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Review

MODERN THERAPY OF RECTAL CARCINOMA

H. Matthaei[1]*, E. Bölke[2]*, M. Schmelzle[1], W. Budach[2], K. Orth[3], R. Engers[4], M. Cohnen[5], C. Matuschek[2], S. Gripp[2], W. T. Knoefel[1], M. Peiper[1]

[1]Klinik für Allgemein-, Viszeral- und Kinderchirurgie, Universitätsklinikum Düsseldorf,
[2]Klinik und Poliklinik für Strahlentherapie und Radiologische Onkologie, Universitätsklinikum Düsseldorf,
[3]Klinik für Allgemein-, Gefäß-, und Thoraxchirurgie, Klinikum Emden,
[4]Institut für Pathologie, Universitätsklinikum Düsseldorf,
[5]Institut für Diagnostische Radiologie, Universitätsklinikum Düsseldorf, Germany

Abstract
Throughout the past decade the treatment of rectal carcinoma has improved remarkably. Today, individualized multimodality treatment allows local and distant tumor freedom with preservation of anorectal and genitourinary function in a majority of patients. Radiotherapy is elementary in reducing the risk of local recurrence whereas chemotherapy including promising novel agents prevents or eliminates distant metastases. However, surgery revolutionized by TME (total mesorectal excision) remains the only curative treatment for rectal carcinoma.

In this study the authors review the developments as well as the current status of modern treatment for rectal carcinoma.

Key words: Rectal carcinoma, total mesorectal excicison, TME, multimodality treatment.

INTRODUCTION

Over the past decades treatment options of rectal carcinoma have improved in a remarkable way.

Local and distant tumor freedom with preservation of anorectal and genitourinary function remain challenging therapy endpoints, requiring a high degree of interdisciplinarity. Therefore, the management of every single patient suffering from a rectal carcinoma has to be embedded in a multidisciplinary tumor board consisting of experienced surgeons, medical and radiation oncologists, gastroenterologists, pathologists as well as stoma therapists.

Radiotherapy reduces the risk of local recurrence, whereas chemotherapy may prevent or eliminate distant metastases. Nevertheless, surgery remains the most effective and the only curative treatment.

Figures 1-4 depict different stages of rectal carcinoma as they present in modern imaging techniques. Today, these progressive diagnostics include endorectal ultrasound, computertomography and high frequency 3-Tesla-MRI allowing a precise preoperative staging, thus providing the basis for a well developed, individually tailored therapy regime according to each patient´s tumor stage.

T1/T2-tumors without signs of local or distant metastases are treated by surgery alone. Primary surgery is also therapy of choice in patients suffering from symptomatic carcinomas with gastrointestinal hemorrhage or ileus. More advanced stages require multimodality treatment concepts.

Total mesorectal excision (TME) was a landmark progress in surgical treatment of carcinomas located in the middle and lower third of the rectum. Developed in 1982, this sphincter preserving technique has now become the gold standard in oncologic rectal surgery. TME has reduced the rate of local recurrences drastically (<10%) in early as well as in locally advanced lesions, temporarily questioning the value of radiotherapy[1-6]. However, more recent studies highlight a clear benefit of preoperative radiotherapy for reducing local recurrence, not survival- even if patients undergo TME thereafter [4, 7, 8].

Numerous prospective studies have analyzed the impact and most favorable sequence of pre- and postoperative radio- and chemotherapy in rectal cancer. Accordingly, tumor resection followed by adjuvant radiochemotherapy was the treatment of choice in locally advanced rectal carcinoma until 2004. However, recent studies demonstrate distinct advantages of preoperative compared to postoperative radiation therapy [9-13].

In particular, a German study by Sauer et al. demonstrated a significantly better local control in patients with rectal carcinoma of UICC Stage II and III after preoperative radiochemotherapy vs. postoperative adjuvant standard treatment. In addition, a decrease in acute as well as long term side effects was noted [10]. Therefore, preoperative radiotherapy has become a standard modality in locally advanced tumors.

Despite the revolutionary successes in local tumor control, distant metastases remain the predominant site of tumor failure. Here, more aggressive combined multimodal therapies are needed particularly in far advanced and/or metastatic disease stages. Ongoing studies are investigating the value of novel substances

* H. Matthaei and E. Bölke contributed equally to this work.

