DEPARTMENT OF CLINICAL ONCOLOGY

ASSESSMENT OF GI-RELATED QUALITY OF LIFE AMONG CERVICAL AND ENDOMETRIAL CANCER PATIENTS WHO RECEIVED CURATIVE RADIOTHERAPY AT BLACK LION SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA

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Title Of Research	ASSESSMENT OF GI-RELATED QUALITY OF LIFE AMONG CERVICAL AND ENDOMETRIAL CANCER PATIENTS WHO RECEIVED CURATIVE RADIOTHERAPY AT BLACK LION SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA
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Summary

Background: Radiation related GI symptoms such as radiation proctitis, enteritis or colitis is a relatively common yet less researched side effect of gynecologic radiotherapy. Beyond the symptoms, affected patients will have significantly low quality of life and impairment of activities of daily living.

Objective: The aim of this study was to assess the symptoms prevalence, quality of life of patients who took radiotherapy for cervical and endometrial cancer, identify associated factors among patients who completed curative gynecologic radiotherapy at TASH radiotherapy center between June 2023 and November 2023.

Methods: A hospital-based cross-sectional study was conducted on 68 Patients who took combined intracavitary and EBRT between June 2023 and November 2023 for cervical and endometrial cancer and fulfill the inclusion criteria for the study. Quality of life was assessed based on EORTC-QLQ-PRT-20 questionnaire and analyzed accordingly. Mann-Whitney U test and Spearmans Correlation test were used and statistical significance was determined at P value less than 0.05

Result: The mean age of the study participants was 52 years and 48 of the 68 patients (70%) reported at least one abnormal symptom. The mean symptom score for bowel and gas, leakage, bowel control, pain and emotion were 32.0, 3.4 ,6.8 ,8.0 and 13.8. Non parametric tests showed significant association between pain score and bladder volume, pain score and number of cycles,bowel control and total rectal EQD2 and bowel gas with maximum rectal diameter and pain score with Period after RT completion (acute vs chronic)

Conclusion: GI related quality of life of uterine and cervical cancer patients after radiotherapy is significantly affected and better patient care and follow ups are needed.

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Acronyms and Abbreviations

TASH----------Tikur Anbessa specialized Hospital

QoL ----------Quality of life

AE----------Adverse events

CT----------Chemotherapy

DVH---------- dose-volume histogram

IMRT----------intensity-modulated radiation therapy

LA----------Locally advanced

NA –----------Neoadjuvant

PTV---------- planning target volume

RT- ----------Radiotherapy

RTOG----------Radiation Therapy Oncology Group

VMAT----------volumetric modulated arc therapy

3DCRT----------three-dimensional conformal radiotherapy

GI----------Gastro-intestinal

RR----------Risk ratio

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1. INTRODUCTION

1.1 Background

Pelvic radiotherapy is a cornerstone treatment for various gynecological(cervical, endometrial and vulva and vaginal) , urological(bladder, prostate and penile) and gastrointestinal(anal, rectal) cancers, where it might be given alone as primary treatment, combined with chemotherapy, or given before or after surgery (1).

Globally, Pelvic primary cancers treatable with radiotherapy, account to nearly 4 million (20.6%) of new cases and 1.4 million (14.4%) of mortality in 2020.(2)

In Ethiopia, these cancers accounted for over 14,000(26.6%) of new cases and over 10,300(26%) of mortality as of 2019. Of these, cervical cancer was the 1st most common cancers with incidence of 6570 and mortality of 3870 while uterine cancer accounted for 590 new cases and 370 death (3).

In gynecologic cancers, depending on the cancer type and stage; the technique of radiotherapy, utilization of chemotherapy, in the neoadjuvant, adjuvant or definitive setting, radiotherapy is associated with improved survival, locoregional control or quality of life in many of these cancers.

However, pelvic radiotherapy inevitably exposes the surrounding normal tissue to some degree of radiation which may cause a cluster of symptoms termed pelvic radiation disease. Pelvic radiation disease is defined as transient or longer-term issues arising in noncancerous tissues from pelvic radiotherapy and it includes sexual disfunction, pain, radiation cystitis and radiation induced gastro intestinal injury; colitis and proctitis.(4)

Various radiation therapy related factors, such as the type of radiotherapy, the size and site of the treatment field, and the dose delivered to the primary and the gastrointestinal tract are correlated with development of bowel injury.(1) The use of concurrent chemotherapy and previous abdominal surgery are also among treatment related factors.(5)

In addition, patient related factors as smoking, co-existing medical conditions or their treatments (such as diabetes, hypertension, IBD and HIV), concurrent medication, genetic factors, and psychological issues have been associated with risk of bowel injury

Gastrointestinal symptoms can be acute (occurring during radiotherapy or within three months), or chronic (persisting or appearing after three months).

