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Early Gastrointestinal Cancers II: Rectal Cancer

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Early Gastrointestinal Cancers II: Rectal Cancer

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Preface

At the second St. Gallen EORTC Gastrointestinal Cancer Conference held in St. Gallen, Switzerland on March 6–8, 2014, a group of renowned international experts came together to discuss the developments in diagnosis and treatment of early, potentially curable gastrointestinal malignancies. Nearly 300 participants from 43 countries took part in the 3-day conference that was organized by St. Gallen Oncology Conferences (SONK) and co-sponsored by the European Organization for Research and Treatment of Cancer (EORTC) and SONK with contribution of the European School of Oncology (ESO).

The focus of this second conference lay on rectal cancer. The experts discussed molecular and pathologic characteristics of rectal cancer, preferred methods for initial staging, novel endoscopic and surgical techniques, multimodal therapeutic approaches including radiation and medical oncology as well as quality-of-life aspects. The concluding day of the conference was dedicated to an attempt on a consensus on diagnosis and treatment of potentially curable rectal cancer. The consensus statement will be published separately in a major oncology journal. The majority of the invited expert contributions to the conference, however, are published in this volume of the internationally well-known series, *Recent Results in Cancer Research*, by Springer. We very much hope you will enjoy reading its content.

The organizers of the conference invite interested clinicians and scientists involved in the field of gastrointestinal malignancies to the next international St. Gallen EORTC Cancer Conference that will be held in St. Gallen/Switzerland, 10–12 March 2016.

St. Gallen, Switzerland — Florian Otto
Saarbrücken, Germany — Manfred P. Lutz

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Imaging Assessment of Early Rectal Cancer

Jo Waage, Fiona Taylor, James Read and Gina Brown

Abstract

Early rectal cancer (ERC) is defined as invasive adenocarcinoma spreading into, but not beyond, the submucosa or muscularis propria—that is a Dukes'A: T1N0 or T2N0 tumour in the tumour node metastasis (TNM) classification (Taylor et al. 2008). Among these tumours it is suggested that the most superficial T1 tumours least likely to metastasize to local lymph nodes than adenocarcinoma invading deeper where the rich lymphatic and venous plexuses within the submucosa provide a mechanism for tumour spread beyond the rectum. Currently, only about 10 % of patients presenting symptomatically with rectal cancer are diagnosed with early disease; however, up to 30 % of screen detected cancers are being identified as Dukes'A. Thus, the overall detection of early stage tumours is likely to increase following greater implementation in screening programs. The goal of this invited review is to provide recommendations based on the consensus discussion on the information from preoperative imaging that is of relevance for clinical decision-making for patients with early rectal cancer.

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1 Assessment and Rationale for Treatment Decisions in Early Rectal Cancer

Total mesorectal excision for invasive rectal cancer guarantees removal of the primary tumour and its draining lymph nodes in an enclosed package and is associated with <3 % risk of local recurrence if no preoperative adverse features are identified and is regarded as a standard of care for malignant lesions arising at a height of 6 cm or more. For low rectal polyps, the additional morbidity and loss of quality of life associated with an ultralow anastomosis or permanent stoma formation means that the options of alternative approaches to enable sphincter preservation while not compromising oncological outcomes increases in importance from the patient's perspective. Precise preoperative staging by imaging and histopathology is essential to enable a balanced risk assessment if more radical surgery is to be avoided.

If local excision or TEM is being considered—preoperative staging of early rectal cancer should enable surgical planning that avoids the risk of subsequent recurrence caused either by tumour perforation beyond the mesorectal envelope or of leaving viable metastatic disease within the mesorectum. In assessing early rectal cancer it is important for radiologists to recognise early stage rectal cancer that is potentially amenable to local excision. Equally, it is important for lesions detected at endoscopy to be staged prior to removal to ensure definitive treatment of high risk early stage rectal cancers for avoidance of piecemeal removal of polyp cancers. MRI or endorectal ultrasound performed prior to a biopsy is likely to be more accurate as oedema/inflammation may distort the submucosal and muscularis propria layer interfaces resulting in potential overstaging.

2 Staging Classification of Early Rectal Cancers

Early rectal cancer can manifest as either a polyp characterised by a rounded or polypoidal mass associated with a fibromuscular stalk or a sessile (flat) lesion. In polyp cancers, tumour spread extends into the stalk and then into the submucosa and beyond.

The principle of staging polyps and sessile lesions is based on knowledge that the deeper and more extensive the tumour spread is into the rich lymphatic and vascular plexuses of the mid and lower thirds of the submucosa, with a higher risk of spread into the lymphatic and venous channels beyond the confines of the rectal wall and into mesorectum.

Pedunculated polyps were originally classified by Haggitt (2008) on a 1–5 point scale to describe the level of polyp invasion and associated risk of metastatic spread to lymph nodes or vessels within the mesorectum. For sessile or flat lesions—the Kikuchi classification describes the depth of submucosal invasion. The Kikuchi classification divides the submucosa into thirds to classify T1 spread as sm1, sm2 and sm3. The upper third of the submucosa is relatively devoid of venous and lymphatic channels and the risk of nodal metastatic disease for sm1 tumours was

originally reported by Kikuchi as 0 %. For increasing submucosal invasion, a higher rate of nodal metastatic disease is seen—rising to 10 % for sm2 and 25 % for sm3 and sm3 is considered equivalent to Haggitt level 4 in terms of nodal risk spread.

Further risk factors for nodal spread have since been identified: resection margin <1 mm (high risk), 1–2 mm (risk factor), poor differentiation, mucinous or signet ring morphology, tumour budding, intramural lymphatic or vascular invasion. These factors, when incorporated into histological staging of polyps form the basis of a risk stratification that enables counselling of patients with regard to the need for definitive surgery or to consider adjuvant therapy following the local excision of an early rectal cancer.

3 Endorectal Ultrasonography

Since Dragsted et al. (1983) introduced ERUS as a method for rectal tumour evaluation, the method has been increasingly accepted as an essential part of the preoperative evaluation regime. Reviews and meta-analyses have indicated that the overall accuracy of ERUS rectal tumour staging is in the range of 80–90 % (Bipat et al. 2004; Puli et al. 2009; Hunerbein 2003). However, a number of papers evaluating the method have been published over the last two decades (see Table 1), demonstrating accuracies ranging from 55 to 97 %. This relatively wide range can, at least in part, be explained by heterogeneity in methods, study design, prevalence of different pT-stages and degree of observer experience. Multi-centre studies tend to report lower accuracies than single-centre studies from high-volume institutions. Studies have also shown that the accuracy of ERUS can be improved from low as 50 % to as high as 90 % with training (Orrom et al. 1990; Badger et al. 2007; Kav and Bayraktar 2010; Li et al. 2010; Morris et al. 2011). Development in ultrasound technology, such as strain elastography, may also contribute to improved staging of ERC (Waage et al. 2011)

4 MRI Technique and Quality

The accuracy of MRI in assessing depth of spread into or beyond the rectal wall, its ability to precisely assess the risk of CRM involvement and local recurrence on baseline and post treatment scans—was based on high quality MRI scans performed according to standardised protocol and images interpreted according to agreed diagnostic criteria, which were standardised through 1 day training workshops. When applied in the multi-centre setting at non-specialised and tertiary referral institutions alike the results were found to be reproducible and consistent. The key to improvements in diagnostic and prognostic accuracy from preoperative MRI assessment of rectal cancers was specialist gastrointestinal radiologists who worked closely with their surgeons, oncologists and pathologists in the MDT setting. The participating radiologists were responsible for reviewing and reporting all newly diagnosed rectal cancers in the MDT meetings at their respective

Table 1 Accuracy is either the reported overall uT-stage accuracy, or the accuracy computed based on information given in the papers

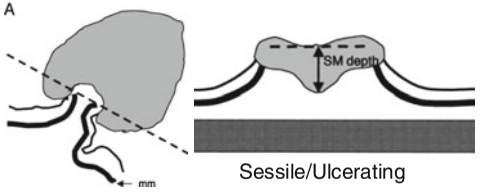
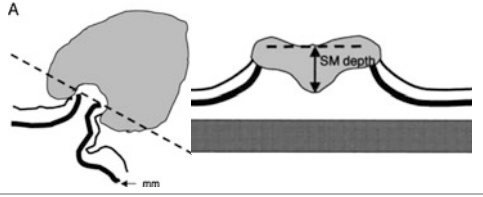
First author (ref.)	Year	Patients (n)	Reported overall uT-stage accuracy
Akahoshi (2000)	2000	39	0.83
Akasu (2009)	1997	150	0.96
Ashraf (2012)	2012	165	0.55
Bali (2004)	2004	29	0.79
Doornebosch et al. (2008)	2008		
Beynon et al. (1986)	1986	33	0.91
Fedyaev et al. (1995)	1995	132	0.91
Garcia-Aguilar et al. (2002)	2002	545	0.69
Giovanniniet al. (2006)	2006	35	0.89
Glaser et al. (1990)	1990	110	0.90
Herzog et al. (1993)	1993	118	0.89
Katsura et al. (1992)	1992	112	0.96
Kulig et al. (2006)	2006	29	0.89
Manger and Stroh (2004)	2004	357	0.77
Nielsen et al. (1996)	1996	100	0.96
Ptok et al. (2006)	2006	3501	0.66
Rafaelsen et al. (1994)	1994	107	0.92
Rifkin	1989	101	0.67
Sailer	1997	162	0.97
Santoro	2001	–	0.82
Yamashita	1988	122	0.96

institutions. Participation in the MERCURY studies showed that with only a minimal investment in training and support development of radiologists—it was possible to harmonise the standards of cancer staging preoperatively.

5 Assessing Nodal Spread Preoperatively

It is now well understood that nodal metastatic spread cannot be reliably excluded using preoperative imaging since a significant majority of metastases measure <0.3 mm in diameter and well beyond the resolution of modern imaging techniques (Landmann et al. 2007). It is also understood that measuring the size of nodes is futile since benign reactive nodes are seen in many patients with and without nodal metastatic disease and reactive nodes can enlarge to any size (Dworak 1991). Therefore, measuring lymph nodes as a means of assessing the

Table 2 Criteria of tumour measured the following characteristics were included when examining the tumours on MRI

MRI characteristic	
Tumour height from anal verge Tumour height from the puborectalis sling	Measured in the sagittal plane from the lower most fibres of the external sphincter Measured in the sagtittal plane from the uppermost border of the puborectalis muscle, verified using axial plane to cross reference anatomic location of puborectalis muscle at point of insertion into symphysis pubis
Morphology	
Diameter of the tumour (D) Diameter of the advancing edge (A) Depth of extension into the submucosa (E) thickness of preserved submucosa at the advancing edge of the tumour (SM)	
Quadrant of the advancing edge or fibromuscular stalk within the rectal wall	Anterior quadrant (10–2 o'clock) Right lateral quadrant (2–4 o'clock) Posterior quadrant (6–8 o'clock) Left lateral quadrant (8–10 o'clock)

(continued)

Table 2 (continued)

MRI characteristic	
Advancing edge	Nodular/irregular Smooth bordered
Venous invasion	Tumour signal expanding course of 1–2 mm extramural vein outside rectal wall Tumour signal expanding course of medium sized vein 3–5 mm vein Tumour expanding anatomic large vessels: superior rectal vein, lateral rectal vein and inferior rectal vein
Nodes	No visible nodes Smooth bordered uniform signal intensity Mixed signal or irregular bordered nodes

likelihood of malignancy is highly inaccurate and is not recommended as good practice in the preoperative assessment of rectal cancer (Brown et al. 2003). The positive identification of nodal or extramural disease relies on resolving tumour signal within a node and its effect on the node, which can manifest as nodal heterogeneity or penetration of the nodal capsule by tumour resulting in nodal border irregularity; this is best seen on high resolution imaging with a minimal voxel resolution of 1.1 mm^3 (Brown et al. 2004).

6 MRI Technique

A 1.5T or 3T system is used with phase array coils. The first series is the sagittal T2-weighted fast spin echo sequence to identify the primary tumour. The second series is the large field of view axial sections of the whole pelvis and the third and subsequent series consists of the high resolution images through the rectal cancer and adjacent tissues. For patients with low tumours, high spatial resolution coronal imaging will optimally show the levator muscles, the sphincter complex, the intersphincteric plane and the relationship to the rectal wall. A sagittal high resolution series will also enable multiplanar assessment of anteriorly located polyps or sessile lesions. Finally, the examination is completed by undertaking further high resolution axial imaging from the upper most border of the tumour to the L5/S1 junction to enable assessment of mesorectal nodes, venous deposits and pelvic sidewall nodes at high resolution.

7 Assessment of Pelvic Lymph Nodes

Nodal assessment with imaging takes place in two settings:

1. The initial assessment of the mesorectum prior to resection/local excision/TEM or preoperative therapy.
2. Following preoperative therapy.
3. During follow up surveillance of the mesorectum if primary radical surgery has been avoided.

In all three scenarios—it is important that the entire mesorectum above the primary tumour is imaged at high resolution, and that this covers the mesorectum to the L5/S1 sacral junction.

The absence of any visible nodes within the mesorectum is strong reassurance that there is an absence of nodal metastatic disease. The natural history of nodes containing micrometastatic disease is unpredictable and is not necessarily associated with adverse outcomes. Clearly, the absence of nodal recurrence in many patients on long-term follow up suggests that the patient's own immune system with and without the use of adjuvant chemoradiotherapy in some high risk cases results in long-term cures. The precise mechanisms for this are poorly understood—however, this favours the possibility that nodal micrometastatic disease—

at least in some patients does not necessarily equate to viable metastatic disease in the long term. Thus, surveillance of nodes is relevant and the lack of progressive change in the morphology of a node is reassuring. On the other hand, a node that changes from smooth bordered and uniform signal to a mixed signal or irregular node should be diagnosed as malignant and such patients can be successfully salvaged by surgery.

8 The Anatomy of the Rectum and Mesorectum at High Resolution

The first demonstration of the layers of the rectal wall using a high resolution MRI technique was achieved by Schnall et al. in a study of 12 patients undergoing endorectal MRI. In this paper, the authors elegantly showed how high resolution imaging depicts the layers of the rectal wall. This has been reproduced using the high resolution pelvic phased array MRI (Fig. 3).

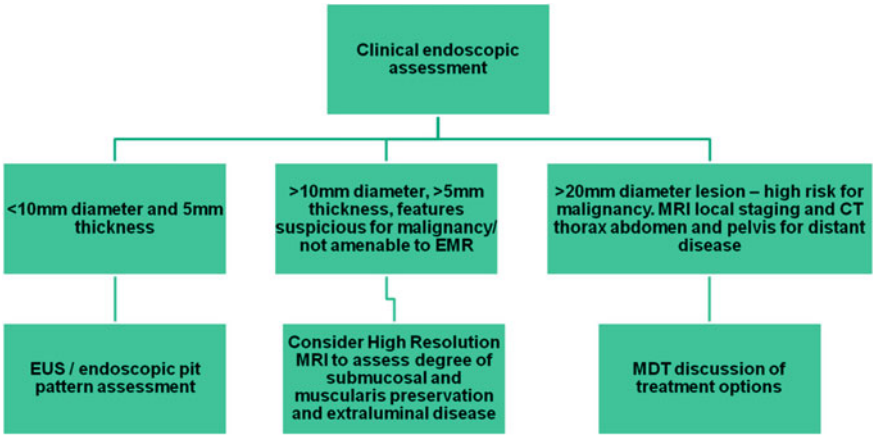
9 Preoperative Evaluation of Primary Early Rectal Cancer

Assessment of polypoidal and sessile lesions

Preoperative evaluation of polypoidal lesions is aimed at firstly determining the site of the stalk and then assessing the extension of tumour into the fibromuscular stalk and beyond. Sessile or flat lesions are characterised by lateral raised rolled edges, which are the non-invasive portions of the lesions, and the central depressed portion, which forms the advancing edge of the tumour. Preoperative assessment of sessile lesions requires detailed evaluation of the central depressed portion of the tumour and the degree of preservation identifiable in the submucosa and muscularis propria at the advancing edge. Multiplanar assessment is essential and if submucosa is evident on any single view at the base of the stalk or at the central invasive base of a sessile tumour—then this enables the confident diagnosis of a T1 lesion amenable to a local excision approach. Assessment of the depth of T stage tumour depth within and beyond the rectal wall is achieved by assessing the extent of the intermediate signal intensity tumour and its extent of spread into the submucosa, muscularis and beyond. The precise depth of extension into submucosa should be attempted, but crucially a measurement of the thickness of preserved submucosa is relevant with a thickness of >1 mm in any plane increases the likelihood of detection of an Sm1 or Sm2 lesion, which could be cured by a local excision approach. The lack of any measurable high signal intensity layer on any plane imaged between the advancing edge of the tumour and the low signal intensity of the muscularis suggests a high probability of a T1sm3 or early T2 tumour. It should be emphasised that the distinction between a T1sm3 and an early T2 is prognostically and clinically irrelevant since it means that a local excision without removal of the full thickness of the underlying muscularis propria will result in a positive deep margin of <1 mm.

In selecting patients for local excision, it is currently understood that T1 sm1 can be safely removed without further therapy since the likelihood of local relapse and tumour recurrence is low in these patients. The current gold standard for patients with T1 tumours sm2 or greater is TME surgery. This is considered a good and safe option for patients amenable to TME surgery with sphincter conservation. However, for low rectal polyps and early stage tumours within 10 mm of the puborectalis sling, surgery most often requires either an abdominoperineal excision or an ultralow intersphincteric anastomosis—both result in significant impact on patient's quality of life due to impairment or loss of sphincter function. Thus, despite the ideal recommendation being definitive surgery many patients opt for the alternative of chemoradiotherapy and surveillance following local excision or TEM of an early stage lesion. Thus, identification of patients with low lying tumours amenable to sphincter preserving approaches is becoming increasingly important.

In order to judge the safety of TEM preoperatively careful documentation of the advancing edge of the tumour is needed, and therefore precise documentation of both the quadrant (clock position) and height of tumour. Certain interfaces may limit the extent for TEM excision: the anterior rectal wall and the prostate, the tumour height and the relationship to levators, distal TME plane and the peritoneal reflection.



Algorithm for staging using MRI and ERUS in early stage rectal cancer

The goal of preoperative imaging in early stage rectal cancer, whether by EUS or MRI, is to determine the safety and feasibility of potentially less radical options such as local excision and TEM. A policy of assessing lesions prior to attempted removal would appear justified if high rates of piecemeal excision or unexpected cancers in locally excised lesions are to be avoided. It is crucial that for both MRI and EUS that appropriately trained expertise and equipment is used to optimally assess early rectal cancer. In this way, patients can be presented with a comprehensive assessment of staging findings and options for treatment, which could

range from local exicision, TEM, or primary TME surgery with and without sphincter preservation and with or without preoperative therapy.

In future studies will need to assess ongoing controversies
What are the documented patterns of recurrence? When do patients relapse after local excision, defining an ideal follow-up schedule and imaging appearances of early relapse. What is the long-term prognostic importance of nodal micrometastatic disease. What is the role of adjuvant chemoradiotherapy and chemotherapy in high risk T1 disease following local excision.

Summary indications for MRI assessment of early rectal cancer lesions
- To assess bulky polyps >5 mm thick.
- Initial assessment of disease remote from the lumen within entire mesorectum.
- Identification of pelvic sidewall disease.
- Road-mapping for surgical planning—identify site location of stalk or invasive border and relationship to puborectalis sling, peritoneal reflection, mesorectal or intersphincteric border.
- Identification of high risk patients with extramural venous invasion.
- Ongoing surveillance of high risk cancer patients opting for conservative approach.

Summary Indications for ERUS
- High frequency EUS to assess flat or depressed lesions <5 mm thick.
- Limited assessment of disease remote from the lumen—therefore for low risk polyp assessment.
- Assisting with planned ESR—identify site location of invasive border.

10 Conclusion

Early stage tumours can be usefully evaluated using high resolution MRI and high frequency ultrasound for superficial lesions.
Technique is important.
Options to consider especially for low lying early stage tumours: results from current trials awaited.
Follow up if less radical therapy is given: MRI surveillance is also important to enable early detection of salvageable regrowth/recurrence (Table 2).

References

Akahoshi K, Kondoh A, Nagaie T, Koyanagi N, Nakanishi K, Harada N et al (2000) Preoperative staging of rectal cancer using a 7.5 MHz front-loading US probe. Gastrointest Endosc 52(4):529–534

Akasu T, Iinuma G, Takawa M, Yamamoto S, Muramatsu Y, Moriyama N (2009) Accuracy of high-resolution magnetic resonance imaging in preoperative staging of rectal cancer. Ann Surg Oncol 16(10):2787–2794

Ashraf S, Hompes R, Slater A, Lindsey I, Bach S, Mortensen NJ et al (2012) A critical appraisal of endorectal ultrasound and transanal endoscopic microsurgery and decision-making in early rectal cancer. Colorectal Dis Off J Assoc Coloproctol Great Br Irel 14(7):821–826

Bipat S, Glas AS, Slors FJ, Zwinderman AH, Bossuyt PM, Stoker J (2004) Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging: a meta-analysis. Radiology 232(3):773–783

Badger SA, Devlin PB, Neilly PJ, Gilliland R (2007) Preoperative staging of rectal carcinoma by endorectal ultrasound: is there a learning curve? Int J Colorectal Dis 22(10):1261–1268

Bali C, Nousias V, Fatouros M, Stefanou D, Kappas AM (2004) Assessment of local stage in rectal cancer using endorectal ultrasonography (EUS). Tech Coloproctol 8(Suppl 1):s170–s173

Beynon J, Mortensen NJ, Foy DM, Channer JL, Virjee J, Goddard P (1986) Endorectal sonography: laboratory and clinical experience in Bristol. Int J Colorectal Dis 1(4):212–215

Brown G, Richards CJ, Bourne MW, Newcombe RG, Radcliffe AG, Dallimore NS et al (2003) Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. Radiology 227(2):371–377

Brown G, Kirkham A, Williams GT, Bourne M, Radcliffe AG, Sayman J et al (2004) High-resolution MRI of the anatomy important in total mesorectal excision of the rectum. AJR Am J Roentgenol 182(2):431–439

Dragsted J, Gammelgaard J (1983) Endoluminal ultrasonic scanning in the evaluation of rectal cancer: a preliminary report of 13 cases. Gastrointest Radiol 8(4):367–369

Doornebosch PG, Bronkhorst PJ, Hop WC, Bode WA, Sing AK, de Graaf EJ (2008) The role of endorectal ultrasound in therapeutic decision-making for local vs. transabdominal resection of rectal tumors. Dis Colon Rectum 51(1):38–42

Dworak O (1991) Morphology of lymph nodes in the resected rectum of patients with rectal carcinoma. Pathol Res Pract 187(8):1020–1024

Fedyaev EB, Volkova EA, Kuznetsova EE (1995) Transrectal and transvaginal ultrasonography in the preoperative staging of rectal carcinoma. Eur J Radiol 20(1):35–38

Garcia-Aguilar J, Pollack J, Lee SH, Hernandez de Anda E, Mellgren A, Wong WD et al (2002) Accuracy of endorectal ultrasonography in preoperative staging of rectal tumors. Dis Colon Rectum 45(1):10–15

Giovannini M, Bories E, Pesenti C, Moutardier V, Lelong B, Delpero JR (2006) Three-dimensional endorectal ultrasound using a new freehand software program: results in 35 patients with rectal cancer. Endoscopy 38(4):339–343

Glaser F, Friedl P, von Ditfurth B, Schlag P, Herfarth C (1990) Influence of endorectal ultrasound on surgical treatment of rectal cancer. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol 16(4):304–311

Hunerbein M (2003) Endorectal ultrasound in rectal cancer. Colorectal dis Off J Assoc Coloproctol Great Br Irel 5(5):402–405

Herzog U, von Flue M, Tondelli P, Schuppisser JP (1993) How accurate is endorectal ultrasound in the preoperative staging of rectal cancer? Dis Colon Rectum 36(2):127–134

Kav T, Bayraktar Y (2010) How useful is rectal endosonography in the staging of rectal cancer? World J Gastroenterol WJG 16(6):691–697

Katsura Y, Yamada K, Ishizawa T, Yoshinaka H, Shimazu H (1992) Endorectal ultrasonography for the assessment of wall invasion and lymph node metastasis in rectal cancer. Dis Colon Rectum 35(4):362–368

Kulig J, Richter P, Gurda-Duda A, Gach T, Klek S (2006) The role and value of endorectal ultrasonography in diagnosing T1 rectal tumors. Ultrasound Med Biol 32(4):469–472

Landmann RG, Wong WD, Hoepfl J, Shia J, Guillem JG, Temple LK et al (2007) Limitations of early rectal cancer nodal staging may explain failure after local excision. Dis Colon Rectum 50(10):1520–1525

Li JC, Liu SY, Lo AW, Hon SS, Ng SS, Lee JF et al (2010) The learning curve for endorectal ultrasonography in rectal cancer staging. Surg Endosc 24(12):3054–3059

Morris OJ, Draganic B, Smith S (2011) Does a learning curve exist in endorectal two-dimensional ultrasound accuracy? Tech Coloproctol 15(3):301–311

Manger T, Stroh C (2004) Accuracy of endorectal ultrasonography in the preoperative staging of rectal cancer. Tech Coloproctol 8(Suppl 1):s14–s15

Nielsen MB, Qvitzau S, Pedersen JF, Christiansen J (1996) Endosonography for preoperative staging of rectal tumours. Acta Radiol 37(5):799–803

Orrom WJ, Wong WD, Rothenberger DA, Jensen LL, Goldberg SM (1990) Endorectal ultrasound in the preoperative staging of rectal tumors: a learning experience. Dis Colon Rectum 33(8):654–659

Puli SR, Bechtold ML, Reddy JB, Choudhary A, Antillon MR, Brugge WR (2009) How good is endoscopic ultrasound in differentiating various T stages of rectal cancer? Meta-analysis and systematic review. Ann Surg Oncol 16(2):254–265

Ptok H, Marusch F, Meyer F, Wendling P, Wenisch HJ, Sendt W et al (2006) Feasibility and accuracy of TRUS in the pre-treatment staging for rectal carcinoma in general practice. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol 32(4):420–425

Rafaelsen SR, Kronborg O, Fenger C (1994) Digital rectal examination and transrectal ultrasonography in staging of rectal cancer: a prospective, blind study. Acta Radiol 35(3):300–304

Taylor FG, Swift RI, Blomqvist L, Brown G (2008) A systematic approach to the interpretation of preoperative staging MRI for rectal cancer. Ajr 191(6):1827–1835

Tytherleigh MG, Warren BF, Mortensen NJ (2008) Management of early rectal cancer. Br J Surg 95(4):409–423

Waage JE, Havre RF, Odegaard S, Leh S, Eide GE, Baatrup G (2011) Endorectal elastography in the evaluation of rectal tumours. Colorectal Dis 13(10):1130–1137

Predicting Lymph Node Metastases in pT1 Rectal Cancer

S. L. Bosch and I. D. Nagtegaal

Abstract

With the widespread introduction of population screening for colorectal cancer in Europe, the number of early rectal cancers is expected to increase. In the past, approximately 25 % of rectal cancers presented with early disease, defined as stage I disease. First, results from population screening in the UK demonstrate an increase to approximately 50 % stage I for screen-detected carcinomas. In the absence of lymph node metastases, local excision of the tumor might be an attractive option, with considerably less morbidity due to surgery and a lower mortality. This option demonstrates the need for a reliable method of lymph node metastasis prediction in early rectal cancer. The overall risk of lymph node metastasis in pT1 tumors is still considerable, 11.4 %. In order to avoid both under—and overtreatment, we need adequate risk factors.

1 Increase in Early Rectal Cancer

Following Council Recommendations of the European Union, many countries have been installing national bowel cancer screening programs. Different screening modalities have been applied, aimed at both a high participation rate and high detection rates. The use of (immunochemical) fecal occult blood testing and (partial) colonoscopy will both result in increased numbers of colorectal

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carcinomas (CRC). However, as already observed in the early screening trials (Hardcastle et al. 1996), screen-detected CRC are detected at an early stage. Recent data from the current UK program show an increase from 14.7 % stage I tumors in the unscreened population (Steele et al. 2012) to 49.9 % in the screen-detected tumors. Patients with these early tumors have an excellent prognosis. Local excision is an attractive option, especially in the pT1 tumors, since it is associated with less morbidity and mortality (Wu et al. 2011). From the oncological point of view, this can be a safe procedure, provided that there are no lymph node metastases (LNM). Local recurrence might be an issue, when resection margins are not free, but this is outside the scope of the current paper.

2 Risk on Lymph Node Metastasis

LNM have since long been recognized as an important risk factor in CRC. The presence of LNM is associated with a poor prognosis, and, as a consequence, adjuvant therapy is indicated after surgery. In tumor staging, the number of involved lymph nodes is important, with a pN1 stage for 1–3 positive nodes, and a pN2 stage for 4 or more LNM. More recent, the number of lymph nodes removed and examined has received considerable attention as an important issue in lymph node staging (Shia et al. 2012). Not only is the number of examined lymph nodes considered an independent prognostic factor (Swanson et al. 2003), but it is also thought that a larger number of lymph nodes is associated with an increased likelihood of detecting LNM. However, there is some debate on the latter, since in general LNM are larger and easier to detect than negative lymph nodes. Whether increasing numbers of lymph nodes also lead to increased numbers of nodes with micrometastases remain to be investigated. The presence of micrometastases is associated with disease recurrence in stage I and II CRC (Sloothaak et al. 2014), and these are hard to detect on preoperative imaging.

In general, the risk on LNM increases with increasing tumor invasion depth and increasing tumor size (Mekenkamp et al. 2009). In pT1 tumors, the overall risk on LNM is 11.4 %, as has been analyzed in a systemic review of 3,621 patients (Bosch et al. 2013). However, there are histological factors that allow for a more individualized risk estimation.

3 What Can We Measure?

As mentioned above, the risk on LNM increases with increasing size and invasion depth of the tumor. Within the pT1 group, this still holds true. Submucosal invasion depth can be subclassified applying a qualitative or a quantitative definition on sessile carcinomas. The qualitative or semiquantitative definition of Kudo (1993) uses the relative submucosal levels: sm1 (uppermost 1/3), sm2 (middle 1/3), and sm3 (deepest 1/3 of the submucosa) (Fig. 1). Indeed, an increasing frequency of lymph nodes are observed: 3.4 % (sm1), 8.5 % (sm2), 22.6 % (sm3) (Bosch et al.

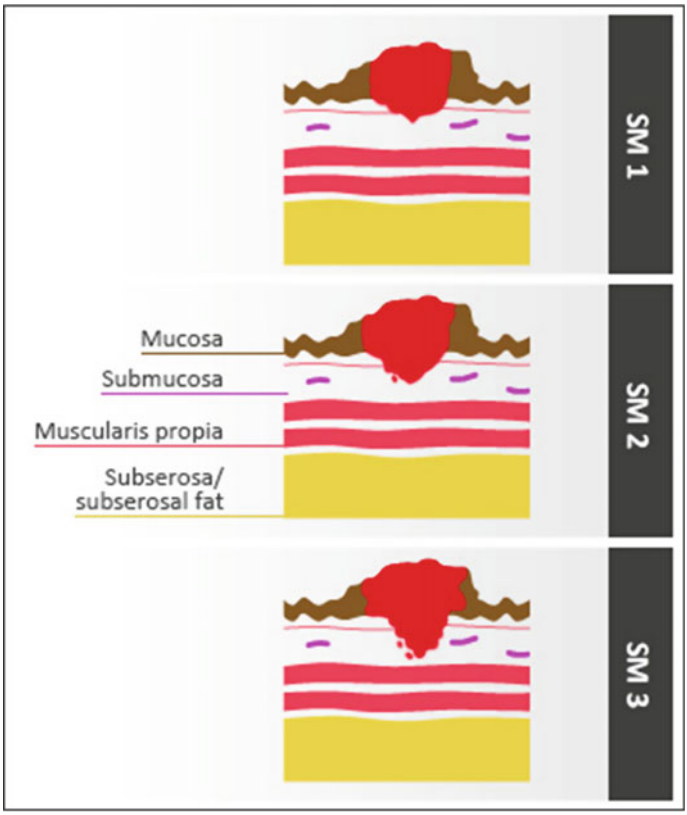

Fig. 1 Kudo classification

2013). However, this method is hard to apply when the muscularis propria is not present in the resection. Alternatively, exact measurements can be used to predict LNM: cut-off levels of 1 and 2 mm have been suggested. Risk on LNM is extremely low in case of an invasion depth less than 1 mm (1.5 %), however, this is a small group of patients (Bosch et al. 2013). Invasion over 1 mm is associated with 12.3 % LNM, and invasion depth over 2 mm is associated with 13.3 % LNM (Bosch et al. 2013). It should be noted that these percentages are only slightly increased compared to the average risk for a pT1 tumor, and as such, these findings in itself do not warrant a radical resection.

For cancers developing in polyps, the measurements of invasion depth are more difficult. A semiquantitative measurement has been introduced by Haggitt et al. (1985) (Fig. 2). A limited number of studies apply this classification, and the increased risk on LNM seems only present in level 4 CRC.

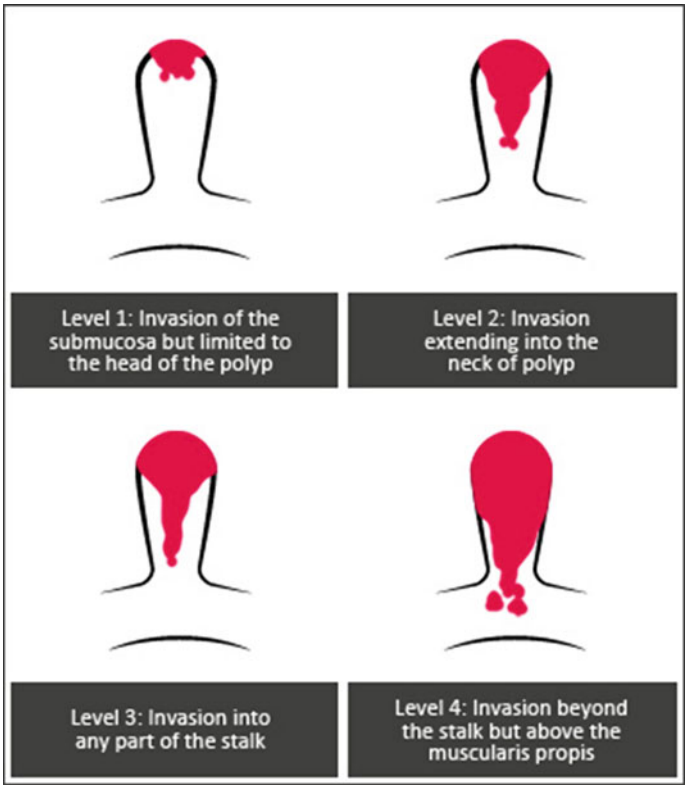

Fig. 2 Haggitt classification

An alternative for tumor size is submucosal width, which is investigated in three studies with a total number of 620 patients (Bosch et al. 2013). Larger tumors with a submucosal width of over 5 mm showed LNM in 17 % compared to 5.6 % in the smaller tumors.

4 Monitoring Tumor Behavior

Risk on LNM is also dependent on tumor biology. Molecular biomarkers are currently being investigated, but none are ready for diagnostic routine. However, growth pattern and interactions with the tumor microenvironment have been investigated in more detail and add relevant information for the risk estimation. Many studies have examined the role of differentiation grade in early adenocarcinomas. Grading is based on the percentage of gland formation in the tumor (World Health Organization. 2010), with a well-differentiated tumor entirely consisting of relatively well-defined glands, and poorly differentiated tumors that consist of areas with a solid growth pattern. For clinical use, the terms low grade (i.e., well and moderately differentiated)

and high grade are preferred. Other tumor types, such as mucinous carcinoma en signet ring cell carcinoma, are in most studies grouped with high-grade tumors. The presence of high grade is associated with an increased risk of LNM, 24.5 versus 8.9 % in low-grade lesions (Bosch et al. 2013).

Separately, the differentiation at the invasive front of the tumor is considered to be important. Sometimes poorly differentiated clusters are observed here (Ueno et al. 2013), that are strongly correlated with the process of budding. Not all studies distinguish these two factors, there might be significant overlap. Budding is sprouting of the tumor, and small groups or single cells infiltrate the microenvironment. While definitions of budding differ per study, tumor buds are in general defined as less single cells or clusters of less than five cells. Poorly differentiated clusters are defined as five cells or more, clustered without evidence of gland formation (Ueno et al. 2013). In the systemic review, the impact of budding on LNM was more pronounced than the effect of the poorly-differentiated clusters (5 vs. 21.3 % and 10.2 vs. 19.2 %, respectively) (Bosch et al. 2013).

In the development of LNM, invasion of the lymphatics play a key role, which is reflected by the high percentage of LNM in the presence of lymphatic invasion (26.7 %) (Bosch et al. 2013). Not all studies report lymphatic invasion as a separate entity, but use lymphovascular invasion as an alternative, grouping lymphatic and vascular invasion. While vascular invasion in itself is associated with a poor prognosis, it is not directly related to the development of LNM and thus not such an adequate risk factor.

5 Overview of Relevant Factors

In a recent meta-analysis, we have studied most of the histological factors that are associated with LNM in pT1 tumors (Bosch et al. 2013). Figure 3 gives an overview of all relevant factors and their impact on the prediction of LNM. In order to establish the value of all factors, sensitivity, specificity, positive, and negative predictive value should be taken into account. Sensitivity is especially high for submucosal invasion depth (1 mm), with 96.7, however, this is accompanied by a low specificity, that causes a high false-positive rate and many unnecessary radical resections. Specificity is high for poor differentiation, which is associated with low sensitivity. Positive predictive values are relatively low for all factors, but negative predictive values are 90 % or above. This illustrates the need for a comprehensive approach, in more factors should be combined for optimal decision-making.

6 Future Considerations

With increasing numbers of patients potentially eligible for local excision of rectal carcinoma, there is an obvious need for adequate risk estimation. Existing studies have identified histological risk factors that can be applied in daily practice, but need confirmation in large populations. We need to focus on combinations of

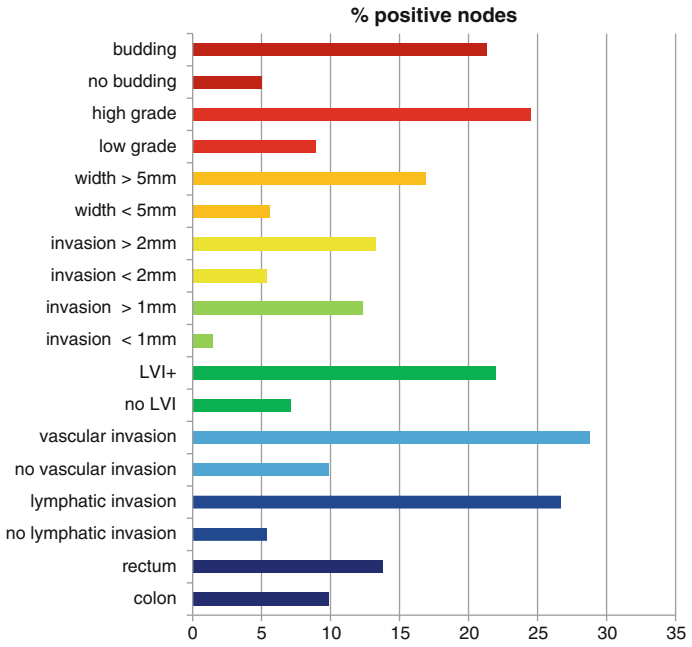

Fig. 3 Histological risk factors for LNM. *Source* Based on the systematic review from Bosch et al. LVI: lymphovascular invasion

factors to stratify patients according to LNM risk. Since the large studies in pT1 tumors originate from Asian countries, with a more extensive pathological workup, we need to validate the risk factors in Western cohorts. In addition, we need validation within screen-detected carcinomas. In breast cancer, it has been suggested that screen-detected carcinomas have a biological distinct background (Dawson et al. 2009), these tumors supposedly are less aggressive. The standardized data collection that is part of the screening programs will offer insights on this issue within a couple of years.

Another issue that needs to be addressed is the application of neoadjuvant therapy. In rectal cancer, this therapeutic strategy has been applied for years, in various combinations of radiotherapy and chemotherapy. In a large number of cases, significant downstaging as a result of treatment made less extensive surgery a possibility. Tumors that decrease in size to ypT0 or ypT1 could potentially be treated with local excisions. However, risk on LNM in these populations might be very different. Even with a complete response of the primary tumor (ypT0), still 7 % of cases present with LNM (Nagtegaal and Marijnen 2008). In these cases, there are no histological risk factors that can be examined. However, risk factors in ypT1 and ypT2 tumors need to be identified, because adequate risk stratification based on histological characteristics may prevent both over and undertreatment of these patients.

References

Bosch SL, Teerenstra S et al (2013) Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy 45(10): 827–834

Dawson SJ, Duffy SW et al (2009) Molecular characteristics of screen-detected vs symptomatic breast cancers and their impact on survival. Br J Cancer 101(8):1338–1344

Haggitt RC, Glotzbach RE et al (1985) Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. Gastroenterology 89(2):328–336

Hardcastle JD, Chamberlain JO et al (1996) Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 348(9040):1472–1477

Kudo S (1993) Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. Endoscopy 25(7):455–461

Mekenkamp LJ, van Krieken JH et al (2009) Lymph node retrieval in rectal cancer is dependent on many factors–the role of the tumor, the patient, the surgeon, the radiotherapist, and the pathologist. Am J Surg Pathol 33(10):1547–1553

Nagtegaal ID, Marijnen CAM (2008) The future of TNM staging in rectal cancer; the era of neoadjuvant therapy. Curr Colorectal Cancer Rep 4:147–154

Shia J, Wang H et al (2012) Lymph node staging in colorectal cancer: revisiting the benchmark of at least 12 lymph nodes in R0 resection. J Am Coll Surg 214(3):348–355

Sloothaak DA, Sahami S et al (2014) The prognostic value of micrometastases and isolated tumour cells in histologically negative lymph nodes of patients with colorectal cancer: a systematic review and meta-analysis. Eur J Surg Oncol 40(3):263–269

Steele RJ, McClements P et al (2012) Interval cancers in a FOBT-based colorectal cancer population screening programme: implications for stage, gender and tumour site. Gut 61(4): 576–581

Swanson RS, Compton CC et al (2003) The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. Ann Surg Oncol 10(1):65–71

Ueno H, Hase K et al (2013) Novel risk factors for lymph node metastasis in early invasive colorectal cancer: a multi-institution pathology review. J Gastroenterol.

World Health Organization (2010) World Health Organization classification of tumours of the digestive system. IARC Press, Lyon

Wu Y, Wu YY et al (2011) TEM and conventional rectal surgery for T1 rectal cancer: a meta-analysis. Hepatogastroenterology 58(106):364–368

Part II
Treatment of Early Rectal Cancer

Endoscopic Resection: When Is EMR/ESD Sufficient?

H. Messmann

Abstract

Endoscopic treatment of malignant lesions in the gastrointestinal tract can be treated curatively if the risk for lymph node metastasis is lower than 1%. In the lower gi-tract (colon and rectum) the low risk criteria for this situaiton are well-defined (G1/G2, LO, invasion depth $\leq$1000μm). However, en-bloc R0-resection is also mandatory. Benign lesions such as lateral spreading tumors (granular-type) can be also treated with piecemeal EMR, however, recurrence rate is up to 30%. All other cases, regardless of size, such as non-granular type lesions or mixed type lesions should be treated with endoscopic submucosal dissection. The definitive histopathology of the resected specimen allows further decision (e.g., surgery if invasion depth of tumor is >1000μm).

Curative endoscopic treatment of early gastrointestinal neoplasia may be possible if the indications for endoscopic resection (ER) are clearly defined.

There is no doubt, that early neoplasia in the gastrointestinal tract invading the submucosa have an increasing risk of lymph node metastasis.

The aim of endoscopic tumor therapy is a R0-resection similar to the approach of surgical procedures. This means, that each early gastrointestinal neoplasia has to be resected en-bloc in one piece. Piece meal resection is by definition not a R0-resection and cannot be accepted as curative resection.

Nevertheless, endoscopic mucosal resection (EMR) is well established for endoscopic removal of colorectal epithelial neoplasms. In lesions larger than 20 mm in diameter but also in smaller lesions with flat morphology EMR leads to

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piecemeal resection. After piecemeal resection, histopathological assessment of R0-resection is mostly impossible and the risk of incomplete resection and recurrence is increased. Recently, published studies on piecemeal EMR of large colorectal lesions (diameter > 20 mm) have reported recurrence rates of 23.5 and 26.3 %, respectively (Hotta et al. 2009; Hochdörffer et al. 2010). ESD can overcome this problem allowing en-bloc resection regardless of a lesions size.

Large studies from Japan showed the advantages of colorectal ESD (high en-bloc resection rate even in large lesions, low recurrence rate) but also its disadvantages (time-consuming procedure, complication risk) (Saito et al. 2010).

Therefore, before starting the ER either with EMR or ESD it is important to differentiate the type of colonic neoplasia. The Japanese classification describes different types of flat polyps as "laterally spreading tumor (LST)." If the lesion shows a homogenous granular surface, the lesion is described as "LST-granular (LST-G) type" and by Paris classification it is a 0-IIa lesion. Lesions with a combination of polypoid nodules and granular surface are so-called "nodular mixed type lesions" (0-IIa, 0-Is + IIa, 0-IIa + Is). Besides LST-G type lesions, we have to differentiate LST-nongranular lesions (LST-NG). This type of lesions are either flat elevated (0-IIa) or pseudo-depressed (0-IIa + IIc, 0-IIc + IIa) (Tanaka et al. 2008). Uraoka et al. showed, that 93 % of LST-G were adenoma or mucosal cancer and submucosal cancer was present in 7 % respectively. In contrast, the LST-NG-type lesions were in 14 % submucosal cancer (Uraoka et al. 2006). Data from the National Cancer Center in Tokyo (personal communication) had in 47 % of the LST-NG larger than 4 cm submucosal invasion.

The German guidelines for colorectal cancer define the polyps, which can be resected endoscopically with a risk of positive lymph nodes <1 %. The low-risk criteria are as follows: G1/2, no invasion of tumor in lymphatic or blood vessel, submucosal infiltration <1,000 μm. In this situation, ER is an appropriate curative treatment and no additional surgery is necessary. In all other cases—high risk cancer (G3/4, L+/V+, sm-filtration > 1,000 μm) the risk of lymph node metastases is higher than 17 % and surgery is indicate (Schmiegel et al. 2005).

Diagnosis of submucosal infiltration is challenging. EUS cannot clearly differentiate between sm-infiltration or not. An additional tool is the so-called "lifting-sign." Those lesions with no lifting sign are not indicated for ER since in the majority deep sm-invasion is present (Kobayash et al. 2007).

As mentioned, EMR has a high risk of recurrence even in lesions of 5–20 mm as shown in a recent publication (Pohl et al. 2013).

ESD has the potential to overcome this problem. ESD is the only local ER technique which allows independent from the size of the lesion an en-bloc resection. The technique consists of several steps: (1) exact location and demarcation of the lesion; (2) injection of special fluid solutions (hyaluronic acid, glycerol, etc.) to achieve lifting and a cushion; (3) circular incision of the lesion using special knives (hook-knife, Dual knife, etc.); (4) submucosal dissection of the lesion.

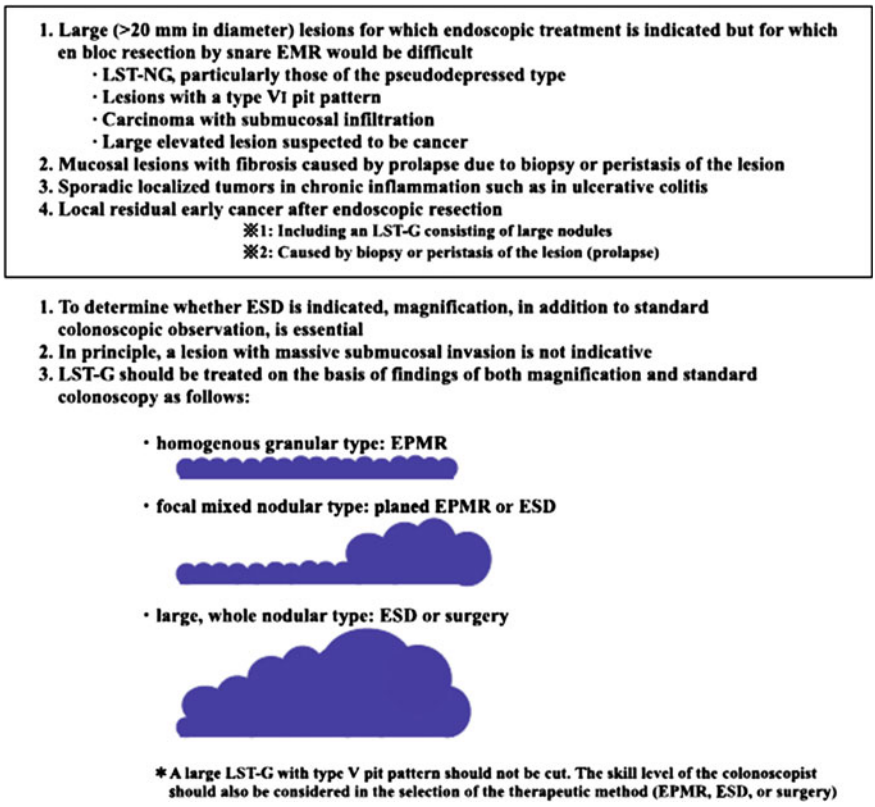

Fig. 1 Indications for colorectal ESD. *EPMR* endoscopic piecemeal mucosal resection, *LST-NG* nongranular laterally spreading tumor (Tanaka et al. 2008)

By using this technique, the risk of recurrence is almost zero and the pathologist has the chance to stage the whole lesions exactly. The Japanese Society for Cancer of the Colon and Rectum has defined lesions which should be resected by ESD and where surgery is indicated. Those lesions larger than 20 mm and difficult to resect by snare in one piece should be resected by ESD. Especially those lesions suspicious for malignancy (LST-NG, pit-pattern Vi), fibrotic lesions, and local recurrence after previous endoscopic treatment (Fig. 1).

Fujishiro et al. published (2006) the first data on ESD in rectal cancer. A total of 32 lesions were treated. The perforation rate was 5.7 % and during a mean follow-up of 3 years 3.1 % recurrences were diagnosed (Tanaka et al. 2007).

Saito compared EMR and ESD in colorectal neoplasia. In both groups, 66 % of the lesions were cancer. In the EMR group (228 lesions), the median size was 28 mm while the size of the lesions in the ESD group ($n = 145$) was 37 mm,

respectively. Nevertheless, the en-bloc resection rate was 33 % in the EMR and 84 % in the ESD group, respectively. However, the procedure time was much longer in the ESD group (108 min) compared to the EMR group (29 min). The recurrence rate was 14% in the EMR and 2 % in the ESD group. Perforation rate was 1.3 % in the EMR and 6.2 % in the ESD group, respectively (Saito et al. 2010).

Tanaka et al. demonstrated a learning curve depending on the number of cases treatred over years. With increasing case load and changing the instruments the perforation rate decreased from initially 18 to 0 % (Tanaka et al. 2007).

Own data confirm the learning curve of ESD. After 10 years performing more than 500 procedures, we could increase the speed of performing ESD and achieved nearly the same results compared to Saito et al. (Probst et al. 2012; Saito et al. 2013). We could increase our en-bloc resection rate from 60 to 96.2 % and the R0-enbloc resection rate from 48 to 85 %, respectively.

A recent study from Japan evaluated EMR and ESD in 18 medium and high volume endoscopy centers. A total of 1,845 patients were analyzed—220 patients had submucosal cancer, 117 with a penetration depth of less than 1000 μm. 88 of these lesions were treated by ESD. The en-bloc resection rate was independent of lesion size between 94 and 96 %, however for EMR the en-bloc resection rate varied between 66.5 (20–29 mm) and 12.3 % (40 mm), demonstrating again the inadequate use of this technique for malignant lesions (Nakajima et al. 2013).

In a recent paper by Ikematsu et al., the long-term outcome for submucosal invasive cancer was analysed. In group A, low-risk tumors were endoscopically resected. The recurrence rate for rectal cancer was significant higher compared to colon cancer group, with no difference in disease-free survival and overall survival. In group B (high risk group), ER was performed and if necessary additional surgery was recommended. Again the recurrence rate was higher in the rectum group, but also the disease free survival decreased in the rectal cancer group. No difference for recurrence, disease free survival and overall survival was found between colon cancer and rectal cancer group if surgery was performed as the only treatment (Ikematsu et al. 2013).

1 Conclusion

Endoscopic treatment of colorectal cancer can be curative—however clear indications and techniques are necessary. Only low-risk colorectal cancer can be treated endoscopically and en-bloc resection is mandatory. Therefore, EMR is in most cases not adequate to treat malignant lesions, but ESD has the potential to overcome this problem.

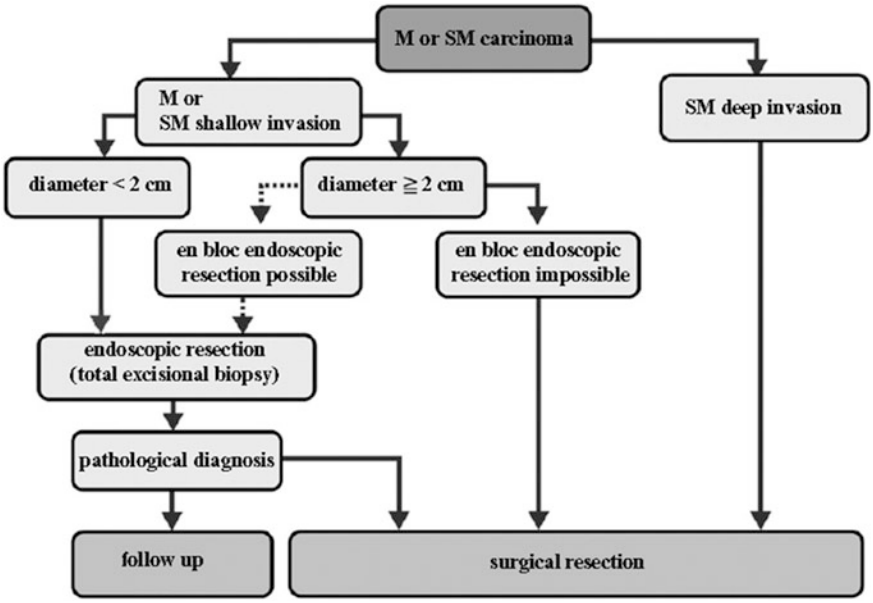

Fig. 2 Therapeutic strategy for lesions diagnosed as M or SM carcinoma (JSCCR Guidelines 2010 for Treatment of Colorectal Cancer) (Ikematsu et al. 2013)

Therefore, the Japanese Society for Cancer of the Colon and Rectum suggested a therapeutic strategy for mucosal and submucosal colorectal cancer (Fig. 2).

References

Fujishiro M, Yahagi N, Nakamura M, Kakushima N, Kodashima N, Ono S, Kobayashi K, Hashimoto T, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M (2006) Endoscopic submucosal dissection for rectal epithelial neoplasia. Endoscopy 38:493–497

Hochdörffer R, Eickhoff A, Apel D et al (2010) Endoscopic resection of "giant" colorectal lesions: long-term outcome and safety. Z Gastroenterol 48:741–747

Hotta K, Fujii T, Saito Y et al (2009) Local recurrence after endoscopic resection of colorectal tumors. Int J Colorect Dis 24:225–230

Ikematsu H, Yoda Y, Matsuda T et al (2013) Long-term outcomes after resection for submucosal invasive colorectal cancers. Gastroenterology 144:551–559

Kobayash N, Saito Y, Sano Y, Uragami N, Michita T, Nasu T, Matsuda T, Fu K, Fujii T, Fujimori T, Ishikawa T, Saito D (2007) Determining the treatment strategy for colorectal neoplastic lesions: endoscopic assessment or the non-lifting sign for diagnosing invasion depth? Endoscopy 39:701–705

Nakajima T, Saito Y, Tanaka S et al (2013) Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan. Surg Endosc 27:3262–3270

Pohl H, Srivastava A, Bensen SP et al (2013) Incomplete polyp resection during colonoscopy—results of the complete adenoma resection (CARE) study. Gastroenterology 144:74–80

Probst A, Golger D, Anthuber M, Märkl B, Messmann H (2012) Endoscopic submucosal dissection in large sessile lesions of the rectosigmoid: learning curve in a European center. Endoscopy 44:660–667

Saito Y, Fukuzawa M, Matsuda T et al (2010) Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. Surg Endosc 24:343–352

Saito Y, Otake Y, Sakamoto T et al (2013) Indications for and technical aspects of colorectal endoscopic submucosal dissection. Gut Liver 7:263–269

Schmiegel W et al (2005) German S3-guideline conference colorectal cancer. Dtsch Med Wochensch 130(Suppl 1):S5–53

Tanaka S, Oka S, Kaneko I et al (2007) Endoscopic submucosal dissection for colorectal neoplasia: possibility of standardization. Gastrointest Endosc 66:100–107

Tanaka S, Oka S, Chayama K (2008) Colorectal endoscopic submucosal dissection: present status and future perspective, including its differentiation from endoscopic mucosal resection. J Gastroenterol 43:641–651

Tanaka S, Terasaki M, Hayashi N et al (2013) Warning for unprincipled colorectal endoscopic submucosal dissection: accurate diagnosis and reasonable treatment strategy. Dig Endosc 25:107–116

Uraoka T, Saito Y, Matsuda T et al (2006) Endoscopic indications for endoscopic mucosal resection of laterally spreading tumors in the colorectum. Gut 55:1592–1597

Transanal Endoscopic Microsurgery

Chris Cunningham

Abstract

There is increasing interest in organ-preserving options in the management of rectal cancer. Excision of small, early stage cancers by transanal endoscopic microsurgery (TEM) is an important part of this approach. Carefully selected cancers can be treated successfully by TEM with acceptably low risk of recurrent disease and overall cancer outcomes similar to radical surgery. The impact of recurrence can be mitigated by early detection of luminal or nodal disease for which a robust surveillance programme is essential. However, patients with high risk features on post-TEM pathology should be offered completion radical surgery which is associated with good oncological results. There may be an opportunity to expand the population of patients who can be offered rectal preservation with the use of radiotherapy in either adjuvant or neo-adjuvant context. Full thickness excision by TEM may be particularly valuable in those demonstrating a clinical complete response to radiotherapy, where diagnosis of complete pathological response can be confirmed. The use of TEM in managing more advanced rectal cancers is exciting, but must be tested within formal clinical trials before being adopted as routine practice.

1 Introduction

Transanal endoscopic microsurgery (TEM) was introduced by Gerhard Buess in the 1980s, initially for use in benign disease (Buess et al. 1988). It became apparent over the subsequent decade that it could play a role in the management of

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early stage rectal cancer (Buess et al. 1992). However, this role remains controversial; local excision for rectal cancer is often perceived as a compromise treatment, suitable only for those unfit for radical surgery (Paty et al. 2002). Removal of the primary tumour by full thickness excision leaves occult nodal disease in situ which, in addition to the risk of tumour re-growth at the TEM site, leads to high rates of local recurrence of 20–40 % for T1-2 cancers. There is no doubt that inappropriate use of local excision can have disastrous outcomes, as highlighted by Paty et al. Delayed diagnosis of recurrent disease makes salvage surgery difficult, highly morbid and associated with poor survival outcomes. However, a proportion of patients with early stage disease, confined to the bowel wall with no lymph node involvement, may be cured by local excision alone. This avoids the short- and long-term morbidity and potential operative mortality of radical surgery, be this total mesorectal excision (TME) or abdomino-perineal excision (APE), while still offering cure for early stage disease. Organ preservation in rectal cancer is gaining considerable momentum and local excision by TEM is just one approach that can be used successfully.

2 Diagnosis and Treatment Selection in Early Rectal Cancer

Locally advanced rectal cancer is diagnosed on clinical suspicion, confirmed by biopsy and staged locally by imaging, most commonly MRI. In early rectal cancer, the pathway may be quite different; malignant polyps and small sessile cancers may be diagnosed and treated simultaneously following removal by polypectomy, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). This may be adequate treatment for very early cancers at low risk of recurrence or lymph node involvement. However, risk of fragmentation and removal of these cancers in the submucosal plane means that final pathology can be difficult to interpret, and is more likely that margins will be involved if there is advanced T1 disease. Therefore, the use of EMR is best restricted to lesions when cancer is not suspected or if the diagnosis of cancer will prompt treatment of the patient with radical surgery or chemo-radiation, i.e., where there is no role for definitive local excision. Incomplete excision by flexible endoscopic techniques can be treated by re-excision with full thickness TEM.

Significant rectal neoplasms, which are confirmed on biopsy as cancer or for which there is a suspicion of malignancy, should be staged completely before considering local excision. Endorectal ultrasound and MRI give information in tumour invasion (T-stage) and lymph node involvement (N-stage). CT scan should exclude metastatic disease in the liver and lung. Cancers staged as cT1N0, may be treated by full thickness excision obtaining a high quality intact specimen comprising all layers of the rectal wall, from mucosa to *muscularis propria*. This allows accurate pathological assessment and prediction of risk of recurrence or occult lymph node involvement.

Full thickness rectal excision can be performed by traditional per-anal excision, but there is good evidence that endoscopic excision by TEM, or similar platform (Barendse et al. 2012), is superior in terms of specimen quality and overall cancer outcome (Moore et al. 2008; Barendse et al. 2012). Full thickness rectal excision is the safest when performed in the extra-peritoneal rectum where the muscle tube of the rectum is usually covered in fatty mesorectum. Breaches into the peritoneal cavity occur in 10 % of TEM cases and are often intentional, i.e., the lesion lies in the intraperitoneal rectum. These can be repaired endoscopically with no apparent increase in complications providing the surgeon has the required technical expertise. There is evidence suggesting little impact on oncological outcome (Baatrup et al. 2009; Morino et al. 2013) when breach is performed during TEM for cancer, but more outcome data are required before this practice can be recommended as the theoretical risk of peritoneal spread of cancer is a concern. Peritoneal breach is more likely in the anterior and lateral aspects of the rectum particularly in women, where the pouch of Douglas may extend to the lower third anteriorly. MRI allows more exact assessment of the location of the cancer, proximity to the peritoneal reflection and the volume of underlying mesorectal fat. TEM in the lower third of the rectum comes with additional complexity. The mesorectal fat is thin, particularly anteriorly, meaning that TEM dissection may open onto the levator muscle, or the prostate or vagina if the pathology is anterior. This has no immediate implications, however, if the patient needs completion radical surgery directed by poor pathology, or indeed develops recurrent disease, more extensive surgery (e.g., APE or even exenterative surgery) may be required compared to that which would have been appropriate for the primary pathology. This needs to be considered in planning suitability of a cancer for TEM and potential compromise should be discussed with patients.

3 Staging

There is no ideal staging modality for early rectal cancer. Endorectal ultrasound (ERUS) is highly accurate (Doornebosch et al. 2008) in assessing T stage but in reality is less impressive in guiding clinical decision making (Ashraf et al. 2012). The risk of over-staging with ERUS is significant, and this may direct a patient unnecessarily to radical surgery. ERUS can provide the surgeon with additional confidence over clinical assessment and decision-making but care must be taken not to rely entirely on this modality. MRI staging is valuable in assessing lymph node involvement and determining the proximity of tumour to peritoneal reflection and adjacent pelvic organs. Assessment of early T-stage by MRI is challenging although possible in expert hands (Taylor et al. 2011). A baseline MRI before TEM surgery is important as a reference against which post-TEM imaging can be compared to enable the early detection of nodal disease or tumour recurrence. Any significant rectal lesion, even with benign histology should have MRI prior to TEM surgery as 20–40 % of cancers have benign histology before TEM. Interpretation of MRI immediately after TEM is largely unhelpful due to the disruption from surgery and presence of reactive lymph nodes.

In the absence of definitive staging, the primary consideration in decision-making in early rectal cancer is to determine if the lesion is safe to treat by TEM. The term 'TEM-able' was coined and this encompasses the size and location of the lesion and includes the individual's skills and preference of the multidisciplinary team over the application of this technique procedure. Careful and experienced endoscopic and digital examination are critical, and this is best performed by the surgeon undertaking the TEM surgery. Tumour morphology (polypoid or ulcerated), location (quadrant and height from anal verge and anorectal junction) and mobility should all be considered and will influence decision-making.

4 Neo-adjuvant Therapy and Local Excision

There is growing enthusiasm for organ preservation in treatment of rectal cancer and the use of TEM is an important component of this. Some patients with more advanced cancers (advanced T1-2) which are still small enough to consider for local excision and do not appear to have involved nodes on MRI scan, may be considered for neo-adjuvant radiotherapy (chemo-radiotherapy or short course radiotherapy) followed by TEM. This approach depends heavily on preoperative staging, which, as indicated above, is imperfect. In addition, because there is a significant downsizing effect of this treatment in early stage disease, the underling pathological stage and histological features may never be determined. The value of this approach needs to be tested with clinical trials offering a non-radiotherapy arm with either TEM and/or radical surgery. Despite this it is clear that the use of neo-adjuvant radiotherapy with a view to considering local excision has leapt into the treatment algorithm for many specialist centres dealing with rectal cancer. The outcomes can be impressive, with studies suggesting no difference in disease-free survival between radical surgery and local excision following radiotherapy for early stage cancer (Lezoche et al. 2008). However, there is considerable selection bias in these groups as a good response to chemo-radiation is itself a favourable prognosticator, therefore, poorer prognostic early stage cancers showing little effect or even progressing during neo-adjuvant treatment will be excluded. In this way, the use of neo-adjuvant therapy may be a means of selecting those small cancers, which can be managed by local excision and proponents of this approach support the liberal use of radiotherapy as primary treatment. Up to 30 % of tumours treated in this way may demonstrate a pathological complete response prompting the question whether TEM surgery should be performed in those displaying a complete clinical response. A cautionary note on the use of TEM after chemo-radiotherapy is provided by the Sao Paolo group, who identify a incidence of recurrent disease perhaps more in keeping with what we might expect from ypT0-2 disease (Perez et al. 2013). Furthermore, the use of TEM after chemo-radiotherapy is associated with increased complication rates over TEM in non-irradiated patients. Wound dehiscence, pelvic sepsis and pain are reported in up to 40 % of patients, many requiring readmission (Perez et al. 2011; Marks et al.

2009). The combined approach of radiotherapy followed by TEM offers a chance to expand the population who may benefit from organ preservation but it warrants thorough and robust testing before being accepted as standard care.

5 Post-TEM Pathology, Risks of Recurrence and Decision-Making

Against the obvious weaknesses in staging modalities before TEM surgery, one benefit of primary treatment with TEM is that a high quality specimen is available for post-TEM histological assessment. There are many factors which have been used as predictors for lymph node involvement after local excision of colorectal cancer (Bosch et al. 2013). A pragmatic approach is derived from analysis of the UK TEM database which considers size of cancer, T-stage invasion and the presence of lymphatic invasion as most important prognosticators (Bach et al. 2009). This work, supported by guidelines issued through the Association of Coloproctology of UK and Ireland, advises restricting TEM as sole treatment to those cancers of less than 3 cm, well or moderately differentiated, with clear resection margins and lacking evidence of lymphatic invasion. With this careful selection on histo-pathological grounds, the estimated local recurrence-free survival should be over 90 %, i.e., 10 % of patients will be expected to develop local recurrence. The entire population treated by TEM for early stage cancer needs to be surveyed effectively to detect recurrent cancer or evolving nodal disease at the earliest stage. This is a high intensity programme that needs to be coordinated and managed effectively through multidisciplinary teams. At present, there is little hard data to guide this surveillance programme but expert opinion advocates 3 monthly endoscopic and MRI assessment for the first 3 years with annual CT to exclude the development of metastatic disease. There is evidence that effective surveillance can detect recurrent cancer at an early stage when standard TME surgery can be performed offering patients oncologically satisfactory outcomes in terms of local control (De Graaf et al. 2009). Less-intensive surveillance for local recurrence with 6–12 monthly MRI may need to continue for up to 10 years, particularly if radiotherapy has been given.

In some patients, post-TEM pathology will convey a risk of recurrence which is unacceptable for that individual. This is a complex assessment and many patients are willing to accept a higher risk trading off oncological excellence in favour of quality of life by avoiding major surgery (Solomon et al. 2003; Johnston et al. 2013). However, the message to patients must be clear; current standard of care for high-risk pathology after local excision is completion surgery. There is good evidence (Bach et al. 2009; Hahnloser et al. 2005) that immediate completion surgery (TME or APER) after TEM with unfavourable pathology effectively returns risk of recurrent cancer to that if radical surgery had been performed as the primary treatment. This implies that a treatment strategy of TEM followed by completion radical surgery does not compromise oncological outcome. This seems

extremely favourable but radical surgery after TEM can be technically challenging and there is some evidence that a subgroup of patients do less well, particularly if there is a poor quality TME specimen (Hompes et al. 2013). This may support the selective use of chemo-radiotherapy prior to completion surgery for those with unfavourable post-TEM pathology.

Many patients are treated by TEM as a compromise and, although post-TEM pathology may be unfavourable, co-morbidity or life expectancy means completion radical surgery is not an option. Short course radiotherapy or chemo-radiotherapy may be considered under these circumstances but there is little data to guide practice. There is a suggestion from the pre-TEM era that local excision followed by radiotherapy can be effective in reducing reduce local recurrence (Minsky et al. 1989). In TEM surgery, Duek reported on 16 patients treated after complete excision of T2 rectal cancer. In this small population, post-TEM radiotherapy reduced local recurrence by 50 % compared to those kept under surveillance (Duek et al. 2008). Post-TEM radiotherapy should be deferred until the TEM site has healed and risks of sepsis are reduced. Radiotherapy fields may be restricted relative to those in advanced disease as it is only the TEM surgical bed and mesorectal lymph nodes that need to be targeted. There may also be a role for brachytherapy techniques, further reducing the chances of radiotherapy-related complications. As many as 40 % of cancers treated by TEM have no definitive cancer diagnosis before surgery, and cannot be considered for primary treatment with chemo-radiotherapy. Adjuvant radiotherapy may have an important role in this population and further investigation defining the role and value of post-TEM adjuvant therapy should be encouraged.