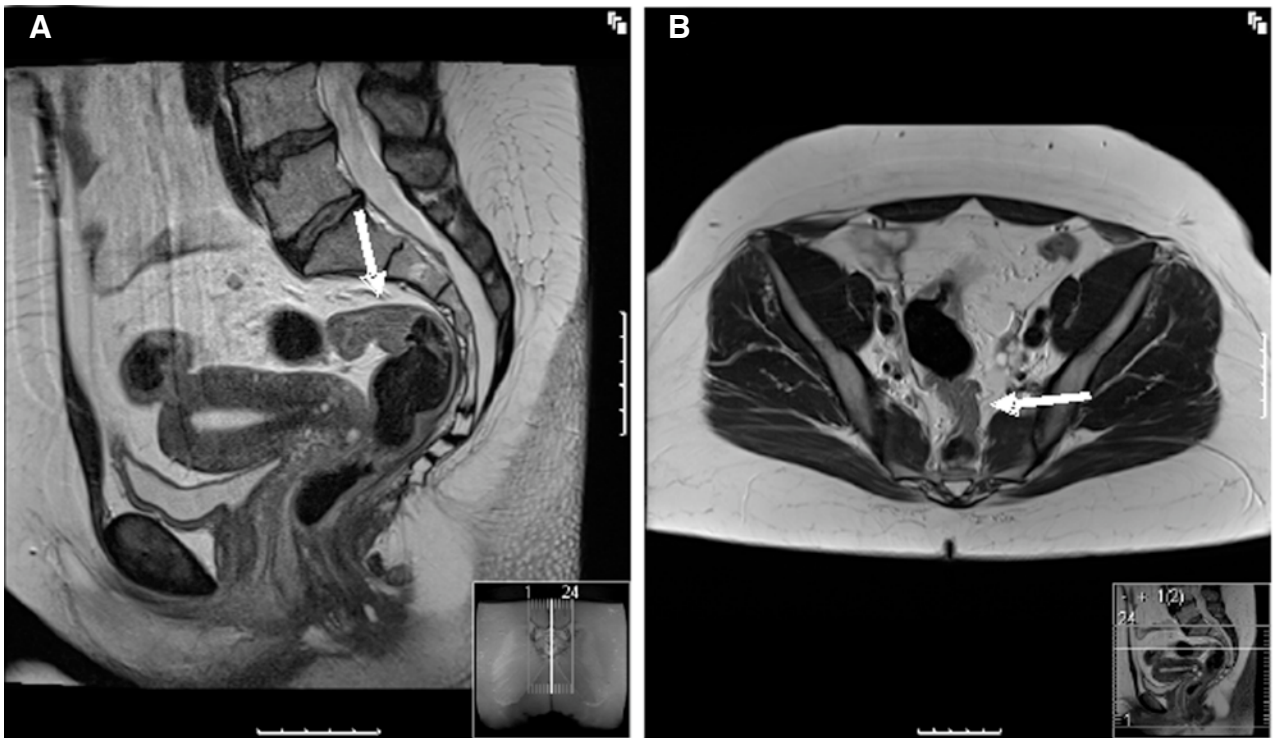

Fig. 1. A: Sagittal T2w MR-image of a T2 rectal cancer (arrow). B: Transverse T2w image delineates the stenosing character of the tumor without perifocal infiltration (arrow).

