Oncological Short-term Effects and Adverse Events of MRI-guided Selective Neoadjuvant Radiochemotherapy for Rectal Cancer

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Abstract. *Aim: To investigate the oncological short-term effects and acute side-effects of magnetic resonance imaging (MRI)-guided selective neoadjuvant radiochemotherapy (nRCT) for rectal cancer. Patients and Methods: In a prospective multicenter cohort study of 230 patients with rectal cancer stage II or III, nRCT was applied in the following situations (n=96) only: cT4 tumors, cT3 tumors of the distal rectum or tumors leaving a circumferential resection margin (CRM) of ≤1 mm between the tumor and the mesorectal fascia (mrCRM+). Pre-therapeutical tumor stage and involvement of mesorectal fascia were assessed by MRI and were compared with the pathological findings of the rectal specimens. Furthermore, tumor regression grades, acute side-effects, and surgical complications were analysed. Results: Using selective nRCT, 62 out of 72 patients (86%) with mrCRM+ had tumor-negative pathological CRM. Reduction of T category was observed in 62% and of N category in 88% of patients. Lymph node metastasis was found by pathology in only 21% of all irradiated patients. Histologically complete tumor regression (ypT0ypN0) was observed in 15% and intermediate regression (more than 25%, but not complete) in 67% of patients. Fifteen percent of patients suffered from grade 3 toxicity, but no grade 4 toxicity occurred. nRCT did not adversely influence surgical morbidity. Conclusion: Despite the negative selection of locally advanced rectal cancer cases for nRCT, impressive rates of tumor down-staging and eradication of tumor from the mesorectal fascia were achieved. The rate of complete regression is comparable to that in the literature. Moreover, the selective use of nRCT spared a considerable percentage of patients with stage II/III rectal cancer severe irradiation toxicity.*

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The recommendation of current guidelines that all rectal carcinomas of International Union Against Cancer (UICC) stage II or III need neoadjuvant radiotherapy or radiochemotherapy is being increasingly challenged (1-3). The current trend is towards selective indication for neoadjuvant therapy on the basis of the minimum distance between the tumor and mesorectal fascia as the anticipated circumferential resection margin (CRM) (4-6). This distance can be reliably assessed by means of magnetic resonance imaging (MRI) (7-13). Nowadays, the concept of total mesorectal excision (TME) is widely accepted and has been successfully introduced by most centers in the Western world, followed by a standardized pathological work-up, focusing particularly on CRM (14-18). The pathologically assessed CRM (pCRM) status seems to be the most important predictor of local recurrence (19-21).

Recently, we published findings demonstrating that, under the premise of the high quality of pre-therapeutic MRI and of the total mesorectal excision (TME) technique, nRCT (nRCT) could be avoided in 45% of patients with UICC stage II or III rectal cancer, without increasing the risk for a positive CRM (22).

In the present study on the same sample of patients, the primary aim was to assess the efficacy of this selectively used nRCT for locally advanced and/or low rectal

carcinomas with regards to down-staging, percentage of histopathologically, complete remission and clearing rate of tumor-infiltrated mesorectal fascia. A second focus was placed on the acute side-effects of nRCT.

Patients and Methods

A prospective observational cohort study of 230 patients with histologically proven, solitary rectal cancer of stages cT2-4, any cN, cM0 was performed in three German centers and one Swiss center from January 2007 to October 2010. All participating surgeons had profound knowledge of the TME technique. We reported that 91% of all rectal specimens exhibited an intact mesorectal fascia and that 94.3% of all rectal specimens exhibited a negative pCRM (22). Although nRCT is recommended in the current guidelines, nRCT was not applied for every UICC stage II or III cancer, but selectively on the basis of the distance of the tumor to the mesorectal fascia, as the anticipated CRM, according to the pre-therapeutic MRI. Details of therapeutic decision-making are shown in Figure 1 and have been previously described by our study group (22). Briefly, for rectal carcinomas <6 cm from the anal verge, nRCT was given for cT3 and cT4 tumors regardless of the anticipated CRM status, because of the progressive paucity of the mesorectum distally and the increased probability of lateral lymph nodes being involved; exceptionally, advanced T2 tumors also fulfilled the criterion for nRCT when the distance between the tumor and the anticipated CRM was 1 mm or less. Tumors of the middle third of the rectum, *i.e.* 6 cm to <12 cm from the anal verge, were treated by nRCT when the mesorectal fascia was anticipated to be infiltrated, *i.e.* ≤1 mm distance between the tumor and the mesorectal fascia; for tumors of the upper third of the rectum, *i.e.* 12-16 cm from the anal verge, the indication for nRCT was at the hospital's discretion (as for middle third cancer or as for colonic carcinomas). The cN status did not influence the indication for nRCT.

