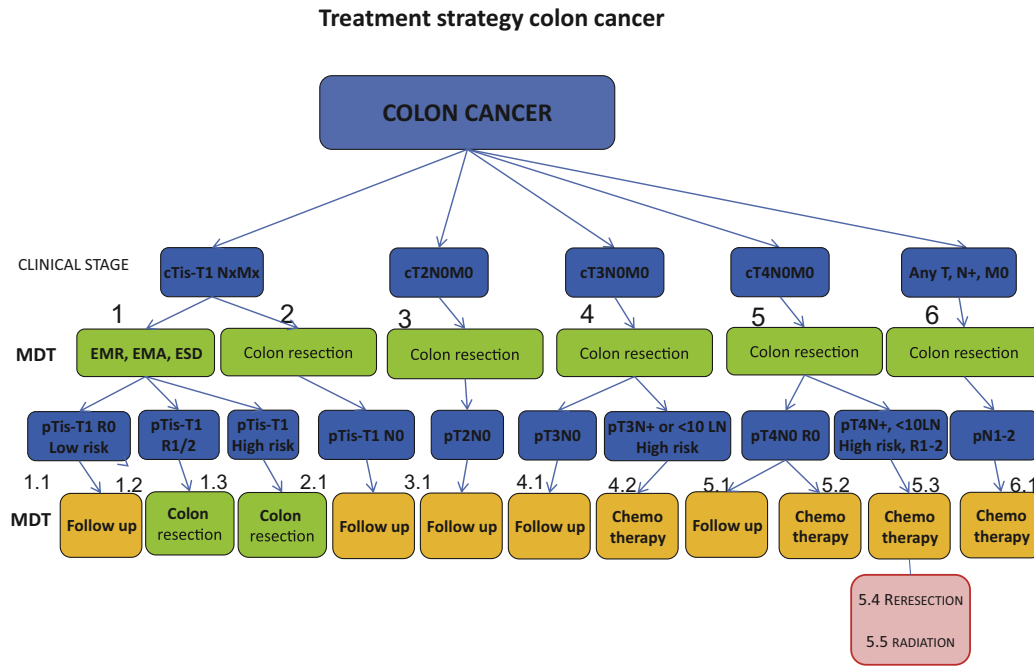


Fig. 3. Treatment algorithm of colon cancer. All proposed MDT treatment decisions, except for decision 5.4 and 5.5, achieved large consensus. No consensus was reached for decision 5.5 to suggest radiation therapy after residual disease in case of a T4 colon tumour with poor histopathological features. Minimum consensus was achieved on decision 5.4 to decide on salvage surgery or re-resection in this patient group.

Table 2

Minimal requirements of the pathological exam.

Grade of cancer
Depth of penetration and extension to adjacent structure(s) (T)
Number of regional lymph nodes evaluated
Number of positive regional lymph nodes (N)
Assessment of the presence of distant metastases to other organs, the peritoneum of an abdominal structure or in non-regional lymph nodes (M)
The status of the margins (proximal, distal and radial margin)
Lymphatic and vascular invasion
Perineural invasion
Extra-nodal tumour deposits

en-bloc in case of T4 stage. In other words, clear pathological margins with adequate lymphadenectomy to avoid locoregional recurrences and tumour seeding. The types of resection are generally defined accordingly: R0 resection (negative microscopic margins), R1 resection (positive microscopic margins without gross residual disease) and R2 resection (incomplete resection with gross residual disease). As a consequence of incomplete resection or aggressive tumour biology; sites of locoregional recurrence could be localised as disease occurring at the suture line or anastomosis (perianastomotic), in the mesentery or nodal basin (mesentery/nodal), retroperitoneum or peritoneum. Locoregional recurrence, constituting 10–20% of all recurrences, is less common than to distant sites [47]. Complete resection is critical for long term survival.

7.3.3. Lymph node yield and pathologic evaluation

Equally important are adequate lymph node yield and its pathologic evaluation. Describing the number of lymph nodes examined is recommended, although the literature is not uniform about the relationship between number of nodes and survival [48–50].

Several cut-off values for total number of examined lymph nodes have been described in literature. There is doubt about the causality and there are conflicting data on the relationship between lymph node yield and survival in the literature, non-alterable factors, such as patient age, sex, tumour stage, size of tumour and tumour location, may influence lymph node yield [51].

TNM and NICE guidelines recommend that at least 12 nodes should be harvested, even if after preoperative treatments it could be more difficult to find them. There is no conclusive evidence about the exact minimum number of examined nodes in the pathological specimen, but it is recommended to examine at least 12 lymph nodes for accurate pN-staging.

It is not recommended to perform sentinel node procedures for colorectal cancer, based on the data of two systematic reviews that show low sensitivity (70–76%) [52,53].

With moderate consensus, patients with less than 10 nodes evaluated should be considered as high risk and could be eligible for adjuvant treatment. This should be discussed in a multidisciplinary team.

8. General considerations in colon cancer

8.1. Laparoscopic versus open colon resection of colon cancer

Laparoscopic colon cancer surgery results in several benefits in the direct postoperative period in comparison to open colonic surgery. Laparoscopic surgery for colon cancer is safe and as effective as open surgery [54–56]. Given the prolonged learning curve associated with laparoscopic surgery, it is very important that the surgeon is adequately trained before practising this technique on his or her own [56]. In randomised trials no difference was found between laparoscopic and open surgery with regard to disease-free and overall survival [55–58].

Patients undergoing late (also called reactive) conversion from laparoscopic to open surgery did worse than patients undergoing primary open colectomy [59]. Laparoscopic resection has some disadvantages such as a long learning curve, longer duration of operation and higher operative costs [54,60,61].

Restrictions in laparoscopic technique are related to previous abdominal surgery (adhesions), and to locally advanced disease (relative contraindication).

With moderate consensus, it was agreed that patients early or pre-emptively converted from laparoscopic to open surgery did similarly to patients undergoing open surgery [54,60].

With minimal consensus, it was agreed that the indication for laparoscopic surgery is not stage dependent and that even combined laparoscopic segmental colon resection and liver metastasectomy can be safely performed in stage IV in expert centers.

8.2. Fast track

Fast Track or Enhanced Recovery After Surgery (ERAS) protocols are designed to attenuate the stress response to surgery and enable rapid recovery [62]. ERAS protocols reduce the length of hospital stay and morbidity rates after both open and laparoscopic colorectal surgery in the elective setting [63–65]. Consider the following perioperative treatment for patients requiring segmental colectomy for colon cancer; laparoscopic resection embedded in a Fast Track programme (data of the LAFA trial [65]), even though more studies are needed to draw consistent evidence.

8.3. Acute obstruction

The literature on stents is currently thought to be biased and well-designed randomised trials ceased patient accrual before reaching the sample sizes needed due to an unacceptably high perforation rate. Implica-

tions of stent perforation, silent and clinically, are not yet fully known, but perforation could compromise long term outcome.

In acute obstructive colon cancer, it is recommended that both the surgeon and the gastroenterologist are required to agree to proceed with emergency surgery or consider using a colonic stent. Patients presenting with acute large bowel obstruction and considering the use of a colonic stent or emergency surgery should be offered a CT of the chest, abdomen and pelvis to confirm the diagnosis of mechanical obstruction, and to determine whether the patient has metastatic disease or colonic perforation. It is not recommended to apply stents to relieve right-sided colonic obstruction or if there is clinical or radiological evidence of colonic perforation or peritonitis. It is discouraged to dilate the tumour before inserting a stent. In the palliative setting, there is no evidence to suggest a survival difference between stent placement and surgery (resection with anastomosis or stoma) in patients with acute obstruction.

With minimal consensus, it was agreed that a stent as a bridge to surgery to avoid a diverting stoma in patients with acute large bowel obstruction could be considered. According to the recent Cochrane analysis, the use of colonic stent in malignant colorectal obstruction appears to have no benefit over emergency surgery [66]. Moreover, clinical success rate was significantly higher in emergency surgery [66].

8.4. T1–T2 colon cancer

For the following sentences it should be taken into account that there are no randomised trial data available about endoscopic resection techniques for T1 colon cancer.

There are indications that surgical resection is not necessary after R0 polypectomy in pTis and pT1N0M0, grade 1 or 2 adenocarcinomas with no lymphovascular invasion and clear margins. Results are from a study of which after endoscopic resection all patients underwent curative oncological colon resection. The 5-year overall survival rate was 96.3% in T1 colon cancer after additional oncological surgical treatment following endoscopic resection. Lymph node metastases occurred in approximately 8.2% [67]. For early colon cancer (Tis–T1), advanced endoscopic techniques such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) or even endoscopic mucosal ablation (EMA) can be considered as alternatives to colectomy [68].

Colon cancer T2 NX should be treated with a colonic resection; the extent of the resection should be based on the vascular supply to the tumour with the accompanying lymphatic drainage (See Fig. 3).

8.5. *pT3 N0, M0 colon cancer*

If less than 10 lymph nodes are found in the specimen, we suggest searching for more lymph nodes in the resected specimen by the pathologist and/or the surgeon. It is recommended looking for unfavourable prognostic risk factors such as lymphovascular invasion. If patients with less than 10 lymph nodes, have more risk factors they might be at higher risk of recurrences and adjuvant chemotherapy should be discussed within the multidisciplinary team and with the patient [69,70]. Consider adjuvant chemotherapy for high risk stage II colon cancer patients [69].

With moderate consensus, it was agreed that high risk stage II colon cancer patients are defined as advanced tumour stage (pT4), <10 lymph nodes analysed, lymphatic and venous invasion, poor tumour grading, extended tumour length, tumour perforation [66]. (See Fig. 3).

8.6. *pT4, N0, M0 colon cancer*

Surgical removal of the tumour en bloc with the draining lymph node basin is the cornerstone of Stage II colon cancer. Patients with pT4N0M0 colon cancer are considered for adjuvant chemotherapy with at least single-agent FU [69,70]. Do not offer preoperative chemotherapy for patients with locally advanced colon cancer unless as part of a clinical trial [71].

With minimal consensus, it was found that adjuvant radiotherapy can be considered in specific cases with expected high rate of local failure such as tumours that invade adjacent organs, exhibit perforation or fistula or are subtotally resected if no re-resection is possible [69]. (See Fig. 3)

8.7. *Any pT, pN1-2, M0 colon cancer*

Upfront surgical removal of the tumour en bloc with the draining lymph node basin is the cornerstone of stage III colon cancer. Adjuvant chemotherapy for stage III colon cancer is recommended. The choice of adjuvant treatment should be made jointly by the patient and the clinician responsible for treatment. In a multidisciplinary board discussion, adjuvant chemotherapy for patients with stage III colon cancer should be considered in line with the patient's preferences [72]. If patients with stage III colon cancer are less fit consider adjuvant monotherapy. Do not offer preoperative chemotherapy alone for patients with locally advanced colon cancer unless as part of a clinical trial [71]. (See Fig. 3).

