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Phase III randomised trial

Gender affects acute organ toxicity during radiochemotherapy for rectal cancer: Long-term results of the German CAO/ARO/AIO-94 phase III trial

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ABSTRACT

Introduction: The CAO/ARO/AIO-94 phase-III-trial demonstrated a significant improvement of preoperative chemoradiotherapy (CRT) versus postoperative CRT on local control for UICC stage II/III rectal cancer patients, but no effect on long-term survival. In this add-on evaluation, we investigated the association of gender and age with acute toxicity and outcome.

Patients and methods: According to actual treatment analyses, 654 of 799 patients had received pre- ($n = 406$) or postoperative CRT ($n = 248$); in 145 patients postoperative CRT was not applied. Gender, age and clinicopathological parameters were correlated with CRT-associated acute toxicity and survival.

Results: The 10-year survival was higher in women than in men, with 72.4% versus 65.6% for time to recurrence ($p = 0.088$) and 62.7% versus 58.4% for overall-survival (OS) ($p = 0.066$), as expected. For patients receiving CRT, women showed higher hematologic ($p < 0.001$) and acute organ toxicity ($p < 0.001$) in the entire cohort as well as in subgroup analyses according to pre- ($p = 0.016$) and postoperative CRT ($p < 0.001$). Lowest OS was seen in patients without acute toxicity ($p = 0.0271$). Multivariate analyses for OS showed that acute organ toxicity ($p = 0.034$) was beneficial while age ($p < 0.001$) was associated with worse OS.

Discussion: Female gender is significantly associated with CRT-induced acute toxicity in rectal cancer. Acute toxicity during CRT may be associated with improved long-term outcome.

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Rectal cancer is one of the most frequent malignancies in the western world and represents a major socioeconomic and health issue [1]. After publication of the intergroup CAO/ARO/AIO-94 [Working Group of Surgical Oncology, Radiation Oncology and Medical Oncology] phase III trial of the German Rectal Cancer Study-Group (GRCSG) in 2004 [2], preoperative radiotherapy combined with intravenous fluorouracil (5-FU) chemotherapy (CRT), total mesorectal excision (TME-surgery) [3], and postoperative (adjuvant) chemotherapy (CTx) with 5-FU became the preferred treatment for patients with locally advanced rectal cancer (clinically staged as UICC stages II/III) in Germany as well as in many other parts of Europe and the US [4–7]. As much as shown in other randomized trials [8,9], preoperative multimodality therapy significantly improves treatment compliance (based on low accompanied toxicity in the overall population) as well as long-term loco-regional control with low relapse rates (between 5% and 10%), but the occurrence of distant metastases in up to 30% of patients still remains the major mode of failure [1,2,7,10].

Therefore, different intensified CRT regimens, including induction [11,12] and concurrent multi-agent chemotherapy approaches [13–18], are currently being tested in clinical trials for better control of systemic disease. The aim of these trials is to increase the rate of histopathologically confirmed complete tumor regression (pCR) as an early surrogate marker and, in particular, to reduce the occurrence of distant metastases to finally improve time to recurrence (TTR) as well as overall survival (OS) [19,20].

Obviously, these approaches with intensification of the multimodality treatment bear risks to increase high-grade acute hematologic as well as organ toxicity, too [15,21,22]. Great efforts are being undertaken to identify subgroups of patients at such higher risk of severe acute toxicity during CRT in order to avoid treatment interruption. It is well known that any delayed or

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incomplete multimodality treatment will not only result in limited patients' compliance but also affects cancer-specific outcome [23].

From the clinical point of view, the identification of reliable parameters that predict both CRT-induced tumor response and treatment-related toxicity would be a promising step toward an individualized risk-adapted treatment for rectal cancer patients.

In this context, molecular markers are being tested extensively, applying cost-intense technologies such as gene expression profiling [24,25]. In contrast, basic clinical parameters such as gender and age have been largely neglected, but could help to stratify for risk-adapted treatment approaches.

Recently, our first monocentric analysis demonstrated a significantly higher proportion of acute organ toxicity in women during preoperative CRT for locally advanced rectal cancer [26]. In order to validate this correlation within an independent and large phase-III study population with long-term follow-up, we now performed an unplanned analysis of a total of 799 eligible patients with UICC stage II/III rectal cancers, treated within the CAO/ARO/AIO-94 trial [6]. We here provide exploratory subgroup analyses of this trial to assess the correlation between gender, age, CRT-associated acute toxicity and long-term outcome.