6 Conclusion

We have seen a dramatic improvement in the surgical management of rectal cancer in the last 30 years with the adoption of TME surgery. Recurrence rates of less than 5 % are reported and these may be reduced further with preoperative radiotherapy. However, there is recognition that this may be over-treatment for a group of patient with early stage disease where local excision is sufficient. Approaches employing local excision and radiotherapy may increase the population to benefit from organ-preserving treatments. These techniques will find a place alongside non-operative management of rectal cancer with chemo-radiotherapy alone (Habr-Gama et al. 2013). Efforts to avoid radical surgery in the treatment of rectal cancer demand careful selection and considerable investment in surveillance coupled with a defined plan of action should abnormalities be detected on follow-up. The optimum system of surveillance and its duration have yet to be determined, but it is likely to be continued for 5–10 years.

References

Ashraf S, Hompes R, Slater A, Lindsey I, Bach S, Mortensen NJ, Cunningham C, On behalf of the Association of Coloproctology of Great B, Ireland Transanal Endoscopic Microsurgery C (2012) A critical appraisal of endorectal ultrasound and transanal endoscopic microsurgery and decision-making in early rectal cancer. Colorectal Dis 14:821–826

Baatrup G, Borschitz T, Cunningham C, Qvist N (2009) Perforation into the peritoneal cavity during transanal endoscopic microsurgery for rectal cancer is not associated with major complications or oncological compromise. Surg Endosc 23:2680–2683

Bach SP, Hill J, Monson JR, Simson JN, Lane L, Merrie A, Warren B, Mortensen NJ (2009) A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer. Br J Surg 96:280–290

Barendse RM, Doornebosch PG, Bemelman WA, Fockens P, Dekker E, De Graaf EJ (2012) Transanal employment of single access ports is feasible for rectal surgery. Ann Surg 256:1030–1033

Bosch SL, Teerenstra S, de Wilt JH, Cunningham C, Nagtegaal ID (2013) Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy 45:827–841

Buess G, Kipfmuller K, Hack D, Grussner R, Heintz A, Junginger T (1988) Technique of transanal endoscopic microsurgery. Surg Endosc 2:71–75

Buess G, Mentges B, Manncke K, Starlinger M, Becker HD (1992) Technique and results of transanal endoscopic microsurgery in early rectal cancer. Am J Surg 163:63–69 (discussion 69–70)

De Graaf EJ, Doornebosch PG, Tollenaar RA, Meershoek-Klein Kranenbarg E, De Boer AC, Bekkering FC, Van De Velde CJ (2009) Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. Eur J Surg Oncol 35:1280–1285

Doornebosch P, Bronkhorst P, Hop W, Bode W, Sing A, de Graaf E (2008) The role of endorectal ultrasound in therapeutic decision-making for local versus transabdominal resection of rectal tumors. Dis Colon Rectum 51:38–42

Duek SD, Issa N, Hershko DD, Krausz MM (2008) Outcome of transanal endoscopic microsurgery and adjuvant radiotherapy in patients with T2 rectal cancer. Dis Colon Rectum 51:379–384 (discussion 384)

Habr-Gama A, Sabbaga J, Gama-Rodrigues J, São Julião GP, Proscurshim I, Aguilar PB, Nadalin W, Perez RO (2013) Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum 56:1109–1117

Hahnloser D, Wolff BG, Larson DW, Ping J, Nivatvongs S (2005) Immediate radical resection after local excision of rectal cancer: an oncologic compromise? Dis Colon Rectum 48:429–437

Hompes R, Mcdonald R, Buskens C, Lindsey I, Armitage N, Hill J, Scott A, Mortensen NJ, Cunningham C, The Association of Coloproctology of Great B, Ireland Transanal Endoscopic Microsurgery C (2013) Completion surgery following transanal endoscopic microsurgery: assessment of quality and short- and long-term outcome. Colorectal Dis 15:e576–e581

Johnston CF, Tomlinson G, Temple LK, Baxter NN (2013) The management of patients with T1 adenocarcinoma of the low rectum: a decision analysis. Dis Colon Rectum 56:400–407

Lezoche G, Baldarelli M, Mario Paganini A, De Sanctis A, Bartolacci S, Lezoche E (2008) A prospective randomized study with a 5-year minimum follow-up evaluation of transanal endoscopic microsurgery versus laparoscopic total mesorectal excision after neoadjuvant therapy. Surg Endosc 22:352–358

Marks JH, Valsdottir EB, Denittis A, Yarandi SS, Newman DA, Nweze I, Mohiuddin M, Marks GJ (2009) Transanal endoscopic microsurgery for the treatment of rectal cancer: comparison of wound complication rates with and without neoadjuvant radiation therapy. Surg Endosc 23:1081–1087

Minsky BD, Rich T, Recht A, Harvey W, Mies C (1989) Selection criteria for local excision with or without adjuvant radiation therapy for rectal cancer. Cancer 63:1421–1429

Moore JS, Cataldo PA, Osler T, Hyman NH (2008) Transanal endoscopic microsurgery is more effective than traditional transanal excision for resection of rectal masses. Dis Colon Rectum 51:1026–1031

Morino M, Allaix M, Famiglietti F, Caldart M, Arezzo A (2013) Does peritoneal perforation affect short- and long-term outcomes after transanal endoscopic microsurgery? Surg Endosc 27:181–188

Paty PB, Nash GM, Baron P, Zakowski M, Minsky BD, Blumberg D, Nathanson DR, Guillem JG, Enker WE, Cohen AM, Wong WD (2002) Long-term results of local excision for rectal cancer. Ann Surg 236:522–529 (discussion 529–530)

Perez RO, Habr-Gama A, Lynn PB, São Julião GP, Bianchi R, Proscurshim I, Gama-Rodrigues J (2013) Transanal endoscopic microsurgery for residual rectal cancer (ypT0-2) following neoadjuvant chemoradiation therapy: another word of caution. Dis Colon Rectum 56:6–13

Perez RO, Habr-Gama A, Sao Juliao GP, Proscurshim I, Neto AS, Gama-Rodrigues J (2011) Transanal endoscopic microsurgery for residual rectal cancer after neoadjuvant chemoradiation therapy is associated with significant immediate pain and hospital readmission rates. Dis Colon Rectum 54:545–551

Solomon M, Pager C, Keshava A, Findlay M, Butow P, Salkeld G, Roberts R (2003) What do patients want? Dis Colon Rectum 46:1351–1357

Taylor FG, Quirke P, Heald RJ, Moran B, Blomqvist L, Swift I, Sebag-Montefiore DJ, Tekkis P, Brown G (2011) 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 253:711–719

Part III
Surgical Treatment of Rectal Cancer

What Is "Good Quality" in Rectal Cancer Surgery? The Pathologist's Perspective

S. L. Bosch and I. D. Nagtegaal

Abstract

High local recurrence rates were a major problem in rectal cancer treatment, with between 30 and 50 % of patients affected, resulting in a very poor quality of life and short survival of patients with rectal cancer. In recent years, prognosis of rectal cancer has markedly improved, due to innovations in surgical treatment in combination with neoadjuvant therapy. Quality evaluation of surgical procedures has become the standard; constant high quality of surgery is one of the major successes in rectal cancer over the last decade. Continuous monitoring of surgical procedures is a new role for the pathologist. Completeness of excision, resection margins, but also numbers of lymph nodes have been firmly established as quality indicators.

1 Quality of Surgery: What Is Important?

Quality evaluation and continuous quality assurance are increasingly important in health care, to ensure optimal treatment of patients. In the field of colorectal cancer, surgical performance is one of the key factors for patient outcome. This is illustrated by the large number of studies that have been published on quality of surgery in colorectal cancer (Fig. 1). Numerous studies have shown that factors such as specialisation and caseload are important prognostic factors. In order to establish these factors, large studies with sufficient follow-up are required. Both

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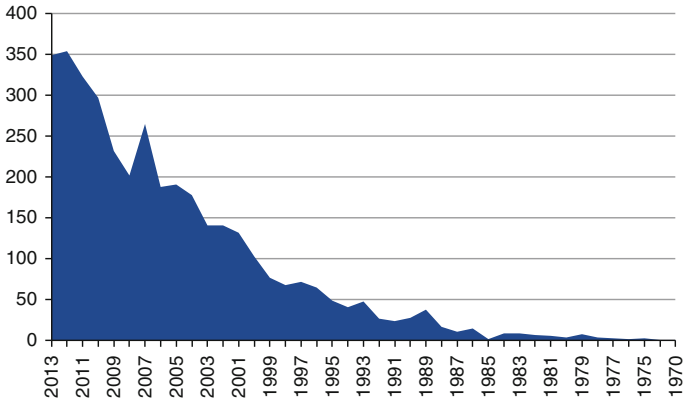

Fig. 1 The increase in publications categorised in PubMed that are retrieved using the combination of "quality of surgery" and "colorectal cancer"

short-term mortality and overall survival can be end-points of these studies, but the bias that is created by case-mix complicates analysis. Moreover, these large studies can provide data on quality evaluation, but are not suitable for continuous quality assurance. In order to continuously improve surgical quality, every individual operation should be evaluated using proven quality indicators. Pathological evaluation can provide several of such quality indicators.

2 Quality Indicators Provided by the Pathologist: Circumferential Resection Margin

The most important margin in rectal cancer surgery is the circumferential margin (CRM); this is the resection margin the surgeon creates in the lateral plane, following Denonvillier's fascia. By doing so, ideally a large fat column separates the tumour and involved lymph nodes from the resection margin (alternatively called: lateral, radial or mesorectal margin). However, in cases with locally advanced tumours this is sometimes hard to achieve, and positive margins occur in various frequencies, depending on the kind of neoadjuvant therapy, the quality of imaging and the skills of the surgeon.

Circumferential margin (CRM) is strongly correlated not only to local recurrence, but also to distant recurrence and survival. With increasing free margins, the risk on poor outcome decreases substantially (Nagtegaal et al. 2002a), therefore it is recommended to provide adequate measurements of the CRM. The international accepted cut-off for a positive resection margin is 1 mm. In a systematic review (Nagtegaal and Quirke 2008) we proved that positive margins in the surgery only setting are associated with a hazard ratio of 2.0 for local recurrence, however, after

neoadjuvant therapy, the hazard ratio is 6.3. This implies that the CRM is more than a surgery quality indicator: it also defines the success of neoadjuvant therapy. In addition, CRM involvement is a powerful prognostic factor. In the neoadjuvant setting, CRM involvement is more important than invasion depth (Gosens et al. 2007; Nagtegaal et al. 2007).

It has been known for a long time that huge differences exist between surgeons in local recurrence and survival rates. Indeed, when studying the CRM, these differences can at least partially be explained (Birbeck et al. 2002). However, a positive CRM might be a multifactorial problem, failure of neoadjuvant therapy, inadequate imaging or incomplete mesorectal excision may all be responsible. Due to analysis of the quality of surgery/completeness of excision as an independent factor, we can investigate this matter and try to improve the future treatment of rectal cancer patients.

3 Quality Indicators Provided by the Pathologist: Distal Resection Margin

The importance of the distal resection margin is less clear than that of the CRM. Although this margin is routinely examined macroscopically, microscopic evaluation is usually limited to those cases in which the tumour approaches the margin. However, there are several ways in which this margin can become involved. Continuous growth can occur either in the lumen of the bowel or intramural. Intramural spread is often subclinical, but can occur in substantial numbers of patients (Williams 1983). Initially, a 5 cm distal margin was advised. More recently, a 1 cm rule was established. In a systematic review, Bujko et al. (2012) demonstrated that, in a series of 948 patients with margins of less than 1 cm compared to 4,626 patients with margins over 1 cm, differences in local recurrence rates could not be substantiated. Alternatively, margins of 5 mm and 2 cm were investigated, but there were no differences in local recurrence rates either.

Distal margins can also become involved by discontinuous growth, by distal spread through lymph and blood vessels, or due to the presence of positive lymph nodes and tumour deposits. When a large number of lymph node metastases occur along the inferior mesenteric artery, lymphatic flow may change to a downward direction, causing distal spread (Shirouzu et al. 1995). In 20 % of the lymph node positive cases, lymphatic spread is observed distal to the primary tumour (in 6.4 % of cases over 2 cm away from the tumour edge) (Morikawa et al. 1994).

For an adequate measurement of the distal margin, fixation induced shrinkage of the bowel has to be recognised: unfixed colorectal segments can undergo shrinkage up to 50 % (Goldstein et al. 1999).

Table 1 Grading system for quality of surgery

	Plane of resection	Definition	Implication
TME	Mesorectal fascia	Smooth CRM, no defects deeper than 5 mm, intact mesorectum	Good prognosis
	Intramesorectal	Irregular mesorectal surface, moderate bulk to the mesorectum	Intermediate prognosis
	Muscularis propria	Defects down onto the muscularis propria, very irregular CRM	Poor prognosis
APR	Outside levator	Cylindrical specimen, with en bloc resection of levators	Good prognosis
	Sphincter	CRM on the surface of the intact sphincteric muscular tube	Intermediate prognosis
	Intramuscular/ submucosa	Perforation or missing areas of muscle	Poor prognosis

In case of an APR resection both gradings should be recorded

4 Quality Indicators Provided by the Pathologist: Quality of the Mesorectum

The plane of surgery achieved after TME, which reflects the completeness of mesorectal excision (Table 1), is a clinically relevant prognostic factor as well as an indicator of quality of surgery (Nagtegaal et al. 2002b). As could be expected, it is closely related to CRM, with a muscularis propria plane of resection automatically leading to a high risk of positive CRM, even in small tumours. However, the measurement of quality of surgery has prognostic value independent of the CRM. In the first series, only 180 patients were included (Nagtegaal et al. 2002b), but more recently these data have been confirmed in the CR07 with 1,117 patients (Quirke et al. 2009) and a systematic review (Bosch and Nagtegaal 2012).

5 Quality Indicators Provided by the Pathologist: Quality of the Sphincter Area

Rectal cancers in the lowest part of the rectum are frequently operated using the abdominoperineal excision (APR), in which the anal sphincter is included in the resection specimen. The surgical removal of this part of the rectum might be difficult, due to the anatomical limitations of the lower pelvis, and consequently perforations and positive margins are relatively common after this procedure. In order to judge the APR surgical technique, a modification (Nagtegaal et al. 2005) has been made to the original quality of surgery grading especially for the anal canal area (Table 1).

6 Quality Indicators Provided by the Pathologist: Lymph Node Counts

Lymph node sampling is an integral part of the pathological workup for resection specimens. Low numbers of examined lymph nodes can be an argument for adjuvant therapy (Benson et al. 2004). Numbers of nodes are dependent on several factors (Mekenkamp et al. 2009), not in the least on the quality of pathology examination. However, there is also a strong correlation with quality of surgery. When the resection plane is on the mesorectal fascia, more lymph nodes can be examined compared to the resection plane on the muscularis propria. In the Dutch Colorectal Surgical Audit 10 or more examined lymph nodes is considered a quality indicator, that is shown to be associated with both risk-adjusted morbidity and risk-adjusted 30-day mortality (Gooiker et al. 2013).

7 What Is Next?

In the era of population screening, an increase in early rectal cancers is expected. Radical treatment with total mesorectal excision might be replaced by local excision in a substantial number of patients. Focus on quality of local excision is important and urgent.

Analogous to the completeness of excision in rectal cancer, a scoring system has been developed for colon cancer (West et al. 2008). In order to accomplish a similar improvement of prognosis as observed in recent years in rectal cancer, we need to implement pathological evaluation of quality of surgery for colon cancer.

References

Benson AB 3rd, Ajani JA et al (2004) Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol 22(14):2918–2926

Birbeck KF, Macklin CP et al (2002) Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. Ann Surg 235(4):449–457

Bosch SL, Nagtegaal ID (2012) The importance of the pathologist's role in assessment of the quality of the mesorectum. Curr Colorectal Cancer Rep 8(2):90–98

Bujko K, Rutkowski A et al (2012) Is the 1-cm rule of distal bowel resection margin in rectal cancer based on clinical evidence? A systematic review. Ann Surg Oncol 19(3):801–808

Goldstein NS, Soman A et al (1999) Disparate surgical margin lengths of colorectal resection specimens between in vivo and in vitro measurements. Anat Pathol 111:349–351

Gooiker GA, Kolfschoten NE et al (2013) Evaluating the validity of quality indicators for colorectal cancer care. J Surg Oncol 108(7):465–471

Gosens MJ, van Krieken JH et al (2007) Improvement of staging by combining tumor and treatment parameters: the value for prognostication in rectal cancer. Clin Gastroenterol Hepatol 5(8):997–1003

Mekenkamp LJ, van Krieken JH et al (2009) Lymph node retrieval in rectal cancer is dependent on many factors—the role of the tumor, the patient, the surgeon, the radiotherapist, and the pathologist. Am J Surg Pathol 33(10):1547–1553

Morikawa E, Yasutomi M et al (1994) Distribution of metastatic lymph nodes in colorectal cancer by the modified clearing method. Dis Colon Rectum 37:219–223

Nagtegaal ID, Gosens MJ et al (2007) Combinations of tumor and treatment parameters are more discriminative for prognosis than the present TNM system in rectal cancer. J Clin Oncol 25(13):1647–1650

Nagtegaal ID, Marijnen CA et al (2002a) Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. Am J Surg Pathol 26(3):350–357

Nagtegaal ID, van de Velde CJ et al (2002b) Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. J Clin Oncol 20(7):1729–1734

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

Nagtegaal ID, van de Velde CJ et al (2005) Low rectal cancer: a call for a change of approach in abdominoperineal resection. J Clin Oncol 23(36):9257–9264

Quirke P, Steele R et al (2009) 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 373(9666):821–828

Shirouzu K, Isomoto H et al (1995) Distal spread of rectal cancer and optimal distal margin of resection for sphincter-preserving surgery. Cancer 76(3):388–392

West NP, Morris EJ et al (2008) Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. Lancet Oncol 9(9):857–865

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

Total Mesorectal Excision: Open, Laparoscopic or Robotic

Monica Young and Alessio Pigazzi

Abstract

Goals Total mesorectal excision (TME) is the gold standard technique for the surgical treatment of rectal cancer. Despite the benefits of minimally invasive surgery, laparoscopic TME (LTME) is a technically challenging procedure with a long learning curve. Robotic TME (RTME) has been advocated as an alternative to conventional LTME, but large studies supporting the efficacy or RTME are scarce. This work will review the current literature on minimally invasive surgery for rectal cancer and discuss future directions in the field. *Methods* A review of recent large single and multicenter studies on minimally invasive surgery for rectal cancer was conducted. *Results* Based on two large randomized clinical studies (CLASICC (Green et al. 2013) and COLOR II (van der Pas et al. 2013)). LTME is safe and feasible for the treatment of rectal cancer. Compared to open surgery, LTME has been shown to result in superior postoperative outcomes and similar oncologic results. However, the conversion rate of LTME is around 17 %. The literature supporting RTME is more limited. Robotic rectal resection appears to have similar postoperative and oncologic outcomes compared to LTME. RTME results in higher costs and possibly lower conversion rates. A large randomized clinical trial (ROLARR) comparing robotic to laparoscopic surgery for rectal cancer is underway. *Conclusions* Despite the technical challenges, current data supports the use of minimally invasive technique for rectal cancer surgery with superior short-term outcomes

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compared to an open approach. The use of robotic surgery is promising, but still limited and awaiting the conclusion of randomized clinical trials.

Keywords
Total mesorectal excision · Laparoscopic TME · Minimally invasive rectal surgery · Robotic TME · Robotic rectal surgery

1 Introduction

Since its introduction by Heald (1979), total mesorectal excision (TME) has been found to reduce local recurrence rates and improve oncologic outcomes (Stewart and Dietz 2007). A sharp, meticulous, en bloc resection of the cancer and surrounding perirectal lymphatic tissue along fascial planes produced superior control of local recurrence compared with nonstandardized surgery (Stewart and Dietz 2007). TME soon emerged as the gold standard technique for the surgical treatment of rectal cancer. Advances in minimally invasive surgery have resulted in the development of laparoscopic as well as robotic TME (RTME). Laparoscopic techniques offer advantages, such as decreased length of hospital stay, reduced postoperative pain, and improved cosmesis (D'Annibale et al. 2013; Jayne et al. 2007; Colon Cancer Laparoscopic or Open Resection Study Groupet al. 2009; Fleshman et al. 2007). However, minimally invasive rectal surgery is technically challenging with a steep learning curve. The pelvis is limited in space and width, making retraction and rectal dissection difficult, especially with laparoscopic instrumentation. Furthermore, concerns have been raised regarding the oncologic outcomes associated with this approach. The advent of a robotic platform has added even more alternatives to the minimally invasive rectal surgery armamentarium. This chapter will review the current literature on minimally invasive surgery for rectal cancer as well as discuss future directions in the field.

2 Open TME

The primary goal of surgical resection in rectal cancer is complete removal of the primary tumor as well as radially spread cancer cells in the mesorectum (van der Pas et al. 2013). The most important variables influencing local recurrence are the presence of involved lymph nodes, lymphovascular invasion, and circumferential resection margin positivity (Stewart and Dietz 2007; Chapuis et al. 2002; Bissett and Hill 2000). While different methods of rectal mobilization have been described, all share the common principle of removing the rectum with its perirectal fat and mesorectal fascia intact (Enker et al. 1995; Heald et al. 1998; Tiret and Pocard 1999; Killingback et al. 2001). The retrorectal plane is key to correct surgical

technique during posterior mobilization of the rectum, as is the retroprostatic or retrovaginal planes for the anterior dissection. Although this dissection historically was done using a blunt or manual technique (Goligher 1960), sharp dissection is now considered the standard operative approach (Beck and Steven 1998). When TME is performed with the proper surgical techniques, local recurrence rates have been reported in the range of less than 10 % (Enker et al. 1995; Aitken 1996). The impact of this proper surgical technique compared to nonstandardized methods has been well described in the literature. Kapiteijn et al. (2002) showed that local recurrence was improved with the adoption of TME techniques and that TME, when compared to conventional rectal resection, was an independent predictor of overall survival.

One of the first large studies published on TME was by Heald and colleagues, who reviewed their experience with 519 patients at North Hampshire Hospital in Basingstoke, England from 1978 to 1997 (Heald et al. 1998). Local recurrence rates were 6 % at 5 years and 8 % at 10 years. The clinically apparent anastomotic leak rate for patients undergoing anterior resection with curative intent was 6.5 %. Law et al. later published another large study on the outcomes of 622 patients with rectal cancer who underwent anterior resection at Queen Mary Hospital in Hong Kong from 1993 to 2002 (Law and Chu 2004). Patients with mid or low rectal cancers were treated with TME (64 %), while rectosigmoid and upper rectal cancers were treated with a partial mesorectal excision (PME, 36 %). The anastomotic leak rate for patients undergoing TME was reported as 8.1 %. On multivariate analysis, TME, male gender, absence of a stoma, and blood loss >500 mL were reported as independent risk factors for anastomotic leak. Local and distant recurrent rates were reported together, and were 6.0 % at 2-year and 9.7 % at 5-year. Due to longer operative times, higher anastomotic leak rates, technically challenging surgery and higher incidence of stoma formation, Law and colleagues concluded that TME should be used selectively, but does produce a good oncologic outcome.

This dramatic improvement in local control due to TME sparked debate as to whether neoadjuvant or adjuvant therapy was still significantly beneficial. As a result, two prospective randomized trials were undertaken to investigate the efficacy of radiation and chemotherapy in combination with TME for the treatment of rectal cancer. The Dutch Colorectal Cancer Group studied 1,861 patients, 924 who underwent preoperative radiotherapy followed by TME and 937 who underwent surgery alone (Kapiteijn et al. 2001). Local recurrence rate was 2.4 % in the radiation group and 8.2 % in the surgery alone group. However, overall survival at 2 years was not significantly different, with a rate of 82 % in the radiation group and 81.8 % in the group treated with surgery alone. The German trial CAO/ARO/AIO-94 examined the efficacy of neoadjuvant chemoradiation versus postoperative radiation in patients undergoing TME for locally advanced (T3/T4) disease (Sauer et al. 2001, 2003). A total of 805 patients were enrolled, with 355 in the neoadjuvant group and 363 in the adjuvant group. Patients in the neoadjuvant group had significantly lower rates of local recurrence, 6 % compared to 13 % local recurrence in the adjuvant group at 5 years. There was no difference in postoperative

morbidity or mortality between treatment groups. Neoadjuvant chemoradiation has subsequently become the standard of care, largely due to the results of this trial.

3 Laparoscopic TME

The widespread adoption of TME in the 1990s to early 2000s was congruent with the implementation of laparoscopy in colorectal operations. Laparoscopic colectomy in the setting of colon cancer was first examined and proved to be safe with less postoperative pain, earlier recovery, and comparable oncologic outcomes with traditional open resection (Colon Cancer Laparoscopic or Open Resection Study Group et al. 2009; Veldkamp et al. 2005; Leung et al. 2004). Although several reports were published demonstrating the safety and feasibility of LTME (Zhou et al. 2004; Scheidbach et al. 2002; Pasupathy et al. 2001), there was limited data regarding long-term impact on oncologic outcomes. These results were summarized in the Cochrane review of laparoscopic versus open TME for rectal cancer in 2006 (Breukink et al. 2006). A total of 48 studies met inclusion criteria, but 28 were case series and only one randomized controlled trial described primary outcome, 3- and 5-year survival rates (Leung et al. 2004). Since this time, additional randomized controlled trials have been performed specifically comparing laparoscopic versus open TME. In 2008, Anderson and colleagues reported a meta-analysis on oncologic outcomes of laparoscopic surgery for rectal cancer (Anderson et al. 2008). Their meta-analysis included 24 publications and examined 1,403 laparoscopic and 1,755 open rectal resections. Overall survival at 3 years was similar between treatment groups (76 % in laparoscopic and 69 % in open cases), as was mean local recurrence rates (7 % for laparoscopic and 8 % for open procedures). Another more recent meta-analysis by Qu et al. analyzed eight randomized controlled trials reported in the Chinese and English literature (Qu et al. 2013). The meta-analysis reviewed 863 patients with middle and low rectal cancers, 438 who underwent LTME and 435 cases of open TME. LTME was associated with significantly less intraoperative blood loss, earlier return of bowel function, shorter hospital length of stay, lower wound infection and lower postoperative bleeding rates compared to open TME. There were no significant differences noted in operative time, number of resected lymph nodes, anastomotic leak, ileus, or abscess formation.

Two large randomized clinical studies have recently been published assessing outcomes of laparoscopic compared to open rectal resection. The COLOR II trial included 30 medical centers across eight countries. A total of 1,044 patients with rectal cancer within 15 cm from the anal verge and no evidence of distant metastases were randomized, 739 in the laparoscopic, and 364 in the open surgery group. The laparoscopic arm was found to have less blood loss, faster return of bowel function, and shorter length of hospital stay, with longer operative time compared to the open arm. The conversion rate was approximately 17 %. There was no difference in oncologic resection margin between groups; the rate of

positive margins (defined as <2 mm) was 10 % in both cohorts. There were no differences in morbidity and mortality.

The UK Medical Research Council recently published their long-term follow-up of the CLASICC trial, which examined outcomes after conventional versus laparoscopic resection in colorectal cancer (Green et al. 2013). A total of 794 patients with colon and rectal cancer at 27 UK medical centers were randomized to laparoscopically assisted or open surgery from 1995 to 2002. For patients with rectal cancer, no statistically significant differences were found between open and laparoscopic groups in median overall survival (65.8 months open vs. 82.7 months laparoscopic, respectively, $p = 0.147$) or median disease-free survival (67.1 months open vs. 70.8 months laparoscopic, respectively, $p = 0.925$). Overall local recurrence was 10.9 % at 10 years and there was no significant difference found between randomized groups.

These studies confirm that minimally invasive rectal surgery is oncologically safe and a suitable alternative to open operations. In-hospital recovery after laparoscopic surgery has been shown to be better than after open surgery. Therefore, in selected patients treated by surgeons skilled in minimally invasive surgery, laparoscopic resection of rectal cancer should be considered (van der Pas et al. 2013). Debate persists on the impact of conversion from laparoscopic to open, as the CLASICC trial previously reported worse outcomes associated with conversion (Green et al. 2013; Jayne et al. 2007). However, in the most recent analysis, reduced disease free survival was only noted in converted patients with colon cancer. Intraoperative conversion did not appear to affect overall survival or disease free survival in patients with rectal cancer. Furthermore, conversion rates appear reduced in nonrandomized studies, ranging from 4.3 % (Yu et al. 2009) to 12 % (Morino et al. 2003).

4 Robotic TME

Robotic rectal resection appears to have similar postoperative and oncologic outcomes compared to LTME; however, the literature supporting RTME is more limited. Several studies have examined the short-term and long-term outcomes of robotic rectal resection (D'Annibale et al. 2013; Baik et al. 2009; Baek et al. 2013a; Biffi et al. 2011; Du et al. 2013; Luca et al. 2013). For a completely robotically performed TME mean operative times ranged from 220 to 270 min and length of stay was reported as 7–8 days. Mean length of stay following hybrid robotic-assisted laparoscopic rectal surgery is slightly lower at 6 days, with a range of 3–9 days. One of the main perceived advantages of robotic-assisted rectal resection is the lower conversion rate to open surgery. This finding was reported in a meta-analysis by Trastulli et al. (2012) who identified eight nonrandomized studies with a total of 854 patients comparing robotic and laparoscopic resection for rectal cancer. The robotic group was found to have a lower conversion rate and no significant differences in operative time, length of hospital stay, postoperative morbidity, postoperative mortality, or oncologic outcomes. A meta-analysis by

Memon et al. (2012) found similar results. However, as large randomized controlled trials are lacking, these lower conversion rates may be due to patient selection or surgeon bias. The majority of the published studies to date are retrospective or prospective nonrandomized trials. A systematic review of the literature published February 2014 by Kim and colleagues found 13 studies examining various types of robotic-assisted rectal resection such as anterior resection, low anterior resection, intersphincteric resection, or abdominoperineal resection (Kim et al. 2014); however, the majority of these publications were comparative studies. Although short-term outcomes appear to be acceptable, oncologic and long-term outcomes of RTME remain unknown. Evidence suggests that robotics may allow for better preservation of urinary and sexual function (Luca et al. 2013); however, further studies are needed to definitely make this conclusion. Randomized clinical trials and long-term follow-up are also needed to evaluate the influence of RTME on recurrence and survival. The ROLARR trial, an international, randomized controlled trial comparing robotic-assisted to laparoscopic resection for rectal cancer is currently in progress. Results of this study should help assess the future impact of RTME.

Key arguments against robotics are longer operative times and higher costs compared to laparoscopic surgery (Baek et al. 2013b). Longer operative times are attributed to setup, docking time of the robot, and time for surgeon to adapt to the robotic system (Kim et al. 2014). Costs are elevated due to longer operative times, robotic instruments, and the initial capital cost of the robotic platform itself. As surgeons and operating room staff become more experienced with robotics, operative times will likely decrease. Modifications have also been made to previously describe robotic techniques as a way to shorten operative time (Pigazzi et al. 2006). Despite the drawback of higher costs, use of robotics is increasing, as shown by Halabi et al. (2013) in his review of the Nationwide Inpatient Sample database from 2009 to 2010. In this study, rectal cancer was the most common indication for robotic-assisted colorectal surgery and increased from 1,188 cases in 2009 to 2,380 cases in 2010. These numbers are expected to be significantly higher today.

5 Future Directions

Transanal TME is a new approach to performing minimally invasive surgery for rectal cancer. Surgical access from the abdomen to the mid and low rectum can be very technically challenging, even for surgeons skilled in laparoscopic techniques. Patients with very distal tumors are particularly good candidates for this minimally invasive approach (Atallah et al. 2013a). Literature published on the initial experience with transanal TME has reported excellent exposure, even in male patients with difficult body habitus and a narrow pelvis (Atallah et al. 2013b). Although this early evidence appears promising, further studies are needed to evaluate the oncological safety and surgical outcomes of this approach.

6 Conclusion

Despite the technical challenges, current data supports the use of minimally invasive techniques for rectal cancer surgery. A review of the literature shows superior short-term outcomes and equivalent oncologic outcomes with LTME compared to an open approach. The use of robotics in rectal surgery is promising but still limited. Further randomized clinical trials are necessary to fully understand the outcomes of RTME. The ROLARR trial is currently in progress to assess outcomes between laparoscopic and robotic surgery for rectal cancer.

References

Aitken RJ (1996) Mesorectal excision for rectal cancer. Br J Surg 83(2):214–216

Anderson C, Uman G, Pigazzi A (2008) Oncologic outcomes of laparoscopic surgery for rectal cancer: a systematic review and meta-analysis of the literature. European J Surg Oncol: J Eur Soc Surg Oncol Br Assoc Surg Oncol 34(10):1135–1142

Atallah S, Martin-Perez B, Albert M et al (2013a) Transanal minimally invasive surgery for total mesorectal excision (TAMIS-TME): results and experience with the first 20 patients undergoing curative-intent rectal cancer surgery at a single institution. Tech Coloproctol

Atallah S, Albert M, DeBeche-Adams T, Nassif G, Polavarapu H, Larach S (2013b) Transanal minimally invasive surgery for total mesorectal excision (TAMIS-TME): a stepwise description of the surgical technique with video demonstration. Tech Coloproctol 17(3):321–325

Baek SJ, Al-Asari S, Jeong DH et al (2013a) Robotic versus laparoscopic coloanal anastomosis with or without intersphincteric resection for rectal cancer. Surg Endosc

Baek SK, Carmichael JC, Pigazzi A (2013b) Robotic surgery: colon and rectum. Cancer J 19(2):140–146

Baik SH, Kwon HY, Kim JS et al (2009) Robotic versus laparoscopic low anterior resection of rectal cancer: short-term outcome of a prospective comparative study. Ann Surg Oncol 16(6):1480–1487

Beck DE, Steven D (1998) Fundamentals of anorectal surgery, 2nd edn. WB Saunders, London

Biffi R, Luca F, Pozzi S et al (2011) Operative blood loss and use of blood products after full robotic and conventional low anterior resection with total mesorectal excision for treatment of rectal cancer. J Robot Surg 5(2):101–107

Bissett IP, Hill GL (2000) Extrafascial excision of the rectum for cancer: a technique for the avoidance of the complications of rectal mobilization. Semin Surg Oncol 18(3):207–215

Breukink S, Pierie J, Wiggers T (2006) Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev 2006(4):CD005200

Chapuis P, Bokey L, Fahrer M, Sinclair G, Bogduk N (2002) Mobilization of the rectum: anatomic concepts and the bookshelf revisited. Dis Colon Rectum 45(1):1–8 (discussion 8–9)

Colon Cancer Laparoscopic or Open Resection Study Group, Buunen M, Veldkamp R et al (2009) Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. Lancet Oncol 10(1):44–52

D'Annibale A, Pernazza G, Monsellato I et al (2013) Total mesorectal excision: a comparison of oncological and functional outcomes between robotic and laparoscopic surgery for rectal cancer. Surg Endosc 27(6):1887–1895

Du XH, Shen D, Li R et al (2013) Robotic anterior resection of rectal cancer: technique and early outcome. Chin Med J 126(1):51–54

Enker WE, Thaler HT, Cranor ML, Polyak T (1995) Total mesorectal excision in the operative treatment of carcinoma of the rectum. J Am Coll Surg 181(4):335–346

Fleshman J, Sargent DJ, Green E et al (2007) Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. Ann of Surg 246(4):655–662 (discussion 662–654)

Goligher JC (1960) Colon, rectum, and anus—surgical. Med Annu 78:40–53

Green BL, Marshall HC, Collinson F et al (2013) Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg 100(1):75–82

Halabi WJ, Kang CY, Jafari MD et al (2013) Robotic-assisted colorectal surgery in the United States: a nationwide analysis of trends and outcomes. World J Surg 37(12):2782–2790

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

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

Jayne DG, Guillou PJ, Thorpe H et al (2007) Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. J Clin Oncol: Off J Am Soc Clin Oncol 25(21):3061–3068

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

Kapiteijn E, Marijnen CA, Nagtegaal ID et al (2001) Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 345(9):638–646

Killingback M, Barron P, Dent OF (2001) Local recurrence after curative resection of cancer of the rectum without total mesorectal excision. Dis Colon Rectum 44(4):473–483 (discussion 483–476)

Kim CW, Kim CH, Baik SH (2014) Outcomes of robotic-assisted colorectal surgery compared with laparoscopic and open surgery: a systematic review. J Gastrointest Surg: Off J Soc Surg Aliment Tract

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

Leung KL, Kwok SP, Lam SC et al (2004) Laparoscopic resection of rectosigmoid carcinoma: prospective randomised trial. Lancet 363(9416):1187–1192

Luca F, Valvo M, Ghezzi TL et al (2013) Impact of robotic surgery on sexual and urinary functions after fully robotic nerve-sparing total mesorectal excision for rectal cancer. Ann Surg 257(4):672–678

Memon S, Heriot AG, Murphy DG, Bressel M, Lynch AC (2012) Robotic versus laparoscopic proctectomy for rectal cancer: a meta-analysis. Ann Surg Oncol 19(7):2095–2101

Morino M, Parini U, Giraudo G, Salval M, Brachet Contul R, Garrone C (2003) Laparoscopic total mesorectal excision: a consecutive series of 100 patients. Ann Surg 237(3):335–342

Pasupathy S, Eu KW, Ho YH, Seow-Choen F (2001) A comparison between open versus laparoscopic assisted colonic pouches for rectal cancer. Tech Coloproctol 5(1):19–22

Pigazzi A, Ellenhorn JD, Ballantyne GH, Paz IB (2006) Robotic-assisted laparoscopic low anterior resection with total mesorectal excision for rectal cancer. Surg Endosc 20(10):1521–1525

Qu C, Yuan RF, Huang J et al (2013) [Meta-analysis of laparoscopic versus open total mesorectal excision for middle and low rectal cancer]. Zhonghua wei chang wai ke za zhi = Chin J Gastrointest Surg 16(8):748–752

Sauer R, Fietkau R, Wittekind C et al (2001) Adjuvant versus neoadjuvant radiochemotherapy for locally advanced rectal cancer. A progress report of a phase-III randomized trial (protocol CAO/ARO/AIO-94). Strahlentherapie und Onkologie: Organ der Deutschen Rontgengesellschaft … [et al] 177(4):173–181

Sauer R, Fietkau R, Wittekind C et al (2003) Adjuvant vs. neoadjuvant radiochemotherapy for locally advanced rectal cancer: the German trial CAO/ARO/AIO-94. Colorectal Dis: Off J Assoc Coloproctol G B Irel 5(5):406–415

Scheidbach H, Schneider C, Konradt J et al (2002) Laparoscopic abdominoperineal resection and anterior resection with curative intent for carcinoma of the rectum. Surg Endosc 16(1):7–13

Stewart DB, Dietz DW (2007) Total mesorectal excision: what are we doing? Clin Colon Rectal Surg 20(3):190–202

Tiret E, Pocard M (1999) Total excision of the mesorectum and preservation of the genitourinary innervation in surgery of rectal cancer. Ann Chir 53(6):507–514

Trastulli S, Farinella E, Cirocchi R et al (2012) Robotic resection compared with laparoscopic rectal resection for cancer: systematic review and meta-analysis of short-term outcome. Colorectal Dis: Off J Assoc Coloproctol G B Irel 14(4):e134–e156

van der Pas MH, Haglind E, Cuesta MA et al (2013) Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol 14(3):210–218

Veldkamp R, Kuhry E, Hop WC et al (2005) Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 6(7):477–484

Yu J, Zhang C, Wang YN, Hu YF, Cheng X, Li GX (2009) [Laparoscopic versus open total mesorectal excision for the middle-lower rectal cancer: a clinical comparative study]. Zhonghua wei chang wai ke za zhi = Chin J Gastrointest Surg 12(6):573–576

Zhou ZG, Hu M, Li Y et al (2004) Laparoscopic versus open total mesorectal excision with anal sphincter preservation for low rectal cancer. Surg Endosc 18(8):1211–1215

Ultra Low Resection Versus Abdomino-Perineal Excision in Low Rectal Cancer

Torbjörn Holm

Abstract

There have been several important improvements in the management of patients with rectal cancer during the recent 20 years. For more accurate local and distant tumour staging, introduction of neoadjuvant treatments, improved surgery, a more precise macroscopic and microscopic evaluation of the specimen and MDT discussions have all been crucial in improving local control and survival. However, the most important factor has been the TME technique with standardisation of the surgical procedure. For patients with low rectal cancer, the decision making is complex with several treatment options, including the choice between neoadjuvant treatment followed by surgery or surgery alone, restorative procedures or APE. If an APE is necessary, this must also be tailored to the individual patient based on patient's characteristics and the extent of local tumour growth.

1 Introduction

The earliest surgical approaches to rectal cancer were via the perineum and the techniques used were exclusively extra-peritoneal. The mortality during and after surgery was high, the postoperative functional results poor and the local recurrence rate ranged up to 90 %. An important step in the development of surgery for rectal cancer was taken by W. Ernest Miles, who on December 19, 1908 in The Lancet

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published a paper entitled '*A method of performing abdomino-perineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon*' (Miles 1908). In Miles original description of the procedure the rectum was bluntly mobilised down to the sacro-coccygeal articulation posteriorly, to the prostate anteriorly and to 'the upper surface of the levatores ani' laterally. A colostomy was brought out and the abdominal wall was closed. The patient was then turned over and placed in the right lateral and semi-prone position. The perineal part of the operation included a wide excision of skin and fat and Miles emphasised that the levator muscles should be divided 'as far outwards as their origin from the white line so as to include the lateral zone of spread'. The specimen was brought out through the perineum and the skin was closed over two drains.

The Lancet paper had an enormous impact on the surgical community and Miles operation became the gold standard procedure for all rectal carcinomas for many decades. However, the concept of removing the entire rectum and the anus in all patients with rectal cancer gradually changed with time, and the increasing experience with bowel reconstruction, including the development of stapling instruments, led to the new concept of anterior resection (AR) and low anterior resection (LAR) which became the standard procedures for tumours in the upper and middle rectum (Collins 1963; Fick et al. 1960; Groves and Harrison 1962; Slanetz et al. 1972; Vandertoll and Beahrs 1965).

For tumours in the lower rectum, most surgeons continued to perform abdomino-perineal excision (APE), although the extensive perineal approach described by Miles was more or less forgotten and the synchronous combined APE was introduced as a feasible procedure, which became popular and gained widespread use in the treatment of low rectal cancer (Schmitz et al. 1958). During the synchronous combined operation, the perineal part is carried out simultaneously with the pelvic part of the abdominal procedure, with the patient in the supine lithotomy or Lloyd Davis position; the rectum with its mesorectum is mobilised down to the pelvic floor and the perineal surgeon then enters the pelvic cavity just in front of the coccyx, the levator muscles are divided on both sides and finally the rectum is dissected off the prostate or the vagina and the specimen is usually delivered through the perineum.

Despite the gradual improvements in rectal cancer treatment during the twentieth century, local control remained a major problem after surgery, with local recurrence rates of up to 50 % after potentially curative resections (Påhlman and Glimelius 1984). Therefore, preoperative radiotherapy was evaluated in several large randomised trials during the 1980s and was shown to reduce the local recurrence rate by 50 % and also to improve cancer-specific survival. Later, a combination of radio- and chemotherapy was shown to further increase local control and survival, especially in locally advanced tumours. Hence, preoperative radio-chemotherapy is an established accessory treatment in rectal cancer.

Even with neoadjuvant treatment, the local recurrence rate was up to 15–20 % and it was not until R. J. Heald described total mesorectal excision (TME) that the picture changed dramatically (Heald et al. 1982; MacFarlane et al. 1993). After extensive educational efforts by professor Heald and others, the TME technique for

rectal cancer resections has been introduced in many countries during the recent 15–20 years and is now considered the standard of care. Subsequently, the results with regard to local control have improved significantly and local recurrence rates are now reported to be less than 10 % in population-based studies (Kapiteijn et al. 2001; Martling et al. 2000; Wibe et al. 2004). The acknowledgement of TME as the standard surgical technique in the treatment of rectal cancer has improved not only local control but also increased the rates of sphincter saving procedures and survival.

2 Low Anterior Resection with Inter-sphincteric Resection

During the typical LAR with TME, the pelvic dissection is performed just outside the mesorectal fascia in loose connective tissue, 'the holy plane', down to the pelvic floor and the top of the puborectal muscle. Special attention is paid to preserve an intact mesorectal fascia and also to identify and preserve autonomic nerves on the pelvic sidewalls. Once the rectum and mesorectum are completely mobilised, the bowel is sealed with a transverse stapler or with a right-angled clamp and the rectal stump is rinsed with sterile water or some other mild cytotoxic agent. Another transverse stapler is applied on the rinsed rectum, the bowel is divided and the specimen removed. Subsequently, a circular stapler is introduced via the anus, the transected proximal colon is connected to the stapler and the anastomosis is completed. Most surgeons advocate a small colonic pouch or an end to side anastomosis in order to create a small reservoir, which improves short-term anorectal function, as compared to a straight anastomosis (Hallböök et al. 1996).

With the development of LAR and TME there has been a constant refinement of the concept of what represents a safe distal resection margin following the excision of rectal cancer, which some consider to be as low as 1 cm in certain circumstances. Therefore, restorative surgery for low rectal cancer, as defined by tumours within 6 cm from the anal verge, has evolved to include excision of all or part of the internal anal sphincter, an adaptation of a technique initially described for use in inflammatory bowel disease. ISR and reconstruction with a hand sewn coloanal anastomosis (CAA) is an attempt to extend the indications for rectal cancer excisions in which the normal route of defecation can be preserved. During the last 10–15 years and with the substantially improved results after TME and LAR, many surgeons have advocated low or ultralow anterior resection for tumours in the lower rectum. It has also been shown that these procedures are feasible and oncologically safe, provided that the tumour can be removed with a clear distal and circumferential margin (Schiessel et al. 2005). In dedicated and highly specialised centres, adopting ISR for appropriate cases, the overall APE rate may be below 10 %.

Some surgeons even perform partial or complete ISR for tumours at or just below the dentate line and the acceptable margin of distal clearance are usually considered to be 1 cm. T1–T2 tumours are usually considered to be resectable by ISR, while this procedure is contraindicated in tumours infiltrating the external sphincter or pelvic floor. Therefore, local tumour staging by MRI, and sometimes endoluminal ultrasound is crucial in patients with low rectal cancer. In addition to

the radiological local staging, digital rectal examination is vital to assess if the tumour is mobile in relation to the external sphincter and pelvic floor.

The oncological results after ISR and CAA are acceptable and comparable to those achieved with LAR and stapled anastomosis above the puborectal muscle, with local recurrence rates usually in the range of 5–10 % and 5-year disease free survival around 80 % (Martin et al. 2012).

Although feasible in selected patients, the functional results after ISR and CAA is often poor with a high rate of low anterior resection syndrome (LARS), including urgency, fragmentation of stools and incontinence. Major LARS at 1 year after surgery has been reported in half of the patients after LAR and this proportion is likely to be even higher after ISR and CAA. Patients with LARS also report poorer quality of life (QoL) than patients without LARS (Emmertsen and Laurberg 2013). Many patients with low rectal cancer will receive radio-chemotherapy before surgery in order to shrink and downsize the tumour, which may make subsequent surgery easier and prevent an involved circumferential resection margin (CRM). However, several studies have shown that radiotherapy in rectal cancer leads to a further deterioration of sexual and anorectal function which is persistent long term after treatment.

The vast majority of patients undergoing ISR and CAA will have a defunctioning ileostomy or transversostomy in order to prevent or diminish the severe and sometimes fatal consequences of an anastomotic leak. Due to different post-operative problems, such as persistent anastomotic leak with pelvic sepsis, other complications and comorbidity, some patients will not have their stoma closed. In other patients the functional results after ISR and CAA are so poor that a conversion to a permanent colostomy is required. It has been reported from different countries that the unintentional permanent stoma rate after LAR is around 20 % after long-term follow-up.

Thus, it is important to realise that ISR and CAA in patients with low rectal cancer should only be performed selectively; in those with early T1–T2 tumours (before or after neoadjuvant treatment) and if the pre-operative anorectal function is good, without any sign of incontinence. In addition, the patients have to be carefully counselled about the risks of poor function and a permanent stoma, despite the attempt to restore bowel continuity.

3 Abdomino-Perineal Excision

The majority of patients with low rectal cancer will need an APE, either because the CRM will not be clear with a sphincter saving procedure or the patient, for different reasons, is not suitable for restoration of bowel continuity. Traditionally, one obvious problem associated with the conventional type of synchronous combined APE was the lack of standardisation. Although the abdominal part of the operation follows the standard TME principles, there has been no apparent agreement on the surgical details of the perineal part of the operation. This probably explains the significant variability in the reported rates of tumour involved margins, bowel

perforations, local recurrence and survival (Birbeck et al. 2002). Also, the results in terms of bowel perforations, tumour involved CRM, local control and survival have been significantly poorer after APE than after AR. In one study based on 561 patients from Leeds, UK, it was reported that patients undergoing APE had a higher local failure rate (22.3 vs. 13.5 %) and a poorer survival (52.3 vs. 65.8 %) compared with patients who had an AR during the same time period (Marr et al. 2005). In another paper based on data from five different European trials it was reported that the APE procedure was associated with an increased risk of circumferential resection margin (CRM) involvement, an increased local recurrence rate and a decreased cancer specific survival (den Dulk et al. 2009).

The difference in oncological results between the two procedures may be explained by several factors, including anatomical difficulties and the surgical technique associated with standard APE surgery. In the lower rectum, the surrounding mesorectum is reduced in size and disappears at the top of the sphincters. Below this level, the sphincter muscle forms the circumferential resection margin (CRM). As mentioned above, the abdominal dissection during a conventional synchronous combined APE is often carried out along the mesorectum, all the way down to the pelvic floor and the top of the puborectalis muscle, with the mesorectum being mobilised off the levator muscles. The perineal dissection then follows the external sphincter to meet the pelvic dissection at the top of the anal canal. With this technique the retrieved specimen often has a typical 'waist' at 3–5 cm from the distal end corresponding to the top of the external sphincter at the level of the puborectalis muscle and the lowest part of the mesorectum.

This inwards coning at the pelvic floor carries the dissection close to the rectal wall and several studies have reported higher rates of bowel perforation and tumour involvement of CRM after APE as compared with AR. Nagtegaal et al. assessed 846 AR specimens and 373 APE specimens from the Dutch TME trial and found that the plane of resection was within the sphincter muscle, the submucosa or lumen in more than 1/3 of the APE cases, and in the remainder was on the sphincter muscles. This resulted in a positive CRM rate of 30.4 % after APE versus 10.7 % after AR and a perforation rate of 13.7 % after APE versus 2.5 % after AR (Nagtegaal et al. 2005).

Due to this variability, and the suboptimal results after APE, there has been a call for a different concept and a more standardised approach to APE (Radcliffe 2006). In recent years, a new concept of APE has therefore evolved, which takes into account the specific anatomical structures of the perineum and the pelvic floor and which aims to adopt and standardise the procedure according to the characteristics of the patient and the tumour. Basically, three types of APE can be described in relation to the perineal approach and the extent of dissection; *the inter-sphincteric APE, the extra-levator APE and the ischio-anal APE*. The mobilisation of the rectum and the mesorectum during the pelvic dissection in the abdominal part of the operation differs between the inter-sphincteric APE and the two other types. In addition, the indications are different for the three procedures, as mentioned below.

3.1 Inter-Sphincteric APE

The abdominal and pelvic dissection in inter-sphincteric APE is identical to that performed during LAR, which means that the mobilisation of the rectum with an intact mesorectum is continued down to the pelvic floor and the puborectal muscle.

To perform the perineal phase of an inter-sphincteric APE the surgeon and assistant move from the abdomen, the patient's legs are elevated and the perineum is exposed. An incision is made around the anus just distal to the inter-sphincteric groove. A self-retaining retractor with hooks is recommended to optimise the view and to facilitate the inter-sphincteric dissection. Once the skin incision is made the anus is closed with a running suture. The dissection then follows the inter-sphincteric plane between the internal and external sphincter, around the circumference of the anal canal, and all the way up to the puborectal sling and into the pelvic cavity. The specimen is then gently removed either through the perineal incision or, if the mesorectum is large and bulky, lifted up from the pelvis and removed from the abdomen via the abdominal incision. The perineal incision is then closed with a running or interrupted suture in the puborectal muscle, external sphincter and skin.

3.2 Extra-Levator APE

The main objective of an extra-levator APE is to diminish the risk of inadvertent bowel perforation and tumour involvement of the CRM. This is a consequence of excision of the levator muscles en bloc with the mesorectum to protect the most distal part of the bowel and thereby avoiding 'the waist' of the specimen, which has been so common after the conventional type of synchronous combined APE. Since the levator muscles should not be separated from the mesorectum, the pelvic dissection during the abdominal part of an ELAPE differs notably from an anterior resection or an inter-sphincteric APE (Holm et al. 2007).

3.2.1 The Pelvic Dissection in ELAPE

The initial abdominal and pelvic dissection is identical to that described above but with one very important difference. In both anterior resection and inter-sphincteric APE the dissection continues all the way down to the pelvic floor and the puborectal muscle and subsequently the mesorectum is lifted off the levator muscles. In ELAPE it is crucial not to take the mobilisation of the rectum and mesorectum as far down as the pelvic floor. Instead, the dissection should proceed only down to the sacro-cocygeal junction dorsally, just beyond the inferior hypogastric plexus antero-laterally, and anteriorly dissection should stop just below the seminal vesicles in men or the cervix uteri in women. By terminating the mobilisation of the rectum and mesorectum at this level, the mesorectum is still attached to the levator muscles of the pelvic floor, which is a crucial feature of the ELAPE.

3.2.2 The Perineal Part of ELAPE

The perineal part of ELAPE differs considerably from the perineal part of the inter-sphincteric APE or LAR with ISR. The perineal phase starts with closure of the anus to avoid any spillage of faeces or mucus which could contain tumour cells. The anal closure thus aims at reducing infection and also reducing the risk of tumour contamination which may result in local recurrence. Closing the anus can be done with a double purse string suture or with an inverting running suture after the skin incision has been made around the anus. The latter technique is especially valuable in very low, advanced tumours which may in fact protrude through the anus. In the ELAPE less skin and ischio-anal fat is excised as compared with Miles original description of the perineal part of the APE procedure. Instead, the skin is incised around the anus with a margin of only about three centimetres anteriorly and laterally, posteriorly the incision is carried up to the level of the lower sacrum i.e. two to three centimetres cranial to the sacro-coccygeal junction.

With gentle traction and counter traction on the skin edges the dissection is now continued in the subcutaneous fat and as dissection proceeds deeper it is important to identify the subcutaneous extension of the external sphincter. These fibres of striated muscle should be kept medially and the dissection follows a plane between the external sphincter and the thin fascia covering the ischio-anal fat in the ischio-anal compartment (also called ischio-rectal fossa) on both sides. At the top of the external sphincter and puborectal muscle, the levator ani muscles are in direct continuity and the dissection is carried along the surface of the levator muscles all the way up to their insertion at the pelvic side wall, i.e. the obturator internus muscle. Once the surface of the levator muscles are exposed all around the circumference the haemostasis must be controlled before entering the pelvic cavity.

In the midline the levator muscles are attached to the anterior surface of the coccyx and continue as the presacral fascia on the anterior, lower aspect of the sacrum. The dissection follows the proximal portion of the levator muscles on both sides of the coccyx so that the coccyx is clearly exposed. Next, an incision is made at the sacro-coccygeal junction, which is easily identified by gentle moving of the coccyx. Once the cartilaginous connection between the sacrum and coccyx has been opened the coccyx is pressed anteriorly to stretch the presacral fascia, which is then divided and an entrance into the pelvic cavity is created. At this stage it is important to identify the mesorectum in order not to injure the mesorectal fascia.

The pelvic floor, i.e. the levator muscle, is now divided from posterior to anterior and as the division of the pelvic floor continues anteriorly it is important to avoid a division of the levator muscles too far laterally and too close to the ischial tuberosity as this may injure the main pudendal nerve and vessels in Alcock's canal. The division of the pelvic floor continues until the dorsolateral part of the prostate or vagina can be palpated and visualised, or preferably one to two centimetres posterior to this point. The specimen is now still attached to the anterior aspect of the levator muscles and to the prostate or posterior wall of the vagina.

The dissection in the anterior plane during the perineal phase of the ELAPE is the most difficult, and potentially most dangerous, part of the procedure because of the

close relationship between the anterior rectal wall and the prostate or posterior vaginal wall. In addition, the neurovascular bundles derived from the inferior hypogastric plexus run anterolaterally on each side of the prostate or vagina and close to the rectum and can easily be damaged if they are not recognised at this stage of the operation. The dissection along the anterior and lateral aspects of the lower rectum must therefore be performed meticulously and with great care. If the dissection is performed close to the rectal wall there is a risk of inadvertent perforation or tumour involved margin and if the dissection is carried out too laterally, or too anteriorly, there is a risk of damage to the neurovascular bundles or to the prostate or vagina. In anteriorly located tumours it may be necessary to include the posterior vaginal wall or a slice of the posterior prostate with the specimen, and sometimes even to sacrifice the neurovascular bundle on one side, to be able to achieve a negative CRM. However, this extension of the procedure should ideally be planned in advanced so that the surgeon is prepared for it and so that the patient is well informed about the consequences which may be impairment of bladder and/or sexual function. To facilitate the anterolateral dissection of the lower part of the rectum it is recommended that the specimen is gently brought out of the pelvic cavity so that the anterior aspect of the bowel can be seen. It is now easy to look into the pelvic cavity and to recognise the seminal vesicles and upper part of the prostate in men and the posterior vaginal wall in women. The plane between Denonvillers fascia and the prostate or posterior vaginal wall is now carefully followed whilst the surgeon should attempt to identify the neurovascular bundles on each side. Gradually, these planes of dissection are developed anteriorly and alternately on the right and left side and the remaining part of the levator muscles that are attached to the lowest part of the rectum are divided. Finally, the puborectal muscle on each side and the perineal body just posterior to the transverse perineal muscle is divided and the specimen can be delivered. The excised specimen is ‘cylindrical’, usually without a waist, due to the fact that the levator muscle is still attached to the mesorectum, forming a cuff around the rectal muscle tube.

3.3 Ischio-Anal APE

In some patients the rectal tumour is locally advanced and may infiltrate or even perforate the pelvic floor, i.e. the levator muscle. In other patients, a perianal abscess may sometimes be the presenting feature of a perforated low rectal cancer, and after drainage a fistula may persist between the low rectum and the perianal skin. In a few very low tumours the growth may extend into the perianal skin. In these instances an ELAPE may not be sufficient to achieve a safe, tumour free CRM and an ischio-anal APE is usually required to obtain an oncologically secure margin. In this situation the levator muscle must be removed and covered with ischio-anal fat and the ischio-anal fat must be removed to include the perianal fistula, which may contain tumour cells. Therefore, the ischio-anal APE is a valid procedure in these special situations.

The abdominal part of the ischio-anal APE is exactly equivalent to the abdominal part of the extra-levator APE. Thus, the dissection stops just above the levator muscle, and leaves the mesorectum attached to the pelvic floor.

3.3.1 The Perineal Part of Ischio-Anal APE

The area of the skin incision in an ischio-anal APE depends on the extent of tumour involvement of the skin. Any tumour infiltration or fistula opening must be included in the excised skin area with a margin of at least 2–3 cm. As soon as the incision deepens into the subcutaneous space the dissection should be directed laterally towards the ischial tuberosity and progresses onto the fascia of the internal obturator muscle. Thus, contrary to an extra-levator APE, the dissection does not follow the external sphincter and levator muscle but is instead carried along the fascia of the internal obturator muscle. The dissection is performed along this plane up to where the levator muscle is inserted onto the internal obturator muscle and hence includes the entire fat compartment of the ischio-anal space. This dissection can be performed unilaterally or bilaterally depending on the extent of tumour growth. When the dissection up to this level is completed the sacro-coccygeal junction is incised and the pelvic cavity is entered in the same fashion as with an ELAPE. The subsequent dissection is also similar to that of the ELAPE, as the levator muscles are divided along the fascia of the internal obturator muscle onto the prostate in men or the vagina in women. Once the specimen has been brought out of the pelvic cavity, the anterior and lateral dissection along the prostate or vagina is also carried out as in an ELAPE. As mentioned above, the difference between an ELAPE and an ischio-anal APE is that the fat in the ischio-anal space is resected en bloc and attached to the levator muscle. This procedure is similar to what Miles described in 1908 in his original paper in The Lancet.

4 Restorative Procedure or APE in Low Rectal Cancer?

Every patient with low rectal cancer should have an appropriate clinical assessment and radiological staging with MRI of the pelvis and CT of the thorax and abdomen. The results of this work up should be presented a multidisciplinary team (MDT) meeting and discussed in relation to current knowledge and the management should be individualised to each patient with rectal cancer.

The choice between a restorative procedure, in terms of ISR and CAA, or APE in low rectal cancer depends on the patient, the tumour and the surgeon. Important patient related factors include comorbidity and anorectal function, tumour characteristics include the height of the tumour from the anal verge and results of preoperative radiological staging in terms of TNM stage, and surgeon-related factors include experience, skill and technical resources.

Thus, ISR with CAA can be performed in patients with an early T1–T2 tumours and good anal function. If the anal function is poor an inter-sphincteric APE is probably a better choice. In patients with tumours threatening or involving the external sphincter or pelvic floor an ELAPE is the procedure of choice and if the tumour is even more advanced, an ischio-anal APE may be necessary.

5 Summary

There have been several important improvements in the management of patients with rectal cancer during the recent 20 years. More accurate local and distant tumour staging, introduction of neoadjuvant treatments, improved surgery, a more precise macroscopic and microscopic evaluation of the specimen and MDT discussions have all been crucial in improving local control and survival. However, the most important factor has been the TME technique with standardisation of the surgical procedure. For patients with low rectal cancer the decision making is complex with several treatment options, including the choice between neoadjuvant treatment followed by surgery or surgery alone, restorative procedures or APE. If an APE is necessary this must also be tailored to the individual patient, based on patient characteristics and the extent of local tumour growth.

References

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

Cancer Collaborative Group (2001) Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. Lancet 358(9290):1291–3304

Collins DC (1963) End-results of the Miles' combined abdominoperineal resection versus the segmental anterior resection. A 25-year postoperative follow-up in 301 patients. Am J Proctol 14:258–261. PubMed PMID: 14041605

den Dulk M, Putter H, Collette L, Marijnen CA, Folkesson J, Bosset JF et al (2009) The abdominoperineal resection itself is associated with an adverse outcome: the European experience based on a pooled analysis of five European randomised clinical trials on rectal cancer. Eur J Cancer 2009 Jan 5. PubMed PMID: 19128956

Emmertsen KJ, Laurberg S, Rectal Cancer Function Study G (2013) Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. Br J Surg 100(10):1377–1387. PubMed PMID: 23939851

Fick TE, Baeten CG, von Meyenfeldt MF, Obertop H (1960) Recurrence and survival after abdominoperineal and low anterior resection for rectal cancer without adjunctive therapy. Eur J Surg Oncol 16:105–108

Groves RA, Harrison RC (1962) Carcinoma of the rectum and lower sigmoid colon: abdominoperineal or anterior resection? Can J Surg 5:393–403

Hallböök O, Påhlman L, Krog M, Wexner SD, Sjödahl R (1996) Randomized comparison of straight and colonic **J** pouch anastomosis after low anterior resection. Ann Surg 224(1):58–65

Heald RJ, Husband EM, Ryall RDH (1982) The mesorectum in rectal cancer surgery - the clue to pelvic recurrence. Br J Surg 69:613–616

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

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

MacFarlane JK, Ryall RD, Heald RJ (1993) Mesorectal excision for rectal cancer [see comments]. Lancet 341(8843):457–460

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

Martin ST, Heneghan HM, Winter DC (2012) Systematic review of outcomes after intersphincteric resection for low rectal cancer. Br J Surg 99(5):603–612

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

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

Nagtegaal ID, van de Velde CJ, Marijnen CA, van Krieken JH, Quirke P (2005) Low rectal cancer: a call for a change of approach in abdominoperineal resection. J Clin Oncol 23(36):9257–9264

Påhlman L, Glimelius B (1984) Local recurrences after surgical treatment for rectal carcinoma. Acta Chir Scand 150:331–335

Radcliffe A (2006) Can the results of anorectal (abdominoperineal) resection be improved: are circumferential resection margins too often positive? Colorectal Dis 8(3):160–167

Schiessel R, Novi G, Holzer B, Rosen HR, Renner K, Holbling N et al. (2005) Technique and long-term results of intersphincteric resection for low rectal cancer. Dis Colon Rectum 48(10):1858–1865; discussion 1865–1867. PubMed PMID: 16086223

Schmitz RL, Nelson PA, Martin GB, Boghossian HM (1958) Synchronous (two-team) abdominoperineal resection of the rectum. AMA Arch Surg 77(4):492–497

Slanetz CA, Herter FP, Grinnell RS (1972) Anterior resection versus abdominoperineal resection for cancer of the rectum and rectosigmoid: an anlysis of 524 cases. Am J Surg 123:110–117

Vandertoll DJ, Beahrs OH (1965) Carcinoma of the rectum and low sigmoid. Evaluation of anterior resection in 1766 favourable lesions. Arch Surg 90:793–798

Wibe A, Syse A, Andersen E, Tretli S, Myrvold HE, Soreide O (2004) Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior versus abdominoperineal resection. Dis Colon Rectum 47(1):48–58

T4 Rectal Cancer: Do We Always Need an Exenteration?

Thomas A. Vermeer, Miranda Kusters and Harm J. T. Rutten

Abstract

The management of rectal cancer has changed dramatically over the last few decades. Due to improvements in the multimodality treatment and the introduction of neoadjuvant chemoradiation, previously irresectable tumours can nowadays be cured by extensive multivisceral resections. These highly complex operations are associated with significant morbidity and mortality. Due to optimization of chemoradiotherapy, the introduction of IORT, increasing knowledge of tumour pathology and patterns of recurrence the need for extensive surgery diminishes. The question arises which patients with T4 rectal cancer really need extensive surgery and who can safely be considered for an organ preserving approach.

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1 Introduction

Due to advances in multimodality rectal cancer treatment, previously untreatable patients with locally advanced disease, now undergo curative multivisceral resections with acceptable oncological outcome. Rectal cancer is a common disease with high incidence rate and a high cancer-related mortality rate. In 10 % of patients present with primary rectal cancer, the tumour penetrates through the mesorectal fascia and threatens the integrity of adjacent organs and structures and an approach according to the TME principles would inevitably lead to an irradical resection (Gebhardt et al. 1999). In these T4 rectal cancer patients, the surgical peripheral margin has to be extended beyond the TME plane (Heald and Ryall 1986). The definition of advanced rectal cancer is very heterogeneous. In this chapter, we discuss T4 rectal cancer, which can be identified better due to its involvement of pelvic organs and structures, which can be easily diagnosed with modern MRI techniques. T4a rectal cancer by definition invades the visceral peritoneum; in upper rectal cancer adjacent organs are not involved (except bowel loop which is located against the peritoneal surface of the upper rectum). T4b rectal cancers always truly invade the adjacent organs. Both, T3+ and T4 tumours are at high risk for local recurrence and worse oncological outcome, but this chapter focuses on T4 tumours.

Despite the current multimodality treatment, the approach of rectal cancer treatment is still based on the importance of the distance of the radial tumour boarder to the MRF, as described by Quirke (1986). This radial margin, called the circumferential resection margin (CRM), is the strongest predictor of an unfavourable oncological outcome; i.e. increase of local recurrence, distant metastasis and poor survival (Nagtegaal and Quirke 2008; Kennelly et al. 2013). In order to fulfil the main goal of rectal cancer surgery, achieving a radical resection, extension beyond the circumferential resection margins will lead to a loss of pelvic structures and organs and subsequent increased morbidity. In low rectal cancers, a T4 tumour will often invade into the funnel-shaped pelvic floor or the anterior genital organs (Fig. 1).

In mid-rectal cancer again the urogenital organs anteriorly, the lateral sidewalls with the neural bundle, the piriformis muscles and the internal iliac vessels as well as the posterior sacral fascia and sacrum are at risk. In high rectal cancer, the uterus, ureters, bladder and major vessels pose a challenge. Therefore, T4 rectal cancer is a very heterogeneous disease, depending on the level and orientation of the tumour (Fig. 2).

