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Side Effects of Neoadjuvant Treatment in Locally Advanced Rectal Cancer

Karoline Horisberger[1] and Pablo Palma[2]
[1]*Department of Surgery, University Hospital Mannheim*
[2]*Division of Colon & Rectal Surgery, University Hospital HUVN Granada*
[1]*Germany*
[2]*Spain*

1. Introduction

Neoadjuvant treatment of locally advanced rectal cancer patients provides undisputable advantages regarding local control (1; 2), and it seems to afford the benefit of survival in patients with preoperative complete regression (3; 4). Furthermore, local control is an important feature in life quality of rectal cancer patients. However, due to the perspicuous interests in oncological effects, the acute and moreover late side effects tend to be neglected. The consequence is that especially late side effects have probably been underestimated until now.

Many patients would perceive a permanent stoma and loss of the anal sphincter as a stigma that lowers their self-esteem (5). Hence, sphincter preservation is a major request of the patients and developed to an important surgical concern. In fact, patients are willing to trade a considerable amount of survival to avoid a colostomy (6). And more than this, they are also disposed to trade survival in order to avoid chemotherapy (6).

Though, with regard to oncological and surgical outcome control late results are important. For all patients quality of life matters are fundamental. This particularly counts for those patients who show an incomplete regression or none and therefore do have only limited benefit from the treatment.

2. Acute side effects

The TME trial was the first large study that compared additional preoperative radiation therapy to TME (Total Mesorectal Excision) surgery alone (1). To register the acute side effects the RTOG (Radiation Therapy Oncology Group) classification 0-5 was used. In general, RTOG 0 represents no complaints and RTOG 5 is a toxicity leading to death. Mild toxic effects are grade 1 and 2; ≥ grade 3 counts as severe toxic effect. The trial showed acute side effects in 26% of the patients within three months of the start of short course radiation therapy (7). It is noticeable in the precise description of the side effects that the most frequent complications were gastrointestinal followed by neurological. 13% of the patients showed gastrointestinal symptoms, most of them grade I or II; only one patient suffered from grade III and none of grade IV (7). It is interesting to know that the scoring system for neurological symptoms was additionally implemented one year after the beginning of the

trial because observations of acute plexopathy in the antecedent Swedish Rectal Cancer Trial were published in 1996 (8). During the first full year of the 4-year trial, no neurological symptoms were recorded in any of the patients (7). In fact, the Swedish Rectal Cancer Trial also compared neoadjuvant short-course radiation with surgery alone; however, this trial was conducted in the era before TME. It has to be noticed that during the recruitment phase of the Swedish Rectal Cancer Trial, the radiation technique changed from three-beam to four-beam (8). The authors explicitly report that no plexopathy was observed after conventional fractionation of the radiotherapy (2Gy/d) but only after short-course hypofractionated 5x5Gy radiation (8).

Neoadjuvant chemoradiation correlates more closely with higher acute toxicity than short-course radiation (9); in fact, it seems to be less harmful than postoperative chemoradiation with regard to acute toxicity (2). Comparing preoperative chemoradiation and long-course radiation with 45 Gy it seems to be obvious that radiation is more tolerable in the acute phase (10; 11). Actually, in most studies only grade 3 and grade 4 toxicities are listed, though the higher rates of grade 1 and 2 toxicities are not mentioned.

Reference	**No. of patients**	**Therapy strategy**	**Toxicity grade III-IV (%)**	**P value**
Marijnen 2002	695 vs. 719	5x5 Gy versus TME	2.4 vs. 0	n.s.
Bujko 2004	155 vs. 157	5x5 Gy versus preoperative chemoradiation (5-FU)	3 vs. 18	0.001
Bosset 2004	398 vs. 400	45 Gy versus preoperative chemoradiation (5-FU)	37.7 vs. 54 *	<0.005
Gérard 2006	367 vs. 375	45 Gy versus preoperative chemoradiation (5-FU)	2.7 vs. 14.6	<0.005
Sauer 2004	404 vs. 394	Pre- versus postoperative chemoradiation (5-FU)	27 vs. 40	0.001
Gérard 2010	293 vs. 291	Cap vs. CapOx preoperative chemoradiation	10.9 vs. 25.4	<0.001

Cap: capecitabine; CapOx: capecitabine and oxaliplatin

Table 1. Acute toxicity ≥ grade III (*toxicities ≥ grade II) in randomised trials.