Patients and methods

This study represents a clinical add-on evaluation of the multicentric, open-label, randomized CAO/ARO/AIO-94 phase III trial conducted by the GRCSG [2]. All analyses were approved by the central and local ethics committees, and each patient had provided written informed consent. The design of the trial was reported previously [2,7].

Patient eligibility and treatment

The trial included patients between 18 and 75 years of age with histopathologically confirmed locally advanced adenocarcinoma of the rectum (clinically staged as UICC stages II/III) with the inferior margin lower than 16 cm above the anal verge as assessed by rigid rectoscopy [7].

Multimodality treatment consisted of either pre- or postoperatively applied radiotherapy (RT) with daily fractions of 1.8 Gy (5 times/week) with a total dose of 50.4 Gy. In the postoperative CRT arm, a boost of 5.4 Gy was applied to the tumor bed. The target volume definition and radiation technique were defined according to the study protocol [2]. Chemotherapy (CTx) was administered concomitantly to RT as continuous 120-h 5-FU infusion, applied in the first and fifth week of RT (1000 mg/m^2 on days 1–5 and 29–33). Total mesorectal excision (TME) surgery was performed 4–6 weeks after completion of neoadjuvant CRT. Adjuvant CTx started 4 weeks after TME-surgery or after completion of postoperative CRT, respectively, and consisted of 4 cycles of 5-FU intravenous bolus (500 mg/m^2), applied on days 1–5, repeated from day 29.

Acute organ toxicity

Initially, hematologic toxicity as well as acute organ toxicity of skin, small bowel and bladder were monitored according to a German classification system that corresponds to the World Health Organization criteria for chemotherapy toxicity and is compatible to the Radiation Therapy Oncology Group (RTOG) and European Organization for Research in Treatment of Cancer (EORTC) acute and late radiation morbidity scoring criteria [27]. After implementation of the NCI Common Toxicity Criteria (CTC), version 2.0 in 2000, toxicity grades were reevaluated retrospectively for final analyses (Supplementary Table S1) [28].

For these analyses, the highest CTC scores for treatment-associated hematologic toxicity, skin reaction, enteritis, or cystitis were assessed for every patient and correlated with survival parameters.

Follow-up

Follow-up visits over a total of five years were scheduled at three-month intervals for the first two years, then at six-month intervals. Each visit consisted of a physical examination, a complete blood count, and blood chemistry. Rigid rectoscopy, abdominal ultrasound, contrast enhanced computed tomography of the abdomen and pelvis as well as chest radiography were conducted according to guidelines of the German Cancer Society [29,30]. In case of local or distant recurrence, histological confirmation was encouraged. Acceptable alternative evaluation criteria were the sequential enlargement of a mass in radiological assessments. Follow-up assessments beyond five years, not specified in the study protocol, were performed on a patient-to-patient basis, and additional information was collected from the participating hospitals and general practitioners using additional case report forms as described recently [7].

Statistical analysis

Within the CAO/ARO/AIO-94 trial 799 of 823 enrolled patients met the inclusion criteria and were randomly assigned to preoperative ($n = 404$ patients) or postoperative CRT ($n = 395$ patients) (intent-to-treat-population), as recently reported [7]. According to the actual treatment population (Supplementary CONSORT diagram) 406 patients received preoperative CRT followed by TME-surgery, and 248 patients were treated with postoperative CRT after TME-surgery. In 145 patients, postoperative CRT was not applied [2,7]. Therefore, the following toxicity analyses were performed in the subset of 654 eligible patients who were actually treated with CRT.

The survival endpoints were defined as followed: TTR was determined according to events defined as local or distant recurrences. OS was calculated as the time interval between randomization and death of any reason or day of last follow-up. All survival analyses were calculated with the Kaplan–Meier method and differences were displayed using the log-rank test. Hazard ratios and 95% confidence intervals (CIs) were computed based on the Cox proportional hazards model. Multivariate analyses were performed using the Cox proportional hazards model on the parameters treatment (pre- or postoperative CRT), grade of toxicity, gender and age as risk factors for cancer recurrence or death. The parameter treatment was defined based on the actual treatment received. Associations among clinical categorical variables (e.g. gender versus treatment) were assessed using the Fisher's Exact Test. Furthermore, associations of categorial and continuous variables (e.g. gender versus age) were determined using the Wilcoxon Test for two group comparisons or the Kruskal–Wallis Test for multigroup comparisons. All statistical analyses were performed using the R statistical computing software (Version: 2.14.1) [31]. Survival analyses were performed using Kaplan–Meier analyses from the R package survival and significance was estimated using the log-rank test. Multivariate survival analyses were performed using the Cox proportional hazards model. A two-sided p-value of less than or equal to 0.05 was considered significant.