The introduction of preoperative long-term radiotherapy with concomitant chemotherapy, i.e. chemoradiotherapy (CRT), has improved oncological outcome in locally advanced rectal cancer. In many cases, it results in downsizing and downstaging of the tumour has been proven effective, but it is still unclear if the oncological prognosis shifts parallel to the extent of the downstaging. More concrete, does it mean when a T4 tumour becomes a T3 or even less, the prognosis also change to that stage? Essentially, this is the controversy whether the tumour

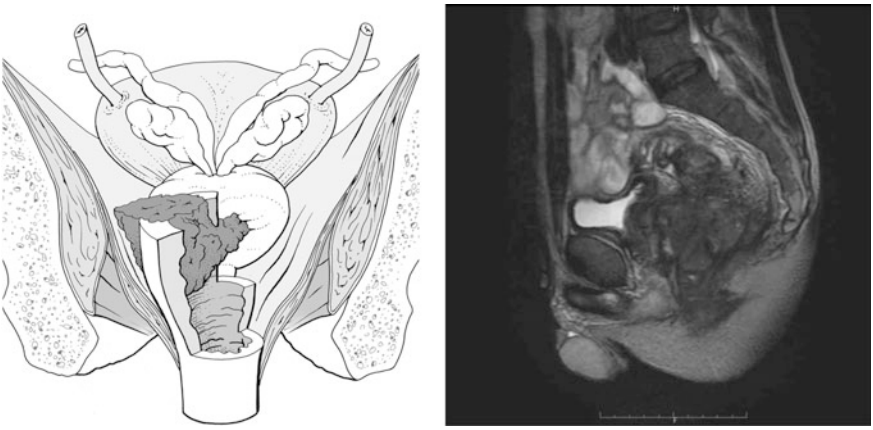

Fig. 1 Tumour invading the prostate and pelvic floor

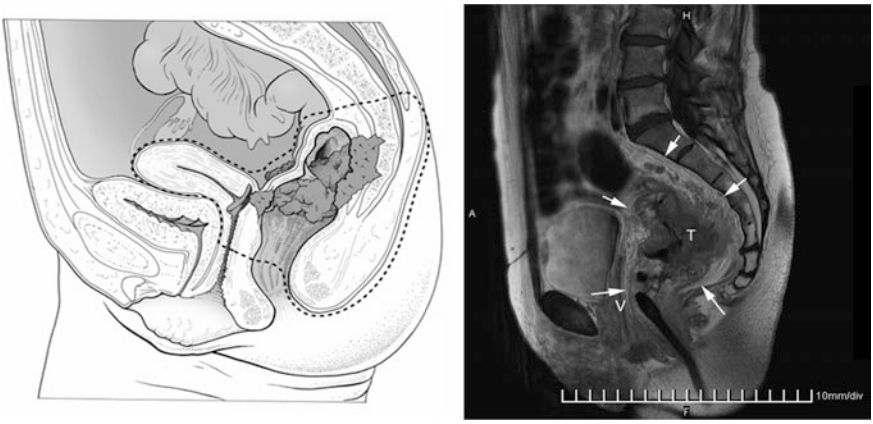

Fig. 2 Large extended resections may be required to achieve a negative surgical margin

should be treated as it primary presented, or does downsizing and downstaging also allow for a downscaled surgical approach meaning that a standard TME resection might be sufficient?

In order to accurately assess whether downstaging has occurred, MRI is used for restaging. But the question arises if it possible to accurately assess downstaging on MRI and subsequently reliably downscale the surgical approach.

Besides neoadjuvant treatment and imaging, several issues will be discussed in this article and two further questions remain to be answered. First, which margin can be considered safe after CRT and does a close or even positive margin result in a poor oncological outcome? Subsequent questions are about the optimal time interval between neoadjuvant treatment and surgery. What is the optimal timing

for restaging, and does prolongation of this interval lead to further regression of the tumour? The second question regards the advantage of intensification of the neoadjuvant treatment. Is there a place for combining multiple drugs as part of the concomitant CRT or would it be better to combine (chemo-) radiotherapy with several courses of systemic chemotherapy? Does intensification of the radiotherapy with additional brachytherapy or intraoperative radiotherapy compensate for close or even affected margins?

2 Neoadjuvant Chemoradiotherapy

Neoadjuvant CRT became the standard treatment for locally advanced rectal cancer, after several studies showed the improvement of downsizing and downstaging of the tumour and its subsequent positive effect on oncological outcome, i.e. increased local control (Frykholm et al. 2001; Valentini et al. 2002). The use of concomitant continuous 5-FU administration as a radiation sensitizer resulted in increased downstaging and local control compared to radiotherapy alone, and 5-FU agents are now a part of the standard neoadjuvant treatment (Bosset et al. 2014; Gerard et al. 2006; Saif et al. 2008). In order to further improve oncological outcome, various chemoradiation schemes have been investigated over the last few decades. Intensified CRT schemes, with additional chemotherapy to the above-mentioned scheme, have been studied in locally advanced rectal cancer. The addition of oxaliplatin showed promising results in different studies with an increased effect on downstaging and even improved oncological outcome (Fakih et al. 2008; Chau et al. 2006; Rutten et al. 2006; de Gramont et al. 2000).

Three randomised controlled multicentre phase III trials could not reproduce these effects on downstaging, and oncological outcome did not improve by intensifying CRT by adding oxaliplatin (Aschele et al. 2011; Rodel et al. 2012; Gerard et al. 2010). In addition, increased toxicity rates were observed and the administration of oxaliplatin was therefore discouraged. A recent update of the ACCORD 12 trial, with a 3-year follow-up did not find any improvement on clinical outcome for this intensified chemoradiation regimen (Gerard et al. 2012). The randomised controlled multicentre CAO/ARO/AIO-04 trial shows contradictory results, with increased pathological complete response without increased acute toxicity rates (Rodel et al. 2012). Despite these results, no impact on R0 resection rate, positive CRM or overall survival was found (Sauer et al. 2012).

Especially in T4 rectal cancer downsizing and downstaging of the tumour is of pivotal importance in order to perform a curative resection or even downscale the surgical approach and prevent the patient form undergoing extensive multivisceral resections. The multicentre phase II CORE study (Capecitabine, Oxaliplatin, Radiotherapy follow by Excision), commenced in 2003 (Rutten et al. 2006). The CORE regimen was significantly associated with tumour regression and high R0 resection rate. This subsequent positive effect of various chemoradiotherapy schemes on R0 resection is confirmed by our data and is shown in Fig. 3 (data presented during the St. Gallen Oncology Conference).

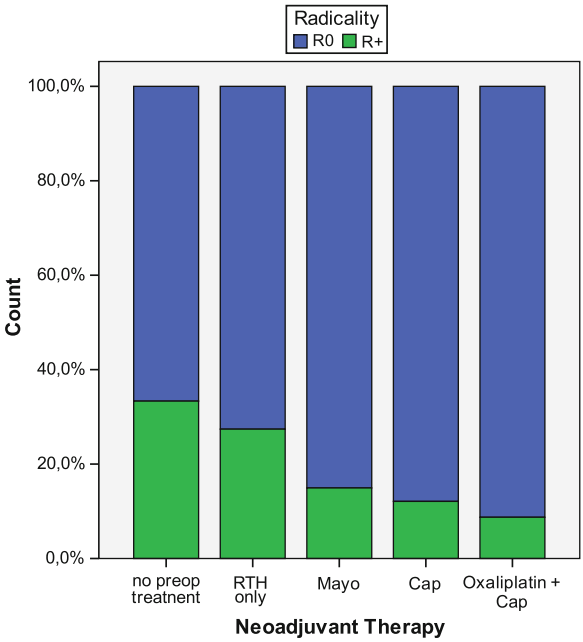

Fig. 3 Intensified radiochemotherapy shows better resection rates in T4 rectal cancer, but the clinical relevance could not be confirmed in several randomised trials (be it that these trials included mostly T3 patients) (unpublished data)

Grade 3 and 4 toxicity rates in the CORE group, 20 and 11 % respectively, were comparable to the other regimens, 18 and 10 % respectively. This intensified CRT scheme significantly improved cancer-specific survival (Martijnse et al. 2012). In this population with mainly T4 rectal cancer patients, the intensified chemoradiation regimen appears effective. Oxaliplatin may only be effective, in those patients with T4 rectal cancer in whom downstaging can induce a resectable tumour. The systemic effects of oxaliplatin are encouraging, with a decrease in distant metastases at the time of surgery (Aschele et al. 2011; Rodel et al. 2012; Gerard et al. 2010) and increased relapse-free survival and cancer-specific survival (Martijnse et al. 2012). Further effects on oncological outcome will be available in the trial updates with increased follow-up.

The administration of additional 5FU-based chemotherapy in the rest period proved to be save with acceptable toxicity and an increase in pCR rates and tumour downstaging, achieving an overall complete response rate of 65 % (Habr-Gama et al. 2009). The FOLFOX phase II trial, demonstrated an increased pCR rate, 25 % versus 16 %, after administration of two cycles of FOLFOX (folinic acid, 5-FU, oxaliplatin) in the rest period (Garcia-Aguilar et al. 2011). Since both studies increased the timing interval compared to previous studies, the attribute of additional chemotherapy cannot be conclusively determined.

3 Staging and Restaging Rectal Cancer

3.1 Staging Rectal Cancer

In order to accurately stage rectal cancer patients and assign them to neoadjuvant treatment, Magnetic Resonance imaging (MRI) has evolved in the most important diagnostic modality. MRI provides detailed images of dissection planes and pelvic fascia's, more specifically the mesorectal fascia (MRF) in rectal cancer, and is therefore the diagnostic modality of choice. High-resolution MRI is superior to Computed Tomography (CT) for imaging rectal tumours and assessment of a threatened or involved MRF. A very good correlation of extramural spread of tumours on MRI and in histopathology was reported by The Mercury study group, confirming the reliability of MRI in predicting tumour invasion (Group MS 2007). But the true value of MRI is its ability to predict a positive CRM or MRF involvement. The best cut-off distance for predicting MRF involvement using MRI is 1 mm between the tumour and the MRF. Using a cut-off point greater than 1 mm did not decrease local recurrence rates below 7 %, while patients with a distance of less than 1 mm on MRI have a 20 % risk to develop a local recurrence (Taylor et al. 2011). Besides local tumour staging, predicting lymph node involvement is an important part of preoperative staging. The prediction of lymph node involvement remains a diagnostic problem for the radiologist even on MRI. Lateral lymph node disease can be assessed with MRI or PET-CT but the accuracy remains insufficient. In order to accurately stage patients prior to treatment, additional diagnostic modalities are used. Abdominal Computer tomography (CT) is used to stage distant disease. Endorectal ultrasound (ERUS) is widely used in staging early rectal cancer. EUS is accurate for the evaluation of the muscularis propria, (Bipat et al. 2004; Kwok et al. 2000; Puli et al. 2009) but it cannot visualise the MRF as reliably as an MRI scan, and the extend of organ involvement cannot be accurately assessed (Bipat et al. 2004; Ref. 28). Therefore, ERUS has no role in primary staging of T4 rectal cancer as a stand-alone diagnostic tool, but it may have an application for determining specific organ involvement, particularly the rectal-prostate interface (Beyond 2013) (Fig. 4).

3.2 Restaging Rectal Cancer

The response to preoperative CRT is evaluated by various diagnostic modalities; i.e. ERUS, CT, MRI, diffusion weight (DW) MRI and FDG-PET/CT. Accurate association between clinical stages predicted by the different diagnostic modalities after CRT and pathological tumour stage is crucial. The question arises whether the surgical strategy can be downscaled if partial or complete tumour response is observed on the different imaging modalities. The tissue transformation induced by chemoradiotherapy causing inflammation and fibrosis, has a major impact on post-CRT radiological imaging and therefore assessment of these diagnostic modalities is crucial (Fig. 5).

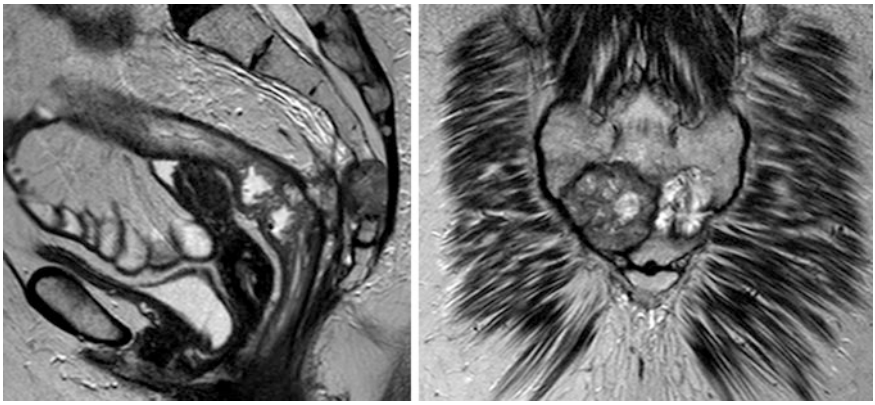

Fig. 4 Accurate delineation of structures and tumour with the help of MRI

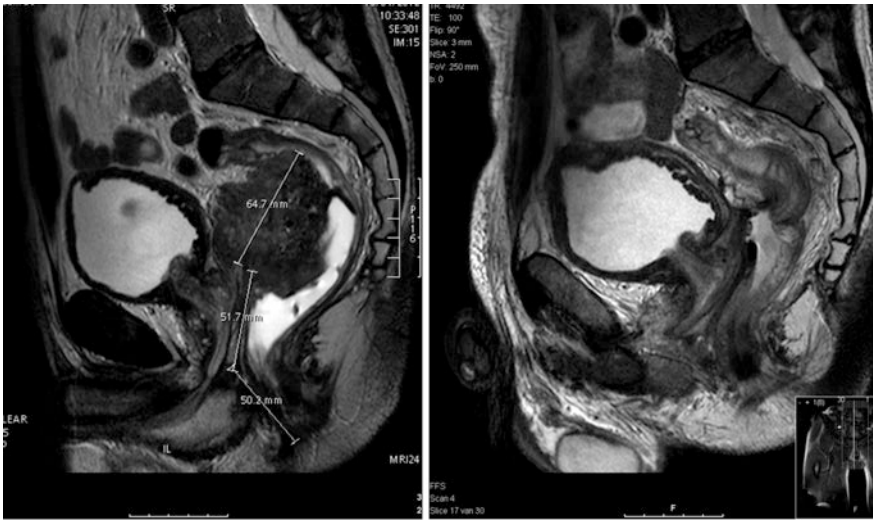

Fig. 5 Restaging with MRI may lead to a new interpretation of the required extent of the resection

The inability to differentiate between tumour and radiation-induced inflammation and fibrosis turns ERUS into an inaccurate diagnostic modality with sensitivity rates between 38 and 48 % (Vanagunas et al. 2004; Mezzi et al. 2009; Huh et al. 2008; Dickman et al. 2013). Similar limitations are encountered using MRI since it cannot completely differentiate between fibrosis and tumour residue and MRI tends to overestimate CRM involvement. Introduction of Diffusion-Weighted (DW) MRI enhanced the diagnostic accuracy compared to conventional MRI in evaluating tumour response, including complete response. The sensitivity for predicting

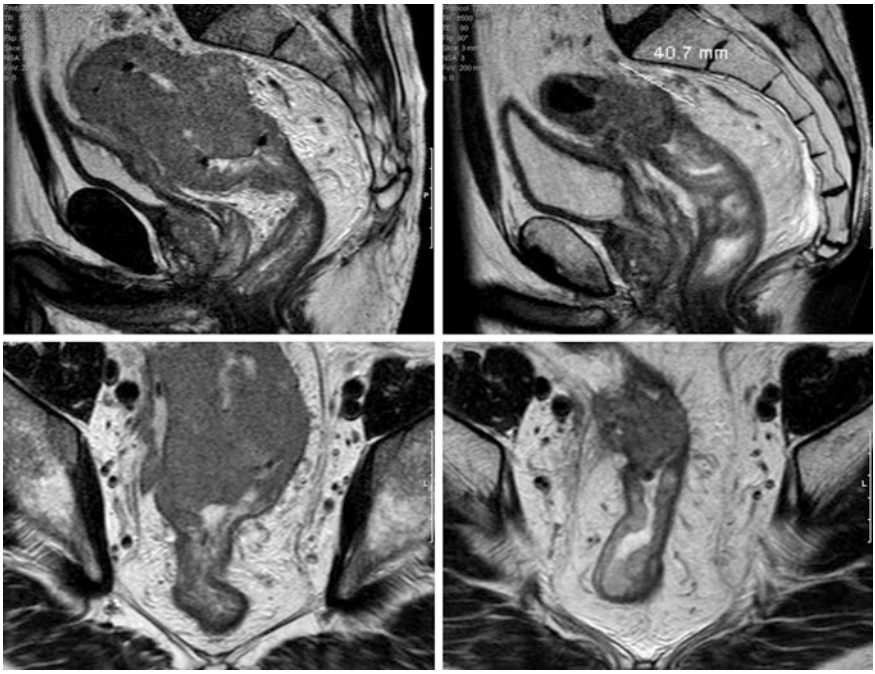

Fig. 6 *Left* before and *right* after radiochemotherapy. No vital tumour cells were found

complete response increased from 55 to 91 % after addition of Diffusion-Weighted Imaging in some series, with an increased inter-observer agreement (Lambregts et al. 2011; Kim et al. 2009). A recent meta-analysis regarding restaging rectal cancer using MRI, confirmed the added value of Diffusion-Weighted Imaging in predicting tumour stage with a sensitivity increase from 50.4 to 83.6 %, with a similar increase in specificity. The sensitivity for evaluation of a tumour-free CRM was 76.3 %, with a specificity of 85.9 %.

In clinical practice, the true value of a diagnostic modality is based on its possibility to modulate the surgical treatment. The identification of those tumours that are confined to the rectal wall and are therefore suitable for downscaled surgery is thus the major challenge in this specific group of patients; i.e. differentiation between T0-3 versus T4 tumours. A specificity and positive predictive value of 98 and 91 % respectively, was found for the prediction of tumour confined to the rectum wall on MRI, T0-2 versus T3-4, by Dresden et al. (2009). These results imply the possibility to downscale surgery based on restaging by MRI after CRT. Evaluation of nodal status showed not to be reliable due to low specificity, 59.8 %, and the inability to differentiate benign from malignant lymphnodes, especially in small nodes (van der Paardt et al. 2013) (Fig. 6).

Multiple recent studies have investigated the role of FDG-PET/CT in restaging rectal cancer patients, with sensitivity ranging from 81 to 85 % and a specificity of

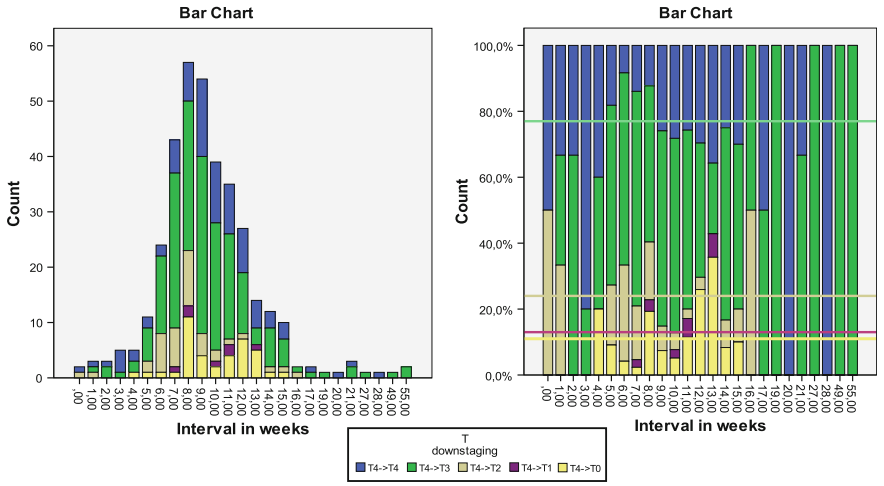

Fig. 7 Relation between 392 T4 rectal cancer patients between timing of surgery and magnitude of T downstaging. *Green*, *beige*, *purple* and *yellow* line indicate 77 % T4 downstaged <= ypT3, 24 % <= ypT2, 13 % <=, 13 % <= ypT1 and 11 % ypT0, respectively (unpublished data)

80 % (Capirci et al. 2009; Kalff et al. 2009; Capirci et al. 2007). The results are promising and suggest a future role for FDG-PET/CT in restaging rectal cancer. Currently, FDG-PET is only able to discriminate responders from non-responders but inaccurate in predicting T stage due to the inability to differentiate tumour from fibrosis (Capirci et al. 2007, 2009; Kalff et al. 2009). In conclusion, none of the currently available imaging modalities is able to 100 % reliably predict tumour response and tumour-free CRM after CRT and surgical planning therefore remains challenging. Overestimating tumour growth, due to the inability to differentiate viable tumour from fibrosis, and poor specificity regarding nodal status are the main drawbacks of the current imaging modalities.

4 Tumour Response and Timing Interval

Since the introduction of chemoradiotherapy as the standard neoadjuvant treatment in advanced rectal cancer, new questions have arisen. The effects of chemoradiotherapy on tumour tissue are well reported but are hardly predictable in clinical practice for individual patients. The goal is to gain optimal tumour response after neoadjuvant treatment without jeopardizing the patients' safety or allowing local tumour increase or distant tumour spread. Finding the optimal timing interval between neoadjuvant treatment and surgery is therefore of pivotal importance (Fig. 7).

Neoadjuvant chemoradiation leads to a pathological complete response (pCR) in 15–20 % of patients with locally advanced rectal cancer. Many studies have been published which have shown that pCR and pathological tumour regression are associated with improved oncological outcome (Maas et al. 2010; Martin et al. 2012; Vecchio et al. 2005; Zorcolo et al. 2012). A recent systematic review by Martin et al., reported a local recurrence rate of 0.7 % at a median follow-up of 55 moths in patients with pCR (Martin et al. 2012). This makes pCR an excellent prognostic factor for local control with minimal risk of developing a local recurrence. Despite a major influence on local control rates, distant failure is not dramatically improved by pCR. Of the patients with pCR, 8.7 % developed metastatic disease. The 5-year overall survival was 90.2 % for patients with pCR, which is a 3.3-fold overall survival advantage over non-complete responders. In addition to pCR, pathological tumour response, or downstaging, is a prognostic factor for improved local failure rates, metastasis-free survival and overall survival (Vecchio et al. 2005; Theodoropoulos et al. 2002). A close relationship between pathological response and outcome has been observed; pT0-2 patients have superior 5-year survival and local control rates regardless of cT stage compared to non- or moderate responders (pT3/4 stage) (Valentini et al. 2002).

Increasing the timing interval, defined as the time between CRT and surgery, has been associated with an increase in pCR rates and subsequent improved oncological outcome (Wolthuis et al. 2012; de Campos-Lobato et al. 2011a, b; Habr-Gama et al. 2008; Tulchinsky et al. 2008). A timing interval >7 weeks is associated with increased pCR rates, 35 % versus 17 % (Tulchinsky et al. 2008) and a timing interval >12 weeks is considered save without a negative influence on oncological outcome (Habr-Gama et al. 2008; Tulchinsky et al. 2008). Based on current literature, the optimal timing interval cannot be considered due to insufficient quality evidence (Foster et al. 2013). However, if this time interval effect also plays a significant role in T4 rectal cancer remains unclear. Therefore, improving tumour response by altered neoadjuvant treatment schemes and optimizing the timing interval should be the subject of additional studies to further improve oncological outcome.

5 Extended Surgery

Despite the increasing effects of neoadjuvant treatment, surgery remains the cornerstone of the current multimodality T4 rectal cancer treatment. The optimisation of preoperative staging and neoadjuvant treatment has one important goal; increasing the radicality rates of the resection and subsequently improving local tumour control and oncological outcome. A radical resection is the most important objective in any case of rectal cancer, and this includes this highly selected group of patients. Since the treatment is associated with high morbidity and mortality rates in these patients, the possibility of an irradical resection and subsequent poor oncological outcome should be reduced by any mean. In T4 rectal cancer, in whom

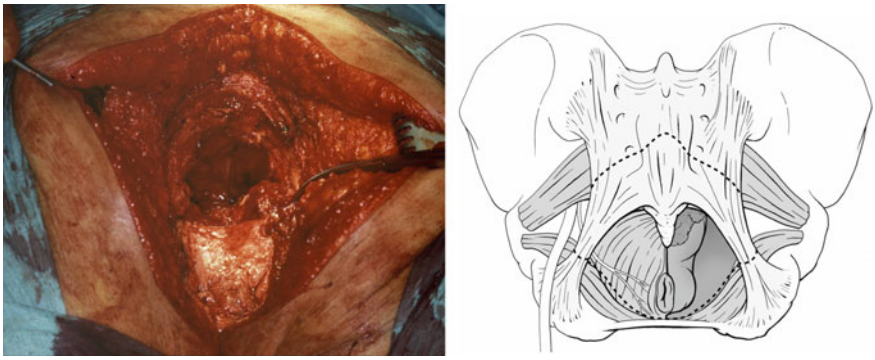

Fig. 8 Resection of the sacrum, uterus, rectum and posterior vaginal wall

despite CRT and restaging, surgery cannot be downscaled and invasion of adjacent organs indicates the need for extended surgery. Adequate preoperative staging followed by a multidisciplinary team meeting in these patients is quintessential in order to tailor the treatment to the individual patients' need. The location of the tumour influences the treatment strategy and oncological outcome. Dorsally located locally advanced rectal tumours invade the pelvic floor muscles, ox coccyx or sacrum when the MRF is breached. Central or anterior located rectal tumours might invade the bladder, prostate or seminal vesicles in men or the vagina and uterus in women. The lateral T4 tumours invade the neural bundle, the piriformis muscles and the internal iliac vessels. Each tumour presents its specific challenges in the treatment process. The location of the tumour itself influences oncological outcome. The more dorsally the tumour is located, the higher the irradicality rate and local recurrence rate is (Park et al. 2009).

5.1 Abdominosacral Resection

Infiltration of the tumour into the sacrum or coccyx typically requires an abdominosacral resection (ASR) if curative surgery is intended. Tumour growth into the lateral pelvic wall or pelvic floor muscles requires a wider dorsal resection for optimisation of dorsal access in order to achieve a radical resection margin and a sacral resection is required (Mannaerts et al. 2001). Sacral resection as high as S1-S2 are described and expected feasible without muscoskeletal disability, but bladder and anorectal dysfunction is inevitable due to nerve transaction at the sacral nerve plexus (Ferenschild et al. 2009; Bhangu et al. 2012). Invasion of the sciatic notch, involvement at the S1/S2 level or a tumour extending beyond the sciatic foramen are usually excluded form surgery and are considered irresectable as a radical resection will lead to unacceptable morbidity (Mannaerts et al. 2001; Ralph et al. 2012) (Fig. 8).

The oncological results for sacral resection in primary rectal cancer as described in the literature are limited. Most studies report data on oncological outcome in recurrent rectal cancer.

An irradical resection is the most important prognostic factor for poor survival, disease-free survival and local recurrence in all series (Mannaerts et al. 2001; Ferenschild et al. 2009; Bhangu et al. 2012; Ralph et al. 2012; Bebenek et al. 2007). Ferenschild et al. and Dudink et al. reported a 5-year overall survival rate of 56 % and local control rates of 88 and 79 % were reported in both series, respectively (Ferenschild et al. 2009; Ralph et al. 2012). Five-year cancer specific survival is reported to be 68 %. Bhangu et al. reported a 3-year local control rate and overall survival rate of 100 % in eight patients after sacral resection for primary rectal cancer (Bhangu et al. 2012). A larger series by Bebenek et al. reported a 60.3 and 73.2 % 5 year overall and relative survival rate respectively for primary rectal cancer patients undergoing a ASR (Bebenek et al. 2007). In this series, similar results were found for patients undergoing a standard abdominal resection, this confirms the role of a radical resection as the most important indicator for oncological outcome. Radical resection rates vary between 72 and 100 % (Mannaerts et al. 2001; Bhangu et al. 2012; Ralph et al. 2012). If the use of IORT in R1 resections is considered a curative approach, the majority of patients with a dorsal T4 tumour invading the sacrum can be treated (Mannaerts et al. 2001).

Overall postoperative complications after ASR are generally high, but morbidity rates vary in literature between 14 and 82 % (Mannaerts et al. 2001; Ferenschild et al. 2009; Bebenek et al. 2007). Sacral resection above S3 is significantly associated with an increased rate of major complications, 60 % versus 27 % (Bhangu et al. 2012). Superficial perineal wound dehiscence, urinary tract infection and urinary incontinence or retention are frequently diagnosed minor complications. Anastomotic leakage, abscess formation and perineal wound dehiscence are considered major complications, which in some series did not differ significantly from complications in standard abdominal resection in primary rectal cancer (Bebenek et al. 2007).

5.2 Multivisceral Resections

In T4 rectal cancer, different adjacent organs may be invaded by the tumour depending on its location. Multivisceral resection (MVR) with en bloc resection of the tumour and adjacent infiltrated organs is required to achieve a complete radical resection. Adequate preoperative staging is crucial in the decision and planning of a MVR. As described earlier, preoperative staging and diagnosing organ invasion is challenging due to the inability of current diagnostic modalities to differentiate fibrosis from tumour remnants. As MVR is associated with significant morbidity and mortality, the decision to perform MVR can be hard. Peroperative distinction of tumour and inflamed or fibrotic tissue is often impossible and therefore preoperative staging is of paramount importance.

A recent meta-analysis for multivisceral resections in colorectal cancer was performed by Mohan et al. A 5-year overall survival rate for MVR in primary rectal cancer of 52.8 % (95 % CI, 52–53.8 %) was published. Survival rates in recurrent rectal cancer are considerably worse, 19.5 % overall 5-year survival, and recurrent rectal cancer should therefore be considered as a different entity (Mohan et al. 2013). Acquisition of an R0 resection resulted in a significant better oncological outcome compared to an R1/R2 resection. A weighed mean radicality rate of 82.5 % was found for primary colorectal cancer.

The inability to peroperatively differentiate tumour residue from fibrosis is confirmed by pathological findings. In more than 20 % of all patients included in the systematic review adjacent organs were negative for tumour residue. A study by Gezen et al., focussing solely on primary colorectal cancer, found a pT4 rate of only 21.3 % for rectal cancer (Gezen et al. 2012). Nakafusa et al. found a 52.8 % pT4 rate after multivisceral resection for combined primary colorectal cancer, with a range in recent literature of 25–84 % (Nakafusa et al. 2004). True invasion did not significantly affect survival in any of the included studies, which is an interesting finding. However, an irradical resection is and downscaled surgery with the risk of an R1 resection, which is the strongest predictor of oncological outcome, is therefore unacceptable (Mohan et al. 2013). Preoperative staging and identifying true tissue invasion therefore remains the biggest challenge. Significant morbidity rates after MVR are reported, with a weighed mean complications rate of 41.5 % and a perioperative mortality rate of 4.2 % (range 0–13 %). Infection, bowel obstruction or ileus, urinary complications and abscess formation and anastomotic leakage form the majority of complications (Gezen et al. 2012).

Morbidity rates after MVR are considerable but when an R0 resection can be achieved, oncological outcome in primary rectal cancer is decent. Selecting those patients in whom an R0 resection can be achieved is therefore crucial, subsequently saving patients from life long morbidity and poor oncological outcome in case of an R1/R2 resection (Fig. 9).

6 Nonstandard Treatment Strategy

In highly selected patients, who are unfit for surgery or who are unwilling to undergo invalidating surgery, a deviation from the usual treatment protocol is sometimes required. A "wait-and-see" policy or local excision with intensive follow-up has been proposed in some series. These treatment strategies are not part of general patient care in our institute and should be taken with caution.

6.1 Wait-and-See

In patients with pCR, after CRT for LARC, no viable tumour residue is present in the specimen, and the question arises whether these patients, in whom the tumour has been sterilised, have to undergo extensive surgery. The superior oncological

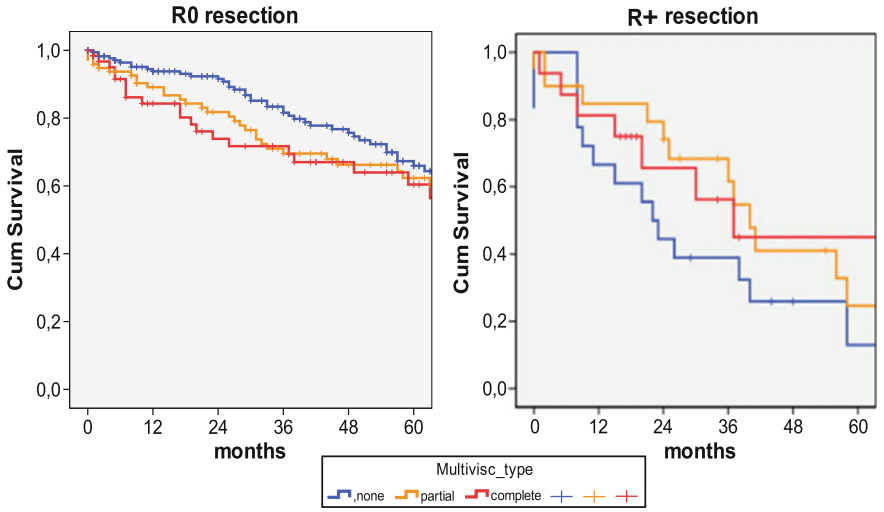

Fig. 9 Multivisceral resections in 392 T4 rectal cancer patients demonstrating that R+ resections carry a significant poorer prognosis (unpublished data)

results for patients with pCR might not be further improved by radical surgery, therefore avoiding the sequel of TME or multivisceral surgery; e.g. surgical morbidity and mortality; may be feasible in patients with clinical complete response (cCR).

This "wait-and-see" policy has been described by various authors over the last decade. Habr-Gama et al. reported a series of 265 patients, including 71 patients (26.8 %) with a cCR after CRT who were treated with a non-operative approach (Habr-Gama et al. 2004). A 5-year overall survival and disease-free survival were 100 and 92 % respectively, in the non-operative group, with a 2.8 % local recurrence rate. A Dutch series by Maas et al., supported these results with a 2-year overall survival and disease-free survival of 91 and 93 %, respectively (Maas et al. 2011). The recurrence rate was low, and could be salvaged by local excision, and no metastatic disease developed during the relative short follow-up. A more recent series by the Habr-Gama group, reported 50 % of patients with a T2-4N0-2M0 treated successfully without undergoing surgery (Habr-Gama et al. 2013). A recent review, regarding the non-operative approach for LARC with cCR after CRT, was not able to identify similar studies with comparable promising results, and a pooled recurrence rate of 33.8 % was found (Glynne-Jones and Hughes 2012).

The assessment of cCR is the first challenge in the "wait-and-see" approach. No general definition is present in the literature and no single diagnostic modality is available to confirm cCR. In a recent pooled analysis, cCR was associated with pCR in 30 % of patients (Glynne-Jones et al. 2008). The superior results published by Habr-Gama et al., are partly due to the extensive methods of defining cCR;

by clinical, endoscopic, radiological and metabolic imaging, confirmed by local excision or biopsy; patient selection; and intensive follow-up (Glynne-Jones and Hughes 2012). The second challenge is the detection of positive lymph nodes after CRT. In pCR after CRT, there is no direct correlation with lymph node sterilisation and in 15–25 % of patients with cCR positive lymph nodes will be present in the mesorectum (Glynne-Jones and Hughes 2012). These lymph nodes could progress and cause a distant recurrence or metastasis. Especially in cT3 and cT4, in whom the risk of nodal metastases is high, up to 50 % at diagnosis, a pelvic recurrence might develop.

In conclusion, the major challenge in the "wait-and-see" approach is patient selection, and the identification of patients with a cCR who also have a pCR. Based on the current literature, no general consensus is present for a "wait-and-see" policy in unselected patients. Patients with a low and small, i.e. non-bulky, rectal tumour, without signs of positive lymph nodes may be selected for the "wait-and-see" approach if cCR is diagnosed using different modalities and follow up is meticulous.

In Fig. 7 is demonstrated that only in 11 % of the presented T4 rectal cancer patients a complete remission was achieved, irrespective of the interval between RCT and surgery.

6.2 Local Excision

The local excision of cT2 tumours, at time of diagnosis, after CRT using TEM has shown to give comparable oncological outcome compared to standard TME surgery (Lezoche et al. 2012). cT4 tumours which are downscaled and downsized to cT2 tumours are different biological tumours and data cannot be simply extrapolated. The inability of diagnostic modalities to restage nodal disease proposes another challenge for selecting patients for local excision. The rate of node positivity in pathological studies with 235 specimens was 2 % for pT0, 15 % for pT1, 17 % for pT2, 38 % for pT3, and 33 % for pT4 cases (Pucciarelli et al. 2005). A more conservative treatment, i.e. local excision, with intensive follow-up may therefore be safe in patients with pCR after CRT for locally advanced rectal cancer. Data regarding local excision in patients with cT1 or cT2 tumours without nodal involvement after CRT is less clear. In a small series by Perez et al., patients with initial LARC with cT0-2 rectal cancer after CRT, were treated with TEM. This resulted in a 15 % local recurrence rate. Only lymphovascular invasion was a prognostic factor for local recurrence; final ypT stage, CRM and tumour regression were not significantly associated with local recurrence (Perez et al. 2013). A multicentre phase II clinical trial, including stage T3N0-1 tumours at diagnosis reported on 63 patients undergoing local excision after CRT. Patients underwent a local excision in case of major tumour response. In case of ypT < 2, negative regional lymph nodes on MRI and negative resection margins patients were considered adequate for follow-up. The authors concluded that patients with a

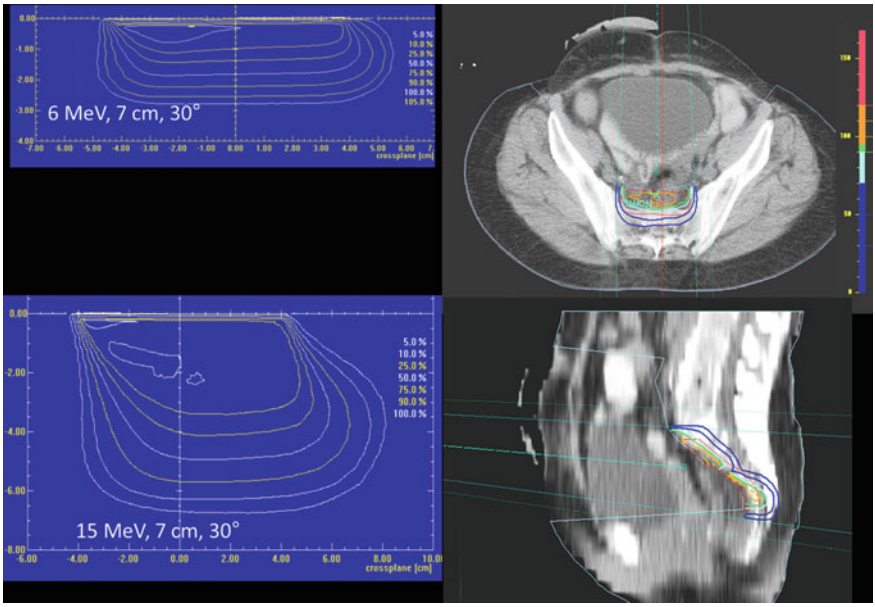

Fig. 10 Demonstrating the principles of an intraoperative electron boost at the area of risk

ypT2 tumour after local excision should undergo subsequent standard TME surgery due to high local recurrence rates, as supported by earlier data (Lezoche et al. 2012; Pucciarelli et al. 2013).

Data regarding local excision and follow-up is very scant and limited to cT $\leq$ 3 tumours at time of diagnosis. Pathological studies with cT3/T4 tumours at time of diagnosis show that in 17 % of pT0-2 tumours residual disease is present in the rectal mesentery and nodes (Bedrosian et al. 2004). Local excision should therefore be recommended with caution. A highly selected group of patients may be eligible for local excision and stringent follow-up. Additional pathological prognostic factors, such as lymphovascular invasion, may be the key to predicting lymph node metastases and local recurrence.

7 IORT

In order to improve oncological outcome in selected complex rectal cancer patients, intraoperative radiation therapy (IORT) has been introduced in the 1990s. The sterilisation of threatened or involved resection margins by high dose locally administered radiation beams is hypothesised to improve local control in rectal cancer patients. The required resection margin of >1 mm as is currently accepted and associated with improved oncological outcome could possibly be reduced in case of effective local radiotherapy. This strategy might lead to a decrease in multivisceral and invalidating extensive resections (Fig. 10).

The administration of IORT as a radiotherapy boost of 10–15 Gy is debatable. The safety of IORT has been established in several studies, without an increase of morbidity and mortality after surgery has been observed (Avizonis et al. 1989; Noyes et al. 1992; Harrison et al. 1998; Mannaerts et al. 2000; Azinovic et al. 2001; Gunderson 1996). Nerve tissue damage is the most important dose-limiting factor, with a linear relationship between radiation dose and limb paralysis (Kinsella et al. 1985). An IORT dose exceeding 12.5 Gy is associated with the development of peripheral neuropathy (Gunderson et al. 1988). In theory IORT reduces the risk of local recurrence in case of microscopic tumour residue (R1) after resection by sterilizing the radiated area. The radiation boost should be administered to this high-risk area. A high-risk area is indicated by a threatened margin on preoperative MRI or perioperative positive frozen section. Some institutes routinely administer the boost to the presacral area as high-risk area (Calvo et al. 2002; Krempien et al. 2006). Studying the patterns of local recurrence has revealed this is associated with development of a local recurrence outside the presacral radiation field in 59–67 % (Calvo et al. 2002; Roeder et al. 2007). IORT to the high-risk area results in less infield local recurrence than routine presacral IORT (Kusters et al. 2009).

Many clinical studies have been published regarding the effect of IORT on oncological outcome, with contradictory results. A positive impact on local control and survival has been reported by several authors in earlier clinical studies (Mannaerts et al. 2000; Calvo et al. 2002). Some series only show improved local control rates without impact on survival (Kusters et al. 2010; Weinstein et al. 1995; Valentini et al. 2009). A recent pooled analysis of 605 European primary rectal cancer patients undergoing IORT-containing multimodality treatment, showed a local recurrence rate of only 12 % in a high-risk group of patients. Furthermore, 55 % of patients with an R1 resection did not develop a local recurrence, which suggests a positive effect of IORT on tumour residue (Kusters et al. 2010). IORT could allow for a margin <1 mm. Our data show that a radical resection is the most important factor in oncological outcome. The oncological outcome after an R0 resection was not affected by the extent of the resection margin. A resection margin <1 mm was not associated with poor oncological outcome, as long as a R0 resection was obtained. This effect might be contributed to the use of IORT. These data support the sterilising effect of IORT on threatened resection margins. In the presence of IORT, surgery could be downscaled as long as an R0 resection is obtained, without a decrease in oncological outcome.

These results are promising but IORT was not identified as a single prognostic factor for local recurrence or survival in this analysis. Despite these promising results, a recent RCT has not been able to find any benefit for the use of IORT in primary rectal cancer (Dubois et al. 2011). Studying the quantitative effect of IORT on oncological outcome remains a challenge and due to the heterogeneous and complex patient population, the conduction of a prospective trial is difficult.

8 Discussion

Locally advanced rectal cancer treatment has evolved from a surgery alone, to a multimodality treatment. Despite this shift in treatment strategy, a radical tumour resection remains the cornerstone of rectal cancer treatment. The implementation of this multimodality treatment has led to the establishment of multidisciplinary teams (MDT's) on a global level. The primary task of the MDT is preoperative staging and planning the treatment strategy. The implementation of MDT's is significantly associated with an increase in R0 resections, decreased recurrent rates and improved oncological outcome (Burton et al. 2006; Palmer et al. 2011; MacDermid et al. 2009). Nowadays no single patient with colorectal cancer should be treated without undergoing meticulous preoperative staging and treatment planning in a MDT meeting. Due to the treatment complexity of locally advanced, T4 stage in particular, and recurrent rectal cancer centralisation is the next step in improving oncological outcome. Complex surgery, in which multivisceral resections including en bloc resection of gynaecological or urological organs are performed, has improved oncological outcome in experienced hands and postoperative morbidity and mortality decreases due to improved perioperative care (de Gramont et al. 2000; Aschele et al. 2011).

The acquisition of pathological complete response (pCR) or downstaging is associated with improved oncological outcome in T4 rectal cancer (Valentini et al. 2002; Maas et al. 2010, 2011; Martin et al. 2012; Vecchio et al. 2005; Zorcolo et al. 2012; Theodoropoulos et al. 2002; Wolthuis et al. 2012; de Campos-Lobato et al. 2011a, b; Habr-Gama et al. 2004, 2008; Tulchinsky et al. 2008) and in selected patients with a major response to CRT a "wait-and-see" policy or local excision may even be sufficient.

In order to achieve optimal tumour downstaging and pCR with subsequent improved oncological outcome, neoadjuvant chemoradiotherapy (CRT) and tumour restaging are of paramount importance. Intensifying standard CRT in T4 rectal cancer by; adding oxaliplatin to 5FU-based chemotherapy; or by administration of an additional cycle of 5-FU based chemotherapy or two cycles of FOLFOX during the resting period; is associated with increased pCR and even improved oncological outcome in some series (Fakih et al. 2008; Chau et al. 2006; Rutten et al. 2006; de Gramont et al. 2000; Martijnse et al. 2012; Habr-Gama et al. 2009; Garcia-Aguilar et al. 2011). Due to contradictory results from different studies or insufficient follow-up in the latter studies, a general consensus regarding intensified CRT is not present. Especially in T4 rectal cancer patients, in whom downstaging can induce a resectable tumour and mean a chance of cure, intensified CRT may be effective.

Increasing the timing interval between CRT and surgery is significantly associated with improved tumour response. The optimal timing interval cannot be considered due to the lack of sufficient evidence, but a timing interval >7 weeks is associated with improved tumour regression and pCR (Wolthuis et al. 2012; de Campos-Lobato et al. 2011a, b; Habr-Gama et al. 2008; Tulchinsky et al. 2008). Further increasing the timing interval beyond 12 weeks in

order to further allow tumour necrosis to occur is save and can be considered in patients in whom downstaging of the tumour is insufficient after the standard timing interval of 6 weeks (Habr-Gama et al. 2008).

Overestimating tumour growth, due to the inability to differentiate viable tumour from fibrosis, and poor specificity regarding nodal status are the main drawbacks of the current imaging modalities (Vanagunas et al. 2004; Mezzi et al. 2009; Huh et al. 2008; Dickman et al. 2013; Lambregts et al. 2011; Kim et al. 2009; Kalff et al. 2009; Capirci et al. 2007, 2009). Differentiating between pT0-2 and pT3-4 stage rectal cancer after CRT with DW-MRI can be done with sufficient specificity and positive predictive value, allowing for less extensive, non-multivisceral resections, in selected patients (Dresen et al. 2009).

In patients in whom a multivisceral resection (MVR) or sacral resection is inevitable due to tumour infiltration, oncological outcome is acceptable in case of an R0 resection. Oncological outcome is even comparable to patients undergoing standard abdominal resection for rectal cancer (Bebenek et al. 2007). An R1 or R2 resection is associated with worse oncological outcome and a major increase in local recurrence. Oncological outcome for patients with locally recurrent rectal cancer is even worse, this means that a radical resection in primary rectal cancer is the patients' best chance for cure and an R0 resection should always be the main goal. Nevertheless, the definition and oncological outcome of a positive margin has evolved over the last few decades. According to initial TME principles, a distal tumour margin of 5 cm was required in order to avoid residual tumour deposits. A recent systematic review concluded that a distal margin <1 cm and even <5 mm in selected patients is save without jeopardizing local recurrence and survival (Bujko et al. 2012). The selection criteria for these patients are unclear; well-differentiated tumours, good response to CRT and short distal intramural tumour spread might be associated with favourable outcome. A small Korean study, with definite limitations, has recently published poor survival rates for patients undergoing a MVR in case of a distal margin $\leq$2 cm, due to the intramural spread which is characteristic for T4 tumours (Kang et al. 2012). In T4 rectal cancer patient's sphincter preserving surgery is possible in an increasing number of patients, but patient selection is important.

The initial TNM definition of a positive CRM and R1 resection is 0 mm. Over the last decade, many pathological and clinical studies have been published regarding tumour, surgical and patient-related factors influencing the CRM. On a pathological level, a margin $\leq$1 mm is considered positive and has an accurate correlation with local recurrence, distant metastasis and survival (Quirke et al. 1986; Nagtegaal and Quirke 2008; Smith et al. 2008). The prognostic value of CRM status nowadays is less clear as the majority of these studies excluded patients with neoadjuvant treatment. The use of CRT might allow for a narrower margin. In a recent series of 563 patients with T3/T4 rectal cancer treated with CRT followed by TME surgery, a CRM $\leq$1 was an independent risk factor for local recurrence and is considered positive (Trakarnsanga et al. 2013). Based on these results, a margin $\leq$1 mm is associated with poor oncological outcome and therefore not acceptable, even in en era with highly optimised chemoradiotherapy.

Our data show that in patients treated with IORT the extend of the resection margin becomes less important, as long as a R0 resection is obtained. These data suggest IORT has a sterilising effect on these high-risk areas.

Poor tumour differentiation, vascular invasion and an ulcerative grow pattern are associated with positive CRM. The increasing knowledge of pathological prognostic factors has lead to optimisation of the surgical treatment of rectal cancer. The introduction of IORT, administered to a high-risk area with threatened margins, further decreased the need for extensive multivisceral resections.

More recent developments in rectal cancer treatment are the "wait-and-see" policy (Habr-Gama et al. 2004, 2013; Maas et al. 2011; Glynne-Jones and Hughes 2012) and local excision (Lezoche et al. 2012; Pucciarelli et al. 2005, 2013; Perez et al. 2013) in patients with pCR or major tumour response after CRT. In highly selected patients with pCR, without signs of nodal involvement, a wait-and-see policy can be considered. Restaging has to be meticulous and follow-up has to be intense in order to acquire sufficient oncological outcome. Especially in T4 rectal cancer, with a high-risk of nodal involvement, and a poor association between pCR and pCR, following a certain approach should be done with caution.

References

Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G et al (2011) Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol Off J Am Soc Clin Oncol 29(20):2773–2780

Avizonis VN, Sause WT, Noyes RD (1989) Morbidity and mortality associated with intraoperative radiotherapy. J Surg Oncol 41(4):240–245

Azinovic I, Calvo FA, Puebla F, Aristu J, Martinez-Monge R (2001) Long-term normal tissue effects of intraoperative electron radiation therapy (IOERT): late sequelae, tumor recurrence, and second malignancies. Int J Radiat Oncol Biol Phys 49(2):597–604

Bebenek M, Pudelko M, Cisarz K, Balcerzak A, Tupikowski W, Wojciechowski L et al (2007) Therapeutic results in low-rectal cancer patients treated with abdominosacral resection are similar to those obtained by means of anterior resection in mid- and upper-rectal cancer cases. Eur J Surg Oncol J Eur Soc Surg Oncol Brit Assoc Surg Oncol 33(3):320–323

Bedrosian I, Rodriguez-Bigas MA, Feig B, Hunt KK, Ellis L, Curley SA, et al (2004) Predicting the node-negative mesorectum after preoperative chemoradiation for locally advanced rectal carcinoma. J Gastrointest Surg Off J Soc Surg Aliment Tract 8(1):56–62 (discussion-3)

Beyond TMEC (2013) Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. Brit J Surg 100(8):E1–E33

Bhangu A, Brown G, Akmal M, Tekkis P (2012) Outcome of abdominosacral resection for locally advanced primary and recurrent rectal cancer. Brit J Surg 99(10):1453–1461

Bipat S, Glas AS, Slors FJ, Zwinderman AH, Bossuyt PM, Stoker J (2004) Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging–a meta-analysis. Radiology 232(3):773–783

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

Bujko KRA, Chang GJ, Michalski W, Chmielik E, Kusnierz J (2012) Is the 1-cm rule of distal bowel resection margin in rectal cancer based on clinical evidence? Syst Rev Ann Surg Oncol 19(3):801–808

Bosset JF, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun RJ et al (2014) Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 15(2):184–190

Capirci C, Rampin L, Erba PA, Galeotti F, Crepaldi G, Banti E et al (2007) Sequential FDG-PET/CT reliably predicts response of locally advanced rectal cancer to neo-adjuvant chemoradiation therapy. Eur J Nucl Med Mol Imaging 34(10):1583–1593

Capirci C, Rubello D, Pasini F, Galeotti F, Bianchini E, Del Favero G et al (2009) The role of dual-time combined 18-fluorodeoxyglucose positron emission tomography and computed tomography in the staging and restaging workup of locally advanced rectal cancer, treated with preoperative chemoradiation therapy and radical surgery. Int J Radiat Oncol Biol Phys 74(5):1461–1469

Calvo FA, Gomez-Espi M, Diaz-Gonzalez JA, Alvarado A, Cantalapiedra R, Marcos P et al (2002) Intraoperative presacral electron boost following preoperative chemoradiation in T3-4Nx rectal cancer: initial local effects and clinical outcome analysis. Radiother Oncol J Eur Soc Ther Radiol Oncol 62(2):201–206

Chau I, Brown G, Cunningham D, Tait D, Wotherspoon A, Norman AR et al (2006) Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. J Clin Oncol Off J Am Soc Clin Oncol 24(4):668–674

de Campos-Lobato LF, Geisler DP, da Luz Moreira A, Stocchi L, Dietz D, Kalady MF (2011a) Neoadjuvant therapy for rectal cancer: the impact of longer interval between chemoradiation and surgery. J Gastrointest Surg Off J Soc Surg Aliment Tract 15(3):444–450

de Campos-Lobato LF, Stocchi L, da Luz Moreira A, Geisler D, Dietz DW, Lavery IC et al (2011b) Pathologic complete response after neoadjuvant treatment for rectal cancer decreases distant recurrence and could eradicate local recurrence. Ann Surg Oncol 18(6):1590–1598

de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J et al (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol Off J Am Soc Clin Oncol 18(16):2938–2947

Dickman R, Kundel Y, Levy-Drummer R, Purim O, Wasserberg N, Fenig E et al (2013) Restaging locally advanced rectal cancer by different imaging modalities after preoperative chemoradiation: a comparative study. Radiat Oncol 8:278

Dubois JB, Bussieres E, Richaud P, Rouanet P, Becouarn Y, Mathoulin-Pelissier S et al (2011) Intra-operative radiotherapy of rectal cancer: results of the French multi-institutional randomized study. Radiother Oncol J Eur Soc Ther Radiol Oncol 98(3):298–303

Dresen RC, Beets GL, Rutten HJ, Engelen SM, Lahaye MJ, Vliegen RF et al (2009) Locally advanced rectal cancer: MR imaging for restaging after neoadjuvant radiation therapy with concomitant chemotherapy-part I. Are we able to predict tumor confined to the rectal wall? Radiology 252(1):71–80

Fakih MG, Bullarddunn K, Yang GY, Pendyala L, Toth K, Andrews C et al (2008) Phase II study of weekly intravenous oxaliplatin combined with oral daily capecitabine and radiotherapy with biologic correlates in neoadjuvant treatment of rectal adenocarcinoma. Int J Radiat Oncol Biol Phys 72(3):650–657

Ferenschild FT, Vermaas M, Verhoef C, Dwarkasing RS, Eggermont AM, de Wilt JH (2009) Abdominosacral resection for locally advanced and recurrent rectal cancer. Brit J Surg 96(11):1341–1347

Foster JD, Jones EL, Falk S, Cooper EJ, Francis NK (2013) Timing of surgery after long-course neoadjuvant chemoradiotherapy for rectal cancer: a systematic review of the literature. Dis Colon Rectum 56(7):921–930

Frykholm GJ, Pahlman L, Glimelius B (2001) Combined chemo- and radiotherapy versus radiotherapy alone in the treatment of primary, nonresectable adenocarcinoma of the rectum. Int J Radiat Oncol Biol Phys 50(2):427–434

Garcia-Aguilar J, Smith DD, Avila K, Bergsland EK, Chu P, Krieg RM et al (2011) Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. Ann Surg 254(1):97–102

Gebhardt C, Meyer W, Ruckriegel S, Meier U (1999) Multivisceral resection of advanced colorectal carcinoma. Langenbeck's Arch Surg Deut Ges Chir 384(2):194–199

Gerard JP, Conroy T, Bonnetain F, Bouche O, Chapet O, Closon-Dejardin MT et al (2006) Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin oncol Off J Am Soc Clin Oncol 24(28):4620–4625

Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL et al (2010) Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol Off J Am Soc Clin Oncol 28(10):1638–1644

Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Lafay I, Hennequin C, Etienne PL et al (2012) Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol Off J Am Soc Clin Oncol 30(36):4558–4565

Gezen C, Kement M, Altuntas YE, Okkabaz N, Seker M, Vural S et al (2012) Results after multivisceral resections of locally advanced colorectal cancers: an analysis on clinical and pathological t4 tumors. World J Surg Oncol 10:39

Glynne-Jones R, Wallace M, Livingstone JI, Meyrick-Thomas J (2008) Complete clinical response after preoperative chemoradiation in rectal cancer: is a "wait-and-see" policy justified? Dis Colon Rectum 51(1):10–19 (discussion 9–20)

Glynne-Jones R, Hughes R (2012) Critical appraisal of the "wait-and-see" approach in rectal cancer for clinical complete responders after chemoradiation. Brit J Surg 99(7):897–909

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

Gunderson LL (1996) Past, present, and future of intraoperative irradiation for colorectal cancer. Int J Radiat Oncol Biol Phys 34(3):741–744

Gunderson LL, Martin JK, Beart RW, Nagorney DM, Fieck JM, Wieand HS et al (1988) Intraoperative and external beam irradiation for locally advanced colorectal cancer. Ann Surg 207(1):52–60

Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U Jr, Silva e Sousa AH Jr et al (2004) Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 240(4):711–717 (discussion 7–8)

Habr-Gama A, Perez RO, Proscurshim I, Nunes Dos Santos RM, Kiss D, Gama-Rodrigues J et al (2008) Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome? Int J Radiat Oncol Biol Phys 71(4):1181–1188

Habr-Gama A, Perez RO, Sabbaga J, Nadalin W, Sao-Juliao GP, Gama-Rodrigues J (2009) Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. Dis Colon Rectum 52(12):1927–1934

Habr-Gama A, Sabbaga J, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Bailao Aguilar P et al (2013) Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum 56(10):1109–1117

Harrison LB, Minsky BD, Enker WE, Mychalczak B, Guillem J, Paty PB et al (1998) High dose rate intraoperative radiation therapy (HDR-IORT) as part of the management strategy for locally advanced primary and recurrent rectal cancer. Int J Radiat Oncol Biol Phys 42(2):325–330

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

Huh JW, Park YA, Jung EJ, Lee KY, Sohn SK (2008) Accuracy of endorectal ultrasonography and computed tomography for restaging rectal cancer after preoperative chemoradiation. J Am Coll Surg 207(1):7–12

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Kalff V, Ware R, Heriot A, Chao M, Drummond E, Hicks RJ (2009) Radiation changes do not interfere with postchemoradiation restaging of patients with rectal cancer by FDG PET/CT before curative surgical therapy. Int J Radiat Oncol Biol Phys 74(1):60–66

Kang HKH, Ju JK, Kim DY (2012) Multivisceral resection for locally advanced rectal cancer: adequate length of distal resection margin. J Korean Surg Soc 82(2):87–93

Kennelly RP, Rogers AC, Winter DC (2013) Abdominoperineal excision study G. multicentre study of circumferential margin positivity and outcomes following abdominoperineal excision for rectal cancer. Brit J Surg 100(1):160–166

Kim SH, Lee JM, Hong SH, Kim GH, Lee JY, Han JK et al (2009) Locally advanced rectal cancer: added value of diffusion-weighted MR imaging in the evaluation of tumor response to neoadjuvant chemo- and radiation therapy. Radiology 253(1):116–125

Kinsella TJ, Sindelar WF, DeLuca AM, Pezeshkpour G, Smith R, Maher M et al (1985) Tolerance of peripheral nerve to intraoperative radiotherapy (IORT): clinical and experimental studies. Int J Radiat Oncol Biol Phys 11(9):1579–1585

Krempien R, Roeder F, Oertel S, Roebel M, Weitz J, Hensley FW et al (2006) Long-term results of intraoperative presacral electron boost radiotherapy (IOERT) in combination with total mesorectal excision (TME) and chemoradiation in patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 66(4):1143–1151

Kusters M, Holman FA, Martijn H, Nieuwenhuijzen GA, Creemers GJ, Daniels-Gooszen AW et al (2009) Patterns of local recurrence in locally advanced rectal cancer after intra-operative radiotherapy containing multimodality treatment. Radiother Oncol J Eur Soc Ther Radiol Oncol 92(2):221–225

Kusters M, Valentini V, Calvo FA, Krempien R, Nieuwenhuijzen GA, Martijn H et al (2010) Results of European pooled analysis of IORT-containing multimodality treatment for locally advanced rectal cancer: adjuvant chemotherapy prevents local recurrence rather than distant metastases. Ann oncol Off J Eur Soc Med Oncol ESMO 21(6):1279–1284

Kwok H, Bissett IP, Hill GL (2000) Preoperative staging of rectal cancer. Int J Colorectal Dis 15(1):9–20

Lambregts DM, Vandecaveye V, Barbaro B, Bakers FC, Lambrecht M, Maas M et al (2011) Diffusion-weighted MRI for selection of complete responders after chemoradiation for locally advanced rectal cancer: a multicenter study. Ann Surg Oncol 18(8):2224–2231

Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M (2012) Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. Brit J Surg 99(9):1211–1218

Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ et al (2010) Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 11(9):835–844

Maas M, Beets-Tan RG, Lambregts DM, Lammering G, Nelemans PJ, Engelen SM et al (2011) Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol Off J Am Soc Clin Oncol 29(35):4633–4640

MacDermid E, Hooton G, MacDonald M, McKay G, Grose D, Mohammed N et al (2009) Improving patient survival with the colorectal cancer multi-disciplinary team. Colorectal Dis Off J Assoc Coloproctol Great Br Irel 11(3):291–295

Mannaerts GH, Rutten HJ, Martijn H, Hanssens PE, Wiggers T (2001) Comparison of intraoperative radiation therapy-containing multimodality treatment with historical treatment modalities for locally recurrent rectal cancer. Dis Colon Rectum 44(12):1749–1758

Martijnse IS, Dudink RL, Kusters M, Vermeer TA, West NP, Nieuwenhuijzen GA et al (2012) T3+ and T4 rectal cancer patients seem to benefit from the addition of oxaliplatin to the neoadjuvant chemoradiation regimen. Ann Surg Oncol 19(2):392–401

Mannaerts GH, Martijn H, Crommelin MA, Dries W (2000) Repelaer van Driel OJ, Rutten HJ. Feasibility and first results of multimodality treatment, combining EBRT, extensive surgery, and IOERT in locally advanced primary rectal cancer. Int J Radiat Oncol Biol Phys 47(2):425–433

Martin ST, Heneghan HM, Winter DC (2012) Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. Brit J Surg 99(7):918–928

Mezzi G, Arcidiacono PG, Carrara S, Perri F, Petrone MC, De Cobelli F et al (2009) Endoscopic ultrasound and magnetic resonance imaging for re-staging rectal cancer after radiotherapy. World J Gastroenterol WJG 15(44):5563–5567

Mohan HM, Evans MD, Larkin JO, Beynon J, Winter DC (2013) Multivisceral resection in colorectal cancer: a systematic review. Ann Surg Oncol 20(9):2929–2936

Nagtegaal ID, Quirke P (2008) What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol Off J Am Soc Clin Oncol 26(2):303–312

Nakafusa Y, Tanaka T, Tanaka M, Kitajima Y, Sato S, Miyazaki K (2004) Comparison of multivisceral resection and standard operation for locally advanced colorectal cancer: analysis of prognostic factors for short-term and long-term outcome. Dis Colon Rectum 47(12):2055–2063

Noyes RD, Weiss SM, Krall JM, Sause WT, Owens JR, Wolkov HB et al (1992) Surgical complications of intraoperative radiation therapy: the radiation therapy oncology group experience. J Surg Oncol 50(4):209–215

Park JK, Kim YW, Hur H, Kim NK, Min BS, Sohn SK et al (2009) Prognostic factors affecting oncologic outcomes in patients with locally recurrent rectal cancer: impact of patterns of pelvic recurrence on curative resection. Langenbeck's Arch Surg Deut Ges Chir 394(1):71–77

Puli SR, Bechtold ML, Reddy JB, Choudhary A, Antillon MR, Brugge WR (2009) How good is endoscopic ultrasound in differentiating various T stages of rectal cancer? Meta-analysis and systematic review. Ann Surg Oncol 16(2):254–265

Palmer G, Martling A, Cedermark B, Holm T (2011) Preoperative tumour staging with multidisciplinary team assessment improves the outcome in locally advanced primary rectal cancer. Colorectal Dis Off J Assoc Coloproctol Great Br Irel 13(12):1361–1369

Perez RO, Habr-Gama A, Lynn PB, Sao Juliao GP, Bianchi R, Proscurshim I et al (2013) Transanal endoscopic microsurgery for residual rectal cancer (ypT0-2) following neoadjuvant chemoradiation therapy: another word of caution. Dis Colon Rectum 56(1):6–13

Pucciarelli S, De Paoli A, Guerrieri M, La Torre G, Maretto I, De Marchi F et al (2013) Local excision after preoperative chemoradiotherapy for rectal cancer: results of a multicenter phase II clinical trial. Dis Colon Rectum 56(12):1349–1356

Pucciarelli S, Capirci C, Emanuele U, Toppan P, Friso ML, Pennelli GM et al (2005) Relationship between pathologic T-stage and nodal metastasis after preoperative chemoradiotherapy for locally advanced rectal cancer. Ann Surg Oncol 12(2):111–116

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

Rutten H, Glynne-Jones DS-MR, Rullier E, Peeters M, Brown G, Van Cutsem E, Ricci S, Van de Velde CJ, Quirke P (2006) Capecitabine, oxaliplatin, radiotherapy, and excision (CORE) in patients with MRI-defined locally advanced rectal adenocarcinoma: results of an international multicenter phase II study. J Clin Oncol 24:3528

Ralph LD, Kusters M, Rutten H (2012) Which Patients Do Benefit from Extended Resections in Case of Locally Advanced Rectal Cancer? In: Valentini V, Schmoll H-J, van de Velde CJH (eds) Multidisciplinary Management of Rectal Cancer Questions and Answers. Springer, pp. 275-290. ISBN: 978-3-642-25004-7

Rodel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T et al (2012) Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 13(7):679–687

Roeder F, Treiber M, Oertel S, Dinkel J, Timke C, Funk A et al (2007) Patterns of failure and local control after intraoperative electron boost radiotherapy to the presacral space in combination with total mesorectal excision in patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 67(5):1381–1388

Saif MW, Hashmi S, Zelterman D, Almhanna K, Kim R (2008) Capecitabine versus continuous infusion 5-FU in neoadjuvant treatment of rectal cancer: a retrospective review. Int J Colorectal Dis 23(2):139–145

Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C et al (2012) 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 Off J Am Soc Clin Oncol 30(16):1926–1933

Smith DKD AJ, Spithoff K, McLeod R, Hunter A, Rumble RB, Langer B (2008) Pathology atEPoCaRCSa. Optim Surg Pathol Qual Perform Radical Surg Colon Rectal Cancer Margins Lymph Nodes

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

Tulchinsky H, Shmueli E, Figer A, Klausner JM, Rabau M (2008) An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. Ann Surg Oncol 15(10):2661–2667

Theodoropoulos G, Wise WE, Padmanabhan A, Kerner BA, Taylor CW, Aguilar PS et al (2002) T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. Dis Colon Rectum 45(7):895–903

Trakarnsanga A, Gonen M, Shia J, Goodman KA, Nash GM, Temple LK et al (2013) What is the significance of the circumferential margin in locally advanced rectal cancer after neoadjuvant chemoradiotherapy? Ann Surg Oncol 20(4):1179–1184

Valentini V, Coco C, Picciocchi A, Morganti AG, Trodella L, Ciabattoni A et al (2002) Does downstaging predict improved outcome after preoperative chemoradiation for extraperitoneal locally advanced rectal cancer? a long-term analysis of 165 patients. Int J Radiat Oncol Biol Phys 53(3):664–674

Vanagunas A, Lin DE, Stryker SJ (2004) Accuracy of endoscopic ultrasound for restaging rectal cancer following neoadjuvant chemoradiation therapy. Am J Gastroenterol 99(1):109–112

van der Paardt MP, Zagers MB, Beets-Tan RG, Stoker J, Bipat S (2013) Patients who undergo preoperative chemoradiotherapy for locally advanced rectal cancer restaged by using diagnostic MR imaging: a systematic review and meta-analysis. Radiology 269(1):101–112

Vecchio FM, Valentini V, Minsky BD, Padula GD, Venkatraman ES, Balducci M et al (2005) The relationship of pathologic tumor regression grade (TRG) and outcomes after preoperative therapy in rectal cancer. Int J Radiat Oncol Biol Phys 62(3):752–760

Valentini V, Coco C, Rizzo G, Manno A, Crucitti A, Mattana C et al (2009) Outcomes of clinical T4M0 extra-peritoneal rectal cancer treated with preoperative radiochemotherapy and surgery: a prospective evaluation of a single institutional experience. Surgery 145(5):486–494

Weinstein GD, Rich TA, Shumate CR, Skibber JM, Cleary KR, Ajani JA et al (1995) Preoperative infusional chemoradiation and surgery with or without an electron beam intraoperative boost for advanced primary rectal cancer. Int J Radiat Oncol Biol Phys 32(1):197–204

Wolthuis AM, Penninckx F, Haustermans K, De Hertogh G, Fieuws S, Van Cutsem E et al (2012) Impact of interval between neoadjuvant chemoradiotherapy and TME for locally advanced rectal cancer on pathologic response and oncologic outcome. Ann Surg Oncol 19(9): 2833–2841

Zorcolo L, Rosman AS, Restivo A, Pisano M, Nigri GR, Fancellu A et al (2012) Complete pathologic response after combined modality treatment for rectal cancer and long-term survival: a meta-analysis. Ann Surg Oncol 19(9):2822–2832

Do T3 Rectal Cancers Always Need Radiochemotherapy?

