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ORIGINAL ARTICLE

Improved treatment outcome and lower skin toxicity with intensity-modulated radiotherapy vs. 3D conventional radiotherapy in anal cancer

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Abstract

Purpose Radiochemotherapy is the standard treatment for anal carcinoma (ACa). Intensity-modulated radiotherapy (IMRT) has been introduced, allowing focused irradiation of the tumor area. Whether physical benefits of IMRT translate to clinical benefits has not been sufficiently demonstrated.

Methods We retrospectively reviewed data from 82 patients with newly diagnosed ACa. Patients treated with IMRT were compared with previous patients treated with conventional three-dimensional computational radiotherapy (3D-CRT). The influence of IMRT on complete remission and acute and chronic side effects was analyzed in univariate and multivariate analyses.

Results 39/40 patients treated with IMRT were in complete remission after 1 year compared to 31/39 patients treated with 3D-CRT ($p = 0.014$). Multivariate analysis confirmed tumor T stage as well as lack of IMRT treatment as risk factors for persistent tumor at 6 months. No significant benefits of IMRT were apparent at later timepoints (median follow up 52 months, IQR: 31.5–71.8 months). Patients treated with IMRT had a significantly lower degree of skin toxicity (median 2 vs. 3 in a scale ranging from 0 to 3, $p = 0.00092$). Rates of hematological toxicity/proctitis were not reduced and rates of acute diarrhea increased ($p = 0.034$). Median length of hospitalization tended to be shorter in patients treated with IMRT (n. s.).

Conclusion We present a real-world experience of shifting radiation technique from conventional 3D-CRT to IMRT. IMRT patients had better tumor control at 1 year and lower degrees of skin toxicity. Our data indicate that IMRT can enable therapies with lower side effects with equal or better oncological results for patients with ACa.

Keywords Anal carcinoma · IMRT · Side effects · Legth of hospitalization · Radiotherapy

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Verbessertes Behandlungsergebnis und geringere Hauttoxizität mit der intensitätsmodulierten Strahlentherapie im Vergleich zur dreidimensionalen konventionellen Strahlentherapie beim Analkarzinom

Zusammenfassung

Hintergrund Die definitive Radiochemotherapie stellt den Goldstandard für die Therapie des Analkarzinoms (ACa) dar. Die in den letzten Jahren eingeführte intensitätsmodulierte Strahlentherapie (IMRT) erlaubt eine fokussierte Bestrahlung des Tumorgebiets unter Schonung der umliegenden Strukturen. Ob diese Vorteile auch einen klinischen Benefit bringen, wurde bis jetzt nur ungenügend untersucht.

Methodik Es erfolgte eine retrospektive Analyse von 82 Patienten mit der Neudiagnose eines ACa, mit einem Vergleich zwischen Patienten, die mit IMRT versus mit der traditionell durchgeführten 3D-konformalen Radiotherapie (3D-CRT) behandelt wurden. Es wurde der Einfluss der IMRT auf das Erreichen einer klinischen Remission sowie auf Rezidivrate und Nebenwirkungen untersucht.

Ergebnisse Die Remissionsrate 1 Jahr nach Ende der Bestrahlung der Patienten lag in der IMRT-Gruppe bei 97,5 % (39/40) vs. 79,5 % (31/39) in der 3D-CRT-Gruppe ($p = 0{,}014$). Die multivariate Analyse bestätigte das T-Stadium als auch die 3D-CRT-Therapie als Risikofaktor für Tumorpersistenz nach 6 Monaten. Weitere Effekte der IMRT-Therapie bei späteren Zeitpunkten wurden nicht beobachtet (medianer Follow-up 52 Monate; IQR 31,5–71,8 Monate). Patienten unter IMRT hatten signifikant weniger schwere Hauttoxizität (median 2 vs. 3 in einer Skala von 0–3; $p = 0{,}00092$). Hämatologische Toxizität/Proktitis waren vergleichbar, akute Diarrhoe trat bei IMRT-Patienten häufiger auf ($p = 0{,}034$). Die mediane Hospitalisierungsdauer war bei IMRT-Patienten tendenziell verkürzt (ohne statistische Signifikanz).

Schlussfolgerung Wir präsentieren „Real-world"-Daten des Übergangs der RT von der 3D-CRT- zur IMRT-Technik. Die IMRT-Patienten hatten eine höhere Remissionsrate nach 6 Monaten und eine niedrigere Rate für Hauttoxizitäten. Die IMRT-Therapie führt beim ACa zu insgesamt weniger Nebenwirkungen bei mindestens gleichwertigem oder sogar besserem onkologischem Outcome.

Schlüsselwörter Analkarzinom · IMRT · Nebenwirkungen · Hospitalisierungsdauer · Strahlentherapie

Abbreviations

3D-CRT	Three-dimensional computational radiotherapy
5-FU	5-Fluorouracil
ACa	Anal carcinoma
CI	Confidence interval
CR	Complete response
CT	Computed tomography
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
IMRT	Intensity-modulated radiotherapy
MMC	Mitomycin
MRI	Magnetic resonance imaging
OR	Odds ratio
RTOG	Radiation Therapy Oncology Group
SIB	Simultaneous integrated boost

Highlights

- We provide a real-world experience of radiotherapy shifting from 3D conventional radiotherapy to intensity-modulated radiotherapy (IMRT)
- In this retrospective study, patients treated with IMRT for anal carcinoma had a lower risk of persistent tumor at 1 year after therapy compared to patients treated with 3D-CRT
- Patients on IMRT also had lower skin toxicity compared to patients on 3D-CRT

Introduction

Anal carcinoma (ACa) is an uncommon gastrointestinal malignancy with an incidence of 2 per 100,000 per year [1]. Therapeutic options for anal carcinoma have improved tremendously during recent decades [2]. Historically, treatment was limited to surgery, i.e., abdominoperineal rectal excision. In the 1970s, Nigro and colleagues demonstrated the efficacy of combined radiochemotherapy [3], offering the possibility of cure with an excellent functional outcome without the necessity of a permanent colostomy. Since then, surgery has been reserved for cases with persistent or recurrent disease. Radiochemotherapy as standard of care was confirmed by additional randomized controlled trials, with radiochemotherapy being superior to radiotherapy alone [4–9].

