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ORIGINAL ARTICLE

Quality of Life Analysis in Anal Squamous Cell Carcinoma Cases Treated with IMRT: A Single-Center Cross-Sectional Study

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OBJECTIVE

The standard treatment for anal cancer involves chemoradiotherapy (CRT), often resulting in long-term side effects that impact patients' quality of life (QoL). The present study aimed to analyse the long-term QoL in anal squamous cell carcinoma (SCC) cases treated with intensity-modulated radiation therapy (IMRT).

METHODS

Between January 2007 and January 2022, 27 anal SCC cases were treated with definitive radiotherapy (RT) or CRT with IMRT. The EORTC QLQ-C30 and EORTC QLQ-CR29 scales were used for data collection.

RESULTS

The mean score for Global Health status/QoL was 72±22.9 and functional scales (range, 84.5-93.8) were generally high, indicating a favourable QoL in the EORTC QLQ-C30 scale. The highest symptom scores were observed for fatigue, insomnia, and financial difficulty. Notably, age (<65 vs. ≥65) was identified as a factor influencing Global Health status/QoL, with patients <65 years of age experiencing a more positive impact. In EORTC QLQ-CR29, although functional scales showed favourable outcomes in body image, anxiety and weight, sexual interest for males (24.8±34.4) and females (10.4±15.7) was impaired, while symptoms like impotence (37.2±32.9) and dyspareunia (31.3±34) scored high. The third-highest symptom was urinary frequency (20.7±27.1). Age ≥65 years was associated with increased symptoms of buttock pain, flatulence and anxiety.

CONCLUSION

Among anal SCC survivors treated with IMRT, functional scores were generally high, whereas clinically relevant sexual function problems were observed. Given the limited sample size and the multiple QoL domains examined, these exploratory findings should be considered hypothesis-generating rather than confirmatory.

Keywords: Anus neoplasms; intensity-modulated radiotherapy; quality of life.
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INTRODUCTION

Anal region cancers are less prevalent compared to other types of gastrointestinal cancer, however, unfavorable trends in anal cancer incidence have been observed over time.[1] Incidence patterns varied by geography and population characteristic, attributed to the distribution of risk factors causing anal cancer in dif-

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ferent regions.[2] In the latest report, age-standardised incidence rates were less than 2.2/100 000 person-years across selected countries worldwide. Germany exhibited the highest incidence rates for both sexes (1.65/100 000 men and 2.16/100 000 women) during 2008–2012, while the lowest rates were found in the Philippines (0.25/100 000 men and 0.18/100 000 women). Notably, female incidence rates remained higher than male rates across nearly all analysed countries.[3] According to another report, anal SCC incidence increased by 2.7% annually from 2001 to 2015. Among white men, incidence steadily rose until age 65–69 years, while white women showed sharp increases from age 30 to 54 years, followed by gradual increases. In contrast, among black men, steep increases occurred at younger ages, whereas among black women, increases persisted until age 65–69 years. Statistically significant increases in incidence were observed for all age groups aged 50 years and older. Among men, the average annual percentage changes for the age groups 50–59, 60–69, and 70 years and older were 4.2%, 2.7%, and 3.8%, respectively. For women, the corresponding changes for the same age groups were 5.0%, 5.3%, and 2.5%, respectively.[4] With the aging global population, the burden of anal cancer is expected to persistently increase and continue to have an impact.

Anal cancer has unique anatomical and histological features that play a pivotal role in their diagnosis, treatment and monitoring. The standard treatment for local-regional disease involves definitive chemoradiotherapy (CRT), as supported by prospective randomized studies.[5,6] The primary goal of treatment is to achieve a complete response while minimizing toxicity. Throughout treatment history, various concurrent chemotherapy (CT) regimens, radiotherapy (RT) techniques and dose applications have been explored to reduce toxicity.[7–9] Despite efforts to minimize toxicity, a significant number of patients still receive high doses of RT as the standard treatment.[10] Consequently, the long-term side effects become inevitable, significantly impacting patients' quality of life (QoL).[11]

In addition, the evaluation of long-term side effects lacks a gold standard method and often tends to provide assessments more aligned with clinicians' perspectives.[12–14] Therefore, QoL scales containing subjective assessments based on the patient's personal experiences play a crucial role. The EORTC core quality of life questionnaire (EORTC QLQ-C30) version 3.0 stands out as the most widely used QoL scale, applicable across various cancer types.[15] Specifically designed for the colorectal region, the EORTC Quality of Life Questionnaire-Colorectal Cancer (EORTC QLQ-CR29) has been recognized as a suitable scale for assessing QoL functions.[16,17] Retrospective and cross-sectional studies conducted up to 2015 and examining the EORTC QLQ-C30 and EORTC QLQ-CR29 scales have reported a decline in QoL and an increase in symptoms.[18] These studies primarily focused on patient populations treated with three-dimensional conformal radiotherapy (3D-CRT) until 2007. Subsequently, the widespread adoption of intensity-modulated radiation therapy (IMRT) has led to a reduction in side effect profiles, albeit with continued effects on QoL.[19,20] Up to date, limited research has assessed the QoL effects of IMRT; therefore, the present study aimed to analyse the QoL of anal squamous cell carcinoma (SCC) cases treated with IMRT and to identify clinical factors associated with QoL.

MATERIALS AND METHODS

Between January 2007 and January 2022, 27 cases of local/local-advanced anal SCC treated with definitive RT/CRT at the Department of Radiation Oncology, Ege University Hospital, were evaluated in the present study. The patient data was accessed retrospectively from archive files. Individuals aged 18 years or older who had a minimum follow-up of 2 years after diagnosis and showed no signs of recurrence were included. Exclusion criteria included metastatic disease at diagnosis, multiple sclerosis, Parkinson's disease, external rectal prolapse, inflammatory bowel disease, diabetic neuropathy, prior RT at diagnosis, and a history of other cancers within the last 3 years. Patients lost to follow-up or unreachable at the time of survey administration were excluded. To assess the QoL of the patients, interviews were conducted using The EORTC QLQ-C30 and EORTC QLQ-CR29 questionnaires in a cross-sectional manner. No serial or prospective PRO collection during treatment was available. This was a cross-sectional survivorship assessment rather than a longitudinal QoL study.

Treatment and Follow-up

Using the sequential boost technique, high-risk clinical target volume (CTV) included gross disease CTV, mesorectum, presacral nodes and bilateral internal and external iliac nodes below the sacroiliac joint.[21] Additional inguinal nodes were included if there was gross inguinal nodal involvement. Low-risk CTV encompassed gross disease CTV, high-risk CTV, presacral, bilateral internal and external iliac nodes above the sacroiliac joint to the L5/S1 vertebral body junction.

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Bilateral inguinal nodes were included if there was no obvious involvement. The dose consisted of 45 Gy at 1.8 Gy per fraction, followed by a 5.4–9 Gy boost at 1.8 Gy per fraction for the high-risk CTV. An additional 5.4–9 Gy boost was administered for the gross disease CTV, reaching a total of 59.4 Gy or 64.8 Gy for stable or progressive cases. Using the Simultaneous Integrated Boost (SIB) technique, single CTV included gross disease CTV, bilateral inguinal nodes, mesorectum, presacral nodes, and bilateral internal and external iliac nodes above the sacroiliac joint to the L5/S1 vertebral body junction.[22] The dose was targeted at 45–54 Gy for single CTV, with a specific 54–59.4 Gy range for gross disease CTV. Concurrent CT was administered with a continuous infusion of 5-Florourasil (5-FU) at a dose of 1,000 mg/m^2/day given intravenously on days 1–4 and 29–32, and Mitomycin C (MMC) as a 10 mg/m^2 intravenous bolus on days 1 and 29 (maximum 20 mg). None of the cases received induction chemotherapy.