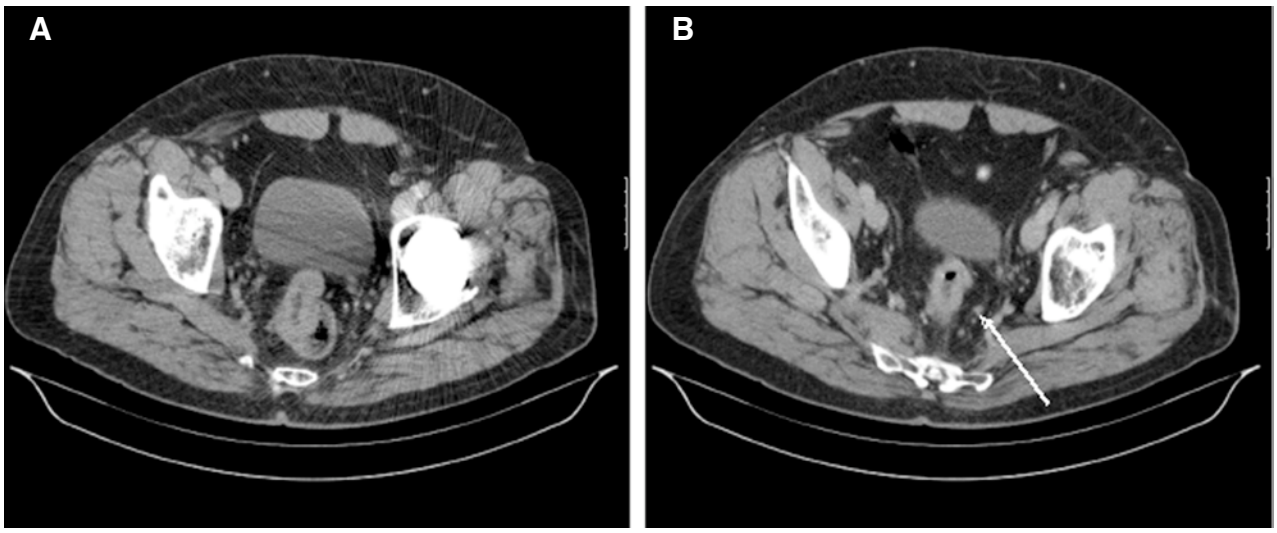

Fig. 2. A: Transverse CT image of a T2 N1 rectal cancer. B: No signs of infiltration either in the perirectal fat or into the bladder (arrow: local lymph node).

(such as Oxaliplatin, Capecitabine, Irinotecane, Bevacizumab or Cetuximab) and first results from preclinical and clinical studies are promising[14-28].

Surgery for Rectal Carcinoma

Radical surgery is the most important part in a curative concept for rectal cancer.

Transanal local excision for T1-tumors has proven to be oncologically adequate for T1a situations. Residual tumor and positive lymph nodes remaining in situ led to high local recurrence rates of 20-30% [29]. Local relapse was observed in 10-23% of patients with T3 tumors treated with local resection and postoperative radiation therapy [30]. Therefore, this technique has to be reserved for selected cases (i.e. in case of severe co-morbidity). Today, radical surgery alone is the treatment of choice in patients without lymph node involvement (N0) and no signs of distant metastases (M0). However, for locally advanced tumors (T3/T4N0) the issue is not fully settled: Especially, wheather surgery in patients with gross sphincter infiltration should be supported by multimodal options including preoperative radiotherapy is discussed contro-