8.8. *Follow up colon cancer*

The site of recurrence does predict surgical success and outcome. Patients with mesenteric/nodal and/or more than two sites of local recurrence had a signifi-

cantly worse prognosis, whereas perianastomotic recurrences were most likely to be completely re-resected with better long-term survival [73]. The main aim of clinical follow-up is to improve survival. This is achieved in two ways, by detecting local or distant recurrences of primary disease and/or a metachronous tumour. Other goals of the follow-up are: management of the post treatment late complications and documenting the quality of the therapy outcome. Post-treatment surveillance colonoscopy of CRC shows (from an analysis of data of 2098 patients enrolled in 18 large adjuvant colon cancer randomised trials) that 80% of recurrences were found in the first 3 years after surgical resection of the primary tumour. In terms of follow-up, enormous variation is seen in frequency, duration, clinical setting and interventions. Use of post-treatment surveillance colonoscopy has not been shown to improve survival through the early detection of recurrence of the original CRC. Surveillance colonoscopy in colon cancer patients should be considered once in the first 2 years. Identifying and removing metachronous polyps are the main goal, since data show that patients with a history of CRC have an increased risk of developing second cancers, particularly in the first 2 years following resection [74]. Early detection of recurrent colorectal cancer following potentially curative resection of the primary tumour confers survival benefit, and in some cases, cures [73]. Post-treatment PET/CT scan is not recommended for routine use, neither for surveillance of patients with resected early-stage CRC nor to detect metastatic disease in the absence of other evidence of such disease.

With minimum consensus, it was found that patients diagnosed with higher risk for recurrences, like stage III disease, should be seen more frequently and should undergo more investigations than patients with the diagnosis of stage I disease, even if there is no evidence to substantiate this.

With moderate consensus, it was agreed that surveillance colonoscopy in colon cancer patients should be considered once in the first 2 years and that identifying and removing metachronous polyps are the main goal, since data show that patients with a history of CRC have an increased risk of developing second cancers, particularly in first 2 years following resection.

9. Rectum

The next sentences were voted on during the consensus process, if less than 80% of agreement was achieved this is indicated clearly in the text or in the legends of table or algorithms.

9.1. *Diagnostics in rectal cancer*

Physical examination, family history of CRC, polyps and other cancers, and CEA should be obtained, if rec-

tal cancer is suspected [31,33]. When at digital examination or at rectoscopy there is high suspicion of rectal cancer a histological confirmation is required. Full colonoscopy has to be performed either at diagnosis preoperatively or postoperatively in case of obstructing tumours or for other reasons.

9.2. Staging rectal cancer

Accurate diagnosis and staging of rectal carcinoma are essential for deciding on treatment strategies in the multidisciplinary team. Local tumour extension, location with respect to the sphincter and the peritoneal reflection, N-stage, potential circumferential resection margins (CRM)/mesorectal fascia (MRF) involvement, and extra-mural or venous invasion need to be discussed. See Fig. 4 for the decision algorithm of staging rectal cancer.

9.3. T Stage

9.3.1. cT1 versus cT2 rectal cancer

Endorectal ultrasound (EUS) is considered the most accurate imaging modality for the assessment of tumour penetration into the rectal wall [75], even if, at times, it is difficult to determine the depth of invasion in large villous lesions. For assessing the depth of tumour growth in the rectal wall EUS has an overall accuracy between 69% and 97% [75]. The highest accuracy is obtained in expert

EUS centres. When EUS is performed in general clinical setting the accuracy significantly drops [76–78]. EUS is not recommended for high seated or obstructive T1–T2 rectal cancer tumours [78]. Endorectal MRI for rectal cancer is not widely performed. Reasons for this are costs, technically demanding for the MR unit and not comfortable for patients. Endorectal MRI in comparative studies with EUS is described to be as accurate as EUS for staging of superficial lesions [79–81]. Phased array MRI and multispiral CT are not reliable in the differentiation between T1 versus T2 lesions [82,83]. There is insufficient evidence to support the routine use of FDG PET/CT in preoperative staging of primary colorectal cancer [37].

9.3.2. cT2 versus cT3 rectal cancer

MRI is the first choice examination for staging of rectal cancer. Phased array MRI fails in the differentiation between T2 versus borderline T3a lesions [84] and overstaging is the main cause of error, however this might not be clinically relevant. The overstaging of stage T2 lesions is caused by a desmoplastic reaction of the peritumoural tissues [85]. It is difficult to distinguish desmoplasia without tumour cells (stage pT2) and desmoplasia with tumour cells by MRI (stage pT3a). EUS has the same limitations as MRI to discriminate between cT2 and cT3 [86].

9.3.3. cT3 rectal cancer

T3 tumours invade beyond the muscularis propria into the peri-rectal fat. Patients who have tumours that

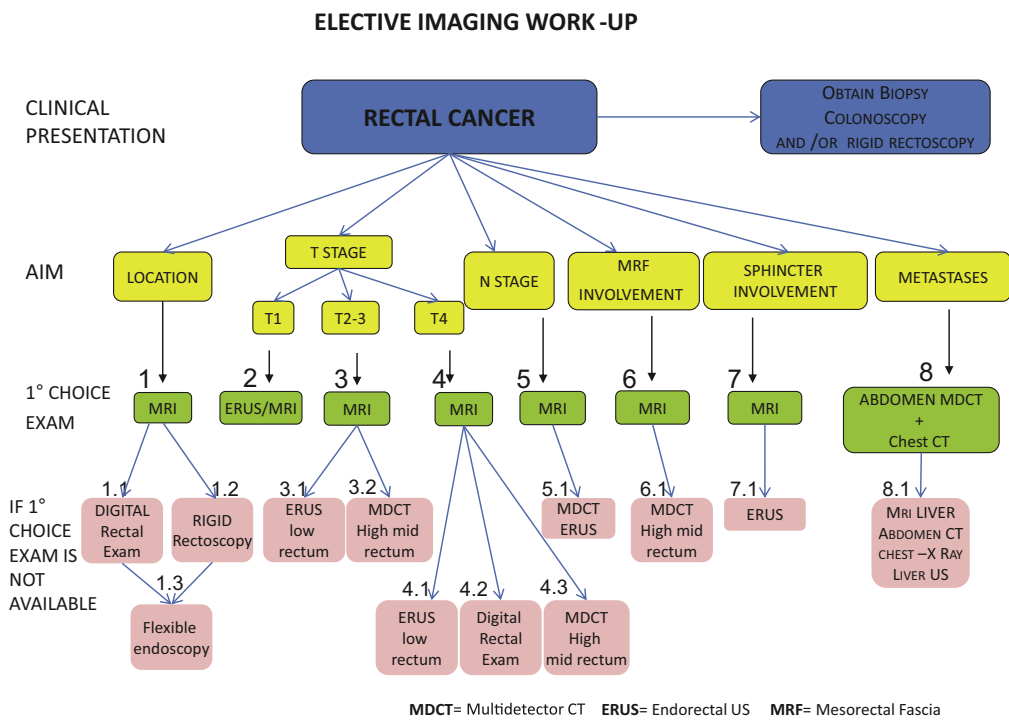


Fig. 4. Elective imaging work up algorithm for rectal cancer. Almost all imaging decisions achieved large consensus with exception of the two lesser choice exam decisions. Moderate consensus was achieved on imaging step 1.1 and moderate consensus on step 3.1.

Table 3

T3 subclassification based on MRI from the rectal wall into the mesorectal fat.

mrT3a	Tumour extends <1 mm beyond muscularis propria
mrT3b	Tumour extends 1–5 mm beyond muscularis propria
mrT3c	Tumour extends >6–15 mm beyond muscularis propria
mrT3d	Tumour extends >15 mm beyond muscularis propria

The mr prefix denotes the staging is based upon MRI.

show greater extension into the mesorectum (>5 mm) have lower 5-year survival and this is independent of lymph node involvement [87,88]. On study population basis, MRI is shown equivalent to histology in measurement of extramural tumour depth [89–91]. A sub-classification of T3 tumours based on MRI according to the depth of tumour extension into the mesorectal fat was developed [89,92], see Table 3. Since the maximal extramural depth of spread, from the outer edge of the low-signal-intensity longitudinal muscularis propria to the outermost edge of the tumour, correlates with cancer-specific survival [88], clinical stage T3 rectal cancers should be subclassified as depicted in Table 3 [93].

Local recurrence rates are similar in patients staged T2 and T3a, whereas rates significantly differ between T3a and T3b, worse in T3b – this is independent of lymph node status [88,94]. The definition of extramural venous invasion (EMVI) is the presence of malignant cells within the endothelial-lined blood vessels beyond the muscularis propria. It can occur in up to 50% of rectal cancer patients. EMVI can be identified pre-operatively on MRI with reasonable accuracy [95]. Assessment of EMVI using MRI must consider the following components: pattern of tumour margin which gives the appearance of nodularity, location of tumour to relevant vessels which makes tumour invasion more likely, calibre of vessel as tumour infiltration can cause an increase in luminal size, and vessel border if the tumour disrupts the vessel itself. EMVI is a poor prognostic factor for overall survival and, more recently, local recurrence [95,96]. The poor prognostic value on overall survival and local recurrence of EMVI is independent of tumour stage [95,96]. See Table 4 for EMVI classification.

9.3.4. Mesorectal fascia (MRF) involvement – MRF+ versus MRF–

Mesorectal fascia involvement (MRF+, = or <1 mm) is the most appropriate term to describe this feature on MRI preoperatively [97]. This term indicates that there is a risk that the circumferential resection margin (CRM) will be involved after surgery if a total mesorectal excision (TME) is done. CRM should be used for the postoperative description. In fact, assessing the resected specimen, a CRM is positive either if there is an involvement of the fascia, when the surgical plane is properly undertaken or if the surgical plane is inside the mesorec-

Table 4

Classification of extramural venous invasion (EMVI) in rectal cancer. Extension of the primary tumour into a vascular structure indicates EMVI. mr is the prefix for MRI.

mrEMVI score	EMVI status	Description
0	Negative	No vessels adjacent to areas of tumour penetration
1	Negative	Minimal stranding but well away from vessels
2	Negative	Stranding within vicinity of vessels but no definite tumour signal
3	Positive	Intermediate signal within slightly expanded vessel
4	Positive	Irregular contour of vessel by definitive tumour signal

tum giving a deficient margin. Patients with a CRM clearance of less than 5mm have a worse outcome (5 year survival) than patients with a larger margin. The group of patients with a margin less than 1mm has the worst 5 year survival. For preoperative staging of rectal cancer, the best cut-off distance for predicting MRF involvement using MRI is 1 mm [94,98].

