European Journal of Cancer 63 (2016) 11–24

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Second St. Gallen European Organisation for Research and Treatment of Cancer Gastrointestinal Cancer Conference: consensus recommendations on controversial issues in the primary treatment of rectal cancer

Manfred P. Lutz [a,*], John R. Zalcberg [b], Rob Glynne-Jones [c], Theo Ruers [d], Michel Ducreux [e], Dirk Arnold [f], Daniela Aust [g], Gina Brown [h], Krzysztof Bujko [i], Christopher Cunningham [j], Serge Evrard [k], Gunnar Folprecht [g], Jean-Pierre Gerard [l], Angelita Habr-Gama [m], Karin Haustermans [n], Torbjörn Holm [o], Koert F. Kuhlmann [d], Florian Lordick [p], Gilles Mentha [q,†], Markus Moehler [r], Iris D. Nagtegaal [s], Alessio Pigazzi [t], Salvatore Puciarelli [u], Arnaud Roth [q], Harm Rutten [v], Hans-Joachim Schmoll [w], Halfdan Sorbye [x,y], Eric Van Cutsem [z], Jürgen Weitz [g], Florian Otto [aa]

[a] *CaritasKlinikum St. Theresia, Saarbrücken, Germany*
[b] *Department of Epidemiology and Preventive Medicine, School of Public Health, Monash University, The Alfred Centre, Melbourne, Australia*
[c] *Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, UK*
[d] *The Netherlands Cancer Institute, Amsterdam, The Netherlands*
[e] *Gustave Roussy, Université Paris-Saclay, Département de Médecine, Villejuif, France*
[f] *CUF Hospitals, Oncology Center, Lisbon, Portugal*
[g] *Universitätsklinikum Carl Gustav Carus, Dresden, Germany*
[h] *Department of Diagnostic Imaging, The Royal Marsden NHS Foundation Trust, London, UK*
[i] *The Maria Sklodowska-Curie Memorial Cancer Centre, Warsaw, Poland*
[j] *Oxford University Hospitals NHS Trust, Oxford, UK*
[k] *Institut Bergonié, Université de Bordeaux, Bordeaux, France*
[l] *Centre A Lacassagne, Nice, France*
[m] *Angelita and Joaquim Gama Institute, São Paulo, Brazil*
[n] *Department of Radiation Oncology, University Hospitals Leuven, Belgium*
[o] *Center for Digestive Diseases, Karolinska University Hospital, Stockholm, Sweden*
[p] *University Cancer Center Leipzig (UCCL), University Medicine Leipzig, Germany*
[q] *Visceral Surgery, HUG, Geneva, Switzerland*

* *Corresponding author*: Caritasklinikum Saarbrücken, St. Theresia, Medizinische Klinik, Rheinstrasse 2, 66113 Saarbrücken, Germany. Tel.: +49 681 406 1001; fax: +49 681 406 1003.
E-mail addresses: m.lutz@caritasklinikum.de (M.P. Lutz).
† Professor Mentha passed away in May 2014.

http://dx.doi.org/10.1016/j.ejca.2016.04.010

[r] I. Med. Klinik und Poliklinik, Johannes Gutenberg Universität Mainz, Mainz, Germany
[s] Department of Pathology, Radboud University Medical Center, Nijmegen, The Netherlands
[t] Department of Surgery, University of California, Irvine, CA, USA
[u] Clinica Chirurgica I, University of Padova, Padua, Italy
[v] Catharina Hospital Eindhoven, Eindhoven and GROW: School of Oncology and Developmental Biology, University Maastricht, Maastricht, The Netherlands
[w] Department of Oncology/Haematology, Martin-Luther-University Halle, Halle (Saale), Germany
[x] Department of Oncology, Haukeland University Hospital, University of Bergen, Norway
[y] Department of Clinical Science, Haukeland University Hospital, University of Bergen, Norway
[z] Digestive Oncology, University Hospitals Gasthuisberg/Leuven, Leuven, Belgium
[aa] Tumor- und Brustzentrum ZeTuP, St. Gallen, Switzerland

Received 20 January 2016; received in revised form 10 April 2016; accepted 17 April 2016
Available online 30 May 2016

KEYWORDS
Rectal cancer;
Staging;
Imaging;
Radiochemotherapy;
Radiotherapy;
Surgery

Abstract Primary treatment of rectal cancer was the focus of the second St. Gallen European Organisation for Research and Treatment of Cancer (EORTC) Gastrointestinal Cancer Conference. In the context of the conference, a multidisciplinary international expert panel discussed and voted on controversial issues which could not be easily answered using published evidence. Main topics included optimal pretherapeutic imaging, indication and type of neoadjuvant treatment, and the treatment strategies in advanced tumours. Here we report the key recommendations and summarise the related evidence. The treatment strategy for localised rectal cancer varies from local excision in early tumours to neoadjuvant radiochemotherapy (RCT) in combination with extended surgery in locally advanced disease. Optimal pretherapeutic staging is a key to any treatment decision. The panel recommended magnetic resonance imaging (MRI) or MRI + endoscopic ultrasonography (EUS) as mandatory staging modalities, except for early T1 cancers with an option for local excision, where EUS in addition to MRI was considered to be most important because of its superior near-field resolution. Primary surgery with total mesorectal excision was recommended by most panellists for some early tumours with limited risk of recurrence (i.e. cT1-2 or cT3a N0 with clear mesorectal fascia on MRI and clearly above the levator muscles), whereas all other stages were considered for multimodal treatment. The consensus panel recommended long-course RCT over short-course radiotherapy for most clinical situations where neoadjuvant treatment is indicated, with the exception of T3a/b N0 tumours where short-course radiotherapy or even no neoadjuvant therapy were regarded to be an option. In patients with potentially resectable tumours and synchronous liver metastases, most panel members did not see an indication to start with classical fluoropyrimidine-based RCT but rather favoured preoperative short-course radiotherapy with systemic combination chemotherapy or alternatively a liver-first resection approach in resectable metastases, which both allow optimal systemic therapy for the metastatic disease. In general, proper patient selection and discussion in an experienced multidisciplinary team was considered as crucial component of care.

1. Introduction

The second St. Gallen European Organisation for Research and Treatment of Cancer (EORTC) Gastrointestinal Cancer Conference 2014 focussed on the primary treatment of rectal cancer. A representative faculty of expert surgeons, radiation oncologists and medical oncologists, pathologists and gastroenterologists reviewed the current knowledge and discussed treatment recommendations in a panel session based on a moderated consensus process. The main interests were controversial issues which could not be easily answered through study of published evidence and guidelines [1–4]. As in the St. Gallen Breast Cancer Conferences, the panel was asked to assess the available evidence and vote on recommendations using a precirculated set of questions. A detailed review of the presentations has been published elsewhere [5]. Here, we summarise the key discussion points of the panel members.

The treatment strategy for localised rectal cancer is based on clinical examination together with endoscopy and imaging using either magnetic resonance imaging (MRI) and/or endoscopic ultrasonography (EUS) and is currently guided mainly by the risk of local recurrence, e.g. European Society for Medical Oncology (ESMO) [1] or the National Comprehensive Cancer Network

(NCCN) guidelines [4]. The most important aim is the prevention of recurrent disease with as little treatment-related morbidity as possible and with maintained bowel, sexual and genitourinary function. Treatment options vary from organ-preserving local excision in very early tumours to a combination of radio-chemotherapy (RCT) with extended surgery in locally advanced disease. If the risk of recurrence or lymphatic invasion is low (i.e. in cT1 sm1 tumours without nodal involvement and without unfavorable prognostic factors like poor differentiation or venous invasion), local excision may be sufficient. Primary extended surgery with total mesorectal excision (TME) is discussed for early tumours with limited risk of recurrence (i.e. mrT1-2 or mrT3a spread <5 mm, mrEMVI negative with clear TME plane), whereas all other substages are commonly considered for multimodal treatment. In any case, optimal pretherapeutic staging is essential for any treatment decision.