Results

Patient and treatment characteristics

In the intergroup CAO/ARO/AIO-94 phase III trial 823 patients were enrolled (Supplementary CONSORT diagram). Of these, 24 patients were excluded as they did not meet the inclusion criteria ($n = 15$) or refused to participate ($n = 9$) in the trial. The remaining 799 patients were randomly assigned to receive either preoperative CRT ($n = 404$) or postoperative CRT ($n = 395$). In both treat-

Table 1
All treated patients and tumor characteristics in relation to gender.

Analyzed study population: $n = 799$	Pre- or postoperative CRT ($n = 654$)		
	Male $n = 457$ (%)	Female $n = 197$ (%)	p-Value
Age (yr)			
Median	61	60	0.98
Range	30–76	29–74	
Distance from anal verge			
0 to <5 cm	119 (26.1)	57 (28.9)	0.23
5 to <10 cm	212 (46.4)	79 (40.1)	
10–16 cm	108 (23.6)	56 (28.4)	
Unknown	18 (3.9)	5 (2.6)	
TNM stage			
pCR/stage 0	25 (5.5)	11 (5.6)	0.88
(y)p I	82 (19.0)	31 (15.7)	
(y)p II	140 (30.6)	64 (32.5)	
(y)p III	171 (37.4)	78 (39.6)	
(y)p IV	33 (7.2)	11 (5.6)	
Unknown/no surgery	6 (1.3)	2 (1.0)	
Type of resection			
Low anterior	286 (62.6)	138 (70.1)	0.26
Intersphincteric	40 (8.8)	14 (7.1)	
Abdominoperineal	126 (27.6)	44 (22.3)	
Other	1 (0.2)	1 (0.5)	
None	4 (0.8)	0 (0)	
Unknown	0 (0)	0 (0)	
Completeness of local resection			
Complete local resection (R0)	436 (95.4)	191 (97.0)	0.36
Incomplete resection (R1)	11 (2.4)	1 (0.5)	
Incomplete resection (R2)	2 (0.4)	1 (0.5)	
(R2)	3 (0.7)	1 (0.5)	
Completeness of scheduled radiotherapy			
Preoperative complete	283 (96.6)	108 (95.6)	0.15
Postoperative complete	154 (93.9)	77 (91.7)	
Completeness of scheduled chemotherapy			
Preoperative complete	267 (95.0)	101 (89.4)	0.22
Postoperative complete	145 (83.5)	69 (82.1)	

ment arms 18 and 20 patients, respectively, requested for a change in therapy. Finally, in 406 patients preoperative CRT was applied according to study protocol followed by TME-surgery ($n = 402$). Postoperative CRT was performed in 248 of the allocated 393 patients after TME-surgery. In 145 patients postoperative CRT was not given due to the histopathological confirmation of <UICC stages II in 75 patients and of UICC stages IV in 19 patients. Additionally, 51 patients did not receive postoperative CRT due to complications or refusal/institutional errors after surgery. Thus, 654 patients (197 women and 457 men) treated with CRT were assessable for analyses focusing on treatment-associated toxicity.

As shown in the CONSORT diagram, preoperative CRT was applied in 113 (57.4%) female patients and postoperative CRT in 84 (42.6%), respectively. In 293 (64.1%) male patients preoperative CRT was given, while 164 (35.9%) men were treated with postoperative CRT. Table 1 summarizes patients' characteristics according to actual treatment received.

Of all patients who had received CRT, 108 (95.6%) of the 113 female and 283 (96.6%) of the 293 male patients received the intended dose of preoperative RT, whereas postoperative RT was fully applied in 77 (91.7%) of female and 154 (93.9%) of male patients, respectively (Table 1). Accordingly, 101 (89.4%) of the women and 267 (95.0%) of the men received full dose of the concomitant CT preoperatively. Postoperatively, the full dose of CT was administered to 69 female (82.1%) and 145 male (83.5%) patients (Table 1).