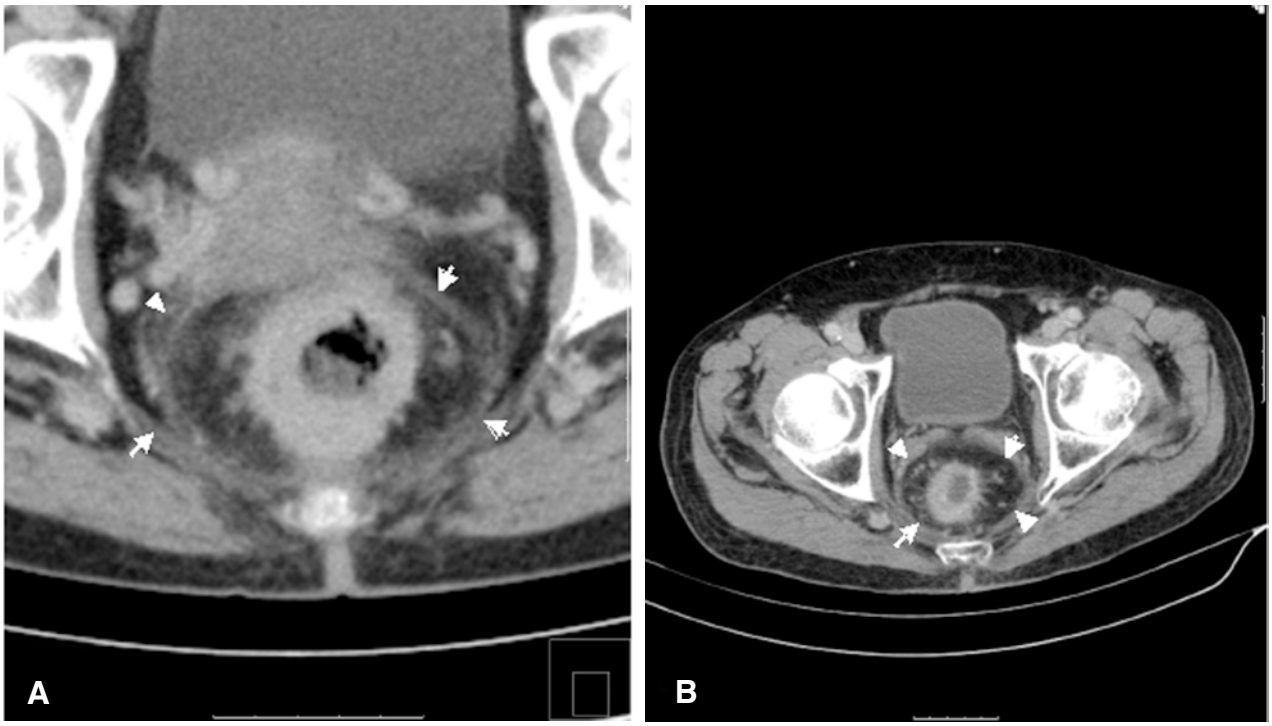

Fig. 3. A: Transverse CT image of a T3 rectal cancer: diffuse infiltration of the perirectal fat whereas uterus and the mesorectal fascia are not involved (arrowheads). B: No signs of infiltration in the perirectal fat (T3 tumor in another patient; seminal vesicles and mesorectal fascia are respected (arrowheads).

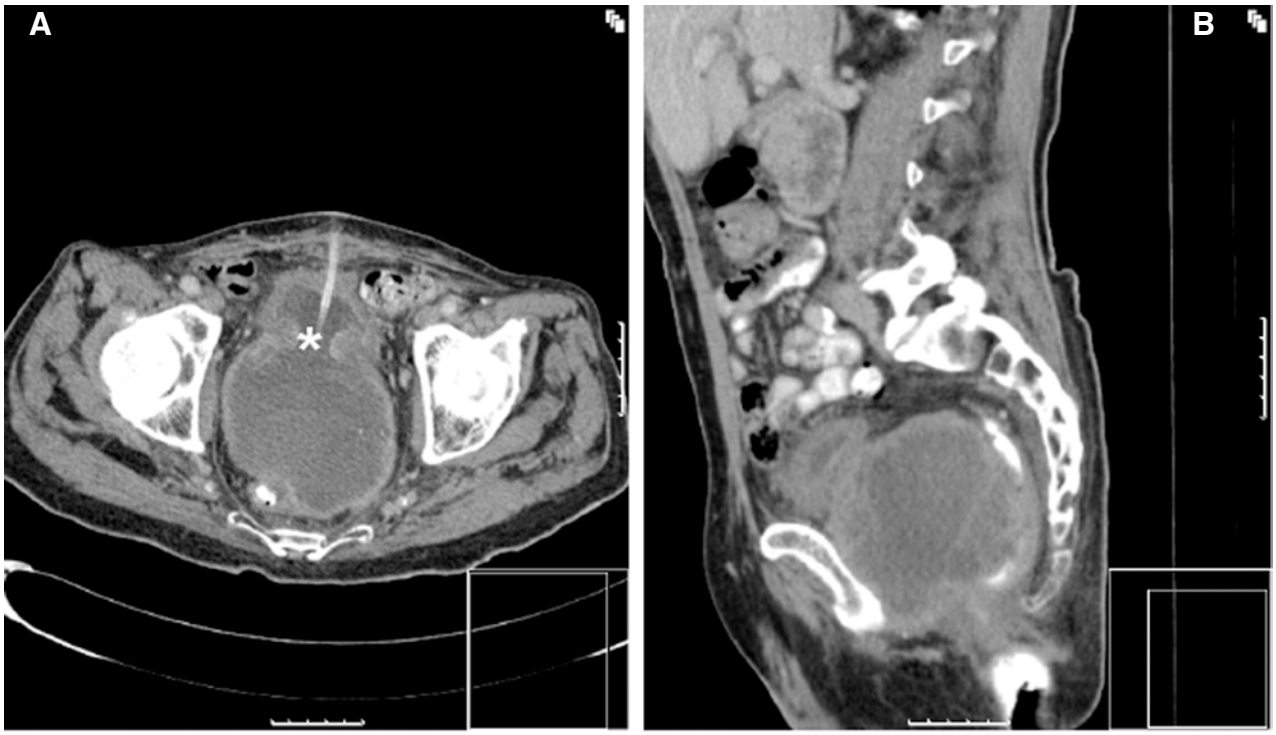

Fig. 4. A: Transverse CT image of a T4 rectal cancer with bladder infiltration (star). B: Large tumor with signs of central necrosis (sagittal reformation).

