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Chronic adverse events and quality of life after radiochemotherapy in anal cancer patients

A single institution experience and review of the literature

In the 1960s, the standard treatment for anal cancer (AC) was abdominoperineal excision with permanent colostomy. Today, radiochemotherapy (RCT) is considered the standard care for AC warranting organ preservation. Depending on the stage of the disease, the 5-year overall survival (OS) rate is about 50–95% [1, 2]. Due to the high number of long-term survivors after RCT, late toxicity and quality of life (QOL) are issues that deserve more attention. All surviving patients might potentially experience some of the late sequelae of the treatment, including stool and urinary incontinence, urgency, dysuria, dyspareunia and erectile dysfunction [1, 2, 3, 4]; some of which might have an impact on the patient's QOL. Only limited data are available on the correlation between CAE and QOL in patients undergoing RCT for AC [3, 4, 5, 6]. The aim of this survey was to report chronic adverse events (CAE) after RCT and analyse their correlation with QOL.

Patients and methods

Between 1988 and 2011, 138 patients with squamous cell AC were treated with RCT at the Department of Radiation Oncology at the Technische Universität München, Germany.

The median radiation dose was 54 Gy (45–59.4 Gy). Radiotherapy (RT) consisted of 36–45 Gy (1.8 Gy per fraction) to the lower part of the pelvis covering the primary tumor bed, perirectal-, presacral-, internal ilical-, external iliacal- and inguinal nodes. A boost with 14.4–21 Gy was delivered to the tumor bed and the enlarged nodes (1.8 Gy per fraction). Concurrent 5-fluorouracil (5-FU; 1,000 mg/m^2/d, days 1–4 and 29–32) + mitomycin C (MMC; 10 mg/m^2/d, days 1 and 29) chemotherapy was administered in 37 patients (89%); 1 patient (2%) received 5-FU alone and 1 patient (2%) received MMC only. Three patients (7%) were treated with RT alone due to T1N0 category (n=1), the patient's refusal of chemotherapy (n=1) and age (n=1).

Of these patients, 44 had died and 9 were lost to follow-up. A minimum interval of 6 months after RT was required for inclusion. The inclusion criteria were fulfilled by 83 patients (18 male; 65 female) and these patients were invited to participate in the study. CAE were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0. We selected the most relevant items for this study, which are detailed in **Tab. 5** at the end of the paper. One physician interviewed the patients regarding the presence/absence/intensity of relevant side effects during the past 2 weeks.

The Functional Assessment of Cancer Therapy-Colorectal (FACT-C) tool was used to assess QOL. This self-report instrument combines common concerns of all cancer patients as addressed by FACT-General (FACT-G; score range 0–108, with higher scores indicating better general well-being) with those of colorectal cancer patients. FACT-C reliability and validity for the assessment of QOL in patients with colorectal cancer has been shown in various publications [7, 8, 9]. Because of the rarity of AC, no specific questionnaire exists for the measurement of QOL in these patients. Considering the similar symptoms and late sequelae in patients with colorectal cancer and AC, the use of FACT-C to assess QOL in these patients seems justified. The questionnaire consists of 34 items in total, with five subscales concerning physical well-being, social/familial well-being, emotional well-being, functional well-being and the colorectal cancer-specific items. The FACT-C score can range from 0 to 136, with higher scores indicating a better