Rob Glynne-Jones

Abstract

The limitation of the traditional method of stratifying patients with rectal cancer for prognosis using magnetic resonance imaging (MRI) and computerised tomography (CT)—TNM staging—is that cT3 tumors comprise the vast majority of rectal cancers. There is a wide variability in outcomes for cT3. Despite this observation, many still advocate routine short course preoperative radiotherapy (SCPRT) or chemoradiation (CRT) for all patients staged as cT3N0 regardless of tumour location, proximity to other structures or extent, despite the fact that advances in imaging with MRI now offer the ability to predict potential outcomes in terms of the risk of local and metastatic recurrence for the individual. Preoperative CRT is designed to reduce local recurrence. The majority of local recurrences historically reflected inadequate quality of the mesorectal resection. Currently, optimal quality-controlled surgery in terms of total mesorectal excision (TME) in the trial setting can be associated with much lower local recurrence rates of less than 10 % whether patients receive radiotherapy or not. Because of the high risk of metastatic disease in selected patients, integrating more active chemotherapy is now attractive. Chemoradiotherapy (CRT) achieves shrinkage and sometimes eradication of tumour—i.e. a pathological complete

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response (pCR), and reduces local recurrence, but has no impact on overall survival. CRT also increases surgical morbidity and impacts on anorectal, urinary and sexual function with an increased risk of second malignancies. Hence, the predominant aims of CRT have been to shrink/downstage a tumour to allow an R0 resection to be performed, or to increase the chances of performing sphincter-sparing surgery. However, it remains unclear why shrinkage/downstaging is meaningful to a patient unless the tumour is initially borderline resectable or unresectable (i.e. the CRM is threatened) or the aim is to perform a lesser operation (i.e. sphincter-sparing or local excision) or for organ-sparing, i.e. to avoid surgery altogether. If it is important to shrink the cancer—ie there is a predicted threat to the CRM, then CRT is currently the treatment of choice. If the cancer is resectable and the aim is simply to lower the risk of local recurrence and preoperative CRT does not impact on survival, can CRT be omitted in selected cases? The answer is yes—with the proviso that we are using good quality MRI and the surgeon is performing good quality TME surgery within the mesorectal plane.

1 Introduction

Preoperative chemoradiation (CRT) has been the standard of care for patients with clinical stage II and III rectal cancer because of the low rates of local recurrence achieved, acceptable levels of toxicity, and the potential for sphincter preservation compared with postoperative chemoradiation. In contrast, parts of Northern Europe have adopted a blanket approach to short course pre-operative radiotherapy (SCPRT) using 25 Gy over 5 days followed by immediate surgery with the predominant aim of reducing the risk of pelvic recurrence. This strategy of preoperative CRT has been extrapolated from postoperative studies, mainly performed in the US which showed a clear benefit for chemoradiation in terms of local recurrence and survival. The GITSG 7175 trial randomly assigned patients to surgery alone, adjuvant chemotherapy, adjuvant radiation therapy or combined adjuvant chemotherapy and radiation. Since then, no large US phase III trial has included a surgery-alone arm.

However, even with the advantage of accurate histopathogical staging unmodified by neoadjuvant treatment, not all patients benefit from postoperative chemoradiation. Data on 3791 patients within phase III US trials examining postoperative adjuvant treatment in rectal cancer prior to the TME era **(NCCTG 794751, NCCTG 864751, and US GI Intergroup 0114)** (Douglas et al. 1986; O'Connell et al. 1994; Tepper et al. 2002) using pooled analyses show a more complex T and N combined classification can predict outcomes and risk of recurrence: low (T1/2N0), intermediate (T1/2N1, T3N0), moderately high (T1/2N2, T3N1, T4N0) and high (T3N2, T4N1/2). In 1060 patients with pT3N0 tumours classified as intermediate-risk, low rates of local recurrence were

associated recurrence (Gunderson 2004) and there was no improvement in disease-free or overall survival when radiation was added to chemotherapy postoperatively. It should be noted that the majority of patients where radiation was omitted, were treated with surgery and chemotherapy rather than surgery alone. This data led to several prospective studies aimed at determining whether patients with T1/2N1 and T3N0 disease could be treated with surgery and chemotherapy, but without radiation therapy **(NSABP R02)** (Wolmark et al. 2000).

The low risk of local recurrence weakens the view that adjuvant radiotherapy always offers added value to radical surgery and hence is a routine requirement for patients with intermediate-risk tumours (T1/2N1 or T3N0). Many authors have questioned whether selected patients with T1-2, N1-2 or T3N0 lesions have a sufficiently low risk of local and distant relapse with surgery alone, that they could avoid radiotherapy (Willett 1999).

Recent improvements in the quality of surgery, MRI and pathogical reporting of the operative specimen, also mean the time has come to question both these approaches (CRT or SCPRT).

The majority of the rectum lies below the peritoneal reflection and has no serosa, allowing tumour growth to extend deeply into peri-rectal fat. Historically, high rates of local pelvic recurrence following radical surgery were described. However, surgical practice has evolved, and the technique of meticulous mesorectal dissection where the surgeon removes all of the surrounding mesorectal fat using sharp dissection in a neat anatomical package is associated with much lower rates of local recurrence and improved survival. With expert total mesorectal excision (TME) consistently performed in specialist centres, metastatic disease is now the predominant problem (Cecil et al. 2004), reflecting the likely presence of distant micrometastases at diagnosis, rather than inadequate surgery. It is true that old meta-analyses have shown that preoperative adjuvant radiotherapy reduces local recurrence rates by almost 50 % and overall mortality by 2–10 %. However, the local recurrence rates were very high in the region of 15–30 %, and importantly the trials included in these meta-analyses all use patient data from long before the introduction of TME surgery, which questions their current relevance.

Conventional therapies for patients with locally advanced rectal cancer appear to have reached a therapeutic plateau, as none of the recent phase III studies investigating the use of radiotherapy or chemoradiation have improved overall survival (OS). This may also reflect the difficulty of performing large scale multicentre studies, where the quality assurance is inevitably more variable.

In addition to the risk of a local recurrence, 10–40 % of patients require extensive surgical procedures, which lead to a permanent stoma. Surgeons will strive to preserve the anal sphincter, but it has been reported that in the United Kingdom that there is a wide variation in the proportion of patients undergoing an abdomino-perineal excision of the rectum (APER) (Morris et al. 2008)—which may either reflect skills and training or the variability in the use of radiotherapy and concerns regarding function after the combination of preoperative radiotherapy and ultra low anterior resection.

In general, we have focussed on avoiding local recurrence and facilitating sphincter sparing in our phase III trials, hoping that improvements in survival would automatically follow if the primary endpoints were achieved. Sadly this has not been the case. Trials suggest that in resectable cancers, where the preoperative MRI predicts the circumferential resection margin (CRM) is not potentially involved, then SCPRT and CRT are equivalent in terms of outcomes such as local recurrence, DFS and OS (Bujko et al. 2006; Ngan 2010). However, none of the trials of radiotherapy alone (Peeters et al. 2007; Sebag-Montefiore et al. 2009) or chemoradiation published in the last decade have impacted on DFS or OS (Sauer et al. 2004; Bosset et al. 2006; Gerard et al. 2006; Roh et al. 2009). Local recurrence is now sufficiently low that (unlike in breast cancer) it fails to impact on overall survival. Alternatively, either the populations in these trials are too low risk to benefit or the inadequacy of the systemic therapy within current chemoradiation schedules may help to explain this finding.

Fluoropyrimidine-based CRT does not employ systemic doses of chemotherapy and delays the integration of adjuvant chemotherapy. Enthusiasm has been stimulated by the efficacy of oxaliplatin in dealing with distant micro-metastases in the adjuvant setting in colon cancer (Kuebler et al. 2007; Andre et al. 2009). However, results of trials using oxaliplatin as a radiosensitizer alone have not been shown to change early outcome measures rate (Aschele et al. 2011; Gerard et al. 2010; Gerard et al. 2012; Roh et al. 2011; Rödel et al. 2012; Schmoll et al. 2013) and toxicity is substantial. The current therapeutic challenge is to optimize all our available non-operative strategies by effective cytotoxic chemotherapy at systemic doses. Incorporating new agents into current therapeutic regimens to reduce the burden of metastases is a priority for research.

In contrast, for more locally advanced cases, where the CRM is breached or threatened according to the MRI, the integration of more active chemotherapy and biological agents into chemoradiation is an attractive strategy. There is an obvious need to improve response to downsize the tumour to achieve a curative resection, and there is a high risk of metastases. In patients where even technically optimised surgery is unlikely to achieve a curative resection—5FU-based chemoradiation has been shown to have a statistically significant effect on resectability and relapse free survival (Frykholm et al. 2001; Braendengen et al. 2008). However, these trials have been underpowered to show a benefit in terms of overall survival. At the time of diagnosis between 20 and 25 % of patients with rectal cancer will be found to have overt metastatic disease, and a further 30–40 % will subsequently develop metastases.

However, the rationale for CRT has been overcalled because of inflated assessments of what is ‘locally advanced disease’, which is facilitated by ultrasound-based rather than MRI-based staging. Hence all cT3 are often considered LARC. There is also a tendency to overstage patients radiologically if the CRM is predicted to be threatened by 2 mm or even 3 mm where 1 mm is sufficient, and the clinical stage migration of cT2 to cT3a engendered by a traditionally cautious approach by radiologists. The delivery of CRT is perpetuated by the reluctance of surgeons to risk a positive margin or the possibility of local recurrence without the safety net of pelvic radiotherapy.

2 Imaging

Initial staging with MRI now offers a high degree of accuracy in predicting peritoneal involvement in upper rectal cancer above the peritoneal reflection, and the depth of extramural spread and CRM involvement in mid and low rectal cancers. In low rectal cancers, the mesorectum thins markedly at the level of levator ani—especially anteriorly in relation to prostate, and predicting potential CRM involvement becomes more difficult.

Recent advances in imaging particularly in terms of the precision available with MRI offer the ability to predict potential outcomes in terms of the risk of local and metastatic recurrence from a range of structural and other features (such as extramural venous invasion, nodal involvement inside and outside the mesorectal fascia, and depth of penetration through the muscularis propria).

The risk of local (pelvic) relapse reflects the degree of tumour extension beyond the rectal wall and to nodal spread. T3c and T3d rectal cancers have markedly worse progression-free and cancer-specific survival compared to T3a and T3b (Pollheimer et al. 2010). This extension can be accurately assessed by MRI within 0.5 mm of tolerance (Mercury 2007).

High spatial resolution coronal imaging also defines the levator muscles, the sphincter complex and intersphincteric plane with sufficient accuracy to allow us to plan the most appropriate plane of surgery (standard TME surgery, intersphincteric resection, APER, or Extralevator abdominoperineal resection, CRT and local excision, TEM). If we can make decisions like this with widely different impacts on QOL, based on MRI appearenaces, then we should also be taking into account the features which predict the risk of local versus metastatic disease.

3 Local Recurrence

The majority of local recurrences historically reflected inadequate mesorectal resection (Syk et al. 2008), which is a common finding on postoperative MRI after partial mesorectal excision (Bondeven et al. 2013). 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 (Quirke et al. 2009). Factors which compromise the performance of good quality TME are well recognised and include patient and disease—related aspects and the surgeon's case volume (Garlipp et al. 2012).

One reason that local recurrence occurs after potentially curative resection is explained by the work of Quirke and colleagues. The presence of microscopic tumour cells within one millimetre of the radial or CRM is clearly demonstrated to be associated with a very high rate of local recurrence and poor survival. High-resolution pelvic MRI using surface phased array coils is now routinely applied in the UK and much of Europe as a preoperative staging and selection tool for the use of neoadjuvant radiation. MRI strongly predicts the likelihood of involvement of

the CRM particularly in the mid-rectum, involvement of the levators in the low rectum and the extramural depth of invasion. The risks of local failure are much lower for cancers in the upper rectum. This MRI preoperative assessment can identify patients at risk of the surgeon being unable to achieve an R0 resection (MERCURY 2007). The accuracy of predicting tumour extent beyond the muscularis propria was within 0.5 mm tolerance in the mid/upper rectum, and suggests MRI can accurately predict ultimate outcome. MRI can also accurately measure the distance between the anorectal junction and/or and the distal part of the tumour and the luminal length of the tumour. However, MRI, multisclice CT and ERUS all remain inadequately accurate to detect involved or uninvolved lymph nodes despite specific imaging features such as size $\geq$8 mm/round/heterogenous/irregular in nodal border. Current studies have also failed to confirm that FDG-PET has improved the accuracy of nodal staging.

Location of the primary tumor (anterior and low confer more risk) and site within the rectum (upper, middle and lower) is also important. MRI is increasingly influencing both the rationale for neoadjuvant radiotherapy, and the design of current trials. Other pathological factors which increase the risk of recurrence include T4 tumours, nodal involvement, extramural vascular invasion, perineural invasion and extranodal deposits (Kusters et al. 2010). Some of these can be identified also on preoperative MRI. Other recognised clinical, individual or social factors that influence the development of recurrence include surgeon variability, grade and sex, and BMI.

However, our sophistication in making decisions and our categorisation of risk for these tumours has not kept pace, since about 65–70 % of rectal cancers are classified as locally advanced rectal cancer (LARC).

The most recent update of the Dutch TME trial in rectal cancer (Van Gijn et al. 2011) reported a 10 year local recurrence cumulative incidence of 5 % in the group assigned to short course preoperative radiotherapy (SCPRT) (5X5 Gy) versus 11 % in the surgery alone group ($P < 0.001$). This 50 % reduction in local recurrence is maintained long-term, and in a non-protocolised subset analysis of 435 TNM stage III patients with a negative CRM, i.e. 23 % of the total population, preoperative radiotherapy appears to improve 10 year OS from 40 to 50 % ($p = 0.032$). However, this finding does not take into account the quality of the mesorectal excision. Node positive patients with defects in the mesorectum are likely to be at high risk of local recurrence, whereas complete mesorectal excision will lead to local recurrence overall in the range 7–8 % (Quirke et al. 2009).

Yet, for all groups the results of the Dutch trial do not show a difference in OS (Van Gijn et al. 2011), which implies that either the result has arisen by chance as a type I error or some population groups within the trial (? node negative) are disadvantaged in terms of survival by radiotherapy.

4 Late Effects of Radiotherapy

There are significant late-effects from pelvic radiotherapy on anorectal, urinary and sexual function (Peeters et al. 2005; Lange et al. 2007), and a increased risk of second malignancies after 10 years (Birgisson et al. 2005; Van Gijn et al. 2011). Small bowel tolerance is a dose-limiting factor. A Cochrane review (Pachler et al. 2012) reported that CRT negatively affect the patient's quality of life in rectal cancer and prompts the need for larger and better designed future prospective studies to examine whether a colostomy is associated with worse QOL.

Effects on sexual functioning (Marijnen et al. 2005), urinary incontinence (Pollack et al. 2006), faecal incontinence (Lange et al. 2007), have been documented after SCPRT. These complications depend on the size of the radiation field, shielding, the overall treatment time, the fraction size and total dose. Mature results of the Swedish Rectal Cancer Trial confirm problems after RT particularly bowel obstruction and abdominal pain (Birgisson et al. 2006). There are also unexplained late cardiac effects (Pollack et al. 2006) and insufficiency fractures in the pelvis (Herman et al. 2009). In addition, in the Dutch TME study deaths from second malignancy were higher in the RT arm than the TME alone arm (13.7 vs. 9.4 %) (Van Gijn et al. 2011). Given this finding is seen after only 11.6 years follow-up—this difference may widen further after 15–25 years. As follow-up in the majority of studies is generally short, the risks of these late effects are likely to be underestimated. It is unclear how much these effects are highlighted in the consent process for radiotherapy. In contrast to radiotherapy, the side effects of chemotherapy are usually short-term, although the neuropathy from oxaliplatin may be permanent.

5 Postoperative Adjuvant Chemotherapy

Because of the high risk of metastatic disease, integrating more active chemotherapy is attractive, and enthusiasm has been stimulated by the efficacy of oxaliplatin in dealing with distant micro-metastases in the adjuvant setting in colon cancer (Kuebler et al. 2007; Andre et al. 2009) although patients with rectal cancer were excluded as ineligible. The possible options for systemic chemotherapy option have expanded, but postoperative adjuvant chemotherapy remains only partially effective, and toxicity (particularly with oxaliplatin) is substantial. The current therapeutic challenge is to optimise all our available non-operative strategies by effective cytotoxic chemotherapy at systemic doses. Incorporating new agents into current therapeutic regimens to reduce the burden of metastases is a priority for research.

Compliance to postoperative chemotherapy following chemoradiation is poor. Neoadjuvant chemotherapy (NACT) offers an alternative strategy. At least 20–25 % of patients in whom chemotherapy with 5FU might be considered may not be sufficiently fit or decline treatment (Sauer et al. 2004; Bosset et al. 2006; Gerard et al. 2006). Compliance to additional postoperative oxaliplatin appears even worse (Rödel et al. 2007).

6 Does Chemotherapy Impact on Local Recurrence?

Systemic chemotherapy has been shown to enhance local control with radiation (Bosset et al. 2006; Bosset et al. 2013; Gerard et al. 2006) after radiation (Bosset et al. 2006; Bosset et al. 2013) or without radiation (Akasu et al. 2006).

In a study of patients with curatively resected stage III rectal cancer, who underwent TME with selective lateral pelvic lymphadenectomy, patients were randomised postoperatively to receive either oral uracil-tegafur (400 mg/m2 tegafur per day) for 12 months or no treatment. The rates of overall local recurrence were 5.8 % (8/139) for the uracil–tegafur group and 9.6 % (13/135) for the surgery-alone group (Akasu et al. 2006). If radiation therapy does not improve survival and systemic chemotherapy enhances local control with or without radiation, and surgical salvage is possible in 50 % if sequential MRIs are performed, then radiation may not always be required. Currently, although local recurrence does increase the risk of distant metastases, local recurrence is reduced to single figures and salvage surgery is effective in more than 50 %.

A recent small prospective trial at Memorial Sloan-Kettering Cancer Center (Schrag et al. 2014) in 32 rectal cancer patients (22 with clinically staged node-positive disease) evaluated the replacement of standard preoperative fluorouracil-based chemoradiation with neoadjuvant FOLFOX (six cycles) and bevacizumab (four cycles) and no radiation. In the 30 patients who completed this neoadjuvant therapy and had a curative TME resection, eight patients (27 %) achieved a pathologic complete response (PCR), and 0/32 patients suffered a local recurrence.

7 Are There Patients for Whom Neoadjuvant Chemotherapy Is an Alternative?

There is clearly a high risk of metastatic disease in locally advanced rectal cancer, yet systemically active doses of chemotherapy are not delivered in CRT schedules, and compliance to postoperative adjuvant chemotherapy is generally poor. Extrapolating from positive studies in colon cancer, many oncologists are encouraged to use a FOLFOX regimen as postoperative chemotherapy for stage III patients after chemoradiation. The optimal number of cycles of such treatment has not been determined. Hence, some groups have extrapolated even further and added chemotherapy either prior to CRT, when compliance to chemotherapy is high (Fernandez-Martos et al. 2010; Fernandez-Martos et al. 2011), or following chemoradiation to increase the response rate (Garcia-Aguilar et al. 2011). Some groups have suggested that this strategy leads to excellent long-term results, but raise concerns for a high early death rate (Chua et al. 2010). Others have proposed NACT alone without radiation (Glynne-Jones et al. 2012).

8 The Importance of Good Surgery

Historically, the majority of local recurrences reflected inadequate mesorectal resection (Syk et al. 2008) as in a series of 2,315 patients operated on by surgeons trained to perform TME; on MRI there was evidence of residual mesorectal tissue in 50/99 local recurrences. Also, unintentional persistent residual mesorectal tissue (defined as mesorectum above the level of the anastomosis) perpendicular to the bowel was observed in a study on postoperative MRI in 54 (40 %) of 136 patients—particularly after partial mesorectal excision in upper rectal cancers (Bondeven et al. 2013). In the Dutch TME study only mobile tumours were selected as eligible, and the local recurrence rates appear too high to validate the claim that the whole series represents 'standardised TME surgery'.

Some surgical authors have stressed the importance of careful dissection particularly in the posterior aspect of a TME specimen as there is a higher prevalence of lymph nodes in this position (Perez et al. 2008), and it is easy to come out of the appropriate surgical plane. It is acknowledged that the quality of TME can be influenced both by the patient's age, morphology and morbidity as well as disease-related factors (site, position and stage) as well as the surgeon's case volume (Garlipp et al. 2012).

The quality of radical surgery has an independent prognostic factor, which may impact on long-term outcomes. Hermanek, Quirke and Nagtegaal have promoted the importance of assessing the quality of the mesorectum in the surgical specimen and recording by means of a photograph. This classification derives from the original findings from Hermanek and Quirke with three grades based on the completeness of the removal of the mesorectum.

A TME specimen ideally should have a smooth surface, without incisions or tearing, as an indication of successful surgery. 'Coning' is a tendency for the surgeon to cut inwards towards the central tube of the rectum during distal dissection, rather than staying outside the visceral mesorectal fascia, which gives the specimen a tapered, conical appearance. This observed feature is an indication of suboptimal surgical quality (Hermanek and Heald Hermanek and Heald 2004).

Two trials—the CLASSICC study of the Medical Research Council in the United Kingdom and the Dutch TME trial have originally defined a protocol to assess the quality of surgery. This classification has been utilised in the MERCURY study and the CRO7 study (Quirke et al. 2009). Multivariate analysis will need to be validated in future randomised studies.

9 Can Radiotherapy Be Omitted?

Several groups have explored omitting radiotherapy when MRI suggests the tumour is easily resectable. This omission does not appear to have increased the local recurrence rate (Taylor et al. 2011; Frasson et al. 2011; Mathis et al. 2012). It seems clear that the surgeon needs to expect to be able to perform an optimal plane

Table 1 Histopathological grading of the quality and completeness of the mesorectum in a total mesorectal excision specimen

	Mesorectum	Defects	Coning	CRM
Complete	Intact, smooth	Not defects deeper than 5 mm	None	Smooth, regular
Nearly complete	Moderate bulk, but irregular	No visible muscularis propria	Moderate	Irregular
Incomplete	Little bulk and very irregular	Down to muscularis propria	Moderate–marked	Irregular

of surgery i.e. to achieve a surgical specimen with an intact mesorectum displaying only minor irregularities over a smooth mesorectal surface; with no defect deeper than 5 mm; with no coning; and with a smooth CRM on slicing (Quirke et al. 2009) (Table 1).

Three feasibility/retrospective studies of NACT alone without radiation (Cercek et al. 2010; Ishii et al. 2010; Fernandez-Martos et al. 2012; Schrag et al. 2014) used FOLFOX plus/minus bevacizumab (Table 2). The pCR rate after chemotherapy alone varied from to 7–35 %, but as small non-randomised studies are unable to show an impact on metastatic disease. The studies are too small and not sufficiently mature to assess the local recurrence rate. However, the proof of principle has given rise to many current studies exploring NACT (Table 3).

10 Are There Clearly Distinguishable Groups Who Do not Need RT?

Accurate information on primary tumour local extension, precise location, potential nodal-stage, potential CRM involvement and extra-mural venous invasion is essential for defining the optimum treatment strategy on an individual basis. Currently, the definition of locally advanced rectal cancer is variable from unit to unit. Currently, in the UK many MDTS categorise patients into 'The good, the bad and the ugly', which allows definition of three different settings where preoperative neoadjuvant treatment may or may not be required. For clinically unresectable cancers or where MRI shows a threatened/breached CRM (10–15 % of cases), or in cancers which require surgical resection beyond the conventional TME plane, then radiation as a component of CRT is clearly necessary. In contrast, early cT1/T2 tumours are not usually treated with radiotherapy because of the low risk of local recurrence. The problem with these above systems is that the intermediate risk represents a wide spectrum, with variable behaviour and should be defined more accurately with further risk groupings. Since in the trials about 50 % of patients are low rectal cancer within 5 cms of the anal margin, probably more than 50 % are stage 2 and up to 30 % are T2 initially. A T3 subclassification has been proposed in 2001 by Merkel from the Erlangen group, who suggested the

Table 2 Phase I/II studies of neoadjuvant chemotherapy without radiation

	No of pts*	Eligibility	Induction Chemotherapy	Toxicity	PCR**	T Mic***	R0	Late outcome
Ishii 2010	26	cT3/T4 N0–2	Irinotecan (80 mg/m^2), FUFA days 1, 8, and 15 for 4 weeks	Not stated	1/15 (7 %)	Not stated	Not stated	5 year RFS 74 % OS 84 %
Schrag 2010	31	Clinical stage II–III (but not T4)	FOLFOXbevacizumab (6 cycles bev 1–4)	2 pts withdrawn (angina arrhythmia)	8/29 (27 %)	Not stated	29/29 (100 %)	No data
Cercek 2010	20	RT contraindicated or presence of synchronous metastases	6 pts FOLFOX 14 pts FOLFOX + Bev	Not stated	7/20 (35 %) 2/6 (33 %) rectal cancer without metastases	Not stated	Not stated	No data

* number entering study
** number having had surgery
*** using regression grading not yp

Table 3 Trials of neoadjuvant chemotherapy in progress

Study (Reference)	Pre-operative treatment	Entry Criteria	Status	RT/CRT	Comments
Phase III trials					
GEMCAD (Fernandez-Martos 2010) 41 patients	Capecitabine/oxaliplatin + bevacizumab 3 cycles then capox = total 4 cycles	MRI defined entry	Recruiting	Selective CRT according to response	Primary endpoint: response rate (RECIST)
RAPIDO Phase III EudraCT number 2010-023957-12 885 patients	SCPRT (5 × 5 Gy) followed by Oxaliplatin/capectabine 6 cycles versus Control Capecitabine +CRT	MRI defined entry	Yet to open	CRT 50.4 Gy/28# with capecitabine	Primary endpoint: 3 year DFS
Polish study EGBRJ 0109 NCT00833131 540 patients	SCPRT (5 × 5 Gy) followed by FOLFOX (3 cycles) then surgery versus Versus 5FU/capecitabine CRT (50 Gy) as control	Unresectable rectal cancer	Recruiting	SCPRT versus CRT	Primary endpoint: the rate of R0 resection
	Randomised phase II trials				
BACCHUS NCRI Randomised phase II 60 patients	FOLFOX +bevacizumab for 5 courses, then final FOLFOX then surgery Versus FOLFOXIRI bevacizumab for 5 courses, then final FOLFOXIRI then surgery	MRI defined entry	Yet to open	SCPRT or CRT only for progression/lack of response	Primary endpoint: pCR
randomised phase II GRECCAR 4 150 patients	FOLFIRINOX 4–8 weeks then reassess/randomised according to response If good cap 50 Gy versus surgery If poor cap 50 Gy versus cap 60 Gy	MRI defined entry	?started	If good cap 50 Gy versus surgery If poor cap 50 Gy versus cap 60 Gy	Primary endpoint: %R0

(continued)

Table 3 (continued)

Study (Reference)	Pre-operative treatment	Entry Criteria	Status	RT/CRT	Comments
French phase II NCT00865189 91 patients	FOLFOX +bevacizumab for 6 courses then CRT(with bevacizumab/ 5FU) versus CRT alone	Not MRI	Ongoing not recruiting		Primary endpoint: pCR
Chinese Randomised phase II NCT01211210 495 patients	FOLFOX (4 cycles) then surgery versus FOLFOX CRT Versus 5FU CRT (control)	Not MRI	Recruiting		Primary endpoint 3 year DFS
SWOG study NCT00070434 Up to 65 patients	Multiple regimens	T4 rectal cancer	Ongoing not recruiting	CRT with cape	Primary endpoint: response

subdivision of T3 into T3a < 5 mm and T3b > 5 mm (Merkel et al. 2001). The Mercury Study Group extended this subclassification further into four groups: 'a' (<1 mm outside the wall), 'b' (1–5 mm), 'c' (5–15 mm) and 'd' (>15 mm) (MERCURY 2007; Smith and Brown 2008). Distinction between cT2 and cT3a remains difficult, but may be less relevant to outcome because the Erlangen data suggests that prognosis is not significantly different for these two groups. MRI can define macroscopic extramural vascular invasion (EMVI), which occurs in about 40 % of patients (Smith et al. 2008). This feature predicts for systemic failure with good concordance between MRI EMVI and eventual pathology EMVI prognostic outcome (Dirschmid et al. 1996; Sternberg et al. 2002), suggesting that patients with macroscopic EMVI have only a 30 % 3 year disease free survival.

A structure which defines three risk groups within the broad intermediate risk category, with low risk of local recurrence/low risk of metastatic disease, low risk of local recurrence/high risk of metastatic disease, high risk of local recurrence/low risk of metastatic disease, high risk of local recurrence/high risk of metastatic disease is therefore proposed (Table 4).

Chemotherapy prior to CRT or SCPRT does not compromise the delivery CRT, but has not increased pCR rates, R0-resection rate, improved DFS or reduced metastases. There is significant late morbidity from pelvic radiotherapy and a doubling of the risk of second malignancy. Hence, NACT alone without radiotherapy could be explored compared with SCPRT or CRT in selected patients with resectable rectal cancer showing adverse features (extramural vascular invasion etc.) in a future research programme.

11 Biomarkers

There has also been a recent focus on predictive and prognostic molecular biomarkers from the longstanding orthodoxy of carcinoembryonic antigen (CEA) through Kras and Nras mutations, to insight regarding phosphoinositide 3-kinase (PI3 K) mutations and wild type p53. Although none of these novel strategies have been validated, they allow us to hope that we can select and stratify patients according to their different molecular and imaging patterns. This knowledge select patients for certain treatments and may also spare other patients from treatment, which is unlikely to be effective. Criteria are therefore emerging, which suggest a possible future role for individually tailored therapy.

12 The Future

A multi-institutional phase II/III randomised, prospective trial (NCCTG-N1048, NCT01515787) currently compares neoadjuvant FOLFOX with selective use of chemoradiation. The study randomises rectal cancer patients with low risk cT1/2N1, cT3N0 and cT3N1 disease, with lesions located 5–12 cm from the anal verge

Table 4 Proposed mid rectal cancer risk categorisation based on MRI and clinical risk factors

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, V2 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 ? Mucinous
Clinical factors	Obesity Male/with anterior tumours Narrow pelvis Previous pelvic surgery Large bulky tumour Sepsis/fistula/perforation			
NICE guidelines low risk +, but does not include T3b < 4 mm	*UK Nice guidelines intermediate risk* 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			NICE guidelines high risk a threatened (<1 mm) or breached resection margin **or** low tumours encroaching onto inter-sphincteric plane or levator involvement
NICE do not give RT	*Nice guidelines (UK)* SCPRT or CRT			NICE CRT recommended
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	SCPRT or CRT depending on whether shrinkage of tumour required or Neoadjuvant chemotherapy alone	SCPRT or CRT depending on whether shrinkage of tumour required or Neoadjuvant chemotherapy alone	Requires Chemoradiation (CRT)

and amenable to sphincter-preserving surgery, to either the standard of preoperative 5-fluorouracil /capecitabine-based chemoradiation, followed by TME and FOLFOX (eight cycles) or to omot radiation and receive neoadjuvant FOLFOX (six cycles). If clinical response ($\geq$20 %) is observed at restaging, then patients undergo surgical resection followed by adjuvant FOLFOX (six cycles). Only those patients with histologically CRM undergo chemoradiation, because of their increased risk of local recurrence. In contrast, if clinical response is <20 %, patients are administered standard combined modality therapy followed by surgery and adjuvant FOLFOX (two additional cycles).

Similarly in the UK, the ongoing BACCHUS randomised phase II study (registered at ClinicalTrials.gov as NCT01650428) evaluates the efficacy of FOLFOXIRI and bevacizumab compared to FOLFOX and bevacizumab omitting radiotherapy. The study aims to examine whether intensive NACT will deliver pathological responses of the primary tumour at least equivalent to CRT as well as reducing the risk of local recurrence and metastasis. If this triple regimen is feasible, effective and tolerable, it would be suitable for testing as the novel arm against the current standards of SCPRT (5 $\times$ 5 Gy) and/or 5FU-based CRT in a future randomised phase III trial.

13 Conclusion

To achieve pelvic control the surgeon needs an R0 resection. Hence, preoperative CRT is an important component of the multimodality treatment of rectal cancer if the CRM is threatened. Pelvic failure gives rise to awful and debilitating symptoms, including intractable pain and intestinal obstruction, and a very poor quality of life. However, for less advanced cases, an R0 resection may be more straightforward, and the risk of metastatic disease now predominates over the risk of local recurrence. It is difficult to understand how monolithic approaches, established by studies conducted more than a decade ago, with none of the modern amenities currently available still drive some to apply the same schedule of SCPRT or CRT for all patients with cT3No resectable rectal cancer irrespective of tumour position, extent and treatment goal (Sebag-Montefiore et al. 2009).

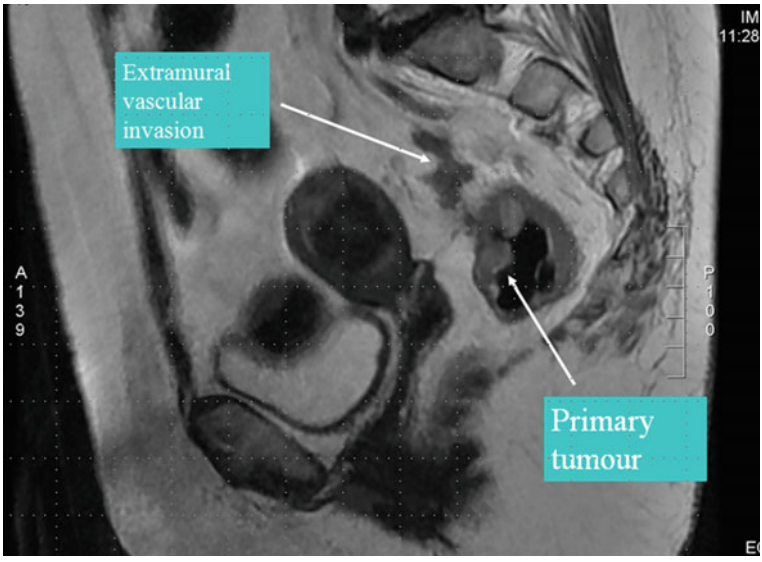
Modern MRI can define patients with a high risk of metastases (EMVI, T3c and T3d)—particularly in the mid rectum. This high risk of metastatic disease means that the use of chemotherapy at systemically-effective doses would seem essential if we are to improve survival in patients with locally advanced rectal cancer. The use of chemoradiation has compromised the integration of full systemic doses and the uptake of postoperative chemotherapy. In contrast NACT has been shown to allow full delivery of chemotherapy in systemic doses and an appropriate intensity without compromising surgery.

The current term of ‘locally advanced rectal cancer’ or ‘T3 /T4’ rectal cancer includes a large proportion of patients who either do not need radiotherapy or equally are not going to benefit in a significant way from chemotherapy, using

analogies of the benefit of chemotherapy in low risk stage II colon cancer. We need a new description /term for locally advanced rectal cancer, which provides an effective risk categorisation. What is the predominant risk? Local recurrence or metastatic disease? A proposal is tabled in this chapter.

All patients with cT3 rectal cancer should be discussed in a well functioning MDT. Patients should be categorised according to clinical stage TNM, site in the rectum, quadrant, and accurate localization in respect to the mesorectal fascia and levators. Other factors, such as cN-stage, and vascular and nerve invasion are important histologically although the prediction of nodal involvement is poor at present and only macroscopic/gross vascular invasion can be imaged at present.

So, can we not do without radiotherapy if the CRM is not threatened? This may be more easily accepted in the upper and mid rectal cancers than in low cancers. But if we still cling to the notion that RT is needed in all cases in the modern TME era, have we simply turned full circle and are back to advocating preoperative radiotherapy to compensate for poor surgical technique? Or can we accept that if we see the surgeon performing good quality surgery in 80–90 % of his specimens within the mesorectal plane and the MRI suggests clear margins, that the benefit from CRT is marginal.



References

Akasu T, Moriya Y, Ohashi Y, Yoshida S, Shirao K, Kodaira S (2006) National surgical adjuvant study of colorectal cancer. adjuvant chemotherapy with uracil-tegafur for pathological stage III rectal cancer after mesorectal excision with selective lateral pelvic lymphadenectomy: a multicenter randomized controlled trial. Jpn J Clin Oncol 36(4):237–244

André T, Boni C, Navarro M et al (2009) Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 27(19):3109–3116

Aschele C, Cionini L, Lonardi S et al (2011) Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 29(20):2773–2780

Birgisson H, Pahlman L, Gunnarsson U, Glimelius B (2005) Occurrence of second cancers in patients treated with radiotherapy for rectal cancer. J Clin Oncol 23:6126–6131

Birgisson H, Pahlman L, Glimelius B (2006) Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish rectal cancer trial. J Clin Oncol 23:8697–8705

Bondeven P, Hagemann-Madsen RH, Bondeven P, Hagemann-Madsen RH, Laurberg S, Pedersen BG (2013) Extent and completeness of mesorectal excision evaluated by postoperative magnetic resonance imaging. Br J Surg 100(10):1357–1367

Bosset JF, Collette L, Calais G et al (2006) Chemoradiotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 355:1114–1123

Bosset JF, Calais G, Mineur L,et al (2014) EORTC radiation oncology group. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 15(2):184–190

Braendengen M, Tveit KM, Berglund A et al (2008) Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol 26(22):3687–3694

Bujko K, Nowacki MP, Nasierowska-Guttmejer A et al (2006) Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 93(10):1215–1223

Cecil DT, Sexton R, Moran BJ, Heald RJ (2004) Total Mesorectal excision results in low local recurrence rates in lymph node-positive rectal cancer. Dis Colon Rectum 47:1145–1150

Cercek A, Weiser MR, Goodman KA, et al (2010) Complete pathological response in the primary of rectal or colon cancer treated with FOLFOX without radiation. J Clin Oncol 28(15S suppl May 20 Supplement):297s (abstract 3649)

Chua YJ, Barbachano Y, Cunningham D et al (2010) Neoadjuvant capecitabine and oxaliplatin before chemoradiation and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol 11(3):241–248

Dirschmid K, Lang A, Mathis G et al (1996) Incidence of extramural venous invasion in colorectal carcinoma: findings with a new technique. Hum Pathol 27(11):1227–1230

Douglas HO Jr, Moertel CG, Mayer RJ, Thomas PR, Lindblad AS, Mittleman A et al (1986) Survival after postoperative combination treatment of rectal cancer. N Engl J Med 315:1294–1295

Fernandez-Martos C, Pericay C, Salud A (2011) Three-year outcomes of GCR-3: a phase II randomized trial comparing conventional preoperative chemoradiation (CRT) followed by surgery and postoperative adjuvant chemotherapy (CT) with induction CT followed by CRT and surgery in locally advanced rectal cancer. J Clin Oncol 29(suppl; abstr 3552)

Fernandez-Martos C, Estevan R, Salud A et al (2012) Neoadjuvant capecitabine, oxaliplatin and bevacizumab (CAPOX-B) in intermedicate-risk rectal cancer (RC) patients defined by magnetic resonance (MR): GEMCAD 0801 trial. J Clinc Oncol 30 (Suppl;abstract 3586)

Fernández-Martos C, Pericay C, Aparicio J et al (2010) Phase II, randomized study of concomitant chemoradiation followed by surgery and adjuvant capecitabine plus oxaliplatin

(capox) compared with induction capox followed by concomitant chemoradiation and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: grupo cancer de recto 3 study. J Clin Oncol 28(5):859–865

Frasson M, Garcia-Granero E, Roda D, et al (2011) Preoperative chemoradiation may not always be needed for patients with T3 and T2N + rectal cancer. Cancer. doi: 10.1002/cncr.25866. (Epub ahead of print)

Frykholm GJ, Pahlman L, Glimerlius B (2001) Combined chemo- and radiotherapy vs. radiotherapy alone in the treatment of primary, nonresectable adenocarcinoma of the rectum. Int J Radiat Oncol Biol Phys 50(2):427–434

Garcia-Aguilar J, Smith DD, Avila K et al (2011) Timing of Rectal Cancer Response to Chemoradiation Consortium. Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. Ann Surg 254(1):97–102

Garlipp B, Ptok H, Schmidt U, Stübs P, Scheidbach H, Meyer F, Gastinger I, Lippert H (2012) Factors influencing the quality of total mesorectal excision. Br J Surg 99(5):714–720

Gerard JP, Conroy T, Bonnetain F et al (2006) Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-T4 rectal cancers: results of FFCD 9203. J Clin Oncol 24:4620–4625

Gerard JP, Azria D, Gourgou-Bourgade S et al (2010) Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the Phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol 28:1638–1644

Gerard JP, Azria D, Gourgou-Bourgade S et al (2012) Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 30(36):4558–4565

Glynne-Jones R, Anyamene N, Moran B, Harrison M (2012) Neoadjuvant chemotherapy in MRI-staged high-risk rectal cancer in addition to or as an alternative to preoperative chemoradiation? Ann Oncol 23(10):2517–2526

Gunderson LL, Sargent DJ, Tepper JE et al (2004) Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. J Clin Oncol 22:1785–1796

Herman MP, Kopetz S, Bhosale PR, Eng C, Skibber JM, Rodriguez-Bigas MA, Feig BW, Chang GJ, Delclos ME, Krishnan S, Crane CH, Das P (2009) Sacral insufficiency fractures after preoperative chemoradiation for rectal cancer: incidence, risk factors, and clinical course. Int J Radiat Oncol Biol Phys 74(3):818–823

Hermanek P, Heald RJ (2004) Pre-operative radiotherapy for rectal carcinoma? Has the case really been made for short course pre-operative radiotherapy if surgical standards for rectal carcinoma are optimal? Colorectal Dis. Review 6(1):10–4

Ishii Y, Hasegawa H, Endo T et al (2010) Medium-termresults of neoadjuvant systemic chemotherapy using irinotecan, 5-fluorouracil, and leucovorin in patients with locally advanced rectal cancer. Eur J Surg Oncol 36(11):1061–1065

Kuebler JP, Wieand HS, O'Connell MJ et al (2007) Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 25(16):2198–2204

Kusters M, Marijnen CA, van de Velde CJ et al (2010) Patterns of local recurrence in rectal cancer; a study of the Dutch TME trial. Eur J Surg Oncol 36(5):470–476

Lange MM, den Dulk M, Bossema ER et al (2007) Risk factors for faecal incontinence after rectal cancer treatment. Cooperative clinical investigators of the Dutch total mesorectal excision trial. Br J Surg 94(10):1278–1284

Marijnen CA, van de Velde CJ, Putter H et al (2005) Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 23(9):1847–1858

Mathis KL, Larson DW, Dozois EJ et al (2012) Outcomes following surgery without radiotherapy for rectal cancer. Br J Surg 99(1):137–143

MERCURY Study Group (2007) Extramural depth of tumour invasion at thin section MR in patients with rectal cancer. Results of the MERCURY Study. Radiology 243:132–139

Merkel S, Mansmann U, Siassi M, Papadopoulus T, Hohenberger W, Heranek P (2001) The prognostic inhomogeneity in pT3 rectal carcinomas. Int J Colorectal Dis 16:298–304

Morris E, Quirke P, Thomas JD et al (2008) Unacceptable variation in abdominoperineal excision rates for rectal cancer: time to intervene? Gut 57(12):1690–1697

Ngan S, Fisher R, Goldstein D et al (2010) TROG, AGITG, CSSANZ, and RACS.A randomized trial comparing local recurrence (LR) rates between short-course (SC) and long-course (LC) preoperative radiotherapy (RT) for clinical T3 rectal cancer: an intergroup trial (TROG, AGITG, CSSANZ, RACS). J Clin Oncol 28(15 Suppl) abstract 3509

O'Connell MJ, Martenson JA, Wieand HS et al (1994) Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 331(8):502–507

Pachler J, Wille-Jørgensen P (2012) Quality of life after rectal resection for cancer, with or without permanent colostomy. Cochrane Database Syst Rev 12:CD004323 (Review)

Peeters KC, van de Velde CJ, Leer JW et al (2005) 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 23(25):6199–6206

Peeters KC, Marijnen CA, Nagtegaal ID, et al (2007) for the Dutch Colorectal Cancer Group. 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 246(5):693–701

Perez RO, Seid VE, Bresciani EH, Bresciani C, Proscurshim I, Pereira DD, Kruglensky D, Rawet V, Habr-Gama A, Kiss D (2008) Distribution of lymph nodes in the mesorectum: how deep is TME necessary? Tech Coloproctol 12(1):39–43

Pollack J, Holm T, Cedermark B et al (2006) Long-term effect of preoperative radiation therapy on anorectal function. Dis Colon Rectum 49(3):345–352

Pollheimer MJ, Kornprat P, Pollheimer VS, Lindtner RA, Schlemmer A, Rehak P, Langner C (2010) Clinical significance of pT sub-classification in surgical pathology of colorectal cancer. Int J Colorectal Dis 25(2):187–196

Quirke P, Steele R, Monson J et al (2009) MRC CR07/NCIC-CTG CO16 Trial Investigators; NCRI colorectal cancer study group. 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 373(9666):821–828

Rödel C, Liersch T, Hermann R et al (2007) Multicenter phase II trial of chemoradiation with oxaliplatin for rectal cancer. J Clin Oncol 25:668–674

Rödel C, Liersch T, Becker H et al (2012) Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 13(7):679–687

Roh MS, Colangelo LH, O'Connell MJ et al (2009) Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP-R03. J Clin Oncol 27:5124–5130

Roh MS, Yothers GA, O'Connell MH et al (2011) The impact of capecitabine and oxaliplatin in the preoperative mutli modality treatment in patients with carinoma of the rectum: NSABP R-04J. Clin Oncol 29(suppl;abstr 3503)

Sauer R, Becker H, Hohenberger W et al (2004) German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351:1731–1740

Schmoll H-J, Haustermans K, Price TJ, et al (2013) Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: first results of the PETACC-6 randomized trial (abstract). J Clin Oncol 31(suppl; abstr 3531)

Schrag D, Weiser MR, Goodman KA et al (2014) Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol 32(6):513–518

Sebag-Montefiore D, Stephens RJ, Steele R et al (2009) Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 373(9666):811–820

Smith N, Brown G (2008) Preoperative staging of rectal cancer. Acta Oncol 47(1):20–31

Smith NJ, Barbachano Y, Norman AR et al (2008) Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. Br J Surg 95(2):229–236

Sternberg A, Amar M, Alfici R, Groisman G (2002) Conclusions from a study of venous invasion in stage IV colorectal adenocarcinoma. J Clin Pathol 55(1):17–21

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

Taylor FG, Quirke P, Heald RJ,et al for the MERCURY study group (2011) 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 that recruited consecutive patients with rectal cancer. Ann Surg 253(4):711–719

Tepper JE, O'Connell, Niedzwiecki D, Hollis DR, Benson AB 3rd, Cummings B, et al (2002) Adjuvant therapy in rectal cancer: analysis of stage, sex and local control—final report of intergroup 0114. J Clin Oncol 20:1744–1750

van Gijn W, Marijnen CA, Nagtegaal ID et al (2011) Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 12(6):575–582

Willett CG, Badizadegan K, Ancukiewicz M et al (1999) Prognostic factors in stage T3N0 Rectal Cancer: Do all patients require postoperative pelvic irradiation and chemotherapy? Dis Colon Rectum 42:167–173

Wolmark N, Wieand HS, Hyams DM, Colangelo L, Dimitrov NV, Romond EH et al (2000) Randomised trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. J Natl Cancer Inst 92:388–396

Quality of Life After Surgery for Rectal Cancer

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Abstract

Patients' health-related quality of life (HRQoL) is now considered a relevant clinical outcome. This study systematically reviewed articles published in the last 5 years, focusing on the impact of rectal cancer treatment on patients' HRQoL. Of the 477 articles retrieved, 56 met the inclusion criteria. The most frequently reported comparisons were between surgical procedures (21 articles), especially between sphincter-preserving and non-sphincter

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preserving surgery or between stoma and stoma-free patients (13 articles), and between multimodality therapies (11 articles). Additionally, twelve articles compared patients' and healthy controls' HRQoL as primary or secondary aim. The majority of the studies were observational (84 %), controlled (66 %), cross-sectional (54 %), prospective (100 %), with a sample of more than 100 patients (59 %), and with more than 60 % of patients treated with neoadjuvant therapy (50 %). The most frequently used instruments were the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30), its colorectal cancer specific module QLQ-CR38, and the Medical Outcomes Study Short-Form 36 items questionnaire. Findings from the included articles are summarised and commented, with a special focus on the comparison between surgical treatments, between irradiated and not-irradiated patients, and between patients and the general population.

Keywords
Rectal cancer · Surgery · Health-related quality of life (HRQoL) · Systematic review

1 Introduction

A milestone in the history of modern medicine has been the shift from a conception of health as the opposite of illness to a multidimensional perspective of health. This conception is reflected in the definition proposed in 1948 by the World Health Organization (WHO) that describes health as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' (WHO 1946). The concept of Quality of Life (QoL) derives from this conception of health. The WHO (WHOQoL Group 1993) defines QoL as 'individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment'.

In medical science, the more specific Health-Related Quality of Life (HRQoL) concept has been introduced, that confines QoL to the health domain and refers to how a disease or a medical condition affects the patient's life (Guyatt et al. 1993). This information is also used by health economics to inform policy making, for example considering Quality-adjusted life-year in cost-effectiveness analyses (Loomes and McKenzie 1989; Detsky 1990).

While there is variation in how QoL and HRQoL are defined and measured, there is a general agreement on several fundamental aspects of the concept of QoL, as used in the medical science (Schumacher et al. 1991; Leplege and Hunt 1997). In fact, it is accepted that QoL is: subjective, multidimensional, dynamic and culturally correlated. The most important dimensions are: physical, psychological, and social functioning and well-being, and physical symptoms that may be related to the specific health condition and its treatment.

QoL can be assessed with generic and specific tools. Generic tools (e.g. Medical Outcomes Study Short-Form 36 items, hereafter SF-36, (Ware 1992)) assess the subjective health status and QoL of various types of patients. Specific tools assess those aspects that can affect QoL of patients with a specific disease and/or a specific treatment (e.g. European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire Core 30, hereafter QLQ-C30 (Aaronson et al. 1993) and its colorectal cancer specific module QLQ-CR38 (Sprangers et al. 1999)) or particular areas of QoL, independently of the disease (e.g. State-Trait Anxiety Inventory (Spielberger et al. 1970)).

Rectal cancer is a common disease in Western countries. In the last decades, the introduction of screening programs, allowing the early detection of the disease, and the advances in surgery interventions and multimodality treatment have improved clinical and oncological outcomes, reducing mortality rate. Presently, the standard of care for locally advanced rectal cancer is neoadjuvant treatment, either as preoperative radiotherapy (pRT) or chemoradiotherapy (pCRT), followed by total mesorectal excision (TME) (National Comprehensive Cancer Network updated). However, this approach is challenging, requiring skilled multidisciplinary teams and it may have severe functional consequences. Similarly to other areas of medicine (Brundage et al. 2011), the shift of focus from assessing exclusively objective oncological outcomes, such as overall and disease-free survival, to subjective and self-reported evaluations of health status and HRQoL is well established (Sprangers et al. 1995; Renner et al. 1999; Dunn et al. 2003).

The information obtained from HRQoL data and, more broadly, from patients' reported outcomes (PROs, i.e. self-reported assessments from patients about how they feel or function in relation to their health condition and therapy) are useful at various levels of decision-making: for individual patients (micro level), for groups of patients (meso level) and at the society level (macro level) (Sutherland and Till 1993; Stiggelbout and de Haes 2001). For example, they allow to monitor the health status of individual patients and to start interventions to support their difficulties. They also represent a parameter for choosing between treatments with similar clinical and oncological outcomes.

Although there is a growing number of studies assessing HRQoL in patients with rectal cancer, findings are often limited by methodological flaws related to the study design, the sample size, the use of non-validated questionnaires, the absence of a baseline assessment, and statistical bias. Moreover, many questionnaires are used to evaluate HRQoL, hindering the comparison of findings from different studies (Brundage et al. 2011, 2013).

The aim of the present study was to review the articles published in the last five years, focusing on HRQoL after surgery in patients with rectal cancer. In particular, we summarised the findings regarding the differences between patients and the general population and the differences between different surgical treatments and oncological approaches.

2 Methods

2.1 Search Strategy

A systematic literature search was performed on PubMed on December 1, 2013, restricting the search to articles published in English from January 2009 to November 2013. The specific terms searched were: ('Rectal Neoplasms'[Mesh]) AND (('Quality of Life'[Mesh] OR (function*) OR (patient-reported)).

2.2 Inclusion and Exclusion Criteria

Studies were included if they measured patients' reported HRQoL after surgery for rectal cancer. QoL could be collected through self-report questionnaires or structured interviews (by telephone or vis-à-vis).

Studies were excluded if: they did not report on primary data; HRQoL was not evaluated; the focus was not on rectal cancer or findings did not distinguish between rectal and colon cancer; the sample size was too small (<20), and other reasons, such as studies performed to validate questionnaires, assessment during neoadjuvant therapy, full text not accessible.

2.3 Coding and Classification

Similarly to our previous reviews (Gavaruzzi et al. 2013; Gavaruzzi et al. 2014), the variables were coded according to the following criteria: comparison between groups of patients, comparisons with general population, study design, sample size, treatment characteristics and instruments used to assess QoL.

Studies were classified based on the comparison between surgical procedures, multimodality therapies, other comparisons such as rectal versus colon cancer patients and finally, no groups compared. It was also noted whether patients' data were compared with reference data or data from healthy controls. Anterior resection (AR), low anterior resection (LAR), ultra low anterior resection (ULAR), intersphincteric resection (ISR) and coloanal anastomosis (CAA) were considered sphincter-preserving procedures. Abdominoperineal resection (APR) also named abdominoperineal excision (APE), extralevator abdominoperineal excision (ELAPE) and pelvic exenteration were considered as non-sphincter preserving procedures.

Based on the statistical design, the studies were classified as: (a) observational or experimental (randomised or not randomised); (b) controlled or not controlled; (c) cross-sectional or longitudinal or before-and-after or longitudinal before-and-after; (d) prospective cohort or retrospective cohort or case-control study.

2.4 Independent Reviewers and Discussion of Cases of Disagreement

Titles and abstracts identified from the literature search were independently reviewed for inclusion by two investigators (GF, GT). The coding of the included articles was performed by one author (GF) and corroborated by a second author (GT). The coding of the study design was performed by a statistician (PDB) and corroborated by a second author (GF). Discrepancies were resolved by discussion with all the authors.

With the exception of articles that compared patients with the general population, when studies reported multiple comparisons between patients according to different criteria (e.g. sex, surgery and stoma), they were classified based on their primary aim and findings are summarised accordingly.

The findings from each included article were reviewed and summarised. For instruments using a 0–100 score, differences of at least 10 points were considered clinically significant (Osoba et al. 1998). When data were not reported numerically but were depicted in figures, information about differences of at least 10 points was extrapolated from the graphs. For instruments using other score ranges, statistical significance was considered.

3 Results

Of 477 articles retrieved and considered for potential inclusion, 421 were excluded. Reasons for exclusion were: no primary (n = 113) or QoL data (n = 243) reported, patients had no rectal cancer (n = 32), sample size < 20 (n = 16), and other reasons (n = 16).

The remaining 56 articles meet the inclusion criteria. Comparisons performed, study design, sample size, patients who received neoadjuvant therapy and QoL instruments used are summarised in Table 1.

3.1 Comparison Between Different Surgical Procedures

Out of 21 studies performed on this issue, nine compared sphincter-preserving surgery (SPS) versus non-SPS (Campos-Lobato et al. 2011; Fischer et al. 2010; Austin et al. 2010; Celasin et al. 2011; Varpe et al. 2011; Konanz et al. 2013; Mrak et al. 2011; How et al. 2012; Kasparek et al. 2011), four compared stoma and

Table 1 Characteristics of the articles

Characteristics		Number (%) of articles	References
Comparisons between patients	Between surgical procedures	21 (37.5 %)	Campos-Lobato et al. (2011), Fischer et al. (2010), Austin et al. (2010), Celasin et al. (2011), Varpe et al. (2011), Konanz et al. (2013), Mrak et al. (2011), How et al. (2012), Kasparek et al. (2011), Yau et al. (2009), Orsini et al. (2013), Bossema et al. (2011), Krouse et al. (2009), Vaughan-Shaw et al. (2012), Kang et al. (2010), Andersson et al. (2013), Li et al. (2010), Dumont et al. (2013), Doeksen et al. (2012), Barisic et al. (2011), Gullà et al. (2011)
	Between multimodality therapies	11 (19.6 %)	Canda et al. (2010), Peng et al. (2011), Thong et al. (2011), Bruheim et al. (2010), Kasparek et al. (2012), Parc et al. (2009), Braendengen et al. (2012), Tiv et al. (2010), Kripp et al. (2012), Guckenberger et al. (2013), Stephens et al. (2010)
	Other comparisons	5 (8.9 %)	Ashburn et al. (2013), Riss et al. (2011), Ohigashi et al. (2011), You et al. (2011), Laforest et al. (2012)
	No comparisons	19 (33.9 %)	Kilic et al. (2012), Bloemen et al. (2009), Pucciarelli et al. (2010), Mahjoubi et al. (2012), Hoerske et al. (2010), Serpentini et al. (2011), Schmidt et al. (2010), Emmertsen (2013), Zutshi et al. (2013), Neuman et al. (2011), Allaix et al. (2011), Pucciarelli et al. (2011), Theodoropoulos et al. (2013), Hennies et al. (2012), Planting et al. (2013), Hirche et al. (2010), Ristvedt and Trinkaus (2009), Carlsson et al. (2010), Caravati-Jouvenceaux et al. (2011)
Comparisons with general population		12 (21.4 %)	Austin et al. (2010), Konanz et al. (2013), Orsini et al. (2013), Thong et al. (2011), Bruheim et al. (2010), Braendengen et al. (2012), Kripp et al. (2012), Guckenberger et al. (2013), Pucciarelli et al.(2010), Serpentini et al. (2011), Carlsson et al. (2010), Caravati-Jouvenceaux et al. (2011)

(continued)

Table 1 (continued)

Characteristics		Number (%) of articles	References
Design	Observational	47 (83.9 %)	Campos-Lobato et al. (2011), Fischer et al. (2010), Austin et al. (2010), Celasin et al. (2011), Varpe et al. (2011), Konanz et al. (2013), Mrak et al. (2011), How et al. (2012), Kasparek et al. (2011), Yau et al. (2009), Orsini et al. (2013), Bossema et al. (2011), Krouse et al. (2009), Vaughan-Shaw et al. (2012), Li et al. (2010), Dumont et al. (2013), Barisic et al. (2011), Gullà et al. (2011), Canda et al. (2010), Peng et al. (2011), Thong et al. (2011), Bruheim et al. (2010), Kasparek et al. (2012), Parc et al. (2009), Guckenberger et al. (2013), Ashburn et al. (2013), Riss et al. (2011), You et al. (2011), Kilic et al. (2012), Bloemen et al. (2009), Pucciarelli et al. (2010), Mahjoubi et al. (2012), Hoerske et al. (2010), Serpentini et al. (2011), Schmidt et al. (2010), Emmertsen (2013), Zutshi et al. (2013), Neuman et al. (2011), Allaix et al. (2011), Pucciarelli et al. (2011), Theodoropoulos et al. (2013), Hennies et al. (2012), Planting et al. (2013), Hirche et al. (2010), Ristvedt and Trinkaus (2009), Carlsson et al. (2010), Caravati-Jouvenceaux et al. (2011)
	Experimental, randomised	6 (10.7 %)	Kang et al. (2010), Andersson et al. (2013), Doeksen et al. (2012), Braendengen et al. (2012), Tiv et al. (2010), Stephens et al. (2010)
	Experimental, quasi-randomised	1 (1.8 %)	Kripp et al. (2012)
	Experimental, not randomised	2 (3.6 %)	Ohigashi et al. (2011), Laforest et al. (2012)

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Table 1 (continued)

Characteristics		Number (%) of articles	References
	Controlled	37 (66.1 %)	Campos-Lobato et al. (2011), Fischer et al. (2010), Austin et al. (2010), Celasin et al. (2011), Varpe et al. (2011), Konanz et al. (2013), Mrak et al. (2011), How et al. (2012), Kasparek et al. (2011), Yau et al. (2009), Orsini et al. (2013), Bossema et al. (2011), Krouse et al. (2009), Vaughan-Shaw et al. (2012), Kang et al. (2010), Andersson et al. (2013), Li et al. (2010), Dumont et al. (2013), Doeksen et al. (2012), Barisic et al. (2011), Gullà et al. (2011), Canda et al. (2010), Peng et al. (2011), Thong et al. (2011), Bruheim et al. (2010), Kasparek et al. (2012), Parc et al. (2009), Braendengen et al. (2012), Tiv et al. (2010), Kripp et al. (2012), Guckenberger et al. (2013), Stephens et al. (2010), Ashburn et al. (2013), Riss et al. (2011), You et al. (2011), Laforest et al. (2012), Caravati-Jouvenceaux et al. (2011)
	Not controlled	19 (33.9 %)	Ohigashi et al. (2011), Kilic et al. (2012), Bloemen et al. (2009), Pucciarelli et al. (2010), Mahjoubi et al. (2012), Hoerske et al. (2010), Serpentini et al. (2011), Schmidt et al. (2010), Emmertsen (2013), Zutshi et al. (2013), Neuman et al. (2011), Allaix et al. (2011), Pucciarelli et al. (2011), Theodoropoulos et al. (2013), Hennies et al. (2012), Planting et al. (2013), Hirche et al. (2010), Ristvedt and Trinkaus (2009), Carlsson et al. (2010)
	Cross-sectional	30 (53.6 %)	Fischer et al. (2010), Austin et al. (2010), Konanz et al. (2013), Mrak et al. (2011), Kasparek et al. (2011), Orsini et al. (2013), Bossema et al. (2011), Krouse et al. (2009), Vaughan-Shaw et al. (2012), Dumont et al. (2013), Barisic et al. (2011), Gullà et al. (2011), Peng et al. (2011), Thong et al. (2011), Bruheim et al. (2010), Kasparek et al. (2012), Tiv et al. (2010), Kripp et al. (2012), Guckenberger et al. (2013), Riss et al. (2011), Laforest et al. (2012), Kilic et al. (2012), Bloemen et al. (2009), Pucciarelli et al. (2010), Mahjoubi et al. (2012), Hoerske et al. (2010), Serpentini et al. (2011), Hirche et al. (2010), Ristvedt and Trinkaus (2009), Caravati-Jouvenceaux et al. (2011)

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Table 1 (continued)

Characteristics		Number (%) of articles	References
	Longitudinal	2 (3.6 %)	Ashburn et al. (2013), Zutshi et al. (2013)
	Before-and-after	7 (12.5 %)	Celasin et al. (2011), Varpe et al. (2011), Kang et al. (2010), Canda et al. (2010), Braendengen et al. (2012), Hennies et al. (2012), Planting et al. (2013)
	Longitudinal before-and-after	16 (28.6 %)	Campos-Lobato et al. (2011), How et al. (2012), Yau et al. (2009), Andersson et al. (2013), Li et al. (2010), Doeksen et al. (2012), Parc et al. (2009), Stephens et al. (2010), You et al. (2011), Schmidt et al. (2010), Emmertsen (2013), Neuman et al. (2011), Allaix et al. (2011), Pucciarelli et al. (2011), Theodoropoulos et al. (2013), Carlsson et al. (2010)
	Mixed: cross sectional and before-and-after	1 (1.78 %)	Ohigashi et al. (2011)
	Prospective cohort	56 (100 %)	Campos-Lobato et al. (2011), Fischer et al. (2010), Austin et al. (2010), Celasin et al. (2011), Varpe et al. (2011), Konanz et al. (2013), Mrak et al. (2011), How et al. (2012), Kasparek et al. (2011), Yau et al. (2009), Orsini et al. (2013), Bossema et al. (2011), Krouse et al. (2009), Vaughan-Shaw et al. (2012), Kang et al. (2010), Andersson et al. (2013), Li et al. (2010), Dumont et al. (2013), Doeksen et al. (2012), Barisic et al. (2011), Gullà et al. (2011), Canda et al. (2010), Peng et al. (2011), Thong et al. (2011), Bruheim et al. (2010), Kasparek et al. (2012), Parc et al. (2009), Braendengen et al. (2012), Tiv et al. (2010), Kripp et al. (2012), Guckenberger et al. (2013), Stephens et al. (2010), Ashburn et al. (2013), Riss et al. (2011), Ohigashi et al. (2011), You et al. (2011), Laforest et al. (2012), Kilic et al. (2012), Bloemen et al. (2009), Pucciarelli et al. (2010), Mahjoubi et al. (2012), Hoerske et al. (2010), Serpentini et al. (2011), Schmidt et al. (2010), Emmertsen (2013), Zutshi et al. (2013), Neuman et al. (2011), Allaix et al. (2011), Pucciarelli et al. (2011), Theodoropoulos et al. (2013), Hennies et al. (2012), Planting et al. (2013), Hirche et al. (2010), Ristvedt and Trinkaus (2009), Carlsson et al. (2010), Caravati-Jouvenceaux et al. (2011)

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Table 1 (continued)

Characteristics		Number (%) of articles	References
	Retrospective cohort	0 (0 %)	no article
	Case-control	0 (0 %)	no article
Sample size	<50 patients	11 (19.6 %)	Austin et al. (2010), Vaughan-Shaw et al. (2012), Dumont et al. (2013), Barisic et al. (2011), Gullà et al. (2011), Riss et al. (2011), Ohigashi et al. (2011), Laforest et al. (2012), Theodoropoulos et al. (2013), Planting et al. (2013), Hirche et al. (2010)
	50–100 patients	12 (21.4 %)	Fischer et al. (2010), Celasin et al. (2011), Varpe et al. (2011), Mrak et al. (2011), How et al. (2012), Canda et al. (2010), Mahjoubi et al. (2012), Neuman et al. (2011), Allaix et al. (2011), Hennies et al. (2012), Ristvedt and Trinkaus (2009, Carlsson et al. (2010)
	>100 patients	33 (58.9 %)	Campos-Lobato et al. (2011), Konanz et al. (2013), Kasparek et al. (2011), Yau et al. (2009), Orsini et al. (2013), Bossema et al. (2011), Krouse et al. (2009), Kang et al. (2010), Andersson et al. (2013), Li et al. (2010), Doeksen et al. (2012), Peng et al. (2011), Thong et al. (2011), Bruheim et al. (2010), Kasparek et al. (2012), Parc et al. (2009), Braendengen et al. (2012), Tiv et al. (2010), Kripp et al. (2012), Guckenberger et al. (2013), Stephens et al. (2010), Ashburn et al. (2013), You et al. (2011), Kilic et al. (2012), Bloemen et al. (2009), Pucciarelli et al. (2010), Hoerske et al. (2010), Serpentini et al. (2011), Schmidt et al. (2010), Emmertsen (2013), Zutshi et al. (2013), Pucciarelli et al. (2011), Caravati-Jouvenceaux et al. (2011)
% of patients who underwent neoadjuvant therapy	0	3 (5.4 %)	Schmidt et al. (2010), Allaix et al. (2011), Ristvedt and Trinkaus (2009)
	<30	9 (16.1 %)	Kasparek et al. (2011), Yau et al. (2009), Krouse et al. (2009), Peng et al. (2011), Kasparek et al. (2012), Ashburn et al. (2013), Emmertsen (2013), Planting et al. (2013), Hirche et al. (2010)

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Table 1 (continued)

Characteristics		Number (%) of articles	References
	30–60	10 (17.9 %)	Fischer et al. (2010), Varpe et al. (2011), Konanz et al. (2013), How et al. (2012), Barisic et al. (2011), Canda et al. (2010), Bruheim et al. (2010), Parc et al. (2009), Stephens et al. (2010), Hoerske et al. (2010)
	61–90	15 (26.8 %)	Campos-Lobato et al. (2011), Celasin et al. (2011), Mrak et al. (2011), Orsini et al. (2013), Vaughan-Shaw et al. (2012), Andersson et al. (2013), Li et al. (2010), Dumont et al. (2013), Thong et al. (2011), Riss et al. (2011), You et al. (2011), Laforest et al. (2012), Bloemen et al. (2009), Serpentini et al. (2011), Carlsson et al. (2010)
	>90	13 (23.2 %)	Kang et al. (2010), Doeksen et al. (2012), Gullà et al. (2011), Braendengen et al. (2012), Tiv et al. (2010), Kripp et al. (2012), Guckenberger et al. (2013), Kilic et al. (2012), Pucciarelli et al. (2010), Zutshi et al. (2013), Neuman et al. (2011), Pucciarelli et al. (2011), Hennies et al. (2012)
	Not specified	6 (10.7 %)	Austin et al. (2010), Bossema et al. (2011), Ohigashi et al. (2011), Mahjoubi et al. (2012), Theodoropoulos et al. (2013), Caravati-Jouvenceaux et al. (2011)
Questionnaires[a]	EORTC QLQ-C30 (Aaronson et al. 1993)	36 (64.3 %)	Fischer et al. (2010), Konanz et al. (2013), Mrak et al. (2011), How et al. (2012), Kasparek et al. (2011), Yau et al. (2009), Bossema et al. (2011), Vaughan-Shaw et al. (2012), Kang et al. (2010), Andersson et al. (2013), Li et al. (2010), Dumont et al. (2013), Barisic et al. (2011), Peng et al. (2011), Bruheim et al. (2010), Kasparek et al. (2012), Braendengen et al. (2012), Tiv et al. (2010), Kripp et al. (2012), Guckenberger et al. (2013), Ohigashi et al. (2011), Kilic et al. (2012), Bloemen et al. (2009), Pucciarelli et al. 2010, Mahjoubi et al. (2012), Hoerske et al. (2010), Schmidt et al. (2010), Emmertsen (2013), Neuman et al. (2011), Allaix et al. (2011), Pucciarelli et al. (2011), Theodoropoulos et al. (2013), Hennies et al. (2012), Planting et al. (2013), Hirche et al. (2010), Caravati-Jouvenceaux et al. (2011)

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Table 1 (continued)

Characteristics		Number (%) of articles	References
	EORTC QLQ-CR38 (Sprangers et al. 1999)	25 (44.6 %)	Fischer et al. (2010), Konanz et al. (2013), How et al. (2012), Kasparek et al. (2011), Orsini et al. (2013), Kang et al. (2010), Andersson et al. (2013), Li et al. (2010), Dumont et al. (2013), Doeksen et al. (2012), Thong et al. (2011), Kasparek et al. (2012), Tiv et al. (2010), Stephens et al. (2010), Kilic et al. (2012), Bloemen et al. (2009), Pucciarelli et al. (2010), Mahjoubi et al. (2012), Hoerske et al. (2010), Neuman et al. (2011), Allaix et al. (2011), Pucciarelli et al. (2011), Hennies et al. (2012), Planting et al. (2013), Hirche et al. (2010)
	EORTC QLQ-CR29 (Whistance et al. 2009)	6 (10.7 %)	Mrak et al. (2011), Vaughan-Shaw et al. (2012, Peng et al. (2011), Kripp et al. (2012), Guckenberger et al. (2013), Theodoropoulos et al. (2013)
	MOS SF-36 (Ware 1992)	16 (28.6 %)	Campos-Lobato et al. (2011), Austin et al. (2010), Celasin et al. (2011), Orsini et al. (2013), Krouse et al. (2009), Doeksen et al. (2012), Thong et al. (2011), Parc et al. (2009), Stephens et al. (2010), Ashburn et al. (2013), Ohigashi et al. (2011), Laforest et al. (2012), Zutshi et al. (2013), Theodoropoulos et al. (2013), Carlsson et al. (2010), Caravati-Jouvenceaux et al. (2011)

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Table 1 (continued)

Characteristics		Number (%) of articles	References
	FIQL (Rockwood et al. 2000)	5 (8.9 %)	Barisic et al. (2011), Canda et al. (2010), Laforest et al. (2012), Allaix et al. (2011), Planting et al. (2013)
	FACT-C (Ward et al. 1999)	3 (5.4 %)	Austin et al. (2010), You et al. (2011), Ristvedt and Trinkaus (2009)
	EQ-5D (Rabin and de Charro 2001)	2 (3.6 %)	Andersson et al. (2013) Allaix et al. (2011)
	Other questionnaires[b]	10 (17.9 %)	Varpe et al. (2011), How et al. (2012), Krouse et al. (2009), Gullà et al. (2011), Ashburn et al. (2013), Riss et al. (2011), Serpentini et al. (2011), Zutshi et al. (2013), Neuman et al. (2011), Theodoropoulos et al. (2013)

[a]Several studies used multiple questionnaires

[b]Other questionnaires used were: CGQL (Fazio et al. 1999); Coloplast stoma QOL questionnaire (Prieto et al. 2005); GIQLI (Eypasch et al. 1995); mCOH-QOL-Ostomy (City of Hope/Beckman Research Institute Pain Resource Center Research Instruments); MOS SF-12 (Ware et al. 1996); PGWBI (Dupuy 1984); RAND 36-item (Hays et al. 1993); SQLI (Marquis et al. 2003); SQOL (Baxter et al. 2006)

List of acronyms CGQL: Cleveland Global Quality of Life; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: EuroQoL 5-D; FACT-C: Functional Assessment of Cancer Therapy-Colorectal; FIQL: Fecal Incontinence Quality of Life questionnaire; GIQLI: Gastrointestinal Quality of Life Index; mCOH-QOL-Ostomy: modified City of Hope Quality of Life Ostomy-specific; MOS SF-36: Medical Outcomes Study Short-Form 36 item; MOS SF-12: Medical Outcomes Study Short-Form 12 item; PGWBI: Psychological General Well-Being Index; QLQ-C30: Quality of Life Questionnaire Core 30; QLQ-CR38: Quality of Life Questionnaire Colorectal 38; QLQ-CR29: Quality of Life Questionnaire Colorectal 29; RAND 36: RAND 36-Item Health Survey; SQLI: Stoma care Quality of Life Index; SQOL: Stoma Quality of Life

non-stoma patients (Yau et al. 2009; Orsini et al. 2013; Bossema et al. 2011; Krouse et al. 2009), four compared open versus laparoscopic surgery (Vaughan-Shaw et al. 2012; Kang et al. 2010; Andersson et al. 2013; Li et al. 2010), two compared different intestinal reconstructions after rectal resection (Dumont et al. 2013; Doeksen et al. 2012), one compared different ISRs (Barisic et al. 2011) and one compared ghost versus standard ileostomy (Gullà et al. 2011).