Radiation of the anal region is challenging due to its proximity to dose-sensitive structures such as skin/genitalia, bladder, rectum, small bowel, bone (pelvis and femoral head), and bone marrow. The selectivity of radiation techniques has improved tremendously during recent decades, first by replacement of 2D planning by 3D CT-guided radiochemotherapy techniques [10, 11]. Later on, intensity-modulated radiotherapy (IMRT) was developed for treatment of cancer of the head and neck region as well as prostate cancer [12–14]. More recently, IMRT has been introduced for anal cancer [15–17]. IMRT allows reduction of radiation dose to adjacent organs, thereby potentially limiting toxicity and allowing application of higher doses within a shorter overall treatment time [2, 18]. However, to the best of our knowledge, there has been no randomized trial comparing conformal 3D radiotherapy with the new IMRT technique and the potential benefits of IMRT have been insufficiently documented. Our aim was therefore to compare IMRT and conventional 3D CT-guided radiation in terms of efficacy and acute and chronic side effects in a retrospective single-center study.

Patients and methods

We performed a retrospective analysis of all patients referred to Triemli Hospital, a tertiary care center and teaching hospital in Zürich, Switzerland, from 1999 until 2013 for treatment of anal carcinoma. Patients were identified by an automated search within the internal clinical information system. Histological prove of anal carcinoma was a requirement for inclusion and all patients with rectal carcinoma were excluded. Patients treated with palliative intent and patients treated for recurrent ACa were excluded from the analysis. The study protocol was approved by the local ethics committee of Zurich county (registration KEK-ZH 2010-0555) and the requirement for informed consent from individual patients was waived by the local ethics committee. The study was performed according to the Declaration of Helsinki.

Treatment of anal carcinoma consisted of radiotherapy over a course of 28 days, either conventionally planned (three-dimensional conformal radiotherapy, 3D-CRT; 1999–2008), or as intensity-modulated radiation therapy (IMRT; 2008–2013). 3D-CRT followed a sequential regimen with 25 fractions of 1.8 Gy to a total dose of 45 Gy to the primary tumor with regional lymph nodes plus a boost of 5 fractions of 1.8 Gy to a total dose of 9 Gy, directed at the primary tumor. IMRT used a sliding window technique or dynamic arc (RapidARC®, Varian Medical Systems, Palo Alto, CA, USA). Thereby, a dose of 1.86 Gy (simultaneous integrated boost, SIB) was applied to the primary tumor and affected lymph nodes to a total dose of 55.8 Gy. The elected lymph drainage region (inguinal and pelvic lymph nodes) was treated with 30 fractions of 1.5 Gy to a total dose of 45 Gy.

Furthermore, patients received 5-fluoruracil (5-FU) using a dose of 1000 mg/m^2 per day on days 1–4 (week 1) and days 29–32 (week 5) as a continuous 24-hour intravenous infusion, and a dose of 10 mg/m^2 of mitomycin as an intravenous bolus at day 1 and 29 (maximum single dose 20 mg).

Data collection and definitions

Our cohort of ACa patients has been described previously [19, 20]. Patient demographics, oncological parameters, details of radiation and chemotherapy as well as outcome parameters were extracted from patient files. Tumor classification followed the seventh edition of the American joint Committee on Cancer TNM staging [21].

After end of therapy, patients were clinically assessed after 3, 6, and 12 months, then every 6 months up to 3 years, then yearly until death or loss to follow-up. Complete response (CR) was defined as lack of evidence of any residual disease in all investigations including history, clinical examination, imaging, and endoscopy at 6 months after the end of therapy. For some patients, suspicious residual lesions remained at 6 months; however, for all these individuals, follow-up at 12 months confirmed complete response and the response rates at 6 and 12 months were identical.

One patient died during radiochemotherapy due to sepsis, and in one patient, metastases were detected immediately after therapy; these two patients were included in the analysis and counted as treatment failures. For 3 patients in the 3D-CRT group, no follow-up information was available. These patients were included into the analysis of acute side effects but were excluded from the analysis of oncological outcome. Therefore, 82 patients were available for the analysis of side effects but only 79 for the follow-up analysis.

Regarding time, the date of diagnosis (histology) was used as a reference: the date was expressed as days after January 1, 2000. For age, the age at the day of diagnosis was used. Radiation side effects were classified using toxicity criteria of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 [22]. Chronic ulceration or fistulae were detected by rectosigmoidoscopy or inspection. Proctitis was defined as an inflammation of the rectum at proctoscopy or sigmoidoscopy. For chronic anal pain, sexual dysfunction, diarrhea, and incontinence, reported patient complaints were used but not standardized questioning was performed. Comorbidities were defined as relevant medical conditions requiring ongoing management including congestive heart failure, HIV infection, COPD, diabetes, or history of neoplasia.