Patients underwent regular follow-up after their treatment, which involved digital rectal

examinations every 3 months for the first 2 years, biannually from year 3 to 5, and yearly thereafter. Females underwent gynecological examinations, and imaging was conducted as necessary.

Data Collection

The EORTC QLQ-C30 and EORTC QLQ-CR29, which have undergone Turkish validations, were utilized in the present study. Permission to use these questionnaires was obtained from the appropriate authorities. All patients were treated and followed at Ege University Hospital, Department of Radiation Oncology, which is also the institution that provided ethics approval for this study (Approval Code: 2024-KAEK-04, No: 24-10/6). The study was performed in line with the principles of the Declaration of Helsinki. Patients treated between 2007 and 2022 were identified retrospectively from institutional archives, and in 2024 the ethics committee approved retrospective contact and administration of the survey. QoL questionnaires were administered once per patient during survivorship follow-up after ethics approval in 2024. A consent form and information sheet, detailing the study's purpose, procedures, risks, benefits, confidentiality measures, and voluntary nature, were obtained from each patient.

The EORTC QLQ-C30 questionnaire was developed by Aaronson et al.[23] and later validated and tested in Turkish by Guzelant et al.[24]. This comprehensive questionnaire comprises 30 questions grouped into three main categories: i) Global health status and QoL; ii) functional scales; iii) and symptom scales. Functional scales assess physical, role, emotional, cognitive and social functions, while symptom scales evaluate fatigue, nausea-vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulty, each with a single question. The first 28 of 30 questions are on a 4-point Likert-type scale (not at all: 1 Point; a little: 2 Points; quite a bit: 3 Points; very much: 4 Points). The final two questions inquire about general well-being, with a scoring range of 1 to 7 (1 point: Very poor; 7 points: Excellent). The overall scoring for subgroups is measured on a scale ranging from 0 to 100, following the EORTC scoring guidelines.[25] A higher score on the global health status/QoL, and functional scales indicates a higher QoL or high functional levels, while a higher score on the symptom scales represents a high level of symptoms or low functional levels.

EORTC QLQ-CR29 was developed by Gujral et al.[16] and Whistance et al.,[17] and the validation and reliability of the Turkish version of the questionnaire were performed by Akduran and Durna.[26] It consists of 29 questions specifically designed for colorectal disease-related complaints, including subheadings for patients with or without stomas. The scale uses a 4-point Likert-type scale for responses (not at all: 1 Point; a little: 2 Points; quite a bit: 3 Points; very much: 4 Points). Additionally, it includes questions about urinary symptoms, pain, hair loss, dry mouth, self-image, health concerns, worries and sexual symptoms.

The EORTC QLQ-CR29 questionnaire is complementary to the EORTC QLQ-C30. It starts with question 31 and ends with question 59. The questions 31–47 cover gastrointestinal symptoms, pain, urinary symptoms, self-image and health concerns. Question 48, a yes-or-no question about the presence of a stoma, is not included in the analysis. The subsequent questions are tailored for patients with a stoma bag, with questions 49–55, and for those without a stoma bag, with questions 49–54. The last four questions inquired about sexual QoL in the past 4 weeks, with two separate questions for each gender (questions 56 and 57 for males, 58 and 59 for females). The overall scoring for subscales is measured on a scale ranging from 0 to 100 according to the EORTC scoring guidelines.[25] Higher scores obtained from the functional scales represent high QoL or high functional levels. For symptom scales, higher scores represent a high level of symptoms or low functional levels.

Statistics

Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM Corp.). The mean values of

QoL scores were examined along with their standard deviations. The relationship between QoL scores and clinical factors was assessed using the Mann-Whitney U test or t-test after normality analysis. P<0.05 was considered to indicate a statistically significant difference. Given the limited sample size and the large number of QoL subscales analyzed, we framed all comparisons as exploratory to avoid overinterpretation. For clarity, only statistically significant mean differences are presented, along with their corresponding 95% confidence intervals and exact p-values. Additionally, time since RT (months) was analyzed as a continuous variable in relation to each EORTC QLQ-C30 and EORTC QLQ-CR29 domain using simple linear regression. Domain scores were treated as dependent variables, while months since RT was the independent variable. Regression coefficients (B), 95% confidence intervals, standardized coefficients (Beta), and p-values were reported.

RESULTS

The patient and tumor characteristics are outlined in Table 1. The median RT dose was 59.4 Gy, with a range of 50.4–64.8 Gy. A total of 85.2% of patients received ≤59.4 Gy, while 14.8% received >59.4 Gy. Regarding boost technique, 70.4% of patients underwent a simultaneous integrated boost (SIB), whereas 29.6% received a sequential boost. The median time since RT was 87 months (range, 12–188 months).

EORTC QLQ-C30

The mean scores for global health status/QoL (mean±SD) and functional scales (mean±SD) are high, indicating a good QoL for most cases. The global health status/QoL score was 72±22.9. Among the functional scales, cognitive function had the highest score (93.8±11.5) (Table 2). When assessing the overall health for the past week (question 29), 22.2% of cases scored 7, 33.3% scored 6 and 22.2% scored 5 points. In the symptom scales (mean±SD), the highest symptom score was observed for fatigue (18.7±18.2), followed by insomnia (18.4±28). Financial difficulty ranked third (11.1±20.6). Other symptom scores were 10 or below (Table 2). Regarding diarrhea, 7.4% of cases reported experiencing it 'quite a bit' or 'very much'. For constipation, all cases responded with 'not at all' or 'a little,' and no cases reported severe constipation.

According to the association between clinical characteristics and the EORTC QLQ-C30, not the median age of 59 but the cut-off value of 65 years (<65 vs. ≥65) was identified as the sole factor related to the Global health status/QoL, indicating a deterioration, especially in the elderly population. Being <65 years old was associated with a positive impact on Global health status/QoL (p=0.029; Mann-Whitney U test) (Table 3).

In regression analyses evaluating time since RT as a continuous variable, no significant associations were observed across global health, the five functional scales, and the eight symptom scales (all p>0.10). Only minor, non-significant trends were noted, suggesting slightly lower physical and social functioning and somewhat higher fatigue and pain with longer follow-up intervals. Effect sizes were modest (e.g., global health B=-0.035, 95% CI -0.219 to 0.150; physical functioning B=-0.139,

Table 1 The patient and tumour characteristics

Characteristic	n (%)
Gender	
Female	19 (70.4)
Male	8 (29.6)
Age, median, years (range)	59 (26–75)
T stage	
T1	3 (11.1)
T2	6 (22.2)
T3	14 (51.9)
T4	4 (14.8)
N Stage	
N0	13 (48.2)
N1a	11 (40.7)
N1b	0 (0)
N1c	3 (11.1)
Stage	
I	2 (7.4)
IIA	4 (14.8)
IIB	7 (26)
IIIA	3 (11.1)
IIIB	0 (0)
IIIC	11 (40.7)
Radiotherapy, median total dose, Gy (range)	59.4 (50.4–64.8)
Median time since radiotherapy, months (range)	87 (12–188)
Radiotherapy dose, Gy	
≤59.4	23 (85.2)
>59.4	4 (14.8)
Radiotherapy boost technique	
Simultaneous integrated boost (SIB)	19 (70.4)
Sequential boost	8 (29.6)
Concurrent chemotherapy	
Yes	25 (92.6)
No	2 (7.4)