Ninety-six out of 230 patients (42%) received nRCT. For the analysis of response to nRCT, one patient had to be excluded due to missing pre-therapeutic MRI data (only computed tomogram was available).

NRCT. Preoperative radiochemotherapy was delivered as a long course with fractions of 1.8 Gy five times weekly to the pelvis using individually shaped portals and a 3- or 4-field box technique. A total of 50.4 Gy was recommended. Concurrent chemotherapy during the first and the fifth week of radiotherapy was given daily using 5-fluorouracil (5-FU) at 1000 mg/m^2 per day. Instead of 5-FU, capecitabine was used for three patients and capecitabine plus oxaliplatin for another three. Surgery was scheduled to take place six weeks after completion of nRCT.

Surgical treatment. Surgical treatment followed the principles of TME surgery, with TME for all tumors of the middle and lower rectum and partial mesorectal excision (PME) for tumors of the upper rectum. In PME, the rectum and the mesorectum were cut in a plane at 90° to the longitudinal axis, 5 cm distal to the macroscopic tumor margin (measured *in situ*). The autonomous pelvic nerves were identified and preserved. For tumors of the upper third of the rectum, an anterior resection was performed; for tumors of the middle and lower third of the rectum, a low anterior or intersphincteric resection was performed; and for tumors close to the sphincter or tumors that invaded the sphincter muscle, an abdominoperineal resection was performed. The decision regarding the surgical technique was up to the individual surgeon.

Assessment of treatment response and acute side-effects. Pre- and post-therapeutic T and N categories were determined according to the sixth Edition of the UICC Classification System of Malignant Tumors (23). The response of the tumor to nRCT, comparing the pre-therapeutic stage assessed by MRI with the post-therapeutic stage assessed by histology of the rectal specimen, was categorized separately for the T category, the N category and the UICC stage, ranging from no down-staging to complete remission, *i.e.* ypT0 ypN0, UICC stage 0. As recommended by the UICC, the outermost layer of the rectum with still vital tumor cells present was decisive for the determination of the ypT category. Scarring fibrous tissue within or beyond the bowel wall without vital tumor cells, was taken as an area free from former adenocarcinoma and was an indirect sign of depth of pre-therapeutic invasion. On MRI, lymph nodes were considered metastatic only if at least one of the three following criteria was fulfilled: non homogenous contrast enhancement, irregular surface of lymph node capsule, or diameter larger than 10 mm (9, 10). The tumor regression was graded both as suggested by Dworak *et al.* (24) and as modified by Rödel *et al.* (25).

Acute side-effects of the nRCT at short-term follow-up were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 (http//ctep.cancer.gov/reporting/ ctc.html).

Ethics and study registration. The study is registered at ClinicalTrials.gov No. NCT01325649. Furthermore, the study was approved by the local Ethics Committee of each participating hospital. Informed consent was obtained from all patients included.

Statistics. Data are presented in detail for all patients, *i.e.* patients of all centers are reported together. In the case of statistically significant differences between centers, the minimum and maximum values are given, as well as the *p*-values. Comparisons between frequencies were performed using the chi-square test or, when appropriate, the Fisher's exact test. Differences of quantitative data between two groups were tested using the Mann Whitney *U*-test and between three or more groups using the Kruskal Wallis H-test. *p*-values ≤0.05 were considered significant. All statistical analyses were carried out using the SPSS 18.0 software for Windows (SPSS Inc., Chicago, IL, USA).

Results

From the total of 230 patients, 96 patients received nRCT. From the remaining 134 patients, a further 78 would have been treated by nRCT according to the current guidelines. These 78 patients corresponded to 45% of all patients with a pre-therapeutic UICC stage II or III.

The complete irradiation dose of 50.4 Gy was tolerated by 93 patients (97%). Irradiation was stopped prematurely in three patients (after 5, 28 and 29 days, respectively) and shortly interrupted in two patients (for 4 and 7 days, respectively). Chemotherapy was tolerated, as prescribed, in 94 patients (98%). Surgery was performed following complete irradiation at 6 weeks in 92% of patients, at 7 weeks in 6%, and at 3 weeks in 1%.