An impression of the difference is given in the publication of the EORTC 22921 study that listed all toxicities ≥ grade 2 and which thereby obtained a toxicity rate of 37.7 resp. 54% comparing 45 Gy with chemoradiation (11). The exclusive subsumption of grade 3 and 4 toxicities of neoadjuvant treatment obtains a toxicity rate below 20% (Table 1). It should be noted that in a direct comparison of 5-FU versus capecitabine in a phase III trial, capecitabine showed to constitute significantly more hand-footsyndrome (31 vs. 2%) but less

leukopenia (25 vs. 35%) (12). Gastrointestinal and skin complications were no different between the arms.

The addition of oxaliplatin to neoadjuvant treatment, either with 5-FU treatment or capecitabine, significantly increased the acute toxicity (particularly diarrhoea) three-fold and 2.5-fold, respectively (13; 14). However, toxicity could be interpreted as feasible as particular grade III toxicities were recorded in not more than 15% of the patients. It was disappointing, however, that the rates of complete response did not change in both trials (13; 14). Unfortunately, there are no other randomised phase III trials that have compared different CRT regimens.

A pooled analysis of three phase I/II trials of patients treated with or without additional cetuximab saw no difference in question of acute toxicity (15).

3. Postoperative complications

Looking at the postoperative complications one can notice that reporting of them is performed on an irregular basis concerning the definition of some complications as well as whether they are reported at all. Few randomised studies (2; 7; 14) report in detail on perioperative complications while others outline the overall rate of complications (Tables 2/3). However, the interpretation of surgical and other complications is complex, even in the case of detailed reports. By way of example, the TME trial meticulously reports a significantly higher rate of postoperative complications in irradiated patients (7). Nevertheless, the rate of all surgical complications is the same for irradiated and non-irradiated patients, although it differs for those with abdominoperineal resection. This is caused by the rate of perineal wound dehiscence that is increased following neoadjuvant radiation, while the rate of anastomotic leakages is no different between the groups. In addition, cardiac and psychological complications that are significantly more frequent in irradiated patients aggravate the higher postoperative complication rate (7).

With regard to the risk of perineal wound dehiscence, the results of the different studies are inconsistent. While it is significantly increased for short-course radiation and chemoradiation in some trials (7; 16), others rule out an influence (2).

The early anastomotic leakage rate has been reported as 8-18% after neoadjuvant treatment and is thereby no different from rates in non-irradiated patients (Table 3) (2; 7; 10; 17; 18). A correlation between neoadjuvant treatment and anastomotic leakage rate cannot be seen in a single study (2; 7; 9; 10; 17). However, in a population-based study from Sweden, the multivariate analysis of 432 out of 6833 patients revealed preoperative radiation to be an independent risk factor for anastomotic leakage (19). The restriction of this publication, however, is the fact that the large majority of these operations were performed without TME. Though, the influence of this fact is in this regard not known.

Besides this, two single-centre studies report a positive correlation between the preoperative regression grade and the risk of anastomotic leakage (Fig. 1) (20; 21).

One main problem of anastomotic leakage reporting is the fact that there is no definition of leakage that has to be reported (Fig. 2/3). While some studies report all clinical apparent leakages as well as the abscess around the anastomosis as leakage (7; 21), others do differ between clinical and radiological leakage (20). Some do not define what they count as leakage (2), others just allude to those complications that require reintervention (9).

Until now, the influence of intensified chemoradiation using oxaliplatin is described by only one phase III trial (14). In this single trial, the rate of anastomotic leakage is no different between patients who received capecitabine and those with additional oxaliplatin (14).