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Table 2 EORTC QLQ-C30 mean scores

	Scale	Mean score	Min-max	SD	Total
QLQ-C30	Global Health status / QoL *	72.2	16–100	22.9	27
	Functional scales*				
	Physical	84.5	20–100	22	27
	Role	86.4	17–100	25.6	27
	Emotional	85.8	34–100	17.7	27
	Cognitive	93.8	66–100	11.5	27
	Social	88.3	34–100	21.9	27
	Symptom scales**				
	Fatigue	18.7	0–45	18.2	27
	Nausea and vomiting	0.5	0–16	3	27
	Pain	9.2	0–66	18.1	27
	Dyspnoea	0	0	0	27
	Insomnia	18.4	0–66	28	27
	Appetite	5	0–34	12.3	27
	Constipation	6.2	0–34	13.4	27
	Diarrhea	9.9	0–100	24.1	27
	Financial impact	11.1	0–66	20.6	27

*: Scores range from 0 to 100, with a higher score representing a higher level of functioning or better functioning; **: Scores range from 0 to 100, with a higher score representing a greater degree of symptoms or less functioning. SD: standard deviation.

Table 3 The relationship between EORTC QLQ-C30 and clinical characteristics

Characteristic	n	Global health status / QoL mean (SD) score (0–100)	Physical mean (SD) score (0–100)	Role mean (SD) score (0–100)	Emotional mean (SD) score (0–100)	Cognitive mean (SD) score (0–100)	Social mean (SD) score (0–100)	Fatigue* mean (SD) score (0–100)	Insomnia* mean (SD) score (0–100)
Gender									
Female	19	73.1 (22)	83.4 (22)	84 (26)	85.5 (18)	92 (16)	88.7 (21)	20.1 (18)	24.4 (30)
Male	8	70.3 (24)	87 (22)	91 (23	86.6 (15)	98 (5)	87.5 (4)	15.5 (19)	4.2 (12)
Age									
<65	19	78 (17)**	85.7 (22)	90 (21)	86.1 (14)	95.3 (11)	91.6 (18)	16.2 (18)	20.2 (30)
≥65	8	56 (26)	79.7 (22)	76.8 (34)	83.5 (25)	89.7 (12)	79.5 (28)	26.7 (14)	16.7 (25)
T stage									
T1-2	9	76.5 (16)	92.2 (13)	96 (12)	94.4 (11)	92.6 (12)	98.2 (5)	11.2 (14)	14.6 (29)
T3-4	18	70.1 (25)	80.6 (24)	81.7 (29)	81.5 (18)	94.4 (11)	83.4 (25)	22.5 (18)	20.3 (28)
N status									
N-	13	73.4 (25)	85.4 (26)	89.8 (24)	91.7 (14)	93.6 (10)	87.2 (25)	13.7 (18)	7.6 (19)
N+	14	71.2 (21)	83.6 (17)	83.5 (26)	80.3 (19)	94 (12)	89.4 (19)	23.3 (16)	28.4 (31)
Stage									
I-II	13	73.4 (25)	85.4 (26)	89.8 (24)	91.7 (14)	93.6 (10)	87.7 (25)	13.7 (18)	7.6 (19)
III	14	71.2 (21)	83.6 (17)	83.7 (26)	80.3 (19)	94 (12)	89.2 (19)	23.5 (16)	28.4 (31)

*: Higher scores indicate higher levels of symptoms or less functioning; **: Mean difference (95% CI): 23.2 (5.2 – 41.1), and p=0.029. SD: Standard deviation; QoL: Quality of life.

-0.307 to 0.030; social functioning B=-0.131, -0.299 to 0.037; fatigue B=0.076, –0.067 to 0.219; pain B=0.087, -0.054 to 0.228), indicating no clear pattern of late recovery or late decline in this survivor cohort.

EORTC QLQ-CR29

Regarding the functional scales (mean±SD), the highest scores were observed in the body image, anxiety and weight subscales, suggesting a favorable QoL. However,

Table 4 EORTC QLQ-CR29 mean scores

	Scale	Mean score	Min-max	SD	Total
QLQ-CR29	Functional scales*				
	Body image	88.4	56–100	15.3	27
	Anxiety	76.1	33–100	20.5	27
	Weight	86.2	33–100	21.4	27
	Sexual interest (male)	24.8	0–100	34.4	8
	Sexual interest (female)	10.4	0–33	15.7	19
	Symptom scales**				
	Urinary frequency	20.7	0–100	27.1	27
	Blood and mucus in stool	6	0–66	14.5	27
	Stool frequency	6	0–100	19.6	27
	Urinary incontinence	12.2	0–100	24.6	27
	Dysuria	1.2	0–33	6.3	27
	Abdominal pain	15.9	0–100	26.6	27
	Buttock pain	11	0–100	24.3	27
	Bloating	8.5	0–100	21.8	27
	Dry mouth	0	0	0	27
	Hair loss	2.4	0–33	8.8	27
	Taste	1.2	0–33	6.3	27
	Flatulence	13.4	0–66	22.8	27
	Faecal incontinence	8.5	0–100	23.6	27
	Sore skin	3.6	0–66	13.9	27
	Embarrassment	7.3	0–100	21.3	27
	Stoma care problems	22	0–33	19	3
	Impotence	37.2	0–100	32.9	8
	Dyspareunia	31.3	0–100	34	19

*: Scores range from 0 to 100, with a higher score representing a higher level of functioning or better functioning; **: Scores range from 0 to 100, with a higher score representing a greater degree of symptoms or less functioning. SD: Standard deviation.

sexual interest for both males and females was associated with impaired function (Table 4). Out of 8 male patients, 4 answered 'not at all' and 3 answered 'a little,' indicating that 87.5% had little to no sexual interest. For female patients, out of 19, 13 answered 'not at all,' and 6 answered 'a little,' indicating that all had little to no sexual interest. Impotence received the highest score (37.2±32.9), followed by dyspareunia (31.3±34) on the symptom scales (mean±SD) (Table 4). Among male patients, 25% reported 'quite a bit' or 'very much' for erection problems. For female patients, 26.3% answered 'quite a bit' or 'very much' regarding pain or discomfort during intercourse. The third-highest symptom was urinary frequency (20.7±27.1). During the day or night, 22.2% of cases reported 'quite a bit' or 'very much' for frequent urination. Abdominal pain was reported as 'quite a bit' by 11.1%, and flatulence by 11.1%. Severe fecal incontinence was reported in 7.4% of cases. Overall, the symptom scales showed favourable outcomes except for impotence, dyspareunia and urinary frequency (Table 4). Three cases had stomas, but the impact of stoma and non-stoma presence on QoL could not be assessed due to the limited number of cases.

Regarding the relationship between clinical characteristics and the EORTC QLQ-CR29, age (<65 vs. ≥65) was the only factor influencing symptoms of buttock pain (p=0.037) and flatulence (p=0.017). Additionally, there was a statistically significant association between age ≥65 and increased anxiety (p=0.049; Mann-Whitney U test) (Table 5).