Follow-up, events and OS according to gender

After a median follow-up of 134 months (range, 90–184) for all 450 surviving patients of the total study population ($n = 799$), the 10-year OS and TTR rates in women were 62.8% and 72.4%, respectively, with a trend toward higher survival rates compared to men (OS: 58.4%, $p = 0.066$; TTR: 65.6%, $p = 0.088$; Fig. 1) [7].

Of all 654 patients who were treated with CRT, 370 (56.6%) were still alive at the last follow-up. Of these 370 patients, all (100%) were followed for at least 5 years, 360 (97%) for at least 8 years, and 261 (71%) for at least 10 years. A total of 280 deaths occurred, of which 180 (64.29%) deaths were related to rectal cancer. No long-term follow-up data were available for 4 patients.

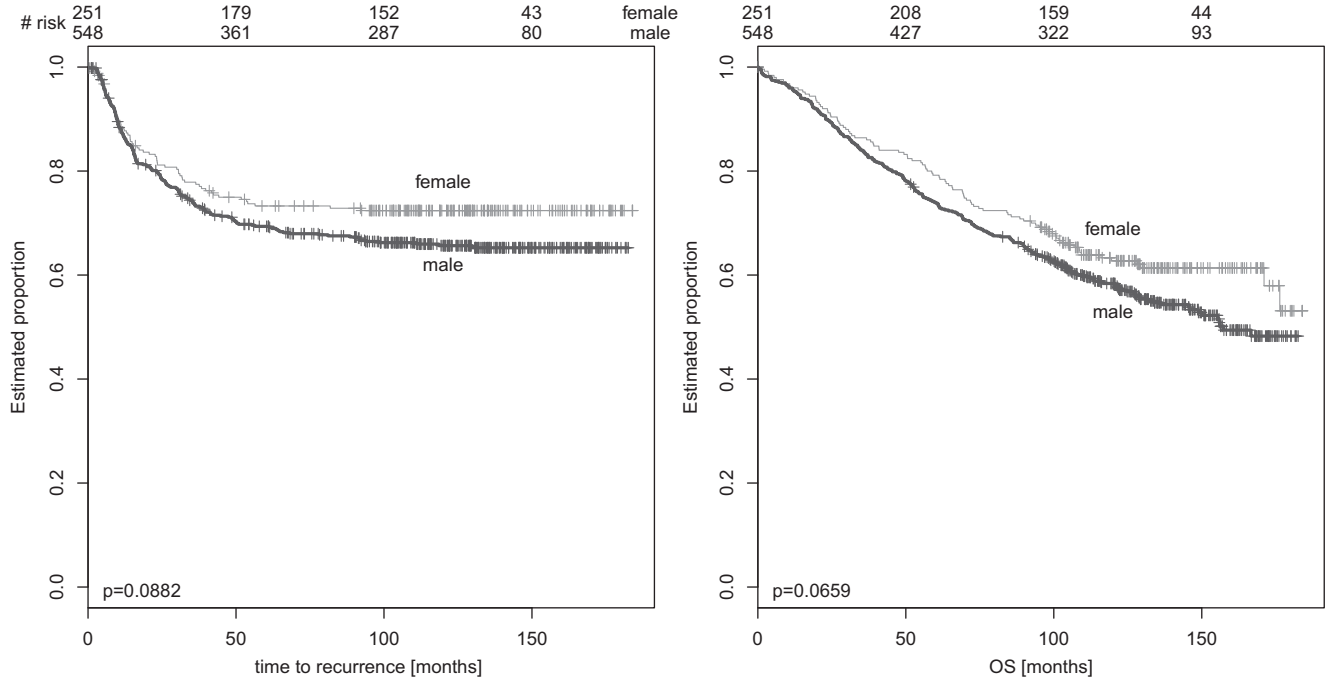

Fig. 1. Kaplan–Meier-curves displaying time to recurrence and overall survival for all treated patients ($n = 799$) in relation to gender.

During follow-up, 208 (31.8%) of the 654 patients receiving preoperative or postoperative CRT had recurrent disease, of which 165 (79.3%) patients had distant metastases alone, 34 (16.4%) in combination with local recurrence, and 9 (4.3%) patients had isolated local recurrence.