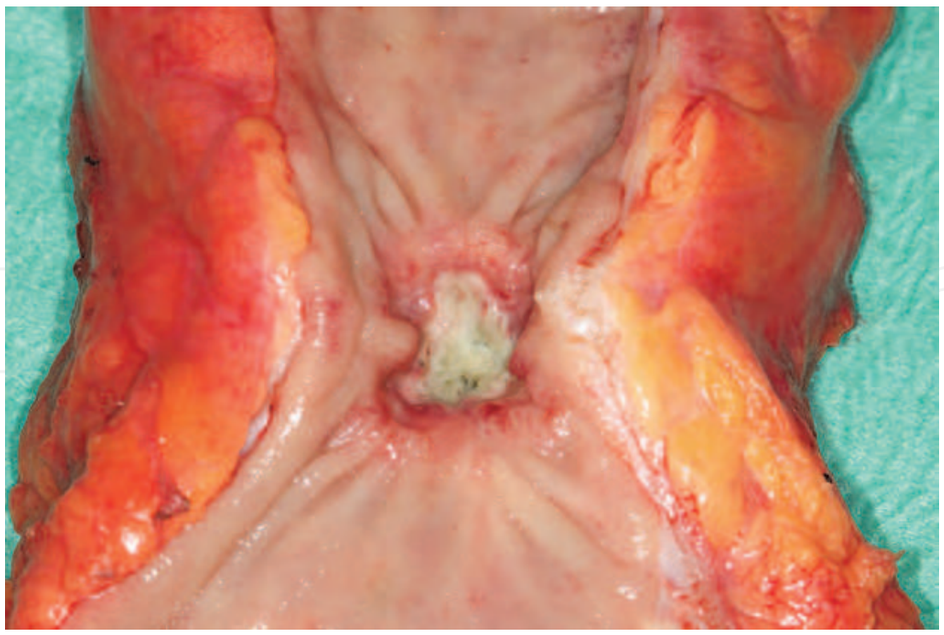

Fig. 1. Rectal cancer after neoadjuvant chemoradiation. Downstaging was histopathologically proven; a distinct fibrosis can be seen macroscopically.

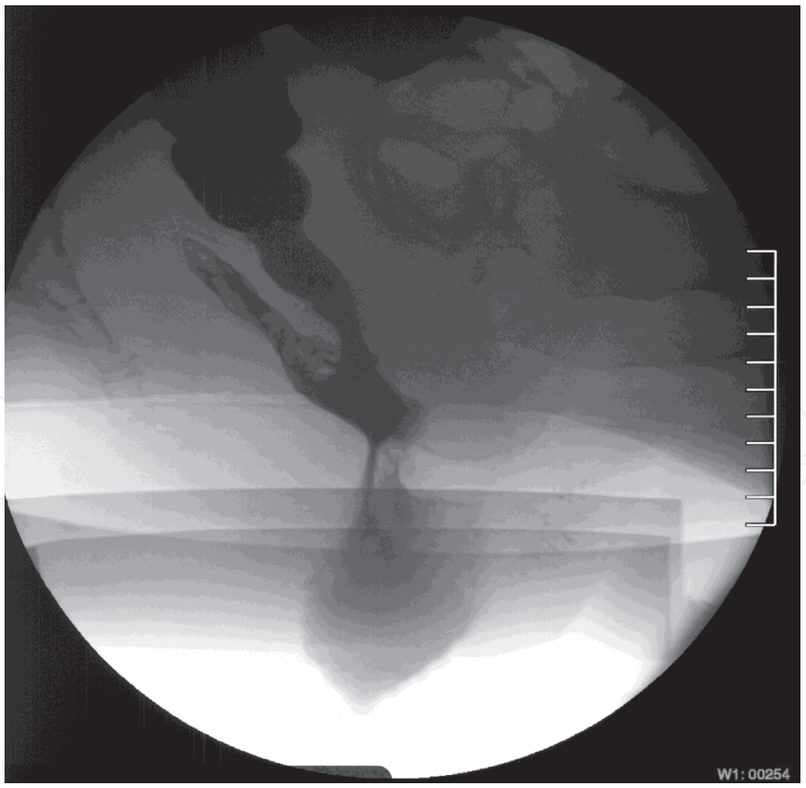

Fig. 2. Radiographically proven old anastomotic leakage that presented years later with outlet obstruction.