Of the preoperative features, the relationship of the tumour to the MRF has emerged as one of the most powerful predictors of outcome [97].

Preoperatively, the extent of the tumour, including pathologic lymph nodes, should be described in relation to an adjacent anatomic structure. In this respect, the MRF is central, but other anatomic structures can also be relevant. If the MRF is involved or if the tumour extends to a point that is within 1 mm from the MRF, there is a clear risk that CRM will be involved after surgery if only a TME is performed [97].

In particularly low rectal tumours, the anal sphincters constitute the corresponding significant border because the MRF does not extend past the puborectal muscle [5]. Phased array MRI is the imaging modality that can most accurately evaluate the potential involvement of the MRF [82,90,92,97,99]. Because several studies have shown that preoperative radiotherapy/chemoradiotherapy is more efficient and less toxic than postoperative therapy, it has become increasingly important to evaluate the risk of MRF+ before the operation [97]. Phased array MR is the first choice exam. EUS and endorectal MRI are not accurate for MRF evaluation. Conventional CT is not helpful for predicting an involved resection margin [91,100,101]. Multi-detector CT appears promising for the prediction of a free mesorectal fascia involvement, but not in low tumours, especially not in those located in the low anterior rectal wall. This modality should be reserved in cases with contraindications for MRI [102]. PET/CT is not reliable in the evaluation of an involved MRF [103,104]. We recommend discussing proximity to or involvement of the mesorectal fascia (MRF) in the multidisciplinary team (MDT) conferences to decide if preoperative treatment should be recommended [97].

9.3.5. *cT3 versus cT4 rectal cancer*

EUS is not considered accurate in the assessment of local tumour extent in bulky T3 and T4 rectal cancer [75]. Multidetector CT is accurate for staging the advanced tumours infiltrating surrounding organs in the middle and high rectum with especially a high NPV, at the expense of lower PPV. The accuracy of CT for low seated rectal tumours is unacceptable [83,89,102]. Careful attention to the technique and the use of high resolution sequences with scans planned perpendicular to the anal canal and coronal scans to show the sphincter complex make MRI superior for lower third rectal tumours [83,89,102]. PET/CT does not add to the accuracy in evaluating the clinical T stage in advanced rectal cancers [103].

9.3.6. *Tumour location evaluation*

Important landmarks to define rectal cancer location are: distance from the anal verge, anterior peritoneal reflexion, puborectal sling, and the distance from the levator plate. Distance from the anal verge to the location of the tumour is important for the surgeon to estimate whether a low anastomosis is feasible. Traditional assessment of the height of tumour was done using a combination of digital rectal examination and rigid sigmoidoscopy. Digital examination is probably the most accurate for mid and lower rectal tumours and mandatory especially for surgical decision making, both these methods can be inaccurate depending on the experience of the person who is performing the examination [105]. Phased array MRI is accurate in measuring the distance between the anorectal junction (puborectal sling) and the distal part of the tumour; it is also accurate for determining the length of the tumour. Flexible endoscopy is not reliable in the definition of the tumour location. EUS is less accurate in the definition of tumour location. However, few studies have examined the staging of tumours with respect to the distance to the intersphincteric plane. The level of the tumour has implications on surgical planning and may be the difference between performing an anterior resection or abdominoperineal resection or deciding to create a defunctioning stoma. In this regard, demonstrating the relationship between the tumour and pelvic floor as well as the sphincter com-

plex is vital. There is still controversy regarding the definition of the extra and intra peritoneal rectum by imaging, even if the external phased array MRI contributes to the identification of the peritoneum in the upper rectum [89].

Minimal consensus was achieved for the following table on estimating tumour location. There is considerable variation in pelvic anatomy, especially the length of the anal canal and the distance between the pelvic floor and the anterior peritoneal reflection. Although this variability exists between different patients (physical constitution, anatomy, sex, etc.), rectal cancers should be categorised to their distal edge measured from the anal verge. Rectal cancers are located up to 15 cm from the anal verge. Definition of low versus mid/high rectal cancer with rigid proctoscopy is accurate and more reliable than flexible endoscopy. Furthermore, MRI is accurate in measuring not only the distance between the anorectal junction and the distal part of the tumour but also in determining the length of the tumour.

Table 5 shows the location of rectal cancer with respect to reference level and imaging method, minimum consensus was achieved on this table.

9.3.7. *Sphincter infiltration*

Sphincter infiltration can be assessed by digital examination and/or EUS if performed by experienced physicians. Phased array MRI is reliable in assessing sphincter infiltration and is the preferred method [106]. EUS is the preferred method when phased array MRI is not available and is recommended over an endoanal coil MR technique [76].

9.3.8. *N stage rectal cancer*

Identifying nodal disease is still a diagnostic problem for the radiologist. Although lymph node size is not accurate for defining lymph node metastases, nodes of >8 mm are suspicious for nodal involvement on CT, MRI and EUS. Despite the identification of lymph nodes as small as 2–3 mm on high spatial resolution imaging, reliable detection of nodal metastases is presently not possible. The radiological assessment of nodal involvement generally relies on morphological criteria such as the shape and the heterogeneity of the nodes [107,128]. Since size is not a good predictor

Table 5
Location of rectal cancer with respect to reference level and imaging method.

Location	Rigid proctoscopy	Flexible endoscopy	MRI
Low	Up to 5 cm	Up to 5 cm	Up to 4 cm
Mid	From >5 to 10 cm	From >5 to 10 cm	From >4 to 8 cm
High	From >10 up to 15 cm	From >10 up to 15 cm	From >8 up to 12 cm
Reference level	Anal verge	Anal verge	Anorectal junction or puborectal sling

for malignancy, it should not be used by itself for defining whether lymph nodes are involved or not. The most reliable method of positively identifying nodal metastases is based on morphological features such as the presence of a round shape, heterogeneity within the lymph node and/or irregularity of the borders of the lymph node due to capsular penetration by malignancy [86,108,109]. The overall accuracy of N-staging is lower than of other prognostic features, such as T-stage, that can be identified more reliably using high resolution MRI scan techniques [110]. MRI is the preferred examination for nodal staging although accuracy is low [86]. EUS and FNA are not recommended for nodal staging. FDG/PET has shown disappointing results for N-staging in rectal cancer, especially in the mesorectum in the presence of a bulky tumour [111].

9.3.9. *M stage rectal cancer*

Abdominal CT, chest X-ray or CT are the minimal requirements for staging of distant metastases. Thoracic and abdominal CT are recommended as part of the staging protocol to detect distant metastases, especially for the high risk rectal cancer [112]. For the characterisation of liver lesions, MRI imaging is superior to helical CT and is recommended in equivocal liver lesions seen on CT. FDG/PET had significantly higher sensitivity on a per-patient basis, but not on a per-lesion basis [113,114]. Sensitivity, per-lesion basis, for MR imaging using liver specific contrast agents were significantly superior to those for helical CT [114]. Bone scan and brain imaging are required for patients with symptoms.

9.3.10. *Imaging after radio(chemo)therapy – responders versus not responders*

The detection of small clusters of residual tumour cells remains a problem and a complete remission after chemoradiation cannot be reliably predicted with non-invasive imaging tools [115]. Although EUS, CT and MRI can show downsizing of the tumour, they are not accurate, especially when there is a fibrotic thickening of the rectal wall, in distinguishing between ypT0, ypT1, ypT2 or ypT3 tumours. The main source of error is overstaging. Reasonably high level of accuracy has been observed by the addition of diffusion weighted imaging (DWI) to standard MR. This is more sensitive than phased array MRI when the end-point is differentiating ypT0-2 versus ypT3. Diffusion Weighted MRI is more sensitive than MRI for prediction of a pathological complete response [116–118]. Many studies have reported a significant decrease of standardised uptake value (SUV) on post radiation FDG–PET in responders when compared to non-responders, but the clinical value of this information remains to be determined [116].

10. Pathology report

10.1. *Assessment of the specimen – rectal cancer*

The macroscopic examination of the specimen is critical and of prognostic significance [119]. From this an understanding of the anatomy and its variability can be obtained: an appreciation of macroscopic features helps to guide pathological analysis [120].

For local excision resection specimens, careful examination of all resection margins should be performed, including examination of the basal resection margin that must be inked. After local excision, in order to adequately predict the presence of lymph node metastases and the subsequent need for radical resection, differentiation grade, lymphatic and vascular invasion and invasion depth (using the Kikuchi classification, sm1-3) as well as completeness of excision should be reported [121].

After TME, the anterior and posterior surfaces should be photographed to record any perforation and the plane of surgical dissection. The specimen is opened anteriorly except for the area of the tumour which is left intact to allow assessment of CRM and peritoneal involvement without the distortion introduced by opening the bowel. The surgically created margin surfaces are painted with ink [119,120]. The specimen should be fixed in formalin for 72 h or longer. It should then be described and the tumour (including 2 cm below and above) should be thinly sliced (3–5 mm). Good fixation allows thinner slices to be taken and thus a better assessment of tumour spread. These slices should be photographed to document the plane of surgical dissection and for radiological audit of extent of spread, EMVI, MRF and nodal involvement [119,120]. The distance of direct tumour spread outside the muscularis propria should be recorded in mm and the area in which tumour spreads closest to the CRM should be identified macroscopically. Blocks should be taken from the area closest to the CRM and any area where the tumour extends to within less than 3 mm from the margin. Other blocks should be taken to include at least 5 blocks of tumour to confirm presence or absence of extramural venous invasion [120].

Although there is a lot of controversy about the significance of lymph node numbers and prognosis, pre-operative treatment does reduce numbers of lymph nodes that are found. Anyway, accurate nodal staging is of critical importance for selecting patients for adjuvant therapies [122]. Careful slicing of the mesorectal fat, visual inspection and palpation are recommended to find sufficient numbers of lymph nodes. Fat clearance or specialist techniques such as GEWF fixation or injection of methylene blue may improve the yield of lymph nodes. However its routine use cannot be recommended.

TNM and NICE guidelines recommend that at least 12 nodes should be harvested, even if after preoperative treatments it could be more difficult to find them. Large variation in lymph node evaluation by hospitals and pathology departments in rectal cancer has consequences for stage distribution and survival [123].

With minimal consensus, it was found that after immediate surgery, in cases of less than 10 lymph nodes, TNM stage II patients could have higher risk of recurrences and could be eligible for adjuvant therapy.

10.2. TNM classification

The version of TNM (5th, 6th or 7th) used should be stated in any publication such as the pathology report [124].