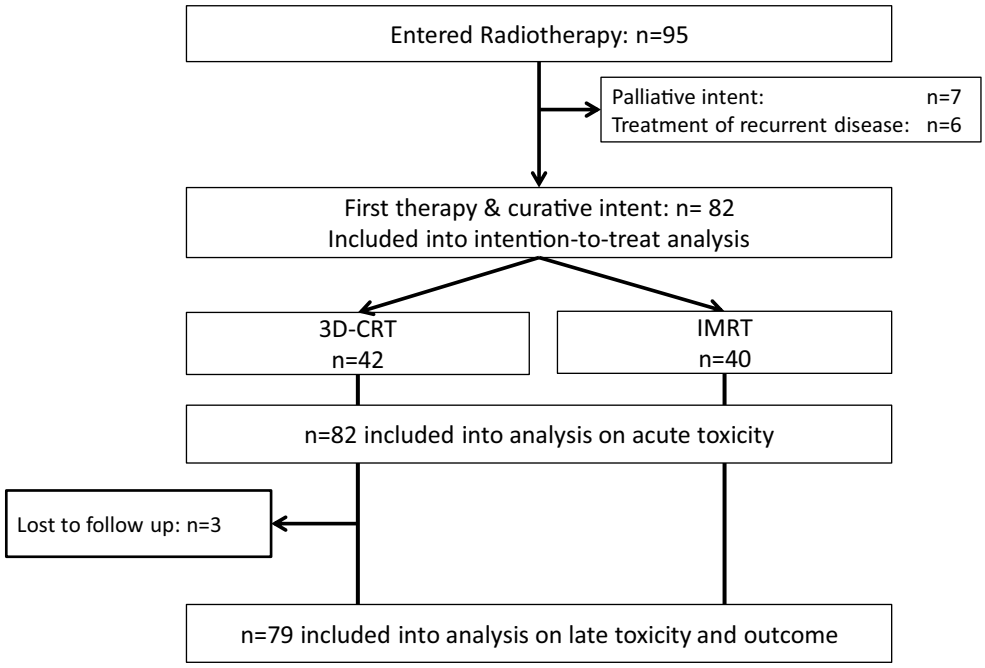

Fig. 1 Flowchart of our study. *3D-CRT* three-dimensional computational radiotherapy, *IMRT* intensity-modulated radiotherapy

Data analysis

To calculate differential effect of radiation techniques, patients treated with IMRT were compared to patients treated with 3D-CRT. For comparisons, the Fisher exact test or the non-parametric Mann–Whitney U test was used. Calculations were performed using Prism (Graphpad, San Diego, CA, USA) version 6.0.

For the multivariate analysis, data were imported into a table in MatLab (version R2017b; MathWorks, Natick, MA, USA). A generalized linear model (GLM) was calculated using the MatLab stepwiseglm function for stepwise optimization of the model. For the calculation predicting the outcome (CR at 6 months or the end of study) as well as acute side effects (diarrhea, proctitis, erythema/skin toxicity, hematological toxicity), we controlled for age, time (first day of treatment), gender, TNM T stage (T1–T4), TNM stage (stage I–IV), radiation dosage, IMRT (yes/no), comorbidities (yes/no), mitomycin treatment (yes/no), and 5-FU treatment (yes/no). Since results for skin toxicity passed the D'Agostino & Pearson omnibus normality test, a normal distribution was assumed. For the prediction of binary variables, a binomial distribution was assumed. A Cox proportional hazard model was calculated using the MatLab coxphit function, controlling for the same confounders as for the generalized linear model.

Literature research

A literature search was performed on January 29, 2018 in PubMed, using the search terms ("anal cancer" OR "anal carcinoma") AND "IMRT." We also performed a Google search using the search terms "anal cancer" AND "IMRT," checking the first 50 results. All publications comparing 3D-CRT with IMRT in either an observational or interventional setting with data on oncological outcome (overall survival, progression-free survival, and/or locoregional tumor control) and/or side effects (general, gastrointestinal, or skin toxicity) were included. No restrictions regarding date of publication or language were applied. Our PubMed search revealed 151 publications, of which 8 publications fulfilled all inclusion criteria [23–30], plus one additional publication via the Google search [31]. One further publication was identified by screening the reference list of identified publications [17]. Heterogeneity of the study design and outcomes reported precluded a formal meta-analysis.

Results

We identified 95 anal carcinoma patients; 6 patients were excluded due to recurrent anal cancer and 7 due to palliative-intent treatment, leaving 82 patients for further analysis (Fig. 1). Histological proof of anal carcinoma was available in all patients. Demographic data, tumor staging, and key parameters of oncological therapy are presented in Table 1. 42 patients were treated with 3D-CRT (years 1999–2008), 40 patients with IMRT (years 2008–2013). Patients from both treatment groups were of similar age, with a similar distribution of gender, T stage, TNM stage, and burden of comorbidities. We noted a trend for higher usage of PET-CT for staging in the IMRT group before therapy (3/42,

Table 1 Epidemiological characteristics of our cohort of ACa patients. Statistical analysis: Fisher's exact test, chi-square test, or Mann–Whitney U test