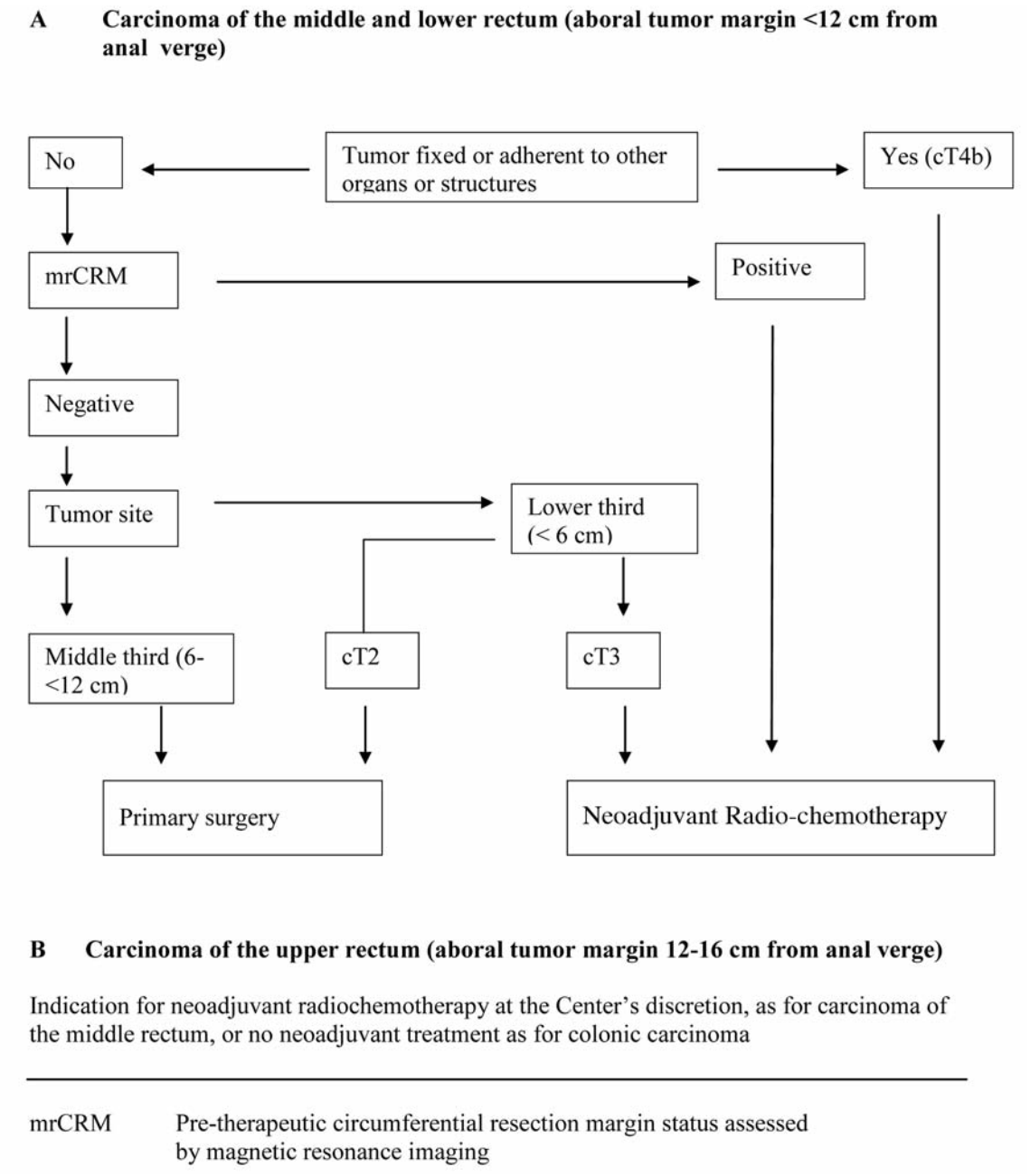

Figure 1. *Indication for neoadjuvant radiochemotherapy. A. Carcinoma of the middle and lower rectum (aboral tumor margin <12 cm from the anal verge). B. Carcinoma of the upper rectum (aboral tumor margin 12-16 cm from anal verge).*

Down-sizing and down-staging by nRCT. Differences between pre-therapeutic and post-therapeutic assessments of CRM status are shown in Table I. The change of CRM status following nRCT is significant ($p<0.0001$). Between the four participating centers, no significant difference was found in the percentage of patients in whom CRM status changed ($p=0.32$), but a significant difference was found in the percentage of questionable MRI-findings ($p=0.049$).