10.3. Evaluation of surgical margins

The most well-known margins of a surgical specimen are the proximal and distal margins of a resection. In rectal cancer, one of the most important margins is the margin around the mesorectum if TME-surgery is performed (Circumferential Resection Margin = CRM). Any small deviation from the correct surgical plane could result in tumour cell deposits, potentially compromising cure [125]. Positive CRM correlates with increased local recurrence rates and decreased survival by half: these data support the importance of clear surgical CRM [94,126]. In each specimen, CRM must be defined as involved if it is less or equal to 1 mm from tumour free margin in order to define risk for local recurrence. CRM should always be measured from the primary tumour and/or involved lymph nodes and given in millimetres in the pathology report. Patients with a CRM of less than 2 mm could be considered at higher risk but more studies are needed to change the value of 1–2 mm in routine practice [127,128]. Therefore, it is important to report the exact CRM in mm. If a positive lymph node or a tumour deposit is closer to the margin, a second CRM measurement should be made and reported. Reporting margins of excision is mandatory in all pathology reports, the R-classification should only be reported in conjunction with clinical information.

10.4. Staging after radio(chemo)therapy

There is good evidence that preoperative chemoradiotherapy is able to downsize and downstage rectal tumours [129–133]. In approximately 8–30% of cases this can lead to a complete pathological response [134].

There are a number of suggested methods for assessing tumour regression after pre-operative treatments. These are modifications of the scoring system developed by Mandard et al. for oesophageal carcinoma [135].

Using similar grading systems the presence of very few or no tumour cells was associated with a much better outcome after therapy. It may be possible to simplify this into tumours that show an excellent response, i.e. no residual tumour cells, a good response, i.e. tumour cells that are difficult to find microscopically or easily identifiable tumour cells and no response at all. Variation in sampling protocols may explain some of the differences in the frequency of complete pathological response described in the literature. A protocol to classify a tumour having a complete pathological response has been recommended from Quirke et al. For a complete pathological response, initially at least 5 tissue blocks should be taken from the tumour site. If there is no tumour present in these, the whole tumour area should be blocked. If still no tumour is present, three levels should be cut from each tumour block. If still no tumour is present, there is a pathological complete response [136].

With moderate consensus, we state that tumour regression grading (TRG) after preoperative treatment has not demonstrated any independent and reproducible prognostic value and currently there is limited indication for the routine reporting of TRG [137,138].

10.5. Documentation of surgical quality

The recording of the frequency of involvement of the MRF or surgical CRM is important for feedback to radiologists for accuracy of prediction as well as to the surgeon as an indicator of the achievement of the appropriate planes and thus an indicator of high quality surgery and the prognosis for the patient [126]. An assessment of the quality of specimen and of the surgical margins should be routinely made by the reporting pathologist [126]. The assessment of abdomino-perineal excision specimens to determine the type of operation performed and its effectiveness in obtaining a clear margin and whether the levator muscle is included in the resection is strongly recommended. This allows an evaluation of the potentially exposed tumour in a similar way as for the mesorectum [139,140].

11. Clinical presentations in rectal cancer

11.1. Laparoscopy in rectal cancer

Evidence on benefits and learning curve of laparoscopic colon surgery apply in a similar way to rectal cancer, although a laparoscopic TME resection is technically more difficult than a laparoscopic segmental colon resection emphasising good quality control. Laparoscopic resection of rectal cancer is safe with similar oncological outcomes and short term advantages compared to open surgery [141].

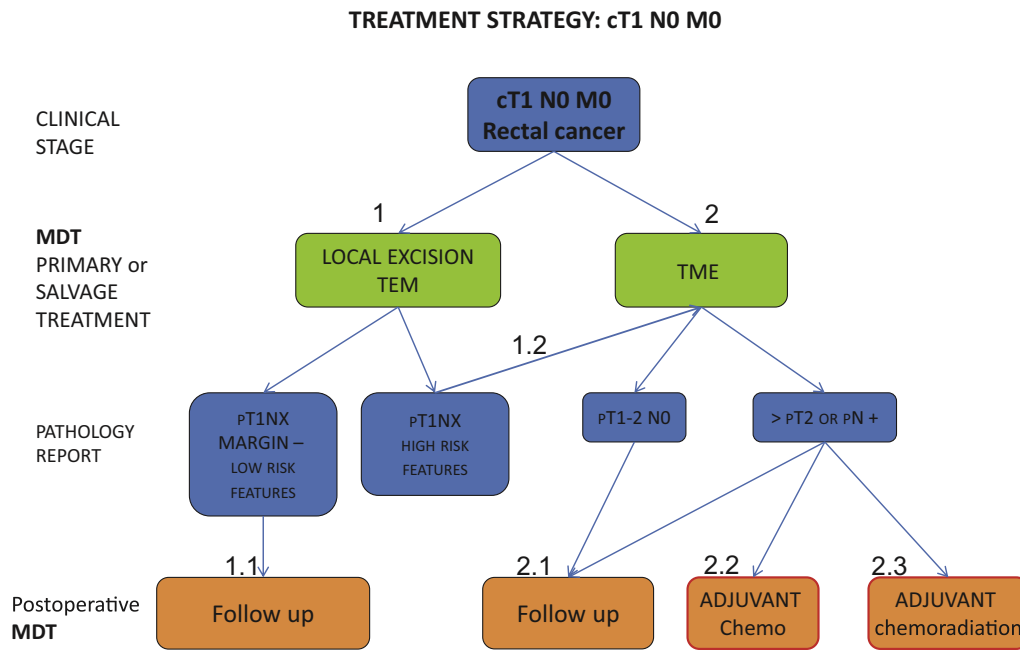


Fig. 5. Treatment strategy rectal cancer: cT1N0M0. Two decisions in the clinical stage 1 rectal cancer treatment algorithm did not achieve large consensus, indicated with red border; being minimal consensus for step 2.2 to give adjuvant chemotherapy after primary TME or salvage TME after TEM; and no consensus was achieved on step 2.3 to decide on postoperative chemotherapy and radiation.

11.2. cT1N0M0 rectal cancer

See Fig. 5 for treatment strategies of CT1N0M0.

cT1, sm1-2, N0, M0 can be treated both with radical TME surgery or resected by local excision, preferably then using trans-anal endoscopic microsurgery (TEM) [142–144]. Local excision is associated with less ano-rectal and genitourinary dysfunction and better quality of life compared with traditional surgery [142]. Technically, the use of local excision requires that there is a non-obstructing tumour and its dimension is less than half of the lumen and/or size less than 4 cm of diameter [144].

The specimen after local excision has to be carefully analysed to evaluate its integrity, the depth of invasion in the bowel wall, the absence of margin infiltration both laterally and deeply, and the presence of adverse pathologic factors: poor grade, blood or lymphatic vessel invasion [120].

Endoscopic mucosal resection (EMR) may be performed [68,145]. However, there is not enough evidence to recommend this procedure as standard treatment. After EMR, pathological analysis of submucosal infiltration is essential to assess the completeness of the resection [68,145]. Trans-anal endoscopic microsurgery (TEM) is a technically reliable option to remove the full thickness rectal wall and to evaluate the completeness of the removed specimen and the tumour as well as whether there are high risk factors for lymph node metastases present (i.e. poorly differentiated tumour, evidence of blood or lymphatic vessel invasion, depth of invasion) [144,146].

After trans-anal excision, in case of confirmed pathological stage pT1, Nx with low risk features (sm1, low grade, no lymphatic or blood invasion), local excision may remain the only treatment. No formal agreement is available for T1sm2, so both treatments are possible options; 1 ‘Close observation’ or 2 proceed to TME surgery. If the pathology report shows a more extensive tumour (\geq pT1sm2) or shows other high risk prognostic factors (i.e. poor grade, blood or lymphatic vessel invasion, sm3) after local excision the patient should undergo TME. There is no evidence to state that postoperative chemoradiation after TEM is as good as TME in early stages with adverse features. Depending on the tumour location salvage surgery after local excision may compromise the ability to perform a sphincter sparing operation. After salvage TME surgery for cT1-2, N0 the patient may be observed in follow-up. There is no evidence to support the following management plan. After salvage TME surgery after local excision if the pathologic stage confirms pT3pN0 with adverse morphological features such as (i.e. high grade, and/or blood or lymphatic vessel invasion, no clear margins) adjuvant treatment should be considered by a multidisciplinary team.

With moderate consensus, it was found that although early salvage TME surgery after TEM appears to be safe when compared to patients undergoing primary TME, several studies are describing disappointing long term results [147–150].

With minimal consensus it was found that if after salvage TME surgery after initial local excision and if the

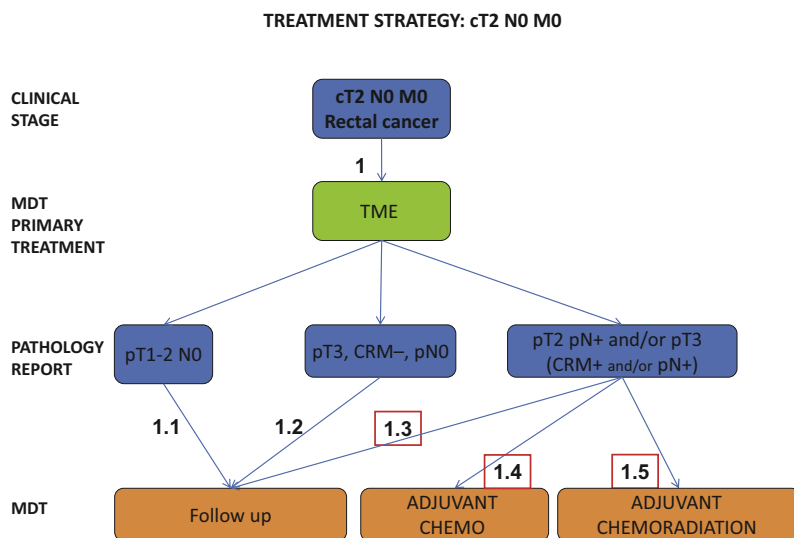


Fig. 6. Treatment strategy: cT2 N0, M0 rectal cancer. Three decisions in the clinical T2 stage treatment algorithm did not achieve large consensus, indicated with red lining; being minimum consensus for step 1.3 to go to follow up in case of positive nodal stage, positive CRM or pT3; and no consensus was achieved on step 1.4 and 1.5 to decide on postoperative chemotherapy and chemoradiation in these patients.

pathologic stage reveals a pT3 pN+, adjuvant treatment could be considered according to the cost–benefits based on the nomogram.

11.3. cT2 N0 M0 rectal cancer

See Fig. 6 for Treatment strategy of cT2 N0, M0.

cT2, N0, M0 is adequately treated with TME surgery as standard resection without preoperative irradiation. After TME surgery, in case of pathological stage pT1-2, pN0, patients are recommended to be observed in follow-up. When the muscular layer is involved by the tumour (T2), the risk of positive lymphatic nodes ranges between 15% and 20%. Local excision is not recommended. After surgery, in case of pathological stage pT3, CRM–, pN0 of the high-mid rectum, patients may be observed in follow-up after a multidisciplinary team discussion.