verserly. No improved survival has been observed within this approach and the benefit concerning local tumor control in these patients is still on debate. Moreover, we believe that even an early diagnosed local relapse after radical surgery for T3/T4N0 carcinomas (assessed through regular aftercare) is operable with curative intention – especially in non-radiated patients. Further studies are needed to clarify this topic. Nevertheless, T3/T4 tumors have a 5% lower risk of a local recurrence but lack of any survival benefit. If

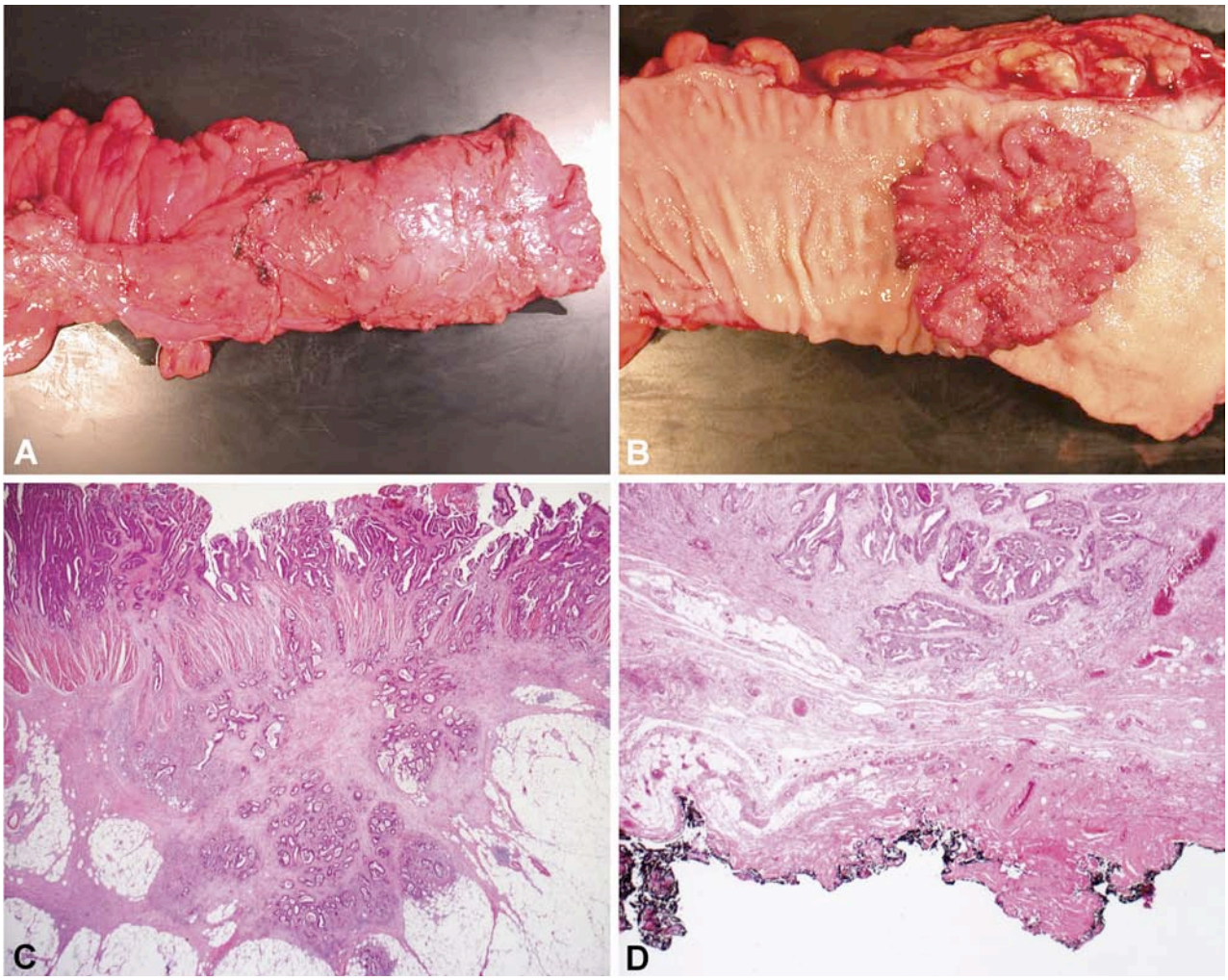

Fig. 5. Pathological evaluation of a representative case of rectal carcinoma treated by total mesorectal excision. A: Surgical specimen with intact circumferential resection margin; B: Typical macroscopic aspect of polypoid rectal carcinoma; C: Histological section, showing a moderately differentiated adenocarcinoma, which deeply invades into the mesorectal fat tissue, but (D) does not reach the ink-marked mesorectal resection margin.

adequate postoperative follow-up is performed, even local recurrences can be detected early enough and resected, even in prior radiated areas. According to the literature, any survial benefit for preoperative radiation therapy might be achieved in T4 situations. .

The most common resection techniques for rectal carcinomas depending on the site of tumor include anterior rectal resection, low anterior rectal resection and abdominoperineal resection of the rectum. Like several other centers, we prefer an intersphincteric (abdominoperianal) rectal resection with hand-sutured coloanal anastomosis for ultra low rectal cancer without signs of massive infiltration of the anal sphincter apparatus. However, this technique requires a high surgical expertise and profound experience.

In terms of reconstruction, we prefer an end-to-end anastomosis or alternatively a colon-J-pouch reconstruction. A diverting ileo- or colostomy is recommended to enhance anastomotic healing and it prevents severe complications in case of a fragile anastomosis. Nevertheless, it should be noted that stomas obviously do not reduce the number of anastomotic leakage.

TME was first described by Heald et al. in 1982 [3]. Since then, it has had a revolutionary impact on surgical therapy for carcinomas of the middle (6 to <12 cm) and lower third (0 to <6 cm) of the rectum. TME involves the sharp dissection under direct visualization of the plane between the endopelvic fascia and the rectal adipose tissue circumferentially, removal of the mesorectum (a fatty tissue directly adjacent to the rectum that contains blood vessels and lymph nodes) with its fascia propria, and the preservation of