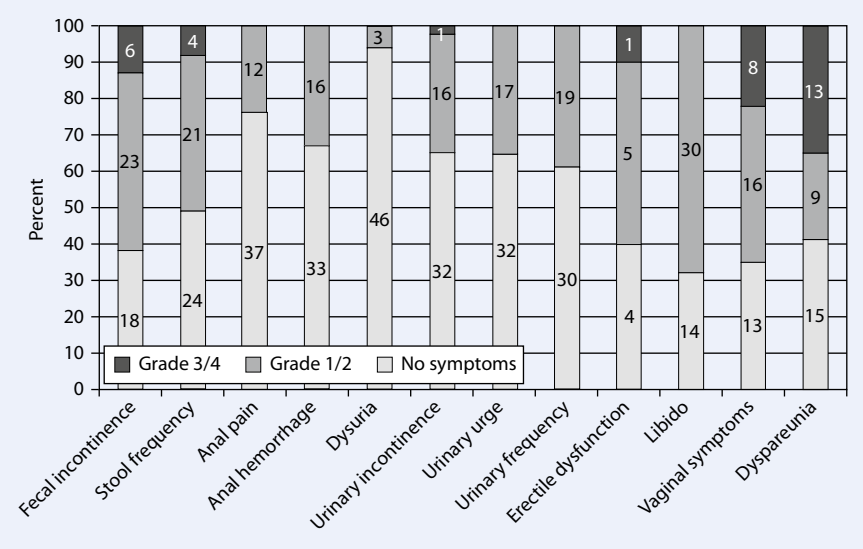

Fig. 1 ▲ Late toxicity in all patients according to the Common Terminology Criteria for Adverse Events v. 4.0. The numbers in the columns indicate the number of patients. The y-axis indicates the percentage of patients

QOL. All questions refer to the last week prior to the interview.

Eight questions concerning demographic characteristics such as marital status, partnership, children, household, education, employment status, economic situation and monthly net income were added.

The study was approved by the Ethics Committee of the Faculty of Medicine of the Technische Universität München.

Eligible patients were invited to visit our department. A total of 51 patients accepted the invitation. Two patients answered the FACT-C questionnaire only and had to be excluded from the study. The other 49 patients answered questions about their CAE. We report the CAE of these 49 patients. Female patients were asked at the appointment if they had performed the vaginal supportive care (vaginal creams, vaginal bath) during, and 8 weeks after the treatment (possible responses were"not at all","irregularly" or"regularly").

For 42 patients, both CAE and FACT-C information was available. To study the correlation of CAE with QOL, we analysed the data of the 42 patients who had completed both questionnaires. The median age of these 42 patients at the time of completing the questionnaires was 64 years (50–86 years). Patient characteristics are summarized in ◘ **Tab. 1.**

No significant differences were noted with regard to demographic-, clinical- or treatment characteristics or to the prevalence of CAE between patients who agreed to participate in the survey and those who did not (data not shown).

The median follow-up time of the patients was 68 months (range 9–222 months).

Statistical analysis

In order to describe differences in the distribution of FACT-C scores between the groups, the median and range of the physical, social/familial, emotional, functional and colorectal subscale scores were reported. The non-parametric Mann–Whitney U test and the Kruskal–Wallis test were used for univariate comparisons of two, or more than two independent subgroups, respectively. Multivariate assessment of the predictive ability of clinical- and sociodemographic patient characteristics on the FACT-C score was performed by multiple linear regression models. A two-sided p-value<0.05 was considered to indicate statistical significance.

Results

CAE

The frequencies of CAE in 49 patients are depicted in ◘ **Fig. 1.** The most common grade 3 CAE were dyspareunia and vaginal symptoms (itching, burning and dryness) in 35 and 22% of female patients, respectively; followed by stool incontinence in 13% of all patients, regardless of gender. Grade 1–3 urinary incontinence was more frequent in female patients (43% vs. 8% in males, p=0.037). Administration of vaginal supportive care (vaginal creams, vaginal bath) during and shortly after RCT was not associated with vaginal CAE (◘ **Tab. 2**).

There was no association between CAE ≥III and hematologic- (p=0.527) or non-hematologic acute toxicity ≥III°(p=0.150). Except for gender, where a trend toward a higher rate of grade 3 CAE was seen in female patients (18 out of 37 women, 49% vs. 2 out of 12 men, 17%; p=0.089), there was no correlation between the incidence of grade 3 CAE and patient- or treatment characteristics (data not shown).