There is an ongoing debate on the ideal modality and sequence of combination treatment for intermediate stages. Influencing factors are depth of extramural spread, the distance from the anal verge, the circumferential location, the distance of the tumours from the mesorectal fascia, and the involvement of extramural vessels (extramural vascular invasion [EMVI]) or nerves. This uncertainty may be exemplified in T3b or less tumours in the upper or middle rectum, which have a low risk of local failure, if the tumour is >1 mm from the mesorectal fascia (MRF). For these stages, the ESMO guidelines consider primary surgery followed by adjuvant treatment if judged necessary after pathological evaluation [1], whereas the NCCN guidelines favour preoperative chemotherapy or preoperative combined RCT and recommend adjuvant treatment for all patients [4].

The choice and sequence of multimodal treatment combinations was another topic. In general, preoperative treatment is preferred because it is less toxic and more effective in local control than adjuvant treatment. Accepted standards for the preoperative approach are either the use of a short course of radiotherapy (SCRT) over 5 d followed by immediate surgery or the combination of fluoropyrimidine-based chemotherapy with a long course of conventionally fractioned RCT followed by surgery after 6–8 weeks. Compliance and immediate toxicity are in favour of SCRT, whereas RCT has the potential of downsizing and downstaging of tumours. In contrast, the standards for postoperative treatment are less well defined. Adjuvant chemotherapy (ACT) is performed in many patients who had already received preoperative RCT, even though the evidence is limited. Postoperative RCT is recommended for all pT3/T4 and/or pN+ tumours which had not been treated preoperatively, a recommendation which may not hold in limited disease (i.e. T3 tumours) or in tumours of the upper rectum.

2. Methods

In preparation for the panel session, which was held on 8th March 2014 with 27 experts, existing guidelines were used to identify areas of uncertainty in order to define the topics for debate. Over 100 questions were circulated between panel members, of which 42 were retained for the joint discussion. During the session, the panel members were asked to assess and comment on the existing data and to recommend treatment strategies as expert opinion. Panel members were given the opportunity to comment on the questions, before and after an electronic vote. Here, we summarise the extent of agreement or disagreement of the panel members.

Even though care was taken to invite a representative spectrum of panellists from relevant disciplines, the general applicability of their conclusions may be limited by an unequal distribution of disciplines and/or underrepresentation of some regions of the world. In addition, generalised treatment recommendations depend also on patient selection. The statements to follow are usually meant for reasonably fit patients with no relevant comorbidities. Many patients in clinical practice will not match the hypothetical model and treatment decisions will need to be made on an individual basis.

3. Pretherapeutic local staging

Accurate pretherapeutic imaging of the tumour and lymph nodes is the key component of any treatment decision, in addition to clinical examination, endoscopy and screening for distant metastases. The vast majority of the expert panel members considered the inclusion of MRI (91% of the panellists) or even MRI + EUS (33%) as mandatory for 'local imaging of the tumour' with no role for EUS or computed tomography (CT) scans alone. Sole exceptions are T1 tumours where organ-sparing surgery or endoscopic en-bloc resection is considered as a potential treatment option. There, EUS was recommended by 88% of the panellists because of its excellent resolution and its superior definition of the infiltration depth, with 38% opting for additional MRI.

To detect 'lymph node involvement', MRI was also considered to be the best imaging tool (92% for MRI alone, 8% together with EUS). The validated parameters using MRI are irregularity of the border and mixed signal intensity [6,7]. Using ultrasound, the roundness, echogenicity, and imaging pattern (architecture) have been described.

Several meta-analyses or systematic reviews examined the quality of T and N staging with various imaging techniques. Summary results of the largest series are listed in Table 1. However, the meta-analyses incorporating such a wide range of imaging standards must be interpreted with caution as many of the older and larger studies included used low-resolution techniques and undefined diagnostic assessment criteria.

Table 1
Pooled estimates of sensitivities and specificities of the routinely used imaging modalities for local staging of rectal cancer.

	T Staging						N Staging	
MRI [74]	T category		CRM involvement				N	
Systematic review and meta-analysis, 22 studies	Sensitivity 87 (81–92)	Specificity 75 (68–80)	Sensitivity 77 (57–90)	Specificity 94 (88–97)			Specificity 71 (58–81)	Sensitivity 77 (69
EUS [75]	T2		T3		T4			
Systematic Review, 42 studies, N = 5,039	Sensitivity 81 (78–83)	Specificity 96 (95–96)	Sensitivity 96 (95–97)	Specificity 91 (90–92)	Sensitivity 95 (92–98)	Specificity 98 (98–99)		
EUS versus MRI versus 1CT [8] Meta-analysis, 90 studies	T2 'muscularis propria invasion'		T3 'perirectal tissue invasion'		T4 'adjacent organ involvement'		N	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
EUS	94 (90–97)	86 (80–90)	90 (88–92)	75 (69–81)	67 (70–73)	78 (71–84)	67 (60–73)	78 (71–84)
MR	94(89–97)	69 (52–82)	82 (74–87)	76 (65–84)	66 (54–76)	76 (59–87)	66 (54–76)	76 (59–87)
CT	–	–	79 (74–84)	78 (73–83)	55 (43–67)	74 (67–80)	55 (43–67)	74 (67–80)

Values are expressed in % with 95% confidence interval in brackets.
CRM, circumferential resection margin; CT, computed tomography; EUS, endoscopic ultrasonography; MRI, magnetic resonance imaging.

Overall, an acceptable accuracy was demonstrated for all three imaging modalities. In a meta-analysis reviewing non–high-resolution techniques and older MRI studies, EUS performed significantly better for the definition of 'invasion into the muscularis propria', i.e. for the distinction of T1 and T2 tumours, where its specificity reached 86% (95% confidence interval [CI]: 80–90%) compared with 69% (95% CI: 52–82%) for MRI [8]. The sensitivity was high in both groups (94%), indicating a greater potential for overstaging with MRI when using older low-resolution techniques and imprecise definitions of assessment of tumour spread [8]. However, the modern high-resolution techniques have proven MRI to assess depth of spread accurately to within 1 mm of histopathology assessments [9]. The use of MRI in selecting patients for local excision rather than TME surgery now hinges on the assessment for the degree of preservation of the muscularis and submucosal layers which enable a judgement of the safety of the excision planes [5]. CT imaging was not compared because of the insufficient resolution of the layers of the rectal wall.

Results for lymph node involvement were comparable for all three modalities with low-sensitivity rates (55–69%). However, EUS can technically only be used to evaluate the perirectal lymph nodes, whereas MRI using high-resolution techniques identifies disease within the entire mesorectum and pelvic sidewall compartment. Based on the morphologic criteria of mixed signal intensity and irregularity of the nodal border rather than size criteria, the prevalence of pelvic sidewall metastatic disease is 11%, and MRI detection of patients with pelvic sidewall nodal disease is associated with poorer overall disease-free survival (DFS) unless RCT is given [9]. CT is used to examine the regional lymph nodes in the pelvis and retroperitoneum. The accuracy is related to T-stage and increases with lymph node size [10]. In a series of EUS-staged rectal cancer, lymph node metastases of increasing size were observed in the resection specimen in 29% of pT1 tumours (median size of 3.3 mm), in 30% of pT2 tumours (median size of 6.2 mm), and in 46% of pT3 tumours (median size of 8.0 mm) with resulting accuracies of preoperative imaging of 48% in pT1, 67% in pT2, and 84% in pT3. Measuring only the size of lymph nodes leads to substantial overstaging because benign reactive nodes are seen in many patients and can enlarge to any size [11]. Nodal heterogeneity or penetration of the outer rim which results in border irregularity in high-resolution images are well-known features of malignancy [6,12,13] which may be used as additional parameters if there is sufficient imaging resolution in larger nodes.