Description	All patients $n=82$	IMRT $n=40$	3D-CRT $n=42$	Comparison
Male n (%)	29 (35.4%)	11 (27.5%)	18 (42.9%)	$P=0.17$
Female n (%)	53 (64.6%)	29 (72.5%)	24 (57.1%)	
Age median (IQR) *range*	64 (53–71) years 32–88 years	62 (52.5–71) years 32–86 years	66 (54–71) years 40–88 years	$P=0.55$
BMI median (IQR) *range*	24.2 (21.3–28.1) kg/m^2 17.7–34.8 kg/m^2	24.2 (21–28.3) kg/m^2 17.7–34.8 kg/m^2	24.4 (21.6–28) kg/m^2 18.8–34.8 kg/m^2	$P=0.61$
Comorbidities	Yes: 27 (33%)	Yes: 14 (35%)	Yes: 13 (31%)	$P=0.82$
HIV status (positive)	7 (8.5%)	5 (12.5%)	2 (4.7%)	$P=0.31$
T Stage n (%)	T1: 8 (9.8%)	T1: 2 (5%)	T1: 6 (14.3%)	$P=0.21$
	T2: 34 (41.5%)	T2: 18 (45%)	T2: 16 (38.1%)	
	T3: 21 (25.6%)	T3: 14 (35%)	T3: 7 (16.7%)	
	T4: 19 (23.2%)	T4: 6 (15%)	T4: 13 (31%)	
N stage n (%)	N0: 39 (48%)	N0: 16 (40%)	N0: 22 (55%)	$P=0.55$
	N1: 27 (33%)	N1: 14 (35%)	N1: 13 (31%)	
	N2: 7 (9%)	N2: 4 (10%)	N2: 3 (7%)	
	N3: 9 (11%)	N3: 6 (15%)	N3: 3 (7%)	
TNM stage n (%)	Stage I: 8 (9.8%)	Stage I: 2 (5%)	Stage I: 6 (14.3%)	$P=0.21$
	Stage II: 27 (32.9%)	Stage II: 13 (32.5%)	Stage II: 14 (33.3%)	
	Stage III: 45 (54.9%)	Stage III: 23 (57.5%)	Stage III: 22 (52.4%)	
	Stage IV: 1 (1.2%)	Stage IV: 1 (2.5%)	Stage IV: 0 (0%)	
Radiation dosage *Median (IQR); range*	55.8 (55.8–55.8) Gy (32.4–60 Gy)	55.8 (55.8–55.8) Gy; (55.8–59.4 Gy)	55.8 (54–55.8) Gy; 32.4–60 Gy	$P=0.01$
5-FU treated	67 (81.7%)	38 (95%)	29 (69%)	$P=0.0033$
5-FU, full dosage	51 (76.1%)	34 (89.5%)	17 (58.6%)	$P=0.0044$
5-FU, dose adjusted	16 (23.9%)	4 (10.5%)	12 (41.4%)	
Mitomycin treated	65 (79.3%)	38 (95%)	27 (64.3%)	$P=0.0075$
Full dosage	49 (0.8%)	28 (73.7%)	21 (77.8%)	$P=0.78$
Dose adjusted	16 (19.5%)	10 (26.3%)	6 (22.2%)	
Length of follow-up	52 months	59 months	43.5 months	$P=0.11$
Median (IQR)	(31.5–71.8)	(34–72)	(18–63.5)	
Range	0–189	19–108	0–189	

IQR interquartile range, *BMI* body mass index, *5-FU* 5-Fluoro-uracil

7.1% for 3D-CRT vs. 6/40, 15% for IMRT, n. s.). Overall, the dosage of radiation was significantly higher upon IMRT treatment ($p=0.01$, Table 1). In the 3D-CRT group, radiation was terminated early in three patients at 32.4, 34, and 40 Gy, respectively, due to severe side effects. Similarly, 5-FU was applied in a higher fraction of individuals receiving IMRT (3D-CRT: 81.7% vs. 95% with IMRT, $p=0.0033$) and the 5-FU dose was adjusted in a lower fraction of patients (10.5% vs. 41.4%, $p=0.0044$). Furthermore, mitomycin was used in more patients with IMRT (3D-CRT: 64.3% vs. 95% with IMRT, $p=0.0075$).

Efficacy of treatment

Overall, 1 year after the end of treatment, complete response (CR) with survival without evidence of residual tumor was reported in 70/79 patients (88.6%; Supplementary Figure S1; Table 2). CR rates were higher in patients receiving IMRT compared to patients with 3D-CRT (79.5% with 3D-CRT vs. 97.5% with IMRT, $p=0.014$). In a multivariate regression analysis, only T stage of the tumor and IMRT treatment were significantly associated with CR at 1 year; other potential confounders such as age, time of treatment, gender, tumor TNM stage, comorbidities, radiation dosage, SIB, VMAT (volumetric-modulated arc therapy), 5-FU, and mitomycin treatment were not significantly associated with CR (Table 3).

At the end of follow-up, 81% of patients were free of detectable disease. A trend toward a better oncological outcome in patients treated with IMRT remains, but CR rates did not differ significantly between 3D-CRT and IMRT (3D-CRT: 29/39 (74.4%) vs. 35/40 (87.5%) with IMRT). In

Table 2 Treatment results and side effects of treatment. Statistical analysis: Fisher's exact test, chi-square test, or Mann–Whitney U test. Radiation side effects were classified using toxicity criteria of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 40 [22]