With minimal consensus, it was agreed that after TME surgery for cT2N0 rectal cancer without preoperative treatment, and in case of pT3 of the low rectum and/or CRM+ or N+, postoperative treatment such as radiotherapy or adjuvant chemotherapy should be considered in a multidisciplinary team discussion.

11.4. cT3 N0 M0 MRF– upper/middle rectum TME surgery

See treatment algorithm Fig. 7 for cT3N0M.

Of importance for treatment strategy of cT3 rectal cancer of the upper/middle rectum is not only the T and N stage but also the site (anterior, lateral or pos-

terior) and height of the tumour, size of the mesorectum, tumour size, extent of the extramural growth (cT3a-d), and skills of the surgical team. In addition patient-related factors are of course of relevance. Both preoperative procedures, i.e. short-course radiation therapy (RT) or chemoradiation, reduce the risk of local relapse, however they are associated with more adverse effects [151–153]. In patients with tumours of the rectum, lymph nodes or other tumour deposits can be found in the mesorectum up to 4 cm distally from the tumour [154]. In tumours located in the upper rectum a Partial Mesorectal Excision (PME) extending 5 cm below lower tumour margin and sparing the distal part of the mesorectum is feasible [155]. However, definitive evidence for this is not available.

After surgery, in case of confirmed pT3, CRM–, pN0 patients may be observed in follow-up after a multidisciplinary team discussion.

With moderate consensus it was agreed that a clinical stageT3 MRF– N0 upper/middle rectum can be managed in three ways:

- Up front resection followed by surveillance only,
- 5 × 5 radiation followed by immediate (2–3 days) surgery [156,157],
- chemoradiation (CRT) followed by delayed (6–8 weeks) surgery [158,159].

With minimum consensus, it was agreed that after TME surgery, in case of a positive CRM, adjuvant radiochemotherapy should be suggested if no preoperative RT was done. This should, however, never happen [157–159].

Also with minimum consensus it was agreed that in case that after surgery, the pathology report shows

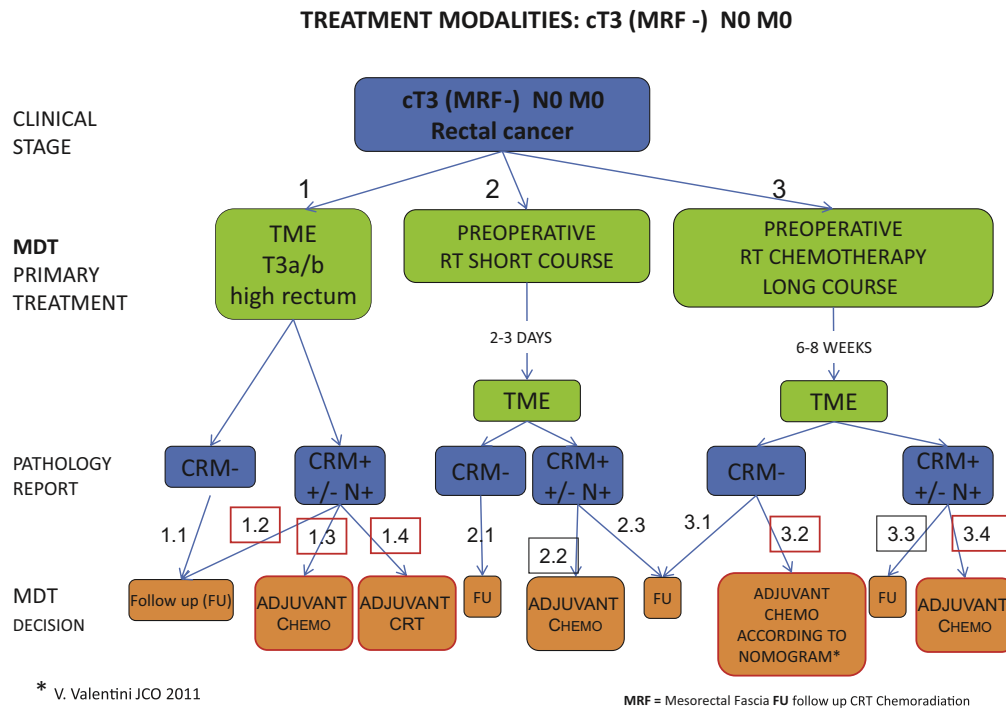


Fig. 7. Treatment strategy: cT3 N0, M0 rectal cancer. Nine decisions in the algorithm did not achieve large consensus. Indicated with red lining is the 'no consensus' for decision 1.3 and 3.2; and 'minimum consensus' for 1.2, 1.4 and 3.4. With moderate consensus it was agreed to decide on step 2, and 3, 2.2 and 3.3.

positive lymph nodes adjuvant treatment should be considered in multidisciplinary discussion [160].

11.5. cT3 N0, M0 MRF- lower rectum

CRT and short course radiotherapy seem to have equivalent outcome in terms of local relapse rate, overall survival and long-term toxicity [159]. Short course radiotherapy has the advantage of less acute toxicity and less cost [161]. Sphincter preservation is considered when tumour does not infiltrate the pelvic floor and if the patient is not incontinent prior to the treatment. Since the mesorectum decreases in size close to the top of the anal canal, tumours arising in this area can easily invade surrounding structures, such as the internal and external sphincters and the levator muscles. This is common if the depth of invasion is beyond cT2. It is important to determine by MRI whether the pelvic floor is involved in very low rectal cancer. In patients with tumours of the rectum, lymph nodes or other tumour deposits can be found in the mesorectum up to 4 cm distally from the tumour. Complete removal of mesorectum distally is always indicated in low rectal tumour locations [126,162].

With moderate consensus it was agreed that in case of cT3 N0 M0 MRF- lower rectum, preoperative treatment followed by surgery (TME) is recommended.

With moderate consensus it was agreed that if the pathology report showed a pT3a/b N0, follow up could be considered.

Minimum consensus was found for the statement that if the pathology report shows a pT3c/d N0 with other high risk features (i.e. poor grade, and/or blood or lymphatic vessel invasion, no clear margins) adjuvant treatment by a multidisciplinary team could be considered [163].

11.6. cT3, N1-2, M0 MRF-

See Fig. 8 for treatment algorithm for this pathological stage.

Standard treatment for cT3N+ MRF- rectal tumours could be:

- Preoperative short course radiotherapy followed by immediate surgery,
- Preoperative chemoradiation followed by delayed (6–8 weeks) surgery.

There is no evidence of an overall survival benefit in the randomised trials using short-course radiotherapy in patients undergoing standardised TME surgery [151,153,156,164]. The reduction in local failure rates in most intermediate risk cancers after TME standardisation is too small to translate into an overall survival benefit irrespective of which radiotherapy modality is used. However population based studies have demonstrated that since standardisation of rectal cancer surgery with TME and the implementation of

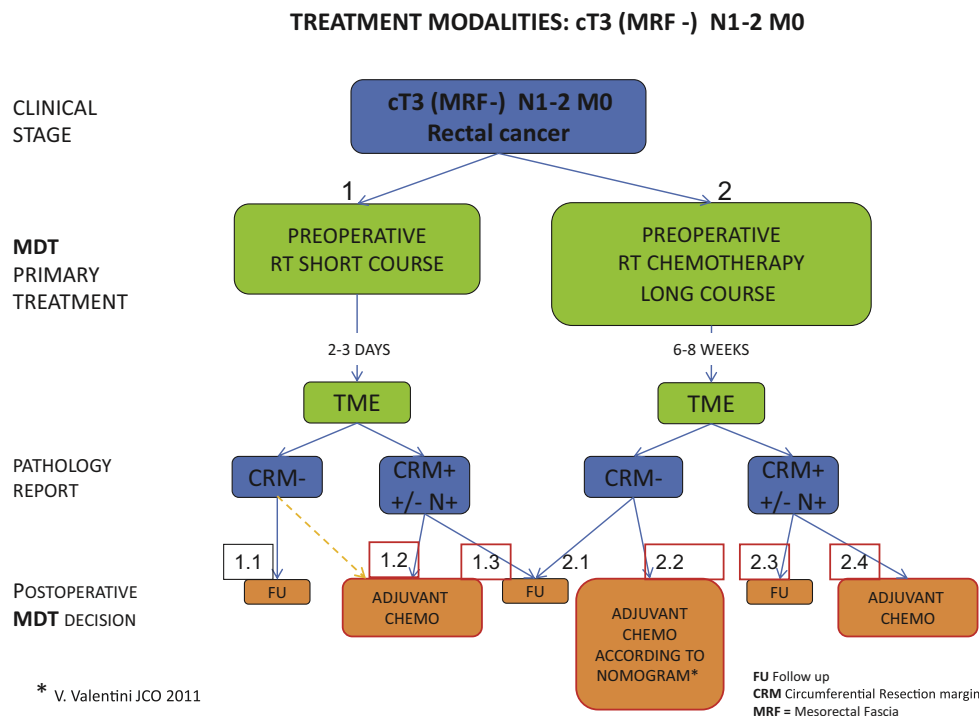


Fig. 8. Treatment strategy: cT3 N+, M0 rectal cancer Six decisions in the algorithm did not achieve large consensus, indicated with red lining; being no consensus for decision 2.2 adjuvant chemotherapy according to the nomogram; minimum consensus for decision 1.2, 1.3, 2.3 and 2.4. There was moderate consensus for decision 1.1. The large variation in agreement illustrates that there is little evidence for adjuvant chemotherapy in rectal cancer.

preoperative radiotherapy, improved survival has been seen in rectal cancer [3]. Two recent randomised trials have shown an improvement in the results of preoperative radiation in patients with locally advanced rectal cancer when 5FU based chemotherapy is added to radiotherapy. A significant decrease in local recurrence was observed in those receiving chemotherapy as well as an increased rate of pCR. Five year overall survival was not changed by the addition of chemotherapy [165,166]. No survival gain was, however, seen in a pooled analysis of these two randomized controlled trials (RCTs), increasing the power of the analysis [167]. After preoperative radiochemotherapy a variable percentage of pathological complete response (pCR) in specimens has been reported. Although some series show no correlation [168], many series report that patients who achieve a pCR following preoperative radiochemotherapy have improved long-term outcomes in terms of excellent local control rates and this is independent of their initial clinical T and N stage [163,169,170]. The increased incidence of pCR in the radiochemotherapy arms did not improve the final outcome of the randomised studies, taking into account that these trials were underpowered to detect this difference in overall survival [166,171]. To increase the efficacy of 5-FU or capecitabine it has been combined, in several phase II studies, with oxaliplatin or irinotecan plus radiation [172,173]. However, none of

the completed phase III trials have to date revealed an improved outcome (except possibly more pCRs) [129,151]. At the present, infused 5-FU or oral fluoropyrimidines remain the standard agents to combine with preoperative radiotherapy.