In regression analyses assessing time since RT as a continuous variable, no significant associations were found for the majority of CR29 domains, including body image, anxiety, weight, urinary and bowel symptoms, embarrassment, and female sexual functioning (all p>0.10). Non-significant positive trends were observed for abdominal pain (p=0.084) and bloating (p=0.127), while other domains such as dysuria and buttock pain also showed mild but non-significant increases with longer follow-up. Importantly, male impotence demonstrated a significant positive association with time since RT (B=0.499, 95% CI 0.155–0.843,

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Table 5 The relationship between EORTC QLQ-CR29 and clinical characteristics

Characteristic	n	Body Image mean (SD) score (0–100)	Anxiety mean (SD) score (0–100)	Weight mean (SD) score (0–100)	Urinary frequency* mean (SD) score (0–100)	Abdominal pain* mean (SD) score (0–100)	Flatulence* mean (SD) score (0–100)	Urinary incontinence* mean (SD) score (0–100)	Buttock pain* mean (SD) score (0–100)
Gender									
Female	19	87.6 (15)	76.7 (19)	85.7 (20)	20.8 (30)	19.1 (29)	13.8 (22)	17.4 (27)	13.9 (27)
Male	8	90.3 (16)	74.6 (23)	87.3 (24)	20.5 (17)	8.2 (15)	12.3 (24)	0 (0)	4.1 (11)
Age									
<65	19	85.8 (17)	80.3	82.2 (23)	23.4 (29)	12.4 (27)	6.9 (17)	10.4 (24)	7 (23)
≥65	8	94.5 (5)	(20)** 66.1 (17)	95.7 (12)	14.3 (18)	24.7 (23)	28.8 (27)**	16.5 (24)	20.6 (24)**
T stage									
T1-2	9	90 (14)	81.1 (17)	88.8 (17)	14.6 (25)	11 (23)	11 (23)	22.1 (37)	11 (23)
T3-4	18	87.6 (16)	73.6 (21)	85 (23)	23.8 (28)	18.3 (28)	14.6 (23)	7.3 (14)	11 (25)
N status									
N-	13	87.2 (17)	79.2 (25)	89.5 (16)	10 (12)	7.6 (14)	12.6	10.1 (20)	5 (12)
N+	14	89.5 (13)	73.2 (14)	83.1 (25)	30.7 (33)	23.6 (32)	14.1	14.2 (28)	16.5 (31)
Stage									
I-II	13	87.2 (17)	79.2 (25)	89.5 (16)	10 (12)	7.6 (14)	12.6 (21)	10.1 (20)	5 (12)
III	14	89.5 (13)	73.2 (14)	83.2 (25)	30.7 (33)	23.6 (32)	14.1 (26)	14.2 (28)	16.5 (31)

*: Higher scores indicate higher levels of symptoms or less functioning; **: Anxiety: Mean difference (95% CI): 21.1 (6.1-31.2), and p=0.049 / Buttock pain: Mean difference (95% CI): -16.2 (-34.4–7.2), and p=0.037/ Flatulence: Mean difference (95% CI): -21.9 (-40.1–-3.8), and p=0.017. SD: Standard deviation; QoL: Quality of life.

p=0.012), indicating a progressive worsening of erectile dysfunction over time. No variability was present for dry mouth, precluding analysis. Overall, these findings suggest that while most quality-of-life domains remain stable over long-term follow-up, male sexual dysfunction may increase with time after RT.

DISCUSSION

In this study, we conducted an analysis of the long-term QoL in cases of anal SCC treated with IMRT. Previous studies investigating EORTC QLQ-C30 in long-term anal cancer survivors before IMRT showed that Global health status/QoL scores ranged from 60 to 71, with functional scales exhibiting variability between 56 and 87. Frequently reported symptoms in the symptom scales were fatigue (range, 27–40), insomnia (range, 23.5–40), and diarrhea (range, 27–35) (Supplementary 1). [11,27–31]

In the IMRT period, the global health status/QoL reported by Yerramilli et al.[32] showed a score of 86.5. This contrasts with scores in other series,[10,33–37] which ranged from 70 to 77.6, consistent with the 3D-CRT period. The present study similarly observed this trend, revealing a Global health status/QoL score of 72.2. Functional scales in our analysis demonstrated favourable outcomes of 85 and above, aligning with Yerramilli's results.[32] Studies mostly reported scales of 80 and above for role, emotional, physical and social functions. [10,33–37] Particularly, cognitive function consistently scored higher than other functional scales in various reports, ranging from 82.5 to 95.8.[33–35] A similar result in cognitive function was also evident in the present study. While no study has directly compared QoL outcomes between IMRT and 3D-CRT, the findings of the present study appear broadly consistent with and comparable to those reported in historical 3D-CRT and IMRT series (Supplementary 1). However, the absence of baseline QoL assessments and a contemporaneous comparison group precludes causal conclusions regarding a QoL advantage associated with IMRT. Notably, previous longitudinal IMRT studies reported that Global health status/QoL and several functional scales returned toward baseline values during follow-up (Supplementary 2).[10,33] However, QoL significantly worsened in the acute period, emphasizing the importance of employing the EORTC QLQ-C30 during this phase. In the late period, focusing on site- or treatment-specific questionnaires may be more logical; however, several of these scales are inevitable extensions of the EORTC QLQ-C30.

Reports indicated that most symptoms in the EORTC QLQ-C30 are commonly observed in the general population,[33,37] similar to the findings reported

in some 3D-CRT studies.[28,29] The two most prevalent symptoms in present data, fatigue and insomnia, pose a significant challenge. Additionally, the EORTC QLQ-C30 addresses only two specific regional issues, namely diarrhea and constipation. Although the present study reported lower scores for diarrhea (9.9±24.1) compared with both the 3D-CRT and IMRT periods, the issue persists. Other studies have reported scores ranging from 14.3 to 22.8,[32–34,36,37] with some reporting higher scores and others lower,[10,35] highlighting the ongoing challenge of effectively managing this side effect, even with IMRT implementation (Supplementary 1).

The EORTC QLQ-CR29, though not specifically designed for the anal region, encompasses the colorectal area and conducts a comprehensive inquiry. Previous studies on anal cancer have consistently reported a decline in sexual interest and an increase in sexually related symptoms.[27,28,38–40] Benztzen et al.[30] reported 24% dyspareunia and 67% impotence with 3D-CRT. Another analysis also revealed a severe decrease in sexual desire in 58% [20 of 33 women (60%) and 3 of 7 men (42.8%)], along with severe dyspareunia in 60% (21 of 35 women) and erection problems in 71% (5 of 7 men) with 3D-CRT.[40] Despite the application of IMRT, significant reports of sexual impairment persisted.[41] Koerber et al.[42] reported a lower incidence of chronic G3 dyspareunia (32% for IMRT vs. 58% for 3D-CRT) and vaginal dryness (41% for IMRT vs. 83% for 3D-CRT) with IMRT. In addition, the same authors identified these issues as major concerns for women undergoing CRT. In the present study, although EORTC QLQ-CR29 function and symptom scores were deemed acceptable, noticeable decreases in sexual interest and an increase in sexual symptoms were also observed with IMRT. Sexual interest severely decreased in 92.2% [19 of 19 in females (100%) and 7 of 8 in males (87.5%)]. While severe dyspareunia was observed in 26.3% (5 of 19), impotence was less frequent at 25% (2 of 8) compared with the previous data. This emphasizes the ongoing challenge of managing sexual side effects. Yet, it should be noted that impotence was evaluated in only 8 patients in our series; therefore, the results should be interpreted with caution.