Description	All patients	IMRT	3D-CRT	Comparison
Complete response at 6 months	70/79 (88.6%)	39/40 (97.5%)	31/39 (79.5%)	$P=0.014$
Complete response at end of follow-up	64/79 (81%)	35/40 (87.5%)	29/39 (74.4%)	$P=0.16$
Acute side effects of treatment				
Acute diarrhea ≥grade 2	56/82 (68.3%)	32/40 (80%)	24/42 (57.1%)	$P=0.034$
Hematological toxicity	14/82 (17.1%)	10/40 (25%)	4/42 (9.5%)	$P=0.081$
Proctitis ≥grade 2	14/81 (17.3%)	9/39 (23.1%)	5/42 (11.9%)	$P=0.24$
Skin toxicity	2.5 (2–3), 0–3	2 (2–3), 0.5–3	3 (2–3), 0–3	$P=0.00092$
Days of hospitalization	10.5 (10–31), 0–84	10 (10–14.5) 0–58	17.5 (10–36), 0–84	$P=0.11$
Chronic side effects of treatment				
Chronic proctitis ≥grade 2	10/72 (13.9%)	4/39 (10.3%)	6/33 (18.2%)	$P=0.50$
Chronic anal pain	14/71 (19.7%)	8/39 (20.5%)	6/32 (18.8%)	$P=1$
Ulcerations	8/69 (11.6%)	4/39 (10.3%)	4/30 (13.3%)	$P=0.72$
Chronic diarrhea ≥grade 2	13/72 (18.1%)	5/39 (12.8%)	8/33 (24.2%)	$P=0.23$
Incontinence	19/72 (26.4%)	11/39 (28.2%)	8/33 (24.4%)	$P=0.79$
Fistula	5/72 (6.9%)	2/39 (5.1%)	3/33 (9.1%)	$P=0.66$
Sexual dysfunction	13/46 (28.3%)	5/26 (19.2%)	8/20 (40%)	$P=0.19$
Males	8/16 (50%)	2/7 (28.6%)	6/9 (66.7%)	$P=0.31$
Females	5/30 (16.7%)	3/19 (15.8%)	2/11 (18.2%)	$P=1$
Pelvic fractures	7/71 (9.9%)	4/39 (10.3%)	3/32 (9.4%)	$P=1$

IMRT intensity-modulated radiotherapy, *3D-CRT* three-dimensional computational radiotherapy

Table 3 Prediction of complete response (CR) at 6 months as well as acute diarrhea and toxicity as multivariate analysis

Prediction of CR at 6 months (n = 79, p = 0.0013)			
Local staging (TNM-T)	OR: 0.37	95% CI: 0.15–0.89	$p=0.027$
IMRT treatment	OR: 9	95% CI: 1.04–78	$p=0.049$
Prediction of acute diarrhea (n = 82, p = 0.0014)			
Tumor size	OR: 0.78	95% CI: 0.63–0.97	$p=0.0165$
IMRT treatment	OR: 5	95% CI: 1.67–15	$p=0.0041$
Radiation dosage	OR: 0.77	95% CI: 0.59–1.02	$p=0.069$
Prediction of degree of skin toxicity (n = 82, p = 0.0011)			
Local staging (TNM-T)	Slope: 0.18	95% CI: 0.02–0.33	$p=0.026$
IMRT treatment	Slope: –0.45	95% CI: –0.74—0.16	$p=0.003$

Multivariate analysis with parameter elimination with the initial parameters age, date of treatment, gender, tumor TNM stage, T stage, tumor size, comorbidities, radiation dosage, IMRT, SIB (simultaneous intergrated boost), VMAT (volumetric-modulated arc therapy), 5-FU, and mitomycin treatment. For all predictions, the number of eligible patients, the p-value of the model as well as the estimate and p-value for each predictor are indicated. For prediction of CR and acute diarrhea, an odds ratio (OR) is provided. For prediction of the degree of skin toxicity (0–3), a slope estimate is given (reading example: according to our model, IMRT decreases the degree of skin toxicity by 0.45 [95%-CI: 0.16–0.74]
IMRT intensity-modulated radiotherapy, *OR* odds ratio, *CI* confidence interval

a Cox proportional hazards analysis, only male gender (HR 1.7, $p=0.045$) and T stage of the tumor (HR 1.5, $p=0.02$) were significantly associated with an unfavorable oncological outcome (persistent disease or recurrence); IMRT was not significantly associated with the oncological outcome in our survival analysis (Table 4). If the analysis was restricted to recurrences, no predictors could be detected.

After complete response at 1 year, 6 recurrences of ACa were observed (2 after 3D-CRT and 4 after IMRT). Recurrences were mainly observed at distant sites (2/2 after 3D-CRT, 3/4 after IMRT) in the liver, brain, small intestine, and lung. Only in a single case (after IMRT) was tumor growth in the anal canal and inguinal lymph nodes observed [19].

Acute side effects of treatment

Relevant side effects were reported by the majority of patients. Overall, diarrhea ≥grade 2 was reported for 68% of patients. Rates of diarrhea were higher for IMRT treatment (Supplementary Figure S2A) and IMRT was associated

Table 4 Prediction of complete response at the end of the study. For a time-dependent analysis, a Cox proportional hazards model was calculated and the hazard ratio with the respective confidence interval and the *p*-value is provided

Complete response at end of follow-up ($n=79$)			
	Hazard ratio	95% confidence interval	*p*-value
IMRT	1.04	0.59–1.84	0.89
Age (per year)	1.02	1–1.05	0.062
Male gender	1.73	1.01–2.95	0.045
TNM stage	1.13	0.71–1.78	0.61
TNM T stage	1.51	1.06–2.15	0.021
Comorbidities (yes/no)	1.41	0.81–2.46	0.23
Radiation dosage	1.04	0.87–1.25	0.64
5-FU chemotherapy	15.8	0.23–1075	0.2
Mitomycin treatment	0.05	0.00068–4.17	0.19

IMRT Intensity modulated radiotherapy, *5-FU* 5-Fluoro-uracil

with a risk for diarrhea in multivariate analysis ($p=0.0041$, Table 3). Hematological toxicity was noted in 25% of patients after IMRT and 10% after 3D-CRT (n. s.). 23 and 12% of patients described proctitis after IMRT and 3D-CRT, respectively (n. s.).