MRI will depict lymph nodes with high sensitivity and the majority of benign reactive nodes will be positioned close to the mesorectal fascia posteriorly. However, audit of specimens has shown that lymph nodes are an extremely rare cause of circumferential resection margin (CRM) involvement occurring in <1.3% of patients and, therefore, caution should be exerted when recommending neoadjuvant therapy solely because an encapsulated lymph node is visualised close to the mesorectal fascia [12]. Both EUS and CT are unable to identify the mesorectal fascia [8]. Optimised MRI performed according to standardised protocols by trained investigators is able to predict the extent of tumour outside the muscularis propria within a tolerance of 0.5 mm and correctly predicted a clear CRM in 94% in the MERCURY trial [14], with 1 mm as best cut-off distance for predicting CRM involvement [15]. Follow-up data indicate that MRI-based pretherapeutic definition of an involved CRM is an independent prognostic factor for 5-year overall survival (62.2% in

MRI-CRM clear as compared to 42.2% in CRM involved), for DFS (67.2% versus 47.3%) and for local recurrence with a hazard ratio of 3.5 (95% CI of 1.53–8.0, $p < 0.05$). MRI-defined EMVI is an additional independent poor prognostic factor for both local recurrence and for DFS in stage II/III rectal cancer [16]. Examples for a minimum technical requirements and reporting are given in Table 2.

4. Do T3 rectal cancers always need RCT or radiotherapy?

Preoperative chemoradiation (RCT) or short-course preoperative radiotherapy (SCRT) are considered standard of care for patients with clinical stage II and III rectal cancer because of the risk of local recurrence with surgery alone and because of the postulated potential for sphincter preservation. Many multidisciplinary teams advocate SCRT or RCT for all patients with rectal cancer staged as cT3 regardless of nodal status, tumour location, and proximity to other structures or extent. However, omitting RCT or SCRT would offer the benefit of improved wound healing, less frequent anastomotic leaks, avoidance of long-term radiation toxicity, and a smaller risk of secondary malignancies [17–21].

The 'site of the primary tumour location and the presence of lymph node metastases' appear crucial to decision making. The consensus panel was asked to choose the optimal preoperative treatment (SCRT, RCT, or primary surgery with no additional multimodal therapy) for three different clinical situations. For units where quality-controlled TME is done, and for easily resectable cancers of the mid-rectum with no detectable lymph node metastases (cT3 cN0), 71% of panellists did not feel combination treatment was required for all patients, but 25% did, albeit there was some debate as to the definition of 'easily resectable', which may be defined as tumours with less than 5 mm infiltration depth into the mesorectal fat and at least 1 mm distance from the mesorectal fascia (see also Table 3). In contrast, for cT3 cN0 low rectal cancer, 66% voted that SCRT or RCT were necessary. The majority of the panellists also considered RCT the best option for treating easily resectable rectal cancer of the mid-rectum with lymph node metastases (cT3 cN+). Only 20% voted that neoadjuvant treatment was not required, and 75% of the panellists considered SCRT to be an appropriate alternative option in this situation. In the interval, data have emerged from the multicentre MERCURY 2 trial which has shown that almost half of patients with tumours arising <6 cm from the anal verge when staged by MRI

Table 2
Minimum technical requirements for MRI and its interpretation and reporting in pretherapeutic staging of rectal cancer [76].

MRI staging of rectal cancer
Technical requirement
- 1.5 or 3 Tesla system with phase array coil
- Standard T2 fast-spin echo for initial localisation/planning
- High-resolution T2-weighed images: minimal voxel density of 1.1 mm^3, e.g. 3-mm sections with in-plane resolution of 0.5–0.8 mm
Scanning protocol
- Sagittal T2-weighted fast-spin echo to identify the tumour
- Large field-view axial sections of the whole pelvis
- High-resolution axial images of the tumour and adjacent tissues (perpendicular to the rectum long axis at the tumour level)
- Lymph node assessment: high-resolution axial imaging of the upper tumour border up to L5/S1
- Low tumours: high-resolution coronal imaging of levator muscles, sphincter complex and their relation to the rectal wall
- Sessile lesions/polyps: high-resolution sagittal series
Interpretation and reporting
- Technique, resolution, quality
- Height of the tumour (from the anal verge)
- Tumour description
○ Size
○ Circumferential location
○ T-stage
○ Infiltration depth beyond muscularis propria (mm)
- Nodal spread
○ Location (perirectal, pelvic)
○ Number
○ Description (size, signal intensity, irregular border)
○ Distance from tumour and MRF
- Extramural vascular invasion
- CRM status (distance to MRF < 1 mm?)

CRM, circumferential resection margin; MRI, magnetic resonance imaging.

Table 3
Proposed mid-rectal cancer risk categorisation based on MRI and clinical risk factors.

Risk stratification for cancer of the mid rectum				
Low risk	Intermediate risk			High risk
Low-risk local recurrence/ low-risk metastases	Low-risk local recurrence/ moderate-risk metastases	Moderate-risk of local recurrence/high-risk metastases	High risk of local recurrence/higher risk metastases	High-risk local recurrence/ high-risk metastases
MRI cT2/T3a/T3b, <4 mm extension into muscularis propria, CRM not threatened (predicted ≥2 mm), cN0, CT M0	MRI cT3b, >4 mm extension into muscularis propria, CRM not threatened (predicted ≥2 mm), cN1, CT M0	MRI cT3b, >4 mm cT3c, cN2, EMVI, CRM not threatened (predicted ≥2 mm), CT M0	MRI cT3d, T4a (resectable), CRM not threatened (predicted ≥2 mm), CT M0	MRI cTany, extension into muscularis propria, T4b, CRM breached or threatened (predicted <1 mm), CT M0 Possibly Mucinous
Potential MRI-directed recommendations				
No requirement for preop radiotherapy Immediate surgery	If surgeon convinced able to perform R0 resection and good quality in mesorectal plane could omit RT	SCRT depending on whether shrinkage of tumour required or neoadjuvant chemotherapy alone	SCRT or RCT depending on whether shrinkage of tumour required or neoadjuvant chemotherapy alone	Requires RCT
Clinical risk factors - Obesity - Male/with anterior tumours - Narrow pelvis - Previous pelvic surgery - Large bulky tumour - Sepsis/fistula/perforation				
UK NICE Guidelines and Recommendations				
Low risk + (but does not include T3b < 4 mm)	Any cT3b or greater, in which the potential surgical margin is not threatened or Any suspicious lymph node not threatening the surgical resection margin or The presence of extramural vascular invasion			Threatened (<1 mm) or breached resection margin or low tumours encroaching onto inter-sphincteric plane or levator involvement
Do not give RT	SCRT or RCT			RCT recommended

CRM, circumferential resection margin; CT, computed tomography; EUS, endoscopic ultrasonography; MRI, magnetic resonance imaging; RCT, radiochemotherapy; SCRT, short course of radiotherapy; NICE, National Institute for Health and Care Excellence; RT, radiotherapy.

are not invading the distal TME/intersphincteric plane. Rectal cancers localised in the upper third of the rectum were exempt from the discussion as they are usually treated by analogy with colon cancer.