3.1.1 Comparison Between Sphincter-Preserving and Non-Sphincter-Preserving Surgery

Out of nine studies comparing SPS and non-SPS, in four there were no differences between the two groups (Campos-Lobato et al. 2011; Fischer et al. 2010; Austin et al. 2010; Celasin et al. 2011), in three the differences favoured SPS (Varpe et al. 2011; Konanz et al. 2013; Mrak et al. 2011), while mixed findings were found in the remaining two studies (How et al. 2012; Kasparek et al. 2011).

Campos-Lobato et al. (Campos-Lobato et al. 2011) compared APR and LAR patients overtime, from baseline up to 36 months from surgery, and found no difference in the summary scores of the SF-36. Fischer et al. (2010) compared a group of APE patients with a group of ULAR patients without secondary stoma and a small group of ULAR patients with a secondary stoma. APE patients reported worse diarrhoea scores than ULAR patients without secondary stoma. At a median of 47 months, Austin et al. (2010) found no differences on the FACT-C scores between patients who underwent pelvic exenteration and a control group of patients who underwent either APE or LAR 3 months earlier. Again, no statistically significant differences were found by Celasin et al. (2011), who longitudinally compared Muslim patients treated with APE, LAR or AR, using the SF-36 questionnaire.

At 1 year after surgery, Varpe et al. (2011) found that AR patients had better scores than APR patients on physical functioning and body pain, measured with the RAND 36 questionnaire (Hays et al. 1993). Konanz et al. (2013) compared three groups of patients who had undergone ISR, LAR or APR using the QLQ-C30 and QLQ-CR38. At a median time of 59 months form surgery, ISR and LAR patients had better scores than APR patients on physical function, body image, sexual functioning and lower male sexual dysfunction, but worse score on diarrhoea, especially for ISR patients. Additionally, LAR patients had better score than APR on role function and future perspectives, but also had worse on constipation, whereas ISR patients had lower female sexual dysfunction, but also more gastrointestinal problems than APR and more defecation problems than LAR patients. At a median follow-up of 74 months, Mrak et al. (2011) reported that patients who underwent ULAR with J-pouch anastomosis reported better HRQoL scores than patients treated with APE. On the QLQ-C30, ULAR patients had higher global health status/QoL, physical, role, emotional, cognitive and social function, and less fatigue, diarrhoea and financial difficulties compared to APE patients. On the QLQ-CR29 (Whistance et al. 2009), ULAR patients had better scores on body pain, weight and sexual interest, and lower problems with urinary frequency, embarrassment and impotence.

Mixed findings were found in two studies (How et al. 2012; Kasparek et al. 2011). How et al. (2012) compared 32 patients who underwent LAR and 30 who underwent APE (19 of them were ELAPE). Using the QLQ-C30 and QLQ-CR38, the authors found that, preoperatively, LAR patients had more symptoms than APE patients, including fatigue, insomnia, defecation problem and male sexual dysfunction, but also less diarrhoea and better scores on sexual functioning and enjoyment and future perspectives. Two years after surgery, LAR patients showed worse role and social function, and more fatigue, pain, insomnia, diarrhoea and gastrointestinal problems, but also better sexual functioning and enjoyment and better cognitive function. The authors' conclusion was that global QoL ratings were comparable in the two groups and that, compared with SPS, the APE should not be regarded as an inferior option for patients with low rectal cancer as concern as the QoL. Kasparek et al. (2011) compared APR patients with CAA patients with or without stoma at a median follow-up of 73 months. On the QLQ-C30 and QLQ-CR38, patients treated with CAA without a stoma had better body image and lower male and female sexual dysfunction, although sexual functioning was also lower than APR patients. In contrast, compared to APR patients, patients treated with CAA and with a stoma had worse global health status/QoL, social function, body image, sexual functioning and future perspectives, and experienced more symptoms related to fatigue, pain and male sexual dysfunction.

3.1.2 Comparison Between Patients With and Without Stoma

While patients treated with non-SPS always have a stoma, patients treated with SPS are not always stoma-free. The primary end-point in the following articles was the comparison between patients with and without stoma.

Yau et al. (2009) used the QLQ-C30 at baseline, during adjuvant therapy, and 3 years after surgery. Patients with either a temporary or a permanent stoma still had worse social function than no-stoma patients at 3 years follow-up. Stoma patients had less constipation at baseline, but this advantage was not found at 3 years. Orsini et al. (2013) compared the effects of having a stoma separately for patients younger or older than 70 at diagnosis using the SF-36 and the QLQ-C30. At a median time from surgery of 3.4 years, younger patients only showed a difference in female sexual dysfunction, higher in stoma than no-stoma patients, whereas older patients with a stoma had more role limitations due to physical and emotional problems, worse body image and more male sexual dysfunction than no-stoma patients. Bossema et al. (2011) used the QLQ-C30 functional scales at a median time from surgery of about 8 years. Stoma patients reported worse physical function, but also improved social function compared to no-stoma patients. Krouse et al. (2009) compared the effects of having a stoma separately for females and males, at a median time from surgery of 11.4 years, using the SF-36 and the modified m-COH-QoL-Ostomy (City of Hope/Beckman Research Institute Pain Resource Center Research Instruments). For males, the only difference found was on social functioning measured with the m-COH-QoL-Ostomy, with stoma patients reporting worse social function. For females, several differences were

clinically meaningful. Female patients with stoma compared to no-stoma patients had worse general health, physical function, social function, vitality, mental health and more limitations due to physical and emotional problems, as measured with the SF-36. Additionally, they had lower scores on the m-COH-QoL-Ostomy for total QoL, social function, and psychological function.

3.1.3 Comparisons Between Laparoscopic and Open Resection

Four studies compared open and laparoscopic surgery, two of them were randomised trials. Vaughan-Shaw et al. (2012) compared QoL of three small groups of patients who underwent ELAPE, standard LAPE and OAPE. Be aware of the bias of the study, the authors concluded that extended APE performed laparoscopically is not associated with deterioration of QoL. In the large randomised COREAN trial comparing laparoscopic and open surgery for rectal cancer up to 9 cm from anal verge, Kang et al. (2010) used the QLQ-C30 and QLQ-CR38 preoperatively and at 3 months or after ileostomy closure. No clinically significant differences were found at either time point between open and laparoscopic surgery arms. In the Andersson et al.'s (2013) study, HRQOL was assessed in a subset of patients enrolled in the COLOR II trial. The EQ-5D (Rabin and de Charro 2001), QLQ-C30, and QLQ-CR38 questionnaires were administered preoperatively and 4 weeks, 6 and 12 months after surgery. There were no differences between groups in any of the questionnaires administered and at any time point measured. Li et al.'s (2010) study compared open and laparoscopic surgery in a prospective but not randomised fashion. QoL assessment was performed preoperatively, and then at 1 week, 3 and 12 months postoperatively using the Chinese version of the QLQ-C30 and QLQ-CR38. The laparoscopic group had less pain 1 week after the surgery, fewer financial difficulties at 1 week and 3 months, and better body image at each time point following surgery, whereas there were no differences in the global health status/QoL scale.

3.1.4 Comparison Between Intestinal Anastomoses Following Rectal Resection

Dumont et al. (2013) compared two small groups of patients, who underwent coloanal anastomosis after ISR or perineal pseudocontinent colostomy (PCC) after APR. At a median of 57.7 months from surgery, using the QLQ-C30 and QLQ-CR38 questionnaires, PCC patients had better functional scores (physical and cognitive function, sexual functioning and enjoyment, and future perspectives), but also more symptoms (fatigue, pain, insomnia, diarrhoea, chemotherapy side effects and defecation problems) than those with ISR. Doeksen et al. (2012) randomised patients to receive J-pouch or side-to-end reconstruction after TME. HRQoL was assessed with the SF-36 and QLQ-CR38 preoperatively and 4 and 12 months postoperatively. Of the 107 patients randomised, only data from 52 of them were analysed. Of the subset of scales reported, there were no differences preoperatively, whereas at both follow-up times, J-pouch patients had better physical function and social function, but also more micturition problems and more

gastrointestinal symptoms than side-to-end patients. General health, sexual functioning and defecation problems did not differ between groups at either follow-up.

3.1.5 Comparison Between Sphincter-Preserving Surgery Procedures

Barisic et al. (2011) compared three small groups of patients who underwent partial, subtotal and total ISR for distal third rectal cancer. At 12 months after ileostomy reversal, no statistically significant differences were found on the QLQ-C30 and only some differences on the FIQL scores (Rockwood et al. 2000) regarding the scales of coping/behaviour and depression/self perception.

3.1.6 Comparison Between Ileostomies

Gullà et al. (2011) compared patients treated with ghost ileostomy or traditional covering stoma, using the Stoma care Quality of Life Index (SQLI) (Marquis et al. 2003). While the authors themselves specified that this questionnaire is divided into 13 subscales, their results reported a single score, whose interpretation is unclear.

3.2 Comparison Between Multimodality Therapies

Of the 11 articles reporting on the effect of multimodality therapies, six included a control group undergoing surgery-only (Canda et al. 2010; Peng et al. 2011; Thong et al. 2011; Bruheim et al. 2010; Kasparek et al. 2012; Parc et al. 2009), whereas five studies did not (Braendengen et al. 2012; Tiv et al. 2010; Kripp et al. 2012; Guckenberger et al. 2013; Stephens et al. 2010).

3.2.1 Studies Including a Control Group

Canda et al. (2010) compared two small groups of patients, one treated with surgery-only, one with pCRT followed by surgery. After a median of 14 months, the two groups did not differ on FIQL scores. Peng et al. (Peng et al. 2011) evaluated four groups of patients who underwent surgery-only, surgery plus adjuvant CT, surgery plus adjuvant CRT and pCRT plus surgery plus adjuvant CT, using the QLQ-C30 and QLQ-CR29 questionnaires. At a median follow-up of 10 months, compared with non-irradiated patients, irradiated patients showed worse scores for faecal incontinence and diarrhoea. Thong et al. (2011) compared SF-36 and QLQ-C38 scores in patients treated with surgery-only or with preoperative radiotheraphy (pRT) followed by surgery, at a median follow-up of 4 years. In patients with a follow-up of less than 5 years, surgery-only patients reported less body pain, and lower male and female sexual dysfunction than pRT patients. For patients with 5 or more years of follow-up, surgery-only patients had better body image and sexual enjoyment, and lower stoma related-problems and male sexual dysfunction than pRT patients. At a median follow-up of 4.8 years, Bruheim et al. (2010) compared irradiated and non-irradiated patients on the functional scales of the QLQ-C30. The only difference was found for social function, which was better in non-irradiated

than in irradiated patients. Kasparek et al. (2012) compared HRQoL in patients who underwent APR without pre or postoperative RT (n = 55), with pRT (n = 53), and with postoperative RT (n = 35). Median follow-up was 52 months and HRQoL was measured with the QLQ-C30 and QLQ-CR38. Apart from females' sexual functioning which scored better in both RT groups and sexual enjoyment which scored better in the pRT group compared to the surgery-only group, the surgery-only group scored better on role function, body image and future perspectives; and showed less constipation, diarrhoea, and male and female sexual dysfunction than pRT patients; and better future perspectives and less female sexual dysfunction than postoperative RT patients. Parc et al. (2009) assessed HRQoL in 364 patients who entered a randomised trial (Fazio et al. 2007) comparing colorectal and coloanal anastomoses after LAR. The SF-36 questionnaire was administered preoperatively, and 4, 12 and 24 months postoperatively. There were no statistically significant differences at any time points between patients treated with or without pRT. However, patients treated with pCRT compared to those treated with pRT had lower physical and mental summary scores at 4 months, and lower mental summary score at 12 months.

3.2.2 Studies not Including a Control Group

Braendengen et al. (2012) evaluated 76 out of 209 patients who were randomised to pRT or pCRT followed by surgery for non-resectable rectal cancer (Brændengen et al. 2008). At a median follow-up of 6 years, there were no differences in QLQ-C30 scores. Tiv et al. (2010) evaluated HRQoL, using the QLQ-C30 and QLQ-CR38 questionnaires, in 207 French patients entered in the 22921 EORTC trial (Bosset et al. 2006). According to the original randomised trial, patients underwent: pRT and surgery, pCRT and surgery, pRT plus surgery plus postoperative CT and pCRT plus surgery plus postoperative CT. Median follow-up from randomisation to HRQoL evaluation was 4.6 years, and results were reported comparing the pRT group with all the other ones. Patients treated with CT had worse social function and more diarrhoea than those treated with pRT only. Kripp et al. (2012) compared 99 locally advanced rectal cancer patients either treated within a phase III (Hofheinz et al. 2011) or Phase I/II trials (Willeke et al. 2007; Horisberger et al. 2009) and randomised to intensified CRT (ICRT) or conventional CRT. The only differences reported on the QLQ-C30 and QLQ-CR29 favoured the ICRT group for urinary frequency and the conventional CRT group for anxiety and diarrhoea. Guckenberger et al. (2013) compared the effects of short-course pRT or long-course pCRT using the QLQ-C30 and QLQ-CR29 questionnaires. At a median follow-up time of 67 months, pCRT patients reported more diarrhoea, financial difficulties and embarrassment, but also less dyspareunia than pRT patients. Stephens et al. (2010) compared SF-36 and QLQ-CR38 scores in patients randomised to short-course pRT and surgery or surgery followed by postoperative CRT (postCRT) in selected patients, i.e. those with positive circumferential margin. Clinical data of this trial were reported elsewhere (Sebag-Montefiore et al. 2009). To note, only 63 out of 676 randomised in the second arm actually received postoperative CRT. HRQoL

was assessed before any treatment, and 3, 6, 12, 18, 24, 30 and 36 months post-operatively. The authors compared the two groups only for the SF-36 general health and physical function scales, and the QLQ-CR38 defection problems and male sexual dysfunction scales. No clinically meaningful differences were found at any time point.

3.3 Other Comparisons

Of the five articles reporting other comparisons, two compared patients with and without anastomotic leakage (Ashburn et al. 2013; Riss et al. 2011), one compared rectal and colon cancer patients (Ohigashi et al. 2011), one compared curative, non-curative, and no surgery (You et al. 2011), and one examined the effect of an anal sphincter training (Laforest et al. 2012).

3.3.1 Anastomotic Leak

Both Ashburn et al. (2013) and Riss et al. (2011) compared a group of patients who experienced an anastomotic leakage with a group of controls. No clinically meaningful differences were found one year from surgery on the two component summary scores of the SF-36 (Ashburn et al. 2013) and after a median of 8.9 years (Riss et al. 2011) on the two component summary scores of the SF-12 (Ware et al. 1996).

3.3.2 Rectal Versus Colon Cancer

No clinically meaningful differences were found on the SF-36 and QLQ-C30 between patients with rectal and colon cancer at a median of 878 days from surgery by Ohigashi et al. (2011).

3.3.3 Other

You et al. (2011) longitudinally surveyed 52 locally recurrent rectal patients with the FACT-C (Ward et al. 1999). No clinically meaningful differences were found between patients treated with curative surgery, non-curative surgery or no surgery. Laforest et al. (2012) assessed the effect of anal sphincter training on patients' HRQoL at a median of 21.5 months after closure of the diverting stoma. The only benefit was found for the depression/self perception scale of the FIQL questionnaire, whereas no differences were found on the SF-36.

3.4 Observational Studies Without Group Comparisons

Out of the 19 articles that did not compare groups, nine used uni- or multi-variate analyses to compare the effect of one or more patients' characteristics on HRQoL (Kilic et al. 2012; Bloemen et al. 2009; Pucciarelli et al. 2010; Mahjoubi et al. 2012; Hoerske et al. 2010; Serpentini et al. 2011; Schmidt et al. 2010; Emmertsen 2013;

Zutshi et al. 2013), six focused on the analysis of HRQoL overtime (Neuman et al. 2011; Allaix et al. 2011; Pucciarelli et al. 2011; Theodoropoulos et al. 2013; Hennies et al. 2012; Planting et al. 2013) and four had a different focus (Hirche et al. 2010; Ristvedt and Trinkaus 2009; Carlsson et al. 2010; Caravati-Jouvenceaux et al. 2011).

3.4.1 Univariate or Multivariate Analyses

Kilic et al. (2012) measured HRQoL with the QLQ-C30 and QLQ-CR38 questionnaires, at a median of 5 years from treatment in patients who underwent adjuvant CRT. Multiple factors were considered, including: age, follow-up time, gender and type of surgery, with a focus on the latter. Compared to APR patients, LAR patients reported better global health status/QoL, emotional and social function, body image and future perspective, and lower symptoms related to fatigue, nausea and vomiting, pain, appetite loss, diarrhoea, financial difficulties, CT side effects and sexual dysfunction. Bloemen et al. (2009) evaluated HRQoL with the QLQ-C30 and QLQ-C38 in a consecutive series of patients, at a median of 36 months form surgery. Patients who suffered postoperative complications had slightly lower physical function, experienced more fatigue, pain and weight loss than those who did not. Patients with a stoma had better future perspectives and slightly less gastrointestinal symptoms, but also more male sexual dysfunction than those without a stoma. In a sample of stoma-free patients, Pucciarelli et al. (2010) assessed HRQoL with the QLQ-C30 and QLQ-CR38 questionnaires, at a median of 43 months from surgery. Univariate analyses were used to assess the impact of a series of clinical variables. The QLQ-C30 functional scales were negatively affected by bowel function-related covariates, whereas clinical factors were associated only with the future perspective and defecation problems scales of the QLQ-CR38. In a sample of Iranian patients with a stoma, Mahjoubi et al. (2012) compared males and females' scores on the QLQ-C30 and QLQ-CR38 at a median of 32 months from surgery. Compared to females, males had better physical function, body image, future perspectives, and sexual functioning and enjoyment, and less CT side effects, gastrointestinal symptoms and stoma-related problems, but also more micturition problems and weight loss. Hoerske et al. (2010) assessed QLQ-C30 functional scales and QLQ-CR38 scores at a median of 13 years from treatment, comparing patients depending on whether they underwent CRT, the tumour site and the need for a permanent stoma. CRT patients had worse role and social function, more defecation problems, stoma related problems, and male and female sexual dysfunction, but also better body image than those who did not undergo CRT. Compared with patients with a tumour in the upper or middle third of the rectum, those with a tumour in lower third of the rectum had worse role and social function, more defecation problems, and male sexual dysfunction, but also better body image and better future perspectives. Patients with a stoma had worse physical, role and social function, worse sexual enjoyment and more male sexual dysfunction, but also better body image, better future perspectives and less female sexual dysfunction. Serpentini et al. (2011) used multivariate

analysis to ascertain clinical and socio-demographic factors independently associated to well-being, measured with the PGWBI (Dupuy 1984), at a median of 68 months from surgery. General health was negatively affected by time from diagnosis and fecal urgency. Positive well-being resulted independently affected by time from diagnosis and occurrence of early major complications self-control was negatively associated with primary education and fecal urgency. Schmidt et al. (2010) measured HRQoL preoperatively, at 3, 6, 12 and 24 months, and compared males and females, different age groups and different surgical procedures (APR vs. AR). The QLQ-C30 was used; however, it is unclear what the authors refer to when reporting results referring to 'functional status' score. Emmertsen et al. (2013) grouped patients treated with sphincter preserving surgery depending on whether they suffered major anterior resection syndrome (LARS). The QLQ-C30 questionnaire was administered before treatment, and at 3 and 12 months after surgery or stoma closure. At 3 months, patients with major LARS had worse global health status/QoL, role and social function; they also experienced more fatigue and more constipation, but also less pain and less diarrhoea. On the contrary, at 12 months, they had better global health status/QoL, role and emotional function, less insomnia and less diarrhoea, while they also had worse social function and more fatigue. Zutshi et al. (2013) compared male and female two component summary scores of the SF-36 and found no differences.

3.4.2 HRQoL Change Overtime

HRQoL changes overtime were assessed by Neuman et al. (2011) in a sample of patients undergoing SPS with a temporary diverting stoma, using the QLQ-C30 and CR-38. Compared to preoperative scores, at stoma closure and at 6 months there were no differences in global health status/QoL, physical, role and social function, body image and gastrointestinal symptoms, whereas future perspectives increased. The other scales were not reported. Allaix et al. (2011) measured HRQoL preoperatively, 3 months, 1 and 5 years after surgery in a sample of patients treated with transanal endoscopic microsurgery (TEM) for extraperitoneal rectal cancer. Compared to preoperative scores, there were no clinically meaningful changes in QLQ-C30 and QLQL-CR38 scores. The mean general QoL score, measured with the EQ-5D visual analogue scale increased significantly at 1 and 5 years compared with preoperative values. Of the four domains of the FIQL questionnaire, no differences were found at 3 months, whereas depression/self perception and embarrassment increased significantly at 1 year and remained higher at 5 years, with an additional increase in the life style score. A series of pCRT patients were evaluated before pCRT, 2/3 weeks after pCRT, and at 6 and 12 months postoperatively by Pucciarelli et al. (2011). Relative to pre-treatment scores, no clinically meaningful changes were observed in QLQ-C30 and QLQ-CR38 scores except for an increase in male sexual dysfunction, which remained higher at each assessment time. Theodoropoulos et al. (2013) prospectively assessed patients treated with laparoscopic colectomy preoperatively, 1, 3, 6 and 12 months after surgery. Patients were personally interviewed using the SF-36, QLQ-C30, QLQ-CR29 and Gastrointestinal

QOL Index (GIQLI) (Eypasch et al. 1995). Compared to preoperative scores, at 1 month there was an improvement in emotional function and levels of anxiety, but a worsening in the global health status/QoL, physical function and role limitation due to physical problems. At 3 months, patients reported better general, emotional and mental health. At 6 months only emotional and mental health was better than preoperative scores, whereas at 12 months several differences were found. Patients had better scores on role limitations due to emotional problems, emotional function, (absence of) anxiety, emotional and mental health, physical function, and global GIQLI score. In a study focusing on the effect of testicular radiation dose, Hennies et al. (2012) assessed HRQoL with the QLQ-C30 and QLQ-CR38. Compared to pre-treatment scores, at 1 year patients reported worse physical, role and social function; worse body image, sexual functioning and enjoyment and increased symptoms, including fatigue, pain, dyspnoea, diarrhoea, financial difficulties, micturition problems, CT side effects, defecation problems and male sexual dysfunction, although future perspectives increased. Planting et al. (2013) used a telephone interview to assess the impact of TEM on HRQoL, measured with the QLQ-C30, QLQ-CR38 and FIQL. The overtime analysis, however, is unreliable, as preoperative scores were assessed retrospectively and biases could have occurred.

3.4.3 Other Focus

Hirche et al. (2010) reported on long-term outcomes of patients with a specific neosphincter reconstruction (perineal spiral cuff plasty) after APR for very low rectal cancer. Ristvedt and Trinkaus (2009) focused on the influence of trait anxiety, measured at the first follow-up visit after surgery, on HRQoL and post-traumatic stress symptoms 2–5 years after surgery. Carlsson et al. (2010) focused on the concerns expressed by stoma patients and how they change overtime. Additionally, HRQoL was measured and results were compared with population norms. Finally, the article by Caravati-Jouvenceaux et al. (2011) also focused on the comparison with healthy controls.

3.5 Comparison with Reference Data from Healthy Population

Out of 56 articles selected for this review, 12 made comparison with healthy subjects. Two articles compared patients' HRQoL with data from the general population at different time points. Carlson et al. (2010) used the 8 subscales of the SF-36 preoperatively and 1, 3 and 6 months postoperatively to compare stoma patients' scores to population norms. Preoperatively, patients had worse scores for: role limitations due to physical health and to emotional problems, social function and mental health. This difference remained clinically significant at 6 months only for role limitations due to physical health and social function. Caravati-Jovenceaux et al. (2011), using the SF-36 and QLQ-C30 questionnaires, compared three cohorts of rectal cancer patients ($n = 198$) with 5, 10 and 15 years of follow-up

with a random sample of the general population ($n = 413$). Clinically meaningful differences were found only for diarrhoea, which was worse in all cohorts of patients. Patients with 10 years of follow-up also showed more constipation and lower social function than the general population.

Most of the other studies comparing patients with the general population focussed on (neo)adjuvant therapies. Thong et al. (2011) compared a group of patients undergoing surgery-only and a group of patients undergoing pRT followed by surgery with the reference data for the SF-36 questionnaires. Additionally, data concerning the sexuality subscale of the QLQ-CR38 were collected from the general population to allow a comparison of sexual functioning as well. While no clinically meaningful differences were found in the SF-36 scores, at a median of 4 years form surgery, both groups of patients showed impaired sexual functioning and reduced sexual enjoyment. Bruheim et al. (2010) compared irradiated and non-irradiated patients with the general population on the functional scales of the QLQ-C30. At a median time of 4.8 years from surgery, the only difference was found for irradiated patients who had worse social function than the general population. Compared to the general population, at a median time from surgery of 5.6 years, patients who underwent either long course pCRT or short course pRT had significantly worse role and emotional functioning, more diarrhoea, more constipation, and more financial difficulties (Guckenbergen et al. 2013). Similarly, Kripp et al. (2012) reported that both patients who underwent conventional or intensified pCRT had worse role and social function and more diarrhoea relative to the general population, and Braendengen et al. (2012) found that patients who underwent pCRT or pRT had worse social functioning and more diarrhoea than the general population at a median time from surgery of 6 years. pCRT patients reported worse constipation and diarrhoea than the general population also in the study by Pucciarelli et al. (2010), although no other differences were found on the QLQ-C30. Konanz et al. (2013) compared three groups of patients with the general population using the QLQ-C30 at a median time from surgery of 4.9 years. All patients showed worse role and social functioning, more constipation, diarrhoea and financial difficulties. Other clinically meaningful differences compared to the general population were found for: global health status (reduced in patients who underwent ISR or APR); physical function (reduced in patients who underwent LAR or APR); cognitive function (reduced in ISR and LAR patients); dyspnoea (increased in ISR and APR patients); fatigue and insomnia (both increased in LAR and APR patients). Orsini et al. (2013) stratified patients with and without a stoma in two age groups and compared their scores with the reference data for the SF-36 questionnaire and the sexuality subscale of the QLQ-CR38. For patients younger than 70, no clinically meaningful differences were found in the SF-36 scores, at a median of 3.4 years form surgery, but both stoma and non-stoma patients showed impaired sexual functioning and reduced sexual enjoyment. Patients older than 70 reported worse sexual enjoyment, but no differences in sexual functioning relative to healthy controls. Stoma patients showed a decreased physical function and non-stoma patients showed increased role limitations due to physical problems. Austin et al. (2010) compared patients who underwent pelvic exenteration to the general

population at a median time of 3.9 years from surgery. Of the two component summary scores of the SF-36 questionnaire, the physical one was significantly worse in patients, whereas the mental score did not differ. Using the PGWBI, after a median time of 68 months, Serpentini et al. (2011) found that patients aged between 65 and 74 years had statistically significant better scores on general health, positive well-being, vitality, anxiety, depressed mood and global index score.

4 Discussion and Conclusion

While the traditional outcomes in rectal cancer research have been overall, disease-free and local recurrence-free survival, in the last decades there has been growing interest in the field of QoL, which is now considered a relevant outcome in clinical trials (Sprangers et al. 1995; Renner et al. 1999; Dunn et al. 2003). Because of the aggressiveness of multimodality approaches, the potentially severe consequences on bowel function, faecal continence, and sexual function, and the high rate of surgical morbidity, the diagnosis and the treatment of rectal cancer may have a significant impact on patients' HRQoL.

The aim of this review was to retrieve, classify and analyse the articles published from January 2009 to November 2013, focusing on HRQoL after surgery in patients with rectal cancer. Fifty-six articles met the inclusion criteria.

As summarised in the Table 1, the majority of the articles focused on the comparison between surgical treatments (37.5 %) and, particularly, on the impact of having a stoma on HRQoL, or on the impact of multimodality treatment on HRQoL (19.6 %). The comparison between patients and the normal population was a principal end point or a secondary aim in twelve (21.4 %) studies. From a methodological point of view, the vast majority of studies (83.9 %) were observational, and only 10.7 % were performed within prospective randomised trials. Two third of the articles were controlled, and more than 50 % were cross-sectional. About 60 % of the studies included more than 100 patients, and in half of the articles, the proportion of patients who had received a neoadjuvant treatment, either pRT or pCRT, was more than 60 %. The most frequent instruments used were the EORTC QLQ-C30, its colorectal module QLQ-CR38 and the MOS SF-36, which were used in 64.3, 44.6 and 28.6 % of the studies, respectively.

Our review highlighted the heterogeneity of design characteristics, and caution should be used in interpreting findings considering methodological limitations. The ideal study on HRQoL should be: prospective, longitudinal, with a baseline assessment prior to any treatment, randomised (when comparing two or more treatments), controlled, with an adequate sample size, powered to detect the expected changes on relevant HRQoL subscales, and HRQoL should be assessed with validated and established questionnaires. Less than 10 % of the studies included in this review presented these characteristics (Austin et al. 2010; Kang et al. 2010; Andersson et al. 2013; Doeksen et al. 2012; Braendengen et al. 2012).

In addition to differences between topics, aims and methodology, the comparison of findings from different studies has also been limited by factors related to the quality of the reporting of HRQoL. For instance, even when using the same instruments, in some cases the authors did not fully report raw data making it difficult to fully judge the presence of clinically meaningful differences or, albeit in fewer cases, the findings from some instruments were not reported. This is in line with previous work showing that the quality of reporting HRQoL data is poor and needs improvement (Brundage et al. 2011). For example, only 14 % of randomised controlled trials including HRQoL data met simultaneously four essential minimal quality indicators, i.e. reporting evidence for the validity of the instrument, stating HRQoL hypothesis, reporting how missing data were handled, and interpreting and discussing HRQoL findings. This issue is especially relevant when considering that findings from different studies have to be aggregated when informing decision-making at all levels (Sutherland and Till 1993; Stiggelbout and de Haes 2001).

Taking into consideration these concerns, we can summarise the main findings in the area of the three most frequently investigated comparisons, namely between surgical treatments, between irradiated and not-irradiated patients and between patients and the general population.

The most frequent comparisons between surgical treatments were between SPSs and non-restorative resections, and between stoma and stoma-free patients. Living with a permanent stoma has for long time been thought to have a negative impact on patients' HRQoL. This conviction has been questioned by the findings of our review, as well as by previous reviews (Pachler and Wille-Jørgensen 2005; Cornish et al. 2007). The findings about the comparison between stoma and no-stoma and between SPSs and non-restorative resections were often disparate and are difficult to summarise. Out of the 13 articles on this topic included in our review (Campos-Lobato et al. 2011; Fischer et al. 2010; Austin et al. 2010; Celasin et al. 2011; Varpe et al. 2011; Konanz et al. 2013; Mrak et al. 2011; How et al. 2012; Kasparek et al. 2011; Yau et al. 2009; Orsini et al. 2013; Bossema et al. 2011; Krouse et al. 2009), four did not find clinically meaningful differences (Campos-Lobato et al. 2011; Fischer et al. 2010; Austin et al. 2010; Celasin et al. 2011). The most frequently impacted HRQoL scales were: social function (8 articles), sexual functioning and male sexual dysfunction (5 articles each), global health status, physical functioning, body pain, diarrhoea and fatigue (4 articles each). Global health status and social functioning were always found to be better in the group without stoma or in the group treated with SPS. Additionally, four of the five studies reporting differences on sexual functioning or male sexual dysfunction favoured stoma-free patients or patients treated with sphincter-preserving interventions. In line with the Cochrane review (Pachler and Wille-Jørgensen 2005) and a previous meta-analysis (Cornish et al. 2007), these findings support the thesis that having a stoma has not a clear negative impact on HRQoL, although none of the articles analysed was clearly in favour of non-restorative surgeries or stoma creation. However, an important point to consider is that the alternative to non-restorative surgery is ULAR or ISR with low colorectal or CAA, often preceded by radiotherapy or chemoradiotherapy. It is

known that these procedures are associated with a high rate of morbidity, including anastomotic leakage, and severe consequences on bowel function and faecal continence. Thus, it is not surprising that many HRQoL scores of stoma-free patients are not dissimilar from those of patients with a permanent stoma.

Other factors that may contribute to the lack of a clear difference between the two groups are related to the ethnic, cultural, economic, stoma care and educational factors (Pachler and Wille-Jørgensen 2005), as well as to proper information, especially about patients' adaptation to stoma and changing concerns overtime (Carlsson et al. 2010). Therefore, when possible, the choice between sphincter- or non-SPS should not be preconceived, should be individualised and should take into account fully informed patient's preferences.

Remaining in the surgical domain, the increasing use of laparoscopy also in the treatment of rectal cancer calls for assessments of whether its use has advantages over the use of open surgical approaches. On this topic, three of the four studies included in this review assessed more than 100 patients. Two of them were randomised, one included all patients randomised in the COREAN trial (Kang et al. 2010) and the other included a subgroup of patients enrolled in the COLOR II trial (Andersson et al. 2013). Both randomised trials found no clinically meaningful differences at any time point assessed. The other non-randomised study found differences concerning body image, which was better in the laparoscopic group at 1 week, 3 months and 1 year after surgery. The sample size, design and ease of comparison between studies using the same HRQoL instruments strongly support the equivalence between the two techniques.

Another frequently addressed topic is the effect of multimodality therapies. The comparison between irradiated and non-irradiated patients was reported in six studies (Canda et al. 2010; Peng et al. 2011; Thong et al. 2011; Bruheim et al. 2010; Kasparek et al. 2012; Parc et al. 2009) and four studies assessed the effect of adding chemotherapy to radiation therapy (Parc et al. 2009; Braendengen et al. 2012; Tiv et al. 2010; Guckenberger et al. 2013). Two studies found no differences between irradiated and non-irradiated patients (Canda et al. 2010; Parc et al. 2009), the others found some differences, favouring non-irradiated patients in the areas of bowel function (2 studies), sexuality (2 studies) and role and social function (1 study each). However, it should be noted that the two groups had often differences in clinical characteristics at baseline. One of the studies assessing the additional effect of CT found no differences (Braendengen et al. 2012), two studies found a negative impact on bowel function (Tiv et al. 2010; Guckenberger et al. 2013), one on social function (Tiv et al. 2010) and one found an effect on mental scores and a temporary effect on physical scores (Parc et al. 2009). These findings are in line with our previous work, suggesting that the most impacted HRQoL dimensions are role and social function and symptoms related to bowel and sexual function (Gavaruzzi et al. 2013; Gavaruzzi et al. 2014).

In total, twelve articles reported on comparisons between patients' and general population's HRQoL scores. The majority (9 out of 11) of the articles that reported on scales assessing global or general health or QoL (QLQ-C30, SF-36, PGWBI) found no differences between patients and the general population (Orsini et al.

2013; Thong et al. 2011; Bruheim et al. 2010; Braendengen et al. 2012; Kripp et al. 2012; Guckenberger et al. 2013; Pucciarelli et al. 2010; Carlsson et al. 2010; Caravati-Jouvenceaux et al. 2011), whereas the other two articles reported contrasting findings, one favouring the general population (Konanz et al. 2013) and one favouring patients (Serpentini et al. 2011). In terms of HRQoL functions, patients were found to have worse scores that the general population on social function (6 out of 10 articles), role function (5 out of 10 articles), physical function (3 out of 11 articles) and emotional function (1 out of 7 articles). In terms of symptoms scales, the most frequently reported differences concerned bowel function (including diarrhoea and constipation, 6 out of 6 articles) and sexual function (assessed with the two functional scales of the QLQ-CR38, 2 out of 2 articles). The finding that general HRQoL scores are similar between patients and healthy controls is in line with previous reviews (Gavaruzzi et al. 2013; Gavaruzzi et al. 2014). In terms of instruments used to assess HRQoL, most studies used the SF-36 or QLQ-C30 questionnaire. While the former is a generic instrument, the latter is a specific instrument designed for all cancer patients and includes also symptoms scales. Given that the most consistent difference between patients and the general population concerns bowel symptoms, our findings support the use of the QLQ-C30 rather than the SF-36 questionnaire. Additionally, two studies also compared patients and healthy controls on the sexual functional scales of the QLQ-CR38, both finding a lower function in patients.

When planning studies comparing patients and the general population or comparing different treatments, particular attention should be paid to the use of instruments that are likely to detect potential differences and to the calculation of sample size based on relevant subscales.

In conclusion, there is no clear evidence that HRQoL is better in stoma-free patients compared with those with a permanent stoma. The choice between SSP or non-SSP should be individualised, not preconceived and should take into account the fully informed patient's preferences. Laparoscopic and open surgery are equivalent in terms of HRQoL. While there is no strong evidence that neoadjuvant therapy has a negative impact on global QOL, our findings suggest that preoperative irradiation do have a negative impact on some scales.

References

Aaronson NK, Ahmedzai S, Bergam B, Bullinger M, Cull A, Duez NJ et al (1993) European Organisation for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85(5):365–376

Allaix ME, Rebecchi F, Giaccone C, Mistrangelo M, Morino M (2011) Long-term functional results and quality of life after transanal endoscopic microsurgery. Br J Surg 98(11):1635–1643. doi:10.1002/bjs.7584

Andersson J, Angenete E, Gellerstedt M, Angerås U, Jess P, Rosenberg J et al (2013) Health-related quality of life after laparoscopic and open surgery for rectal cancer in a randomized trial. Br J Surg 100(7):941–949. doi:10.1002/bjs.9144

Ashburn JH, Stocchi L, Kiran RP, Dietz DW, Remzi FH (2013) Consequences of anastomotic leak after restorative proctectomy for cancer: effect on long-term function and quality of life. Dis Colon Rectum 56(3):275–280. doi:10.1097/DCR.0b013e318277e8a5

Austin KK, Young JM, Solomon MJ (2010) Quality of life of survivors after pelvic exenteration for rectal cancer. Dis Colon Rectum 53(8):1121–1126. doi:10.1007/DCR.0b013e3181e10c46

Barisic G, Markovic V, Popovic M, Dimitrijevic I, Gavrilovic P, Krivokapic Z (2011) Function after intersphincteric resection for low rectal cancer and its influence on quality of life. Colorectal Dis 13(6):638–643. doi:10.1111/j.1463-1318.2010.02244.x

Baxter NN, Novotny PJ, Jacobson T, Maidl LJ, Sloan J, Young-Fadok TM (2006) A stoma quality of life scale. Dis Colon Rectum 49:205–212. doi:10.1007/s10350-005-0275-6

Bloemen JG, Visschers RG, Truin W, Beets GL, Konsten JL (2009) Long-term quality of life in patients with rectal cancer: association with severe postoperative complications and presence of a stoma. Dis Colon Rectum 52(7):1251–1258. doi:10.1007/DCR.0b013e3181a74322

Bossema ER, Seuntiëns MW, Marijnen CA, Baas-Thijssen MC, van de Velde CJ, Stiggelbout AM (2011) The relation between illness cognitions and quality of life in people with and without a stoma following rectal cancer treatment. Psychooncology 20(4):428–434. doi:10.1002/pon.1758

Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L et al (2006) Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 355:114–123. doi:10.1056/NEJMoa060829

Brændengen M, Tveit KM, Berglund Å, Birkemeyer E, Frykholm G, Påhlman L et al (2008) Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectables rectal cancer. J Clin Oncol 26:3687–3694. doi:10.1200/JCO.2007.15.3858

Braendengen M, Tveit KM, Hjermstad MJ, Johansson H, Berglund Å, Brandberg Y et al (2012) Health-related quality of life (HRQoL) after multimodal treatment for primarily non-resectable rectal cancer. Long-term results from a phase III study. Eur J Cancer 48(6):813–819. doi:10.1016/j.ejca.2011.06.035

Bruheim K, Guren MG, Skovlund E, Hjermstad MJ, Dahl O, Frykholm G et al (2010) Late side effects and quality of life after radiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys 76(4):1005–1011. doi:10.1016/j.ijrobp.2009.03.010

Brundage M, Bass B, Davidson J, Queenan J, Bezjak A, Ringash J et al (2011) Patterns of reporting health-related quality of life outcomes in randomized clinical trials: implications for clinicians and quality of life researchers. Qual Life Res 20(5):653–664. doi:10.1007/s11136-010-9793-3

Brundage M, Blazeby J, Revicki D, Bass B, de Vet H, Duffy H et al (2013) Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. Qual Life Res 22(6):1161–1175. doi:10.1007/s11136-012-0252-1

Campos-Lobato LF, Alves-Ferreira PC, Lavery IC, Kiran RP (2011) Abdominoperineal resection does not decrease quality of life in patients with low rectal cancer. Clinics (Sao Paulo) 66(6):1035–1040

Canda AE, Terzi C, Gorken IB, Oztop I, Sokmen S, Fuzun M (2010) Effects of preoperative chemoradiotherapy on anal sphincter functions and quality of life in rectal cancer patients. Int J Colorectal Dis 25(2):197–204. doi:10.1007/s00384-009-0807-y

Caravati-Jouvenceaux A, Launoy G, Klein D, Henry-Amar M, Abeilard E, Danzon A et al (2011) Health-related quality of life among long-term survivors of colorectal cancer: a population-based study. Oncologist 16(11):1626–1636. doi:10.1634/theoncologist.2011-0036

Carlsson E, Berndtsson I, Hallén AM, Lindholm E, Persson E (2010) Concerns and quality of life before surgery and during the recovery period in patients with rectal cancer and an ostomy. J Wound Ostomy Continence Nurs 37(6):654–661. doi:10.1097/WON.0b013e3181f90f0c

Celasin H, Karakoyun R, Yılmaz S, Elhan AH, Erkek B, Kuzu MA (2011) Quality of life measures in Islamic rectal carcinoma patients receiving counselling. Colorectal Dis 13(7):e170–e175. doi:10.1111/j.1463-1318.2011.02649.x

City of Hope/Beckman Research Institute Pain Resource Center Research Instruments. http://prc.coh.org/pdf/Quality%20of%20Life%20Ostomy.pdf

Cornish JA, Tilney HS, Heriot AG, Lavery IC, Fazio VW (2007) Tekkis PP. A meta-analysis of quality of life for abdominoperineal excision of rectum versus anterior resection for rectal cancer. Ann Surg Oncol 14(7):2056–2068. doi:10.1245/s10434-007-9402-z

Detsky AS, Naglie IG (1990) A clinician's guide to cost-effectiveness analysis. Ann Intern Med 113(2):147–154

Doeksen A, Bakx R, Vincent A, van Tets WF, Sprangers MA, Gerhards MF et al (2012) J-pouch vs side-to-end coloanal anastomosis after preoperative radiotherapy and total mesorectal excision for rectal cancer: a multicentre randomized trial. Colorectal Dis 14(6):705–713. doi:10.1111/j.1463-1318.2011.02725.x

Dumont F, Ayadi M, Goéré D, Honoré C, Elias D (2013) Comparison of fecal continence and quality of life between intersphincteric resection and abdominoperineal resection plus perineal colostomy for ultra-low rectal cancer. J Surg Oncol 108(4):225–229. doi:10.1002/jso.23379

Dunn J, Lynch B, Aitken J, Leggett B, Pakenham K, Newman B (2003) Quality of life and colorectal cancer: a review. Aust N Z J Public Health 27(1):41–53

Dupuy HJ (1984) The psychological general well being (PGWB) index. In: Wenger NK, Mattson ME, Furberg CD, Elinson J (eds) Assessment of quality of life in clinical trials of cardiovascular therapies. Le Jacq Publishing Inc, New York, pp 170–183

Emmertsen KJ, Laurberg S (2013) Rectal cancer function study group. Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. Br J Surg 100(10):1377–1387. doi:10.1002/bjs.9223

Eypasch E, Williams JI, Wood-Dauphinee S, Ure BM, Schmulling C, Neugebauer E et al (1995) Gastrointestinal quality of life index: development, validation and application of a new instrument. Br J Surg 82:216–222. doi:10.1002/bjs.1800820229

Fazio VW, O'Riordain MG, Lavery IC, Church JM, Lau P, Strong SA et al (1999) Long-term functional outcome and quality of life after stapled restorative proctocolectomy. Ann Surg 230:575–584. doi:10.1097/00000658-199910000-00013

Fazio VW, Zutshi M, Remzi FH, Parc Y, Ruppert R, Fürst A et al (2007) A randomized multicentre trial to compare long-term functional outcome, quality of life, and complications of surgical procedures for low rectal cancers. Ann Surg 246:4818. doi:10.1097/SLA.0b013e3181485617

Fischer A, Tarantino I, Warschkow R, Lange J, Zerz A, Hetzer FH (2010) Is sphincter preservation reasonable in all patients with rectal cancer? Int J Colorectal Dis 25(4):425–432. doi:10.1007/s00384-010-0876-y

Gavaruzzi T, Giandomenico F, Pucciarelli S (2013) Quality of Life and Function After Chemoradiation for Rectal Cancer: a systematic review of recent publications. Curr Colorectal Cancer Rep. 9(2):157–167

Gavaruzzi T, Lotto L, Giandomenico F, Perin A, Pucciarelli S (2014) Patient reported outcomes after neoadjuvant therapy for rectal cancer: a systematic review. Expert Rev Anticancer Ther. doi: 10.1586/14737140.2014.911090

Guckenberger M, Saur G, Wehner D, Thalheimer A, Kim M, Germer CT et al (2013) Long-term quality-of-life after neoadjuvant short-course radiotherapy and long-course radiochemotherapy for locally advanced rectal cancer. Radiother Oncol 108(2):326–330. doi:10.1016/j.radonc.2013.08.022

Gullà N, Trastulli S, Boselli C, Cirocchi R, Cavaliere D, Verdecchia GM et al (2011) Ghost ileostomy after anterior resection for rectal cancer: a preliminary experience. Langenbecks Arch Surg 396(7):997–1007. doi:10.1007/s00423-011-0793-8

Guyatt GH, Feeny DH, Patrick DL (1993) Measuring health-related quality of life. Ann Intern Med 118(8):622–629

Hays RD, Sherbourne CD, Mazel RM (1993) The RAND 36-item health survey 1.0. Health economics 2(3):217–227. doi: 10.1002/hec.4730020305

Hennies S, Wolff HA, Jung K, Rave-Fränk M, Gaedcke J, Ghadimi M et al (2012) Testicular radiation dose after multimodal curative therapy for locally advanced rectal cancer. Influence on hormone levels, quality of life, and sexual functioning. Strahlenther Onkol 188(10): 926–932

Hirche C, Mrak K, Kneif S, Mohr Z, Slisow W, Hünerbein M et al (2010) Perineal colostomy with spiral smooth muscle graft for neosphincter reconstruction following abdominoperineal resection of very low rectal cancer: long-term outcome. Dis Colon Rectum 53(9):1272–1279. doi:10.1007/DCR.0b013e3181e74c1f

Hoerske C, Weber K, Goehl J, Hohenberger W, Merkel S (2010) Long-term outcomes and quality of life after rectal carcinoma surgery. Br J Surg 97(8):1295–1303. doi:10.1002/bjs.7105

Hofheinz R, Wenz Z, Post S et al (2011) Capecitabine (Cape) versus 5-fluorouracil (5-FU) -based (neo)adjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC): long-term results of a randomized, phase III trial. J Clin Oncol 29(Suppl.):3504 [abstr.]

Horisberger K, Treschl A, Mai S, Barreto-Miranda M, Kienle P, Ströbel P et al (2009) Cetuximab in combination with capecitabine, irinotecan, and radiotherapy for patients with locally advanced rectal cancer: results of a Phase II MARGIT trial. Int Radiat Oncol Biol Phys 74:1487–1493. doi:10.1016/j.ijrobp.2008.10.014

How P, Stelzner S, Branagan G, Bundy K, Chandrakumaran K, Heald RJ et al (2012) Comparative quality of life in patients following abdominoperineal excision and low anterior resection for low rectal cancer. Dis Colon Rectum 55(4):400–406. doi:10.1097/DCR.0b013e3182444fd1

Kang SB, Park JW, Jeong SY, Nam BH, Choi HS, Kim DW et al (2010) Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial. Lancet Oncol 11(7):637–645. doi:10.1016/S1470-2045(10)70131-5

Kasparek MS, Hassan I, Cima RR, Larson DR, Gullerud RE, Wolff BG (2011) Quality of life after coloanal anastomosis and abdominoperineal resection for distal rectal cancers: sphincter preservation vs quality of life. Colorectal Dis 13(8):872–877. doi:10.1111/j.1463-1318.2010.02347.x

Kasparek MS, Hassan I, Cima RR, Larson DR, Gullerud RE, Wolff BG (2012) Long-term quality of life and sexual and urinary function after abdominoperineal resection for distal rectal cancer. Dis Colon Rectum 55(2):147–154. doi:10.1097/DCR.0b013e31823d2606

Kilic D, Yalman D, Aksu G, Atasoy BM, Igdem S, Dincbas FO et al (2012) Impact of adjuvant chemoradiotherapy for rectal cancer on the long-term quality of life and late side effects: a multicentric clinical evaluation by the Turkish Oncology Group. Asian Pac J Cancer Prev 13(11):5741–5746

Konanz J, Herrle F, Weiss C, Post S, Kienle P (2013) Quality of life of patients after low anterior, intersphincteric, and abdominoperineal resection for rectal cancer–a matched-pair analysis. Int J Colorectal Dis 28(5):679–688. doi:10.1007/s00384-013-1683-z

Kripp M, Wieneke J, Kienle P, Welzel G, Brade J, Horisberger K et al (2012) Intensified neoadjuvant chemoradiotherapy in locally advanced rectal cancer—impact on long-term quality of life. Eur J Surg Oncol 38(6):472–477. doi:10.1016/j.ejso.2012.02.002

Krouse RS, Herrinton LJ, Grant M, Wendel CS, Green SB, Mohler MJ et al (2009) Health-related quality of life among long-term rectal cancer survivors with an ostomy: manifestations by sex. J Clin Oncol 27(28):4664–4670. doi:10.1200/JCO.2008.20.9502

Laforest A, Bretagnol F, Mouazan AS, Maggiori L, Ferron M, Panis Y (2012) Functional disorders after rectal cancer resection: does a rehabilitation programme improve anal continence and quality of life? Colorectal Dis 14(10):1231–1237. doi:10.1111/j.1463-1318.2012.02956.x

Leplege A, Hunt S (1997) The problem of quality of life in medicine. JAMA 278(1):47–50

Li J, Chen R, Xu YQ, Wang XC, Zheng S, Zhang SZ et al (2010) Impact of a laparoscopic resection on the quality of life in rectal cancer patients: results of 135 patients. Surg Today 40(10):917–922. doi:10.1007/s00595-009-4156-9

Loomes G, McKenzie L (1989) The use of QALYs in health care decision making. Soc Sci Med 28(4):299–308

Mahjoubi B, Mirzaei R, Azizi R, Jafarinia M, Zahedi-Shoolami L (2012) A cross-sectional survey of quality of life in colostomates: a report from Iran. Health Qual Life Outcomes 10:136. doi:10.1186/1477-7525-10-136

Marquis P, Marrel A, Jambon B (2003) Quality of life in patients with stomas: the Montreux study. Ostomy/Wound Manage 49:48–55

Mrak K, Jagoditsch M, Eberl T, Klingler A, Tschmelitsch J (2011) Long-term quality of life in pouch patients compared with stoma patients following rectal cancer surgery. Colorectal Dis 13(12):e403–e410. doi:10.1111/j.1463-1318.2011.02740.x

National Comprehensive Cancer Network, Inc. (updated) NCCN guidelines version 4.2013: rectal cancer. http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

Neuman HB, Patil S, Fuzesi S, Wong WD, Weiser MR, Guillem JG et al (2011) Impact of a temporary stoma on the quality of life of rectal cancer patients undergoing treatment. Ann Surg Oncol 18(5):1397–1403. doi:10.1245/s10434-010-1446-9

Ohigashi S, Hoshino Y, Ohde S, Onodera H (2011) Functional outcome, quality of life, and efficacy of probiotics in postoperative patients with colorectal cancer. Surg Today 41(9):1200–1206. doi:10.1007/s00595-010-4450-6

Orsini RG, Thong MS, van de Poll-Franse LV, Slooter GD, Nieuwenhuijzen GA, Rutten HJ et al (2013) Quality of life of older rectal cancer patients is not impaired by a permanent stoma. Eur J Surg Oncol 39(2):164–170. doi:10.1016/j.ejso.2012.10.005

Osoba D, Rodrigues G, Myles J, Zee B, Pater J (1998) Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 16(1):139–144

Pachler J, Wille-Jørgensen P (2005) Quality of life after rectal resection for cancer, with or without permanent colostomy. Cochrane Database Syst Rev 2. doi:10.1002/14651858.CD004323.pub4

Parc Y, Zutshi M, Zalinski S, Ruppert R, Fürst A, Fazio VW (2009) Preoperative radiotherapy is associated with worse functional results after coloanal anastomosis for rectal cancer. Dis Colon Rectum 52(12):2004–2014. doi:10.1007/DCR.0b013e3181beb4d8

Peng J, Shi D, Goodman KA, Goldstein D, Xiao C, Guan Z et al (2011) Early results of quality of life for curatively treated rectal cancers in Chinese patients with EORTC QLQ-CR29. Radiat Oncol 6:93. doi:10.1186/1748-717X-6-93

Planting A, Phang PT, Raval MJ, Brown CJ (2013) Transanal endoscopic microsurgery: impact on fecal incontinence and quality of life. Can J Surg 56(4):243–248

Prieto L, Thorsen H, Juul K (2005) Development and validation of a quality of life questionnaire for patients with colostomy or ileostomy. Health Qual Life Outcomes 3(1):62. doi:10.1186/1477-7525-3-62

Pucciarelli S, Del Bianco P, Efficace F, Toppan P, Serpentini S, Friso ML et al (2010) Health-related quality of life, faecal continence and bowel function in rectal cancer patients after chemoradiotherapy followed by radical surgery. Support Care Cancer 18(5):601–608. doi:10.1007/s00520-009-0699-y

Pucciarelli S, Del Bianco P, Efficace F, Serpentini S, Capirci C, De Paoli A et al (2011) Patient-reported outcomes after neoadjuvant chemoradiotherapy for rectal cancer: a multicentre prospective observational study. Ann Surg 253(1):71–77. doi:10.1097/SLA.0b013e3181fcb856

Rabin R, de Charro F (2001) EQ-5D: a measure of health status from the EuroQol Group. Ann Med 33:337–343

Renner K, Rosen HR, Novi G, Hölbling N, Schiessel R (1999) Quality of life after surgery for rectal cancer. Dis Colon Rectum 42(9):1160–1167

Riss S, Stremitzer S, Riss K, Mittlböck M, Bergmann M, Stift A (2011) Pelvic organ function and quality of life after anastomotic leakage following rectal cancer surgery. Wien Klin Wochenschr 123(1–2):53–57. doi:10.1007/s00508-010-1514-y

Ristvedt SL, Trinkaus KM (2009) Trait anxiety as an independent predictor of poor health-related quality of life and post-traumatic stress symptoms in rectal cancer. Br J Health Psychol 14(4):701–715. doi:10.1348/135910708X400462

Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG et al (2000) Fecal incontinence quality of life scale: quality of life instrument for patients with fecal incontinence. Dis Colon Rectum 43(1):9–16. doi:10.1007/BF02237236

Schmidt C, Daun A, Malchow B, Küchler T (2010) Sexual impairment and its effects on quality of life in patients with rectal cancer. Dtsch Arztebl Int 107(8):123–130. doi:10.3238/arztebl.2010.0123

Schumacher M, Olschewski M, Schulgen G (1991) Assessment of quality of life in clinical trials. Stat Med 10(12):1915–1930

Sebag-Montefiore D, Stephens RJ, Steel R, Monson J, Grieve R, Khanna S et al (2009) Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC CTG C016): a multicentre randomised trial. Lancet 373:811–820. doi:10.1016/S0140-6736(09)60484-0

Serpentini S, Del Bianco P, Alducci E, Toppan P, Ferretti F, Folin M et al (2011) Psychological well-being outcomes in disease-free survivors of mid-low rectal cancer following curative surgery. Psychooncology 20(7):706–714. doi:10.1002/pon.1763

Spielberger CD, Gorsuch RL, Lushene RE (1970) Manual for the state-trait anxiety inventory. Consulting Psychologists Press, Palo Alto

Sprangers MA, Taal BG, Aaronson NK, Te Velde A (1995) Quality of life in colorectal cancer. Dis Colon Rectum 38(4):361–369

Sprangers M, Te Velde A, Aaronson N (1999) The construction and testing of the EORTC colorectal cancer-specific quality of life questionnaire module. (QLQ-CR38). Eur J Cancer 35(2):238–247

Stephens RJ, Thompson LC, Quirke P, Steele R, Grieve R, Couture J et al (2010) Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the medical research council CR07/national cancer institute of Canada clinical trials group C016 randomized clinical trial. J Clin Oncol 28(27):4233–4239. doi:10.1200/JCO.2009.26.5264

Stiggelbout AM, de Haes JC (2001) Patient preference for cancer therapy: an overview of measurement approaches. J Clin Oncol 19(1):220–230

Sutherland HJ, Till JE (1993) Quality of life assessments and levels of decision making: differentiating objectives. Qual Life Res 2(4):297–303

Theodoropoulos GE, Karantanos T, Stamopoulos P, Zografos G (2013) Prospective evaluation of health-related quality of life after laparoscopic colectomy for cancer. Tech Coloproctol 17(1):27–38. doi:10.1007/s10151-012-0869-7

Thong MS, Mols F, Lemmens VE, Rutten HJ, Roukema JA, Martijn H et al (2011) Impact of preoperative radiotherapy on general and disease-specific health status of rectal cancer survivors: a population-based study. Int J Radiat Oncol Biol Phys 81(3):e49–e58. doi:10.1016/j.ijrobp.2010.12.030

Tiv M, Puyraveau M, Mineur L, Calais G, Maingon P, Bardet E et al (2010) Long-term quality of life in patients with rectal cancer treated with preoperative (chemo)-radiotherapy within a randomized trial. Cancer Radiother 14(6–7):530–534. doi:10.1016/j.canrad.2010.06.017

Varpe P, Huhtinen H, Rantala A, Salminen P, Rautava P, Hurme S et al (2011) Quality of life after surgery for rectal cancer with special reference to pelvic floor dysfunction. Colorectal Dis 13(4):399–405. doi:10.1111/j.1463-1318.2009.02165.x

Vaughan-Shaw PG, Cheung T, Knight JS, Nichols PH, Pilkington SA, Mirnezami AH (2012) A prospective case-control study of extralevator abdominoperineal excision (ELAPE) of the rectum versus conventional laparoscopic and open abdominoperineal excision: comparative analysis of short-term outcomes and quality of life. Tech Coloproctol 16(5):355–362. doi:10.1007/s10151-012-0851-4

Ward WL, Hahn EA, Mo F, Hernandez L, Tulsky DS, Cella D (1999) Reliability and validity of the functional assessment of cancer therapy-colorectal (FACT-C) quality of life instrument. Qual Life Res 8:181–195. doi:10.1016/j.jpainsymman.2004.12.009

Ware JE Jr, Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Med Care 30(6):473–483

Ware J Jr, Kosinski M, Keller SD (1996) A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 34(3):220–233. doi:10.1097/00005650-199603000-00003

Whistance RN, Conroy T, Chie W, Costantini A, Sezer O, Koller M et al (2009) European organisation for research and treatment of cancer quality of life group. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. Eur J Cancer 45(17):3017–3026. doi:10.1016/j.ejca.2009.08.014

WHO (1946) Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19–22 June, 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no 2, p 100) and entered into force on 7 April 1948

WHOQoL Group (1993) Measuring quality of life: the development of a world health organisation quality of life instrument (WHOQoL). WHO, Geneva

Willeke F, Horisberger K, Kraus-Tiefenbacher U, Wenz F, Leitner A, Hochhaus A et al (2007) A phase II study of capecitabine and irinotecan in combination with concurrent pelvic radiotherapy (CapIri-RT) as neoadjuvant treatment of locally advanced rectal cancer. Br J Cancer 96:912–917. doi:10.1038/sj.bjc.6603645

Yau T, Watkins D, Cunningham D, Barbachano Y, Chau I, Chong G (2009) Longitudinal assessment of quality of life in rectal cancer patients with or without stomas following primary resection. Dis Colon Rectum 52(4):669–677. doi:10.1007/DCR.0b013e31819eb970

You YN, Habiba H, Chang GJ, Rodriguez-bigas MA, Skibber JM (2011) Prognostic value of quality of life and pain in patients with locally recurrent rectal cancer. Ann Surg Oncol 18(4):989–996. doi:10.1245/s10434-010-1218-6

Zutshi M, Hull T, Shedda S, Lavery I, Hammel J (2013) Gender differences in mortality, quality of life and function after restorative procedures for rectal cancer. Colorectal Dis 15(1):66–73. doi:10.1111/j.1463-1318.2012.03075.x

Part IV
Combined Modality Therapy in Rectal Cancer

Aims of Combined Modality Therapy in Rectal Cancer (M0)

J. P. Gerard, K. Benezery, J. Doyen and E. Francois

Abstract

Optimizing the Cost/benefit ratio of treatment: Evidence Based The aim of a cancer treatment is always to achieve the maximum of cure rate with a minimum of toxicity and best quality of life at an acceptable cost for the society. It is always a multifactorial challenge depending on the patient, the tumor, the doctor, and the society cultural and financial backgrounds. The goal is to find the best cost/benefit ratio between all possible strategies in agreement with a well-informed patient. In rectal cancer (M0) surgery is the cornerstone of treatment. Combined modality therapies aim at optimizing the cost/benefit ratio of possible strategies and only randomized trials can bring strong evidence regarding their results and recommendations. *Lessons from randomized trials: quite modest* During the past decades many phase III trials have shown that: (1) neoadjuvant treatment even with "TME" surgery was better than adjuvant, (2) chemoradiotherapy (CRT) was better than RT alone, (3) long course CRT was probably more efficient (in terms of ypCR) than short course (25/5), and (4) capecitabine was as efficient as 5 FU but oxaliplatin was not adding benefit. Overall, the gains of nCRT remain modest and it is mainly a reduction in local relapse not exceeding 5 %, but no benefit in survival and neither in sphincter saving surgery has been proven. *The way forwards organ preservation in case of CCR.* Local

Conflict of interest: JP Gérard is the medical advisor of the Ariane Medical Systems company

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control: can probably be improved for T4 tumors by RT dose escalation. Survival: can be increased by innovative medical treatment either before or after surgery. Toxicity: may be reduced by a less aggressive treatment in elderly. Conservative treatment: A new field of clinical research is to achieve "organ preservation" (and not only sphincter saving). To modify the surgical approach and preserve the whole rectum, neoadjuvant treatment must achieve safely a *clinical complete response*. As rectal adenocarcinoma is a relatively radioresistant tumor endocavitary irradiation (contact X-Ray) is a promising safe approach and this hypothesis will be addressed by the OPERA randomized trial.

Keywords
Rectal cancer · Multimodality therapy · Organ preservation · Conservative treatment

1 Optimizing the Cost–Benefit Ratio of Treatment According to Evidence-Based Medicine

Since Hippocrates the aim of a curative medical treatment is to achieve the most efficient result against the disease and the less toxic effect for the patient. One the first curative treatments for rectal cancer was introduced by Miles in 1908 using "a radical abdomino-perineal resection" (APR) with an acceptable (although high) operative mortality. Since then surgery has been (and will remain) the cornerstone of the treatment of rectal cancer. The modern era of rectal surgery started with the introduction of the so-called "TME surgery" removing the mesorectum along the "holly plane" with sharp dissection under vision control (Heald and Ryall 1986). To improve local control and survival radiotherapy and chemotherapy have been used in association with surgery. Due to the many confounding factors, the results of such combined treatments can be evaluated only using randomized control trial. The ultimate aim is to reach 100 % cure with 0 % toxicity. Most of the new treatments aiming at better local control or survival use radiation dose escalation or more efficient multidrug medical treatments. The main limiting factor to this intensification is the induced toxicity. It is the merit of the "TME surgery" to be at the same time able to achieve a better local control by reducing the breaching of the rectal fascia and a lower toxicity by sparing the latero-pelvic nerves. It is probably the advantage of the laparoscopic approach to reach similar results by reducing further the operative health constraint for the patient (Panis et al. 2011). May be one of the most significant progress in the past decades impacting survival was the dramatic reduction in the rate of operative mortality. Intensive care, improved anesthesia, reduction of radiation toxicity with smaller irradiated volume, and better surgical bleeding and infection control have reduced the 60 days postoperative mortality from 10 % to close to 1 %. Only in elderly, frail patients surgery is remaining a significant trauma (Rutten et al. 2008).

When analyzing the benefits of the various combined multimodality treatments associated to surgery it is crucial to take into consideration the two aspects of the balance (benefit vs. cost) and to include in the cost all the sustainable aspects relevant to the patient, the healthcare system, and the society. Most probably in this subtle equilibrium between benefit and cost, toxicity is the main parameter because it is, since Hippocrates again, the key ethical message of medicine: "Primum non nocere" which in modern language may be assimilated to the "Principe de précaution." In such a complex situation and as the improvements are generally (and unfortunately) small only RCT can bring reliable scientific evidence, which remains the best way leading to changes of practice in the medical community.