Almost all patients described at least some degree of skin affection (erythema or erosions), but significantly lower degrees of skin toxicity were reported for IMRT treatment (Supplementary Figure S2D, $p<0.001$). A multivariate analysis confirmed protective effects of IMRT treatment for more skin toxicity ($p=0.00092$, Table 3).

Length of hospitalization

Radiochemotherapy was performed as an in-patient procedure for most patients (70/80, 77%; rates for in-patient treatment: 87.5% with IMRT, 65% with 3D-RCT, not significant). The number of days spent in the hospital for in-patients tended to be shorter for IMRT treatment (median 10 days vs. 17.5 days, Supplementary Figure S2C); however, this difference did not yield statistical significance. Furthermore, in a multivariate analysis, IMRT treatment was not significantly associated with the length of hospitalization (not shown).

Long-term effects of treatment

Median follow-up time was 52 months (IQR 31.5–71.8, range 0–189). Several chronic problems including proctitis (14%), anal pain (18%), anal ulcerations (12%), intermittent chronic diarrhea (18%), some degree of incontinence (26%), and fistulae (7%) were noted (Table 2, Supplementary Figure S3). Several patients also reported some degree of sexual dysfunction (28%) and pelvic fractures (9%). The rates of these side effects did not differ significantly between IMRT and 3D-CRT, and no multivariate regression analysis was performed.

Systematic literature search

Our systematic literature search for studies comparing effects and side effects of 3D-CRT and IMRT revealed 10 publications (Table 5; [17, 23–31]). Nearly all studies reported reduced acute toxicity for IMRT compared to 3D-CRT, even though not all studies reported significant results. Likely due to reduced toxicity, treatment breaks were less frequent with IMRT. In most studies, overall survival, progression-free survival, and locoregional tumor control were identical or highly similar between the two radiation techniques. However, one seminal study reported significantly better oncological outcomes for IMRT [23].

Discussion

In this study, we provide a comprehensive description of success rates and short- and long-term time side effects of radiochemotherapy of anal carcinoma with IMRT vs. standard radiation therapy. We report better tumor control, less skin toxicity, and a trend toward shorter hospitalization in patients treated with IMRT.

Strikingly, skin toxicity was significantly reduced upon IMRT treatment and this difference remained robust in a univariate and a multivariate analysis. Skin toxicity upon IMRT was reported in our study and in seven previous studies comparing IMRT with 3D-CRT (Table 5; [17, 23–29]). Reduction of skin toxicity (defined as ≥grade 2 or 3) was significant in three studies [17, 24, 28], with a clear trend towards lower skin toxicity in IMRT in four of the other publications. Of studies with beneficial effects, the study by Kachnic et al. is the largest and most detailed, comparing prospective data from the RTOG-0529 trial with IMRT to historical 3D-CRT data of the RTOG-9811 trial [17].

Reduced skin toxicity is likely due to better focusing of radiation, avoiding the integument. In our study, reduced skin toxicity appears remarkable in light of the more aggressive treatment performed in the IMRT group: radiation dosage was increased, along with a higher fraction of individuals receiving 5-FU and mitomycin treatment, and a lower fraction of individuals with a 5-FU dose reduction. Since skin affections frequently limit radiation treatment, IMRT might have enabled more aggressive treatment in some patients.

However, not all side effects of radiation treatment were superior in the IMRT group. We noted a significantly increased rate of diarrhea upon IMRT treatment, observed in univariate and multivariate analyses, which is not entirely clear. One possible explanation could be a different dis-

Table 5 Overview of studies comparing outcomes and side effects of IMRT vs. 3D CRT