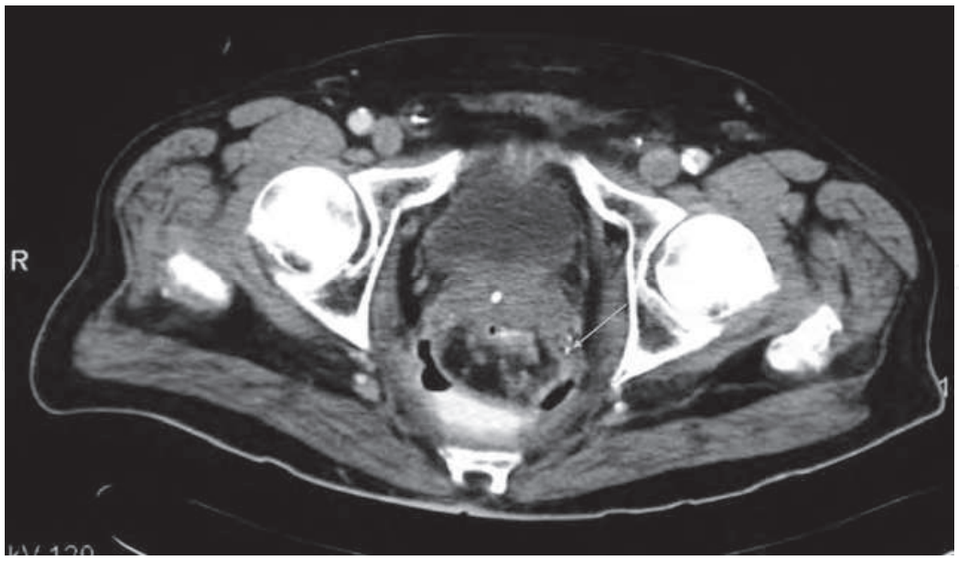

Fig. 3. Radiographically proven anastomotic leakage with extraluminal contrast agent (arrow).

Reference	No. of patients	Therapy strategy	Overall rate of postoperative complications (%)	P value
Marijnen 2002	695 vs. 719	5x5 Gy versus TME	48 vs. 41	0.008
Bujko 2004	155 vs. 157	5x5 Gy versus preoperative chemoradiation (5-FU)	23 vs. 15*	0.12
Bosset 2004	398 vs. 400	45 Gy versus preoperative chemoradiation (5-FU)	22.2 vs. 22.8*	n.s.
Gérard 2006	367 vs. 375	45 Gy versus preoperative chemoradiation (5-FU)	26.9 vs. 20.9	n.s.
Sauer 2004	404 vs. 394	Pre- versus postoperative chemoradiation (5-FU)	36 vs. 34	0.68
Gérard 2010	293 vs. 291	Cap vs. CapOx preoperative chemoradiation	33.8 vs. 30.6	n.s.

* Complication criteria not defined

Table 2. Postoperative complications in randomised trials.

Reference	Anastomotic leakage rate (%)	P value	Surgical reintervention rate (%)	P value
Marijnen 2002	11 vs. 12	n.s.	14.8 vs. 13.6	n.s.
Bujko 2004	Not reported		12 vs.9	0.38
Bosset 2004	Not reported		Not reported	
Gérard 2006	7.6 vs. 7.4	n.s.	Not reported	
Sauer 2004	11 vs. 12	0.77	Not reported	
Gérard 2010	18.9 vs. 16.7 *	n.s.	12.9 vs. 12.5	0.9

*Rate of surgically treated anastomotic fistula; Additional conservatively treated fistula: 8.5% vs. 7.7%; n.s.

Table 3. Anastomotic leakage rate and surgical reintervention rate in randomised trials.

The rate of diverting stoma creation is not mentioned in some large trials (2; 10; 11; 22). Others merely report the late rate of permanent stoma (23). In fact, only some studies have reported the rate of defunctioning stomas and identified in addition the different rates between stoma created initially and those created subsequently as a result of another complication (7; 17); altogether, the rates are hardly comparable.
Mortality rate is the same in patients with or without neoadjuvant treatment (1; 2; 9 - 11; 18; 24). It is to be noted that the intensified neoadjuvant chemoradiation with oxaliplatin does not influence the mortality rate (13; 14).

4. Late side effects

Improving the oncological results of rectal cancer patients also directed the scientific focus on late side effects, late functional results and long-term quality of life.
However, results of the late functional investigations of 597 patients of the Dutch TME trial were disappointing (Tab.4) (25). Patients with a local recurrence were excluded from this follow-up, so that the functional results were not disease-related. 5 years after the primary treatment, 68% of irradiated patients suffered from incontinence during the day and 32% from incontinence at night. These were 24% resp. 15% more than in non-irradiated patients. There were statistically significant differences in terms of bowel frequency, blood loss and mucus loss (25). Pad use as evidence of incontinence was evaluated in 56% of the irradiated patients while 33% of the directly operated patients had the same need ($p<0.001$) (25). Fractionated defecation with the sensation of incomplete evacuation is elicited in 35-58% of irradiated patients (26–28). Irradiated patients were significantly impaired in their daily activities and social function (29).
It is understandable from the information above that irradiated patients without a stoma were significantly less satisfied than non-irradiated patients. If patients had a stoma, the rate of satisfaction did not differ between those that were radiated and those that were non-irradiated (25). It is to be noted that impairment of the sphincter function may have been so