2 Recent Results Gained Through Randomized Trials

2.1 Quite Modest Even if Local Recurrence Rate Is Now Below 7 %

Until the end of the twentieth century radical surgery followed by adjuvant chemoradiotherapy (CRT) was the standard treatment for rectal cancer (stage M0) (Conference 1990; Krook et al. 1991; O'Connell et al. 1994) (Table 1). It was the merit of the Swedish and mainly German trials (Folkesson et al. 2005; Pahlman and Glimelius 1990; Frykholm et al. 1993; Sauer et al. 2004, 2012) to demonstrate that neoadjuvant CRT (nCRT) was more efficient and possibly less toxic than adjuvant CRT (Park et al. 2011). As "TME surgery" was introduced in early 2000, it was one of the main conclusion of the Dutch trial to show that even with a "TME surgery" preoperative radiotherapy (short course) was improving local control (Kapiteijn et al. 2001; van Gijn et al. 2011). Other more recent trials demonstrated that nCRT was more efficient for long-term local control than radiotherapy alone (Bosset et al. 2006, 2014; Gerard et al. 2006), that capecitabine was as efficient as Fluorouracile (5FU) (Gerard et al. 2010, 2012; Aschele et al. 2011; Schmoll et al 2013; Roh et al. 2011) that radiation dose escalation using external beam radiotherapy (EBRT) from 45 Gy/5 weeks up to 50 Gy/5w was producing more pathologic sterilization of the tumor (ypCR) without increase in 3-year toxicity, but without other clinical significant benefits (Gerard et al. 2012) and that oxaliplatine was not to be given concurrently with EBRT and Capecitabine (or 5FU) (Schmoll et al. 2013; Roh et al. 2011). As local control is at the present time close to 95 % in T2-3 M0 tumors the only way to improve survival is to find an efficient (and not too toxic) medical treatment. First-line chemotherapy has been proven possible without compromising nRT and surgery (Fernandez-Martos et al. 2010; Chua et al. 2010). With increasing knowledge about the molecular abnormalities driving cell growth, immune reaction, and tumor proliferation various molecular targeted drugs (MTD) have been tested. So far the results have not been totally convincing using as neoadjuvant

Table 1 Overview of some of the main messages and conclusion derived from recent randomized control trials

Study	Regimen	5-year local recurrence (%)	5-year overall survival (%)	Sphincter preservation (%)	Comments
Krook et al. (1991) (1980–1986) $n = 204$	Postoperative radiotherapy (45 Gy) versus postoperative concurrent chemoradiotherapy (45 Gy and 5-FU)	25 versus 13.5 ($P = 0.03$)	48 versus 58	50 versus 50	Postoperative concurrent chemoradiotherapy improves local control and survival; becomes standard treatment
Pahlman and Glimelius (1990), Frykholm et al. (1993) (1987–1990) $n = 908$	Surgery alone versus preoperative radiotherapy (25 Gy in 5 fractions)	25 versus 8 ($P = 0.001$)	55 versus 63 ($P = 0.008$)	44 versus 40	Postoperative death in experimental arm was reduced from 15 to 4 % by reducing the radiation volume ($P = 0.001$)
Marsh et al. (1994) (1982–1986) $n = 284$	Surgery alone versus preoperative radiotherapy (20 Gy in 4 fractions) small field (10 × 10 cm)	36.5 versus 12.8 ($P = 0.0001$)	50 versus 56	48 versus 46	4 MV linear accelerator and small fields in the posterior pelvis reduce local recurrence without toxicity
Kapiteijn et al. (Pettersson et al. 2010) (1996–1999) $n = 1{,}861$	Total mesorectal excision versus preoperative radiotherapy (25 Gy in 5 fractions)	11 versus 6 ($P = 0.001$)	63 versus 64	67 versus 65	Short course preoperative radiotherapy improves local control even with total mesorectal excision surgery
Lyon R96–02 (Gerard et al. 2004; Ortholan et al. 2012) (1996–2001) $n = 88$	Preoperative radiotherapy versus preoperative radiotherapy and CBX (85 Gy in 3 fractions)	11 versus 8	67 versus 67	44 versus 76 ($P = 0.004$)	Safe high-dose RT escalation with CBX enables improved sphincter and rectal preservation
CAO/ARO/AIO (Sauer et al. 2004, 2012) (1995–2002) $n = 823$	Postoperative concurrent chemoradiotherapy (45 Gy in 25 fractions and 5-FU) versus preoperative concurrent chemoradiotherapy (45 Gy in 25 fractions and 5-FU)	13 versus 6 ($P = 0.006$)	74 versus 76	71 versus 69	*Preoperative concurrent chemoradiotherapy* superior in terms of local control and early toxicity; *becomes standard treatment*

(continued)

Table 1 (continued)

Study	Regimen	5-year local recurrence (%)	5-year overall survival (%)	Sphincter preservation (%)	Comments
FFCD 9203 (Géard 2006) (1993–2003) $n = 762$	Preoperative radiotherapy (45 Gy in 25 fractions) versus preoperative concurrent chemoradiotherapy (45 Gy in 25 fractions and 5-FU)	16 versus 8	67 versus 67	50 versus 50	Properative concurrent chemoradiotherapy is superior to radiotherapy alone in terms of local control
MRC CRO7 (Sebag 2009) (1998–2005) $n = 1{,}350$	Preoperative radiotherapy (25 Gy in 5 fractions) versus selective postoperative concurrent chemoradiotherapy (45 Gy and 5–FU)	10.6 versus 4.4	70 versus 68	63 versus 65	Confirmation of Kapiteijn et al. (Pettersson et al. 2010) with minimal radiation toxicity; local control improved with preoperative radiotherapy versus postoperative concurrent chemoradiotherapy
ACCORD 12 (Gerard et al. 2003) (2005–2008) $n = 598$	Preoperative concurrent chemoradiotherapy (45 Gy and capecitabine) versus preoperative concurrent chemoradiotherapy (50 Gy and capecitabine and oxaliplatin)	6.1 versus 4.7[§]	85 versus 83[§]	74 versus 76	A sterilized operative specimen was observed in 13 % of cases in first arm and 19 % in second Local relapse at 3 years <5 % with 50 Gy radiotherapy
STAR 01 (Aschele 2011) (2003–2008) $n = 747$	Preoperative concurrent chemoradiotherapy (50.4 Gy in 28 fractions and 5-FU) versus preoperative concurrent chemoradiotherapy (50.4 Gy in 28 fractions and oxaliplatin)	NR	NR	79 versus 81	A sterilized operative specimen was observed in 16 % of cases in both arms. Oxaliplatin associated with higher early grade 3 toxic events and does not increase tumor sterilization

(continued)

Table 1 (continued)

Study	Regimen	5-year local recurrence (%)	5-year overall survival (%)	Sphincter preservation (%)	Comments
KOREA (Park et al. 2011) $N = 220$	Preoperative versus postoperative chemoradiotherapy (CAP50)	4 % versus 6 %	77 % versus 73 %	80 % versus 72 %	Despite more ypCR in preop group no significant difference in sphincter preservation. Post op less toxic than preop
		(4 year)	(3y DFS)	(NS)	
CAO/ARO04 (Rodel et al. 2012) 1236 pts	Preop RT (46 Gy + 5Fu ± oxaliplatin)	NR	NR	88 % (no different)	FU+ oxalipt give a higher reate of ypCR without excessive toxicity. Waiting for endpoints 3y DFS
PETTAC6 (Schmoll et al. 2013) $N = 1094$	Néoadjuvant and adjuvant treatment using capecitabine + oxaliplatin versus capecitabine alone	NR	NR	68 % (no difference)	Oxaliplatin does not increase tumor response or local control or survival but gives more toxicity
NSABP R04 (Roh et al. 2011) $N = 1608$	2 × 2 format 5FU versus capecitabine with or without oxaliplatin néoadjuvants	NR	NR	62 % (no difference)	Capecitabine is equivalent to 5FU. Oxaliplatin no benefit more early toxicity

treatment either anti EGFR MDT (Dewdney et al. 2012) or anti-VEGF concurrently with radiotherapy. Such MDT can provide sometimes increased toxicity (Crane et al. 2003) or decreased radiosensitivity (Machiels et al. 2007; Willett et al. 2009).

2.2 Does Neoadjuvant Treatment Reduce the Rate of Permanent Stoma? Surprisingly NO

One of the most common medical beliefs is that preoperative treatment especially nCRT with long interval will "downsize" the tumor (T2-T3-T4) and increase the chance of a conservative treatment, namely sphincter saving surgery (SSS) using either low anterior resection (LAR) or inter sphincteric resection (ISR) (Rullier et al. 2013). In fact, conservative treatment of rectal cancer is a very complex situation with the interaction of many multifactorial parameters related to the tumor, the patient, the surgeon, and the general culture of a specific country or area. Here, more than everywhere else, only randomized trials can give strong evidence regarding the benefit of any preoperative treatment in terms of conservative treatment. Two literature reviews have analyzed this question (Bujko et al. 2006; Gerard et al. 2012). Both authors came to the same conclusion: for T2-3 (4) rectal cancers the rate of permanent stoma (for distal and middle rectum) have dramatically decreased during the past decades from 70 to 25 % (and sometimes 10 %), but this increase in sphincter preservation was due to technical surgical innovation and new concepts regarding the distal margin to be respected (from 5 to 2 even 1 cm) (Pahlman et al. 2013). In none of the randomized trials the group using the experimental treatment showed a significant increase in the rate of SSS despite often an increase in sterilization (ypCR) of the operative specimen (Fig. 1). A recent randomized trial performed in South Korea (Park et al. 2011) compared (as in the German CAO/ARO trial) postoperative CRT with nCRT. Despite a highly significant difference in the rate of ypCR (0 vs. 20 %) there was a non-significant increase in the rate of sphinter saving surgery (62 vs. 70 %). In a Nordic trial (Braendengen et al. 2008; Braendengen et al. 2011) nCRT when compared to short course RT with immediate surgery for T4 tumor was able to increase R0 surgery, local control, and sphincter preservation.

2.3 The Clinical Complete Response Hypothesis

The Lyon R96-2 trial using sphincter preservation as the main endpoint was the only trial showing a benefit of the neoadjuvant treatment to improve the rate of conservative treatment (Table 2). The addition of a boost using contact Brachytherapy X Ray 50 kV (CBX) 90 Gy in 3 fractions to EBRT increased the SSS rate from 44 to 76 % without increase in toxicity and preservation of a good bowel function (Gerard et al. 2004). Two points were of interest in this trial: first the rate of clinical complete response (CCR) was increased in the CBX boost group from 2 to 29 % and this finding may explain why the surgeons were more in favor of a

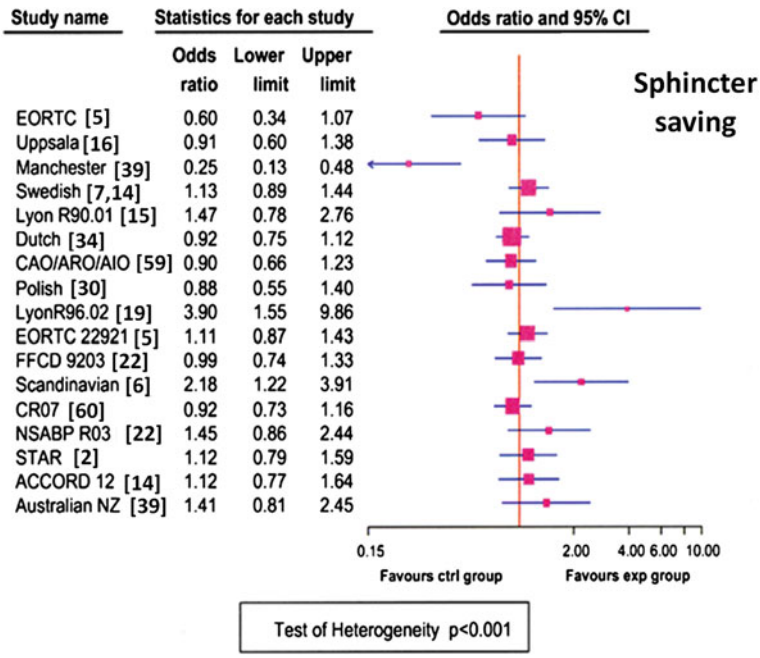

Fig. 1 Forest plot summarizing the results of recent randomized trials about sphincter preservation and showing the lack of benefit of neo adjuvant treatment (with the exception of the Lyon R 96-2 trial)

conservative approach in the boost group. When the surgeon see only a partial response he does not modify his surgical initial decision, but when he cannot see or palpate anymore a lesion he may reappraise his decision and perform a more conservative technique (Ortholan et al. 2006). Second, not only Anterior Resection was more frequent in the boost group, but also most of all "organ preservation" as 10 patients out of 45 in the CBX group were able to preserve the whole rectum after CCR using either a local excision or only a careful surveillance (Watch and wait). These data has been updated after 10 years of follow-up and the gain in stoma-free rate was maintained on the long-term without detrimental effect on local control or survival (Ortholan et al. 2012).

2.4 How to Increase Safely the Rate of CCR to Perform More Conservative Treatment

There are mainly three ways to increase the CCR rate:

(1) Increase the *interval* between the end of the neoadjuvant treatment and the surgery: the Lyon R 90-1 trial compared an interval of 2 versus 6 weeks. An increase in ypCR was observed (2 vs. 13 % p: 0.005), but it did not translate in

Table 2 Lyon R96-02 randomized trial 1996–2001 (Géard 2004; Ortholan et al. 2012)

Inclusion criteria		T2-T3 <½ circumference ≤6 cm from anal verge (distal rectum) Operable patient-any age >18	
Randomization		A- Preoperative EBRT alone (39 Gy/13 F/3 W)	
		B- Preoperative same EBRT + boost CBX (90 Gy/3F) Boost usually given before EBRT. Surgery TME: 5 weeks after end EBRT. No chemoradiotherapy	
Endpoint		Sphincter preservation	
		Hypothesis: A: 40 % B: 70 %	
1996–2001		88 patients included	
		EBRT (43 pts)	CBX + EBRT (45 points)
Med age		67	69
T2		12	10
T3		29	33
CCR		1 (2 %)	11 (29 %)
APE		24	11
Sph. Savint Tt		19 (44 %)	34 (76 %) p = 0.004
Watch and Wait Loc Excision	Organ preserved	0 0 — 0	7 3 — 10
Distant meta 3 y		11	9
10 year ov. Surv		56 %	55 %
10 year loc rec		5 (15 %)	4 (10 %)
10 year stoma free		27 %	61 % p < 0.001

At 10 years, 9 patients with organ preserved with no local recurrence, good anorectal function for all. Rectal bleeding G2 during the first 3 years. *CCR* Clinical Complete Response, *APE* Abdomino-Perineal Excision

a better SSS rate (Francois et al. 1999; Glehen et al. 2003). In Sao Paulo, Habr Gama has been for many years a strong advocate of a conservative treatment in case of CCR after nCRT. By increasing the interval before evaluation of the response from 5 to 12 weeks habr gama was able to increase the rate of CCR from 30 to 55 % (Habr-Gama et al. 2009; Habr-Gama et al. 2014). In the stockholm trial after short course an interval of 5 weeks (compared to immediate surgery) increased the ypCR without difference in toxicity, but without increase in SSS (Pettersson et al. 2010, 2012). It is probably after 2 to 3 months after the end of the nCRT that the optimal tumor response can be seen (Sloothaak et al. 2013; Wang et al. 2005).

(2) Concurrent use of one or two *chemotherapy* with radiotherapy: The FFCD 9203 and EORTC 22921 trials have shown that the addition of 5FU to preoperative irradiation is increasing ypCR and most of all local control in T3-4

rectal cancer, but without gain in SSS (Bosset et al. 2006; Gerard et al. 2006). The addition of oxaliplatin to 5FU or Capecitabine is not adding any benefit to the patient and may increase the risk of diarrhea (Gerard et al. 2010; Aschele et al. 2011; Schmoll et al. 2013).

(3) *Radiation dose escalation* is probably the most efficient way so far. In Toronto the dose escalation from 40 to 45 until 50 Gy was associated with a progressive increase of ypCR from 10 to 19 % (Wiltshire et al. 2006). In the ACCORD 12 trial a biological dose escalation of 15 % (from 45 to 50 Gy with the same protraction time of 5 weeks) increased the ypCR from 13 to 19 % (Gerard et al. 2010). The main limitation of such dose escalation, even with modern RT technique as IMRT or Proton therapy is the tolerance of the normal pelvic tissues and OAR (Gerard et al. 2004, 2003). The most efficient way to escalate the RT dose with regards to the "Toxicity/Benefit" ratio is using endocavitary irradiation, which can concentrate the dose to the primary tumor without arming too severely the surrounding OAR. With HDR Iridium combined with EBRT it is possible to achieve in T3 tumors a CCR rate of 70 % (Vuong et al. 2007). The randomized trial performed in Danemark (Jakobsen et al. 2006, 2012) despite an increase in ypCR in the group treated with Ir HDR did not show an increase in SSS and lead to more toxicity. Same findings in a phase III trial in Pakistan (Tunio et al. 2010). On the other hand as previously reported a safe dose escalation using CBX 50 kV was able to significantly increase CCR, sphincter saving, and most of all organ preservation. Unfortunately, this trial performed in a single institution in a limited number of patient has not influenced clinical practices (Gerard et al. 2004; Ortholan et al. 2012).

3 Aim of the Ongoing and Upcoming Randomized Trials

The most relevant and standard endpoint of CRT is overall survival, but in practice this endpoint is seldom used because it requires to include more than 1,000 patients and a very long follow-up. Disease Free Survival at 3 years is often the main endpoint of trial aiming at increasing survival. Other endpoints as ypCR, TRS (tumor regression score) (Taylor et al. 2011; Patel et al. 2011; Nougaret et al. 2013), R0 surgery may be used, but none can be considered as a robust surrogate endpoint of overall survival (Methy et al. 2010). Toxicity, rate of organ preservation, quality of life, and bowel or sexual functions are always major endpoints (Table 3). From a pragmatic point of view neo or adjuvant treatments are aiming at improved four clinical objectives:

(1) *Local Control* In T2 T3 tumors it will be difficult to demonstrate a further improvement over 95 % local control. In T4 following the trial of Braendegen (Braendengen et al. 2008, 2011), the GRECCAR 4 trial (EUDRACT N° 1234556…) is comparing a standard radiation dose of 50 Gy combined with capecitabine to 60 Gy dose in a reduced boost volume. Different techniques of

Table 3 Ongoing or up coming randomized control trials in operable T2-3-4 Nx M0 rectal cancer

Study	Inclusion criteria	Regimen	Endpoint	N° pt
RAPIDO	T3 c-d	• Cap50 + TME	3y DFS	600
Sweden ongoing	T4	• 5 × 5-chemo (folfox) TME	60–70 %	
	Nx			
PRODIGE23	T3-T4	• Cap 50 + TME	3y DFS	500
France NCT	Nx	• Folfirinox-cap 50	65–75 %	
01804790		+TME		
Ongoing				
Aristotle	T3-T4	• Cap45 TME	3y DFS	600
UK	Nx	• Capiri 45 TME	60–70 %	
Ongoing				
GRECCAR4	T3-T4	First-line chemo	R0 resection	250
France		Folfirinox poor response	85 → 95 %	
Ongoing		• Cap50-TME		
N1048		• Cap60-TME		
GRECCAR4	T3-T4	First-line chemo folfirinox	RO resection	250
France ongoing		Good response	95 versus 95 %	
		• CAP50-TME		
		• TME		
PRODIGE X	T3-T4	• CAP50-TME	Toxicity - Q.L	250
France up coming	Age >70 years	• 5 × 5-TME		
OPERA	T2 T3a-b	CAP45	Organ preserved 5–25 %	236
European		• EBRT boost 5.4 Gy		
up coming		• CBX boost 90 Gy/3F		
NCCTG	T3	• Folfox + TME	• R0	1060
N1048 (US)		if response >20 %	• Survival	
		• nCRT		
BACCHUS (UK) up coming	T3	±6 cycles bevacizumab with FOLFOX or FOLFOXIRI preop		
COPERNICUS (UK) up coming	T3	Firs line chemo + 5 × 5		

(continued)

Table 3 (continued)

Study	Inclusion criteria	Regimen	Endpoint	N° pt
Poland NCT00738790	T2-T3a	Preop 5 × 5 versus CRT 6 weeks local excision	Local control pCR	200
GRECCAR7 NCT01648894	T3-4	CRT and interval 7 weeks versus 11 weeks: TME	Pathological response	250
Rectum 51B UZB NCT01224392	T3-4	CRT versus RT with simultaneous integrated TBODSV	pCR	
Rectum TEM spain NCT01308190	T2T3	CRT TEM versus TME	Local control	

radiotherapy are tested to increase the tumor dose without increasing toxicity. Proton therapy if financially available is a promising technology (Thariat et al. 2013) to be used for rectal adenocarcinoma, which require dose above 90 Gy for 80–90 % rate of ypCR (Appelt et al. 2013).

(2) *Survival* As none of the medical regimens tested in RCT has so far been able to increase survival (in opposition with colon cancers), various trials are testing different drugs combination and strategy to try to reduce the rate of distant metastases without detrimental effect on the local control and the overall toxicity rates. The Swedish RAPIDO trial is using a first-line chemotherapy with a short course (5 × 5 gy) versus a standard long course CRT in T3c-d T4 M0 tumors. The French Prodige 23 is comparing in T3T4 M0 a standard "Cap 50" regimen versus the same regimen preceded by four cycles of first-line chemotherapy using a Folfirinox regimen. The British Aristotle RCT is comparing Cap 45 versus the same treatment with the addition of concurrent irinotecan. With the growing development of targeted treatment toward specific molecular pathways some RCT intend to select patients according to some specific mutations and to use an adapted MTD.

(3) *Toxicity and constraint reduction* in the French ACCORD 12 trial it was observed that in patients over 70 years of age the rate of treatment interruption, surgery not performed and postoperative toxicity was significantly increased using Capox 50 (or Cap 50) when compared to younger patients (Francois et al. 2014). A new Prodige randomized trial is upcoming who will test the hypothesis that after 70 years of age a short course radiotherapy (5 × 5 Gy in a small posterior pelvic volume) with delayed surgery will be better tolerated than the Standard Cap 50 and will lead to more patients able to undergo with reduced toxicity a TME surgery. No randomized trial has ever proved that in "goodT3 tumors" a surgery alone was as efficient as CRT (or 5 × 5 Gy) to achieve an optimal local control. Some institutions with a highly dedicated colorectal team tend to expect that TME alone can be proposed for these "good T3 tumors". In Greccar 4 these patients staged with MRI are treated with a first-line chemotherapy using a Folfirinox regimen. In case of "good response"

judged on MRI the patients are randomized between a standard Cap 50 nCRT or a TME without any a nCRT. So far no RCT is comparing the standard nCRT strategy versus TME surgery first-line. In MSKCC New York, following a phase II study using first-line Folfox and Bevacizumab with a 25 % ypCR in T3 tumors (Schrag et al. 2014) an upcoming phase III trial is testing the hypothesis that combined first-line chemotherapy and MTD may replace n CRT. It is not sure that replacing the toxicity of radiotherapy by the toxicity (cardio-vascular) of this new approach will benefit the patient.

Following all recent trials capecitabine (oral) is replacing 5FU (iv), which is for the patients a benefit in terms of simplicity and toxic risk.

(4) *Conservative treatment* This is possibly one of the most promising hypothesis. How to increase not so much Sphincter Saving using AR or ISR (Rullier et al. 2013), but organ preservation after CCR? The upcoming European trial OPERA (Organ Preservation for Early Rectal Adenocarcinoma) will include T2 T3a-b and after Cap 45 will compare a boost using EBRT (5.4 Gy) versus a boost using CBX (90 Gy). The hypothesis is that taking advantage of an increase in CCR in the CBX group the organ preservation rate will increase from 5 to 25 %. One still controversial question in case of CCR is to decide between local excision as proposed by Lezocche (Lezoche et al. 2012) or Garcia-Aguilar et al.(2012) (Sauer et al. 2004) and the GRECCAR group (Rullier et al. 2013) or close surveillance (Habr-Gama et al. 2014; Perez et al. 2013; Maas et al. 2011).

4 Conclusion

Important improvements have been made in the past decade in the treatment of rectal cancers and its overall prognosis is now slightly better than colon cancer. Chemotherapy and new molecular targeted drugs should be able to improve survival in the future. Robust prognostic and predictive markers will be necessary to tailor and optimize these "targeted" treatments for each individual patients. The growing development of colorectal screening will lead to the discovery of more early rectal cancers. In these patients and especially when elderly and frail, organ preservation (as for squamous cell carcinoma of the anal canal) should be an important step forward to better quality of life. Only well-conducted randomized control trials will bring strong enough evidence to influence and modify the clinical and surgical practices.

References

Appelt AL et al (2013) Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. Int J Radiat Oncol Biol Phys 85(1):74–80

Aschele C et al (2011) Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 29(20):2773–2780

Bosset JF et al (2006) Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 355(11):1114–1123

Bosset JF et al (2014) Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 15(2):184–190

Braendengen M et al (2008) Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol 26(22):3687–3694

Braendengen M et al (2011) Late patient-reported toxicity after preoperative radiotherapy or chemoradiotherapy in nonresectable rectal cancer: results from a randomized Phase III study. Int J Radiat Oncol Biol Phys 81(4):1017–1024

Bujko K et al (2006) Does rectal cancer shrinkage induced by preoperative radio(chemo)therapy increase the likelihood of anterior resection? A systematic review of randomised trials. Radiother Oncol 80(1):4–12

Conference NC (1990) Adjuvant therapy for patients with colon and rectal cancer. JAMA 264:1444–1450

Chua YJ et al (2010) Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol 11(3):241–248

Crane CH et al (2003) Response to preoperative chemoradiation increases the use of sphincter-preserving surgery in patients with locally advanced low rectal carcinoma. Cancer 97(2):517–524

Dewdney A et al (2012) Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol 30(14):1620–1627

Fernandez-Martos C et al (2010) Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 28(5):859–865

Folkesson J et al (2005) Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 23(24):5644–5650

Francois Y et al (1999) Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol 17(8):2396

Francois E et al (2014) Results in the elderly with locally advanced rectal cancer from the ACCOR12/PRODIGE 2 phase III trial: tolerance and efficacy. Radiother Oncol (2014)

Frykholm GJ, Glimelius B, Pahlman L (1993) Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. Dis Colon Rectum 36(6):564–572

Garcia-Aguilar J, Shi Q, Thomas CR, Jr., et al (2012) A phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer : preliminary results of the ACOSOG Z6041 trial. Ann Surg Oncol 19:384–391

Gérard JP, Romestaing P, Chapet O (2003) Radiotherapy alone in the curative treatment of rectal carcinoma. Lancet Oncol 4(3):158–166

Gerard JP et al (2004) Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: the lyon R96-02 randomized trial. J Clin Oncol 22(12):2404–2409

Gerard JP et al (2006) Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 24(28):4620–4625

Gerard JP et al (2010) Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol 28(10):1638–1644

Gerard JP et al (2012) Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 30(36):4558–4565
Gerard JP et al (2012) Can we increase the chance of sphincter saving surgery in rectal cancer with neoadjuvant treatments: lessons from a systematic review of recent randomized trials. Crit Rev Oncol Hematol 81(1):21–28
Glehen O et al (2003) Long-term results of the Lyons R90-01 randomized trial of preoperative radiotherapy with delayed surgery and its effect on sphincter-saving surgery in rectal cancer. Br J Surg 90(8):996–998
Habr-Gama A et al (2009) Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. Dis Colon Rectum 52(12):1927–1934
Habr-Gama A et al (2014) 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 88:822–828
Heald RJ, Ryall RD (1986) Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1(8496):1479–1482
Jakobsen A et al (2006) Preoperative chemoradiation of locally advanced T3 rectal cancer combined with an endorectal boost. Int J Radiat Oncol Biol Phys 64(2):461–465
Jakobsen A et al (2012) Dose-effect relationship in chemoradiotherapy for locally advanced rectal cancer: a randomized trial comparing two radiation doses. Int J Radiat Oncol Biol Phys 84(4):949–954
Kapiteijn E et al (2001) Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 345(9):638–646
Krook JE et al (1991) Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 324(11):709–715
Lezoche E et al (2012) Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. Br J Surg 99(9):1211–1218
Maas M et al (2011) Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 29(35):4633–4640
Machiels JP et al (2007) Phase I/II study of preoperative cetuximab, capecitabine, and external beam radiotherapy in patients with rectal cancer. Ann Oncol 18(4):738–744
Marsh PJ, James RD, Schofield PF (1994) Adjuvant preoperative radiotherapy for locally advanced rectal carcinoma. Results of a prospective, randomized trial. Dis Colon Rectum 37(12):1205–1214
Methy N et al (2010) Surrogate end points for overall survival and local control in neoadjuvant rectal cancer trials: statistical evaluation based on the FFCD 9203 trial. Ann Oncol 21(3):518–524
Nougaret S et al (2013) The use of MR imaging in treatment planning for patients with rectal carcinoma: have you checked the "DISTANCE"? Radiology 268(2):330–344
O'Connell MJ et al (1994) Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 331(8):502–507
Ortholan C et al (2006) Role of radiotherapy with surgery for T3 and resectable T4 rectal cancer: evidence from randomized trials. Dis Colon Rectum 49(3):302–310
Ortholan C et al (2012) Correlation in rectal cancer between clinical tumor response after neoadjuvant radiotherapy and sphincter or organ preservation: 10-year results of the Lyon R 96-02 randomized trial. Int J Radiat Oncol Biol Phys 83(2):e165–e171
Pahlman L, Glimelius B (1990) Pre- or postoperative radiotherapy in rectal and rectosigmoid carcinoma. Report from a randomized multicenter trial. Ann Surg 211(2):187–195
Pahlman L et al (2013) Altering the therapeutic paradigm towards a distal bowel margin of < 1 cm in patients with low-lying rectal cancer: a systematic review and commentary. Colorectal Dis 15(4):e166–e174

Park JH et al (2011) Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. Cancer 117(16):3703–3712

Patel UB et al (2011) Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. J Clin Oncol 29(28):3753–3760

Panis Y et al (2011) Mortality after colorectal cancer surgery: a French survey of more than 84,000 patients. Ann Surg 254(5):738–743 (discussion 743–744)

Pettersson D et al (2010) Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. Br J Surg 97(4):580–587

Pettersson D et al (2012) Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer. Br J Surg 99(4):577–583

Perez RO et al (2013) Transanal endoscopic microsurgery for residual rectal cancer (ypT0-2) following neoadjuvant chemoradiation therapy: another word of caution. Dis Colon Rectum 56(1):6–13

Rodel C et al (2012) Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 13(7):679–687

Rutten HJ et al (2008) Controversies of total mesorectal excision for rectal cancer in elderly patients. Lancet Oncol 9(5):494–501

Roh MS et al. (2011) The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP 5-04. J Clin Oncol 29(221s): p. suppl 15; abstr 3503

Rullier E et al (2013) Low rectal cancer: classification and standardization of surgery. Dis Colon Rectum 56(5):560–567

Sauer R et al (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351(17):1731–1740

Sauer R et al (2012) 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 30(16):1926–1933

Schrag D et al (2014) Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol 32(6):513–518

Sebag-Montefiore D, Stephens RJ, Steele R et al (2009) Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016) : a multicentre, randomised trial. Lancet 373:811–820

Sloothaak DA et al (2013) Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. Br J Surg 100(7):933–939

Schmoll HJ, Haustermans K et al (2013) Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: first results of the PETACC-6 randomized phase III trial; ASCO, Abstract, p 3531

Taylor FG et al (2011) 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 253(4):711–719

Thariat J et al (2013) Past, present, and future of radiotherapy for the benefit of patients. Nat Rev Clin Oncol 10(1):52–60

Tunio MA et al (2010) High-dose-rate intraluminal brachytherapy during preoperative chemoradiation for locally advanced rectal cancers. World J Gastroenterol 16(35):4436–4442

van Gijn W et al (2011) Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 12(6):575–582

Vuong T, Devic S, Podgorsak E (2007) High dose rate endorectal brachytherapy as a neoadjuvant treatment for patients with resectable rectal cancer. Clin Oncol (R Coll Radiol) 19(9):701–705

Wang Y et al (2005) Primary radical external beam radiotherapy of rectal adenocarcinoma: long term outcome of 271 patients. Radiother Oncol 77(2):126–132

Wiltshire KL et al (2006) Preoperative radiation with concurrent chemotherapy for resectable rectal cancer: effect of dose escalation on pathologic complete response, local recurrence-free survival, disease-free survival, and overall survival. Int J Radiat Oncol Biol Phys 64(3):709–716

Willett CG et al (2009) Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: a multidisciplinary phase II study. J Clin Oncol 27(18):3020–3026

Neoadjuvant Radiotherapy (5 × 5 Gy): Immediate Versus Delayed Surgery

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Abstract

Goals: To evaluate the role of length of the interval between 5 × 5 Gy and surgery. *Methods*: PubMed was searched to perform a systematic review. *Results*: There were 10 studies on 5 × 5 Gy with delayed surgery (no of patients (n) = 1343), and six studies on 5 × 5 Gy with consolidation chemotherapy delivered over a long interval prior to surgery in a tight sequence (n = 244). In total, there were four randomized studies, five phase II studies, and seven retrospective studies. Trials that compared immediate with delayed surgery after 5 × 5 Gy showed a benefit in terms of lower rate of severe acute post-radiation toxicity (4.2 % absolute difference) in the immediate-surgery group. However, this benefit was counterbalanced by the increase in minor postoperative complications (13 % of absolute difference) in the group with immediate surgery compared with that with the delayed surgery. The pathological complete response (pCR) rate was about 10 % higher in the delayed-surgery group. There were no differences in sphincter preservation and R0 resection rate between the two groups. Small studies suggest no differences in the oncological outcomes. Regarding elderly patients who were unfit for chemotherapy, short-course radiotherapy with delayed surgery produced favourable outcomes for "unresectable" cancer or for small cancer after full-thickness local excision. A watch-and-wait policy in complete responders after short-course radiotherapy is feasible. A pCR of over 20 % was recorded after

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short-course radiotherapy and consolidation chemotherapy compared with about 10 % after 5 × 5 Gy and delayed surgery. Favourable outcomes after short-course radiotherapy and consolidation chemotherapy were observed in patients with potentially resectable stage IV disease. *Conclusions*: Evidence showed that 5 × 5 Gy with delayed surgery can be used routinely for the management of elderly patients who are unfit for chemotherapy in case of "unresectable" cancer or early cancer prior to local excision. Short-course radiotherapy with consolidation chemotherapy is a promising treatment that can be used routinely for potentially resectable stage IV disease.

Keywords
Rectal cancer · Pre-operative short-course radiotherapy

1 Introduction

In the treatment of rectal cancer, pre-operative radiotherapy is preferable to post-operative radiotherapy because of its higher efficacy regarding the reduction of the risk of local relapse and lower toxicity (Sauer et al. 2004; Frykholm et al. 1993). Short-course radiation (five fractions of 5 Gy over 1 week) with immediate surgery (i.e., surgery performed within the subsequent week) has been the neoadjuvant radiotherapy regimen for resectable rectal cancer that was tested most extensively in randomized trials (Frykholm et al. 1993; Bujko et al. 2006; Ngan et al. 2012; Folkesson et al. 2005; Martling et al. 2001; Peeters et al. 2007; Sebag-Montefiore et al. 2009; Stockholm Colorectal Cancer Study Group 1990). This treatment resulted in a relative reduction of local recurrence of about 60 % compared with surgery alone, and was associated with acceptable toxicity. In addition, this treatment is cheap (only five fractions are administered) and convenient. Less is known about the results of short-course radiotherapy and delayed surgery. Therefore, the current systematic review focused on papers that described this regimen.

2 Materials and Methods

A search of PubMed was performed up until February 2014 using the terms "rectal cancer" and "short-course radiotherapy" or "5 × 5 Gy" and the related citation function. In addition, abstracts of the ESTRO, ASTRO or ECCO conferences from 2010 to 2013 were searched. Original articles qualified for this review if the original data had shown results after short-course radiation (5 × 5 Gy) and surgery delayed for more than 2 weeks. Additional studies were searched manually from the reference lists of relevant articles. Only English-language studies were included. The literature search and data extraction using a data-collection form

were performed independently by the two authors. Any disagreements were resolved by consensus.

3 Results

The PubMed search yielded a total of 543 records. After exclusion of reviews, duplicates, case reports or irrelevant studies, 47 abstracts of potential relevance were obtained. Moreover, four papers of potential interest were identified in the reference lists. In total, 51 full-text copies of the original articles were acquired. Of these, 17 articles describing 16 studies met the entry criteria and constituted the material used in this review (Tables 1 and 2). The studies were divided into the following two groups: 10 studies on 5 × 5 Gy with delayed surgery (Table 1) (Pettersson et al. 2010, 2012, 2013; Pach et al. 2012; Latkauskas et al. 2012; Yeo et al. 2013; Faria et al. 2014; Bujko et al. 2013a; Pettersson et al. 2012; Radu et al. 2008; Hatfield et al. 2009; Veenhof et al. 2007), and six studies on 5 × 5 Gy with consolidation chemotherapy delivered over a long interval prior to surgery (Radu et al. 2008; Bujko et al. 2013b; van Dijk et al. 2013; Myerson et al. 2014; Widder et al. 2005; Shin et al. 2011) (Table 2).

Pre-operative short-course radiation alone was used in 1343 patients. There were three randomized studies; two compared short-course radiotherapy and immediate surgery with short-course radiotherapy and delayed surgery (Pettersson et al. 2010, 2012, 2013; Pach et al. 2012), whereas the third one compared short-course radiotherapy and delayed surgery with long-course chemoradiation and delayed surgery (Latkauskas et al. 2012). There were three phase II studies (Yeo et al. 2013; Faria et al. 2014; Bujko et al. 2013a). The four remaining studies were retrospective (Pettersson et al. 2012; Radu et al. 2008; Hatfield et al. 2009; Veenhof et al. 2007).

Pre-operative short-course radiation with consolidation chemotherapy was used in 244 patients. There was one randomized study that compared this treatment with long-course chemoradiation (Bujko et al. 2013b), two phase II studies (van Dijk et al. 2013; Myerson et al. 2014) and three retrospective studies (Radu et al. 2008; Widder et al. 2005; Shin et al. 2011).

3.1 Acute Radiation Adverse Effects

Acute toxicity occurring over the 5 days of short-course radiation delivery has been described well in previous randomized studies that evaluated short-course radiation and immediate surgery (Bujko et al. 2004; Marijnen et al. 2002). The studies presented here (Pettersson et al. 2010; Bujko et al. 2013a, b) confirmed previous observations. Acute toxicity during short-course radiotherapy, most often of grade I–II severity, occurred in about 10 % of patients. Gastrointestinal symptoms or sacral pain of short duration were observed most frequently. However, most of the post-radiation toxicity, such as abdominal pain and cramps,

Table 1 Studies using short-course radiotherapy (5 × 5 Gy) alone and delayed surgery in rectal cancer

Author, study type, no of patients	Patients' characteristics	Treatment	Interval from day 1 of radiation therapy to surgery in weeks	% of acute toxicity	% of sphincter preservation	% of postoperative complications	% of pCR	% of R1 + R2 resections	Median follow-up in months	% of local recurrence	% of survival
Pattersson (2010, 2012, 2013) Stockholm III randomized, interim analyses of 303, 398, and 585 patients	Stage II–III resectable cancers	5 × 5 Gy immediate surgery versus 5 × 5 Gy delayed surgery versus 25 × 2 Gy delayed surgery	1.4 versus 7 versus planned 9–13	Severe-0 versus 4.2 versus 5	68 versus 62 versus 79	Total: 52.5 versus 39.4 versus 41, p = 0.01 Severe: 11.1 versus 9.8 versus 4 p = 0.132 Post-operative deaths: 0.8 versus 1.2 versus 1	0.4 versus 9.8 versus 2	7 versus 7 versus n.d.	n.d.	n.d.	n.d.
Pach et al. (2012), Polish randomized, N = 154	Stage I–III resectable cancers	5 × 5 Gy and immediate surgery versus 5 × 5 Gy and delayed surgery	Planned: 1.7–2.2 versus 5-6	n.d.	53 versus 57 p = 0.63	n.d.	0 versus 10 p = 0.003	16 versus 8 p = 0.24	86	2 versus 10#	63 versus 73 at 5 years, p = 0.24
Latkauskas et al. (2012), Lithuanian randomized, N = 83, interim analysis	Stage II-III resectable cancers	5 × 5 Gy and delayed surgery versus chemoradiation 25 × 2 Gy 5-FU and Lv	7.1 versus 11.3	n.d.	76 versus 85 p = NS	41 versus 26 p = NS	3 versus 13	13 versus 9 p = NS	n.d.	n.d.	n.d.

(continued)

Table 1 (continued)

Author, study type, no of patients	Patients' characteristics	Treatment	Interval from day 1 of radiation therapy to surgery in weeks	% of acute toxicity	% of sphincter preservation	% of postoperative complications	% of pCR	% of R1 + R2 resections	Median follow-up in months	% of local recurrence	% of survival
Yeo (2013), prospective, phase II, N = 71	Stage II–III resectable cancers	5 × 5 Gy concurrent 5-FU, Lv	8	Grade 3+: 34	99	15	1	6	n.d.	n.d.	n.d.
Faria et al. (2014), phase II, N = 52	Stage II–III resectable cancers	5 × 6 Gy delayed surgery	8.4	Total: 42 Grade 3: 8	73	37	10	0	23	2	n.d.
Bujko (2013), phase II, N = 89	Stage I–II ≤3 cm	5 × 5 Gy + 4 Gy boost or 28 × 1.8 Gy +3 × 1.8 Gy boost, 5-FU, Lv, local excision for good responders	8 versus 13.3	Total: 27 versus 64 p = 0.001 Grade 3–2 versus 8	Local excision: 67 versus 80 p = 0.30	19 versus 32 p = 0.18	36 versus 64 p = 0.016	8	24	After local excision 11.8 versus 6.2 at 2 years, p = 0.53	n.d.
Pattersson et al. (2012), retrospective, N = 112	Mostly because of unresectable cT4, unfit for chemotherapy	5 × 5 Gy delayed surgery	8	Grade 3: 5.4	55	38	8	14	38	n.d.	n.d.
Radu et al. (2008), retrospective, N = 24	unresectable cT4 or unfit for chemotherapy	5 × 5 Gy delayed surgery	7.7	Grade 3: 4	57	n.d.	9	9	26	12.5 at 3 years	62.5 at 3 years

(continued)

Table 1 (continued)

Author, study type, no of patients	Patients' characteristics	Treatment	Interval from day 1 of radiation therapy to surgery in weeks	% of acute toxicity	% of sphincter preservation	% of postoperative complications	% of pCR	% of R1 + R2 resections	Median follow-up in months	% of local recurrence	% of survival
Hatfield et al. (2009), retrospective, N = 43	cT2–4, unfit for chemotherapy	5 × 5 Gy delayed surgery	9	Grade 3+: 5	62.5	31	8	15	18	0	75 at 2 years
Veenhof et al. (2007), retrospective, N = 108	Stage II–III resectable cancers	5 × 5 Gy immediate surgery or 5 × 5 Gy delayed surgery	1.3 versus 7	n.d.	44 versus 49	Major: 30 versus 35 p = 0.54 Minor: 51 versus 53 p = 0.83	0 versus 12 p < 0.01	17 versus 12	34	2 versus 4# p = 0.60	66 versus 73 at 5 years, p = 0.12

Abbreviations used pCR—pathological complete response, n.d.—no data, Lv—lecovorin, NS—non significant
crude rates
Lack of p-value in the table confers that it was not provided by the authors

Table 2 Studies using short-course (5 × 5 Gy) radiotherapy with consolidation chemotherapy and delayed surgery in rectal cancer

Author, study type, no of patients	Patients' characteristics	Treatment	Interval from day 1 of radiation therapy to surgery in weeks	% of patients with acute toxicity	% of patients with sphincter preservation	% of patients with post-operative complications	% of pCR	% of R1 + R2 resections	Median follow-up in months	% of local recurrence	% of survival
Bujko (2013b), randomized, interim analysis, N = 97	Unresectable stage II–III cancers	5 × 5 Gy after one week 3 cycles of FOLFOX versus chemoradiation (50.4 Gy, FOLOX) delayed surgery	12 versus 12.3	Grade ≥3: 26 versus 25	61 versus 60	27 versus 16	21 versus 8	5 versus 15	n.d.	n.d.	n.d.
Van Dijk et al. (2013), phase II (), N = 50	Potentially resectable stage IV disease	5 × 5 Gy within 2 weeks up to 6 cycles of CAPOX + bevacizumab delayed surgery	26.5	Grade3 + : 39	70	31	26	9	n.d.	6#	80 at 2 years
Myerson et al. (2014), phase II, N = 76	Stage II–III, 9 % M1 cancers	5 × 5 Gy after 2 weeks 4 cycles of FOLFOX delayed surgery	17.3	Grade ≥3: 27 % haematological 20 % nonhaematological	75	n.d.	25	5	26	5 at 30 months	87 disease-free at 30 months for M0 patients
Radu et al. (2008), retrospective, N = 13	Potentially resectable stage IV disease	FOLFOX, 5 × 5 Gy after one week 2 cycles of FOLFOX	8	1 toxic death	7 of 9	n.d.	2 of 9	3 of 9	31	50 at 3 years	0 at 3 years
Widder et al. (2005) retrospective, N = 2	Stage III resectable cancers	5 × 5 Gy after 1 week 3 cycles of CAPOX delayed surgery	15, 19	Grade 2: 2 of 2	1/2	0	2 of 2	0	n.d.	n.d.	n.d.
Shin et al. (2011), retrospective, N = 6	Potentially resectable stage IV	4–9 cycles of FOLFOX, 5 × 5 Gy after one week 2–5 cycles of FOLFOX	14	Grade 3: 50	100	n.d.	1 of 6	1 of 6	17	0	100

Abbreviations used pCR—pathological complete response, n.d.—no data, Lv—lecovorin, FOLFOX—5-FU, lecovorin and oxaliplatin combination, CAPOX—capecitabine, lecovorin and oxaliplatin combination

crude rates

Lack of p-value in the table confers that it was not provided by the authors

urgency, and diarrhoea occurred not during but 3–7 days after the completion of radiotherapy. This toxicity was reported in 27–41 % of patients (Pettersson et al. 2010, 2012; Faria et al. 2014; Bujko et al. 2013a, b; Radu et al. 2008; Hatfield et al. 2009; van Dijk et al. 2013) (Tables 1 and 2). Usually, toxicity was minor (grade I–II). Severe side-effects occurred in 2–5 % of patients. The symptoms resolved within the subsequent week. Because in the immediate surgery schedule, operation takes place before the occurrence of acute post-radiation toxicity, more side effects were seen when surgery was delayed. Pattersson et al. (2010), in the interim analysis of the Stockholm III randomized trial, reported severe acute toxicity in 4.2 % of patients in the 5 × 5 Gy and delayed-surgery group and in none of the patients in the 5 × 5 Gy and immediate-surgery group. One prospective study that compared long-course chemoradiation ($n = 25$) with 5 × 5 Gy and delayed surgery ($n = 64$) reported that acute toxicity was seen more often in the chemoradiation group (64 % vs. 27 % of patients, $P = 0.001$) (Bujko et al. 2013a). Severe complications were reported in 8 and 2 % of these patients, respectively.

In only one study, reported by Yeo et al. (2013), was short-course radiation simultaneously combined with 5-Fu and leucovorin. Surgery was delayed for 7 weeks. Grade III–IV acute toxicity occurred in 38 % of patients. Surprisingly, the pathological complete response (pCR) rate in this study was only 1 %. Lower toxicity was reported when short-course radiation was combined with sequential consolidation chemotherapy delivered after a 1–2 week interval from completion of irradiation (Bujko et al. 2013b; van Dijk et al. 2013; Myerson et al. 2014). Grade III–IV toxicity was reported in 26–50 % of patients (Table 2). Most of the acute side-effects occurred during the delivery of chemotherapy. The interim analysis of the randomized trial that compared the above schedule with long-course chemoradiation did not reveal differences in acute toxicity (26 % vs. 25 %) (Bujko et al. 2013b).

3.2 Sphincter or Organ Preservation

Three randomized studies that compared short-course radiotherapy and delayed surgery with other schedules showed that the rates of anterior resection were not different between the treatment-assigned groups (Pettersson et al. 2013; Pach et al. 2012; Latkauskas et al. 2012) (Table 1).

Short-course radiation was administered 6 weeks prior to full-thickness local excision in patients with cT1-3 N0 small tumours (≤3 cm) (Table 1) (Bujko et al. 2013a). Good response to radiation (pCR or downstaging to ypT1 cancer with negative margin) was diagnosed in the local excision specimen in 67 % of patients. No further treatment was administered in this group. In patients with poor response, conversion to abdominal surgery was required. The local recurrence rate in patients with good response to radiation was 11.8 % at 2 years; all of these patients underwent rescue radical surgery.

A study aimed at evaluating the watch-and-wait policy in clinical complete responders 10 weeks after short-course radiation among elderly patients who were

unfit for chemotherapy is currently ongoing (ClinicalTrials.gov: NCT01963862). Tumours smaller than 5 cm and involving less than 60 % of the bowel wall circumference qualify for this study. Six patients have been treated thus far (unpublished data). Clinical complete response was observed in three of them. Among them, one patient developed local recurrence, and the remaining two patients had sustained complete response at the last follow-up (6 and 12 months from irradiation).

3.3 Postoperative Complications

The Stockholm III randomized trial showed the presence of more post-operative complications in the short-course radiotherapy and immediate-surgery group than in the short-course radiotherapy and delayed-surgery group (52.5 % vs. 39.4 %; $P = 0.01$) (Pettersson et al. 2013). However, the rates of severe complications, namely post-operative deaths and complications requiring re-operation, were not different between these groups (Table 1). No difference in post-operative complications was observed in a small retrospective study that compared the two schedules described above (Veenhof et al. 2007) (Table 1).

No differences in post-operative complication rates were detected in the randomized trials that compared short-course radiotherapy and delayed surgery with long-course chemoradiation or with short-course radiotherapy and consolidation chemotherapy (Latkauskas et al. 2012; Bujko et al. 2013b) (Tables 1 and 2).

3.4 Radical Resection Rate

In all randomized trials shown in the Tables 1 and 2, there were no significant differences in the rates of positive surgical margin between the treatment-assigned groups (Pettersson et al. 2012; Pach et al. 2012; Latkauskas et al. 2012; Bujko et al. 2013b).

3.5 Pathological Complete Response

pCR after short-course radiotherapy and delayed surgery was most often diagnosed in about 10 % of patients and varied between 1 and 12 % (Table 1). In patients with tumours with a size $\leq$3 cm, the pCR rate was as high as 34 % (Bujko et al. 2013a). Two randomized studies that compared short-course radiotherapy and immediate surgery with short-course radiotherapy and delayed surgery (Pettersson et al. 2013; Pach et al. 2012) reported a higher rate of pCR in the delayed-surgery group (Table 1). The comparison of short-course radiotherapy and delayed surgery with long-course chemoradiation in a randomized study (Latkauskas et al. 2012) or in a phase II study (Bujko et al. 2013a) revealed that the pCR rate was higher in the chemoradiation groups (Table 1). The rates of pCR after short-course radiotherapy

and consolidation chemotherapy varied between 21 and 26 % (Table 2). An interim analysis of a randomized study that compared short-course radiotherapy and consolidation chemotherapy with long-course chemoradiation revealed a higher pCR rate in the short-course radiotherapy group (21 % vs. 8 %; the *P*-value was not given) (Bujko et al. 2013b).

3.6 Long-Term Oncological Outcomes

Data on the long-term outcomes after short-course radiotherapy and long interval to surgery are scarce and are based on a small number of patients. The oncological outcomes in this setting seem to be similar to those observed in other studies that used long-course pre-operative radio(chemo)therapy for similar cancer stages. A small randomized study that compared short-course radiotherapy and immediate surgery with short-course radiotherapy and delayed surgery showed more local recurrences in the delayed-surgery group: 2 % versus 10 % (the *P*-value was not given) (Pach et al. 2012). However, this difference did not translate into a survival benefit (Table 1). No differences in local recurrence and survival were observed in a retrospective study that compared the two schedules mentioned above (Veenhof et al. 2007).

4 Discussion

The indications for using a long or short interval between 5 × 5 Gy and surgery in relation to the characteristics of patients or tumours are discussed below.

4.1 Resectable Cancer

The evidence is too weak to allow the recommendation of short-course pre-operative radiotherapy and delayed surgery for resectable cancer. Whether delaying surgery by 4–8 weeks is beneficial is unknown, because the full results of the large Stockholm III trial have not been published. Local-recurrence evaluation (primary end-point) will be available in 2015 (Glimelius 2013).

The interim analysis of the Stockholm III trial has revealed the presence of benefit in terms of lower rate of post-operative complications (13 % of absolute difference) in the delayed-surgery group compared with the immediate-surgery group (Pettersson et al. 2013) (Table 1). The lack of pelvic bone-marrow recovery after immediate surgery, which manifests itself as insufficient production of leukocytes, is probably a main cause of this increased risk of post-operative complications (Pettersson et al. 2013). However, the benefit of fewer post-operative complications associated with delayed surgery was counterbalanced by the increase in acute adverse post-radiation effects in this group. About 5 % more patients had severe post-radiation complications in the case of delayed surgery

compared with immediate surgery (Table 1) (Pettersson et al. 2010). This is because the organ at risk (rectum) is removed before radiation damage is manifested clinically in cases in which surgery is performed immediately.

Recently, several articles have evaluated whether delaying surgery for a few days has an impact on these patients. The Dutch trial showed that, for elderly patients treated with short-course radiation and immediate surgery, the rate of non-cancer-related mortality at 1 year post-treatment was lower when surgery was performed at 0–3 days compared with 4–7 days (van den Broek et al. 2013). Similar results were observed in a pooled analysis of the Stockholm I and II trials (Fokstuen et al. 2009) and in one retrospective study (Hartley et al. 2002). However, this was not confirmed by the verification set of 600 patients (van den Broek et al. 2013) and by the interim analysis of the Stockholm III trial (Pettersson et al. 2012). In this trial, the rate of post-operative complications was 52.5 % in patients in whom surgery was performed within 5 days after the last fraction of irradiation compared with 55 % in patients in whom surgery was delayed between 5 and 30 days (hazard ratio, 1.11; 95 % confidence interval, 0.53–2.30). One possible explanation for this discrepancy may be that, in some studies, surgery was postponed in patients with poor condition after consultation with the anaesthetist, which would result in a bias (van den Broek et al. 2013).

4.2 "Unresectable" Cancer

"Unresectable" cancer in this article was defined as a large fixed lesion involving mesorectal fascia or neighbouring organs. Tumour shrinkage is required for radical surgery of such advanced cancers. Long-course chemoradiation with an interval of about 6 weeks before surgery is used routinely, because the long chemoradiation period and the long interval to surgery cause significant tumour shrinkage and downstaging in the majority of patients (Braendengen et al. 2008).

However, often, chemotherapy cannot be used in elderly patients with comorbidity. Because tumour shrinkage and downstaging increase with time (Graf et al. 1997; Francois et al. 1999), short-course radiation and delayed surgery seem to be a logical management for those patients (Radu et al. 2008). In fact, this treatment produced favourable long-term outcomes with acceptable acute toxicity (Pettersson et al. 2012; Radu et al. 2008; Hatfield et al. 2009) (Table 1). Less acute toxicity is observed in patients after short-course radiation and delayed surgery compared with what is observed after long-course chemoradiation (Bujko et al. 2013a). There are sufficient data to conclude that, for patients who are unfit for chemotherapy, short-course radiation and delayed surgery can be used routinely. However, there are insufficient data to conclude that this treatment can be used routinely also for fit patients. Thus, long-course chemoradiation remains the standard procedure.

This standard procedure was compared with short-course radiation combined with sequential consolidation chemotherapy in a randomized study (Bujko et al. 2013b) (Table 2). The planned accrual of 540 patients was recently completed.

Results are expected at the beginning of 2015. The similarly designed RAPIDO trial is ongoing (Nilsson et al. 2013).

Interestingly, after 5 × 5 Gy and consolidation chemotherapy (Table 2), the pCR rate is doubled compared to short-course radiation alone with a long interval to surgery (Table 1). However, it remains unknown whether this difference is related to the longer interval between the onset of radiation and surgery when consolidation chemotherapy was added, or to enhance local effectiveness caused by the addition of chemotherapy.

4.3 Potentially Resectable Stage IV Disease

The Dutch phase II study reported by van Dijk et al. (2013) showed favourable results in patients with potentially resectable stage IV disease after the use of 5 × 5 Gy and consolidation chemotherapy delivered in a tight sequence (Table 2). The main rationale for this approach is that chemotherapy can be delivered in full doses, whereas, if traditionally combined simultaneously with long-course irradiation, the chemotherapy doses must be reduced. The results of this study, together with the results of the other studies presented in Table 2, strongly suggest the routine use of 5 × 5 Gy and consolidation chemotherapy either for potentially resectable (van Dijk et al. 2013; Myerson et al. 2014) or unresectable (Radu et al. 2008; Tyc-Szczepaniak et al. 2013) stage IV disease.

4.4 Organ Preservation

Organ preservation (both the sphincter and rectum) after long-course chemoradiation was assessed either after using a watch-and-wait policy for complete responders (Habr-Gama et al. 2014) or local excision for good responders (Bujko et al. 2013a; Pucciarelli et al. 2013). Such procedures are expected to be especially beneficial for elderly patients with co-morbidity because of low morbidity and lack of post-operative deaths. The post-operative death rate in elderly patients, when measured within a period of 3–6 months after total mesorectal excision, is higher than it is commonly believed. For example, a Dutch population-based study reported 16 % of post-operative mortality at 6 months in patients older than 75 years compared with 4 % in younger patients (Rutten et al. 2007). Because elderly patients are often unfit for chemotherapy, the question arises regarding whether, for organ preservation, short-course radiation assures similar oncological results and yields less early adverse post-radiation effects than does long-course chemoradiation. A small prospective study provided a positive answer to this question by using full-thickness local excision (Bujko et al. 2013a) (Table 1). However, that study should be interpreted with caution because of the small number of patients included and the short follow-up. A watch-and-wait policy for complete clinical responders after 5 × 5 Gy is feasible.

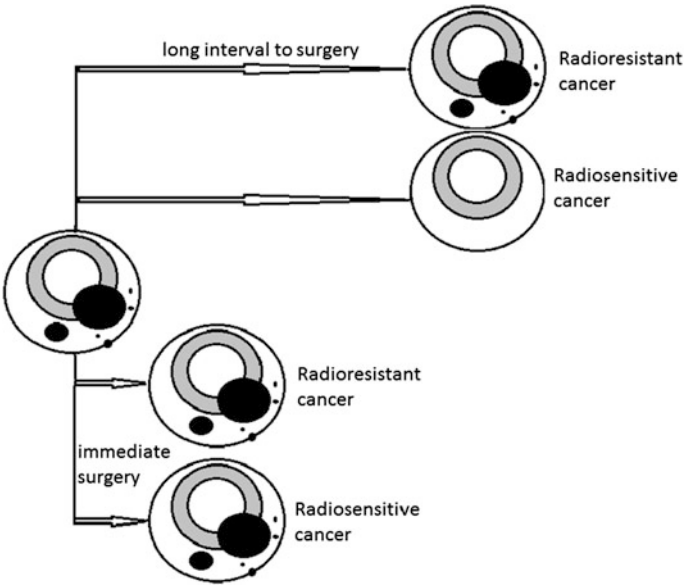

Fig. 1 Response of radiosensitive or radioresistant cancer to short-course radiotherapy in relation to the duration of the rest period between irradiation and surgery. Irreparable DNA damage, which ceases unlimited cancer cell division, occurs only at the time of irradiation. Extending the rest period between radiation and surgery does not produce additional DNA damage. In radiosensitive cancers, DNA damage eventually leads to a pathological complete response (pCR). The manifestation of pCR is heavily dependent on the duration of the interval between the beginning of radiation and surgery (Graf et al. 1997; Francois et al. 1999). Within a few days following the start of radiation, non-viable cancer cells look morphologically intact (Suit and Gallager 1964) and no downstaging occurs (Marijnen et al. 2001) (*lower* scenario). If the interval to surgery is extended to 6–8 weeks, non-viable cancer cells undergo lyses (Francois et al. 1999; Suit and Gallager 1964) (*upper* scenario). This figure explains why a lack of downstaging after short-course radiotherapy and immediate surgery does not confer poor prognosis. It is well known that pCR and downstaging are associated with an excellent prognosis (Maas et al. 2010; Bujko et al. 2007). In the context described above, a long rest period serves as a prognostic test for indentifying patients with excellent prognosis and for guiding further treatment, for example, local excision or a watch-and-wait policy without surgery

4.5 Radiobiological Considerations

Numerous articles have presented outcomes in relation to the length of the interval between long-course radiotherapy or chemoradiotherapy and surgery, which provide additional insight into the issue in question. Four randomized trials (Bujko et al. 2006; Ngan et al. 2012; Francois et al. 1999; Saglam et al. 2014), one population-based study (Sloothaak et al. 2013), one systematic review (Foster et al. 2013), and one meta-analysis (Petrelli et al. 2013) addressed this issue. The body of evidence from these studies and evidence presented in the "Results" section of the present article show that, with a longer interval to surgery, the pCR

rate and downstaging increase, whereas long-term outcomes remain much the same. It is also well known that pCR and downstaging are associated with an excellent prognosis (Maas et al. 2010; Bujko et al. 2007). Thus, the question arises regarding why pCR and downstaging rates are not surrogate prognostic end-points in patients with a long rest interval; pCR or downstaging confers excellent prognosis only for patients with these features, and not in a total group. This question is answered in Fig. 1. In conclusion, there are two ways to obtain enhanced downstaging or pCR: 1) by extending the rest period; then, local control remains much the same (Fig. 1); or 2) by enhancing the tumoricidal effect of radiation (by adding concomitant chemotherapy, for example), which demonstrates the benefits of local control (Bosset et al. 2006).

In two studies that compared short-course radiation and delayed surgery with long-course chemoradiation and delayed surgery, the pCR rates were lower in the short-course radiotherapy groups than in the chemoradiation groups (Latkauskas et al. 2012; Bujko et al. 2013a) (Table 1). However, this does not necessarily mean that local control will be lower. Although the rest period between the completion of radiotherapy and surgery was the same in both groups (6–7 weeks), the interval between the onset of irradiation and surgery was 1 month longer in the long-course chemoradiation groups. The interval should be measured between the start of radiation and surgery, and not between the completion of radiation and surgery. This is because each fraction of radiation sterilizes the same proportion (not number) of cancer cells (Benzen 2009). Thus, overwhelming cell killing occurs during the first 1–2 fractions. For this reason, an inherent bias favouring the chemoradiation group was inadvertently introduced into the design of the trials mentioned above.

With delayed surgery, there is a risk of tumour regrowth and the development of a cancer phenotype that produces distant metastases. If one imagines that the interval from irradiation to surgery lasts a few months instead of weeks, then most tumours would inevitably regrow. When does a tumour repopulation start? The evaluation of a labelling index showed the accelerated proliferation of cancer cells in some tumours 1 month after 5 × 5 Gy (Gasinska et al. 2007). Based on PET/CT examinations, another study showed decreased metabolic activity at 6 weeks from chemoradiation compared with the baseline values (Perez et al. 2012). However, increased metabolic activity in some tumours was observed between 6 and 12 weeks after chemoradiation. Thus, the long interval potentially jeopardizes oncological outcomes. This effect was not shown in the randomized studies (Bujko et al. 2006; Ngan et al. 2012; Francois et al. 1999; Saglam et al. 2014) or in the meta-analysis (Petrelli et al. 2013).

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References

Bujko K, Michalski W, Kepka L et al (2007) Association between pathologic response in metastatic lymph nodes after preoperative radiochemotherapy and the risk for distant metastases in rectal cancer: an analysis of outcomes in a randomized trial. Int J Rad Oncol Biol Phys 67:369–377

Benzen SM (2009) Dose-response relationship in radiotherapy. In: Joiner M, van der Kogel A (eds) Basic clinical radiobiology, 4th edn. Edward Arnold, London, pp 56–67

Bujko K, Nowacki MP, Nasierowska-Guttmejer A et al (2004) Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomized trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 72:15–24

Bujko K, Richter P, Smith FM et al (2013a) Preoperative radiotherapy and local excision of rectal cancer with immediate radical re-operation for poor responders: a prospective multicentre study. Radiother Oncol 106:198–205

Bujko K, Nasierowska-Guttmejer A, Wyrwicz L et al (2013b) Neoadjuvant treatment for unresectable rectal cancer: an interim analysis of a multicentre randomized study. Radiother Oncol 107:171–177

Bujko K, Nowacki MP, Nasierowska-Guttmejer A et al (2006) Long-term results of randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 93:1215–1223

Braendengen M, Tveit KM, Berglund A et al (2008) Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol 26:3687–3694

Bosset JF, Collette L, Calais G et al (2006) Chemoradiotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 355:1114–1123

Faria S, Kopek N, Hijal T et al (2014) Phase II trial of short-course radiotherapy followed by delayed surgery for locoregionally advanced rectal cancer. Colorectal Dis 16:66–70

Francois Y, Nemoz CJ, Bauliex J et al (1999) Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. J Clin Oncol 17:2396–2402

Foster JD, Jones EL, Falk S et al (2013) Timing of surgery after long-course neoadjuvant chemoradiotherapy for rectal cancer: a systematic review of the literature. Dis Colon Rectum 56:921–930

Fokstuen T, Holm T, Glimelius B (2009) Postoperative morbidity and mortality in relation to leukocyte counts and time to surgery after short-course preoperative radiotherapy for rectal cancer. Radiother Oncol 93:293–297

Frykholm GJ, Glimelius B, Pahlman L et al (1993) Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and evaluation of late secondary effects. Dis Colon Rectum 36:564–572

Folkesson J, Birgisson H, Pahlman L et al (2005) Swedish rectal cancer trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 23:5644–5650

Gasinska A, Skolyszewski J, Popiela T et al (2007) Bromodeoxyuridine labeling index as an indicator of early tumor response to preoperative radiotherapy in patients with rectal cancer. J Gastrointest Surg 11:520–528

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

Graf W, Dahlberg M, Osman MM et al (1997) Short-term preoperative radiotherapy results in down-staging of rectal cancer: a study of 1316 patients. Radiother Oncol 43:133–137

Habr-Gama A, Gama-Rodrigues J et al (2014) 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 88:822–828

Hatfield P, Hingorani M, Radhakrishna G et al (2009) Short-course radiotherapy, with elective delay prior to surgery, in patients with unresectable rectal cancer who have poor performance status or significant co-morbidity. Radiother Oncol 92:210–214

Hartley A, Giridharan S, Gray L et al (2002) Retrospective study of acute toxicity following short-course preoperative radiotherapy. Br J Surg 89:889–895

Latkauskas T, Pauzas H, Gineikiene I et al (2012) Initial results of a randomised 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 14:294–298

Maas M, Nelemans PJ, Valentini V et al (2010) Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 11:835–844

Marijnen CA, Nagtegaal ID, Klein Kranenbarg E et al (2001) No downstaging after short-term preoperative radiotherapy in rectal cancer patients. J Clin Oncol 19:1976–1984

Martling AL, Holm T, Johansson H et al (2001) The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. Cancer 92:896–902

Marijnen CA, Kapiteijn E, van de Velde CJ et al (2002) Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 20:817–825

Myerson RJ, Tan B, Hunt S et al (2014) Five fractions of radiation therapy followed by 4 cycles of FOLFOX chemotherapy as preoperative treatment for rectal cancer. Int J Radiat Oncol Biol Phys 88:829–836

Ngan SY, Burmeister B, Fisher RJ et al (2012) 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 30:3827–3833

Nilsson PJ, van Etten B, Hospers GA et al (2013) Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer–the RAPIDO trial. BMC Cancer 13:279

Pach R, Kulig J, Richter P et al (2012) Randomized clinical trial on preoperative radiotherapy 25 Gy in rectal cancer: treatment results at 5-year follow-up. Langenbecks Arch Surg 397:801–807

Peeters KC, Marijnen CA, Nagtegaal ID et al (2007) 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 246:693–701

Pettersson D, Cedermark B, Holm T et al (2010) Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. Br J Surg 97:580–587

Pettersson D, Glimelius B, Iversen H et al (2013) Impaired postoperative leucocyte counts after preoperative radiotherapy for rectal cancer in the Stockholm III Trial. Br J Surg 100:969–975

Pettersson D, Lorinc E, Holm T et al (2012) Tumour regression and pathological outcomes in the randomized Stockholm III trial of different radiotherapy regiments in rectal cancer. Preoperative radiotherapy in rectal cancer: aspects of different regimens. Thesis, Karolinska Institutet, Stockholm

Pettersson D, Holm T, Iversen H et al (2012b) Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer. Br J Surg 99:577–583

Perez RO, Habr-Gama A, São Julião GP et al (2012) Optimal timing for assessment of tumor response to neoadjuvant chemoradiation in patients with rectal cancer: do all patients benefit from waiting longer than 6 weeks? Int J Radiat Oncol Biol Phys 84:1159–1165

Petrelli F, Sgroi G, Sarti E et al (2013) Increasing the interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer: a meta-analysis of published studies. Ann Surg (Epub ahead of print)

Pucciarelli S, De Paoli A, Guerrieri M et al (2013) Local excision after preoperative chemoradiotherapy for rectal cancer: results of a multicenter phase II clinical trial. Dis Colon Rectum 56:1349–1356

Radu C, Berglund A, Pahlman L et al (2008) Short course preoperative radiotherapy with delayed surgery in rectal cancer: a retrospective study. Radiother Oncol 87:343–349

Rutten H, den Dulk M, Lemmens V et al (2007) Survival of elderly rectal cancer patients not improved: analysis of population based data on the impact of TME surgery. Eur J Cancer 3:2295–2300

Sauer R, Becker H, Hohenberger W et al (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351:1731–1740

Sebag-Montefiore D, Stephens RJ, Steele R et al (2009) Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 373:811–820

Shin SJ, Yoon HI, Kim NK et al (2011) Upfront systemic chemotherapy and preoperative short-course radiotherapy with delayed surgery for locally advanced rectal cancer with distant metastases. Radiat Oncol 6:99–106

Stockholm Colorectal Cancer Study Group (1990) Preoperative short-term radiation therapy in operable rectal carcinoma: a prospective randomized trial. Cancer 66:49–55

Saglam S, Bugra D, Saglam EK et al (2014) Fourth versus eighth week surgery after neoadjuvant radiochemotherapy in T3-4/N0 + rectal cancer: Istanbul R-01 study. J Gastrointest Oncol 5:9–17

Sloothaak DA, Geijsen DE, van Leersum NJ et al (2013) Dutch surgical colorectal audit: optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. Br J Surg 100:933–993

Suit HD, Gallager HS (1964) Intact tumor cells in irradiated tissue. Arch Pathol 78:648–651

Tyc-Szczepaniak D, Wyrwicz L, Kepka et al (2013) Palliative radiotherapy and chemotherapy instead of surgery in symptomatic rectal cancer with synchronous unresectable metastases: a phase II study. Ann Oncol 24:2829–2834

van den Broek CB, Vermeer TA, Bastiaannet E et al (2013) Impact of the interval between short-course radiotherapy and surgery on outcomes of rectal cancer patients. Eur J Cancer 49:3131–3139

van Dijk TH, Tamas K, Beukema JC et al (2013) 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 24:1762–1769

Veenhof AA, Kropman RH, Engel AF et al (2007) Preoperative radiation therapy for locally advanced rectal cancer: a comparison between two different time intervals to surgery. Int J Colorectal Dis 22:507–513

Widder J, Herbst F, Scheithauer W (2005) Preoperative sequential short-term radiotherapy plus chemotherapy can induce complete remission in T3N2 rectal cancer. Acta Oncol 44:921–923

Yeo SG, Oh JH, Kim DY et al (2013) Preoperative short-course concurrent chemoradiation therapy followed by delayed surgery for locally advanced rectal cancer: a phase 2 multicenter study (KROG 10-01). Int J Radiat Oncol Biol Phys 86:34–39

Early and Late Toxicity of Radiotherapy for Rectal Cancer

Ines Joye and Karin Haustermans

Abstract

With the implementation of total mesorectal excision surgery and neoadjuvant (chemo) radiotherapy, the outcome of rectal cancer patients has improved and a substantial proportion of them have become long-term survivors. These advances come at the expense of radiation- and chemotherapy-related toxicity which remains an underestimated problem. Radiation-induced early toxicity in rectal cancer treatment mainly includes diarrhea, cystitis, and perineal dermatitis, while bowel dysfunction, fecal incontinence, bleeding, and perforation, genitourinary dysfunction, and pelvic fractures constitute the majority of late toxicity. It is now generally accepted that short-course radiotherapy (SCRT) and immediate surgery is associated with less early toxicity compared to conventionally fractionated chemoradiotherapy with delayed surgery. There are no significant differences in late toxicity between both treatment regimens. While there is hardly an increase in early toxicity after preoperative SCRT with immediate surgery, late toxicity is substantial compared to surgery alone. Early toxicity is more frequent when a longer interval between SCRT and surgery is used and is comparable to the toxicity observed with conventionally fractionated radiotherapy except that it occurs after the end of the radiotherapy. So far, randomized phase III trials failed to demonstrate a substantial gain in tumoural response when oxaliplatin or molecular agents are added to the multimodality treatment. Moreover, the addition of these drugs increases toxicity and remains therefore experimental.