Author	Year	Number of patients	Follow-up (months)	Overall survival	Locoregional control	Progression-free survival	Treatment breaks, *n* (%)	Non-hematological toxicity	GI-toxicity	Skin toxicity	Toxicity criteria
Bazan et al. [23]	2011	$n=45$ CRT: 17 IMRT: 29	Overall: 58 CRT: 26 IMRT: 32	3 years: CRT: 52% IMRT: 88% $p<0.01$	3 years: CRT: 57% IMRT: 92% $p<0.01$	3 years: CRT: 57% IMRT: 85% $p<0.01$	CRT: 15 (88%) IMRT: 10 (34%) $p<0.0001$	Grade ≥3: CRT: 65% IMRT: 21% $p=0.003$	Grade ≥3: CRT: 5 (29%) IMRT: 2 (7%) p: n.a.	Grade ≥3: CRT: 7 (41%) IMRT: 6 (21%) p: n.a.	CTCAE V3.0
Dewas et al. [26]	2012	$n=51$ CRT: 27 IMRT: 24	Overall: 40 CRT: 60 IMRT: 20	2 years: CRT: 81% IMRT: 89% n. s.	2 years: CRT: 76% IMRT: 63% n. s.	n.a.	CRT 4 IMRT 5 n. s.	n.a.	Grade ≥3: CRT: 1 (%) IMRT: 5 (%) $p=0.08$	Grade ≥3: CRT: 9 (33%) IMRT:9 (38%) n. s.	CTCAE V3.0
Chuong et al. [24]	2012	$n=89$ CRT: 37 IMRT: 52	Overall: 27 CRT: 62 IMRT: 20	3 years: CRT: 83% IMRT: 91% n. s.	3 years: CRT: 92% IMRT: 91% n. s.	3 years: CRT: 73% IMRT: 82% n. s.	CRT: 11 (30%) IMRT: 4 (8%) $p<0.006$	Grade ≥3: CRT: (21%) IMRT: (60%) $p<0.0001$	Grade ≥3: CRT: 11 (30%) IMRT: 5 (10%) $p=0.06$	Grade ≥3: CRT: (64%) IMRT: (12%) $p<0.0001$	CTCAE V4.0
Dasgupta et al. [25]	2013	$n=223$ CRT: 178 IMRT: 45	Overall: 60 CRT: 73 IMRT: 28	2 years: CRT: 90% IMRT: 93% n. s.	2 years: CRT: 82% IMRT: 83% n. s.	n.a.	n.a.	n.a.	n.a.	n.a.	Information not given
Kachnic et al. [17]	2013	CRT = 341[a] IMRT = 52	n.a.	n.a.	n.a.	n.a.	CRT[a]: 62% IMRT: 49% $p=0.09$	n.a.	Grade ≥3: CRT (36%) IMRT (21%) $P<0.0082$	Grade ≥3: CRT (49%) IMRT (23%) $p<0.0001$	CTCAE version 3.0 in 0529 CTC version 2.0 in 9811
Koerber et al. [28]	2014	$n=105$ CRT: 37 IMRT: 68	Overall: 41 CRT: 98 IMRT: 31	3 years: CRT: 70% IMRT: 83% n. s.	3 years: CRT: 78 IMRT:75 n. s.	3 years CRT: 67% IMRT: 67% n. s.	n.a.	n.a.	Grade ≥2: CRT: 25 (68%) IMRT: 32 (47%) $p=0.03$	Grade ≥2: CRT: 35 (95%) IMRT: 43 (63%) $p<0.001$	CTCAE V4.0
Kemmerer et al. [31]	2016	$n=22$ CRT: 10 IMRT: 12	n.a.	n.a.	n.a.	n.a.	CRT: 11 (92%) IMRT: 5 (50%) n. s.	n.a.	n.a.	n.a.	Information not given
Fredman et al. [27]	2017	$n=165$ CRT: 104 IMRT: 61	CRT: 46 IMRT: 15	IMRT: not reached CRT: 64.2 n. s.	"No difference"	"no difference"	CRT: 41% IMRT: 28% n. s.	Less "overall toxicity" with IMRT	n.a.	Grade ≥3: CRT: (18%) IMRT: (8%) $p=0.067$	CTCAE V3.0

Table 5 (Continued)

Author	Year	Number of patients	Follow-up (months)	Overall survival	Locoregional control	Progression-free survival	Treatment breaks, *n* (%)	Non-hematological toxicity	GI-toxicity	Skin toxicity	Toxicity criteria
Pollom et al. [30]	2017	$n = 1165$ CRT: 700 IMRT: 465	Overall: 47	2 years: CRT: 80% IMRT: 80% n. s.	n.a.	n.a.	n.a.	Lower risk of hospitalization with IMRT (HR 0.70, $p < 0.002$)	n.a.	n.a.	Information not given
Muirhead et al. [29]	2017	$n = 232$ CRT: 51 IMRT: 180 Including stage IV	n.a.	n.a.	n.a.	n.a.	CRT: 4 (8%) IMRT: 7 (4%) *p*: n.a.	CRT 22 (49%) IMRT: 51 (40%) *p*: n.a.	CRT 5 (11%) IMRT: 17 (13%) *p*: n.a.	CRT: 18 (40%) IMRT: 32 (25%) *p*: n.a.	CTCAE V4.03

CRT computational radiotherapy, *HR* hazard ratio, *IMRT* intensity-modulated radiotherapy, *n.a.* not available, *n. s.* not significant
[a]The 3D-CRT data were taken from historical data from [46]

tribution of radiation in the small intestine. As shown in a simulation by Cendales et al. [32], there was less high-dose radiation to the small intestine on IMRT, whereas low-dose radiation (e.g., 30 Gy dose bath) was more extensive in IMRT than in 3D-CRT. This difference, together with higher treatment rates and dosages for 5-FU and mitomycin in the IMRT group, might to some extent explain the increase in acute diarrhea in the IMRT group.

GI toxicity was also reported in 6 previous studies with mixed results [17, 23, 24, 26, 28, 29]. Three studies reported on GI side effects in general [17, 23, 24], the others also reported on single symptoms such as diarrhea and/or rectal bleeding [26, 28, 29]. Two of the six showed significantly lower GI toxicity upon IMRT, whereas 3 showed only trend towards lower GI toxicity; one study even showed a trend toward more GI toxicity in IMRT (5 vs. 1 patient in CRT) [26], Table 5. Our study also demonstrated a trend toward higher hematological toxicity in the IMRT group. In contrast, lower hematological toxicity for IMRT compared to 3D-CRT for the treatment of cervical cancer was demonstrated in some [33] but not all studies [34].

Altogether, the combination of beneficial effects of IMRT and a more aggressive treatment approach might result in a similar overall tolerability of IMRT treatment, indicated by a trend toward shorter duration of hospitalization. While the average length of hospitalization was shorter upon IMRT treatment, and especially long-term hospitalizations beyond 58 days did not occur in the IMRT group, this difference failed to reach statistical significance. A significantly reduced risk of hospitalization in the first 6 months *after therapy* was noted for IMRT in a previous study (hazard ratio 0.70; 95% CI 0.58–0.84; $p < 0.0002$) [30] and a shorter treatment time was reported in a large database analysis [35].