The response of the tumor to nRCT with regard to the T category is shown in Table II, comparing the cT category with the ypT category of each tumor as described in the Material and Methods section. Change to a lower T category was seen in 59/95 patients (62%); in 13/95 patients (14%), a change to a ypT0, *i.e.* pathologically complete regression of the primary tumor was achieved. No significant differences in response to nRCT were observed between the four centers.

Table I. *Change of circumferential resection margin (CRM) status following neoadjuvant radiochemotherapy.*

mrCRM		pCRM		*p*-Value
		Negative	Positive	
Positive	72 (76%)	62 (86%)	10 (14%)	<0.0001
Negative	19 (20%)	18 (95%)	1 (5%)	
Questionable	4 (4%)	4 (100%)	0	
Total*	95 (100%)	84 (88%)	11 (12%)	

mrCRM: Circumferential resection margin pre-therapeutically anticipated at the mesorectal fascia plane by MRI; pCRM: histopathologically assessed CRM; *excluding one patient due to missing pre-therapeutic MRI.

Table II. *Influence of neoadjuvant radiochemotherapy on T category.*

cT category	n	No change ypT=cT	Reduction		Change to ypTis	Change to ypT0
			One category	Two categories		
cT4	24	0	15 (63%)	7 (29%)	0	2 (8%)
cT3	67	34 (51%)	18 (27%)	4 (6%)	2 (3%)	9 (13%)
cT2	4	2 (50%)	0	0	0	2 (50%)
Total*	95	36 (38%)	33 (35%)	11 (12%)	2 (2%)	13 (14%)
p-Value		<0.001	<0.001	0.044	0.628	0.032

n: Number of patients; ypTis: *in situ* carcinoma, pathologically assessed following nRCT; *excluding one patient due to missing pre-therapeutic MRI.

The potential down-staging of the lymph node status by means of nRCT is shown in Table III. cN2 disease changed significantly less often to ypN0 than did cN1 disease (52% *vs*. 84%, $p=0.005$). Taken together, a change from any cN+ to ypN0 was achieved in 48/67 patients (72%). No significant differences in nodal down-staging were found between the four centers.

Table IV summarizes the down-staging effect of nRCT regarding the UICC stage. Any type of down-staging was found in 60% (57/95); a down-staging to ypT0 or ypTis was found in 16% (15/95) of patients. No significant differences in down-staging of UICC stage were observed between the four centers.

The gradings of tumor regression are shown in Table V. The differences in the percentages of poor regression (grade 0 and 1) between the centers ranged from 0% to 38% ($p=0.012$). No significant differences in the percentages of intermediate and complete regressions were found between the centers (data not shown).

Influence of nRCT on lymph nodes. Following primary surgery, the median number of the removed and histologically investigated lymph nodes was 26 (10-79), and following nRCT the number was 19 (3-56). This reduction of the median number of lymph nodes examined by nRCT was significant ($p<0.001$). The minimum number of 12 lymph nodes assessed, as requested by the UICC, was found in 133 out of 134 cases from primary surgery (one patient had had irradiation for cancer of the cervix in the past), but only in 86 out of 96 (89.6%) cases following nRCT ($p=0.001$). The four centers revealed differences in the median number of lymph nodes after primary surgery ranging from 22 (10-79) to 29 (19-62) ($p=0.019$), but not after nRCT, ranging from 16 (4-43) to 20 (10-56) ($p=0.226$).

Focusing on the median number of metastatic lymph nodes, no significant difference was found between the group of primary surgery and the group of nRCT: 2 (1-13) *vs*. 1 (1-7) ($p=0.284$). Similarly, no significant difference in lymph node ratio (LNR), defined as the ratio of the number of lymph nodes with metastasis and the total number of lymph nodes examined, was detected for patients with lymph node-positive disease: the mean LNR was 0.12 (±0.03) after nRCT and 0.18 (±0.03) after primary surgery ($p=0.272$).

Table III. *Influence of neoadjuvant radiochemotherapy on N category*

cN category	n	Any change	Change to ypN0	Change to ypN1
cN2 + cN1	58	50 (86%)	42 (72%)	n.a.
cN2	21	18 (86%)	11 (52%)	7 (33%)
cN1	37	32 (86%)	31 (84%)	n.a.
cN+ n.o.s.	9	9 (100%)	6 (67%)	n.a.
Total all cN+	67	59 (88%)	48 (72%)	n.a.
Incl. N0	28	n.a.	n.a.	n.a.
Total*	95	59 (62%)	48 (51%)	n.a.

n: Number of patients; cN+ n.o.s.: patients with clinically suspected lymph node metastasis not otherwise specified; n.a.: not applicable; *excluding one patient due to missing pre-therapeutic MRI.