severe that significantly more patients would have been satisfied if they had had a stoma than if they had not (25). This result is interesting due to the fact that sphincter-preservation is seen to be one of the main objectives of neoadjuvant and surgical therapy (2). It is often suggested that patients with a stoma generally have lower quality of life and as a consequence, sphincter-sparing surgery has been forced (5). Already when low anastomosis started coming up, the problem of reduced social functioning of both colostomy and impaired anal sphincter was seen and could not be clearly weighed up (30). It is meaningful that the surgical and oncological aims seem not to correspond completely with the demand of the patients (31). In a survey of healthy individuals it turned out that the majority would prefer a treatment with better functional outcome even when they would have to accept a higher risk of local recurrence (31). In another study was revealed that patients and even oncologist and surgeons would trade survival for quality of life. 52% of the questioned patients – and 88 and 90% resp. of the surgeons and oncologist - would trade life to avoid colostomy (6).

A Norwegian study that evaluated the functional outcome of 199 patients 4.8 years after initial treatment found a significant correlation between incontinence of liquid stool and overall quality of life (29). In the really long-term results, 15 years after radiation, 69% of the irradiated versus 43% of the non-irradiated patients had incontinence complications (32). More than twice as many patients suffered from fecal incontinence after irradiation. However, this data was generated from the Swedish Rectal Cancer Trial, which means that the patients were operated on without using the TME procedure. Although there is no randomised trial that would compare conventional rectal cancer surgery and TME procedure – and due to the definitely favourable results of the TME procedure there will never be one – several smaller in-hospital series compare functional results of the two procedures. In those studies the postoperative impairment of urination and genital function rather improved when TME was introduced (33;34).

The poor functional results seem to be the same or even worse following chemoradiation (Tab. 4) (35; 36). Good anal function was stated in one study that compared chemoradiation with radiation in 11% versus 30%, resp. of the patients seen (p=0.04) (36).

The results concerning urinary incontinence after radiation are inconsistent. While the late results of the Dutch TME study do not find a correlation to preoperative radiation, this correlation is to be found in a Norwegian study of 199 irradiated patients (25; 29; 37).

From the Dutch TME trial, we know that former sexually active male and female patients are significantly impaired in their sexual activity in an evaluation two years after surgery (38). Two other studies that described a significant lack of lubrication or more vaginal dryness, dyspareunia and reduced vaginal dimension in irradiated patients confirmed this data. However, women were not concerned about their sexual life (36; 39). It is to be noted that one study did not discriminate between pre- and postoperative irradiation (39) and the other one was performed with initially nonresectable rectal cancer (36).

In male patients, both erection and ejaculation functions were impaired after 5x5Gy radiation therapy (38). As the impaired sexual functions differ significantly in direct comparison to only operated patients, there must be a direct influence from radiation in addition to the possible surgical damage to the pelvic autonomic nerves. Whether or not this influence consists of radiation damage to the nerves itself, a postirradiated reduced tolerance to surgery-caused ischemia or to technically hindered surgery after radiation cannot be clarified (40).

Reference	No. of patients	Therapy strategy	Follow-up (yrs; median)	Fecal incontinence (%)	P value
Peeters 2005	177 vs. 185	5x5 Gy versus TME	5.1	62 vs. 38*	<0.001
Pollack 2006	21 vs. 43	5x5 Gy versus conventional surgery	14	57 vs. 26	0.013
Brændengen 2006	18 vs. 19	Preop. RTX versus RCTX	4-12	58 vs. 38° 75 vs. 56 ∆	
Coco 2007	100	50.4Gy	12	46 ∆ 14 ¥	
Urso † 2006	12	Pre- and postoperative	19 mths	75 ¥	
Bruheim † 2010	69 vs. 240	Pre- and postoperative versus TME	4.8	71 vs. 58∆ 52 vs. 13 ¥	0.01 <0.001

* Incontinence by day; Incontinence at night: 32 vs. 17%(P=0.001); ° Incontinence to stool;
∆ Incontinence to gas; ¥ Defined as: requirement of pad use
†Urso (2006): Preoperative chemoradiation (50.4Gy) with 5-FU and oxaliplatin, postoperative 5-FU-based chemotherapy. Bruheim (2010): Pre- or postoperative radiation (50Gy) with chemotherapy (in 40% of neoadjuvant radiation; in 75% of adjuvant radiation).