A large majority of panellists believe RCT to be required if clinical staging suggests the status is 'cN+'. Also, when MRI shows a 'threatened/breached CRM' (10–15% of cases), or in cancers which require surgical resection beyond the conventional TME and in clinically unresectable cancers, downstaging is required and RCT was considered the modality of choice [22]. As a consequence, 66% of the panellists considered it necessary to distinguish between patients with MRI criteria which predict a high risk of local recurrence versus those with a high risk of metastases (i.e. EMVI) and tailor treatment appropriately.

The results from the Dutch TME trial [23] show a marginal benefit for SCRT in stage II (N0) patients (local recurrence [LR], 5.3% versus 7.2%), arguing against any preoperative therapy, but the MRC CR07 trial [24] demonstrated a reduction of LR from 6.4% to 1.9%, again with SCRT. However, none of these trials nor any of the chemoradiation trials published in the last decade have shown any difference in overall survival [25–28]. None of these trials used modern MRI staging techniques to assess CRM, mrEMVI status or depth of tumour spread beyond the muscularis propria. Norwegian population data suggested low rates of local recurrence for patients with pathological findings of a clear CRM >3 mm and pN0 [29]. Several groups, which are known to perform high-quality surgery, have recently explored omitting radiotherapy when MRI suggests the tumour is easily resectable and the mesorectal fascia is not threatened regardless of nodal stage. This omission is associated with the local recurrence rates of <5% [30–33].

The 'quality of surgery' is crucial. The majority of local recurrences historically reflected inadequate mesorectal resection [34], which is a common finding on postoperative MRI after partial mesorectal excision [35]. Careful dissection particularly in the posterior aspect of a TME specimen with its higher prevalence of lymph nodes is important [36]. Currently, optimal quality-controlled surgery in terms of TME in the trial setting can be associated with local recurrence rates of less than 10% whether patients receive radiotherapy or not [37].

There are also significant 'late effects from pelvic radiotherapy' on anorectal, urinary and sexual function [17,38,39], unexplained late cardiac effects [17], insufficiency fractures in the pelvis [40], and an increased risk of secondary malignancies after 10 years [20,21]—all of which need to be balanced against the risk of local recurrence.

Some have, therefore, questioned the routine use of both these approaches (RCT and SCRT). Fluoropyrimidine-based RCT does not employ full systemically active doses of chemotherapy and delays the integration of ACT. Many current investigative approaches in rectal cancer take the view that better results might be obtained by adding and/or extending more intensive chemotherapy into the neoadjuvant setting. The question is, whether radiotherapy is needed at all?

5. Neoadjuvant long-course RCT versus SCRT

The aims of neoadjuvant therapy in locally advanced rectal cancer (LARC) are to decrease the risk of locoregional relapse and to downsize/downstage tumours that threaten the mesorectal fascia or to facilitate sphincter preservation. Long-course RCT or SCRT is currently used (Tables 4 and 5). In the latter, the original protocol scheduled the operation for the week following radiation therapy. More recently, protocols for delayed surgery have been evaluated in clinical trials [41].

The consensus panel discussed the indications for RCT and SCRT in various clinical situations. Rectal cancers localised in the upper third of the rectum were exempt from the discussion as they are usually treated similarly to colon cancer.

For easily resectable rectal cancer of the mid-rectum with no detectable lymph node metastases (cT3 cN0), an equal number of panellists favoured either option, if a combined therapy was indicated. In the trials directly comparing SCRT and RCT [19,42], LR rates were similar and 75% of the panellists considered SCRT to be acceptable in this situation. As discussed above, the indication for preoperative therapy in this group of patients has been questioned since the introduction of TME has significantly reduced the rate of LR.

However, more than half of the panellists considered RCT the best option for cancer of the mid-rectum with lymph node metastases (cT3 cN+) even when it was easily resectable, with only very few voting against any neoadjuvant treatment. Both the Dutch and the MRC trials [23,24] show a significant decrease of LR in node-positive tumours in the TME era. However, analysis of the surgical specimen quality in the CR07 trial has also shown that pelvic recurrence rates were 20% for poor-grade TME compared with only 6% for good-quality CRM-negative TME node-positive patients which compared favourably with 5% local recurrence rates in node-negative patients in good-grade TME specimens [37]. Approximately 18% of audited TME specimens in the Dutch TME trial were poor grade and preoperative CRM status had not been assessed in either CR07 or Dutch TME trials. Therefore, a neoadjuvant approach seems indicated in node-positive disease if the quality of the TME surgery is in doubt and preoperative assessment of the MRI-validated prognostic factors linked to local recurrence, i.e. mrCRM, mrT substage and mrEMVI, is not established.

For rectal cancer situated in the 'low rectum' (without lymph node metastases), three quarters of the panellists favoured RCT and only one quarter considered SCRT the best option. The risk for LR for tumours in the low rectum even in the TME era and after neoadjuvant therapy is relatively high (10.1% LR in the German trial) [43]. Implementation of an MRI-based low rectal cancer staging classification enables identification of patients for primary surgery with a 98% clear margin rate in just under half of the patients presenting with low-risk rectal cancers at <6 cm from the anal verge. Preoperative therapy of high-risk MR low rectal cancer tumours followed by a good mrTRG and regression of tumour from the intersphincteric plane results in 0% pCRM rates. A poor response necessitates the use of a beyond TME approach in order to achieve clear margins either by extralevator APE or in some cases exenterative surgery [44].

The role of SCRT was first established in the 1990s by a series of randomised trials [45–47] in resectable and early rectal cancers with the aim of reducing the risk of

Table 4
Comparison of treatment and performance characteristics of SCRT or RCT for rectal cancer.

	SCRT Short-course radiotherapy	RCT Long-course radiochemotherapy
Total radiation dose	25 Gy	45–50.4 Gy
Fraction size/number	5 Gy in five fractions	1.8–2 Gy in 23–28 fractions
Radiation duration	1 week	5–5.5 weeks
BED, acute effects	37.5 Gy	37.5–44.4 Gy
BED, late effects	66.7	72–84 Gy
Overall time to surgery	10 d	10–14 weeks
Concomitant chemotherapy	No	Yes
Acute toxicity	Minimal if immediate surgery	10–24% G3
Late toxicity	G3/G4 8–10%	G3/G4 8–10%
Downsizing/downstaging	No (unless surgery delayed)	Yes

BED, biologically effective dose; RCT, radiochemotherapy; SCRT, short course of radiotherapy.

Table 5
Summary results of randomised radiotherapy trials in rectal cancer.