In terms of EORTC QLQ-CR29 scores with IMRT, a previous study indicated the highest QoL scores; however, they also reported the highest scores for dyspareunia (48.5±38.1) and impotence (50±39.8).[32] Dyspareunia scores varied between 26.6 and 42, and impotence scores were in the range of 39.4 to 52 in other studies (Supplementary 3).[10,33,34,36,37] Across all studies, it was found that males had more sexual symptoms than females, but conversely, females had higher levels of sexual aversion. Our findings revealed that both male and female sexual interest was lower than reported in the literature. While the dyspareunia score (31.3±34) was consistent with ranges reported in previous data, impotence (37.2±32.9) was less pronounced, despite higher scores in preliminary data. Most patients expressed satisfaction with their bodies.

Contradictory data in various studies suggested that sexual scores either returned to the pre-treatment baseline or worsened in the 12th month after treatment (Supplementary 2). [10,33,34,36] When compared with the general population, Bentzen et al.[30] reported lower levels of dyspareunia (28±34) but higher levels of impotence (69±37) in anal SCC cases with 3D-CRT. It should be noted that in several series, patient age negatively affects sexual desire.[43] It is possible that similar symptoms were present before treatment. A prospective observational survey of non-institutionalized men aged 40–70 years found that 52% of men reported erectile dysfunction and erectile dysfunction is observed more frequently with increasing age.[44] In addition, most reports emphasize the physical aspects of sexuality (dyspareunia, changes in the vagina and decreased sexual activity) and may not adequately represent the psychological (decreased libido, alterations in body image, anxiety related to sexual performance) and social (difficulty maintaining previous sexual roles, emotional distancing from partners, perceived change in partner's level of sexual interest) aspects of female cancer survivors.[45] Although EORTC QLQ-CR29 addresses physical aspects and psychological effects, including decreased libido and alterations in body image, it does not inquire about anxiety related to sexual performance. The question about anxiety addresses concerns related to the future. Additionally, social aspects are overlooked.

Clinicians, primarily focused on survival, often disregard the evaluation of sexual function. Gender differences and social norms also contribute to this phenomenon. Consequently, patients are typically examined by gynecologists and urologists in the late period. Although complementary medical strategies in the post-treatment phase (e.g., guidance on the use of vaginal dilators and lubricants) are recommended, efficacy has been the subject of controversial discussion in the literature.[38]

Nevertheless, a more effective approach remains elusive at present. Clinicians, therefore, should adopt the approach known as pre-rehabilitation, or 'pre-hab,' as a pre-treatment strategy. While pre-hab research often centers on nutrition and exercise, it could also involve teaching pelvic floor exercises, starting moisturizer regimens, and recommending lubricant use before

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treatment.[46] Psychological evaluation should not be overlooked both before and after the treatment process. Future studies are required to explore the role of supportive care (including more intensive approaches and/or new agents) during and after CRT.

Based on these findings and in line with current survivorship recommendations, routine screening for sexual dysfunction should be integrated into follow-up visits, with structured referral pathways (urology, gynecology, pelvic floor physiotherapy, psycho-oncology) when indicated. Counseling should cover both physical (e.g., dyspareunia, erectile dysfunction) and psychosocial (e.g., libido, body image, partner communication) aspects. Furthermore, pre-habilitation should be expanded to include sexual health interventions prior to CRT, such as pelvic floor exercises, moisturizers, and lubricants, delivered by a multidisciplinary team.

In the current study, the present authors observed that urinary frequency (20.7±27.1) emerged as the most prevalent symptom, following impotence and dyspareunia regarding the EORTC QLQ-CR29 symptom scales. This aligns with frequencies reported in other IMRT studies, ranging from 14 to 32.7 (Supplementary 3).[10,32–34,36,37] In comparison with baseline values, it is observed that urinary symptoms mostly improve after treatment, except for the result reported by Joseph et al.[33] (Supplementary 2). Management of urinary tract symptoms after pelvic RT involves lifestyle modifications, such as fluid intake adjustments and avoiding bladder irritants like caffeine and alcohol. Pelvic floor muscle training has shown efficacy in improving symptoms, especially when combined with counseling and physical therapy. Hyperbaric oxygen therapy is promising for managing urinary tract symptoms after pelvic RT, particularly for patients who completed pelvic RT more than 6 months prior.[47] Initial management strategies include behavioral modifications and keeping a 72-hour voiding diary. Anticholinergic and beta-3 agonist medications are options for managing irritative symptoms in female patients post-RT, while third-line treatments like a botulinum toxin A, percutaneous tibial nerve stimulation or sacral neuromodulation may be considered for those with uninhibited bladder contractions. In cases of decreased bladder compliance, more invasive treatments like catheterization or urinary diversion may be necessary, with regular upper urinary tract monitoring recommended.[48]

On the other hand, the present results indicated lower rates of fecal incontinence (8.5±23.6) and flatulence (13.4±22.8) compared with previous data, which reported fecal incontinence in the range of 14–29 and flatulence between 17.2 and 40.2 (Supplementary 3).[10,31–33,35,36] Severe fecal incontinence, reported by Lefevre et al.[37] at 7%, was also found in the present study at the same rate. However, the prevalence of flatulence was lower in the present study at 11.1%, compared with the reported 25%.

Regarding the RT dose, the median value was 59.4 Gy in the current series. Notably, some reports suggest an increase in side effects with doses exceeding >60 Gy.[49,50] Therefore, the adherence of the present study to a lower dose may have contributed to the positive QoL outcomes observed.

When analysing the clinical factors influencing EORTC QLQ-C30 and QLQ-CR29 in anal SCC, limited studies are available. Allal et al.[27] reported lower physical scale scores in elderly patients without a significant relationship with the EORTC QLQ-C30 scale and clinical factors. Sauter et al.[35] also found favourable scores for Global health status/QoL, physical and role functioning with EORTC QLQ-C30 in patients under 70 years old, however, observed no significant relationship with treatment-related factors and functional and symptom scales. By contrast, Das et al.[39] identified a trend toward lower QoL scores in patients under 51 years old. In the present analysis of EORTC QLQ-C30, individuals <65 years old exhibited improved Global health status/QoL. For EORTC QLQ-CR29, cases aged ≥65 showed a tendency for anxiety. Additionally, hip/anal pain and flatulence symptoms were statistically higher in cases aged ≥65 years again indicating age is an important factor for a patient's well-being. These age-related differences may reflect a combination of treatment-related late effects, age-related physiological changes, and a greater burden of comorbidities in older survivors. Age-associated changes in bowel function, pelvic floor function, musculoskeletal symptoms, and psychological well-being may produce symptoms similar to those associated with pelvic treatment. Because pretreatment QoL and detailed comorbidity data were not available, the relative contributions of treatment, aging, and comorbidity could not be determined. Therefore, these findings should be interpreted cautiously and regarded as exploratory.

The present study has several limitations that need consideration. Firstly, the inability to compare the present patient population with the general population, coupled with the small number of cases, are notable drawbacks. In addition, the study population consisted exclusively of recurrence-free survivors who remained available for follow-up and completed the questionnaires. Therefore, survivorship and potential nonresponse bias

may have contributed to the relatively favourable QoL scores observed. Patients who developed recurrence, experienced greater morbidity, were lost to follow-up, or were otherwise unavailable for survey completion were not represented, which may limit the generalizability of the findings to the entire treated population. Due to the cross-sectional nature of the study, baseline values at the time of diagnosis are unknown. However, it is essential to recognize that anal cancer is a rare malignancy, and the analysis of long-term QoL with IMRT is inherently limited. Given the distinctive nature of the anal region and its treatment differing from other colorectal cancers, a specific QoL scale, the EORTC Quality of Life Questionnaire-Anal Cancer (EORTC QLQ-ANL27), has been developed. This scale comprises 27 questions addressing ongoing gastrointestinal symptoms, skin symptoms, lifestyle adjustments, stoma concerns, and sexual symptoms, following the EORTC QLQ-C30 scale.[51] Notably, the lack of Turkish validation and reliability analysis for this scale and its non-utilization in the present study poses additional limitations. Therefore, it should not be concluded that the sexual function items in the CR29 are direct and sole indicators of anal function.