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Keywords
Rectal cancer · Toxicity · Neoadjuvant treatment

Abbreviations

CRT	Chemoradiotherapy
SCRT	Short-course radiotherapy
TME	Total mesorectal excision

1 Introduction

For patients with rectal cancer two preoperative radiation approaches are commonly used: preoperative short-course radiotherapy (SCRT) (5 × 5 Gy) followed by immediate surgery, and preoperative long-course chemoradiotherapy (CRT) with a radiation dose to 45–50.4 Gy in fractions of 1.8 to 2 Gy combined with fluoropyrimidine-based chemotherapy followed by total mesorectal excision (TME) 6–8 weeks after the end of the CRT (Kapiteijn et al. 2001; Sauer et al. 2004; Sebag-Montefiore et al. 2009; Swedish Rectal Cancer Trial 1997). Over the past years, outcome of rectal cancer patients has improved and a substantial proportion of them have become long-term survivors. These advances come at the expense of treatment-related toxicities which remain an underestimated problem. Radiation-induced bowel injury is more common than Crohn's disease. Only a fifth of the patients with these complaints visit a gastroenterologist and most who do so are managed ineffectively (Andreyev et al. 2013).

Increased awareness and recognition of treatment-related toxicity is of major importance as the associated morbidity affects quality of life. Nowadays, radiation-induced toxicity is no longer regarded as a constellation of vague and poorly defined symptoms, but as a real disease which needs to be investigated and can be treated appropriately. Treatment-related toxicity is classified as early and late, depending on the onset of symptoms. Early side-effects are observed during or shortly after treatment. In contrast, late toxicity develops after latent times of months to many years. The cut-off time to distinguish early from late effects has arbitrarily been set to 90 days after the onset of radiotherapy. Diarrhea, cystitis, and perineal dermatitis constitute the majority of radiation-induced early toxicity in rectal cancer treatment. Late toxicity mainly includes bowel dysfunction, fecal incontinence, bleeding and perforation, genitourinary dysfunction, and pelvic fractures. Progressive cell depletion and inflammation are the leading mechanisms of early side-effects. The pathogenetic pathways of late toxicity are more complex and involve processes as vascular sclerosis and fibrosis (Bentzen 2006; Denham et al. 2000). It is clear that early and late radiation effects are independent with regard to their pathogenesis and, in general, conclusions from the severity of early toxicity on the risk of late effects cannot be drawn. However, interactions between

acute and chronic toxicities have been described in early-responding tissues that have a protective function against mechanical and/or chemical exposures. These consequential late effects have been demonstrated in intestine, urinary tract, oral mucosa, skin, and lung tissues (Dörr and Hendry 2001; Dörr et al. 2005).

The fractionation sensitivity of tissues differs and is reflected by the α/β ratio. A higher α/β ratio means that tissue responses are less dependent on the amount of radiation administered with each fraction. Conversely, tissues with a lower α/β ratio are more sensitive to fractionation which means that a larger dose of radiation per fraction can enhance tumor response, but can also increase side-effects. Acutely responding tissues typically have an α/β ratio in the range of 7–20 Gy while for late-responding tissues, α/β ranges from 0.5 to 6 Gy (Joiner and van der Kogel 2009).

The aim of this paper is to provide an overview of the evidence on early and late treatment-related toxicity in patients treated with SCRT and CRT. Because of the plethora of reports and the wide variety in treatment schedules, we mainly focus on toxicity data available from large phase III randomized trials.

2 Toxicity Profiles

2.1 SCRT + Surgery Versus Surgery Alone

With the implementation of TME surgery and the administration of SCRT local recurrence rates of locally advanced rectal cancer have decreased from 30 to 50 % to less than 15 % (Heald and Ryall 1986; Kapiteijn et al. 2001; Swedish Rectal Cancer Trial 1997; van Gijn et al. 2011). In the Swedish Rectal Cancer Trial it was shown that preoperative SCRT improved the 5-year overall survival rate from 48 to 58 % (Swedish Rectal Cancer Trial 1997). Long-term follow-up of the Dutch TME trial could not confirm the benefit in overall survival, but showed preoperative radiotherapy improved 10-year survival in patients with cTNM stage III cancer and a negative circumferential resection margin (van Gijn et al. 2011). The gains in outcome have to be balanced against the acute and late adverse effects of treatment. This is of particular concern in patients with a low risk of local recurrence.

The Dutch TME trial showed that there was hardly an increase in early toxicity after preoperative SCRT followed by surgery within 1 week (Marijnen et al. 2002). Twenty-six percent of all irradiated patients experienced adverse effects, mostly grade I, representing only minor complaints. Grade 2 or 3 complications occurred in 7 % of the patients.

Of special concern is the acute lumbosacral plexopathy, causing long-lasting pain, and/or neurologic symptoms at the level of the lower lumbar plexus (Frykholm et al. 1996). Several patients treated with SCRT in Sweden developed acute pain in the back, in the gluteal region or in the legs during radiotherapy. Some of them suffered from chronic severe pain and permanent neurological symptoms. In the Dutch trial 53 patients experienced pain or discomfort in the legs

or in the gluteal region and treatment was interrupted or medication was needed in 18 patients (Marijnen et al. 2002). However, longstanding pain or neurologic symptoms did not occur after a median follow-up of 25.4 months. The difference between both series might be attributed to the location of the upper border of the radiation field (L5–S1 in the Dutch trial versus. mid L4 in the Swedish series) and to the shielding of the lordotic area at the dorsum of the sacrum in 90 % of the patients in the Dutch trial.

In contrast to early toxicity, late toxicity after SCRT immediately followed by surgery is substantial. Late toxicity data are extensively reported by Swedish series. The Stockholm I and II trials randomized 1,406 patients with clinically resectable rectal cancer between surgery with or without preoperative radiotherapy (Martling et al. 2001; Stockholm Rectal Cancer Study Group 1990). In the Stockholm I trial, a two-field technique was used and the beam limits extended from the upper border of the L2 vertebra down to the anal verge. The Stockholm II trial had a slightly different radiation protocol: a four-field box technique was used and a smaller volume was irradiated (beam limits were from the upper border of the L4 vertebra down to and including the anal canal).

Long-term toxicity results of the Stockholm trials, the Swedish rectal cancer trial and the Dutch TME trial uniformly showed irradiated patients had significantly more bowel movements and fecal incontinence compared to nonirradiated patients (Dahlberg et al. 1998; Peeters et al. 2005; Pollack et al. 2006a, b). Swedish patients also had an increased risk of hospital admissions during the first 6 months from the primary treatment, mainly for infections and gastrointestinal disorders (Birgisson et al. 2005a). Six months after treatment, irradiated patients in the Swedish series had in increased relative risk of small bowel obstruction and abdominal pain (Birgisson et al. 2005a, 2008; Holm et al. 1996). The higher incidence of small bowel obstruction in irradiated patients was not confirmed by the Dutch TME trial. The fact that Swedish series used extensive radiotherapy fields (the upper border including L2), limited portals and did not mandate blocking can explain this difference.

Late follow-up of the Stockholm trials showed an increased urinary incontinence in irradiated patients (Pollack et al. 2006a). Voiding problems were not significantly different in the Dutch TME trial between irradiated and nonirradiated patients. However, urinary dysfunction was of concern since approximately 39 % of the patients reported to be incontinent for urine in both groups and 57 % of patients wore pads (Peeters et al. 2005).

Interestingly, after a mean follow-up of 15 years, an increased incidence in cardiovascular disease was found in irradiated patients in the Stockholm trials (Pollack et al. 2006a). It was hypothesized pelvic irradiation invokes an inflammatory response in the pelvic arteries and an increased secretion of growth factors into the bloodstream has been suggested to accelerate the atherosclerotic process in remote arteries (Baerlocher et al. 2004; Chuang 1994). However, long-term follow-up of the Swedish Rectal Cancer Trial and the Dutch TME trial did not confirm the increased risk of cardiovascular disease after preoperative irradiation (Birgisson et al. 2005a; Peeters et al. 2005).

Currently, one paper showed an increased risk of secondary cancer in patients treated with SCRT (Birgisson et al. 2005b). After a follow-up of 14 years 9.5 % of the radiotherapy patients developed a secondary cancer, compared to 4.3 % of the nonirradiated patients. The secondary cancers mainly involved organs within or adjacent to the irradiated volume (colon, prostate, bladder, ureter).

The Dutch TME trial analyzed the grade of sexual dysfunction between irradiated and nonirradiated patients (Marijnen et al. 2005). SCRT had a negative impact on sexual function in males and females. Irradiated males experienced more ejaculation disorders, further deteriorating over time, which can be explained by the fact that seminal vesicles have been irradiated and might stopped functioning. For up to 2 years, irradiated men had a decrease in erectile function, suggesting late radiation damage to the small vessels.

While data from the Stockholm trials showed an increase in the number of femoral head or pelvic fractures in patients receiving preoperative radiotherapy, there was no difference in bony fractures in the Dutch TME trial (Holm et al. 1996; Peeters et al. 2005). This could be explained by the fact that the Dutch TME trial used a three- or four-field technique compared to the two-field technique used in the Stockholm I trial.

There is no consensus on whether late toxicity impairs social life: Pollack and colleagues reported no significant difference in quality of life scores between irradiated and nonirradiated patients (Pollack et al. 2006b). However, Dahlberg et al. showed an impaired social life in 30 % of the irradiated patients compared to 10 % of the surgery alone group (Dahlberg et al. 1998). In the Dutch TME trial, it was shown that despite the significant increase in fecal incontinence and sexual dysfunction in irradiated patients, there were few differences in quality of life between patients with and without SCRT (Marijnen et al. 2005). Interestingly, there was no significant difference in the overall perceived health between patients who underwent an abdominoperineal resection (APR) compared to those who underwent a low anterior resection. APR patients had fewer physical and psychological problems. This finding suggests that sphincter saving surgery may not always improve the quality of life.

2.2 Preoperative SCRT Versus Preoperative CRT

Three randomized trials directly compared preoperative SCRT with preoperative CRT (Bujko et al. 2006; Ngan et al. 2012; Siegel et al. 2009). The Polish and Australian trials showed that local recurrence and overall survival were similar between SCRT and CRT. However, the Australian trial indicated CRT may be more effective than SCRT in reducing the risk of local recurrence, especially for distal tumors. As shown by both trials, overall and grade III–IV early toxicity is more frequent in patients treated with CRT compared to those treated with SCRT (Table 1) (Bujko et al. 2004; Ngan et al. 2007). After a median follow-up of 4 years, the Polish study group found no significant differences in severe late toxicity, anorectal, and sexual dysfunction, treatment compliance or quality of life

Table 1 Early and late toxicity in phase III trials randomizing between SCRT and CRT

	Trial	Toxicity parameter	Preop SCRT (%)	Preop CRT (%)	*p*-value
Acute toxicity	Polish trial (Bujko et al. 2004)	Grade 3–4 adverse effects	3.2 (5/155)	18.2 (29/157)	$p < 0.001$
		All complications	24 (37/155)	85 (132/157)	$p < 0.001$
		Compliance	97.9	69.2	
	TROG trial (Ngan et al. 2007)	Grade 3–4 adverse effects	1.9	28	
Late toxicity	Polish trial (Bujko et al. 2006)	Overall toxicity	28.3 (39/138)	27.0 (38/141)	$p = 0.810$
		Severe toxicity[a]	10.1 (14/138)	7.1 (10/141)	$p = 0.360$
	TROG trial (Ngan et al. 2012)	Grade 3–4 small or large intestine toxicity	3.2 (5/155)	5.1 (8/158)	$p = 0.53$
		Grade 3–4 adverse effects	5.8 (9/155)	8.2 (13/158)	$p = 0.53$

[a]Toxicity was scored as severe when it met any of the following criteria: toxic death, grade III-IV or requiring major surgical intervention or hospitalization
SCRT = short-course radiotherapy; CRT = chemoradiotherapy

(Bujko et al. 2006; Pietrzak et al. 2007). The similar late toxicity profile of the two treatment regimens was confirmed by the Australian study. After a median follow-up of 5.9 years grade III and IV late toxicity occurred in 5.8 % after SCRT versus 8.2 % after LCRT ($p = 0.53$). Outcome and toxicity data from the Berlin study will be analyzed after a median follow-up of 5 years (Siegel et al. 2009).

2.3 Preoperative CRT Versus Postoperative CRT

The German CAO/ARO/AIO-94 trial randomized 823 patients with stage II and III rectal cancer between preoperative and postoperative CRT (Sauer et al. 2004). Long-term results after a median follow-up of 11 years showed preoperative CRT improved local control, but had no effect on overall survival, disease-free survival or distant metastases (Sauer et al. 2012). The overall rates of acute and long-term adverse effects were lower with the preoperative approach than with the postoperative approach, especially with respect to acute and chronic diarrhea and the development of strictures at the anastomotic site (Sauer et al. 2004). This resulted in an improved compliance with the chemoradiotherapy regimen if it was given before major surgery. Women showed higher hematologic and acute organ toxicity in the entire cohort as well as in the subgroup analyses according to pre- and postoperative CRT (Wolff et al. 2013). Interestingly, it was suggested acute toxicity was associated with an improved long-term outcome (Wolff et al. 2013).

2.4 CRT Versus Long-Course Radiotherapy

Three trials randomized patients with rectal cancer between long-course radiotherapy with or without fluoropyrimidine-based chemotherapy (Bosset et al. 2006; Brændengen et al. 2008; Gérard et al. 2006). While the EORTC 22921 and the FFCD 9203 trials included patients with resectable T3/T4 Nx M0 rectal cancer, Braendengen et al. investigated the role of chemotherapy in patients with unresectable T4 primary rectal carcinoma or with local recurrence from rectal carcinoma (Brændengen et al. 2008). The three trials led to similar outcome and toxicity results. Patients treated with chemotherapy had less local recurrences and a higher chance of pathological complete remission (pCR) of the tumor. The EORTC and French studies did not reveal any survival gains, whereas Braendengen et al. showed significant benefits related to time to treatment failure and cancer-specific survival for patients treated with CRT. The gains in outcome of the CRT group come at the expense of an increased acute toxicity, mainly due to gastrointestinal morbidity (i.e., diarrhea). There is a tendency towards more late toxicity in the CRT group, which frequently occurs as fecal and urinary incontinence and erectile dysfunction (Brændengen et al. 2011). The addition of chemotherapy to preoperative radiation therapy can impair social functioning (Brændengen et al. 2012; Tiv et al. 2010). However, Braendengen et al. showed there was no statistically significant difference in health-related quality of life between patients who received chemotherapy and those who did not (Brændengen et al. 2012).

2.5 SCRT Versus SCRT with Delayed Surgery

In an attempt to increase the efficiency of radiotherapy for elderly patients with co-morbidities and unresectable rectal cancer, SCRT has been associated with a prolonged interval to surgery. The idea is to obtain similar downstaging and downsizing of the tumor as when CRT is applied. This treatment is more toxic than SCRT with immediate surgery, primarily because the main organ at risk for early toxicity (the rectum) is not removed before the occurrence of adverse effects.

Retrospective series showed SCRT with a prolonged interval to surgery was associated with early toxicity rates less than 10 % (Hatfield et al. 2009; Pettersson et al. 2012; Radu et al. 2008). However, such series tend to underestimate toxicity as they are affected by reporting bias (e.g., Hatfield et al. restricted the assessment of severe early toxicity as to whether hospital-admission was necessary) (Hatfield et al. 2009). In prospective studies toxicity grades I and II are more accurately scored and therefore higher—and more reliable—toxicity rates are reported. Whether SCRT with delayed surgery is a valuable option for all rectal cancer patients is not yet known. The multicentric randomized Stockholm III trial will probably give more evidence. In this 3-arm trial, patients with primary resectable rectal cancer are randomized to preoperative SCRT followed by surgery within

1 week or after 4–8 weeks, or long-course preoperative RT (25 × 2 Gy) with surgery after 4–8 weeks. In an interim analysis no significant difference in early toxicity could be detected between the different treatment schedules (Pettersson et al. 2010).

2.6 Influence of Cytotoxic Agents

Randomized trials have shown that the addition of 5-fluorouracil (5-FU) or its prodrug capecitabine to preoperative radiotherapy increases pCR and local control rates over radiotherapy alone. However, with the exception of the Swedish trial, phase III clinical trials failed to show that addition of (C) RT to TME surgery results in an improved survival (Bosset et al. 2006; Gérard et al. 2012; Peeters et al. 2007). Current strategies therefore aim at improving the outcome by the addition of other drugs to the multimodality treatment.

Oxaliplatin in combination with 5-FU has shown to enhance tumor response in metastatic colorectal cancer and to improve survival in the adjuvant setting (André et al. 2004; Goldberg et al. 2004). It was expected that oxaliplatin to standard preoperative CRT in rectal cancer might both increase pCR and reduce micrometastases at distant sites. Unfortunately, most phase III trials so far failed to show an improvement in tumoural response (Aschele et al. 2011; Gérard et al. 2010; Gérard et al. 2012; Rödel et al. 2012; Roh et al. 2009; Schmoll et al. 2013). While an increase in pCR rate was only shown in the German CAO/ARO/AIO-04 trial, 3 other trials reported an increase in grade 3 and 4 toxicity when oxaliplatin was added to the preoperative regimen. Patients mainly suffered from diarrhea, nausea, dermatitis, fatigue, and peripheral neuropathy. Hematological problems were less frequent. Although the addition of oxaliplatin to the preoperative regimen significantly increased acute grade 3 or 4 toxicity, it did not result in more surgical complication or postoperative deaths within 60 days. The 3-year follow-up results of the ACCORD trial showed, grade 3 or 4 toxicity was equal (5.4 vs. 6.5 % with and without oxaliplatin respectively) and mainly involved gastrointestinal or sexual problems (Gérard et al. 2012). There was no significant difference in bowel incontinence, erectile dysfunction, and social life disturbance between both groups. A meta-analysis concluded the combination of oxaliplatin and fluorouracil in the preoperative setting still seems promising, either with a modified schedule or as induction therapy prior to CRT or after CRT, prior to surgery (An et al. 2013). It is clear longer follow-up is needed to assess further impact on efficacy end points.

In an attempt to further enhance tumoural response, phase I/II studies evaluated the addition of targeted agents as radiosensitizers in rectal cancer (Dewdney et al. 2012; Marquardt et al. 2009). Up to now, studies with epidermal growth factor receptor inhibitors (i.e., cetuximab) and with VEGF inhibitors (i.e., bevacizumab) have failed to show a significant benefit in pCR compared to standard CRT. Moreover, caution is needed regarding the toxicity pattern (diarrhea, skin toxicity, perforations) and surgical complications (wound healing, bleeding, fistulisation)

(Marquardt et al. 2009). No randomized phase III studies are currently available. Therefore, the use of these agents in the preoperative treatment for rectal cancer remains experimental.

3 Toxicity Management

With the strict application of dose-volume constraints and with the use of advanced radiation delivery techniques, radiation-induced side-effects are reduced, but not abolished. The first step for the correct management of radiation toxicity is to identify the pathophysiological mechanisms of the symptoms. The effects of dietary manipulation and cytoprotective and anti-inflammatory drugs have been investigated (Fuccio et al. 2012; Wedlake et al. 2013). To date, there is insufficient evidence to recommend nutritional intervention or administration of cytoprotective drugs during pelvic radiotherapy. In severe toxicity total replacement of diet with elemental formula may be appropriate. Probiotics seem promising in reducing the incidence and severity of radiation-induced diarrhea but can only be introduced into clinical practice with rigorous safety analysis, especially in immunocompromised patients (Chitapanarux et al. 2010; Delia et al. 2007).

Optimal toxicity management requires close collaboration between general practitioners, gastro-enterologists, radiation oncologists, oncologists, dieticians, nurses, and surgeons. Andreyev et al. reported that patients who were given targeted intervention in a detailed clinical algorithm had better improvements in radiotherapy-induced gastrointestinal symptoms than did patients who were given usual care (Andreyev et al. 2013). The authors also found that this algorithm-based care could be managed by a trained nurse.

4 Future Prospects

Efforts are made to decrease the incidence of radiation-induced toxicity. In radiotherapy, conformal techniques have been developed to precisely deliver high doses of radiation to the tumor mass while the surrounding normal tissue is spared. In that way, intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT) and proton therapy allow for a precise dose delivery to the target volume, thereby reducing the doses to the organs a risk (i.e., small bowel) (Samuelian et al. 2012; Wolff et al. 2012). It remains to be seen whether the dosimetrical benefits of these highly conformal radiation techniques will translate into less acute and late toxicity.

Currently, studies are undertaken investigating parameters that predict treatment-related toxicity. Identification of these parameters would be a promising step towards an individualized risk-adapted treatment for rectal cancer patients. It remains to be seen whether new treatment schedules (e.g., SCRT followed by neoadjuvant chemotherapy and surgery), RAPIDO trial will shed new light on toxicity profiles in rectal cancer treatment (Nilsson et al. 2013).

5 Conclusions

Treatment-related toxicity in rectal cancer patients is substantial and depends on the type of neoadjuvant treatment and the timing of surgery. With the advent of new treatment techniques, some patients with rectal cancer can be considered long-term survivors. Awareness and recognition of treatment-related toxicity has gained in importance. In their decision-making of which treatment to prescribe, physicians consider toxicity, need for downsizing, treatment costs, convenience, and patients' preference. Results from ongoing randomized trials are expected to shed new light on toxicity profiles in rectal cancer.

References

An X, Lin X, Wang FH et al (2013) Short term results of neoadjuvant chemoradiotherapy with fluoropyrimidine alone or in combination with oxaliplatin in locally advanced rectal cancer: a meta analysis. Eur J Cancer 49:843–851

André T, Boni C, Mounedji-Boudiaf L et al (2004) Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350:2343–2351

Andreyev HJ, Benton BE, Lalji A et al (2013) Algorithm-based management of patients with gastrointestinal symptoms in patients after pelvic radiation treatment (ORBIT): a randomised controlled trial. Lancet 382:2084–2092

Aschele C, Cionini L, Lonardi S et al (2011) Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomised phase III trial. J Clin Oncol 29:2773–2780

Baerlocher MO, Rajan DK, Ing DJ, Rubin BB (2004) Primary stenting of bilateral radiation-induced external iliac stenoses. J Vasc Surg 40:1028–1031

Bentzen SM (2006) Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. Nat Rev Cancer 6:702–713

Birgisson H, Påhlman L, Gunnarson U, Glimelius B (2005a) Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. J Clin Oncol 23:8697–8705

Birgisson H, Påhlman L, Gunnarsson U, Glimelius B (2005b) Occurrence of second cancers in patients treated with radiotherapy for rectal cancer. J Clin Oncol 23:6126–6131

Birgisson H, Påhlman L, Gunnarson U, Glimelius B (2008) Late gastrointestinal disorders after rectal cancer surgery with and without preoperative radiation therapy. Br J Surg 95:206–213

Bosset JF, Collette L, Calais G et al (2006) Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 355:1114–1123

Brændengen M, Tveit KM, Berglund A et al (2008) Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol 26:3687–3694

Brændengen M, Tveit KM, Bruheim K, Cvancarova M, Berglund Å, Glimelius B (2011) Late patient-reported toxicity after preoperative radiotherapy or chemoradiotherapy in nonresectable rectal cancer: results from a randomized Phase III study. Int J Radiat Oncol Biol Phys 81:1017–1024

Brændengen M, Tveit KM, Hjermstad MJ et al (2012) Health-related quality of life (HRQoL) after multimodal treatment for primarily non-resectable rectal cancer. Long-term results from a phase III study. Eur J Cancer 48:813–819

Bujko K, Nowacki M, Nasierwska-Guttmejer A et al (2006) Long-term results of a randomised trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 93:1215–1223

Bujko K, Nowacki M, Nasierwska-Guttmejer A et al (2004) Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy versus conventionally fractionated radiochemotherapy. Radiother Oncol 72:15–24

Chitapanarux I, Chitapanarux T, Traisathit P, Kudumpee S, Tharavichitkul E, Lorvidhaya V (2010) Randomized controlled trial of live Lactobacillus acidophilus plus Bifidobacterium bifidum in prophylaxis of diarrhea during radiotherapy in cervical cancer patients. Radiat Oncol 5:31

Chuang VP (1994) Radiation-induced arteritis. Semin Roentgenol 29:64–69

Dahlberg M, Glimelius B, Graf W, Påhlman L (1998) Preoperative irradiation affects functional results after surgery for rectal cancer: results from a randomized study. Dis Colon Rectum 41:543–549

Delia P, Sansotta G, Donato V et al (2007) Use of probiotics for prevention of radiation-induced diarrhea. Tumori 93(Suppl 2):1–6

Denham JW, Hauer-Jensen M, Kron T, Langberg CW (2000) Treatment-time-dependence models of early and delayed radiation injury in rat small intestine. Int J Radiat Oncol Biol Phys 48:871–887

Dewdney A, Cunningham D, Tabernero J et al (2012) Multicenter randomised phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol 30:1620–1627

Dörr W, Hendry JH (2001) Consequential late effects in normal tissues. Radiother Oncol 61:223–231

Dörr W, Bertmann S, Hermann T (2005) Radiation induced lung reactions in breast cancer therapy. Modulating factors and consequential effects. Strahlenther Onkol 181:567–573

Fuccio L, Guida A, Andreyev HJ (2012) Management of intestinal complications in patients with pelvic radiation disease. Clin Gastroenterol Hepatol 10:1326–1334

Frykholm GJ, Sintorn K, Montelius A, Jung B, Påhlman L, Glimelius B (1996) Early lumbosacral plexopathy during and after preoperative radiotherapy of rectal adenocarcinoma. Radiother Oncol 38:121–130

Gérard JP, Conroy T, Bonnetain F et al (2006) Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 24:4620–4625

Gérard JP, Azria D, Gourgou-Bourgade S et al (2010) Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol 28:1638–1644

Gérard JP, Azria D, Gourgou-Bourgade S et al (2012) Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomised trial in rectal cancer. J Clin Oncol 30:4558–4565

Goldberg RM, Sargent DJ, Morton RF et al (2004) A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 22:23–30

Hatfield P, Hingorani M, Radhakrishna G et al (2009) Short-course radiotherapy, with elective delay prior to surgery, in patients with unresectable rectal cancer who have poor performance status or significant co-morbidity. Radiother Oncol 92:210–214

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

Holm T, Singnomklao T, Rutqvist LE, Cedermark B (1996) Adjuvant preoperative radiotherapy in patients with rectal carcinoma. Adverse effects during long term follow-up of two randomized trials. Cancer 78:968–976

Joiner M, van der Kogel A (2009) Basic Clinial Radiobiology. Hodder Arnold, London

Kapiteijn E, Marijnen CA, Nagtegaal ID et al., Dutch Colorectal Cancer Group (2001) Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 345:638–646

Marijnen CA, Kapiteijn E, van de Velde CJ et al., Cooperative Investigators of the Dutch Colorectal Cancer Group (2002) Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 20:817–825

Marijnen CA, van de Velde CJ, Putter H et al (2005) Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomised trial. J Clin Oncol 23:1847–1858

Marquardt F, Rödel F, Capalbo G, Weiss C, Rödel C. (2009) Molecular targeted treatment and radiation therapy for rectal cancer. Strahlenther Onkol 185:371–378

Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B (2001) The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. Cancer 92:896–902

Ngan S, Fisher R, Mackay J et al (2007) Early adverse events in a randomised trial of short course versus long course preoperative radiotherapy for T3 adenocarcinoma of rectum: a trans-tasman radiation oncology group trial (TROG01.04). Eur J Cancer 5:237(Abstract)

Ngan SY, Burmeister B, Fisher RJ et al (2012) Randomised 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 30:3827–3833

Nilsson PJ, van Etten B, Hospers GA et al (2013) Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer–the RAPIDO trial. BMC Cancer 13:279

Peeters KC, van de Velde CJ, Leer JW et al (2005) 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 23:6199–6206

Peeters KC, Marijnen CA, Nagtegaal ID et al (2007) 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 246:693–701

Pettersson D, Cedermark B, Holm T et al (2010) Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. Br J Surg 97:580–587

Pettersson D, Holm T, Iversen H, Blomqvist L, Glimelius B, Martling A (2012) Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer. Br J Surg 99:577–583

Pietrzak L, Bujko K, Nowacki MP et al., Polish Colorectal Study Group (2007) Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: report of a randomised trial. Radiother Oncol 84:217–25

Pollack J, Holm T, Cedermark B et al (2006a) Late adverse effects of short-course preoperative radiotherapy in rectal cancer. Br J Surg 93:1519–1525

Pollack J, Holm T, Cedermark B, Holmström B, Mellgren A (2006b) Long-term effect of preoperative radiation therapy on anorectal function. Dis Colon Rectum 49:345–352

Radu C, Berglund A, Påhlman L, Glimelius B (2008) Short-course preoperative radiotherapy with delayed surgery in rectal cancer - a retrospective study. Radiother Oncol 87:343–349

Rödel C, Liersch T, Becker H et al (2012) Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 13:679–687

Roh MS, Colangelo LH, O'Connell MJ et al (2009) Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol 31:5124–5130

Samuelian JM, Callister MD, Ashman JB, Young-Fadok TM, Borad MJ, Gunderson LL (2012) Reduced early bowel toxicity in patients treated with intensity-modulated radiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys 82:1981–1987

Sauer R, Becker H, Hohenberger W et al., German Rectal Cancer Study Group (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351:1731–1740

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

Schmoll HJ, Haustermans K, Price T et al (2013) Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: response to the local treatment after chemoradiation and surgery as secondary endpoint. Ann Oncol 24:iv11–24

Sebag-Montefiore D, Stephens RJ, Steele R et al (2009) Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 373:811–820

Siegel R, Burock S, Wernecke KD et al (2009) Preoperative short-course radiotherapy versus combined radiochemotherapy in locally advanced rectal cancer: a multi-centre prospectively randomised study of the Berlin Cancer Society. BMC Cancer 9:50

Stockholm Rectal Cancer Study Group (1990) Preoperative short-term radiation therapy in operable rectal carcinoma. A prospective randomised trial. Cancer 66:49–55

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

Tiv M, Puyreveau M, Mineur L et al (2010) Long-term quaity of life in patients with rectal cancer treated with preoperative (chemo)-radiotherapy within a randomized trial. Cancer Radiother 14:530–534

van Gijn W, Marijnen CA, Nagtegaal ID et al., Dutch Colorectal Cancer Group (2011) Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 12:575–82

Wedlake LJ, Shaw C, Whelan K, Andreyec HJ (2013) Systematic review: the efficacy of nutritional interventions to counteract acute gastrointestinal toxicity during therapeutic pelvic radiotherapy. Aliment Pharmacol Ther 37:1046–1056

Wolff HA, Wagner DM, Conradi LC et al (2012) Irradiation with protons for the individualized treatment of patients with locally advanced rectal cancer: a planning study with clinical implications. Radiother Oncol 102:30–37

Wolff HA, Conradi LC, Beissbarth T et al (2013) Gender affects acute organ toxicity during radiochemotherapy for rectal cancer: long-term results of the German CAO/ARO/AIO-94 phase III trial. Radiother Oncol 108:48–54

Immediate Surgery or Clinical Follow-Up After a Complete Clinical Response?

Angelita Habr-Gama and Rodrigo Oliva Perez

Abstract

Neoadjuvant chemoradiation (CRT) is considered as one of the preferred treatment strategies for patients with locally advanced rectal cancer. This treatment strategy may lead to significant tumor regression, ultimately leading to complete pathological response in up to 42% of patients. Assessment of tumor response following CRT and before radical surgery may identify patients with complete clinical response that could be managed non operatively with strict follow-up (Watch & Wait Strategy).

Radical surgery has always been the mainstay of the treatment of rectal cancer. However, local recurrence rates were still considerably high in a subset of patients even after appropriate surgery including total mesorectal excision (Simunovic et al. 2003). The concern for local recurrences prompted the surgical and radiation oncology community to consider additional therapy in selected patients considered to be at a higher risk for local disease relapse. Indeed, additional postoperative radiation (adjuvant) did improve local disease control even though at a considerably high cost in terms of toxicity and long-term complications (Ooi et al. 1999). The solution for this problem was the use of preoperative therapy in patients with locally invasive rectal cancer that was shown to improve local disease control and

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significantly decrease immediate and long-term toxicities. The addition of chemotherapy to radiation therapy in these patients seems to be beneficial in terms of local disease control (Sauer et al. 2004).

The benefits of neoadjuvant chemoradiation were not restricted to long-term local disease control as confirmed by an update of the German Trial after 11 years of follow-up (Sauer et al. 2012). One of its main consequences is that it may lead to variable degrees of tumor regression, reflected by primary tumor reduction in size (downsizing), in-depth penetration, and possible perirectal node sterilization (downstaging). In up to 42 % of the cases, complete pathological tumor regression has been reported (Sanghera et al. 2008). Such findings challenged the role of standardized radical resection in all patients with rectal cancer particularly after complete tumor response to neoadjuvant therapy. One could ask about the oncological benefit in a patient following radical rectal resection where not a single cancer cell is removed (Habr-Gama et al. 1998; Habr-Gama et al. 2004).

But the solution for this riddle is not straightforward, as it seems. Assuring complete tumor regression is not an easy task, even when radical resection is performed (Chen et al. 2011). However, exposing patients to considerable morbid procedure leading to variable rates of urinary, sexual and fecal dysfunctions, the requirement for temporary or permanent stomas and the expected procedure-related mortality may not be considered the best alternative (Mass et al. 2012; Habr-Gama et al. 2004).

In addition, the degree of tumor regression may be influenced by several different factors that should be taken into account. Obviously, radiation doses and chemotherapy regimens may both influence the rates of complete tumor regression. Indeed, experimental studies suggest that cancer cells significantly lose their metastatic potential after being treated with 45 Gy of radiation (Withers and Haustermans 2004). However, studies have not definitively explained the reasons why after similar doses some tumors respond completely while others seem to be absolutely resistant to such therapy. Recent studies in molecular biology have provided initial hints of possible specific combinations of genetic mutations rendering cancer cells either sensitive or resistant to chemoradiation (Kim et al. 2007).

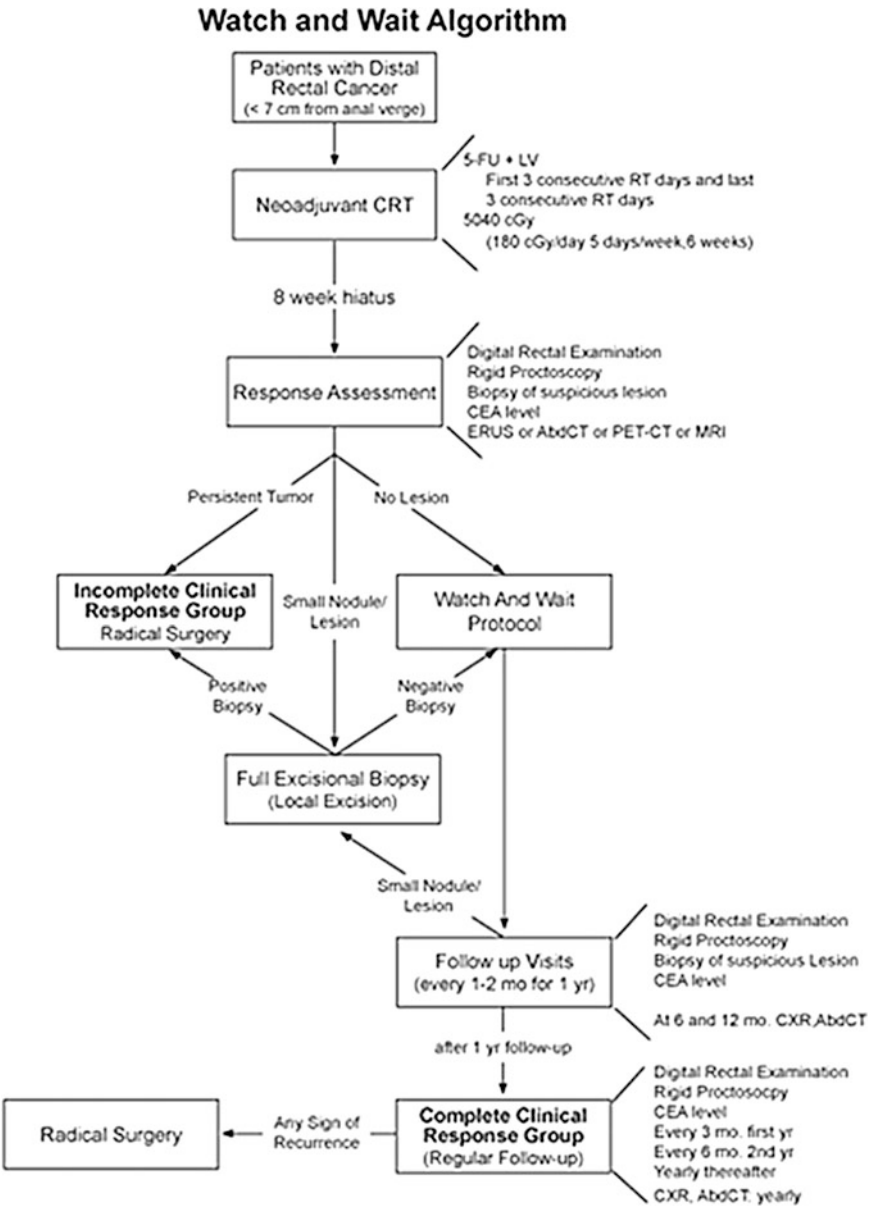
Another factor that seems to influence tumor regression to neoadjuvant therapy is the time elapsed between completion of treatment and response assessment. This was first suggested by data of patients with anal cancer that exhibited and significant increase in tumor response simply by waiting 8 weeks after completion of therapy instead of 4 weeks (Deniaud-Alexandre et al. 2003). In rectal cancer, retrospective studies also indicated that longer interval periods were associated with increased rates of complete tumor regression (Moore et al. 2004). This fact was more recently demonstrated in studies supporting the idea that degree of tumor downstaging is probably time-dependent suggesting that the more you wait, the more you get in terms of tumor regression (Tulchinsky et al. 2008; Kalady et al. 2009).

Interestingly, chemoradiation seems to exert significant effects in perirectal nodes in addition to the primary tumor. First, tumors treated by neoadjuvant CRT have consistently resulted in decreased rates of stage III or node-positive disease

(Sauer et al. 2004). The rates of micrometastases among perirectal nodes seem to be decreased by neoadjuvant CRT (Perez et al. 2005). The observation of residual mucinous deposits among lymph nodes in the absence of cancer cells also suggests the possibility of lymph node sterilization as a result of CRT (Perez et al. 2005). Finally, the overall number of recovered nodes is significantly decreased in patients after neoadjuvant therapy (Habr-Gama et al. 2008b; Sermier et al. 2006); again, this effect has also been shown to be time-dependent since longer interval periods between CRT completion and surgery was associated with fewer recovered nodes (Sermier et al. 2006).

In this setting, patients with apparent complete clinical tumor regression would be ideal candidates for alternative treatment strategies including no immediate surgery and rigorous close observation.

The main obstacle to this approach is the risk of leaving microscopic residual disease within the rectum or in perirectal nodes. Indeed, distinguishing transmural fibrosis from microscopic residual disease may be quite difficult. Clinical assessment alone has been shown quite disappointing sensitivity and specificity rates in previous retrospective studies. However, some of these studies included tumor response assessment performed at 6 weeks from CRT completion, possibly too early and reflecting the detection of residual disease in the setting of ongoing necrosis (Hiotis et al. 2002). Also, studies have detected residual microscopic nodal disease in patients with complete pathological primary tumor regression (ypT0). Again, these studies included patients managed by radical surgery after 6 weeks from CRT completion and may also reflect potential interruption of ongoing radiation-related tumor necrosis (Zmora et al. 2004). This is suggested by the observation of absence of residual nodal disease in patients with ypT0 after periods of longer intervals than 6 weeks after CRT completion (Habr-Gama et al. 2008b).



It has been our strategy to assess tumor response at least after 8 weeks from CRT completion including clinical assessment with digital rectal examination, rigid proctoscopy and CEA levels in combination with radiological assessment, mainly performed to rule out residual extra-luminal disease (Habr-Gama et al. 2010).

Only patients fulfilling these stringent criteria have been considered for this nonoperative approach (Watch & Wait) (Perez et al. 2009). Patients with any small residual nodule or excisable scar are managed by a full-thickness transanal excision primarily as a diagnostic (or eventually as therapeutic) approach (Perez et al. 2013). Only patients with no detectable residual disease or without microscopic disease after FTLE (ypT0) are considered for observation alone (Habr-Gama 2006).

In a retrospective analysis of patients managed by this approach, patients with complete clinical response did no worse than patients managed by radical surgery and pathological complete response in terms of survival (Habr-Gama et al. 2004). Late local relapses occurred in approximately 10 % of these patients not immediately operated on and in a considerably longer interval when compared to systemic relapses. In addition, patients with exclusive local relapse were all amenable to salvage resection (Habr-Gama et al. 2006). Recently, other institutions have observed similar results further supporting this treatment strategy in highly selected patients (Maas et al. 2012).

Still, assessment of tumor response remains a challenging issue. Clinical assessment is associated with a learning curve and probably has improved over time during our 15-year experience period. Even so, a subset of patients who were initially considered as complete responders presented with residual disease or early tumor regrowth/recurrence within 12 months of follow-up. It is worth mentioning that we have arbitrarily considered this period of 12 months as the minimum to consider a sustained complete clinical response in these patients (Habr-Gamaet al. 2006).

One of the main concerns with this "Watch & Wait Strategy" would be the risk of harming these particular patients misdiagnosed as complete clinical responses after delayed surgery. However, in a retrospective review, there was no survival compromise in patients with initial suspicion for complete clinical response who had undergone delayed surgery for early tumor regrowth (Habr-Gama et al. 2008a).

The task of identifying patients with complete tumor regression is one of the most difficult challenges faced by colorectal surgeons. Up till now, this aims at nearly 30–40 % of patients with distal rectal cancers but this share may actually increase with modern and newer CRT drugs and regimens. In fact, the addition of chemotherapy cycles during the RT and the "resting" period between RT and surgery with a modest increase in RT dose (50.4–54 Gy) has led to a significant increase in complete clinical response rates to over 50 % of patients (Habr-Gama et al. 2009; Habr-Gama et al. 2013).

In addition, assessment of tumor response may further improve its accuracy by the combination of different radiological modalities such as PET/CT and MRI imaging brought together in a single radiological study as well as using individualized intervals between CRT completion and assessment of tumor response for different groups of patients.

1 Conclusions

Complete clinical response may be observed in up to 50 % of patients with rectal cancer following neoadjuvant chemoradiation. The actual percentage of patients that will develop complete response may vary according to baseline staging, type of chemoradiation regimen, and timing of assessment of response. Specific clinical, endoscopic, and radiological features may identify patients likely to have a complete pathological response. Management of these highly selected patients without immediate radical surgery and strict surveillance ("Watch & Wait") may provide an interesting alternative avoiding significant morbidity and mortality associated with radical surgery without compromising oncological outcomes. As understanding of molecular biology aspects associated with these tumors grows, additional tools may further improve selection of appropriate candidates for this organ-sparing procedure in patients with distal rectal cancer.

References

Chen Z, Duldulao MP, Li W, Lee W, Kim J, Garcia-Aguilar J (2011) Molecular diagnosis of response to neoadjuvant chemoradiation therapy in patients with locally advanced rectal cancer. J Am Coll Surg 212(6):1008–1017

Deniaud-Alexandre E, Touboul E, Tiret E, Sezeur A, Houry S, Gallot D, Parc R, Huang R, Qu SH, Huart J, Pene F, Schlienger M (2003) Results of definitive irradiation in a series of 305 epidermoid carcinomas of the anal canal. Int J Radiat Oncol Biol Phys 56:1259–1273

Habr-Gama A (2006) Assessment and management of the complete clinical response of rectal cancer to chemoradiotherapy. Colorectal Dis 8(Suppl 3):21–24

Habr-Gama A, de Souza PM, Ribeiro U Jr, Nadalin W, Gansl R, Sousa AH Jr, Campos FG, Gama-Rodrigues J (1998) Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. Dis Colon Rectum 41:1087–1096

Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Jr., Silva e Sousa AH, Jr., Campos FG, Kiss DR, Gama-Rodrigues J (2004) Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 240:711–717 (discussion 7–8)

Habr-Gama A, Perez RO, Proscurshim I, Campos FG, Nadalin W, Kiss D, Gama-Rodrigues J (2006) Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. J Gastrointest Surg 10:1319–1328 (discussion 28–29)

Habr-Gama A, Perez RO, Proscurshim I, Nunes Dos Santos RM, Kiss D, Gama-Rodrigues J, Cecconello I (2008a) Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome? Int J Radiat Oncol Biol Phys 71:1181–1188

Habr-Gama A, Perez RO, Proscurshim I, Rawet V, Pereira DD, Sousa AH, Kiss D, Cecconello I (2008b) Absence of lymph nodes in the resected specimen after radical surgery for distal rectal cancer and neoadjuvant chemoradiation therapy: what does it mean? Dis Colon Rectum 51:277–283

Habr-Gama A, Perez RO, Sabbaga J, Nadalin W, Sao Juliao GP, Gama-Rodrigues J (2009) Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. Dis Colon Rectum 52:1927–1934

Habr-Gama A, Perez RO, Wynn G, Marks J, Kessler H, Gama-Rodrigues J (2010) Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: characterization of clinical and endoscopic findings for standardization. Dis Colon Rectum 53:1692–1698

Habr-Gama A, Sabbaga J, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Bailao Aguilar P (2013) Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management. Dis Colon Rectum 56(10):1109–1117

Hassan I, Cima RR (2007) Quality of life after rectal resection and multimodality therapy. J Surg Oncol 96:684–692

Hiotis SP, Weber SM, Cohen AM, Minsky BD, Paty PB, Guillem JG, Wagman R, Saltz LB, Wong WD (2002) Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: an analysis of 488 patients. J Am Coll Surg 194:131–135 (discussion 5–6)

Kalady MF, de Campos-Lobato LF, Stocchi L, Geisler DP, Dietz D, Lavery IC (2009) Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. Ann Surg 250(4):582–589

Kim IJ, Lim SB, Kang HC, Chang HJ, Ahn SA, Park HW, Jang SG, Park JH, Kim DY, Jung KH, Choi HS, Jeong SY, Sohn DK, Kim DW, Park JG (2007) Microarray gene expression profiling for predicting complete response to preoperative chemoradiotherapy in patients with advanced rectal cancer. Dis Colon Rectum 50:1342–1353

Maas M, Beets-Tan RG, Lambregts DM, Lammering G, Nelemans PJ, Engelen SM, van Dam RM, Jansen RL, Sosef M, Leijtens JW, Hulsewe KW, Buijsen J, Beets GL (2012) Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 29:4633–4640

Moore HG, Gittleman AE, Minsky BD, Wong D, Paty PB, Weiser M, Temple L, Saltz L, Shia J, Guillem JG (2004) Rate of pathologic complete response with increased interval between preoperative combined modality therapy and rectal cancer resection. Dis Colon Rectum 47:279–286

Ooi BS, Tjandra JJ, Green MD (1999) Morbidities of adjuvant chemotherapy and radiotherapy for resectable rectal cancer: an overview. Dis Colon Rectum 42:403–418

Perez RO, Habr-Gama A, Nishida Arazawa ST, Rawet V, Coelho Siqueira SA, Kiss DR, Gama-Rodrigues JJ (2005) Lymph node micrometastasis in stage II distal rectal cancer following neoadjuvant chemoradiation therapy. Int J Colorectal Dis 20:434–439

Perez RO, Sao Juliao GP, Habr-Gama A, Kiss D, Proscurshim I, Campos FG, Gama-Rodrigues JJ (2009) Cecconello I. The role of carcinoembriogenic antigen in predicting response and survival to neoadjuvant chemoradiotherapy for distal rectal cancer. Dis Colon Rectum 52:1137–1143

Perez RO, Habr-Gama A, Lynn PB, Sao Juliao GP, Bianchi R, Proscurshim I, Gama-Rodrigues J (2013) Transanal endoscopic microsurgery for residual rectal cancer (ypT0-2) following neoadjuvant chemoradiation therapy: another word of caution. Dis Colon Rectum 56:6–13

Sanghera P, Wong DW, McConkey CC, Geh JI, Hartley A (2008) Chemoradiotherapy for rectal cancer: an updated analysis of factors affecting pathological response. Clin Oncol 20(2):176–183

Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351:1731–1740

Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, Becker H, Raab HR, Villanueva MT, Witzigmann H, Wittekind C, Beissbarth T, Rodel C (2012) 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 30:1926–1933

Sermier A, Gervaz P, Egger JF, Dao M, Allal AS, Bonet M, Morel P (2006) Lymph node retrieval in abdominoperineal surgical specimen is radiation time-dependent. World J Surg Oncol 4:29

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

Tulchinsky H, Shmueli E, Figer A, Klausner JM, Rabau M (2008) An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. Ann Surg Oncol 15:2661–2667

Withers HR, Haustermans K (2004) Where next with preoperative radiation therapy for rectal cancer? Int J Radiat Oncol Biol Phys 58:597–602

Zmora O, Dasilva GM, Gurland B, Pfeffer R, Koller M, Nogueras JJ, Wexner SD (2004) Does rectal wall tumor eradication with preoperative chemoradiation permit a change in the operative strategy? Dis Colon Rectum 47:1607–1612

Part V
Rectal Cancer with Synchronous Liver Metastases

Limits of Colorectal Liver Metastases Resectability: How and Why to Overcome Them?

For Progress in Cancer Research

Serge Evrard

Abstract

Offering surgery is to date the best case scenario for patients with colorectal liver metastases (CRLM). Few oncological topics have progressed as much as the treatment of CRLM. New surgical techniques, conversion therapies, and imaging allow us to pursue the ultimate limit for surgery of CLM before compromising patient benefits. Pushing the limits of surgery involves pushing the limits of conversion therapies too, increasingly taking risks in the surgical process. Finally, toxicities add up and the patient benefit could disappear. The apparent paradox of efficiency and toxicity might be addressed by separating the two treatment targets: (1) The metastatic burden for which a clear escalation in medical and surgical aggressiveness is still required. (2) The healthy parenchyma which should be preserved as much as possible and for which a clear de-escalation is anticipated. A new strategy exists that integrates both fundamental endpoints in the battle against CLM.

Keywords

Colorectal liver metastases · Liver resection · Ablation · Chemotherapy · Cancer target therapy · Cancer survival · Quality of life

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1 Introduction

Articles on colorectal liver metastases (CRLM) frequently start by arguing, first of all that resection is the only chance for cure with 5-year survivals ranging from 33 (Adam et al. 2009) to 56 % (Karanicolas et al. 2013), and second, that unfortunately only a few patients, probably less than 20 % of the total, will be suitable for surgery. Some of them present with easily resectable CRLM, and the only uncertainty lies in whether they should go to perioperative chemotherapy based on the EORTC EPOC trial results (Nordlinger et al. 2008) or not considering the negative data on overall survival (OS) recently published (Nordlinger et al. 2013). Consequently, the reader should understand that increasing resectability in mainly borderline resectable or initially unresectable lesions is the major preoccupation of the liver surgeon. That being said, two new facts that should be understood when exposing the situation. The first deals with the strategy: a median 40-month OS has been reported for CRLM treated by palliative chemotherapy (Ruers et al. 2012). As a consequence, a cut-off should exist beyond which R0 resection is no longer of profit for the patient compared to a chemotherapy-only palliative approach. The second concerns the technique: initially unresectable CRLM should not be managed with a radical approach such as extensive hepatectomies, (Cauchy et al. 2012) but through a de-escalation process using iterative treatments on a lesion-per-lesion basis (Gold et al. 2008), and especially intraoperative ablation combined with resection (Karanicolas et al. 2013; Evrard et al. 2013a). In an effort to reflect the new technical reality, operability should be used in favor of resectability, which is becoming increasingly confusing.

That being said, deciding for resectability or, better said, operability is a challenge for the surgeon who has to deal subjectively with multiple objective parameters. The Celim study has clearly demonstrated that several expert liver surgeons can decide differently on the same case (Folprecht et al. 2010). Such decision-making involves identifying where the limits are, how to overcome them, and ultimately how the patient could profit from such a demanding procedure.

2 Nature of the Limits?

Resectability limits are mainly based on the necessity to respect the hepatic capital and its functions. Technical challenges may additionally represent a concern, and finally, the surgical decision has to be consistent with the oncologic multidisciplinary approach designed to manage the tumor.

3 Patient Limits and Tolerance

Immediate iatrogenicity, i.e., mortality and morbidity—is the main concern for the surgeon dealing with CLM surgery. The primary aim of the liver surgeon is not to lose his patient in the postoperative period. Hemorrhage, liver failure, and septic complications are major drawbacks that can be the direct consequences of pushing the limits of surgery too far. A 1 or 2 % mortality figure is usually reported for hepatectomies or series combining resection and ablation but higher rates ranging from 6.4 (Brouquet et al. 2011b) to 10.3 % (Cauchy et al. 2012) have been recorded when using aggressive procedures, respectively, 2-stage and extensive hepatectomies, which clearly exceed the accepted standard. The second limit is less obvious and directly linked to postoperative morbidity. Several studies have demonstrated that postoperative complications diminish the 5-year OS (Matsuda et al. 2013), as far as dividing them by two (Evrard et al. 2012). In surgical oncology, a maturing strategy always evolved toward a de-escalation profile, aiming to achieve the same therapeutical results but diminishing the morbi-mortality. The oldest paradigm is breast surgery and more recently laparoscopic surgery. Consequently *Primum non nocere* should be the first "commandment" for the liver surgeon wanting to push the limits of CRLM surgery without causing any harm to patients.

4 Anatomical "Capital"

Patients' original liver anatomy may limit the surgical options. An unfavorable right/left repartition of the parenchyma can sometimes be a real challenge. Figure 1 exhibits a female patient with a dominant right liver having a 12 mm CRLM stuck on the right hepatic vein. This right/left repartition precludes a right hepatectomy; indeed the risk of right portal vein embolization cannot be envisaged since it could lead to a fatal liver failure. The only possible solution remains a local treatment of the metastasis.

Other anatomical restrictions may arise from previous hepatectomies. A second, a third, and sometimes a fourth hepatectomy may be possible but with progressive reduction in the liver capital:

- In fact, liver homeostasis possibilities decrease after each line of surgery. The limits of parenchymal regeneration are due to the depletion of cellular homeostasis but also to the diminution of the vascular input (portal and arterial vessels) and output structures (hepatic veins).
- Previous surgery induces more or less adhesions between the liver and the diaphragm. Scarred remaining liver may be a limit by itself (Dupre et al. 2013). Dividing adhesion can sometimes lead to important hemorrhage, and some liver fracture, limiting the resection possibilities. As far as that goes, dividing perihepatic adhesions alters the Glisson's capsulae which impairs the ultra sounds transmission into the parenchyma. The consequence is a blind area for surgery and a reduction in therapeutic possibilities. Respecting Glisson's capsulae as much as possible is therefore a conservative approach optimizing the surgical care.

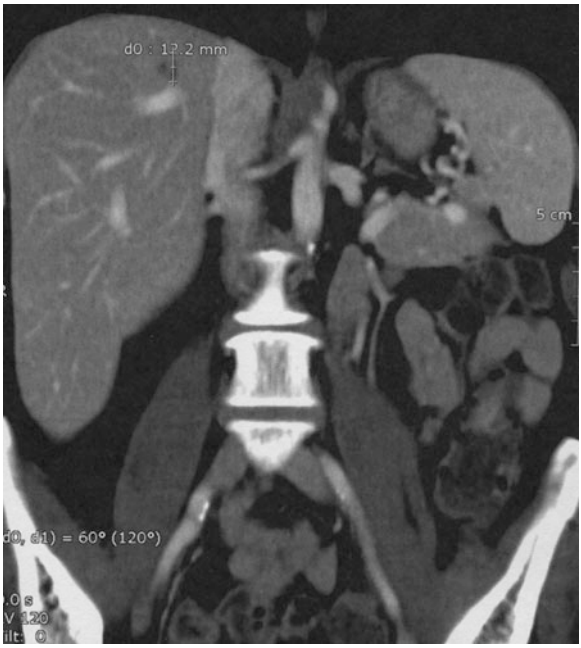

Fig. 1 Female patient with right dominant liver. To be noticed, a 12 mm diameter colorectal liver metastasis stuck on the right hepatic vein

5 Liver Functions

The concept of hepatic capital must also be understood functionally. The quantity, but also the quality of liver parenchyma, and the vascular flow irrigating it are parameters of liver functions to be considered.

5.1 Parenchyma Volume and Functions

Before chemotherapy was used for neoadjuvant or induction strategies, the rule of parenchymal-sparing by hepatectomies was strictly based on volume estimates. It was widely accepted that up to 75 % of the liver could be retrieved with a healthy parenchyma. When the patient receives more than 6 or sometimes more than 12 preoperative chemotherapy cycles based on Folfox or Folfiri regimens, the remaining liver volume must be at least 40 % of the total volume. Some authors have proposed a prediction of postoperative morbidity and mortality based on an functional remnant liver volume (RLV)/body weight (BW) ratio. In the series reported by Truant et al., no deaths occurred in patients with an RLV/BW $>$ 0.5 % (Truant et al. 2007).

Hepatic steatosis may occur after treatment with 5-fluorouracil and is associated with increased postoperative morbidity. Steatohepatitis including inflammation and hepatocyte damage can occur after treatment with irinotecan. Irinotecan-associated

steatohepatitis can affect hepatic reserve and increase morbidity and mortality after hepatectomy (Zorzi et al. 2007). Hepatic sinusoidal obstruction syndrome can occur in patients treated with oxaliplatin. Some authors claim that it does not appear to be associated with an increased risk of perioperative death (Zorzi et al. 2007). Some others report compromise perioperative outcome, early recurrence, and decreased survival in the long term (Tamandl et al. 2011).

5.2 Input and Output Vascular Flow

It is generally accepted that at least one portal pedicle, as the input flow, two contiguous segments and one hepatic vein, as the output flow are the minimum required anatomic structures to be spared. Most of the time, this extreme strategy has to use portal induced atropho-hypertrophy in order to enhance the volume of the two residual segments. It should be emphasized that any vascular structure, especially the portal output vessels, is precious and must be preserved whenever possible. The direct hepatic veins originating from segment 1 must never be cut only to mobilize the liver. Indeed, the necessity to cut a main hepatic vein (right, median, or left) can be avoided by direct hepatic veins allowing saving a segment.

6 Vascular Technical Limits

LM in close contact with a major portal pedicle are most of the time resected R1 if the pedicle cannot be sacrificed. An invasion of both right and left portal pedicles is a definitive surgical contraindication. Invasion of one major (right or left) portal pedicle plus an invasion of the median and contralateral hepatic veins can be considered as a relative unresectablity scenario. Invasion of hepatic veins does not represent a definitive contra-indication as some surgical techniques sometimes allow clearing or reconstructing the vessels.

7 Oncologic Limits

By respecting oncologic limits the relevance of the surgical procedure is guaranteed. In other words, a surgeon is not allowed to define what is feasible under exclusive technical considerations. The first oncologic rule to be observed is the R0 rule: all visible disease has to be removed. It will be later discussed that R1 resection might be acceptable under certain circumstances.

7.1 Systemic Control of the Disease

5FU was first introduced at the beginning of the 1980s. Due to the moderate efficiency of 5 FU and FUFOL regimens, the maximum number of lesions accepted was three. "No more than 3" was an active rule for 15 years. In 1986, Starzl's team (Iwatsuki et al. 1986) reported that no patient operated on from more than 4 CRLM was alive 3 years later. In a review published in 1991, Muller et al. (Muller et al. 1991) evidenced that only solitary or very small and unilateral metastases may profit from surgery. The introduction of oxaliplatin and irinotecan in the Folfox and Folfiri regimens extended the efficacy perimeter. Progressively, the number of metastases and the bilaterality were no longer a limitation (Minagawa et al. 2000); attention was focused not on what have to be retrieved from the liver but rather on what had to stay. The introduction of cetuximab and bevacizumab supported this trend. In the joined analysis of their strategies over time, the Mayo Clinic and the MD Anderson observed a clear increase in the OS of patients due to a concomitant use of polychemotherapies and biological therapies and the increased number of hepatectomies (Kopetz et al. 2009), especially after 2004. The more chemotherapies and biological are used, the more hepatectomies are performed and the better the survival. If we accept this correlation between systemic medical treatment and surgery, it means that each period of time has its own oncological limits. As suggested by some authors (Boige et al. 2007; Cardona et al. 2013; Gallagher et al. 2007), the intraarterial use of chemotherapy would provide a greater number of technical possibilities. In the future, major progresses in systemic treatment could lead to the end of the R0 rule. A new concept of R2 debulking surgery could become useful and pertinent for the patient, providing that medical treatment controlled the rest of the disease.

In this respect, we should critically analyze the respective role of chemotherapy and surgery. Indeed, for 3–6 CLM, surgery is evidently the main curative treatment, whereas systemic treatments are adjuvant to surgery. For 12 bilateral CRLM however, are the roles inverted? Is not chemotherapy the main treatment and surgery adjuvant to medical treatments? That implies that there must be a turning point between curative and palliative strategy in CRLM care which is so far unknown. The Clocc trial reported an unexpected long survival of 40 months in the control arm treated by chemotherapy only. An increased PFS of 10.6 % at 3 years was reported compared with 27.6 % in the control arm, but there was no statistical difference of OS at 5 years. The use of PFS as a surrogate marker of OS in colorectal cancer (Buyse et al. 2007) is not as pertinent as thought. The EORTC EPOC trial made the same disappointing observation (Nordlinger et al. 2013).

7.2 Extrahepatic Disease

Lung and peritoneum are the two main extrahepatic locations for metastases. Some authors claim that they are not contraindications to treat CRLM (Brouquet et al. 2011a; Allard et al. 2013) but the series published are, most of the time, highly

selective. Paucy extrahepatic locations may not preclude CRLM surgery, but they clearly diminish the OS (Adam et al. 2009). In a series combining resection and intraoperative ablation of CRLM, 3-year OS decreased by two (30 months vs. 60) in patients with extrahepatic disease (Evrard et al. 2013a). Other extrahepatic metastases like adrenal gland, bone, and muscle are usually contraindications.

7.3 Margin Clearance

The clear surgical resection margin accepted to achieve cure has evolved from 10 (Cady et al. 1992) to 2 mm (Kokudo et al. 2002), and more recently to 0 mm (de Haas et al. 2008). So, there does not seem to be a margin limitation, but the size of the margin may be dictated by the location of the CLM in the liver structures. In other words, a lesion resected with a 1 mm margin may have a worse recurrence outcome due to worst anatomical topography. Some authors remain committed to the R1 and R0 resection distinction (Andreou et al. 2013). Nevetheless, a large series of 2,715 patients analyzed by a propensity score case-match approach concluded that a 1 mm cancer-free resection margin achieved in patients with CLM should be considered the standard of care (Hamady et al. 2014).

8 How to Overcome Limits?

The surgeon has to consider the limits of resectability and push them, guided by a pertinent multidisplinary strategy that makes sense from an oncological point of view, only if the patient is not harmed. The question remains though—how can this challenging and paradoxical job be carried out? Going further from an oncological point of view but offering a better outcome for the patient, this strategy has to take into account a major characteristic of CLM disease, the high rate of recurrence.

8.1 Increasing the Remaining Liver Function

8.1.1 Decrease Chemotherapy Toxicities

Both oxaliplatin and irinotecan induce liver toxicities that potentially impair resectability (see above). Preoperative chemotherapy is sometimes mandatory as a conversion strategy to surgery, but also because it allows testing the chemosensibility of the tumors, which is a major prognostic factor. Decreasing preoperative chemotherapy and the toxicity of targeted therapies increase surgical possibilities. Ideally, the patient should undergo surgery as soon as the surgeon approves, which means that the role of the MDT decision to discuss the file every four cures of chemo is key.

8.1.2 Parenchyma Atropho-Hypertrophy

Liver is the only organ capable of homeostasis, which offers fantastic therapeutic opportunities. The idea is to get atrophy of the invaded segments and hypertrophy of the healthy parenchyma. Two techniques are available.

Portal Vein Occlusion

Introduced by Kinoshita et al. (Kinoshita et al. 1986) in 1986, it is the oldest and the best-known technique. The principle is to obliterate a portal vein to induce hypertrophy in the contralateral segments. Portal Vein Occlusion (PVO) can be performed in the preoperative setting by a radiologist to prepare an extensive hepatectomy, or intraoperatively by the surgeon to prepare a 2-stage procedure. Obliteration can be performed proximally by ligation or using a plug or distally with coils, glue, lipiodol. Several studies suggest that these different approaches would yield comparable results (Aussilhou et al. 2008). A logical drawback of PVO may be a growth stimulation not only for the healthy parenchyma but also for the metastases (Elias et al. 1999). Some authors reported the concomitant use of neoadjuvant chemotherapy after PVO without diminishing neither hypertrophy of the future remnant liver nor additional toxicity (Covey et al. 2008). PVO results are appreciated after 4 weeks by a CT-scan and can lead to either 1-stage or 2-stage surgeries.

ALPPS

First described in Regensburg, Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS), is a new 2-step technique for obtaining short-term parenchymal hypertrophy in patients requiring extended right hepatic resection with limited functional reserve. A first step includes a right portal vein ligation (PVL) and an in situ splitting (ISS) of the liver parenchyma letting the targeted liver volume vascularized by the artery only. The ischemic part of the liver is retrieved approximately 9 days later. Schnitzbauer et al. reported an increase of the median volume of the future remnant liver of 74 % but with a high mortality rate of 12 % (Schnitzbauer et al. 2012). The experience is preliminary and a registry for a prospective study is open to collect data.

8.1.3 2 Stage with or Without PVO

The two-stage procedure is also based on liver function homeostasis: to retrieve all the CLM in one procedure when it is not feasible, one hemi-liver can be treated after the other, avoiding liver failure (Adam et al. 2000). In between, a PVO can be added to enhance the growing capacities of the future remnant liver. This artful strategy has no equivalent in surgical oncology, and allows treating more patients. In a selected population, a 2-stage procedure offers good survival results as seen in the MD Anderson series (Brouquet et al. 2011a) with a 64 % 5-year OS. Nevertheless, mortality was 2 % after the first stage and 6 % after the second, and only 75 % of the patients were apt to proceed to the second stage. For this group, the survival was worse compared to a group treated by chemotherapy only (13 vs.

42 %). A 2-stage procedure is very useful but complex and costly (Dupre et al. 2013; Abbott et al. 2013) and needs a good selection of patients, especially to avoid failure at the second step.

8.1.4 Nonanatomical Resection

Liver transplant surgery during the 1980s and the 1990s contributed a great deal to the development of resectional liver surgery. Liver transplant surgery is based on vascular principles that imply a respect of the anatomical structures. As evidence, if the segment unit is respected, its vascular and biliary structures are automatically intact. At this time, the number of CLM which was authorized was among 3. Thus, having anatomical resections was not a challenge. Nevertheless, the number of CLM to resect progressively increased and some authors claimed that anatomical resections would be better than nonanatomical (DeMatteo et al. 2000), probably with the idea that surgical margins would be the largest.

After more than 10 years of controversies, nonanatomical resections were finally accepted as a de-escalation strategy (Gold et al. 2008; Sui et al. 2012) resulting in superior oncological outcomes, a better iterativity and a lower consumption of healthy parenchyma.