	Treatment arms	TME	Stages	Adjuvant chemotherapy	LR (5 years)	DR (5 years)	OS (5 years)	Remarks
Trials with RCT (long-course RCT)								
EORTC 22921 [51], N = 1011	25 × 1.8 Gy 25 × 1.8 Gy/preop 5FU 25 × 1.8 Gy/postop 5FU 25 × 1.8 Gy/preop + postop	n.a.	II–III	4 Cycles 5FU/LV (depending on treatment arm)	21.9% 10.9% 13.7% 10.7%	36.9% 32.1% 33.5% 29.8%	No significant difference at 10 years	Bolus 5FU/LV with radiotherapy (depending on treatment arm)
FFCD 92032 [27], N = 733	25 × 1.8 Gy 25 × 1.8 Gy/bolus 5FU	Rec.	II–III	4 Cycles 5FU/LV	16.5% 8.1%	19.3% 24.3%	67.9% 67.4%	Bolus 5FU/LV with radiotherapy
NSABP R-03 [28], N = 267	Preop 28 × 1.8 Gy/5FU Postop 28 × 1.8 Gy/5FU	n.a.	II–III	5 Cycles 5FU/LV	10.7% 10.7%	n.a.	74.5% 65.6%	Bolus 5FU/LV with radiotherapy
CAO/ARO/AIO-94 Trial [43], N = 823	Preop 28 × 1.8 Gy/5FU Postop 28 × 1.8 Gy/5FU	Yes	II–III	4 Cycles 5FU/LV	5.0% 9.7%	29.8% (10 years) 29.6%	59.6% (10 years) 59.9%	CIV 5FU with radiotherapy
Trials with SCRT (short-course radiotherapy)								
Swedish Rectal Cancer Trial [45], N = 1168	None 5 × 5 Gy	No	I–III	No	26% (13 years) 9%	34% (13 years) 34%	30% (13 years) 38%	Equal effects for mid and low rectum
Dutch Colorectal Cancer [46] Group Trial 2, N = 1861	None 5 × 5 Gy	Yes	I–III (–IV)	No	10.9% 5.6%	28.3% 25.8%	63.5% 64.2%	Little effect for high and low rectum
MRC CR-07/NCIC-CTG C016 [24] N = 1350	5 × 5 Gy (postop 25 × 1.8 Gy, 5FU)	Rec.	I–III	According to local policy	4.7% 11.5%	19% 21%	70.3% 67.9%	Postop. RCT for involved circumferential margin only
Polish Rectal Cancer Trial [19], N = 312	5 × 5 Gy 28 × 1.8 Gy, bolus 5FU	Yes	T3/4 N0-2	Optional	9.0% (4 years) 14.2%	31.4% (4 years) 34.6%	67.2% (4 years) 66.2%	
Trans-Tasman Trial 01.04 [42], N = 326	5 × 5 Gy 28 × 1.8 Gy, 5FU CIV	Yes	T3 N0-2	Mandated FUFA 6/12	7.5% (3 years) 4.4%	27% 30%	74% 70%	Imbalance regarding location of primary
Pach *et al.* [77], N = 154	5 × 5 Gy surgery 7–10 d 5 × 5 Gy surgery 4–5 weeks	n.a.	I–III	Not stated	1.5% 7%		63% 73%	Delayed surgery may require longer interval

EORTC, European Organisation for Research and Treatment of Cancer; n.a., not applicable; TME, percentage of patients treated with total mesorectal excision; LR, local recurrence; DR, distal recurrence; OS, overall survival; preop, preoperative; postop, postoperative; RCT, radiochemotherapy; Rec., recommended; FFCD, Fédération Francophone de Cancérologie Digestive; NSABP, National Adjuvant Breast and Bowel Project; CAO/ARO/AIO, Chirurgische Arbeitsgemeinschaft Onkologie/Arbeitsgemeinschaft Radioonkologie/Arbeitsgemeinschaft Internistische Onkologie; MRC, Medical Research Council; NCIC-CTG, National Cancer Institute of Canada Clinical Trials Group; LV, leucovorin; 5FU, 5-fluorouracil.

local recurrence, which was 20–30% after surgery alone, reflecting the suboptimal surgical practice at that time. Two subsequent, more modern trials early in the TME era, addressed the key question: did SCRT simply compensate for poor surgical technique? These trials tested whether SCRT still reduced local recurrence even if TME was performed [24,46]. In the control group, postoperative radiotherapy or RCT was intended to be given in the event of a histopathological positive CRM in the Dutch TME study and the CR07 trial, respectively. Both trials demonstrated a reduction in local recurrence, but overall survival was not improved, and the risk of metastases predominated over local recurrence [21,24,37,46].

The second radiation option is combined RCT with daily radiation fractions of 1.8 − 2.0 Gy up to a total dose of 45 − 50 Gy. Concurrently, a fluoropyrimidine-based chemotherapy is given, most often infusional 5-fluorouracil (5FU) or capecitabine, which has been extrapolated from the successful strategy of postoperative 5FU-based RCT for patients with stage II or III rectal cancer. Several groups performed randomised trials of preoperative 5FU-based RCT and demonstrated an improvement in locoregional control [25–27] but this did not translate into an improvement in DFS or OS. Only in more advanced unresectable or borderline resectable cases did RCT result in improved resectability and DFS [22].

With the increased accuracy of preoperative imaging to define the potential for curative resection, RCT has been taken up more widely, particularly when the CRM is predicted to be compromised. In contrast, SCRT and immediate surgery is primarily not intended to achieve significant shrinkage or pathological downstaging. The Dutch TME trial found no significant difference in TNM stage distribution between SCRT and surgery-alone groups [46], but T-stage downstaging was observed if surgery was delayed for more than 10 d following the completion of SCRT [48]. Further extension of the interval following SCRT to surgery of at least 6 weeks does demonstrate more downstaging, but the optimal interval has not been defined [41,49]. Whether the same degree of tumour shrinkage to that seen with RCT can be achieved with SCRT and an extended interval to surgery is currently unclear. Recent preliminary data from a Polish trial comparing two neoadjuvant treatment protocols (SCRT followed by 4 × FOLFOX4 or RCT with bolus 5FU/leucovorin (LV) and oxaliplatin) resulted in comparable local efficacy and possibly improved overall survival with SCRT (ASCO GI 2016, Abstract # 489).

Overall, the consensus panel recommended long-course RCT over short-course radiotherapy for most clinical situations in which neoadjuvant treatment is indicated, with the exception of T3a/b N0 tumours with clear mesorectal fascia (>1 mm) where short-course radiotherapy or no therapy were regarded to be equivalent.

6. Adjuvant chemotherapy

Most cancer-related deaths in patients with rectal cancer are due to distant metastases. ACT in colon cancer reduces the incidence of distant relapse and improves overall survival. In analogy, ACT was integrated into postoperative and perioperative treatment strategies in rectal cancer. However, although ACT after preoperative RCT and surgery is currently recommended in most guidelines [50], the contribution of the adjuvant part to the benefit of the perioperative therapy had not been formally tested in a randomised trial at the time of the St. Gallen 2014 consensus meeting. The first indication that ACT may not improve local or distant relapse rate after preoperative RCT came from the EORTC 22921 trial [51] and was further questioned in other trials [52–54] (see Table 6).

At the consensus session, most panellists (83%) recommended against ACT for cN0/ypN0 tumours. However, for tumours that were initially lymph node positive but became lymph node negative after RCT (i.e. cN+/ypN0), the panellists' opinion on ACT was divided (pro 41%, con 59%). In cases with histologically confirmed positive lymph nodes after neoadjuvant RCT

Table 6
Adjuvant chemotherapy trials in rectal cancer and meta-analysis.

	Treatment Arms	Stages	DFS	OS	Remarks
EORTC 22921 [51]	Follow-up	II–III	47%	51.8%	At 10 years
N = 1011	5FU/LV		43.7%	48.4%	
Chronicle [52]	Follow-up	I–III	71.3%	87.8%	At 3 years
N = 113	Xelox		77.5%	88.8%	
I-CNR-RT [54]	Follow-up	II–III	62.8%	70%	At 5 years
N = 655	5FU/LV		65.3%	69.1%	
PROCTOR/SCRIPT [53]	Follow-up	II–III	55.4%	79.2%	At 5 years
N = 823	5FU/LV or cape		62.7%	80.4%	
Meta-analysis [55]	Follow-up	II–III	HR 0.91	HR 0.97	10–15 cm from anal verge
N = 1196	Adjuvant chemotherapy		(0.77–1.07)	(0.81–1.17)	HR for DFS 0.59 (0.40–0.85)

cape, capecitabine; DFS, disease-free survival; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; OS, overall survival.