Acute toxicity, age, gender, and treatment

Based on all 654 CRT patients, overall hematologic toxicity (leukopenia, anemia, and thrombocytopenia) was significantly higher in female patients ($p < 0.001$) as shown in Table 2. Especially transient leucopenia (WHO grade I–III) and mild anemia (WHO grade I) occurred more often in female patients, whereas severe leucopenia WHO grade IV was restricted to men. Additional analysis did not reveal any correlation between the occurrence of hematologic toxicity and age (Kendalĺs correlation coefficient −0.034 resulting in a p-value of 0.34).

The maximum acute organ toxicity grades recorded for the skin, bladder, and intestine, were used to create box plots showing toxicity grades in relation to gender and age (Supplementary Fig. S1). Remarkably, there was no apparent correlation between patientś age and acute organ toxicity ($p = 0.97$). Conversely, severity of acute organ toxicity was significantly higher in female patients, as shown in Table 1 for the entire cohort ($p < 0.001$) as well as for the preoperative ($p = 0.016$) and postoperative ($p < 0.001$) treatment cohorts, respectively. The main impact on this distribution resulted from toxicity of the intestine, whereas skin toxicity showed only a trend for higher incidences and grades in female patients ($p = 0.091$). The bladder toxicity showed no differences regarding gender ($p = 0.46$).

Treatment associated hematologic ($p = 0.0007$) as well as maximum acute organ toxicity ($p < 0.001$) was higher in female patients than in men in both treatment arms ($p = 0.016$ and $p < 0.001$). The detailed distribution of treatment related acute toxicity is summarized in Table 2.

TTR and OS according to acute toxicity

Fig. 2 displays Kaplan–Meier analyses for OS and TTR rates for all 654 patients according to the highest acute organ toxicity score for at least one item of skin, bladder, or intestine toxicity. There was no apparent correlation between hematologic or organ toxicity and OS or TTR. Interestingly, the lowest OS rates were observed in patients without any acute toxicity (no toxicity versus toxicity groups: $p = 0.0271$).

Influence of acute organ toxicity on OS and TTR

Furthermore, gender-specific survival analyses revealed that OS in male patients was significantly lower when no acute organ toxicities occurred (Fig. 2, $p = 0.0187$). When TTR was analyzed, there was only a trend for male patients without any toxicity, although these results were not significant ($p = 0.522$). In detail, after a follow-up of 10 years, 6.6% ($n = 30$) of all male patients suffered from local failure and 31.5% ($n = 144$) developed distant metastases. For female patients, the results were 6.6% ($n = 13$) and 27.9% ($n = 55$), respectively. Remarkably, for women no correlation was detectable between grade of toxicity and OS ($p = 0.88$) or TTR ($p = 0.992$).

In addition to the univariate analyses, multivariate analyses for OS, but not for TTR, revealed that acute organ toxicity as well as age were significant prognostic parameters for OS, independent of pre- or postoperative CRT and gender (Table 3).

Table 2
Overall hematologic toxicity as well as maximum acute organ toxicity of intestine, bladder and skin according to gender and treatment arm.