- Minimum consensus was found about the condition that after surgery, in case of positive CRM, postoperative radio-chemotherapy should be delivered if no preoperative RT had been performed.
- Minimum consensus was achieved for the following that two recent pooled analyses of randomised and non-randomised trials have indicated that preoperative CRT impacted on distant metastases and overall survival [163].
- In patients who received preoperative treatment, no consensus was reached for the statement that after surgery, in case of confirmed pT3 pN0 CRM-, adjuvant chemotherapy could be considered according to the cost-benefits based on the nomogram in a multidisciplinary team discussion [163] (see Fig. 9).
- No consensus was reached for the decision that in case of a cT3N0 that after surgery results in a pathological report of a pN+, an adjuvant treatment should be considered in a multidisciplinary team discussion [166].

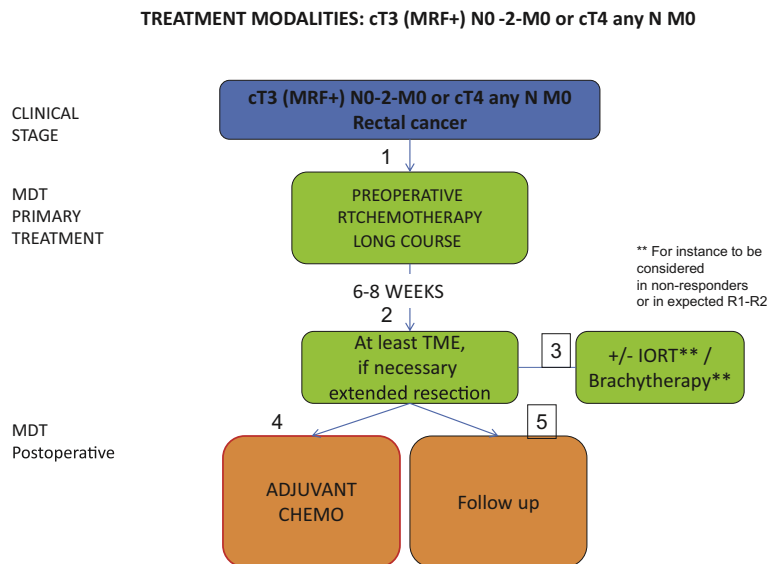


Fig. 9. Treatment modalities: cT3 (MRF+) any N M0 or cT4 any N Moderate consensus was achieved for step 3 and 5, minimum consensus indicated with red borders was achieved for step 4 in the decision making.

11.7. cT3 N1-2 M0 MRF+

In order to achieve tumour shrinkage, for MRF+ patients showing, high risk of local or distant recurrence and poorer overall survival, preoperative CRT is recommended followed by TME surgery [174]. In rectal cancer patients with a clinical stage with positive lymph nodes and a positive mesorectal fascia, preoperative chemoradiotherapy is recommended even though there is no direct evidence showing better outcome in this specific subgroup [175]. In case of concomitant morbidity prohibiting chemoradiation, short course radiotherapy with delayed surgery can be considered, although this approach has not been tested in a randomised study in this particular subgroup of patients [161,176].

Some studies, using concomitant boost, are ongoing to explore the efficacy of intensified radiotherapy doses with the aim to increase tumour response and R0 resectability [178,179].

In patients who received a preoperative treatment, no consensus was found for the statement that after surgery, if high risk features are present in the pathological report, adjuvant chemotherapy could be considered according to the cost–benefits based on the nomogram in a multidisciplinary team discussion [163] (see Fig. 9).

11.8. cT4 any cN rectal cancer

Locally advanced tumours are defined as tumours extending beyond the rectal wall with infiltration in surrounding organs or structures, and/or perforation of the visceral peritoneum (c/p T4 N0-2 M0). The evaluation of resectability depends on the extent of the operation the surgeon is able to perform as well as the degree of

morbidity the patient is willing to accept. The heterogeneity of the presentation and a definition of resectability based on clinical rather than objective criteria make it difficult to compare the results between series. Only randomised trials may give evidence of superiority of one treatment above another [180]. Preoperative radiochemotherapy includes radiation in the range of 50–54 Gy plus 5FU-based chemotherapy with the goal of increasing R0 resectability [181–183]. Doses above 50.4 Gy are associated with a higher complication rate especially using techniques that are not able to conform the radiation dose with high precision to the tumour and positive lymph nodes. Positive evidence of the role of higher dose is still to be confirmed in randomised studies [184–187]. Referral centres, in single institution studies, suggest a favourable local control rate also in patients with positive margins or microscopic residual disease treated with a large single dose (10–20 Gy) of radiation by electron beam or brachytherapy (intraoperative radiation or IORT) [188–190]. However, not all series show a benefit [191]. The results (and recommended dose) of IORT depend on whether the margins of resection are negative or whether there is microscopic or gross residual disease. IORT does not compensate for suboptimal surgery. In general, series have used 10–20 Gy. IORT-related toxicity increases with IORT doses >18–20 Gy. In patients who are not medically able to receive long-course chemoradiation, short-course RT followed by delayed surgery is the recommended treatment since it can result in substantial down staging, downsizing and frequent R0-resections. This group of patients is otherwise left with palliative measures only [177]. Given the limitation of the total radiotherapy dose which can be delivered to the bulky tumour in the pelvis and the frequent problem of local recurrence, the surgeon, on the resectable cases,

should achieve a complete resection. Extended surgery to the infiltrated organs should be considered particularly if there is a favourable response after preoperative therapy. Even in patients who do not respond adequately to the preoperative therapy, surgery can be indicated, balancing gains and losses [192].

With moderate consensus, it was agreed that cT4 rectal cancer can be sub-divided into readily resectable, potentially resectable after induction treatment (in case of favourable response), and unresectable, depending on the possibility to have a potentially curative surgical resection or not.

With minimum consensus, it was agreed that all patients with a cT4 disease – resectable or unresectable – should receive up front chemoradiation, if this is possible considering biologic age and co-morbidity.

No consensus was reached about the statement that after surgery, if high risk features are present in the pathological report, adjuvant chemotherapy could be considered according to the cost-benefits based on the nomogram in a multidisciplinary team discussion [163]. (Fig. 9).

11.9. Follow up rectal cancer

The follow up after surgery for rectal cancer is an important issue; however, we have little evidence to substantiate the statements made.

11.10. Design and cost-effectiveness

The value of following patients after radical resection for colorectal cancer is still controversial, and scientific evidence supporting it remains sparse. Many cohort and case-control studies have supported the effectiveness of follow-up [193,194], but very few randomised controlled trials have been performed. Moreover, the frequency of follow-up is also debated. Outcome of follow-up programmes must be considered from both efficacy and cost perspectives. Despite limited evidence, extensive follow-up programmes are being used in most clinics and support a continued relationship with the patients [193,194]. The published studies imply that finding extra luminal recurrences (local recurrence after rectal cancer and liver metastases after colorectal cancer) is the main benefit in the follow-up programme. Since local recurrence after colorectal cancer surgery is much less common than historical data, the principal benefit remains detecting liver and possibly lung metastases, allowing the opportunity for a second curative procedure. The search and identification of an intra luminal recurrence does not change mortality, however, the detection of metachronous colorectal malignancy may be worthwhile. The calculated annual incidence is 0.35% for the identification of metachronous lesions, with a cumulative incidence at 18 years of 6.3%. Moderate consensus was reached for the statement

that an annual follow-up CT for high risk patients seems to be justified [193].

11.11. Early localised rectal cancer

In patients who undergo traditional surgery (anterior resection or APR with TME) for early rectal cancer, the risk of local and distant recurrence is very low. A colonoscopy is recommended at 3 years and then, if normal, once every 5/6 years thereafter, to rule out polyps, advanced adenomas or metachronous colorectal cancer [193–197]. After local excision, follow-up should include regular endoscopic surveillance of the rectum, especially the scar [198]. Careful follow-up to diagnose local recurrence early is necessary so that salvage surgery can be performed [199]. The use of modern imaging (endorectal ultrasonography, MRI and PET) to detect local recurrence is recommended after local excision, but the appropriate modality and frequency is subject of debate and firm data are pending [199].

With moderate consensus, it was agreed that digital rectal examination and sigmoidoscopy are recommended, after local excision, every 3 months for the first 2 years, every 4 months for the third year and every 6 months for the next 2 years and then annually. However, this examination frequency is not unanimously agreed upon.

11.12. Intermediate and locally advanced tumours

Carcino-embryonic Antigen (CEA): even if 30% of all colorectal cancer recurrences do not produce CEA, elevated CEA levels, if confirmed by retesting, warrant further evaluation for metastatic disease but do not justify systemic therapy for presumed metastatic disease [193–196]. Complete Blood Cell Count (CBC): Currently there is no evidence to suggest the use of CBC in routine follow-up after colorectal cancer resection [196]. Liver function test (LFTs): No studies have shown the usefulness of LFTs in the monitoring of patients after colorectal cancer resection. Because of low specificity, routine use of LFTs in surveillance of colorectal cancer is not recommended [196]. Colonoscopy: A second or synchronous malignancy at a different location within the colon or rectum is found in 3–5% of patients who have undergone resection. Another 25% of these patients will have adenomas that require removal. Numerous studies have attempted to document the usefulness of colonoscopy or flexible procto-sigmoidoscopy in the detection of recurrent colorectal cancer. These studies have found that they were rarely the first indicator of recurrence (0–19%) [196]. Despite their low cost, chest X-rays have a low frequency of initially detecting pulmonary metastasis (range, 3–20%) and the advantage in outcome is small. The current available data do not support routine

chest X-ray in the follow-up evaluation of colorectal cancer [196]. In patients who have symptoms suggestive of pulmonary disease, a CT scan should be considered [196]. The use of periodic CT scans in the postoperative setting is unproven. No studies have proven that the routine use of CT scan can identify curable metastatic disease before other imaging modalities. However, the CT scan is useful to evaluate suspicious signs and symptoms in patients such as increasing CEA level, abdominal pain and abnormal LFTs. Further studies are needed to evaluate the role of routine CT scanning in patients with non-CEA producing tumours [196]. MRI showed superior accuracy to conventional CT in the detection of rectal cancer recurrence by the combination of the signal intensity on T2 weighed images, the shape of the margins of the mass and the presence of greater than 40% contrast enhancement [200–202]. A meta-analysis compared the diagnostic value of US, CT, MRI and PET in the detection of gastrointestinal cancer metastases. FDG–PET with CT is the most sensitive method for detection of metastases, with a mean weighted sensitivity of 90–92% [203]. There is insufficient evidence that routine use of FDG–PET is cost-effective. In patients who receive neoadjuvant therapy, recurrences after 5 years from surgery can occur [153,204].