Table IV. *Influence of neoadjuvant radiochemotherapy on clinical stage.*

Pre-therapeutic clinical stage	n	Any type of down-staging	Down-staging to ypT0 or ypTis
III	67	47 (70%)	11 (16%)
II	27	9 (33%)	3 (11%)
I	1	1 (100%)	1 (100%)
Total	95*	57 (60 %)	15 (16%)
p-Value (III *vs*. II)		0.009	1.0

n: Number of patients; *excluding one patient due to missing pre-therapeutic MRI.

Table V. *Tumor regression grading*.

Regression grade	0 (no R)	1 (<25%)	2 (25-50%)	3 (>50%)	4 (CR)
	Poor		Intermediate		Complete
According to Dworak *et al*. (24)	2 (2%)	16 (17%)	31 (32%)	33 (34%)	14 (15%)
Modified by Rödel et al. (25)	18 (19%)		64 (67%)		14 (15%)

R: Tumor regression; CR: complete tumor regression.

Acute toxicity of nRCT. From 96 patients treated with nRCT, data with regards to acute side-effects of nRCT were obtained from 81 patients. Forty-seven patients (58.0%) had signs of acute toxicity. Grades 1 and 2 acute severe events (34/81, 42.0%) were significantly more frequent than those of grade 3 (12/81, 14.8%) (p=0.001). Grading of toxicity was not possible in one patient due to severe depression. The frequency of acute adverse effects varied between centers from 32% to 71% (p=0.037).

Grade 3 toxicities consisted of stomatitis (6 patients), diarrhea (4 patients), proctitis and dehydratation (2 patients each). Furthermore, colitis, perianal ulcers, atrial fibrillation and nausea were encountered in one patient each.

Grade 1/2 toxicities comprised diarrhea in 21, proctitis in 7, colitis in 3, stomatitis in 5, skin diseases in 9, nausea in 3 and tiredness in 3 patients.

Surgical complications and reoperation. Intraoperative complications were recorded in 4/230 patients (1.7%): in 1/134 patients with primary surgery (ureter lesion) and in 3/96 with nRCT (p=0.314; one splenic lesion, one perforation of the vagina and one defect of the rectal stump necessitating perineal extirpation of the anus).

Postoperative complications were experienced in 54/230 patients (23.5%), 35/134 (26.0%) after primary surgery and 19/96 (20%) after nRCT (p=0.275). Out of these 54 patients, 42 patients had surgical complications, 10 patients had general complications, and 2 patients had both surgical and general complications. The most frequent surgical complications were wound infection (7.4%) and clinically symptomatic leak of bowel anastomosis (3.9%). Surgical complications were not more frequent in the group of patients with nRCT (p=0.750).

Re-operations were similarly frequent in patients with primary surgery compared to patients with nRCT and surgery: 10/134 (7.5%) *vs*. 9/96 (9.0%) (p=0.603).

Three patients died in the postoperative course (1.3%), all of them from the group of primary surgery, and two of them within 30 days after surgery.

Discussion

Differing from most recent investigations on stage II / III rectal cancer, nRCT was used selectively in the present study. nRCT was applied when pre-therapeutic MRI showed a T3 tumor of the distal part of the rectum or when the tumor was 1 mm or less from the mesorectal fascia. The focus of this analysis was the oncological short-term effects in this negatively selected study population with locally advanced stages or challengingly distal tumor site.

nRCT led to a reduction of the T category in 62% (Table II) and a reduction of the N category in 88% of patients with cN positive disease (Table III). The down-staging was in accordance with a recent study in stage II rectal cancer (53). This tumor shrinkage or even tumor eradication led to the most important effect of the nRCT: a pre-therapeutic positive CRM converted into a negative one in the pathological work-up in 86%. A negative CRM, *i.e*. a clear lateral margin, is crucial with regard to local recurrence rate and 5-year survival (20, 21, 26).