Acute toxicity grade (CTC)	Male	Female	p-Value
Acute hematologic toxicity in relation to gender			
Leukopenia			
0	288 (63.0)	109 (55.3)	0.007
1	90 (19.7)	46 (23.4)	
2	32 (7.0)	26 (13.2)	
3	3 (0.7)	4 (2.0)	
4	3 (0.7)	0 (0.0)	
Missing	41 (9.0)	12 (6.1)	
Thrombocytopenia			
0	406 (88.8)	183 (92.9)	0.222
1	5 (1.1)	2 (1.0)	
2	2 (0.4)	0 (0.0)	
3	3 (0.7)	0 (0.0)	
4	1 (0.2)	0 (0.0)	
Missing	40 (8.8)	12 (6.1)	
Anemia			
0	371 (81.2)	143 (72.6)	0.0002
1	36 (7.9)	38 (19.3)	
2	7 (1.5)	3 (1.5)	
3	2 (0.4)	1 (0.5)	
4	0 (0.0)	0 (0.0)	
Missing	41 (9.0)	12 (6.1)	
Overall Hematologic toxicity			
0	259 (56.7)	87 (44.2)	0.0007
1	110 (24.1)	67 (34.0)	
2	39 (8.5)	26 (13.2)	
3	6 (1.3)	5 (2.5)	
4	3 (0.7)	0 (0.0)	
Missing	40 (8.8)	12 (6.1)	
Acute organ toxicity of intestine, bladder and skin in relation to gender			
Maximum per patient, both arms			
0	31 (6.8)	7 (3.6)	<0.001
1	157 (34.4)	33 (17.0)	
2	123 (26.9)	73 (37.6)	
3	136 (29.7)	74 (38.1)	
4	7 (1.5)	7 (3.6)	
Missing	3 (0.7)	3 (1.5)	
Maximum per patient, preoperative arm			
0	16 (5.5)	5 (4.4)	0.016
1	111 (37.9)	26 (23.0)	
2	71 (24.2)	37 (32.7)	
3	89 (30.4)	40 (35.4)	
4	3 (1.0)	3 (2.7)	
Missing	3 (1.0)	2 (1.8)	
Maximum per patient, postoperative arm			
0	15 (9.1)	2 (2.4)	<0.001
1	46 (28.0)	7 (8.3)	
2	52 (31.7)	36 (42.8)	
3	47 (28.8)	34 (40.5)	
4	4 (2.4)	4 (4.8)	
Missing	0 (0.0)	1 (1.2)	
Intestinal toxicity per patient, both arms			
0	117 (25.9)	25 (12.9)	<0.001
1	193 (42.8)	52 (26.8)	
2	120 (26.6)	89 (45.9)	
3	20 (4.4)	24 (12.4)	
4	1 (0.2)	4 (2.0)	
Bladder toxicity per patient both arms			
0	303 (67.0)	123 (64.4%)	0.46
1	122 (27.0)	53 (27.8%)	
2	23 (5.1)	15 (7.9%)	
3	4 (0.9)	0 (0.0%)	
4	0 (0.0)	0 (0.0%)	
Skin toxicity per patient, both arms			
0	100 (22.1)	37 (19.3)	0.091
1	159 (35.2)	55 (28.7)	
2	62 (13.7)	36 (18.8)	
3	125 (27.7)	61 (31.8)	
4	6 (1.3)	3 (1.6)	

Discussion

This unplanned add-on study of participants of the German CAO/AIO/ARO-94 trial was motivated by intriguing results derived from our monocentric analysis on 196 patients with locally advanced rectal cancer (UICC stages II and III) [26]. In this cohort study we found significantly more high-grade acute organ toxici-

ties in women undergoing preoperative CRT. To validate our findings, the present confirmatory analysis was conducted, analyzing 654 patients of the CAO/ARO/AIO-94-trial based on actual treatment received and providing a median follow-up of 10 years. We again identified gender as a significant risk factor for CRT-induced acute toxicity: the overall maximum organ toxicity was significantly higher in female compared to male patients.

In the overall trial population, the 10-year OS rates were in trend higher in women than in men (62.7% vs. 58.4%; $p = 0.066$) which could be expected since life expectancy in general is higher in women compared to men. In this context, significant age-related sex differences in the incidence and maybe also in the prognosis of colorectal cancer were described recently while the underlying reasons remain unillucidated, so far [32].

Moreover, OS in male patients was significantly lower when no acute organ toxicities occurred, and acute organ toxicity turned out to be a significant prognostic parameter for OS in multivariate analysis. The lack of acute toxicity therefore seemed to be associated with higher chance of dying owing to causes other then rectal cancer.

Even if the statistical power of this restrospective add-on analysis can be discussed, the possible underlying reasons for lower OS in patients without any acute toxicity remain unclear. All patients received the same treatment according to the trial protocol, and compliance with all components of multimodality treatment, including RT, CTx, and TME-surgery (Table 1), was comparable between men and women. Patients' age was equally distributed in both genders and did not correlate with hematologic toxicity or acute organ toxicity.

In the literature, only few reports on RT or CRT of solid cancers have specifically addressed either gender-specific risks for treatment-related organ toxicity or a correlation of gender and toxicity with long-term outcomes. Dahl et al. [33] described a significant correlation between acute side-effects to the normal bowel and sensitivity of rectal carcinomas to preoperative RT. In this study, comprising 159 patients, high-grade acute toxicity was significantly related to tumor regression at the time of surgery compared to patients without high-grade bowel toxicity.