It is crucial to acknowledge that QoL is a result of side effects, and QoL questionnaires play a valuable role in assessing patients individually, shedding light on the symptoms experienced by cases. However, every individual's perception of QoL varies significantly. Additionally, functional conditions and symptoms are not directly observed in real life. Scales based on individual responses given during visits may mask some functional losses and symptoms. Recognizing that symptoms can develop over time underscores the importance of repeatable assessments during visits. A comprehensive analysis of the patient's symptoms at the time of diagnosis is crucial for evaluating long-term outcomes after treatment.

CONCLUSION

In conclusion, the long-term QoL outcomes of anal SCC survivors treated with IMRT presented a mixed profile, with relatively high functional scores and persistent challenges in selected symptom domains. Given the limited sample size and the multiple QoL domains examined, these exploratory findings should be interpreted as hypothesis-generating rather than confirmatory. Future research should focus on addressing the specific needs of this patient population, incorporating targeted interventions, and developing comprehensive, culturally validated assessment tools to enhance the understanding and management of long-term effects.

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Supplementary 1. Comparison of mean scores in studies utilizing EORTC QLQ-C30 for 3D-CRT and IMRT

	3D-CRT						IMRT							
QLQ-C30	Allal (27) (1999) n=41	Jephcott (11) (2004) n=50	Provencher (28) (2010) n=30	Welzel[§] (29) (2011) n=52	Bentzen (30) (2013) n=128	Knowles[†] (31) (2015) n=42	Han[#] (10) (2014) n=58	Joseph[#] (33) (2016) n=54	Yeramilli (32) (2020) n=42	Gilbert[#] (34) (2020) n=57[‖]	Sauter[††] (35) (2022) n=52	Hosni[#] (36) (2022) n=72	Lefèvre[#] (37) (2023) n=232[‖]	Balci Topuz (current study) n=27
Global Health status / QoL *	71 (21)	66 (28)	70 (25)	60 (n/a)	68 (25)	66.7 (n/a)	70 (20)	72.2 (18.3)	86.5 (16.3)	72.8 (19.5)	77.6 (13)	72.7 (n/a)	71.6 (21.6)	72.2 (22.9)
Functional scales*														
Physical	79.5 (22)	74 (29)	87 (14)	70 (n/a)	77 (22)	86.7 (n/a)	88 (15)	84.9 (17.2)	91 (12.9)	84 (20.7)	82.3 (17)	85.5 (n/a)	84.8 (19.3)	84.5 (22)
Role	85 (21)	76 (33)	77 (26)	60 (n/a)	69 (31)	66.7 (n/a)	86 (25)	79.4 (23.1)	91.7 (16)	81 (24.1)	70.5 (22)	82.9 (n/a)	80 (26.7)	86.4 (25.6)
Emotional	77 (25)	74 (28)	77 (26)	56 (n/a)	77 (25)	66.7 (n/a)	78 (21)	77 (21.9)	87.3 (12.1)	80.3 (23.1)	70.5 (15)	79.2 (n/a)	81.9 (18.7)	85.8 (17.7)
Cognitive	76 (23)	75 (24)	85 (25)	75 (n/a)	77 (26)	83.3 (n/a)	79 (18)	82.5 (23.9)	90.9 (12.3)	84.8 (20.9)	95.8 (12.5)	82.9 (n/a)	84.5 (21.6)	93.8 (11.5)
Social	82 (28)	73 (35)	74 (34)	60 (n/a)	71 (29)	66.7 (n/a)	83 (20)	81.1 (22.3)	90.5 (15.2)	76.6 (27.1)	83.0 (11)	83.8 (n/a)	84.8 (23.6)	88.3 (21.9)
Symptom scales**														
Fatigue	27 (22)	36 (30)	28 (29)	40 (n/a)	38 (28)	33.3 (n/a)	24 (18)	27.2 (19.6)	15.6 (16.1)	26.2 (22.8)	21.1 (18)	26 (n/a)	26.3 (24.6)	18.7 (18.2)
Nausea/vomiting	6 (15)	6 (17)	1 (4)	5 (n/a)	6 (13)	0 (0)	6 (16)	7.46 (15.8)	1.59 (6.17)	4.09 (10.5)	(n/a) (n/a)	5.7 (n/a)	4.0 (10.4)	0.5 (3)
Pain	15 (21)	23 (31)	20 (25)	32 (n/a)	25 (30)	16.7 (n/a)	19 (24)	18.4 (21.9)	9.13 (21.5)	15.5 (23.7)	(n/a) (n/a)	20 (n/a)	19.0 (24.8)	9.2 (18.1)
Dyspnoea	13 (22)	23 (33)	18 (26)	30 (n/a)	27 (33)	(n/a) (n/a)	9 (15)	14.0 (21.4)	8.33 (19.6)	14 (23.3)	(n/a) (n/a)	11.6 (n/a)	13.1 (24.8)	0 (0)
Insomnia	23.5 (29)	29 (32)	26 (31)	40 (n/a)	35 (35)	(n/a) (n/a)	29 (27)	33.3 (30)	17.5 (21.3)	25.7 (30.8)	(n/a) (n/a)	28.1 (n/a)	23.4 (30)	18.4 (28)
Appetite	10 (19)	13 (22)	10 (23)	13 (n/a)	14 (24)	(n/a) (n/a)	11 (20)	9.7 (23.1)	4.17 (13.5)	8.9 (19.5)	(n/a) (n/a)	10 (n/a)	8.5 (20.8)	5 (12.3)
Constipation	15 (21)	24 (32)	7 (19)	15 (n/a)	22 (28)	(n/a) (n/a)	8 (17)	4.4 (15.8)	7.32 (14)	9.9 (18.8)	18.6 (30)	10.5 (n/a)	11.3 (21.5)	6.2 (13.4)
Diarrhea	28 (36)	27 (32)	28 (40)	35 (n/a)	27 (32)	(n/a) (n/a)	12 (21)	22.8 (27)	14.3 (19.7)	18.2 (22.9)	38.5 (19)	18.1 (n/a)	20.9 (25.8)	9.9 (24.1)
Financial impact	15 (28)	23 (37)	20 (31)	32 (n/a)	14 (27)	(n/a) (n/a)	19 (29)	16.7 (24.2)	8.73 (18.1)	16.3 (23.8)	(n/a) (n/a)	17.1 (n/a)	7.8 (20.8)	11.1 (20.6)

Scores for the late phase of the 12th month are provided.
§ The approximate mean scores were obtained from the presented figure 1 in the study.
† Median scores are provided.
†† 38 patients were treated with IMRT, while 14 were treated with 3D-CRT.
|| Patient number for the late phase of the 12th month are provided.
* Scores range from 0 to 100, with a higher score representing a higher level of functioning or better functioning
** Scores range from 0 to 100, with a higher score representing a greater degree of symptoms or less functioning
The standard deviation is indicated within parentheses.
n/a, not available

Supplementary 2. Comparing long-term QoL outcomes utilizing EORTC QLQ-C30 and CR29 for anal cancer with IMRT in published studies