On lymph nodes, the down-staging effect of nRCT seems to be even more pronounced than on the primary tumor. Eighty-eight percent (59/67) of patients with clinically assessed lymph node metastasis experienced a reduction of the N category following nRCT and down-staging of a node-positive status to ypN0 occurred in 72% (Table III) of these patients. Correspondingly, down-staging of tumors with clinical stage UICC III was encountered significantly, more often than tumors with clinical stage UICC II [47/67 (70%) *vs*. 9/27 (38%); p=0.009, Table IV]. Taking all irradiated patients together, only 20/96 (21%) had the prognostically relevant stage ypN+. This figure is rather low when compared to the recent literature, where the percentage of ypN+ patients ranged from 20.4%-33.3% (27-33). Interestingly, the corresponding mean value for ypN+ rates in these articles, that all reported a 5-FU based nRCT, was 28.6% and did not differ significantly from the ypN+ rates following nRCT with capecitabine (30.5%), and capecitabine plus oxaliplatin (28.5%) (34).

nRCT is known to have a decreasing effect on lymphatic tissue. Therefore, response to nRCT should not only result in a reduction of the number of metastatic lymph nodes but also in a reduction of the number of retrieved and examined lymph nodes. Indeed, following nRCT, we assessed a significantly lower median number of lymph nodes than after primary surgery (19 *vs*. 26; p<0.001). Compared with recent literature, reporting median numbers of examined lymph

nodes following nRCT of 5.2 (n=157) (35), 8.7 (n=303) (27), 12 (n=565) (34), and 17.8 (n=121) (28), the median number of 19 in the present series might reflect the expertise of the participating surgeons and pathologists.

With regard to the concept of watchful-waiting in the case of complete remission following nRCT, as proposed by Habr-Gama *et al*. (36), the percentage of complete responses gains importance. In the present study, we found a pathologically complete response (pCR), *i.e*. ypT0ypN0cM0, in 14 out of 96 cases (15%) (Table V). This figure is in accordance with those in five recently published meta-analyses and reviews, reporting pooled rates of pCR between 11.1% and 22.5%, with extreme values for single studies between 3% and 47% (27, 37-40). The use of newer drugs such as oxaliplatine or irinotecan might increase the rate of pCR, however, probably at the price of higher toxicity (29, 34, 41-43). Intermediate regression of 67% and poor regression of 19% in the present study were similar to the data published by Rödel *et al*. (66% and 25%) (29) and by Park *et al*. (76% and 6%) (30).

The interval between the conclusion of radiotherapy and surgery was a median of 46 days in this series. Since Francois *et al*. (44) have shown that tumor regression increased if the waiting time until surgery was extended to 6 – 8 weeks following radiotherapy, the standard interval of at least 6 weeks is widely accepted. Recent data from Tulchinski *et al*. (45) favour at least 7 weeks waiting time, and those of Kalady *et al*. even 8 weeks (46). However, further prolongation of the interval between radiotherapy and surgery did not have any advantage (19, 20, 47).

It is noteworthy that postoperative short-term complications did not occur more frequently after nRCT than after surgery alone (20% *vs*. 26%, p=0.275). The total postoperative complication rate of 23.5% compares favourably with 41.8% postoperative complications reported in the Swedish rectal cancer registry 1995-2003 (48), 35% in the German CAO/ARO/AIO trial 1994 (49), as well as 32.5% in a study from Heidelberg (50). In accordance with our trial, none of these studies demonstrated an adverse perioperative outcome following nRCT. As most frequent postoperative complications, we found disturbed wound healing in 7.4% and a clinically obvious anastomotic leak in 3.9% of patients. Again for comparison, a meta-analysis comprising of 84 studies reported a pooled leak rate of 11% (2291 out of 22102 patients, 95% confidence interval=10-12%) (51).

With regards to acute side-effects of nRCT, grade 4 toxicity was not encountered in this series.

Three current meta-analyses served as a basis for the comparison of toxicities (38, 39, 52). All three meta-analyses enrolled only randomized controlled trials, and in all these single trials, 5-FU was used as a radiosensitizer. Similar frequencies of grade 3/4 toxicity were found in two, but not in one study: 14.8% (this series) *vs*. 14.9% (38), *vs*. 13.6% (39), *vs*. 45.3% (52).

Conclusion

Despite an MRI-based selective indication for nRCT and therefore a negative selection of cases of locally advanced rectal cancer for nRCT, impressive rates of tumor down-staging and eradication of tumor from the mesorectal fascia was achieved. The rate of complete regression is comparable to that reported in the literature and hardly seems to depend on the tumor size or the depth of invasion. Moreover, the selective use of nRCT spared a considerable percentage of patients with stage II/III rectal cancer severe irradiation toxicity.

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