Interestingly, in anal cancer, also a significant correlation between CRT-induced acute toxicity and improved loco-regional tumor response as well as long-term outcome was observed [34]. Detailed analyses showed high-grade acute organ toxicity as an independent prognostic factor in multivariate analysis and a benefit for female patients reaching a significantly better loco-regional control rate in comparison to male patients (5-years: 87% vs. 53%; $p = 0.01$).

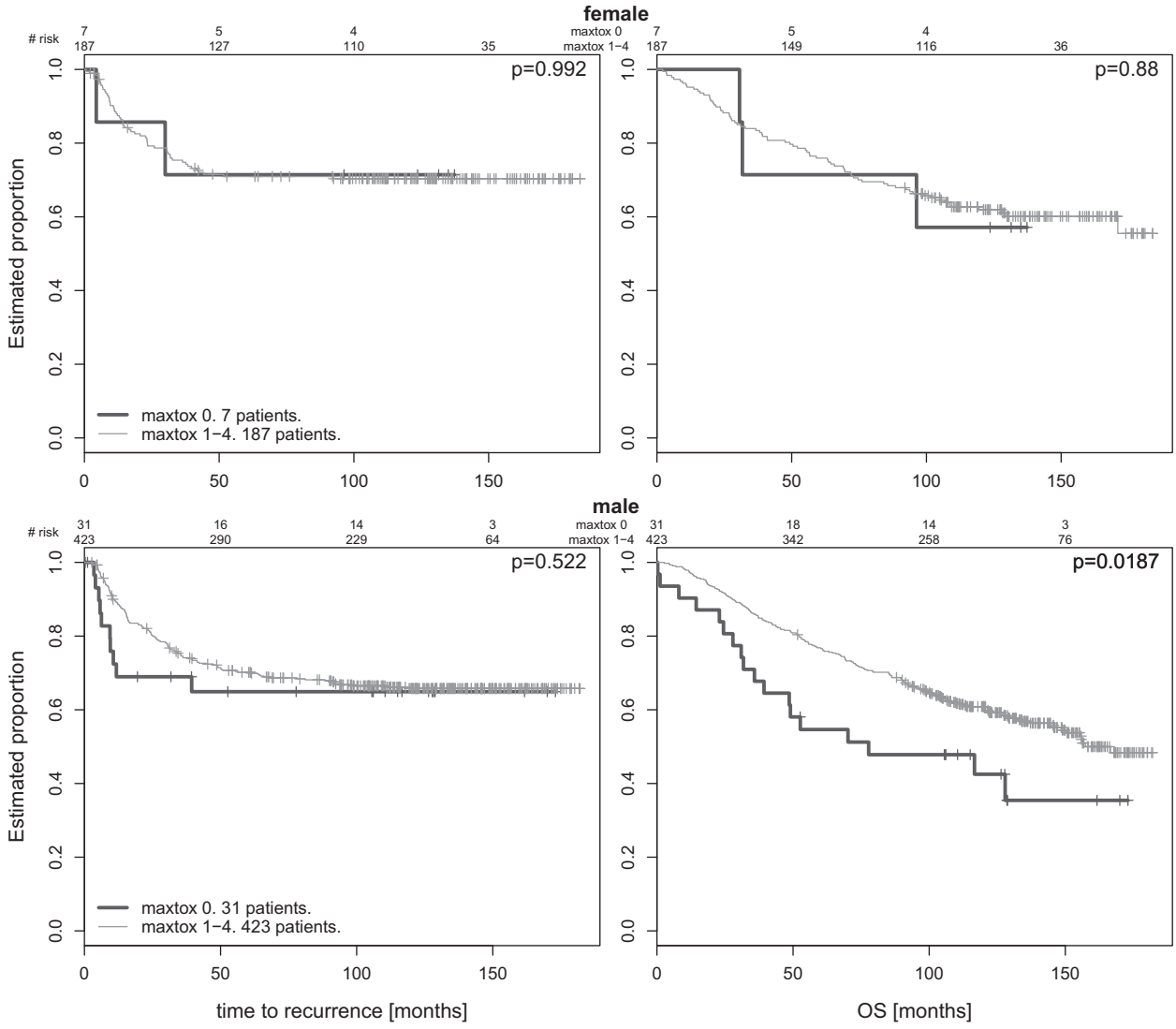

Fig. 2. Kaplan–Meier-curves displaying time to recurrence and overall survival for all patients and in relation to gender.