the pelvic fascia and the autonomic nerve plexus. This technique is thought to extirpate the primary tumor en bloc by "no-touch isolation technique" including potential satellite metastases of the mesorectum. Notably, "coning", defined as the continually dissection of thinner slides of the mesorectum with the risk of remaining contaminated tissue in situ, should be avoided with regard to the area located above the pelvic muscles.

The overwhelming results of many large centers performing TME revealed consistently low local recurrence rates of <10%. In addition, improved survival rates were achieved while preserving patient`s genitourinary and anorectal function [1, 2, 4-6, 31, 32]. National TME training programs have proven to be successful with subsequent outcome improvements [32].

Over the past few years, the CRM (circumferential resection margin: the plane created by dissecting the rectum from its surroundings) has become an important prognostic marker in rectal cancer. This parameter seems to be strongly associated with local recurrence and survival. It has been shown that apart from adequate surgery, the tumor freedom of the CRM depends on neoadjuvant therapy [33]. Not surprisingly, histopathological investigations revealed that TME was able to reduce the rate of CRM involvement below 10% [5]. However, to allow proper evaluation of the CRM by the pathologist, it is essential that the CRM remains intact during the surgical procedure. Figures 5A-D show a representative rectal carcinoma treated by TME with complete CRM.

Whether all patients with rectal cancer should undergo TME regardless of tumor stage and site is still on debate. For tumors located in the middle or distal rectum the excision of the entire mesorectum is mandatory.

For proximal rectal carcinomas (12 to 16 cm) as well as for tumors of the rectosigmoid, a partial mesorectal excision (PME) seems to be sufficient. The PME delivers equal oncologic outcomes and a reduced risk of surgery associated complications such as anastomotic leakage or nerve damage [34].

Radiotherapy

Radiotherapy was formerly implemented within palliative treatment concepts for advanced rectal cancer. Today it is an essential part of standard treatment in order to reduce the rate of local recurrence. Local relapses in rectal cancer are often difficult to handle and overall they have a severe impact on the patient`s quality of life.

Not only quality of surgery has improved over the past decades. Also radiotherapy has ameliorated steadily. For example, an area-wide implementation of linear accelerators and 3-D treatment planning have increased effectiveness and reduced the side-effects of radiotherapy.