Correlation of CAE with QOL

The median total FACT-C score was 110±20 (40–132) out of a possible maximum of 136. The median total FACT-G score was 89±17 (29–106) out of a possible maximum of 108. The median scores in the subscales were (median ± standard deviation/possible maximum score): physical: 24±6/28, social/familial: 23±5/28, emotional: 20±3/24, functional: 22±6/28 and colorectal: 22±4/28. The results of the univariate and multivariate analyses for factors associated with FACT-C are shown in ◘ **Tab. 3**. The results of the univariate analyses demonstrating a significant association between CAE (which was significantly associated with lower QOL scores in the multivariate analysis) and the subscales of FACT-C are shown in ◘ **Tab. 4.**

The highest score-difference between the compared groups was observed in patients with grade 3 stool incontinence (vs. no incontinence), with a median difference of 37 points (p=0.009). High dif-

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Chronic adverse events and quality of life after radiochemotherapy in anal cancer patients. A single institution experience and review of the literature

Abstract

Purpose. To report on chronic adverse events (CAE) and quality of life (QOL) after radiochemotherapy (RCT) in patients with anal cancer (AC).

Patients and methods. Of 83 patients who had received RCT at our department between 1988 and 2011, 51 accepted the invitation to participate in this QOL study. CAE were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0 and QOL was assessed with the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) questionnaire.

Results. CAE could be evaluated in 49 patients. There was a tendency toward a higher rate of grade 3 CAE in female patients, i.e. 18 out of 37 (49%) vs. 2 out of 12 (17%) male patients (p=0.089). The most common grade 3 CAE were dyspareunia and vaginal symptoms (itching, burning and dryness) in 35 and 22% of female patients, respectively, followed by stool incontinence in 13% of all patients (6 out of 49). Both FACT-C and CAE information were available for 42 patients, allowing evaluation of the impact of CAE on QOL. The median total FACT-C score was 110 (40–132) out of a possible maximum of 136. The absence of grade 3 CAE (115 vs. 94, p=0.001); an interval of ≥67 months after the end of the treatment (111 vs. 107, p=0.010), no stool incontinence vs. grade 3 stool incontinence (111 vs. 74, p=0.009), higher education (114 vs. 107, p=0.013) and no dyspareunia vs. grade 3 dyspareunia (116 vs. 93, p=0.012) were significantly associated with a higher median FACT-C score.

Conclusion. The majority of AC patients treated with RCT have acceptable overall QOL scores, which are comparable to those of the normal population. Patients with grade 3 CAE—particularly dyspareunia and fecal incontinence—have a poorer QOL compared to patients without CAE. In order to improve long-term QOL, future strategies might aim at a reduction in dose to the genitalia and more intensive patient support measures.

Keywords

Chemotherapy · Dyspareunia · Fecal incontinence · Toxicity · Survival

Chronische Nebenwirkungen und Lebensqualität nach Radiochemotherapie bei Analkarzinompatienten. Die Erfahrungen einer Klinik und ein Literaturüberblick

Zusammenfassung

Ziel. Bericht über chronische Nebenwirkungen (CAE) und die Lebensqualität (QOL) nach Radiochemotherapie (RCT) bei Patienten mit Analkarzinom (AC).

Patienten und Methode. Von 83 Patienten, die in unserer Klinik zwischen 1988 und 2011 mit einer RCT behandelt wurden, folgten 51 Patienten der Einladung zur QOL-Studienteilnahme. Die chronischen Nebenwirkungen wurden anhand der „Criteria for Adverse Events" (CTCAE v4.0) und die Lebensqualität mit dem „Functional-Assessment-of-Cancer-Therapy-Colorectal"-(FACT-C-)Fragebogen erfasst.