Table 3
Multivariate analyses of the time to recurrence and overall survival according to actual treatment, CTC grade of acute organ toxicity, gender and age.

Variables	Hazard ratio [95% CI]	*p*-Value
TTR univariate		
Treatment arm (postoperative)	1.11 [0.84–1.47]	0.45
Grade of toxicity (I–IV)	0.84 [0.47–1.50]	0.55
Gender (male)	1.28 [0.96–1.69]	0.089
Age	1.00 [0.99–1.01]	0.934
TTR multivariate		
Treatment arm (postoperative)	1.13 [0.86–1.50]	0.376
Grade of toxicity (I–IV)	0.85 [0.47–1.53]	0.593
Gender (male)	1.16 [0.85–1.58]	0.347
Age	1.00 [0.98–1.01]	0.838
OS univariate		
Treatment arm (postoperative)	1.06 [0.84–1.35]	0.61
Grade of toxicity (I–IV)	0.61 [0.39–0.95]	**0.029**
Gender (male)	1.25 [0.99–1.58]	0.066
Age	1.03 [1.02–1.05]	**<0.001**
OS multivariate		
Treatment arm (postoperative)	1.08 [0.85–1.38]	0.521
Grade of toxicity (I–IV)	0.62 [0.40–0.96]	**0.034**
Gender (male)	1.13 [0.87–1.48]	0.359
Age	1.03 [1.02–1.05]	**<0.001**

CI, confidence interval; TTR, time to recurrence; OS, overall survival.

One possible explanation for the gender-specific difference of acute hematologic and organ toxicity in our analyses, especially for the intestine, could be explained by enzyme levels of dihydropyrimidine dehydrogenase (DPD). This enzyme is the rate-limiting factor in the catabolism of 5-FU. DPD has been reported to correlate with the toxicity and effectiveness of 5-FU-based cancer treatment. Yamashita et al., among others, found significantly lower levels of DPD in females in a cohort of 97 colorectal cancer patients [35]. Subsequently, lower DPD-levels in women could result in higher plasma levels of 5-FU causing higher toxicity and also a better long-term outcome. Thus, it may be clinically useful to individually adjust chemotherapy dosages to DPD-activity and/or plasma-levels of 5-FU in future clinical trials [36].

Our analyses were conducted in the setting of the CAO/ARO/AIO-94-phase-III-trial which established the present gold-standard in the treatment of locally advanced rectal cancer: preoperative 5-FU-based CRT followed by TME-surgery, and adjuvant 5-FU chemotherapy. The aim of currently ongoing trials, e.g. CAO/ARO/AIO-04-phase-III-trial [16], is either to integrate more effective CTx regimens to preoperative RT or to include multi-agent CTx as inductive chemotherapy approaches [12,37], in order to enhance the rate of pCR and in particular, to reduce the occurrence of distant metastases leading to improved TTR as well as OS [11,13].

Any intensification of treatment components bears the risk of high-grade acute organ toxicity [21,22,38,39]. Thus, basic pre-treatment parameters that allow the identification of subgroups of patients at a higher risk of severe acute organ toxicity would help to improve the clinical management of these patients. Additionally, it should enforce optimized standard of supportive care to successfully complete the planned multimodality therapy. Even though in this add-on evaluation of the CAO/ARO/AIO-94-trial a high proportion of 96.3% (RT) and 90.6% (CTx) of patients received the planned dosages preoperatively versus 93.1% (RT) and 86.3% (CTx) postoperatively these are comparably lower in other studies [40].

To increase the treatment adherence even under intensified treatment protocols [13,16,18], further optimization of every part of the multimodal treatment is mandatory. Therefore, like the already standardized use of a belly-board during RT [41], new and more protective techniques such as intensity modulated volumetric arcs or irradiation with protons [42] might further reduce the exposure of organs at risk and of normal tissues [43] without compromising tumor control rates, in the future.

In conclusion, our results suggest that basic patient characteristics such as gender may predict the occurrence of CRT-induced acute organ toxicity that affects long-term outcome. Together with further identified reliable biomarkers this may help to tailor treatment modalities in a cost effective manner. Finally, this may lead to early preventative interventions to avoid severe adverse effects during multimodality treatment and ultimately to improve patients' outcomes.

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Conflict of interest

The authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.05.009.

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