	Number of patients	Design	Aim	Treatment	Scoring system	Main result
Han (10) (2014)	58	Single-center, longitudinal cohort study	Evaluation of acute and long-term toxicities as well as QoL at baseline, after treatment, and during follow-up	*Primary tumor:* Tumors ≤2 cm: 45 Gy in 25 fractions Tumors 2.1 to 4 cm: 54 Gy in 30 fractions Tumors >4 cm or poorly differentiated: 63 Gy in 35 fractions *Lymph nodes:* Nodes >2 cm: 63 Gy in 35 fractions Nodes ≤2 cm: Initial phase: 36 Gy in 20 fractions Follow-up phase: 22.5 Gy in 15 fractions *Sites of excised involved nodes:* 54 Gy in 30 fractions *Node-negative regions:* T1N0 disease: 27 Gy in 15 fractions	QLQ-C30 QLQ-CR29	QOQ-C30: Global QoL/health status was significantly worse at the end of treatment but returned to baseline levels, remaining stable at 12 months. Social functioning and appetite scores improved significantly at 12 months. QOQ-CR29: Skin and defecation problems worsened significantly at the end of treatment but returned to baseline levels, remaining stable at 12 months. Impotence significantly worsened from a baseline mean score of 30 to 52 at 12 months. Dosimetric parameters correlated with toxicities, showing IMRT's benefits in reducing toxicities without compromising control.

				All other stages: 36 Gy in 20 fractions Fraction size: 1.8 Gy Chemotherapy: 5-FU/MMC		
Joseph (33) (2016)	54	Single-center, longitudinal cohort study	Evaluation of QoL at baseline, after treatment, and during follow-up	*Primary tumor:* 54 Gy delivered to 95% of the volume in 30 fx *Region at risk of disease spread:* 45 Gy delivered to 95% of the volume in 30 fx Fraction size: 1.8 Gy Chemotherapy: 5-FU/MMC	QLQ-C30 QLQ-CR29	QOQ-C30: Functional scales returned to baseline or slightly improved at 12 weeks post-treatment. Symptoms worsened initially, including medium deterioration in diarrhea, which persisted for up to 12 months. QOQ-CR29: Dyspareunia worsened and remained elevated throughout period. Impotence improved at 12 weeks post-treatment. Urinary frequency and dysuria returned to baseline at 12 weeks, but urinary incontinence persisted. The study supported the routine use of IMRT and emphasized the importance of evaluating sexual, urinary, and anorectal functions before starting treatment.

Yeramilli (32) (2020)	42	Single-center, cross-sectional	Evaluation of long-term QoL, patient-reported sexual function, and mood	*T2N0 tumors:* Elective nodal volumes: 42 Gy Primary tumor: 50.4 Gy Fractionation: 28 fx *T3-4, N0-3 tumors*: Elective nodal volumes: 45 Gy Lymph nodes ≤3 cm: 50.4 Gy Lymph nodes >3 cm: 54 Gy Primary tumor: 54 Gy Fractionation: 30 fx Chemotherapy: 5-FU/MMC, 5-FU/cisplatin	QLQ-C30 QLQ-CR29	QOQ-C30: Overall quality of life scores were relatively high, with a mean global quality of life score of 86.5. QOQ-CR29: Both male and female patients reported poor sexual interest, with mean scores of 54.2 (±30.5) and 17.9 (±21.2), respectively. For the 18 symptom scales, patients reported particularly high scores corresponding to worse symptoms for impotence and dyspareunia. Patients undergoing pelvic radiation therapy for anal cancer may experience changes in sexual function, but they typically report mild mood symptoms and display high QOL scores.
Gilbert (34) (2020)	57[l][l]	Multicenter, longitudinal cohort study	Evaluation of QoL at baseline, after treatment, and one-year follow-up	*T1/2 tumors:* Median dose 50.4 Gy in 28 fx (Range 30-54 Gy in 10-30 fx) *T3/ 4 tumors:* Median dose 53.2 Gy in 28 fx (Range 40-54 Gy in 15-30 fx) Chemotherapy: 5-FU/MMC, Capecitabine/MMC	QLQ-C30 QLQ-CR29	QOQ-C30: At one-year follow-up, significant improvements were observed in pain, constipation, appetite loss with moderate improvements in emotional and role functioning. QOQ-CR29: Impotence scores remained relatively poor at one year but did not significantly worsen after treatment. Dyspareunia worsened moderately for women after

						treatment, with an overall one-year mean score indicating mild. At one year, flatulence, impotence, libido (for both genders), and health anxiety had the most severe symptom mean scores, with moderate or small improvements observed for health anxiety and female libido.
Sauter [††] (35) (2022)	52	Single-center, cross-sectional	Evaluation of long-term QoL between healthy people and anal cancer patients	*Minimum dose*: 45 Gy *Boost for advanced tumors and affected lymph nodes:* 9–14 Gy Fraction size: 1.8 Gy Chemotherapy: 5-FU/MMC, Capecitabine/MMC	QLQ-C30 QLQ-ANL27	QLQ-C30: Anal cancer patients showed lower role, emotional, and social functioning, but higher cognitive functioning and overall global health compared to the German reference population. Constipation and diarrhea scores were higher in anal cancer patients. Physical and role functioning strongly impacted global QoL. Fatigue notably impacted QoL negatively. IMRT patients did not differ significantly from 3D-CRT patients.
Hosni (36) (2022)	72	Single-center, longitudinal cohor	Evaluation of QoL at baseline, after treatment, and during follow-up	*Elective targets:* 36 Gy/20 fractions, except for T1N0 cancer which received 27 Gy/15 fractions. *T1N0 disease:* 45 Gy/27 fractions	QLQ-C30 QLQ-CR29	QLQ-C30: Clinically and statistically significant improvements above baseline were observed in role functioning, emotional functioning, appetite loss, pain, social functioning, nausea/vomiting, insomnia, fatigue, and financial problems in long-term.

		t study		*All T1N+ or selected T2 any N with low/intermediate-grade tumor of <4 cm:* 54 Gy/30 fractions *Advanced tumors (T3 and T4) or T2 with high-grade and/or ≥4 cm:* 63 Gy/35 fractions. Chemotherapy: 5-FU/MMC		Baseline QOL did not significantly correlate with long-term QoL, except for specific scales like physical functioning, social functioning, constipation, and financial problems. QOQ-CR29: Anxiety and abdominal/pelvic pain improved significantly above baseline. Body image, bowel embarrassment, fecal incontinence, and hair loss worsened statistically, but not clinically in long-term. Impotence worsened both statistically and clinically. No significant correlation was found between baseline and long-term QoL.
Lefèvre (37) (2022)	232[II]	Multicenter longitudinal cohort study	Evaluation of QoL at baseline, after treatment, and one-year follow-up	*Elective targets:* 48 to 51.2 Gy *Tumor and pathological lymph nodes:* 60 to 64 Gy Fraction size: 2 Gy Chemotherapy: Induction chemotherapy, concomitant cisplatin, concomitant 5-FU, concomitant cisplatin/5-FU, concomitant capecitabine	QLQ-C30 QLQ-CR29	QLQ-C30: Significant minor score improvements were observed in four items: Global health status/QoL, Emotional functioning, Insomnia, and Appetite. No items showed moderate or major changes, and none worsened from baseline to one year. QOQ-CR29: Of the bowel and bladder items, two worsened significantly from baseline to one year after treatment. These were fecal incontinence, which experienced a minor change, and flatulence, which

						experienced a moderate change. Erectile dysfunction also worsened slightly by 9.4 points. Patients had a low bowel symptom burden and symptom scores one year after treatment, and most patients with high bowel and bladder symptoms before treatment experienced improvement one year after treatment.
Balci Topuz (current study)	27	Single-center, cross-sectional	Evaluation of long-term QoL	*Sequential boost technique:* 45 Gy followed by a 5.4-9 Gy for the high-risk CTV, and additional 5.4-9 Gy boost for the gross disease CTV, reaching a total of 59.4 Gy or 64.8 Gy for stable or progressive cases. Fraction size: 1.8 Gy *Simultaneous Integrated Boost technique:* 45–54 Gy for single CTV, with a range of 54–59.4 Gy for gross disease CTV. Chemotherapy: 5-FU/MMC	QLQ-C30 QLQ-CR29	QOQ-C30: Overall QoL scores were relatively high, with lower scores reported for most symptoms, particularly diarrhea and constipation. QOQ-CR29: Sexual interest decreased for both genders, with urinary frequency [20.7±27.1] being the most prevalent symptom, followed by impotence [37.2±32.9] and dyspareunia [31.3±34].

|| Patient number for the late phase of the 12th month are provided.