Table 4. Late functional results; RTX: radiation therapy; RCTX: radiochemotherapy

Hip fracture is a rarely mentioned late complication but seems to be significantly increased in irradiated patients (29; 41). In the Norwegian study by Bruheim, et al. the incidence of pelvic fracture was five times higher in the irradiated patients (5% versus 1%) (29). Furthermore, in the group of irradiated patients female sex seems to be the only independent predictor for fracture (42). However, in the late follow-up of the Dutch TME trial hip fracture rate did not differ between irradiated and non-irradiated patients (25).
Reports concerning second malignancies following radiation of the Swedish Rectal Cancer Trial (43) are refuted by a large population-based analysis of 20,910 patients that showed that the rare event of second primary malignancies is not more frequent in irradiated patients (44). The occurrence of a second malignancy in an adjacent organ of the irradiated volume seems to be weighted between the radiation-induced malignancies and those spontaneous malignancies accidentally avoided by radiation (44).
Anal stricture or late anastomotic stricture is reported in some publications (35; 45). However, a difference between irradiated and non-irradiated patients is not seen in the long-term follow-up of the Dutch TME trial (25) and a difference between patients with preoperative and postoperative chemoradiation cannot be seen either (45).

5. Discussion

Besides the side effects reported above there are few further thoughts regarding neoadjuvant treatment as a source of possible harm. With the current staging methods an

overtreatment is performed in probably 18% of the patients, most of them wrongly staged as cT3N0 (2). However, this overtreatment is intentional as 22% of the pT3 tumours had a previously undetected involvement of mesorectal lymph nodes and would have poorer local control with postoperative treatment (46). This means that at present the incidence of side effects in overtreated patients who would require nothing other than surgery unfortunately has to be accepted to include most of the patients to neoadjuvant treatment who really need it.

Another cause of medical discomfiture is the group of patients without any signs of regression. Those non-responders do have the correct indication for the treatment but instead of benefit they only see the side effects of the treatment. To date, there is no predictive resistance marker that could exclude those patients from neoadjuvant treatment.

For short-course radiotherapy where there is a short amount of time until the operation it must be taken into account that there is no downstaging. Patients in whom an involvement of the circumferential margin is suspected should maybe treated with chemoradiation as a preference. In case of showing an involved circumferential resection margin after neoadjuvant treatment the long-term is even worse than having an involved margin after direct surgical resection (47;48). Chemoradiation alone can provide preoperative downstaging, however, the long-term functional results are even worse than those following radiation.

Another critical point is that the improved local control of neoadjuvant short-course radiation has to be put into a certain sense of perspective by the fact that the oncological benefit may be only valid for mid-rectal cancers from 5 to 10 cm from the anal verge (47). Conversely, the low rectal cancer patients and those with tumours in the upper third seem not to profit from the benefit that short-course radiation might offer.

6. Conclusion

In addition to acute side effects that seem to be feasible, it is assumed that there are surgical and other perioperative complications that are not reported as a matter of routine. It is evident, that a regular report system of acute and late side effects concerning medical and surgical problems is not implemented yet.

In particular the late complications appear to limit the patient in their functional abilities and quality of life. Moreover, the late side effects are probably still underestimated. To date, the impairment of social life by poor anorectal function and the psychological consequences of sexual dysfunction have barely been evaluated. It has to be assumed by a lack of studies evaluating late side effects, that the unreported number of cases exceeds the published ones. A certain number of unreported cases should however also be assumed as many patients do not answer honestly due to a sense of shame. Unfortunately, the evidenced poor functional results after rectal cancer surgery seem to be worsened by neoadjuvant treatment. It is easier said than done, but the patients have to be individually balanced in terms of their potential oncological benefit against the probable functional deficiency that is likely to compound over the years.

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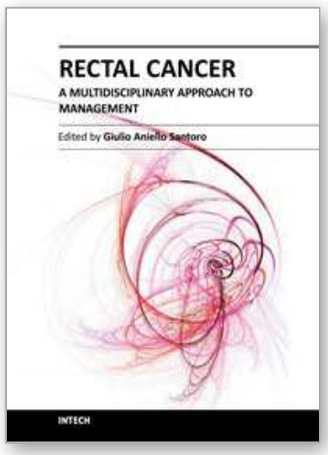

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Dramatic improvements in medicine over the last few years have resulted in more reliable and accessible diagnostics and treatment of rectal cancer. Given the complex physiopathology of this tumor, the approach should not be limited to a single specialty but should involve a number of specialties (surgery, gastroenterology, radiology, biology, oncology, radiotherapy, nuclear medicine, physiotherapy) in an integrated fashion. The subtitle of this book "A Multidisciplinary Approach to Management" encompasses this concept. We have endeavored, with the help of an international group of contributors, to provide an up-to-date and authoritative account of the management of rectal tumor.

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