No consensus was reached about the following statement concerning history and physical examination: even if there is no evidence that directly addresses the contribution of the history and physical examination to outcomes of colorectal cancer surveillance, a clinical history and pertinent physical examination could be

considered every 6 months for the first 3 years and annually thereafter [195].

With minimum consensus, it was agreed that Multidetector-row CT (MDCT) has a major role in the follow-up of rectal cancer patients, especially to detect metastases, because it provides good imaging of the liver and the abdomen and chest in one session. Several studies have assessed the value of using thin slices to improve detection of small metastases [205].

No consensus was reached for the statement that Multidetector CT and FDG–PET–CT are similarly accurate in the definition of the presence of a local recurrence [206].

Minimum consensus was found that for the high risk group (stage III) CT of the chest plus abdomen is preferred as follow-up tool for metastases.

With minimum consensus, it was decided that for individualised follow-up, based on tumour stage and age of the patients, the usage of nomograms assessing the risk of local recurrence, distant metastases and survival should be recommended [163].

With moderate consensus, it was agreed that recurrences beyond the 5th year from diagnosis can happen; decision to continue follow up should be made on an individual basis.

12. Advanced presentations, stage IV

The next sentences were voted on during the consensus process, if less than 80% of agreement was achieved this is indicated clearly in text at the end of the

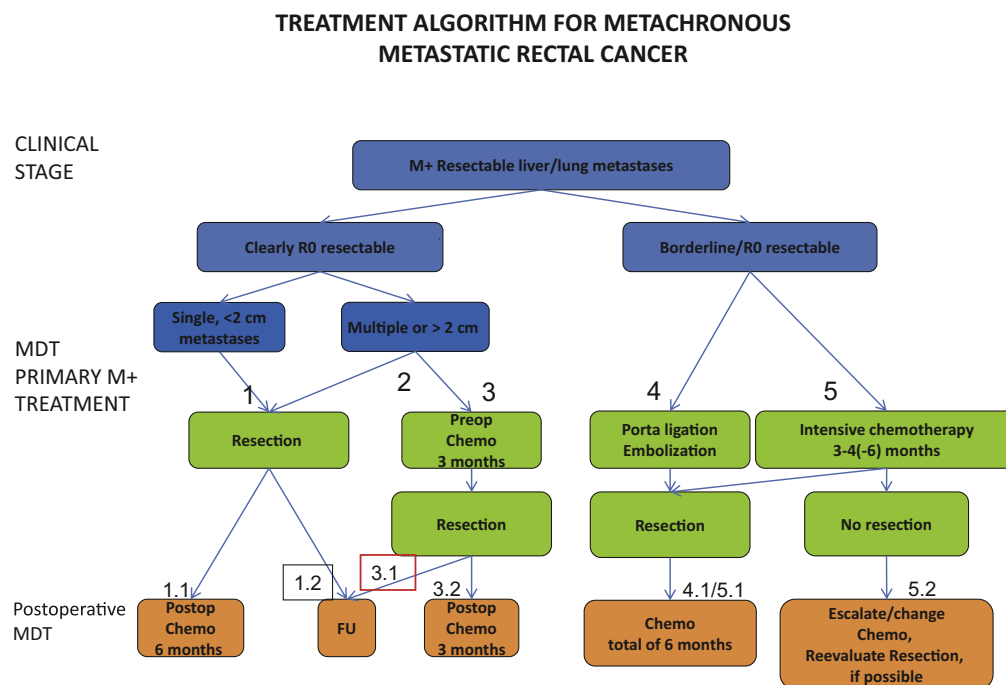


Fig. 10. Treatment algorithm for metachronous metastatic rectal cancer Moderate consensus was achieved for decision 1.2 and minimum consensus was reached for decision 3.1, indicated with red borders.

paragraph or in the legends of table or algorithms. For this section, please also look at the recommendations of ESMO consensus [72].

12.1. Metachronous colorectal metastases

For treatment algorithm see Fig. 10.

12.2. R0 resectable liver +/- lung metastases

Patients with multiple resectable metastases or metastases larger than 2 cm could be considered to receive 3 months of preoperative chemotherapy, surgical resection and then 3 months of postoperative chemotherapy [207]. The EORTC 40983 trial, showed that the approach of 3 months preoperative chemotherapy, resection and 3 months postoperative chemotherapy resulted in improvement of progression-free survival but not overall survival in patients with up to four liver metastases, no extrahepatic disease and no previous treatment with oxaliplatin [207]. Patients failing response, within 12 month of previous adjuvant oxaliplatin based treatment should not receive perioperative FOLFOX (FOL – folinic acid (leucovorin); F – fluorouracil (5-FU); OX – oxaliplatin (eloxatin)), rather another active protocol, in the same manner of pre/postoperative treatment, or immediate surgery if feasible. To achieve complete response to chemotherapy is of major prognostic importance for liver metastases but should be avoided in order to enable resection (before complete disappearance) [208,209]. Therefore, close follow up with imaging and multidisciplinary discussion is mandatory. If an anatomical resection can be performed, preoperative chemotherapy leading to complete response is not a major problem, because resection will be based on initial sites of liver metastases. In case of complete response on chemotherapy and no option for anatomical resection, different imaging methods might be used (MRI with liver-specific contrast agents, PET /CT, contrast-enhanced ultrasound) or resection might be delayed until relapse occurs. In patients with a single small (<2 cm) liver metastasis, postoperative chemotherapy with FOLFOX for 6 months is recommended according to a multidisciplinary team discussion:

- FU + oxaliplatin for 6 months.
- Single agent FU is also an option, mainly for patients with a contraindication to oxaliplatin. In case of R1 resection postoperative chemotherapy should be continued as planned [210]. Resection is superior to radiofrequency ablation (RFA) in the treatment of resectable colorectal liver metastases [211]. In case of R2-resection the intention of further treatment should be re-evaluated.

In patients who might still be candidates for a curative approach, chemotherapy should be modified and/or intensified according to a multidisciplinary team discussion. In patients who are not amenable for a curative approach treatment may be resumed. In case of contraindications against surgery or unresectable oligometastases (size up to 3–4cm for RFA and 4–5cm for SBRT, if properly located) local ablative measures (RFA, SBRT) could be considered in a multidisciplinary team discussion [212–214]. In the case of primary progression during preoperative chemotherapy, the best available salvage treatment may be preferred, instead of straight resection according to a multidisciplinary team discussion.

With minimum consensus, it was found that patients with a single resectable liver or lung metastases of less than 2 cm could be primarily resected and are recommended to receive post-operative chemotherapy for 6 months [187].

With moderate consensus, it was agreed that patients with larger or multiple liver metastases suitable for hemi-hepatectomy or extended hemi-hepatectomy, can also be considered for up front surgery as enough remnant liver is left behind for regeneration [215].

12.3. Borderline R0 resectable or initially unresectable

Borderline resectable or unresectable patients should receive, as current standard, 3–4(–6) months of induction chemotherapy. After re-evaluation resectable patients should undergo surgery and complete postoperative chemotherapy for a total of 6 months. If metastases remain unresectable after chemotherapy, chemotherapy should be escalated or changed, then patients should be re-evaluated for resectability according to a multidisciplinary team discussion. Patients with larger or multiple liver metastasis, deemed borderline resectable can also be considered for surgery. Several techniques could be considered such as two stage procedure, selective portal vein ligation or embolisation to shrink the affected liver lobes and induce growth of the later remnant liver.

12.4. Never resectable symptomatic metastatic disease and metastases not becoming resectable

Patients with multiple metastatic sites with rapid tumour progression and/or tumour related symptoms, risk of rapid deterioration and co-morbidities are candidates for palliative treatment, allowing intensive treatments according to a multidisciplinary team discussion. The treatment aim is palliative rather than curative, (with individual exceptions e.g. in case of high chemosensitivity and major or complete response to therapy) aiming for the rapid regression of metastases to relieve symptoms, tumour associated complications

and improve the quality of life. An escalation strategy (single agent followed by combination) might have the risk that the first line treatment is not effective and switch to more effective second line treatment either will or cannot be performed or might be established too late. Therefore, very active 1° line treatment with a high likelihood to induce regression of metastases in a short time appears appropriate for most of these patients.

12.5. Never resectable and not becoming resectable metastatic disease with no major tumour related symptoms

It is not recommended to give intensive systemic treatment to asymptomatic patients with multiple metastases who will not become candidates for resection or those who have severe comorbidities according to a multidisciplinary team discussion. In these patients maximal shrinkage of metastases is not a treatment aim. Without present or imminent symptoms and limited risk for rapid deterioration, the aim is prevention of tumour progression thus avoiding the appearance of symptoms and prolongation of life with minimal treatment burden. Treatment selection is according to the disease characteristics and patients' preference regarding toxicity and efficacy. Besides a 'watchful waiting' approach, an escalation strategy seems to be appropriate, starting with single agent or well tolerated two-drug combination reserving an exceptional role to triplet combinations.

13. Synchronous colorectal metastases

13.1. Peritoneal carcinomatosis

Peritoneal carcinomatosis as single site of disease in advanced colorectal cancer represents a special biologic entity with a poor prognosis using systemic chemotherapy alone. Current data including one randomised controlled trial and numerous prospective and retrospective studies suggest a role for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) within the multimodal treatment regimen and may improve PFS as well as overall survival for selected patients with peritoneal carcinomatosis [216–218]. The procedure can be performed with acceptable morbidity and low mortality in specialised centres. Nevertheless, preoperative patient selection is crucial for the success of the combined treatment concept. Main selection criteria are good general health status, limited intraperitoneal tumour dissemination (peritoneal cancer index, PCI < 20), limited small bowel disease and no extra-abdominal metastases. Options should be offered to the patient according to the multidisciplinary team discussion. Furthermore localisation, histology and lymph node status of the primary tumour as well as response to systemic chemotherapy should be considered.

13.2. R0 resectable liver +/- lung metastases

Approximately 2–5% of colorectal cancers are diagnosed with one or a few synchronous metastases in one organ, usually liver. These patients are staged as having oligometastatic disease, and can be treated in a potentially curative fashion. The treatment strategy for synchronous oligometastatic rectal cancer should be based on the possibility to achieve R0-resection, either initially or after induction treatment for both the systemic disease and the primary tumour in a multidisciplinary team discussion [72]. It has been shown that surgical resection of colorectal liver/lung metastases (CLM) is a potentially curative treatment, with reported 5-year survival rates ranging from 30% to 50% [215,219–225]. The limited evidence does not identify the best timing for the surgery of the primary: either concomitant with resection of the metastases or delayed until after (chemo)radiation. It should be based on the individual patient by a multidisciplinary team discussion.