†† 38 patients were treated with IMRT, while 14 were treated with 3D-CRT.

CTV, Clinical target volume; IMRT, Intensity-modulated radiation therapy; MMC, Mitomycin C; QoL, Quality of life; 3D-CRT, Three-dimensional conformal radiotherapy; 5-FU, 5-Florourasil.

Supplementary 3. Comparison of mean scores in studies utilizing EORTC QLQ-CR29 for 3D-CRT and IMRT

	3D-CRT		IMRT						
QLQ-CR29	Provencher (28) (2010) n=30	Bentzen (30) (2013) n=128	Han[#] (10) (2014) n=58	Joseph[#] (33) (2016) n=54	Yeramilli (32) (2020) n=42	Gilbert[#] (34) (2020) n=57[‖]	Hosni[#] (36) (2022) n=72	Lefèvre[#] (37) (2022) n=232[‖]	Balci Topuz (current study) n=27
Functional scales*									
Body Image	(n/a) (n/a)	72 (31)	87 (17)	81.0 (22.3)	78.3 (29.2)	76 (28.9)	83.7 (n/a)	80.9 (26.4)	88.4 (15.3)
Anxiety	(n/a) (n/a)	62 (33)	73 (19)	71.3 (25.4)	75.6 (26.9)	60.7 (29.2)	73.8 (n/a)	67.4 (28.8)	76.1 (20.5)
Weight	(n/a) (n/a)	76 (31)	(n/a) (n/a)	81.5 (23.2)	74.6 (27.4)	75.5 (29.4)	(n/a) (n/a)	81.5 (27.9)	86.2 (21.4)
Sexual interest (male)	(n/a) (n/a)	44 (32)	60 (29)	36.4 (31.5)	54.2 (30.5)	28.8 (27.7)	62.6 (n/a)	48.7 (27.9)	24.8 (34.4)
Sexual interest (female)	(n/a) (n/a)	23 (27)	84 (21)	24.2 (23.4)	17.9 (21.2)	18.9 (26.6)	81.8 (n/a)	16.5 (24.3)	10.4 (15.7)
Symptom scales**									
Urinary frequency	(n/a) (n/a)	29 (28)	14[††] (19)	23.6 (22.3)	21.8 (22.2)	32.7 (22)	16[††] (n/a)	20.8 (23.0)	20.7 (27.1)
Blood and mucus in stool	(n/a) (n/a)	13 (17)	18[§] (13)	15.2 (17.3)	9.76 (13.9)	14.6 (17.9)	17.2[§] (n/a)	17.4 (19.2)	6 (14.5)
Stool frequency	(n/a) (n/a)	19 (21)	18[§] (13)	18.1 (17.1)	14 (13.7)	20 (20.9)	17.2[§] (n/a)	16.9 (16.3)	6 (19.6)
Urinary incontinence	(n/a) (n/a)	17 (26)	14[††] (19)	14.8 (21.7)	15.9 26.8)	13.1 (21.7)	16[††] (n/a)	7.6 (19.5)	12.2 (24.6)
Dysuria	(n/a) (n/a)	8 (19)	14[††] (19)	4.6 (11.7)	1.59 (7.18)	2.97 (n/a)	16[††] (n/a)	3.5 (11.9)	1.2 (6.3)
Abdominal pain	(n/a) (n/a)	14 (22)	9 (10)	16.7 (24.6)	3.17 (9.90)	9.52 (18.7)	9.6 (n/a)	13.4 (21.2)	15.9 (26.6)
Buttock pain	(n/a) (n/a)	25 (32)	9 (10)	17.6 (20.3)	13.5 (25.6)	23.3 (25.3)	9.6 (n/a)	20.4 (26.5)	11 (24.3)
Bloating	(n/a) (n/a)	31 (29)	18 (23)	13.9 (20.1)	9.52 (16.9)	(n/a) (n/a)	20.1 (n/a)	26.9 (27.8)	8.5 (21.8)
Dry mouth	(n/a) (n/a)	(n/a) (n/a)	17 (23)	11.1 (17.8)	12.7 (20.8)	23.2 (32.9)	18.6 (n/a)	18.3 (26.3)	0.0 (0.0)
Hair loss	(n/a) (n/a)	(n/a) (n/a)	12 (16)	5.6 (12.6)	20.6 (29.4)	5.3 (13.8)	11.4 (n/a)	7.5 (18.7)	2.4 (8.8)
Taste	(n/a) (n/a)	(n/a) (n/a)	8 (17)	7.4 (18.0)	4.76 (11.8)	10.1 (24.5)	8.3 (n/a)	8.3 (19.8)	1.2 (6.3)
Flatulence	(n/a) (n/a)	47 (32)	18[§] (13)	31.5 (22.5)	28 (27.3)	40.2 (28.3)	17.2[§] (n/a)	34.8 (27.1)	13.4 (22.8)
Faecal incontinence	(n/a) (n/a)	29 (31)	26 (21)	19.4 (23.1)	14 (18.8)	19.3 (27)	29 (n/a)	18.0 (23.4)	8.5 (23.6)

Sore skin	(n/a) (n/a)	(n/a) (n/a)	22 (22)	20.4 (21.5)	20.4 (23.8)	22.7 (30.3)	20.5 (n/a)	23.8 (24.6)	3.6 (13.9)
Embarrassment	(n/a) (n/a)	(n/a) (n/a)	13 (24)	15.7 (23.2)	17.8 (25.9)	25.2 (31.9)	17.9 (n/a)	11.8 (23.1)	7.3 (21.3)
Stoma care problems	(n/a) (n/a)	(n/a) (n/a)	(n/a) (n/a)	0.0 (0.0)	8.33 (16.7)	(n/a) (n/a)	33.3 (n/a)	0.0 (0.0)	22 (19)
Impotence	(n/a) (n/a)	69 (37)	52 (43)	39.4 (46.7)	50 (39.8)	46.7 (39.4)	49.5 (n/a)	47.6 (39.1)	37.2 (32.9)
Dyspareunia	(n/a) (n/a)	28 (34)	42 (34)	37.8 (27.8)	48.5 (38.1)	29.5 (38)	30 (n/a)	26.6 (34.8)	31.3 (34)

Scores for the late phase of the 12th month are provided.
§ Defined as defecation problems
†† Defined as micturition problems
|| Patient number for the late phase of the 12th month are provided.
* Scores range from 0 to 100, with a higher score representing a higher level of functioning or better functioning
** Scores range from 0 to 100, with a higher score representing a greater degree of symptoms or less functioning
The standard deviation is indicated within parentheses.
n/a, not available