(ypN+), the majority of panellists (77%) voted in favour of ACT.

About half the panellists (47%) were in favour of ACT that included oxaliplatin with 16% against this option. When ACT is indicated, most panellists (68%) agreed that a colostomy should be closed after completion of chemotherapy to avoid an interruption that might mitigate the effect of the ACT.

After the consensus meeting, results from a number of clinical trials investigating the role of ACT in this situation were published (Table 6). Since these results have the potential to change clinical practice, we compiled the evidence in a table without additional panel voting. These new data do not support the further use of ACT as a standard in mid and low rectal cancer (less than 10 cm from the anal verge) after neoadjuvant RCT and R0 resection, irrespective of T stage and nodal status [55]. However, for upper rectal cancer between 10 and 15 cm from the anal verge, ACT can be considered as standard for lymph node–positive tumours (either cN+ before neoadjuvant therapy and/or ypN+) [55]. This regimen should usually include oxaliplatin (panel: 47% yes, 16% no, 37% abstain), which is supported by data from colon cancer and from a phase II trial in rectal cancer [56].

7. Clinical complete response after preoperative long-course RCT

After RCT, some patients experience a complete clinical response of their tumour. Managing these patients without immediate surgery, but with frequent surveillance presents an option that may obviate the need for a surgical intervention for some of them [57]. To test the limits of this strategy, the panellists were asked whether this 'watch and wait' strategy was also justified in lymph node–positive, low rectal cancer. In this situation, the panel was equally divided for and against. Half of the panellists were in favour of 'adjuvant' chemotherapy after achieving a complete clinical response by RCT provided careful follow up was feasible, thus avoiding a primary operation. We did not ask if local excision with organ preservation was also considered as an option.

8. Rectal cancer with synchronous liver metastases

The incidence of synchronous liver metastases in patients with primary rectal cancer is approximately 15% [58]. The principle treatment goal is complete resection of all primary and metastatic lesions with a curative approach, but the choice and sequence of the available treatment modalities depend on the clinical situation. Patients can grossly be divided into two groups: those with initially resectable and potentially resectable disease after conversion therapy and those patients in whom complete resection of the primary tumour or the metastases will not be achievable.

In patients with 'unresectable metastatic rectal cancer', the primary treatment goal is maintaining quality of life, improving tumour-related symptoms and minimising treatment-related side-effects. Accordingly, if the primary tumour was not going to be removed, the panel voted against pelvic radiotherapy in patients with an asymptomatic rectal tumour and synchronous liver metastases (79% no) and also against local ablative treatment by surgery or radiologic intervention even if the hepatic lesions were small and few (80% no).

Reported mortality after resection of the primary tumour in patients with incurable stage IV colorectal cancer ranges from 1.3% to 16%, which is significantly higher than resection for colorectal cancer in general [59,60]. For this reason, there is a tendency towards a conservative approach, especially in asymptomatic patients. A deviating loop colostomy (preferably by laparoscopy) is often an effective alternative. Palliative pelvic radiotherapy was analysed in a systematic review by Cameron *et al.* [62] and showed a pooled overall symptom response rate of 75%, although toxicity results were not available [61]. SCRT with chemotherapy has even been shown to spare palliative surgery in 80% of symptomatic patients in a phase II trial. A stent can be placed to treat obstructing rectal cancer, but endoscopic stenting options for low-lying rectal tumours are limited and may cause significant side-effects. A randomised study by Fiori *et al.* [63] analysed 22 patients with stage IV unresectable rectosigmoid cancer with symptoms of subacute obstruction. Patients were treated by either endoscopic placement of an expandable stent or diverting proximal colostomy and were followed until death. There were no differences between treatment-related morbidity or mortality, but hospital stay and restoration of oral feeding and bowel function were shorter after stenting.

In 'potentially resectable disease', treatment of the primary rectal tumour per se consists of surgery after SCRT or RCT. Most patients with synchronous liver metastases present with advanced rectal disease and, thus, formally have an indication for prior RCT [64]. However, standard RCT based on a fluoropyrimidine-alone chemotherapy backbone likely results in under-treatment of the metastatic disease for a substantial time interval which may be further prolonged by postoperative complications if the rectal tumour is removed first. Therefore, the panel did not see an indication to start with fluoropyrimidine-based RCT in these patients (83% no).

As SCRT and delayed (4–8 weeks) rectal surgery in resectable cancers can result in local tumour regression in 74% of patients and has a low-toxicity profile [65], it may offer both local control and, more importantly, the opportunity to start systemic therapy almost instantly, optimising the treatment of metastatic disease. The feasibility of such an approach has been demonstrated in a phase II trial, where SCRT was followed by capecitabine, oxaliplatin, and bevacizumab for up to six

cycles and surgery 6–8 weeks after the last cycle [66]. Radical R0 surgery of all tumour sites was possible in 36 of 50 (72%) patients. An interim analysis of a randomised trial in patients with fixed cT3 or cT4 or locally recurrent rectal cancer showed this strategy (SCRT + FOLFOX) achieved a microscopically radical resection (primary end-point) in 73% [67].

'Systemic therapy alone' can also induce significant response of the tumour. A case series of 22 patients with rectal cancer demonstrated an objective pathological response in 12 patients, including one patient with a complete response [68]. Prior to the start of treatment, symptomatic rectal tumours with clinical signs of obstruction should be decompressed with a colostomy to avoid treatment delays for emergency intervention. However, in patients with an endoscopically obstructing tumour only (with no clinical symptoms or signs of obstruction), a diversion colostomy seems not needed. Patel *et al*. [69] showed progression to complete obstruction needing surgery in only 2 of 85 patients during neoadjuvant systemic therapy in patients with endoscopically obstructing rectal tumours. As to the panel, all members elected combination regimens for initial treatment.

Traditionally, the strategy for surgical management of colorectal carcinoma with resectable liver metastases was resection of the primary tumour followed by treatment of the liver metastases, with or without perioperative systemic therapy. This approach has been challenged by a 'liver-first approach' because the prognosis is usually related to the liver metastases. Furthermore, the liver-first approach has a higher percentage of patients completing the full treatment protocol and it avoids delay due to complications of rectal surgery [70]. The St. Gallen panel saw a place for the primary resection of a small resectable liver lesion before the start of RCT for LARC (52% yes versus 43% no).

In a systematic review of patients with colorectal tumours, the common treatment sequence in four studies comprised neoadjuvant systemic chemotherapy, liver resection, RCT for the rectal tumours, followed by colorectal resection and ACT; 90 of the 121 (74%) patients in this review completed the full treatment protocol and disease progression occurred in 23 patients (19%). In the study describing patients with rectal cancer only, 73% (16 of 22) completed the full protocol with a 5-year survival rate of 67% and a median progression-free survival of 19 months [71]. Another argument to choose a liver-first strategy in patients with synchronous rectal cancer is the chance of a complete response of the primary tumour after chemoradiation of 15–25% and, thus, the possibility of a wait-and-see policy [72]. Synchronous resection has been proposed as an alternative approach with less abdominal interventions, but this approach has not been compared to others in a randomised trial [73]. An important factor seems to be patient selection by an experienced multidisciplinary team.