Ergebnisse. Chronische Nebenwirkungen konnten bei 49 Patienten ausgewertet werden. Es bestand eine Tendenz zu einer höheren Grad-3-CAE-Rate bei weiblichen Patienten im Vergleich zu männlichen Patienten (18/37 vs. 2/12; 49% vs. 17%; p=0,089). Die häufigsten Grad-3-CAEs waren Dyspareunie und vaginale Symptome (Jucken, Brennen, Trockenheit) bei jeweils 35% bzw. 22% der Frauen, gefolgt von Stuhlinkontinenz bei 13% aller Patienten (6/49). Bei 42 Patienten lagen Daten zu FACT-C und CAE vor, so dass der Einfluss von CAE auf den QOL evaluiert werden konnte. Der mediane Gesamt-FACT-C-Score betrug 110 (40–132) bei einem maximal erreichbarem Wert von 136. Das Fehlen von chronischen Grad-3-Nebenwirkungen (115 vs. 94; p=0,001), ein Zeitabstand von ≥67 Monaten nach Behandlungsende (111 vs. 107; p=0,010) sowie fehlende Stuhlinkontinenz vs. Grad-3-Stuhlinkontinenz (111 vs. 74; p=0,009), höhere Schulbildung (114 vs. 107; p=0,013) und fehlende Dyspareunie vs. Grad-3-Dyspareunie (116 vs. 93; p=0,012) waren signifikant mit einem höheren medianen FACT-C-Score assoziiert.

Schlussfolgerung. Die Mehrzahl der Analkarzinompatienten erreicht nach einer RCT eine akzeptable globale Lebensqualität, die jener der Normalbevölkerung entspricht. Patienten mit chronischen Grad-3-Nebenwirkungen – insbesondere Dyspareunie und Stuhlinkontinenz – haben eine schlechtere Lebensqualität als Patienten ohne chronische Nebenwirkungen. Zukünftige Strategien könnten auf eine Dosisreduktion bei den Genitalien und auf intensivere Supportivmaßnahmen abzielen, um die Langzeitlebensqualität zu verbessern.

Schlüsselwörter

Chemotherapie · Dyspareunie · Fäkale Inkontinenz · Toxizität · Überleben

ferences in median scores were also observed between grade 3 stool frequency (36 points, p=0.011), grade 3 dyspareunia (23 points, p=0.012) and stool urge (20 points, p=0.033) as compared to grade 0 of these symptoms.

There was a considerable FACT-C score-difference of 17 points between grade 3 and grade 1–2 dyspareunia, and between grade 3 and grade 1–2 stool incontinence (33 points).

The difference in the FACT-C scores of patients with higher education and those without high school degree was only 7 points, although this factor was significantly associated with QOL in the multivariate analysis (p=0.013). The median FACT-C score of patients with a follow-up time <67 months was only 4 points lower than that of patients with a follow-up time ≥67 months. However, this variable was significantly associated with QOL in the univariate- (Spearman's ρ=+0.33, p=0.031) and multivariate analyses (p=0.010) (**Tab. 3.**).

A possible correlation between recurrence or distant metastasis and QOL could not be assessed due to insufficient patient numbers; only 1 patient had distant metastasis (FACT-C score of 73) and only 2 had local recurrent disease (FACT-C scores of 116 and 126).

Tab. 1 Characteristics of the 42 patients who answered both quality of life and toxicity questionnaires

Characteristics	N=42 (100%)
Age[a](years)	
Median	64
Range	50–86
Gender	
Male	10 (24)
Female	32 (76)
Tumor site	
Anal canal	38 (90)
Anal margin	3 (7)
Overlapping	1 (2)
TNM stage	
cT1/T2	31 (74)
cT3/T4	11 (26)
cN 0	34 (81)
cN +	8 (19)
UICC stage	
I/II	35 (83)
IIIA/B	7 (17)
Grade	
G1/G2	28 (67)
G3/G4	12 (29)
Gx	2 (5)
RT dose (Gy)	
Median	54
Range	45–59.4
Chemotherapy	
5-FU/MMC	37 (89)
5-FU only	1 (2)
MMC only	1 (2)
Only RT	3 (7)
Follow-up time (months)	
Median	68
Range	9–222

G grade, *RT* radiotherapy, *MMC* mitomycin C, *5-FU* 5-fluorouracil [a]At the time of the completion of the questionnaires.