Our data suggest better local tumor control upon IMRT treatment. Out of 39 patients treated with 3D-CRT, no complete response at 1 year was achieved in 8, compared with only 1 patient without CR treated with IMRT. Apparently, IMRT allows a more localized focus of radiation in the primary tumor area which might have received more radiation volume and/or more homogenous radiation over its entire volume for maximum oncological effects. However, we cannot exclude that higher rates and intensities of 5-FU and mitomycin treatment in the IMRT group contributed to better tumor control.

In line with good local tumor control in the IMRT group, tumor progression was detected within the 6 months after treatment in 6 individuals with 3D-CRT vs. 1 with IMRT. Tumor progression was mainly local and/or in the inguinal lymph nodes (4/6 individuals with 3D-CRT vs. 1 individual with IMRT). Of note, most recurrences occurred at systemic sites (2/2 for 3D-CRT, 3/4 for IMRT), confirming good local control of the tumor after radiochemotherapy.

To the best of our knowledge, there is no randomized controlled comparison for IMRT vs. 3D-CRT in anal cancer. Our literature research identified 10 retrospective observational studies comparing IMRT and 3D-CRT [17, 23–31] (see also Table 5). Better local tumor control, progression-free survival, and overall survival were reported in one previous study [23]; however, most studies reported highly similar oncological outcomes for IMRT and 3D-CRT (Table 5; [24–28, 30]), with an overall survival at 2–3 years of 71–93%, and a progression-free survival of 67–82% [24–26]. It should be noted that in the single study with favorable oncological outcome upon IMRT treatment vs. 3D-CRT, the outcome of the 3D-CRT group was considerably worse (52% overall survival after 3 years) than in all other studies, including ours [23]. Improvement of local tumor control in our study upon IMRT treatment is encouraging; however, it remains unclear why this effect has not been observed in most previous studies. However, in a very recent large database study with 6814 patients (57.4% 3D-CRT, 42.6% IMRT), a significantly better overall survival was observed (80.8% vs. 78.9%, $p = 0.0036$), which was robust after a propensity score-matched analysis [35]. This suggests that better local control will translate into small improvements in overall outcomes, detectable only in very large analyses.

Radiochemotherapy was accompanied by long-term side effects in a significant fraction of patients. Local side effects including proctitis, anal pain, ulcerations, fistulae, and functional impairments resulting in incontinence were similar in the IMRT and 3D-CRT groups. These side effects would be due to radiation of the tumor and its immediate neighborhood, which would be unchanged or even increased upon IMRT treatment. Therefore, the perception of diarrhea during treatment might result from increased radiation to the distal rectum with critical functionality for defecation. In our multivariate analysis (Table 3) and in direct comparisons (not shown), neither 5-FU nor mitomycin treatment was associated with diarrhea. In any case, the initial negative effect of IMRT on acute diarrhea during the initial stages of treatment (Supplementary Fig. 2A) was not observed in long-term follow-up (Supplementary Figure S3F) and might thus be transient. Sexual dysfunction was common in males and females but did not differ between IMRT and 3D-CRT treatment.

Treatment of ACa continues to evolve, and besides the introduction of IMRT, a number of potential improvements in ACa therapy have been advanced in recent years. Dose escalation in primary radiochemotherapy has been suggested; however, no benefit was apparent in a recent randomized controlled trial (Unicancer ACCORD 03 trial) [36]. The checkpoint inhibitor nivolumab, used in treatment of many different malignancies such as melanoma and head and neck cancers [37, 38], has been successful in treatment of metastatic anal cancer [39, 40], with response in up to 24% of patients. The question remains whether checkpoint inhibitors could also increase response rates and overall survival in the primary treatment of locally advanced anal carcinoma [41]. Cetuximab, an epidermal growth factor receptor (EGFR) antibody, might improve response to treatment; however, the high toxicity prevents it from general use apart from in highly selected populations [42, 43]. Deep regional hyperthermia is another potential add-on modality, which has, in small studies, shown a beneficial effect when added to conventional chemoradiotherapy [44, 45]. Larger studies are needed to show whether it should find its way into clinical practice.

Our study has several limitations: i) in our institution, treatment was shifted from 3D-CRT to IMRT in 2008. We therefore cannot entirely exclude the possibility that in addition to IMRT, other treatment variables were improved in parallel, incrementally affecting outcome and side effects. For this reason, time was included as a confounder in all multivariate analyses, but IMRT was consistently found to explain any given variation better than the continuous variable "time." However, a randomized controlled trial would be needed to definitively clarify benefits of IMRT vs. 3D-CRT; ii) all data were collected retrospectively from patient charts, which is similar to most studies comparing IMRT vs. 3D-CRT of which only a single study prospectively collected patient information [17]; iii) 3D-CRT patients were diagnosed and treated 5–10 years prior to IMRT patients and changes in diagnostic procedures such as wider use of PET-CT for staging before therapy in the IMRT group might account for some of the difference in outcome; iv) no patient-reported outcomes regarding sexual function, pain, diarrhea, etc. are available; v) the number of 82 patients might be too small to detect all relevant associations. Nevertheless, our data provide a real-world experience on how switching from IMRT to 3D-CRT might change outcome and side effects in radiochemotherapy for anal carcinoma.

In summary, our data show that IMRT can reduce local side effects of radiochemotherapy such as skin toxicity and enable a more aggressive radiochemotherapy. We found better tumor control rates with IMRT at 6 months to 1 year after the end of treatment, suggesting significant oncological benefits of IMRT over 3D-CRT.

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Conflict of interest M. Sauter, N. Lombriser, S. Bütikofer, G. Keilholz, H. Kranzbühler, H. Heinrich, G. Rogler, S.R. Vavricka, and B. Misselwitz declare that they have no competing interests.

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