In summary, optimised MRI with standardised protocols or MRI + EUS were considered as corner stones of pretherapeutic imaging. Early tumours with limited risk of recurrence were considered as candidates for primary surgery whereas all others should receive multimodal treatment. In general, long-course RCT was preferred over short-course radiotherapy, if neoadjuvant treatment is indicated. In patients with resectable synchronous liver metastases, a treatment strategy with optimum systemic chemotherapy supported by short-course radiotherapy of the primary tumour was the favoured approach.

Conflict of interest statement

None declared.

Acknowledgements

This meeting was made possible through the financial support of St. Gallen Oncology Conferences. We wish to thank Hans-Jörg Senn and Agnes Glaus for sharing their expertise from the St. Gallen Breast Cancer Conference as well as Judith Eberhardt for the excellent operational management of the meeting.

References

[1] Glimelius B, Tiret E, Cervantes A, Arnold D, Group EGW. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(Suppl. 6):vi81–8.
[2] Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol 2012;23(10):2479–516.
[3] Monson JR, Probst CP, Wexner SD, Remzi FH, Fleshman JW, Garcia-Aguilar J, et al. Failure of evidence-based cancer care in the United States: the association between rectal cancer treatment, cancer center volume, and geography. Ann Surg 2014;260(4):625–31. discussion 631–2.
[4] Benson 3rd AB, Venook AP, Bekaii-Saab T, Chan E, Chen YJ, Cooper HS, et al. Rectal cancer, version 2.2015. J Natl Compr Canc Netw 2015;13(6):719–28. quiz 728.
[5] Otto F, Lutz MP. Early gastrointestinal cancers II: rectal cancer. In: Recent results in cancer research. Cham: Imprint: Springer; 2014. VIII. 252 S.
[6] Brown G, Richards CJ, Bourne MW, Newcombe RG, Radcliffe AG, Dallimore NS, et al. Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. Radiology 2003;227(2):371–7.
[7] Yu SK, Tait D, Chau I, Brown G. MRI predictive factors for tumor response in rectal cancer following neoadjuvant chemoradiation therapy–implications for induction chemotherapy? Int J Radiat Oncol Biol Phys 2013;87(3):505–11.
[8] Bipat S, Glas AS, Slors FJ, Zwinderman AH, Bossuyt PM, Stoker J. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging–a meta-analysis. Radiology 2004;232(3):773–83.
[9] Group MS, Shihab OC, Taylor F, Bees N, Blake H, Jeyadevan N, et al. Relevance of magnetic resonance imaging-detected pelvic

sidewall lymph node involvement in rectal cancer. Br J Surg 2011; 98(12):1798–804.
[10] Landmann RG, Wong WD, Hoepfl J, Shia J, Guillem JG, Temple LK, et al. Limitations of early rectal cancer nodal staging may explain failure after local excision. Dis Colon Rectum 2007; 50(10):1520–5.
[11] Dworak O. Number and size of lymph nodes and node metastases in rectal carcinomas. Surg Endosc 1989;3(2):96–9.
[12] Brown G. Local radiological staging of rectal cancer. Clin Radiol 2004;59(3):213–4.
[13] Kim JH, Beets GL, Kim MJ, Kessels AG, Beets-Tan RG. High-resolution MR imaging for nodal staging in rectal cancer: are there any criteria in addition to the size? Eur J Radiol 2004;52(1): 78–83.
[14] Group MS. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ 2006;333(7572):779.
[15] Taylor FG, Quirke P, Heald RJ, Moran B, Blomqvist L, Swift I, et al. One millimetre is the safe cut-off for magnetic resonance imaging prediction of surgical margin status in rectal cancer. Br J Surg 2011;98(6):872–9.
[16] Smith NJ, Barbachano Y, Norman AR, Swift RI, Abulafi AM, Brown G. Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. Br J Surg 2008;95(2):229–36.
[17] Pollack J, Holm T, Cedermark B, Altman D, Holmstrom B, Glimelius B, et al. Late adverse effects of short-course preoperative radiotherapy in rectal cancer. Br J Surg 2006;93(12):1519–25.
[18] Teo MT, Sebag-Montefiore D, Donnellan CF. Prevention and Management of Radiation-induced Late Gastrointestinal Toxicity. Clin Oncol (R Coll Radiol) 2015;27(11):656–67.
[19] Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93(10):1215–23.
[20] Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Occurrence of second cancers in patients treated with radiotherapy for rectal cancer. J Clin Oncol 2005;23(25):6126–31.
[21] van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011;12(6):575–82.
[22] Braendengen M, Tveit KM, Berglund A, Birkemeyer E, Frykholm G, Pahlman L, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol 2008;26(22): 3687–94.
[23] Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 2007;246(5):693–701.
[24] Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009;373(9666):811–20.
[25] Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351(17): 1731–40.
[26] Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355(11):1114–23.
[27] Gerard JP, Conroy T, Bonnetain F, Bouche O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;24(28):4620–5.
[28] Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Allegra CJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 2009;27(31):5124–30.
[29] Eriksen MT, Wibe A, Hestvik UE, Haffner J, Wiig JN, Norwegian Rectal Cancer G, et al. Surgical treatment of primary locally advanced rectal cancer in Norway. Eur J Surg Oncol 2006;32(2): 174–80.
[30] Taylor FG, Quirke P, Heald RJ, Moran B, Blomqvist L, Swift I, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone: a prospective, multicenter, European study. Ann Surg 2011;253(4):711–9.
[31] Frasson M, Garcia-Granero E, Roda D, Flor-Lorente B, Rosello S, Esclapez P, et al. Preoperative chemoradiation may not always be needed for patients with T3 and T2N+ rectal cancer. Cancer 2011;117(14):3118–25.
[32] Mathis KL, Larson DW, Dozois EJ, Cima RR, Huebner M, Haddock MG, et al. Outcomes following surgery without radiotherapy for rectal cancer. Br J Surg 2012;99(1):137–43.
[33] Marinello FG, Frasson M, Baguena G, Flor-Lorente B, Cervantes A, Rosello S, et al. Selective approach for upper rectal cancer treatment: total mesorectal excision and preoperative chemoradiation are seldom necessary. Dis Colon Rectum 2015; 58(6):556–65.
[34] Syk E, Torkzad MR, Blomqvist L, Nilsson PJ, Glimelius B. Local recurrence in rectal cancer: anatomic localization and effect on radiation target. Int J Radiat Oncol Biol Phys 2008;72(3): 658–64.
[35] Bondeven P, Hagemann-Madsen RH, Laurberg S, Pedersen BG. Extent and completeness of mesorectal excision evaluated by postoperative magnetic resonance imaging. Br J Surg 2013; 100(10):1357–67.
[36] Perez RO, Seid VE, Bresciani EH, Bresciani C, Proscurshim I, Pereira DD, et al. Distribution of lymph nodes in the mesorectum: how deep is TME necessary? Tech Coloproctol 2008; 12(1):39–43.
[37] Quirke P, Steele R, Monson J, Grieve R, Khanna S, Couture J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. Lancet 2009;373(9666):821–8.
[38] Peeters KC, van de Velde CJ, Leer JW, Martijn H, Junggeburt JM, Kranenbarg EK, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients–a Dutch colorectal cancer group study. J Clin Oncol 2005;23(25):6199–206.
[39] Lange MM, den Dulk M, Bossema ER, Maas CP, Peeters KC, Rutten HJ, et al. Risk factors for faecal incontinence after rectal cancer treatment. Br J Surg 2007;94(10):1278–84.
[40] Herman MP, Kopetz S, Bhosale PR, Eng C, Skibber JM, Rodriguez-Bigas MA, et al. Sacral insufficiency fractures after preoperative chemoradiation for rectal cancer: incidence, risk factors, and clinical course. Int J Radiat Oncol Biol Phys 2009; 74(3):818–23.
[41] Pettersson D, Lorinc E, Holm T, Iversen H, Cedermark B, Glimelius B, et al. Tumour regression in the randomized Stockholm III trial of radiotherapy regimens for rectal cancer. Br J Surg 2015;102(8):972–8. discussion 978.
[42] Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30(31): 3827–33.