Tab. 2 Extent of supportive care in female patients correlated to chronic dyspareunia according to the Common Terminology Criteria for Adverse Events v. 4.0

	No. of patients performing supportive care				Total patients
	Not at all	Irregularly	Regularly	Not reported	
Dyspareunia Grade 0	7	2	2	1	**12**
Dyspareunia Grade 1/2	1	5	0	3	**9**
Dyspareunia Grade 3	1	3	6	3	**13**
Not reported	1	0	0	2	**3**
Total No.	**10**	**10**	**8**	**9**	**37**

Discussion

Depending on the clinical stage, 50–90% of all AC patients survive for more than 5 years. Therefore, late toxicity and long-term QOL are of importance for the clinical management of this disease. As AC is a rare disease, there are only a few studies reporting on long-term QOL—with or without correlation to late toxicity [3, 4, 5, 6, 10, 11].

Das et al. [5] evaluated the QOL and sexual function in 32 AC patients after a median follow-up of 5 years using the FACT-C and Medical Outcomes Study (MOS) sexual problems scale. They reported a median FACT-C score of 108 (47–128), which is consistent with our results (median FACT-C score 110). They observed significantly lower QOL scores in patients <51 years old and in those with a history of anxiety/depression. The authors described poor sexual functioning in their cohort of AC patients: 75% reported a lack of sexual interest as a problem; 71% of patients reported that the inability to relax and enjoy sex was a problem and 72% of patients reported that difficulty in becoming sexually aroused was a problem. Among 6 male patients in their group, 4 (67%) reported erectile dysfunction. Among 20 female patients, 14 (70%) reported problems having an orgasm.

In our series, 60% of male patients had some degree of erectile dysfunction. Interestingly, this did not significantly affect the QOL, which might be due to the small number of male patients participating in the study (n=10).

Jephcott et al. [10] were the first investigators to compare the QOL of AC survivors (n=50) with that of healthy volunteers (n=50). Useing the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-CR38 QOL questionnaires, they reported significantly higher scores for overall QOL, as well as for physical and sexual functioning scales in healthy volunteers. They observed poorer scores for AC patients vs. healthy volunteers in several symptom scales, including fatigue (36 vs. 20), nausea (6 vs. 1), diarrhea (27 vs. 5), gastrointestinal symptoms (27 vs. 9), defecation problems (20 vs. 6) and sexual problems (85 vs. 19 in male patients; 51 vs. 21 in female patients). However, only in areas of sexual enjoyment (a numerical difference of 24 points) and sexual problems did the differences reach "very much changed" levels.

In line with the studies of Jephcott et al. and Das et al., about one third of female patients in our group suffered from grade 3 vaginal symptoms and/or dyspareunia, which negatively affected QOL. It is of note that about two thirds of the female patients in our group reported some degree of vaginal symptoms and dyspareunia.

Although several reports of vaginal symptoms and dyspareunia after pelvic RT for gynecological cancers indicate a prevalence of 2–60% [12, 13, 14, 15, 16], female sexual morbidity remains a neglected aspect of routine follow-up and cancer survival. White et al. [17] reported that during follow-up after pelvic RT, physical toxicity assessment was focused mainly on bowel (81%) and bladder (70%) symptoms, whereas vaginal toxicity and sexual issues were explored in only 42% and 25% of consultations, respectively. Many female patients have difficulty talking about their sexual complaints and asking about solutions or treatment options. In our group, 7 female patients did not initially want to answer the questions regarding vaginal symptoms and dyspareunia, until a senior female colleague asked them to talk about these issues in a separate session. Of these 7 patients, 5 had some degree of dyspareunia and found it embarrassing to talk about or report on this issue, despite the anonymous nature of the questionnaire.