8.1.5 Intraoperative Ablation and the CARe Concept

After the imposition of nonanatomical resection the question arose on the place of intraoperative ablation to continue the concept of tumoral focused treatment with a high propensity to spare healthy parenchyma. Enthusiastically introduced by Elias et al. (2000) and Curley et al. (1999) from both sides of the Atlantic Ocean, radiofrequency ablation was rapidly ostracized (Abdalla et al. 2004). The reason was a competition with radiologists who wanted to conquer the CLM market by using RF percutaneously. By comparing the results on resection to treat easily resectable lesions to those on ablation to treat lesions without any possibility of clear margin, they attempted to discredit RF (Abdalla et al. 2004). The first attempt was to separate results from intraoperative RF and pecutanous route. Clearly, the local recurrence rates were less than 10 % in the surgical arm and more than 25 % in the percutaneous arm (Evrard and Mathoulin-Pélissier 2006). Intraoperative ablation progressively evolving toward a new concept of complementarity to resection rather than toward being a competitor (Leblanc et al. 2008). In 2012, two prospective studies (Ruers et al. 2012; Evrard et al. 2012) were published confirming the place of intraoperative RF to complement resection for nonresectable CLM. Local recurrence rates of ablated lesions were inferior to 9 % (Ruers et al. 2012) and 5-year OS reached 43 % (Evrard et al. 2012). A confirmation study, based on a large international population was realized by joining four prospective databases. Preliminary results have already been reported (Evrard et al. 2013a) and a branded concept of CARe (Combined Ablation plus Resection) will be soon published. Currently, several surgeons (including the author) believe that ablation should be indicated not only for unresectable CLM but to face complex situations including bilateral diseases (Karanicolas et al. 2013; Leblanc et al. 2008). In some

cases it could substitute 2-stage procedures and result in better survival and lowest cost (Abbott et al. 2013). Anatomical resections, nonanatomical resections, 2-stage resections, and finally CARe are the four successive main steps in the history of CLM surgery. A de-escalation story …

8.1.6 Increasing the Radicality of Surgery

Approaches to enhance surgical radicality include intensifying the preoperative medical strategy, the second include more specific technical options.

Increase Chemotherapy and Targeted Therapies Efficacy

Unresectable or borderline resectable CLM are treated by downsizing chemotherapy regimens including targeted therapies. Some studies have reported conversion rates ranging from 19 (Adam et al. 2009) to 28 % (Folprecht et al. 2010). These regimens were based on Folfox and Folfiri, more or less associated with cetuximab or bevacuzimab. More aggressive strategies are tested like triplet chemotherapy (Folfirinox), triplet plus antigiogenics, new antigiogenics, etc. It is too early to hypothesize the level of conversion that will be reached in the future. What is clear, however, is that aggressive conversion strategies are a major trend and that the surgeon who operates following chemotherapy has to take it into account. It has been shown that after more than 12 cycles of preoperative chemotherapy, extensive radical hepatectomies should be avoided due to poor surgical outcomes and poor survivals (Cauchy et al. 2012).

Another way to increase downsizing treatments is to change the route of administration like with the arterial pump and hepatic artery infusion (HAI) (Cardona et al. 2013; Goere et al. 2010; Ammori et al. 2013). For initially unresectable CLM, a 24 % rate of resection was obtained with HAI by oxaliplatin and intravenous 5 FU and a 5-year OS of 56 % (Goere et al. 2010). HAI of oxaliplatin plus irinotecan plus intravenous FUDR—dexamethasone led to a conversion rate of 47 %. When HAI was performed in first line, a 5-year 51 % rate was observed (Kemeny et al. 2009). Even if aggressive, this conversion approach is gaining increasing acceptance.

This being said, this chapter does not contradict a previous one where it was claimed that the MDT should decide to go to surgery, as soon as the surgeon approves.

Treating Invaded Vessels

Invaded vessels are a major reason for unresectability. For portal pedicles, there is no technical joker. A lesion in close contact with a portal pedicle can be resected R1 if the pedicle cannot be sacrificed. Vascular resections followed by a reconstruction are not used for CLM and hyperthermic ablation cannot be used due to biliary duct sensitivity.

For hepatic vein, more aggressive techniques are available. Techniques of resection plus grafting reconstruction have been reported but with mediocre results (Hemming et al. 2002; Aoki et al. 2004). Mortality after vascular reconstruction could be as high as 33 % (4/12) (Cauchy et al. 2012). On the contrary, ablation

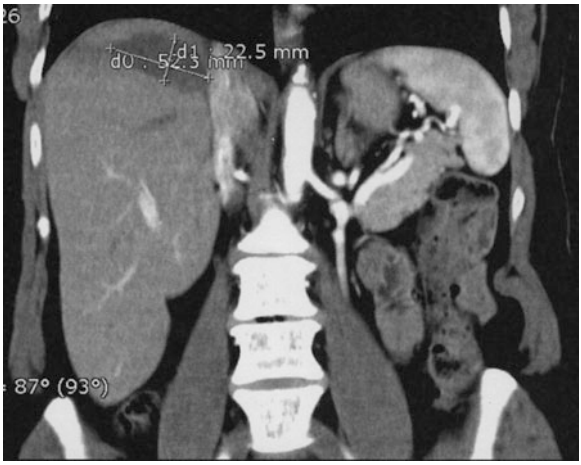

Fig. 2 The same patient after an intraoperative RF with vascular exclusion. Complete destruction of the lesion without harming the right liver veinous drainage

with vascular exclusion is a good indication to treat LM close to them (Evrard et al. 2013b). Indeed, portal vascular endothelium is highly resistant to heat (Sato et al. 2005). Vascular exclusion is required to prevent blood cooling and local recurrences. Nevertheless, new technologies like powerful RF generators (up to 200 watts compared with 50 watts for the first generation of generators) or microwaves generators allow to treat such lesions without vascular clamping. Figure 2 illustrates such an intraoperative ablation.

Hanging Maneuvers for Big Lesions

Big lesions have their own concerns as shown in Fig. 3. Some of them preclude the division of the right triangle ligament which usually is realized first. It is thus necessary to cut first the liver without any mobilization which is dangerous. The liver hanging maneuver, which is a technique of passing a tape along the retrohepatic avascular space and suspending the liver during parenchymal transection, facilitates anterior approach of major hepatectomy. The liver hanging maneuver has 94 % feasibility. Absolute contraindication is tumor infiltration to the retrohepatic avascular space (Ogata et al. 2007).

Radical Extensive Hepatectomy

Extensive hepatectomy is sometimes necessary to remove the metastases burden. A PVO is often necessary. The question if extensive radical hepatectomy should be done as a standard based on the concept of retrieving a maximum of unknown micrometastases, has a clear negative answer. In the Beaujon Hospital series, patients with initially unresectable CLM without extrahepatic diseases responding to chemotherapy had a 5-year PFS of 13 % and a 5-year OS of 40 % after major hepatic resection. Mortality, however, was high at 10 %, and margins were involved in 39 % of the cases. Patients requiring more than 12 cycles of chemotherapy to achieve resectability had more postoperative complications, a 3-year DFS of 0 % and a 5-year OS of less than 30 %. Authors clearly concluded

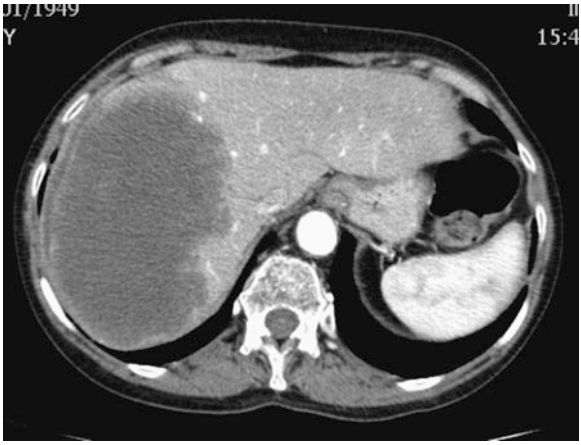

Fig. 3 Massive solitary CLM of the right liver with major adhesions with the diaphragm. Impossibility to mobilize the right liver first and thus a hanging maneuver was necessary for anterior hepatotomy

(Cauchy et al. 2012) that patients responding only after 12 chemotherapy cycles should undergo conservative strategies including repeated resection, ablation, or intraarterial chemotherapy instead of extensive radical surgery.

Ex Vivo Surgery

These exceptional procedures may be indicated in very particular cases of vena cava involvement (Malde et al. 2011; Magge et al. 2013)

Isolated Liver Perfusion

Isolated hepatic perfusion (Ammori et al. 2013) was proposed 20 years ago as an aggressive treatment limited to the liver (Bartlett et al. 2001). This approach stayed confidential both because of the spread of active systemic treatments and because of the complexity and the cost of the procedure. Some attempts of percutaneous isolation have been reported (Miao et al. 2008; van Etten et al. 2004).

Liver Transplant

CLM is a classical contraindication for liver transplant, and it probably should stay so. A limited number of experiences have been reported (Hagness et al. 2013) that show an interesting pattern of recurrence observed after transplantation. If pulmonary recurrence were of indolent character, re-metastases to the liver transplant were prognostically adverse and confirm that delayed metastases in CR cancer may originate from previous metastases (Klein 2009).

9 Increasing Surgeon's Skill

There is a clear deficit in practicing intraoperative ultrasounds (IOUS) in liver surgery, even in some of the most renowned HPB teams. Indeed, in these teams, the surgical decision is made preoperatively, usually based on an MRI, and the surgery has just to execute the plan. The main explanation for why intraoperative ablation

was hard to break is the weak diffusion of IOUS. Moreover, some teams that decided to make intraoperative ablation felt the necessity to call a radiologist in the OP room to perform the IOUS. Yet, IOUS are the surgeons' eyes. They allow perfect guidance to determine the cutting plan, to push down a needle, and to discover among 20 % of additional lesions (Torzilli and Makuuchi 2003). Contrast-enhanced IOUS is now available (Fioole et al. 2007; Shah et al. 2010). Some advanced HPB courses offer specific IOUS subjects (ESSO course, University of Milan).

10 For the Benefit of Which Patient ?

As already mentioned, the main concern when extending the frontier of resectability is to not harm the patient. The last one, but not the least, should be to determine how the patient really benefits from the efforts and finally the question of quality of live (QoL) should be asked.

Overall survival is the primary endpoint for the patient and surgery will remain indicated as long as it provides longer OSs compared to a systemic treatment. For extended CLM diseases, surgery acts as a closing treatment in the efficiency perimeter delineated by the systemic treatment. This perimeter increases with time and progresses in surgery and in systemic treatments provide a synergistic result (Kopetz et al. 2009). In the surgical world that abides by the R0 rule, the perimeter of surgery will never overcome that of systemic treatments, like nothing travels faster than the speed of light. Violating this rule would mean creating a new paradigmatic world where the patient would never be cured and instead would benefit from becoming chronic. This new R2 oncological rule inaugurates a new concept that will need one or two decades before breaking it. Not only invasive surgery but also interventional radiology, percutaneous ablation, HIFU, and stereotaxic radiotherapies will invest this scope of action.

But back in the old R0 world, extending the limits of resectability cannot be infinite; a cut-off exists beyond which the gain in OS will not be significant. But where? At the present time the answer to this question is unknown. What is sure is that an R0 surgery brings additional PFS as demonstrated by the CLOCC trial (Ruers et al. 2012). The ARF2003 study demonstrated that QoL improved during the period of clinical remission. Consequently, the PFS is a good surrogate marker of QoL rather than of OS. Extending the limits of resectability or operability could thus provide, at least, an improvement in the quality of life of patients.

11 Conclusion

Resectability must give way to operability as the CARe concept is now evidence of the modern surgical approach that allows treating more and more patients. To be more proactive but less toxic is the main watchword to intensify the surgical fight, facing the escalation in medical conversion therapies. Therapeutical endpoints must be well-defined and understood through the real patient benefit they provide.

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References

Abbott DE, Sohn VY, Hanseman D et al (2013) Cost-effectiveness of simultaneous resection and RFA versus 2-stage hepatectomy for bilobar colorectal liver metastases. J Surg Oncol doi: 10.1002/jso.23539. [Epub ahead of print]

Abdalla EK, Vauthey JN, Ellis LM et al (2004) Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Data validation in an economic evaluation of surgery for colon cancer. Ann Surg 239:818–825

Adam R, Laurent A, Azoulay D et al (2000) Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors. Ann Surg 232:777–785

Adam R, Wicherts DA, de Haas RJ et al (2009) Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? J Clin Oncol 27:1829–1835

Allard MA, Adam R, Ruiz A et al (2013) Is unexpected peritoneal carcinomatosis still a contraindication for resection of colorectal liver metastases? Combined resection of colorectal liver metastases with peritoneal deposits discovered intra-operatively. Eur J Surg Oncol 39:981–987

Ammori JB, Kemeny NE, Fong Y et al (2013) Conversion to complete resection and/or ablation using hepatic artery infusional chemotherapy in patients with unresectable liver metastases from colorectal cancer: a decade of experience at a single institution. Ann Surg Oncol 20:2901–2907

Andreou A, Aloia TA, Brouquet A et al (2013) Margin status remains an important determinant of survival after surgical resection of colorectal liver metastases in the era of modern chemotherapy. Ann Surg 257:1079–1088

Aoki T, Sugawara Y, Imamura H et al (2004) Hepatic resection with reconstruction of the inferior vena cava or hepatic venous confluence for metastatic liver tumor from colorectal cancer. J Am Coll Surg 198:366–372

Aussilhou B, Lesurtel M, Sauvanet A et al (2008) Right portal vein ligation is as efficient as portal vein embolization to induce hypertrophy of the left liver remnant. J Gastrointest Surg 12(2):297–303

Bartlett DL, Libutti SK, Figg WD et al (2001) Isolated hepatic perfusion for unresectable hepatic metastases from colorectal cancer. Surgery 129:176–187

Boige V, Malka D, Elias D et al (2007) Hepatic arterial infusion of oxaliplatin and intravenous LV5FU2 in unresectable liver metastases from colorectal cancer after systemic chemotherapy failure. Ann Surg Oncol 14:3188–3194

Brouquet A, Abdalla EK, Kopetz S et al (2011a) High survival rate after two-stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. J Clin Oncol 29:1083–1090

Brouquet A, Vauthey JN, Contreras CM et al (2011b) Improved survival after resection of liver and lung colorectal metastases compared with liver-only metastases: a study of 112 patients with limited lung metastatic disease. J Am Coll Surg 213:62–69

Buyse M, Burzykowski T, Carroll K et al (2007) Progression-free survival is a surrogate for survival in advanced colorectal cancer. J Clin Oncol 25:5218–5224

Cady B, Stone MD, McDermott WV Jr et al (1992) Technical and biological factors in disease-free survival after hepatic resection for colorectal cancer metastases. Arch Surg 127:561–568

Cardona K, Donataccio D, Peter KT et al (2013) Treatment of extensive metastatic colorectal cancer to the liver with systemic and hepatic arterial infusion chemotherapy and two-stage hepatic resection: the role of salvage therapy for recurrent disease. Ann Surg Oncol 21(3):815–821

Cauchy F, Aussilhou B, Dokmak S et al (2012) Reappraisal of the risks and benefits of major liver resection in patients with initially unresectable colorectal liver metastases. Ann Surg 256:746–752

Covey AM, Brown KT, Jarnagin WR et al (2008) Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. Ann Surg 247:451–455

Curley SA, Izzo F, Delrio P et al (1999) Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: results in 123 patients. Ann Surg 230:1–8

de Haas RJ, Wicherts DA, Flores E et al (2008) R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? Ann Surg 248:626–637

DeMatteo RP, Palese C, Jarnagin WR et al (2000) Anatomic segmental hepatic resection is superior to wedge resection as an oncologic operation for colorectal liver metastases. J Gastrointest Surg 4:178–184

Dupre A, Lefranc A, Buc E et al (2013) Use of bioresorbable membranes to reduce abdominal and perihepatic adhesions in 2-stage hepatectomy of liver metastases from colorectal cancer: results of a prospective, randomized controlled phase II trial. Ann Surg 258:30–36

Elias D, de Baère T, Roche A et al (1999) During liver regeneration following right portal embolization the growth rate of liver metastases is more rapid than that of the liver parenchyma. Br J Surg 86:784–788

Elias D, Goharin A, El Otmany A et al (2000) Usefulness of intraoperative radiofrequency thermoablation of liver tumours associated or not with hepatectomy. Eur J Surg Oncol 26:763–769

Evrard S, Mathoulin-Pélissier S (2006) Controversies between surgical and percutaneous radiofrequency ablation. Eur J Surg Oncol 32:3–5

Evrard S, Rivoire M, Arnaud J et al (2012) Unresectable colorectal cancer liver metastases treated by intraoperative radiofrequency ablation with or without resection. Br J Surg 99:558–565

Evrard S, Diallo A, Brouste V et al (2013a) Survival after resection plus intra-operative radiofrequency ablation (IRFA). In: Proceedings of the results presented at the 49th annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago, IL. J Clin Oncol 31 (suppl): abstr, p 3558

Evrard S, Brouste V, McKelvie-Sebileau P et al (2013b) Liver metastases in close contact to hepatic veins ablated under vascular exclusion. Eur J Surg Oncol 39:1400–1406

Fioole B, de Haas RJ, Wicherts DA et al (2007) Additional value of contrast enhanced intraoperative ultrasound for colorectal liver metastases. Eur J Radiol 67(1):169–176

Folprecht G, Gruenberger T, Bechstein WO et al (2010) Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol 11:38–47

Gallagher DJ, Capanu M, Raggio G et al (2007) Hepatic arterial infusion plus systemic irinotecan in patients with unresectable hepatic metastases from colorectal cancer previously treated with systemic oxaliplatin: a retrospective analysis. Ann Oncol 18:1995–1999

Goere D, Deshaies I, de Baère T et al (2010) Prolonged survival of initially unresectable hepatic colorectal cancer patients treated with hepatic arterial infusion of oxaliplatin followed by radical surgery of metastases. Ann Surg 251:686–691

Gold JS, Are C, Kornprat P et al (2008) Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. Ann Surg 247:109–117

Hagness M, Foss A, Line PD et al (2013) Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg 257:800–806

Hamady ZZ, Lodge JP, Welsh FK et al (2014) One-millimeter cancer-free margin is curative for colorectal liver metastases: a propensity score case-match approach. Ann Surg 259(3):543–548

Hemming AW, Reed AI, Langham MR et al (2002) Hepatic vein reconstruction for resection of hepatic tumors. Ann Surg 235:850–858
Iwatsuki S, Esquivel CO, Gordon RD et al (1986) Liver resection for metastatic colorectal cancer. Surgery 100:804–810
Karanicolas PJ, Jarnagin WR, Gonen M et al (2013) Long-term outcomes following tumor ablation for treatment of bilateral colorectal liver metastases. JAMA Surg 148:597–601
Kemeny NE, Melendez FD, Capanu M et al (2009) Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma. J Clin Oncol 27:3465–3471
Kinoshita H, Sakai K, Hirohashi K et al (1986) Preoperative portal vein embolization for hepatocellular carcinoma. World J Surg 10:803–808
Klein CA (2009) Parallel progression of primary tumours and metastases. Nat Rev Cancer 9:302–312
Kokudo N, Miki Y, Sugai S et al (2002) Genetic and histological assessment of surgical margins in resected liver metastases from colorectal carcinoma: minimum surgical margins for successful resection. Arch Surg 137:833–840
Kopetz S, Chang GJ, Overman MJ et al (2009) Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 27:3677–3683
Leblanc F, Fonck M, Brunet R et al (2008) Comparison of hepatic recurrences after resection or intraoperative radiofrequency ablation indicated by size and topographical characteristics of the metastases. Eur J Surg Oncol 34:185–190
Magge D, Choudry HA, Zeh HJ III et al (2014) Outcome analysis of a decade-long experience of isolated hepatic perfusion for unresectable liver metastases at a single institution. Ann Surg 259(5):953–959
Malde DJ, Khan A, Prasad KR et al (2011) Inferior vena cava resection with hepatectomy: challenging but justified. HPB (Oxford) 13:802–810
Matsuda A, Matsumoto S, Seya T et al (2013) Does postoperative complication have a negative impact on long-term outcomes following hepatic resection for colorectal liver metastasis?: a meta-analysis. Ann Surg Oncol 20:2485–2492
Miao N, Pingpank JF, Alexander HR et al (2008) Percutaneous hepatic perfusion in patients with metastatic liver cancer: anesthetic, hemodynamic, and metabolic considerations. Ann Surg Oncol 3:815–823
Minagawa M, Makuuchi M, Torzilli G et al (2000) Extension of the frontiers of surgical indications in the treatment of liver metastases from colorectal cancer: long-term results. Ann Surg 231:487–499
Muller JM, Schmidt A, Strauss JM et al (1991) Resection of liver metastases of colorectal carcinoma: claims and reality. Dtsch Med Wochenschr 116:681–688
Nordlinger B, Sorbye H, Glimelius B et al (2008) Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 371:1007–1016
Nordlinger B, Sorbye H, Glimelius B et al (2013) Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 14:1208–1215
Ogata S, Belghiti J, Varma D et al (2007) Two hundred liver hanging maneuvers for major hepatectomy: a single-center experience. Ann Surg 245:31–35
Ruers T, Punt C, Van CF et al (2012) Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). Ann Oncol 23:2619–2626
Sato K, Nakamura K, Hamuro M et al (2005) The influence of radiofrequency ablation on hepatic vessels in porcine liver. Hepatogastroenterology 52:571–574

Schnitzbauer AA, Lang SA, Goessmann H et al (2012) Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 255:405–414

Shah AJ, Callaway M, Thomas MG et al (2010) Contrast-enhanced intraoperative ultrasound improves detection of liver metastases during surgery for primary colorectal cancer. HPB (Oxford) 12:181–187

Sui CJ, Cao L, Li B et al (2012) Anatomical versus nonanatomical resection of colorectal liver metastases: a meta-analysis. Int J Colorectal Dis 27 (7):939–946

Tamandl D, Klinger M, Eipeldauer S et al (2011) Sinusoidal obstruction syndrome impairs long-term outcome of colorectal liver metastases treated with resection after neoadjuvant chemotherapy. Ann Surg Oncol 18(2):421–430

Torzilli G, Makuuchi M (2003) Intraoperative ultrasonography in liver cancer. Surg Oncol Clin N Am 12:91–103

Truant S, Oberlin O, Sergent G et al (2007) Remnant liver volume to body weight ratio >/ =0.5 %: a new cut-off to estimate postoperative risks after extended resection in noncirrhotic liver. J Am Coll Surg 204:22–33

van Etten B, Brunstein F, van Ijken MG et al (2004) Isolated hypoxic hepatic perfusion with orthograde or retrograde flow in patients with irresectable liver metastases using percutaneous balloon catheter techniques: a phase I and II study. Ann Surg Oncol 11:598–605

Zorzi D, Laurent A, Pawlik TM et al (2007) Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg 94:274–286

Rectal Cancer with Synchronous Liver Metastases: Leave It All in? When (not) to Resect the Primary?

Florian Lordick

Abstract

Rectal cancer with synchronous distant metastases is challenging the choice of optimal treatment. Today, it is unknown if and when the primary tumor should or should not be resected. The current literature was reviewed. Data on the safety of a primary chemotherapy approach are reported. These publications indicate that at least in selected situations without severe symptoms or complications resulting from the primary, the rectum can be left in situ without major risks for the patient. However, retrospective analyses from randomized controlled trials indicate a potential prognostic advantage for patients having the primary tumor resected. The reason for this observation is largely unknown and requires further investigation. Due to the lack of data from prospective randomized controlled trials illuminating the situation of rectal cancer with synchronous distant metastases and due to the rapid changes evolving in the field of systemic treatment of metastatic colorectal cancer, no clear conclusions can be drawn at this stage. But a practical algorithm that may reflect current European treatment patterns is presented in this article.

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Keywords
Rectal cancer · Liver metastasis · Synchronous metastases · Resection · Chemotherapy

1 Two Cases

The following two cases illustrate two contrary strategies for the treatment of rectal cancer with synchronous distant metastases.

1.1 Patient 1

A 42-year-old man presented with locally advanced rectal cancer. He underwent anterior resection followed by external beam radiotherapy combined with chemotherapy 8 weeks later. He relapsed within 6 months with hepatic metastases and started treatment with bevacizumab 5 mg/kg every other week plus irinotecan, infusional 5-fluorouracil, and folinic acid. During the first 4 weeks of treatment with bevacizumab, he experienced severe perianal pain requiring opioids. Digital rectal examination revealed a hard luminal mass adherent to the bowel wall. On endoscopy, wall thickening accompanied by ulcerative lesions around the anastomosis similar to the mucosal changes seen in ulcerative colitis was present (Fig. 1). MRI showed thickening of the intestinal and vesical wall in the borders of the previous pelvic irradiation. Multiple biopsies revealed no malignant areas. The specimens were consistent with mucosal damage, such as seen in ischemic colitis. Treatment with bevacizumab was stopped, and systemic analgesics and anti-inflammatory enemas were administered. The patient was still symptomatic after 5 months of follow-up. In addition, a circumscribed necrotic destruction of the bowel wall developed covered by the surrounding tissue, still without evidence of tumor. The patient recovered slowly from his symptoms and lived with metastatic disease for 5 years.

1.2 Patient 2

A 45-year-old man presented with rectal cancer in the upper rectal third (Fig. 2) with synchronous multiple lung and liver metastases (Fig. 3). He had lost 3 kg of weight and suffered from moderate diarrhea. Serum CEA was elevated to 1,727 μg/l (normal range < 5); LDH was elevated to 1,182 U/l (normal range < 220). Chemotherapy with irinotecan plus 5-fluorouracil/folinic acid (FOLFIRI) plus cetuximab was started. Apart from acneiform rash grade 3 and a severe infusion reaction at the time of the first cetuximab infusion, he tolerated chemotherapy well until 6 weeks later he presented with an acute abdomen that was caused by a rectal perforation leading peritonitis and ileus (Fig. 4). The liver metastases and the primary tumor had responded to treatment. He received an

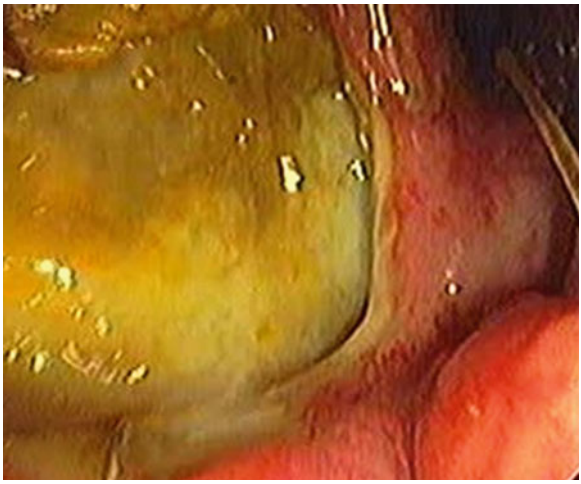

Fig. 1 Endoscopic aspect of ulcerous pseudotumor of the neorectum in patient 1 who underwent treatment with bevacizumab after previous anterior resection of the rectum and adjuvant chemoradiotherapy

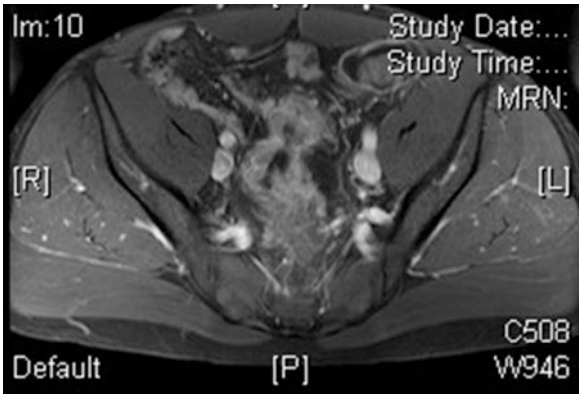

Fig. 2 Rectal cancer in the upper third in patient 2. Magnetic resonance imaging (MRI)

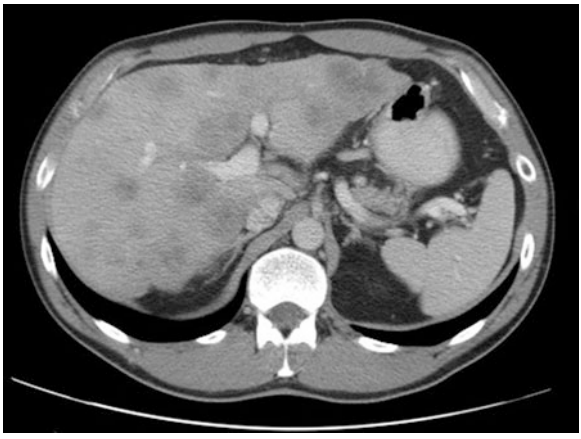

Fig. 3 Multiple liver metastases in patient 2. Computed tomography (CT)

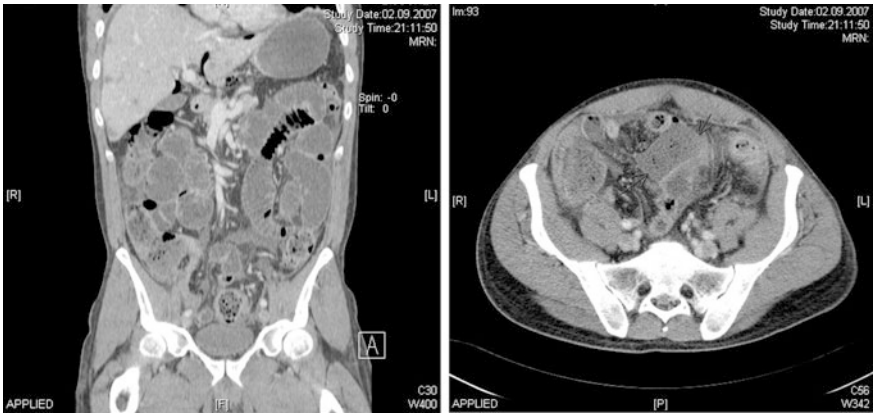

Fig. 4 CT scans of patient 2 six weeks after initiation of chemoimmunotherapy, illustrating an ileus due to peritonitis caused by a rectosigmoid perforation

anterior rectal resection and a descendostoma as an emergency operation which led to his fast recovery. Four weeks later, chemoimmunotherapy could be continued. This man lived for 4 years with his metastatic disease.

These two cases, one of which has been published previously (Lordick et al. 2006) illustrate that both strategies, i.e., primary tumor resection followed by systemic chemotherapy and primary systemic chemotherapy without resection of the primary tumor are common practice in the management of rectal cancer with synchronous distant metastases. The two cases show that both approaches can lead to complications in due course. The question is: which approach should be preferred in which situation?

2 How Do We Make a Clinical Decision?

Usually, clinicians and multidisciplinary tumor boards want to be informed about the following issues when a decision on treatment sequences in colorectal cancer with synchronous metastases has to be taken:

1. Is the primary tumor symptomatic (obstruction, bleeding, and pain)?
2. How advanced is the metastatic tumor load?
3. Can the disease be treated curatively?

In case of a symptomatic primary, the indication for early resection is more evident, but other means of controlling symptoms (e.g., colonostomy or stent insertion for obstruction, radiation for bleeding or pain) can be considered.

Massive metastatic disease, especially when associated with an inflammatory systemic reaction composed of weight loss, fever, night sweats, increase of serum acute phase proteins (C-reactive protein), or cytokines (Interleukin-6) indicate an imminent need for early and maximally active systemic treatment. Treatment of

the primary tumor is then usually postponed or will never be performed, especially when the situation deteriorates in the further course.

If cure seems achievable, different strategies are to be considered. Most centers start with systemic chemotherapy for 3 months as used in the EORTC 40983 study (Nordlinger et al. 2009). Following induction chemotherapy, a rectal-surgery-first approach must be weighed against a liver-surgery-first approach (Mentha et al. 2006). The risk of progression of resectable liver metastases during neoadjuvant chemoradiation, especially if this contains oxaliplatin, has probably been overestimated in the past (Manceau et al. 2013).

3 Is It Safe to Leave the Primary Tumor in Situ?

3.1 Cohort Studies

Dutch authors collected the outcome data of 850 patients from seven cohort studies (Scheer et al. 2008). Only patients with asymptomatic primary colorectal cancers were included. Leaving the primary tumor in situ was shown to be a relatively safe strategy: the mean complications were intestinal obstruction in 13.9 % [95 % confidence interval (CI) 9.6–18.8 %] and hemorrhage in only 3.0 % (95 % CI 0.95–6.0 %) of the patients. After resection, the overall postoperative morbidity ranged from 18.8–47.0 %. The authors conclude: "For patients with stage IV colorectal cancer, resection of the asymptomatic primary tumor provides only minimal palliative benefit, can give rise to major morbidity and mortality and therefore potentially delays beneficial systemic chemotherapy. When presenting with asymptomatic disease, initial chemotherapy should be started and resection of the primary tumor should be reserved for the small portion of patients who develop major complications from the primary tumor." However, in this publication, the proportion of patients presenting with rectal cancer is not specified and is not subject to detailed subgroup analyses.

3.2 MSKCC Series

Another more recent case series from the Memorial Sloan Kettering Cancer Center, New York, reports that from 233 patients with synchronous metastases and an unresected primary tumor, 217 (93 %) never required surgical palliation of their primary (Poultsides et al. 2009). Sixteen patients (7 %) required emergent surgery for primary tumor obstruction or perforation, 10 patients (4 %) required nonoperative intervention (stent or radiotherapy), and 213 (89 %) never required any direct symptomatic management for their intact primary tumor. Of those 213 patients, 47 patients (20 %) ultimately underwent elective colon resection at the time of metastasectomy. Of note, location of the primary tumor in the rectum, and metastatic disease burden were not associated with increased intervention rate. Also, the use of bevacizumab had no impact on complication or intervention rates.

The authors therefore concluded that "most patients with synchronous, stage IV colorectal cancer who receive up-front modern combination chemotherapy never require palliative surgery for their intact primary tumor. These data support the use of chemotherapy, without routine prophylactic resection, as the appropriate standard practice for patients with neither obstructed nor hemorrhaging primary colorectal tumors in the setting of metastatic disease."

4 The Effect of Systemic Chemotherapy on the Primary Tumor

It has been hypothesized that the effect of systemic chemotherapy on the primary tumor is not as high as on liver or other hematogenous metastases. Therefore, long-term control of the primary may not be achievable. This question has not been investigated in larger series, but a very recent study from the MSKCC gives some insight (Schrag et al. 2014). Thirty-two patients with clinical stages II–III rectal cancer participated in this single-center phase II trial. All were candidates for low anterior resection with total mesorectal excision (TME). Patients were to receive six cycles of FOLFOX, with bevacizumab included for cycles 1–4. Patients with stable/progressive disease were to have radiation before TME, whereas responders were to have immediate TME. Postoperative radiation was planned if R0 resection was not achieved. Postoperative FOLFOX-6 was recommended, but adjuvant regimens were left to clinician discretion. The primary outcome was R0 resection rate. Thirty-two (100 %) of 32 study participants had R0 resections. Two did not complete preoperative chemotherapy secondary to cardiovascular toxicity. Both had preoperative chemoradiotherapy and then R0 resections. Of 30 patients completing preoperative chemotherapy, all had tumor regression and TME without preoperative chemoradiotherapy. The pathologic complete response rate to chemotherapy alone was 8 of 32 (25 %; 95 % CI, 11–43 %). The 4-year local recurrence rate was 0 % (95 % CI, 0–11 %); the 4-year disease-free survival was 84 % (95 % CI, 67–94 %). The authors conclude that "for selected patients with clinical stages II–III rectal cancer, neoadjuvant chemotherapy and selective radiation does not seem to compromise outcomes. Preoperative Radiation or Selective Preoperative Radiation and Evaluation Before Chemotherapy and TME (PROSPECT), a randomized phase III trial to validate this experience, is now open in the US cooperative group network."

This study indicates that systemic chemotherapy has a high activity in primary rectal tumors.

5 Does Resection of the Primary Tumor Confer with a Better Prognosis?

A crucial question is if resection of the primary tumor confers with a better prognosis. There is little direct evidence that this is the case in colorectal cancer. The only disease where this has been studied in randomized controlled trials is metastatic renal cell cancer (Flanigan et al. 2001; Mickisch et al. 2001). The larger of the two studies showed that the median survival of 120 eligible patients assigned to surgery followed by interferon was 11.1 months, while among the 121 eligible patients assigned to interferon alone was 8.1 months ($P = 0.05$). The difference in median survival between the two groups was independent of performance status, metastatic site, and the presence or absence of a measurable metastatic lesion. The smaller of the two studies that was recruited in the EORTC Genitourinary Group confirmed these results.

In conclusion, resection of the primary followed by systemic therapy resulted in longer survival among patients with metastatic renal cell cancer than systemic therapy alone.

5.1 SEER Data

Can the observations from renal cell cancer be transferred to metastatic colorectal cancer? Data from the Surveillance, Epidemiology and End Results (SEER) data registry of the National Cancer Institute indicate that the percentage of patients receiving resection of primary stage IV colorectal tumors is steadily decreasing from 1988 to 2000 (Cook et al. 2005). The investigators analyzed data from 26,754 patients with stage IV colorectal cancer diagnosed between 1988 and 2000. A total of 17,658 patients received resection of their primary tumor. A better overall survival was observed after primary tumor resection compared with a nonresection strategy. For rectal cancer, the difference was 16 months versus 6 months, and the 1-year-survival was 45 % versus 12 % ($p < 0.001$). Such a series, however, cannot inform us about the reasons why survival for patients having the primary tumor resected may have been longer. The authors themselves state that "The proportion of patients undergoing resection depends on patient's age and race and the anatomical location of the primary tumor. The degree to which case selection explains the treatment and survival differences observed is not known." Clearly, more detailed information from prospective trials is warranted.

5.2 CAIRO Studies

The Dutch Colorectal Cancer Group retrospectively analyzed the outcome of stage IV colorectal cancer patients with or without resection of the primary tumor treated in the phase III CAIRO and CAIRO2 studies (Venderbosch et al. 2011). In these two

studies, 258 and 289 patients had undergone a primary tumor resection and 141 and 159 patients had not. In the CAIRO study, a significantly better median overall survival and progression-free survival was observed for the resection compared to the nonresection group, with 16.7 versus 11.4 months [$P < 0.0001$, hazard ratio (HR) 0.61], and 6.7 versus 5.9 months ($P = 0.004$; HR 0.74), respectively. In the CAIRO2 study, median overall survival and progression-free survival were also significantly better for the resection compared to the nonresection group, with 20.7 versus 13.4 months ($P < 0.0001$; HR 0.65) and 10.5 versus 7.8 months ($P = 0.014$; HR 0.78), respectively. These differences remained significant in multivariate analyses. The authors concluded: "Our results as well as data from literature indicate that resection of the primary tumor is a prognostic factor for survival in stage IV colorectal cancer patients. The potential bias of these results warrants prospective studies on the value of resection of the primary tumor in this setting."

Do the results from the CAIRO study help us to guide our decisions in rectal cancer presenting with synchronous distant metastases? Not necessarily. The publication is dealing with stage IV colorectal cancer without a special focus on the situation of synchronous metastases. Moreover, no particular focus is put on the location of the tumor. No subgroup analysis for rectal cancers has been shown.

5.3 FFCD 96-01

This is the strength of a recent French publication from the Fédération Francophone de Cancérologie Digestive (FFCD) 96-01 study (Ferrand et al. 2013). Among the 294 patients with nonresectable colorectal metastases enrolled in the FFCD 96-01 phase III trial, which compared different first-line, single-agent chemotherapy regimens, 216 patients (73 %) presented with synchronous metastases at study entry and constituted the study population. Potential baseline prognostic variables including prior primary tumor resection were assessed by univariate and multivariate Cox analyses. Among the 216 patients with stage IV colorectal cancer, 156 patients (72 %) had undergone resection of their primary tumor prior to study entry. The resection and nonresection groups did not differ for baseline characteristics except for primary tumor location: rectal cancers were more often not resected: 14 % versus 35 % ($p = 0.0006$). In a multivariate analysis, resection of the primary was the strongest independent prognostic factor for progression-free survival (PFS) (hazard ratio (HR), 0.5; 95 % confidence interval [CI], 0.4–0.8; $p = 0.0002$) and overall survival (OS) (HR, 0.4; CI, 0.3–0.6; $p < 0.0001$). Both median PFS (5.1 [4.6–5.6] versus 2.9 [2.2–4.1] months; $p = 0.001$) and OS (16.3 [13.7–19.2] versus 9.6 [7.4–12.5]; $p < 0.0001$) were significantly higher in the resection group. These differences in patient survival were maintained after exclusion of patients with rectal primary ($n = 43$). The authors conclude that "resection of the primary tumor may be associated with longer PFS and OS in patients with stage IV colorectal cancer starting first-line, single-agent chemotherapy."

Limitations of this publication, as stated by the authors themselves are: First, assessing the impact of primary colorectal cancer resection on survival was not the primary aim of the FFCD 96-01 trial, which furthermore excluded patients whose condition worsened after primary tumor resection. As such, the study must be viewed as an exploratory, hypothesis-generating, post hoc analysis of a prospective trial. Second, indications for primary resection before patient inclusion in the FFCD 96-01 trial are unknown, as the study protocol did not require to collecting such information. Thus, the analysis probably mixed patients who had primary-related symptoms or complications at diagnosis and patients who had not.

In conclusion, the Dutch and the French retrospective analyses from prospective randomized trials support the hypothesis that resection of the primary tumor in case of synchronous distant metastases may improve progression-free and overall survival. The reason for this potential difference is thus far unknown. This clinical research question merits prospective investigation.

6 Current Ongoing Studies

Two randomized controlled trials with a comparable design are currently recruiting patients in Europe: *Synchronous* is recruiting patients in Germany while *CAIRO-4* is active in the Netherlands (Rahbari et al. 2012). Both studies enroll patients with colon cancer with synchronous nonresectable metastases. The study hypotheses are based on the prognostic differences seen in the previous retrospective analyses outlined earlier. Of note, both studies exclude patients with primary rectal tumors, as the study chairs see this situation different from colon cancers. Therefore, the results of these two important studies will not finally resolve the question how to manage rectal cancer with synchronous distant metastases.

7 Practical Consequences

The published data indicate that primary chemotherapy can be administered relatively safely in asymptomatic (colo-)rectal cancer with synchronous metastases. The severity of symptoms does usually guide the strategy. If severe symptoms result from the primary tumor, local treatment (colostomy, radiation, stenting, or resection) is usually administered up-front. The choice of local treatment is tailored to the individual needs.

In patients without symptoms from the primary tumor or with far advanced metastatic disease or with severe symptoms from metastatic disease, primary systemic treatment should be given first.

Figure 5 is illustrating the strategy followed in the University Cancer Center of Leipzig (Fig. 5). This practical algorithm may reflect one of the preferred algorithms that are currently preferred in Cancer Centers in Europe.

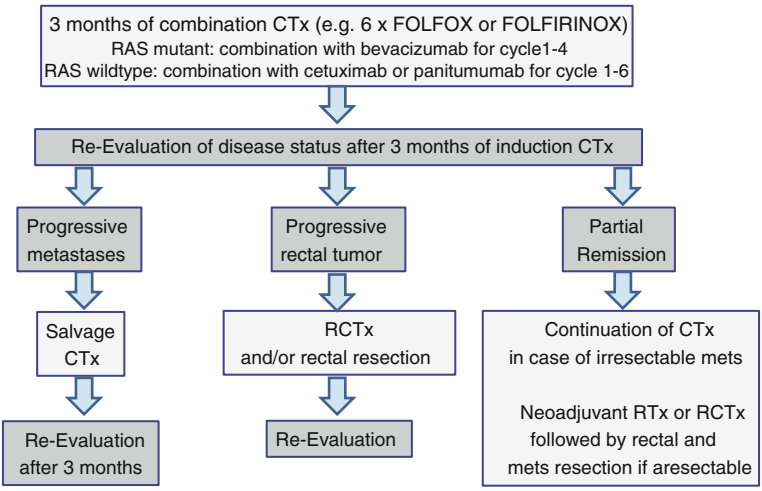

Fig. 5 Treatment algorithm of the University Cancer Center Leipzig (UCCL) for patients with asymptomatic rectal cancer with synchronous distant metastases. *Legend* CTx = chemotherapy, mets = metastases, RCTx = radiochemotherapy RTx = radiotherapy

References

Cook AD, Single R, McCahill LE et al (2005) Surgical resection of primary tumors in patients who present with stage IV colorectal cancer: an analysis of surveillance, epidemiology, and end results data, 1988 to 2000. Ann Surg Oncol 12:637–645

Ferrand F, Malka D, Bouuredjem A et al (2013) Impact of primary tumour resection on survival of patients with colorectal cancer and synchronous metastases treated by chemotherapy: results from the multicenter, randomised trial Fédération Francophone de Cancérologie Digestive 9601. Eur J Cancer 49:90–97

Flanigan RS, Salmon SE, Blumenstein BA et al (2001) Nephrectomy followed by interferon alfa-2b compared with interferon alpha-2b alone for metastatic renal-cell cancer. N Engl J Med 345:1655–1659

Lordick F, Geinitz H, Theisen J et al (2006) Increased risk of ischemic bowel complications during treatment with bevacizumab after pelvic irradiation: report of three cases. Int J Radiat Oncol Biol Phys 64:1295–1298

Manceau G, Brouquet A, Bachet JB et al (2013) Response of liver metastases to preoperative radiochemotherapy in patients with locally advanced rectal cancer and resectable synchronous liver metastases. Surgery 154:528–535

Mentha G, Majno PE, Andres A et al (2006) Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. Br J Surg 93:872–878

Mickisch GHJ, Garin A, van Poppel H et al (2001) Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet 358:966–970

Nordlinger B, Sorbye H, Glimelius B et al (2009) Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet 371:1007–1016

Poultsides GA, Servais EL, Saltz LB et al (2009) Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. J Clin Oncol 27:3379–3384

Rahbari NN, Lordick F, Falk C et al (2012) Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): synchronous—a randomised controlled multicentre trial (ISRCTN30964555). BMC Cancer 12:142

Scheer MGW, Sloots CEJ, van de Wilt GJ, Ruers TJM (2008) Management of patients with asymptomatic colorectal cancer and synchronous irresectable metastases. Ann Oncol 19:1829–1835

Schrag D, Weiser MR, Goodman KA et al (2014) Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol 32:513–518

Venderbosch S, de Wilt JH, Teerenstra S et al (2011) Prognostic value of resection of primary tumor in patients with stage IV colorectal cancer: retrospective analysis of two randomized studies and a review of the literature. Ann Surg Oncol 18:3252–3260

Recurrence Patterns After Resection of Liver Metastases from Colorectal Cancer

Halfdan Sorbye

Abstract

Recurrence of metastatic disease after resection of liver metastases from colorectal cancer remains a major problem as 70–80 % of patients will have a recurrence, most commonly in the liver or lung. To predict patterns of recurrence and outcome may guide follow-up and further treatment, as patients with recurrence might be candidates for repeated surgery or ablation therapy. A summary of studies shows that after hepatectomy 20–43 % will have a recurrence only in the remaining liver without extrahepatic disease, whereas 15–37 % will have a recurrence only to the lung. Early recurrence is associated with poorer outcome compared to late recurrence. Site of first recurrence after resection of liver metastases is predicted by several baseline variables; synchronous disease, primary tumor site, hepatic tumor size, CEA level, number of hepatic lesions, and RAS mutation status. Pattern of recurrence is a predictor for survival after hepatectomy, with liver-only and lung-only recurrences having the best survival. In the majority of patients with isolated hepatic or lung recurrence, repeated metastasectomy is possible resulting in a 40 % 5-year survival rate. Perioperative chemotherapy reduces the risk of liver recurrence after hepatectomy of colorectal cancer liver metastases.

Keywords

Colorectal · Cancer · Liver · Hepatectomy · Recurrence · Patterns · Metastases · Resection

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1 Metastatic Disease from Colorectal Cancer

In patients diagnosed with colorectal cancer (CRC), synchronous or metachronous metastatic disease occurs in about 30–40 % of cases. In a recent follow-up study, recurrent disease after primary surgery only developed in 20 % of patients, less than prior reported (Grossmann et al. 2014). The decrease was explained by improvements in treatment and a stage shift due to routine preoperative CT staging. The reported incidence of synchronous metastases has increased over time from 10–15 % up to 30 % in current series. Localization of recurrent disease after primary surgery has also undergone changes as compared to historical reports. Local recurrences have become less common, whereas lung metastases are found more often (39 % vs. 4–14 %) probably due to increased use of chest CT. Metastases are now more often located to one organ site. In a recent study, recurrence was confined to one organ in 58 % of patients, most often liver-only and lung-only (Grossmann et al. 2014). The eligibility for curative treatment of first recurrence seems to have increased, with 28 % in this observational cohort compared to approximately 20 % in older follow-up trials (Grossmann et al. 2014). Curative treatment of recurrent disease was possible in 33 % for liver metastases and 20 % for lung metastases. Patients having lung resection of pulmonary metastasis have an expected 5-year survival of 45 % and a median survival of 50 months (Inoue et al. 2004). Compared to colon cancer, rectal cancers have a higher risk of developing synchronous and metachronous lung metastases (Mitry et al. 2010). Advanced age, recent year of diagnosis and a rectal primary were significantly associated with synchronous pulmonary metastases in a national cohort of CRC (Nordholm-Carstensen et al. 2014). Molecular mechanisms seem to predict for recurrence and site of recurrence after primary surgery. KRAS mutation is associated with lung relapse but not liver relapse (Tie et al. 2011). BRAF mutant tumors have higher rates of peritoneal metastases, distant lymph node metastases, and lower rates of lung metastases (Tran et al. 2011).

2 Resection of Liver Metastases from Colorectal Cancer

The liver is the most common site of distant metastatic spread from CRC. Liver metastases are present in nearly 80 % of stage IV patients and the sole site of disease in approximately 40 % of these (Grossmann et al. 2014; Siegel et al. 2012; Sorbye et al. 2007). Hepatic resection is the standard therapy for resectable metastases and offers the only chance of long-term survival. Radical surgical treatment or ablation of liver metastases is possible in approximately 20 % of patients with metastatic disease. When surgical resection of liver metastases is possible, 5-year survival approaches 35–40 % (Fong et al. 1997). However, relapse is common and occurs in 50–75 % of the patients (Kopetz et al. 2009) (Table 1). Patients undergoing

Table 1 Location of first recurrence after liver resection in mCRC patients in retrospective studies with >175 patients

	Liver resection/ ablation	Recurrence (%)	Location of recurrence, percentage of all recurrences					Local recurrence (%)
			Liver only (%)	Lung only (%)	Extra hepatic only (%)	Liver all (%)	Lung all (%)	
de Jong et al. (2009)	1,669	57	43		36	64		
Saiura et al. (2012)[a]	736	75	38	18		61	30	
D'Angelica et al. (2011)	637	62	31	27		52	45	
Hughes and Cuthbertson (1962)[b]	607	70	40	19		50	25	9
Kato et al. (2003)	585	68				61	28	
Pawlik et al. (2005)	557	40	34		36	64		
Fong et al. (1997)	456	52	41	21		42	26	
Malik et al. (2007)	430	67	20			68	31	
Karanjia et al. (2009)	283	48	35		54	46		
Mise et al. (2010)	216	73	43	15		66	29	
Vauthey et al. (2013)[a]	193	65	42	37		70	66	
Butte et al. (2012)	185[c]	70	27	29		49	45	7

[a]Additional unpublished data given by personal communication with the author
[b]Site of first recurrence available for 376 cases, percentage calculated from this
[c]Rectal primary with synchronous metastatic disease

resection of metachronous colorectal liver metastases after adjuvant chemotherapy with FOLFOX, had increased rate of KRAS mutations in liver metastases compared with patients treated with 5-FU only (Andreou et al. 2012).

3 Recurrence After Resection of Liver Metastases from CRC

Metastatic recurrence after curative resection of liver metastases from CRC remains a major problem, with disease-free survival at 10 years only 18 %. The liver and lung are the most common sites of recurrence after hepatectomy with recurrence rates of 40–74 % (D'Angelica et al. 2011) (Table 1). Most liver recurrences are not local relapses of treated lesions. Local intrahepatic relapse was only 5.5 % per lesion in the perioperative chemotherapy arm of the 40983 EORTC study (Tanis et al. 2014). After radiofrequency ablation, local intrahepatic relapse was 6 % per lesion (Tanis et al. 2014). Tumor and patient-related characteristics might offer predictive value for outcome, recurrence, and treatment of recurrence. To predict patterns of recurrence and outcome may guide follow-up and further treatment, as patients who develop recurrence after liver surgery might be candidates for repeated surgery or ablation therapy.

3.1 Factors that Predict Recurrence After Resection of Liver Metastases

The prognostic determinants of recurrence and survival after hepatectomy are well-known and include factors such as; elevated carcinoembryonic antigen (CEA) level, number of liver metastases, size of largest hepatic tumor, bilateral liver involvement, nodal status of the primary tumor, male gender, synchronous metastatic disease, presence of extrahepatic disease, and short disease-free interval (Rees et al. 2008). A number of clinical scoring systems have been proposed to synthesize these data and help assessing the patient's prognosis after resection of liver metastases and whether surgery is worthwhile (Fong et al. 1999; Nordlinger et al. 1996). However, the proposed scoring systems demonstrate limited external validation and their clinical utility remains controversial. Treatment-related prognostic factors for recurrence are surgical margins and radiological or pathological response to chemotherapy. Larger metastases and node positivity in the colorectal primary predict early (within 6 m) intrahepatic recurrence, whereas a positive resection margin was the only predictor for a late recurrence (Malik et al. 2007). Perioperative chemotherapy reduces recurrences with an 8–10 % increase in PFS and increased overall survival (Nordlinger et al. 2008, 2013). Patients with elevated CEA and a good performance status seem to benefit the most from perioperative chemotherapy (Sorbye et al. 2012). Molecular markers may predict recurrence. KRAS mutation was an independent factor for increased recurrence risk and worse survival in patients with liver surgery for CRC metastases (Nash et al. 2010; Stremitzer et al. 2012; Karagkounis et al. 2013). In contrast, metastasis associated in colon cancer 1 (MACC1) mRNA, but not KRAS mutation was found to be an independent predictive factor for recurrence after resection of CRC liver metastases (Isella et al. 2013). In patients with hepatic colorectal liver metastases treated with resection and modern chemotherapy, increased expression of

thymidylate synthase improves outcome (Maithel et al. 2012). Gene expression profiles can predict outcome following liver resection in patients with metastatic CRC (Ito et al. 2013).

3.2 Location of Recurrences After Liver Resection

The site of first recurrence is usually liver or lung. A summary of studies shows that 20–43 % will have a recurrence only in the remaining liver without extrahepatic disease, whereas 15–37 % will have a recurrence only to the lung (Table 1).

3.3 Factors Predicting Site of First Recurrence After Resection of Liver Metastases

Several factors are associated with an increased risk of intrahepatic disease or lung as the first site of recurrence after liver resection. Synchronous presentation of the primary tumor and hepatic metastasis, receipt of chemotherapy, R1 margin status, and history of ablation were associated with an increased risk of intrahepatic recurrence as the initial site of failure (de Jong et al. 2009). In multivariate analysis, R1 margin status and history of ablation remained associated with intrahepatic recurrence. When extrahepatic disease as the first site of recurrence was analyzed in the same study, primary rectal tumor site, primary tumor lymph node metastasis, hepatic tumor size >5 cm, hepatic tumor number >4 and receipt of chemotherapy were each associated with an increased risk of extrahepatic recurrence. In multivariate analysis, rectal primary tumor site and tumor number >4 each remained associated with the risk of extrahepatic recurrence (de Jong et al. 2009). Lung recurrence occurred more frequently after hepatectomy when the primary was located in the lower rectal tumor, whereas liver recurrence was more frequent when the primary was located in colon (Lee et al. 2014). In a Japanese publication, patients with >4 liver metastases and size of hepatic tumor >5 cm more often had recurrence in liver and less in lung after hepatectomy for CRC metastases (Hirokawa et al. 2014). However, time to recurrence was similar. In a US study, CEA > 200 ng/ml, liver tumor size >5 cm and >1 liver metastasis were independent predictors for other sites of recurrence than a liver-only or lung-only pattern (Hill et al. 2012). Minor pathologic response to chemotherapy was an independent predictor of lung and liver recurrences after liver surgery for CRC metastases (Vauthey et al. 2013).

Few studies have focused on molecular markers and site of recurrence after hepatectomy in CRC patients. A recent study indicated that KRAS mutation was predictive for lung recurrence, but not for liver recurrence (Vauthey et al. 2013). RAS mutation was associated with a shorter 3-year lung recurrence free survival rate, but not with a shorter liver recurrence free survival rate. At the last follow-up in this study, lung recurrence was observed in 65 % of patients with RAS mutation

versus 38 % of patients with wild-type RAS (Vauthey et al. 2013). The cumulative incidence of liver recurrence did not correlate significantly with RAS mutation status. These results suggest a propensity for RAS-mutated tumors to metastasize to lung, and are in line with previous studies showing higher KRAS mutation rates in lung and brain colorectal metastases compared to colorectal liver metastases (Tie et al. 2011; Kim et al. 2012). After hepatic resection for colorectal liver metastases, lack of the CXCR4 tumor expression (a chemokine receptor) was associated with a lower overall rate of recurrence and associated with a liver-only or lung-only pattern of recurrence (Yopp et al. 2012).

3.4 Survival According to Recurrence Patterns After Liver Surgery

Pattern of recurrence seems to be a predictor for survival after hepatectomy. The median overall survival for patients with posthepatectomy recurrence was 35 months (Hill et al. 2012). Whereas a liver-only or lung-only recurrence had a median survival of 44 months, other recurrences had a median survival of about 28 months (Hill et al. 2012). Lung-only recurrence was associated with the best survival measured from the time of recurrence (median 36 months) (D'Angelica et al. 2011). Survival was shorter for patients with liver-only (24 m) or other single sites of recurrence (17 m), whereas those with multiple sites had the worst outcome (13 m). In one study, however, recurrence–free survival was 16–17 months regardless of site of recurrence after hepatectomy (intrahepatic vs. extrahepatic vs. intra and extrahepatic) (de Jong et al. 2009). Patients who developed recurrence at only one metastatic site had significantly greater long-term survival than patients who developed recurrences at multiple anatomical sites (40 vs. 27 m) (Assumpcao et al. 2008). Whereas the number of recurrent sites had an important effect on survival, the location of the recurrent disease did not seem to affect survival.

The time interval from hepatectomy to recurrence is related to the recurrence pattern and to survival. Initial lung-only recurrence was associated with a late presentation. Only 28 % of patients with lung-only recurrence experienced recurrence within the first year, whereas about 50 % of patients with liver-only, other single sites, or multiple sites of recurrence experienced recurrence within the first year (D'Angelica et al. 2011). Time to recurrence was an independent factor for survival (16 m for early vs. 30 m for late recurrence) (D'Angelica et al. 2011). In another study, 20 % of patients developed early recurrence, i.e., recurrence within 6 months (Malik et al. 2007). Early recurrence was associated with poorer survival when compared to late recurrence (22 vs. 41 m). An independent predictor of early recurrence was the presence of eight or more metastases.

3.5 Resection of Recurrence After Liver Surgery

Patients with limited posthepatectomy recurrence in anatomically favorable locations might be candidates for further resection. Especially patients with a liver-only or lung-only recurrence might benefit from repeated surgery. For patients undergoing a second liver resection, 5-year survival rates between 30–58 % have been reported (Adair et al. 2012; Kulik et al. 2013; Wicherts et al. 2013). Median survival was 42–46 months. After initial hepatectomy, more than half of lung recurrences were resected (D'Angelica et al. 2011). This resulted in a median survival of 51 months compared to 34 months in patients with resection of a liver recurrence. In another study, 98 of the 166 patients with recurrence underwent repeated metastasectomy with curative intent and 85 % of patients with isolated hepatic or lung recurrence were resected (Mise et al. 2010). The 5-year survival rate of 37–39 % after repeated resection was similar for hepatic and pulmonary recurrences (Mise et al. 2010). In one study, 29 % of patients with a recurrence after hepatectomy underwent another operation with curative intent, resulting in a 3- and 5-year survival rate of 77 and 39 %, respectively (Assumpcao et al. 2008). Another study found a 5-year survival of 47 % after repeated curative intent surgery for recurrent colorectal liver metastases (de Jong et al. 2009). The presence of eight or more initial liver metastases predict for developing a unresectable recurrence (Malik et al. 2007). Although 50 % of patients with negative CXCR4 tumor expression developed a recurrence, the pattern of recurrence was frequently amenable to salvage therapy with resection or ablation resulting in long-term survival free of disease in most cases (Yopp et al. 2012).

4 Perioperative Chemotherapy and Recurrence Patterns After Resection of Liver Metastases

In the EORTC 40983 study, 364 patients with 1–4 resectable liver metastases were randomized between surgery alone and surgery + perioperative FOLFOX (Nordlinger et al. 2013). Place of first recurrence and time to first recurrence according to baseline factors and perioperative chemotherapy was analyzed and presented at the 2nd St. Gallen EORTC Gastrointestinal Cancer Conference. The risk for lung as first place of recurrence increased when CEA was elevated at baseline, if regional lymph node metastases had been present or when the size of the largest liver metastasis was >3 cm. Synchronous metastatic disease or presence of more than one liver metastasis increased the risk for liver recurrence. Primary tumor location had no effect on recurrence patterns. Perioperative chemotherapy reduced the number of liver recurrences. Perioperative chemotherapy reduced liver recurrence in the subgroups of patients with one of the following characteristics: CEA > 30 ng/ml, one liver metastases or initial N1-2 disease. Median survival after recurrence was 40 months for liver-only (39 % 5-year survival) and 47 months for lung-only (36 % 5-year) and not significantly different.

5 Conclusion

Several baseline prognostic variables predict site of first recurrence after resection of liver metastases from CRC; synchronous disease, primary tumor site, hepatic tumor size, CEA level, number of hepatic lesions, and RAS mutation status. Pattern of recurrence is a predictor for survival after hepatectomy, with a liver-only or lung-only recurrence having the best survival. In the majority of patients with isolated hepatic or lung recurrence, repeated metastasectomy is a possibility, resulting in a 40 % 5-year survival rate. Perioperative chemotherapy reduces the risk of liver recurrence after hepatectomy in CRC patients.

References

Adair RA, Young AL, Cockbain AJ et al (2012) Repeat hepatic resection for colorectal liver metastases. Br J Surg 99:1278–1283

Andreou A, Kopetz S, Maru DM et al (2012) Adjuvant chemotherapy with FOLFOX for primary colorectal cancer is associated with increased somatic gene mutations and inferior survival in patients undergoing hepatectomy for metachronous liver metastases. Ann Surg 256:642–650

Assumpcao L, Choti MA, Gleisner AL et al (2008) Patterns of recurrence following liver resection for colorectal metastases: effect of primary rectal tumor site. Arch Surg 143:743–749

Butte JM, Gonen M, Ding P et al (2012) Patterns of failure in patients with early onset (synchronous) resectable liver metastases from rectal cancer. Cancer 118:5414–5423

D'Angelica M, Kornprat P, Gonen M et al (2011) Effect on outcome of recurrence patterns after hepatectomy for colorectal metastases. Ann Surg Oncol 18:1096–1103

de Jong MC, Pulitano C, Ribero D et al (2009) Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1,669 patients. Ann Surg 250:440–448

Fong Y, Cohen AM, Fortner JG et al (1997) Liver resection for colorectal metastases. J Clin Oncol 15:938–946

Fong Y, Fortner J, Sun RL et al (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 230:309–318

Grossmann I, Doornbos PM, Klaase JM et al (2014) Changing patterns of recurrent disease in colorectal cancer. Eur J Surg Oncol 40:234–239

Hill CR, Chagpar RB, Callender GG et al (2012) Recurrence following hepatectomy for metastatic colorectal cancer: development of a model that predicts patterns of recurrence and survival. Ann Surg Oncol 19:139–144

Hirokawa F, Hayashi M, Miyamoto Y et al (2014) Reconsideration of the indications for adjuvant chemotherapy for liver metastases from colorectal cancer after initial hepatectomy. Ann Surg Oncol 21:139–146

Hughes ES, Cuthbertson AM (1962) Recurrence after curative excision of carcinoma of the large bowel. JAMA 182:1303–1306

Inoue M, Ohta M, Iuchi K et al (2004) Benefits of surgery for patients with pulmonary metastases from colorectal carcinoma. Ann Thorac Surg 78:238–244

Isella C, Mellano A, Galimi F et al (2013) MACC1 mRNA levels predict cancer recurrence after resection of colorectal cancer liver metastases. Ann Surg 257:1089–1095

Ito H, Mo Q, Qin LX, Viale A et al (2013) Gene expression profiles accurately predict outcome following liver resection in patients with metastatic colorectal cancer. PLoS One (E pub 10 Dec 2013)

Karagkounis G, Torbenson MS, Daniel HD et al (2013) Incidence and prognostic impact of KRAS and BRAF mutation in patients undergoing liver surgery for colorectal metastases. Cancer 119:4137–4144

Karanjia ND, Lordan JT, Fawcett WJ et al (2009) Survival and recurrence after neo-adjuvant chemotherapy and liver resection for colorectal metastases: a ten year study. Eur J Surg Oncol 35:838–843

Kato T, Yasui K, Hirai T et al (2003) Therapeutic results for hepatic metastasis of colorectal cancer with special reference to effectiveness of hepatectomy: analysis of prognostic factors for 763 cases recorded at 18 institutions. Dis Colon Rectum 46:S22–S31

Kim MJ, Lee HS, Kim JH et al (2012) Different metastatic pattern according to the KRAS mutational status and site-specific discordance of KRAS status in patients with colorectal cancer. BMC Cancer 12:347

Kopetz S, Chang GJ, Overman MJ et al (2009) Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 27:3677–3683

Kulik U, Bektas H, Klempnauer J, Lehner F (2013) Repeat liver resection for colorectal metastases. Br J Surg 100:926–932

Lee H, Choi DW, Cho YB, et al (2014) Recurrence pattern depends on the location of colon cancer in the patients with synchronous colorectal liver metastasis. Ann Surg Oncol (E pub 5 Feb 2014)

Maithel SK, Gönen M, Ito H et al (2012) Improving the clinical risk score: an analysis of molecular biomarkers in the era of modern chemotherapy for resectable hepatic colorectal cancer metastases. Surgery 151:162–170

Malik HZ, Gomez D, Wong V et al (2007) Predictors of early disease recurrence following hepatic resection for colorectal cancer metastasis. Eur J Surg Oncol 33:1003–1009

Mise Y, Imamura H, Hashimoto T et al (2010) Cohort study of the survival benefit of resection for recurrent hepatic and/or pulmonary metastases after primary hepatectomy for colorectal metastases. Ann Surg 251:902–909

Mitry E, Guiu B, Cosconea S et al (2010) Epidemiology, management and prognosis of colorectal cancer with lung metastases: a 30-year population-based study. Gut 59:1383–1388

Nash GM, Gimbel M, Shia J et al (2010) KRAS mutation correlates with accelerated metastatic progression in patients with colorectal liver metastases. Ann Surg Oncol 17:572–578

Nordholm-Carstensen A, Krarup PM, Jorgensen LN et al (2014) Danish colorectal cancer group. Occurrence and survival of synchronous pulmonary metastases in colorectal cancer: a nationwide cohort study. Eur J Cancer 50:447–456

Nordlinger B, Guiguet M, Vaillant JC et al (1996) Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1,568 patients. Cancer 77:1254–1262

Nordlinger B, Sorbye H, Glimelius B et al (2008) Preoperative chemotherapy with FOLFOX4 and surgery for resectable liver metastases form colorectal cancer. Lancet 371:1007–1016

Nordlinger B, Sorbye H, Glimelius B et al (2013) Perioperative FOLFOX4 chemotherapy and surgery for resectable liver metastases from colorectal cancer: long-term survival results of the EORTC Intergroup phase III study 40983. Lancet Oncol 14:1208–1215

Pawlik TM, Scoggins CR, Zorzi D et al (2005) Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg 241:715–722

Rees M, Tekkis PP, Welsh FK et al (2008) Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg 247:125–135

Saiura A, Yamamoto J, Hasegawa K et al (2012) Liver resection for multiple colorectal liver metastases with surgery up-front approach: bi-institutional analysis of 736 consecutive cases. World J Surg 36:2171–2178

Siegel RL, Ward EM, Jemal A et al (2012) Trends in colorectal cancer incidence rates in the United States by tumor location and stage, 1992–2008. Cancer Epidemiol Biomark Prev 21:411–416

Sorbye H, Kohne CH, Sargent D, Glimelius B (2007) Patient characteristics and stratification in medical treatment studies for metastatic colorectal cancer. Ann Oncol 18:1666–1672

Sorbye H, Mauer M, Gruenberger T et al (2012) Predictive factors for the benefit of peri-operative FOLFOX for resectable liver metastasis in colorectal cancer patients (EORTC Intergroup Trial 40983). Ann Surg 255:534–539

Stremitzer S, Stift J, Gruenberger B et al (2012) KRAS status and outcome of liver resection after neoadjuvant chemotherapy including bevacizumab. Br J Surg 99:1575–1582

Tanis E, Nordlinger B, Mauer M et al (2014) Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983. Eur J Cancer (E pub 7 Jan 2014)

Tie J, Lipton L, Desai J et al (2011) KRAS mutation is associated with lung metastasis in patients with curatively resected colorectal cancer. Clin Cancer Res 17:1122–1130

Tran B, Kopetz S, Tie J et al (2011) Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. Cancer 117:4623–4632

Vauthey JN, Zimmitti G, Kopetz SE et al (2013) RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. Ann Surg 258:619–626

Wicherts DA, de Haas RJ, Salloum C et al (2013) Repeat hepatectomy for recurrent colorectal metastases. Br J Surg 100:808–818

Yopp AC, Shia J, Butte JM et al (2012) CXCR4 expression predicts patient outcome and recurrence patterns after hepatic resection for colorectal liver metastases. Ann Surg Oncol 19(Suppl 3):S339–S346