Today, there is evidence that preoperative radiotherapy is more effective than postoperative radiotherapy [9-13]. The disadvantages of postoperative radiotherapy comparing to preoperative radiation may be explained by different hypotheses:

First, the interval between operation and radiotherapy gives potentially remaining tumor cells time to proliferate. Second, a reduced postoperative blood circulation in the operating field with subsequent hypooxygenation is believed to increase radioresistance. Finally, adverse effects have proven to be higher after adjuvant radiation therapy.

For preoperative radiation, a distinct dosage-effect relation was observed. As an example, cumulative doses of 20 Gy showed no significant improvements whereas patients treated with doses of >32 Gy had significant fewer local recurrences [35].

As mentioned, TME was able to reduce local recurrence rates dramatically, questioning the necessity of radiotherapy. However, a large study from the Netherlands (n=1861) revealed a significantly lower local recurrence rate (5.6%) in patients treated with preoperative radiotherapy and TME compared to the local recurrence rate after TME alone (10.9%). The effect was most obvious in UICC stage III rectal carcinomas as well as in tumors of the middle and lower rectum [4].

Recent results from the MRC-CR-07 study underlined the benefit of combining TME with preoperative radiotherapy. In this trial, preoperative radiotherapy with 5 x 5 Gy was compared with postoperative radiotherapy in patients with positive circumferential resection margin (CRM+). The latter had a significantly higher local recurrence rate and a significantly reduced disease free survival (DFS) [7, 8].

According to these findings, neoadjuvant radiotherapy has become the gold standard.

Solely or in combination with chemotherapy, it is considered as the treatment of choice in rectal cancer in order to minimize the risk of a local recurrence.

Chemotherapy and Multimodality Treatment

In the 1980ies, various American studies outlined the superiority of the combination of surgery with radiotherapy and chemotherapy versus the application of one modality alone in the treatment of rectal cancer [36]. This finding was supported by additional latter studies [11]. Today it seems evident that best clinical results are achieved if both modalities are applicable [37-41].

As local relapse could be drastically reduced by TME and radiotherapy, distant metastases are today the predominant site of tumor failure, generating an urgent need for more effective systemic drugs in the adjuvant setting.

In the past, a variety of protocols in order to evaluate the optimal schedule and sequence of radiotherapy and 5-FU/ folinic acid based chemotherapy have been presented.

The EORTC-22921 trial compared outcomes after neoadjuvant conventional fractionized radiation (45 Gy) with or without 5-FU/ folinic acid. Postoperatively, patients were treated either with or without adjuvant chemotherapy. Herein, remission rates as well as local tumor control were significantly higher in the combined radiochemotherapy arm whereas no significant survival benefit could be assessed [42].

Similar results were revealed in a French study that included patients with cT3-, T4- Nx-patients. Here, patients treated with neoaduvant radiochemotherapy (45 Gy and 5-FU/ folinic acid) also had a lower local recurrence rate of 8% as compared to patients that underwent only radiotherapy in the neoadjuvant setting [22]

Accordingly, a combined neoadjuvant radiochemotherapy seems more effective in patients with cT3-, T4- Nx patients than radiation alone, even if chemotherapy is given postoperatively.

Today, a set of novel chemotherapeutic agents has been proven more effective than 5-FU alone in advanced colorectal disease. However, results from larger studies are not available for all of these substances.

Capecitabine (Xeloda,) represents an orally administered fluoropyrimidine. Capecitabine is converted to 5-FU intrahepatically and in the tumor cells them-

selves by the enzyme "thymidine phosphorylase". Preclinical studies have identified an activation of this enzyme and therefore an improved antitumor effect through radiotiotherapy [25]. Moreover, it could be demonstrated that capecitabine applied in metastatic colorectal cancer had comparable effects on tumor relapse, toxicity and survival as compared to conventional 5-FU/ folinic acid regimes [19-21]. No data concerning phase III studies (such as NSABP-R04 trial) are available, so far.

Oxaliplatin (Eloxatin,) together with fluorouracil and folinic acid it is part of the FOLFOX scheme for the treatment of colorectal cancer. Compared to cisplatin oxaliplatin showed an improved antitumor activity and proved to be a radiosensitizer [24]. However, the exact molecular mechanisms of action of oxaliplatin remain elusive. Whether it should be administered before or after radiation is still on discussion. In a phase III trial in colorectal cancer patients it has been shown that combining oxaliplatin with 5-FU/ folinic acid is more beneficial concerning tumor progression than 5-FU/ folinic acid alone [23]. Also in combination with preoperative radiation oxaliplation showed no increased side-effects [18].