Vaginal symptoms such as dryness, itching and bleeding, as well as sexual morbidity most likely result from late radiation damage. The incidence and sever-

Tab. 3 FACT-C scores in different subgroups of patients with univariate and multivariate analyses

Factor		No.	Median score (range)	p-value (univariate)	p-value (multivariate)
Gender	Male	10	111 (40–130)	0.626	
	Female	32	109 (61–132)		
Education	High school	17	114 (73–132)	0.047*	0.013*
	Lower	25	107 (40–130)		
Economic situation	No financial problems	20	113 (73–132)	0.057	
	Financial problems	22	107 (40–125)		
UICC Stage	I/II	35	111 (40–132)	0.280	
	IIIA/B	7	104 (86–120)		
RT dose	≤54 Gy	14	110 (74–123)	0.852	
	>54 Gy	28	110 (40–132)		
Cx administered?	No	3	111 (40–123)	0.883	
	Yes	39	109 (61–132)		
CAE grade 3 present?	No	26	115 (83–132)	0.001*	0.001*
	Yes	16	94 (40–123)		
Stool incontinence	0	16	111 (73–130)	0.009*	0.009*
	G1–2	19	107 (73–132)		
	G3	5	74 (40–114)		
Stool frequency	0	19	116 (73–132)	0.011*	
	G1–2	19	108 (40–123)		
	G3	4	80 (61–96)		
Stool urge	0	11	115 (73–132)	0.033*	
	G1–2	19	108 (61–130)		
	G3	10	95 (40–120)		
Urinary incontinence	0	28	111(61–132)	0.204	
	G1	12	110 (73–126)		
	G2	2	68 (40–96)		
Dyspareunia	0	12	116 (85–132)	0.021*	0.012*
	G1–2	8	110 (106–120)		
	G3	11	93 (61–123)		
	No comment	1	116 (101–116)		
Erectile dysfunction[a]	0	3	111 (107–126)	0.928	
	G1	3	111 (83–130)		
	G2	2	105 (90–120)		
	No comment	2	82 (40–123)		
Follow-up time (months)	<67	21	107 (40–132)	0.031*	0.010*
	≥67	28	111 (86–130)		

RT radiotherapy, *Cx* chemotherapy, *UICC* Union for International Cancer Control, *G* grade, *CAE* chronic adverse events *Statistically significant p-value [a]Considering the appropriate gender.

ity of these morbidities are related to dose and combined chemotherapy [6, 14, 15, 16]. A few studies have demonstrated that intensity-modulated radiation therapy (IMRT) can reduce radiation dose to the genitalia in patients with AC [18, 19, 20, 21]. Nevertheless, additional dosimetric and clinical studies are required to assess whether sophisticated RT techniques and modalities such as tomotherapy and positron-emission tomography/computed tomography (PET-CT) for radiation planning [22, 23, 24, 25]; or simple supportive positioning instruments such as intravaginal cuffs or cylinders, could allow a reduction in the dose delivered to (parts of) the internal and/or external genitalia, and whether this has any impact on the incidence of CAE and QOL in AC patients.

Another important undefined issue concerns supportive care to prevent sexual morbidity and the appropriate treatment options. The efficacy of conventional supportive care comprising vaginal baths, vaginal creams and vaginal expander sets has been the topic of controversial discussion in the literature [14, 15, 26, 27]. While these measures might help in a subgroup of patients, they seem to be insufficient to prevent or treat vaginal symptoms for a considerable portion of patients—including 14 (out of 37) female patients in our group (**Tab. 2**) who applied the supportive care at least partially. There are a few reports about other types of supportive care and treatment options to prevent late toxicity, such as hyperbaric oxygen therapy [28, 29]. However, their role in improvement of gynecologic symptoms is still uncertain. Future studies are needed to investigate the role of supportive care (more intensive or/and new agents) during and after RCT.

In a recently published study, Welzel et al. [6] reported that the global health QOL in AC patients was comparable to that of previously published reference data from the (age-adjusted) general German population [30]. They assessed QOL using QLQ-C30 and QLQ-CR38 and CAE according to the late effects in normal tissues subjective, objective, management, and analytic (LENT/SOMA) scale in 52 patients (37 female and 15 male) with a median follow-up interval of 36 months (range 5–137 months). AC patients had a

Tab. 4 Correlation between the CAE associated with lower QOL in the multivariate analysis with the subscales of FACT-C. Presentation of significant p-values as determined using Mann–Whitney U and Kruskal–Wallis tests