[43] Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012;30(16):1926–33.
[44] Battersby NJ, How P, Moran B, Stelzner S, West NP, Branagan G, et al. Prospective validation of a low rectal cancer magnetic resonance imaging staging system and development of a local recurrence risk stratification model: The MERCURY II study. Ann Surg 2016;263(4):751–60.
[45] Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005;23(24):5644–50.
[46] Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345(9):638–46.
[47] Cedermark B, Johansson H, Rutqvist LE, Wilking N. The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. Stockholm Colorectal Cancer Study Group. Cancer 1995;75(9):2269–75.
[48] Marijnen CA, Nagtegaal ID, Klein Kranenbarg E, Hermans J, van de Velde CJ, Leer JW, et al. No downstaging after short-term preoperative radiotherapy in rectal cancer patients. J Clin Oncol 2001;19(7):1976–84.
[49] Latkauskas T, Pauzas H, Gineikiene I, Janciauskiene R, Juozaityte E, Saladzinskas Z, et al. Initial results of a randomized controlled trial comparing clinical and pathological downstaging of rectal cancer after preoperative short-course radiotherapy or long-term chemoradiotherapy, both with delayed surgery. Colorectal Dis 2012;14(3):294–8.
[50] Poulsen LO, Qvortrup C, Pfeiffer P, Yilmaz M, Falkmer U, Sorbye H. Review on adjuvant chemotherapy for rectal cancer why do treatment guidelines differ so much? Acta Oncol 2015;54(4):437–46.
[51] Bosset JF, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun RJ, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 2014;15(2):184–90.
[52] Glynne-Jones R, Counsell N, Quirke P, Mortensen N, Maraveyas A, Meadows HM, et al. Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control. Ann Oncol 2014;25(7):1356–62.
[53] Breugom AJ, van Gijn W, Muller EW, Berglund A, van den Broek CB, Fokstuen T, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. Ann Oncol 2015;26(4):696–701.
[54] Sainato A, Cernusco Luna Nunzia V, Valentini V, De Paoli A, Maurizi ER, Lupattelli M, et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): long term results of a randomized trial (I-CNR-RT). Radiother Oncol 2014;113(2):223–9.
[55] Breugom AJ, Swets M, Bosset JF, Collette L, Sainato A, Cionini L, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015;16(2):200–7.
[56] Hong YS, Nam BH, Kim KP, Kim JE, Park SJ, Park YS, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. Lancet Oncol 2014;15(11):1245–53.
[57] Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Sabbagh C, Lynn PB, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys 2014;88(4):822–8.
[58] Mantke R, Schmidt U, Wolff S, Kube R, Lippert H. Incidence of synchronous liver metastases in patients with colorectal cancer in relationship to clinico-pathologic characteristics. Results of a German prospective multicentre observational study. Eur J Surg Oncol 2012;38(3):259–65.
[59] Evans MD, Escofet X, Karandikar SS, Stamatakis JD. Outcomes of resection and non-resection strategies in management of patients with advanced colorectal cancer. World J Surg Oncol 2009;7:28.
[60] Eisenberger A, Whelan RL, Neugut AI. Survival and symptomatic benefit from palliative primary tumor resection in patients with metastatic colorectal cancer: a review. Int J Colorectal Dis 2008;23(6):559–68.
[61] Cameron MG, Kersten C, Vistad I, Fossa S, Guren MG. Palliative pelvic radiotherapy of symptomatic incurable rectal cancer a systematic review. Acta Oncol 2014;53(2):164–73.
[62] Tyc-Szczepaniak D, Wyrwicz L, Kepka L, Michalski W, Olszyna-Serementa M, Palucki J, et al. Palliative radiotherapy and chemotherapy instead of surgery in symptomatic rectal cancer with synchronous unresectable metastases: a phase II study. Ann Oncol 2013;24(11):2829–34.
[63] Fiori E, Lamazza A, Schillaci A, Femia S, Demasi E, Decesare A, et al. Palliative management for patients with subacute obstruction and stage IV unresectable rectosigmoid cancer: colostomy versus endoscopic stenting: final results of a prospective randomized trial. Am J Surg 2012;204(3):321–6.
[64] Assumpcao L, Choti MA, Gleisner AL, Schulick RD, Swartz M, Herman J, et al. Patterns of recurrence following liver resection for colorectal metastases: effect of primary rectal tumor site. Arch Surg 2008;143(8):743–9. discussion 749–50.
[65] Pettersson D, Holm T, Iversen H, Blomqvist L, Glimelius B, Martling A. Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer. Br J Surg 2012;99(4):577–83.
[66] van Dijk TH, Tamas K, Beukema JC, Beets GL, Gelderblom AJ, de Jong KP, et al. Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. Ann Oncol 2013;24(7):1762–9.
[67] Bujko K, Nasierowska-Guttmejer A, Wyrwicz L, Malinowska M, Krynski J, Kosakowska E, et al. Neoadjuvant treatment for unresectable rectal cancer: an interim analysis of a multicentre randomized study. Radiother Oncol 2013;107(2):171–7.
[68] Bensignor T, Brouquet A, Dariane C, Thirot-Bidault A, Lazure T, Julie C, et al. Pathological response of locally advanced rectal cancer to preoperative chemotherapy without pelvic irradiation. Colorectal Dis 2015;17(6):491–8.
[69] Patel JA, Fleshman JW, Hunt SR, Safar B, Birnbaum EH, Lin AY, et al. Is an elective diverting colostomy warranted in patients with an endoscopically obstructing rectal cancer before neoadjuvant chemotherapy? Dis Colon Rectum 2012;55(3):249–55.
[70] Jegatheeswaran S, Mason JM, Hancock HC, Siriwardena AK. The liver-first approach to the management of colorectal cancer with synchronous hepatic metastases: a systematic review. JAMA Surg 2013;148(4):385–91.
[71] Ayez N, Burger JW, van der Pool AE, Eggermont AM, Grunhagen DJ, de Wilt JH, et al. Long-term results of the "liver first" approach in patients with locally advanced rectal cancer and

synchronous liver metastases. Dis Colon Rectum 2013;56(3):281–7.

[72] Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11(9):835–44.

[73] Silberhumer GR, Paty PB, Temple LK, Araujo RL, Denton B, Gonen M, et al. Simultaneous resection for rectal cancer with synchronous liver metastasis is a safe procedure. Am J Surg 2015;209(6):935–42.

[74] Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schmocker S, et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol 2012;19(7):2212–23.

[75] Puli SR, Bechtold ML, Reddy JB, Choudhary A, Antillon MR, Brugge WR. How good is endoscopic ultrasound in differentiating various T stages of rectal cancer? Meta-analysis and systematic review. Ann Surg Oncol 2009;16(2):254–65.

[76] Taylor FG, Swift RI, Blomqvist L, Brown G. A systematic approach to the interpretation of preoperative staging MRI for rectal cancer. AJR Am J Roentgenol 2008;191(6):1827–35.

[77] Pach R, Kulig J, Richter P, Gach T, Szura M, Kowalska T. Randomized clinical trial on preoperative radiotherapy 25 Gy in rectal cancer–treatment results at 5-year follow-up. Langenbecks Arch Surg 2012;397(5):801–7.