Irinotecane (Camptosar,) is a topoisomerase-1-inhibitor that blocks DNA replication as well as transcription. Together with 5-FU, folinic acid, irinotecane is used for metastatic colorectal cancer within the FOLFIRI scheme. Severe diarrhea and a strong suppression of the immune system are two major side-effects of irinotecane. Nevertheless, experiences from phase I/II of combined-modality schemes integrating Irinotecane show that toxicity is overall tolerable and remission rates as well as outcomes are promising [27].

Cetuximab (Erbitux,) is a chimeric monoclonal antibody directed against the epidermal growth factor receptor (EGFR). The latter is over-expressed in colorectal cancer cells leading to increased proliferation, angiogenesis, migration and inhibition of apoptosis. Results from first line phase II trials of combined modality schemes integrating Cetuximab are hopeful and showed high response rates [15, 16]. Similarly, in recent phase III trials, including patients with chemotherapy-refractory metastatic colorectal cancer, a new fully humanized monoclonal EGFR antibody, referred to as Panitumumab, was shown to significantly increase progression free survival [43, 44]. Interestingly, the therapeutic success or failure of Panitumumab and/or Cetuximab seems to depend largely on the mutation status of the KRAS oncogene. Whereas up to 33% of tumors with wild type KRAS responded to this therapeutic approach, none of the tumors with activating mutations in codon 12 or 13 of KRAS did [45, 46]. Thus, analysis of the KRAS mutation status seems to be predictive in terms of whether or not a therapeutic approach with Panitumumab and/or Cetuximab is justified and consequently, approval of Panitumumab in colorectal cancer therapy by the European Medicines Agency (EMEA) is exclusively restricted to tumors with wild type KRAS.

Bevacizumab (Avastin,) is also a monoclonal antibody directed against the vascular endothelial growth factor receptor (VEGFR). It inhibits the formation of new blood vessels by targeting the function of VEGF. Moreover, Bevacizumab seems to enhance radiotherapy [17]. One important side effect in some patients is hypertension. Phase I/II studies integrating Bevacizumab in combined modality schemes for rectal have proven to be tolerable, with encouraging response rates [14].

Conclusion and Current Practical Advice

The treatment of rectal carcinoma requires a multidisciplinary team of experts.

According to findings from ever improving diagnostics, every patient should be referred to an individual, tailored therapy.

Therein, radical surgery is the most important curative part. TME (total mesorectal excision) has had a revolutionary impact on local tumor control and has become the standard technique in middle or low rectal carcinomas. PME (partial mesorectal excision) has proved to be appropriate in proximal rectal tumors. Distal sphincter infiltrating tumors are treated by abdomino perineal rectum extirpation. However, ultralow abdominoperanal rectal resection with sphincter preservation should be applied wherever feasible.

The detailed postoperative histopathological investigation includes the assessment of the CRM by an experienced pathologist. The results contribute to further treatment decisions.

In localized rectal cancer (T1 to T3 and N0), radical surgery alone seems to be sufficient. However, in T4N0 tumors the issue is not completely settled as preoperative radiotherapy does not improve survival in these patients and the effect on long-term local control is limited. However, in far advanced tumors (uT3n+) a combined multimodality scheme with preoperative radiochemotherapy implementing new systemic drugs (such as Capecitabine, Oxaliplatin, Irinotecan, Cetuximab, Bevacizumab) is recommended. Phase I/II studies revealed promising results. Now, there is a need for phase III studies (Germany: CAO/ARO/AIO-04; Europe: PETACC6; USA: NSAPB-R04, E5204 Intergroup Trial) to examine whether these approaches are superior to 5-FU based combined modality and to assess long-term toxicity.

Concluding, no adjuvant scheme can compensate for inadequate surgery.

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Address for correspondence:
PD Dr. med. Matthias Peiper
Klinik für Allgemein-, Viszeral- und Kinderchirurgie
Universitätsklinikum Düsseldorf
Moorenstr. 5
40225 Düsseldorf
Germany.
Fax: +49-(0)211-8119099
Tel.: +49-(0)211-8116398
E-mail: matthias.peiper@uni-duesseldorf.de