13.3. Colon

In case of R0-resectable primary tumour and liver +/- lung metastases up front chemotherapy with FOLFOX for 3 months followed by resection (primary or synchronous) followed by postoperative FOLFOX for 3 months could be applied [207]. In case of symptomatic primary tumour of the colon, upfront resection of primary tumour could be performed, followed by surgery for resectable metastases and postoperative adjuvant chemotherapy for 6 months. Alternatively, in case of symptomatic primary tumour of the colon, after resection of primary tumour, the perioperative approach with 3 months pre-/postoperatively chemotherapy and resection of metastases may be pursued. In selected symptomatic cases for not resectable metastases up front chemotherapy could be considered to reduce symptoms by tumour shrinkage in a multidisciplinary team discussion [72].

13.4. Rectum

In early primary tumours (<T3 N0), resection of primary and resectable metastases followed by postoperative treatment with FOLFOX for a total of 6 months should be considered [72]. In a patient who received immediate surgery, a postoperative multimodality treatment should be considered, according to the pathological stage of the tumour and the patient condition in a multidisciplinary team discussion.

With moderate consensus, it was agreed that in a patient who received immediate surgery a postoperative multimodality treatment should be considered, according to the pathological stage of the tumour and

the patient condition in a multidisciplinary team discussion.

With moderate consensus, it was agreed that when few resectable metastases in one organ are present, perioperative chemotherapy may also be considered with 3 months of preoperative FOLFOX, followed by resection of the primary and the metastases [207] and, if necessary, by postoperative chemoradiation (e.g. CRM+) with 3 months of FOLFOX in a multidisciplinary team discussion.

13.5. Potentially resectable metastatic disease after chemotherapy

For the treatment algorithm see Fig. 11.

13.6. Colon

For initially unresectable synchronous metastatic disease and an asymptomatic colon primary the most active available induction treatment should be chosen [72]. If metastases become resectable, surgery for the primary and the metastases should be performed, followed by postoperative continuation of the same regimen for a total of 6 months (including preoperative). Options should be offered to the patient according to a multidisciplinary team discussion. If metastases remain unresectable, treatment should be continued or switched, depending on quality of response.

table, treatment should be continued or switched, depending on quality of response.

13.7. Rectum

For initially unresectable metastatic disease, the most active available induction treatment should be chosen. If metastases become resectable, local treatment according to stage for the primary tumour followed by resection of primary and metastases should be performed (preoperative short course RT, preferably with a delay to surgery if locally advanced or CRT) (less optimal since the chemotherapy has limited systemic effects), followed by postoperative continuation of the same regimen for a total of 6 months (including preoperative). Options should be offered to the patients according to the multidisciplinary team discussion. If metastases remain unresectable, treatment should be continued or switched, depending on quality of response. After continuation/second line chemotherapy, if the metastases become resectable, the same flowchart as for resectable metastases after first line chemotherapy should be followed [72]. If resectability of metastases is not achieved, surgery should be avoided and local treatment should be considered for the asymptomatic primary: CRT or short course RT or brachytherapy for locally advanced tumours. In case of a symptomatic primary of the rectum, a diverting stoma or other local radiation treatment should be applied.

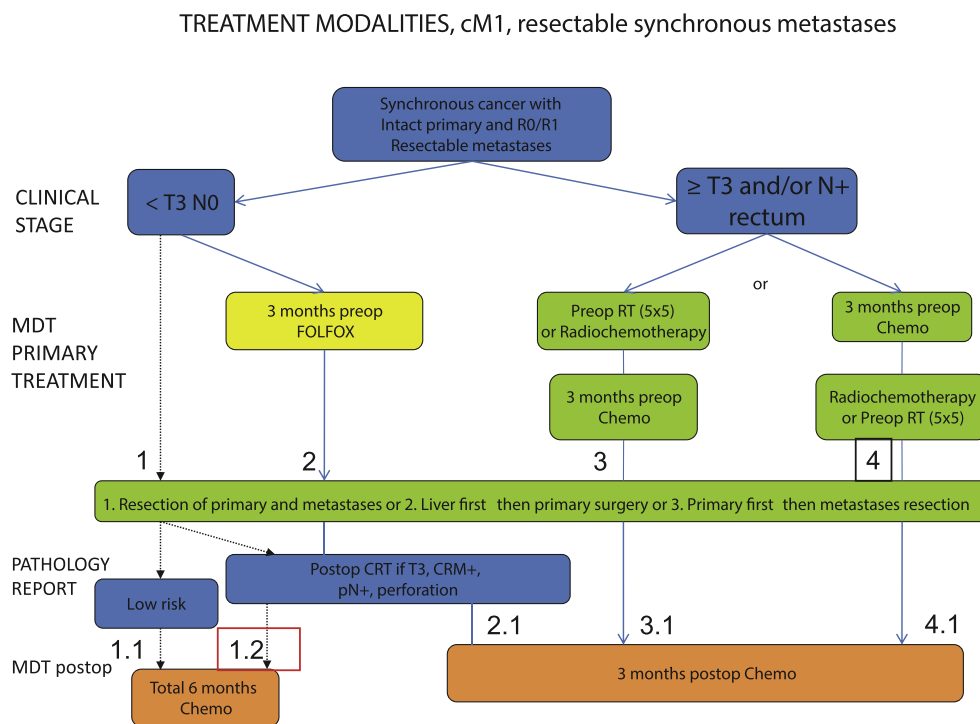


Fig. 11. Treatment modalities, cM1, resectable synchronous metastases For patients with resectable synchronous colorectal metastases, with moderate consensus it was agreed on decision 4; decision 1.2 was agreed with minimum consensus indicated by red borders.

TREATMENT MODALITIES, cM1, unresectable synchronous metastases

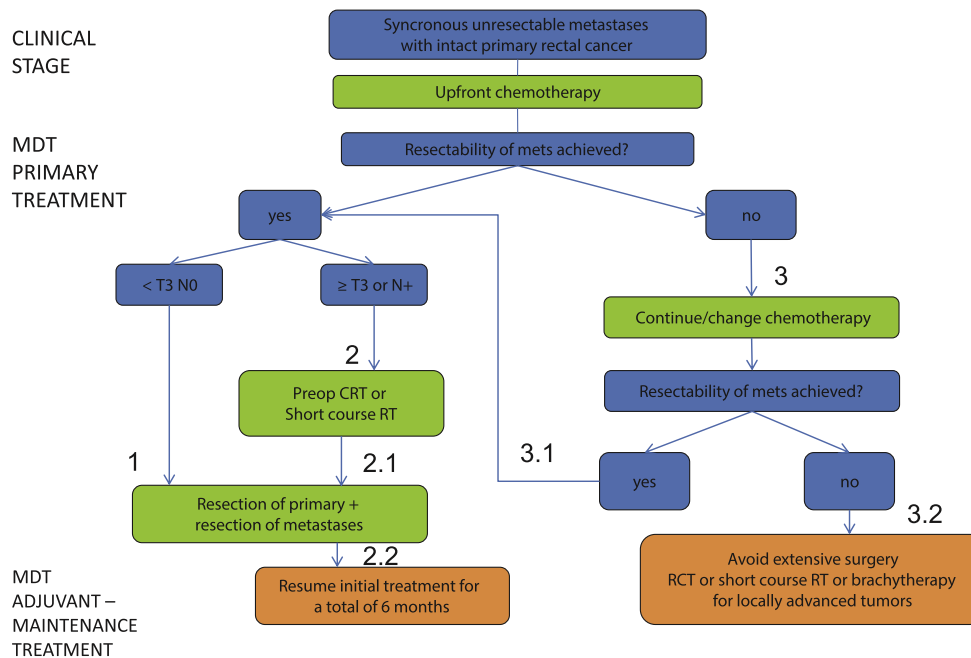


Fig. 12. Treatment modalities, cM+, unresectable synchronous metastases. All decisions were agreed with large consensus.

13.8. Never resectable metastatic disease and metastases not becoming resectable

For the treatment algorithm see Fig. 12.

Patients with multiple metastatic sites are candidates for palliative treatments [72]. They may be divided into 2 major groups:

- Group 1: Multiple sites of metastases with rapid tumour progression and/or tumour related symptoms, risk of rapid deterioration, and co-morbidities allowing intensive treatments.
- Group 2: Multiple sites metastases with no option for resection, and/or no major symptoms or risk of rapid deterioration, and/or severe comorbidities not allowing intensive systemic treatment

The treatment aim is palliative (with individual exceptions e.g. in case of high chemosensitivity and a major response) in both groups. Options should be offered to the patients according to the multidisciplinary team discussion. The main treatment goal, in the absence of symptoms, is to prevent further progression of the tumour with a minimal treatment burden or considering a ‘watchful waiting’ approach in case of an indolent disease. Options should be offered to the patients according to a multidisciplinary team discussion [72].

13.9. Colon

Upfront surgery of the primary tumour for an asymptomatic primary tumour in cases of unresectable systemic disease should not occur. In the case of unresectable disease after systemic treatment then palliative surgery, stenting or laser ablation should be confined to bleeding or obstruction and be either non-invasive measures or as minimally invasive as possible. Options should be offered to the patients according to a multidisciplinary team discussion. Up front chemotherapy should be started in the case of asymptomatic primary and unresectable systemic disease [226,227]. In case of a symptomatic primary of the colon, local measures (e.g. insertion of a stent, stoma) or resection could be performed initially; however up front chemotherapy is mostly active in eliminating local tumour related symptoms.

13.10. Rectum

The treatment aim is palliation and chemotherapy should be chosen accordingly. Options should be offered to the patient according to the multidisciplinary team discussion. Radical and mutilating surgery of the primary should be avoided, unless necessary due to an emergency presentation. Chemoradiation or 5×5 RT should be restricted to otherwise uncontrollable local tumour symptoms. Options should be offered to the

patient according to the multidisciplinary team discussion [72]. In case of a symptomatic primary of the rectum, local measures (e.g. insertion of a stent, stoma) should be performed initially and only in specific circumstances palliative surgical resection undertaken. Options should be offered to the patient according to the multidisciplinary team discussion [72].

14. Conclusion

This general consensus document was an inventory of all sentences voted on as well as discussed during the consensus meeting on the multidisciplinary care for colon and rectal cancer patients held in Perugia in 2012. The results of the Delphi consensus method are described in the text, clearly indicating the minority of the sentences that did not reach large consensus. If no large consensus was reached this is highlighted in the diagnostic and treatment algorithms. This consensus document was created for multidisciplinary teams taking care of patients with colorectal cancer. Experts review will be written to support multidisciplinary teams in their clinical decision making with interpretations of the consensus scientific evidence as well as the described controversies in diagnosis and treatment. In collaboration with EuropaColon, an executive summary expressed in a lay patient friendly language will be produced to inform patients of the recommended requirements of colorectal cancer management. Our mission is to enhance the quality assurance of the diagnosis and treatment of colorectal cancer.

Conflict of interest statement

On behalf of the authors we state that the consensus meeting was possible due to a non-restrictive unconditional grant from ESSO. No other conflict of interest for this publication.

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