Factor	PWB	SWB	EWB	FWB	CCS
CAE grade 3	**0.004**	0.054	**0.007**	**0.001**	**0.001**
Stool incontinence	0.211	0.728	0.122	0.119	**0.001**
Dyspareunia	0.057	**0.040**	0.143	**0.016**	0.103

CAE chronic adverse events, *QOL* quality of life, *PWB* physical well-being, *SWB* social well-being, *EWB* emotional well-being, *FWB* functional well-being, *CCS* colorectal cancer subscale[a]Considering the appropriate gender.

clinically and statistically significant impaired cancer-specific QOL on all functioning scales. They described problems relating to cancer-specific psychosocial QOL, fatigue, insomnia, urological/gastrointestinal complaints and impairment of sexual function as the five main concerns in their series. Using the LENT/SOMA scale, these authors report a grade 3 stool incontinence level of only 6%, which is much lower than in our series. Additionally, Welzel et al. reported a significant correlation between gastrointestinal toxicity and QOL, which is consistent with our results. In their series, tumor stage, tumor location, a RT dose >50.4 Gy, time since RT, surgical treatment, male gender, physically inactivity, gastrointestinal toxicity and sphincter insufficiency were independent risk factors for poor QOL.

Welzel et al. were the first to report on the correlation between demographic and socioeconomic characteristics and QOL in AC patients. In their series, marital status significantly influenced female sexual function and employment status was significantly associated with emotional functioning, social functioning, sexual enjoyment and gastrointestinal symptoms in the univariate analysis. In our group of patients, high school graduation or a higher level of education was significantly associated with a better QOL in the multivariate analysis, but marital- and employment status had no impact on QOL (data not shown).

In one of the first reported series on QOL in AC patients, Vordermark et al. [3] evaluated the late gastrointestinal sequelae of RCT and QOL (instrument: Gastrointestinal Quality of Life Index, GIQOL [31]) in 22 colostomy-free survivors after a median follow-up time of 3 years. They performed anorectal manometry in 16 of the 22 patients and reported a complete continence rate of 56% (9 out of 16 patients). The median GIQOL values in continent patients were significantly higher than in those with fecal incontinence (126 vs. 108 points on a scale of 0–144). They compared their results (n=22, 114 points) with the published results of Sailer et al. [32], who reported the GIQOL of healthy volunteers (n=150, 121 points) and patients with other benign anorectal diseases (n=325, 113 points), whereby they found QOL scores among their AC patients to be similar to those in healthy volunteers and patients with benign disease. Vordermark et al. concluded that adaptation to symptoms and satisfaction with the apparent cure of malignant disease might be the reason for this. This is in line with our results, which indicate that patients with a longer follow-up interval (and thus more time to adapt to symptoms) have slightly higher QOL scores.

In another report from the late 1990s, Allal et al. [4] evaluated QOL in 41 patients using the EORTC QLQ-C30 and QLQ-CR38 questionnaires. They reported that the QOL score was significantly affected by the severity of late complications, which is consistent with our results. However, Allal and coworkers did not observe any effect of follow-up time on QOL; they found no difference in QOL values between patients with a follow-up time of less than 10 years and more than 10 years. Similar results were reported by Provencher et al. [11]. They evaluated QOL in 30 patients before, or 5 years after completion of treatment and observed no time-related changes in global QOL score. One should note that in the study by Allal et al., all patients had a minimum follow-up time of 3 years and the cutoff interval was set to 10 years. In the study by Provencher et al., 95% of the patients who answered the questionnaires had a minimum interval of 2 years to the last day of RCT. We hypothesize that the adaptation to symptoms and improvement in QOL reported by Vordermark and the current study probably occur during the first 2 years after treatment—a period not evaluated by Allal et al. or and Provencher et al. in their series.

Using the QLQ-C30 and QLQ-CR38 questionnaires, Oehler-Jänne et al. [33] compared the QOL in 17 AC survivors who were treated with external beam radiation therapy (EBRT) + EBRT boost with that of 17 AC survivors who were treated with EBRT + brachytherapy (IBT). They observed higher QOL values for patients treated with an EBRT boost compared to an IBT boost (86 vs.72 points), although this did not reach statistical significance. Allal ET. al. [4] reported a similar tendency toward a decrease in QOL scores and increase in CAE after IBT, which also did not reach statistical significance. The lack of statistical significance is most probably due to the small number of patients in both of these studies.

Tournier-Rangeard et al. [34] conducted a short-term, longitudinal randomized controlled trial, using the QLQ-C30 questionnaire to evaluate QOL before and 2 months after RCT in 119 patients. The authors report that QOL scores 2 months after RCT were higher than those recorded before treatment in regard to global health status, emotional- and intestinal function. They also observed a significant decrease in insomnia, appetite loss and pain. Unfortunately, the long-term CAE and QOL values were not published at the time of the current study. As RCT is the main treatment modality for the management of AC, an important goal for radiation oncologists is to improve or preserve the health-related QOL in these patients. The median FACT-G score of our patients (89±17) is similar to those of published series taken from the general population in the United States (80±16), Australia (86±15) and Austria (87±15), as well as to that of patients that received RCT for a variety of other pelvic malignancies (85±13) [35, 36, 37, 38]. However, a considerable number of AC patients experi-

Tab. 5 List of the relevant items of the Common Terminology Criteria for Adverse Events v. 4.0, which were used for this study

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	–	–
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Stool urgency	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	–	–
Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	–	–
Anal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Dysuria	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	–	–
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self-care ADL	–	–
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	–	–	–
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	–	–	–
Erectile dysfunction	Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)	Decrease in erectile function (frequency/rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump)	Decrease in erectile function (frequency/rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)	–	–
Decreased libido	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	–	–	–
Vaginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function or causing frequent discomfort	Severe vaginal dryness resulting in dyspareunia or severe discomfort	–	–
Vaginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	–	–	–
Dyspareunia	Mild discomfort or pain associated with vaginal penetration; discomfort relieved with use of vaginal lubricants or estrogen	Moderate discomfort or pain associated with vaginal penetration; discomfort or pain partially relieved with use of vaginal lubricants or estrogen	Severe discomfort or pain associated with vaginal penetration; discomfort or pain unrelieved by vaginal lubricants or estrogen	–	–
Gastrointestinal disorders; other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Reproductive system and breast disorders; other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Tab. 5 List of the relevant items of the Common Terminology Criteria for Adverse Events v. 4.0, which were used for this study (Continued)

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Renal and urinary disorders; other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or non-invasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

ADL Activity of daily living.

enced late adverse effects (LAE) of RCT, which significantly affected their QOL.

The correlation between acute and late toxicity has been the topic of controversial discussion in the literature. Some studies indicate a correlation between acute- and late normal tissue injury after RT in the pelvic region [39, 40], whereas others report no-, or only a weak correlation between the incidence and severity of acute- and late reactions [41, 42].

In our series we could not observe any correlation between acute and late toxicity.

Our series had a number of limitations. Firstly, it was a retrospective analysis of a small group of patients, thus the uni- and multivariate analyses have to be interpreted cautiously—they allow for general conclusions, but specific ones might be elusive. Secondly, we did not provide a dose–volume histogram for the organs at risk. Thus it was not possible to examine any potential correlations between the dosimetric parameters of the normal organs and the occurrence/severity of CAE or QOL. Similarly, patients' hormonal statuses were not available to examine if an imbalance exists due to RT in the pelvic region.

However, this study indicates a correlation between CAE and QOL and highlights the necessity of further efforts to prevent CAE. Some patients are ashamed to talk about their genital/sexual CAE (about 20% of women in our study). The respective physician has to gain a patients' confidence, such that they start to talk about their sequelae and accept help in the form of the presently available supportive care.

Conclusion

The majority of AC patients have acceptable overall QOL scores that are comparable to those of the normal population. However, in a considerable number of these patients, long-term grade 3 CAE—particularly dyspareunia and fecal incontinence—were associated with impaired QOL. In order to improve long-term QOL, future strategies might aim at reducing the dose to the genitalia and intensifying supportive care.

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