Acute symptoms, including diarrhea, abdominal pain, nausea, bloating, rectal bleeding, and urgency, typically begin during the second week of treatment and peak at four to five weeks.(6)

Chronic symptoms, including fecal incontinence, urgency, rectal bleeding, flatulence, and abdominal pain, can follow acute symptoms or arise on their own or sometime later. (6)

Chronic symptoms are very common, with up to 90% of patients reporting a permanent change in their bowel habits, and up to 30%, 40% and 66% respectively of urological, gynecological and colorectal cancer survivors experiencing chronic gastrointestinal symptoms that negatively affect their quality of life.(5)

A better understanding of patient and radiotherapy related parameters and; their relationship with the incidence of RT related GI toxicity will help to improve the quality of life of patients with cervical and uterine cancer. Therefore, this study will analyze the association of dose, techniques used and GI dosimetric parameters with the development of RT related GI sideeffects and QOL among cervical and uterine cancer patients who underwent curative intent pelvic radiotherapy.

1.2 Statement of the problem

Earlier study by Andreyev et.al reported that up to 300,000 patients per year undergo pelvic radiotherapy worldwide.(5) With increasing incidence of gynecologic cancers and an epidemiological shift from incidence of communicable to non-communicable diseases in Africa and; improving utilization of pelvic radiotherapy in developing countries, radiotherapy related toxicities are predicted to increase.

Radiotherapy related GI symptoms is a relatively common yet underreported complication of pelvic radiotherapy.(7) The largest obstacles to the successful management of these patients are failure to screen patients for symptoms and accurately diagnose and lack of access to effective treatments. The diagnostic difficulty was addressed by by a prospective cohort of patients with new-onset gastrointestinal symptoms after pelvic radiation therapy and fewer than half of the patients had a singular gastrointestinal diagnosis, and one-third of diagnoses were unrelated to prior radiation therapy.(8) To add to this problem are the sensitive nature of the sideeffects due to which patients hide their symptoms unless actively triggered and when they inform their physicians, their symptoms are ignored due to the lack of awareness on the need of gastro-enterolgist evaluation or due inaccessibility of gastro-enterology care. A study in United Kingdom showed that only a fifth of patients with chronic radiotherapy related GI sideeffects will be referred for Gastro-enterologist evaluation.(9)

It is estimated that 50 to 70% of patients who are treated with pelvic radiation will experience acute injury of the rectum and approximately 10 to 20% of them may develop chronic symptoms (10) The true incidence of RP is probably underestimated, as clinical evaluation usually utilizes toxicity scales that focus on rectal bleeding and do not asses symptoms as mucus discharge, fecal urgency or incontinence(11)

In addition to the physical impact, radiotherapy related GI symptoms can have a profound impact on patients' psychosocial wellbeing, affect day-to-day activities, occupational, and sexual functioning.(4,12,13)

The limited choices of treatment modality together with high cost of the medication and scarcity of Gastro-enterologists and oncologists makes treating radiotherapy related GI symptoms in Ethiopia challenging and decreases the satisfaction of patients.

The studies done on impact of radiotherapy related GI symptoms on quality of life in Ethiopian patients remains insufficient. The only research done on this issue in Ethiopia, at the same hospital, TASH, is before LINAC EBRT machine and Brachytherapy afterloading systems were employed, only on cobalt 60 teletherapy machine, with no standard quality of life assessment and difficult to represent current treatment cohorts(14).

Despite the recent rise in utilization of pelvic radiotherapy and patients reporting radiotherapy related GI sideeffects during the course of gynecologic radiotherapy and on follow-up afterwards, no single study was done to assess the prevalence of radiotherapy related GI symptoms and related Quality of life at TASH radiotherapy center.

Therefore, The aim of this study is to assess the symptoms prevalence, quality of life of patients who took gynecologic radiotherapy, and identify associated factors among patients who completed curative pelvic radiotherapy at TASH radiotherapy center

1.3 Significance of the Study

Although Radiotherapy related GI toxicity is common complication of gynecologic radiotherapy with wide range of diagnostic requirements and treatment modality, multiple factors contribute to delay in recognition and patient dissatisfaction. the This has marked impairment on the patients physical, psychosocial and social wellbeing.

On the part of the patients, withholding information for fear of stigma, the non-specific nature of the symptoms frequently attributed to various infectious disease and, lack of awareness of the need for proper physician evaluation coupled with the distance of patient's residence to oncology and gastro-intestinal subspecialty centers contributes to delay in proper evaluation. The lack of dedicated follow-up to trigger symptom reporting, lack of comprehensive symptom screening tool and frustration with the lack of ready access to gastroenterological evaluation and treatment modalities maybe factors contributing to less diagnosis of this sideeffects.

In Ethiopia little is known about the exact prevalence of the various defining symptoms of radiotherapy related GI toxicity and only few treatment options are accessible and affordable. Radiotherapy related treatment practices are also not studied. When evaluating radiotherapy related sideeffects, there is lack of rigorous screening and proper grading for symptoms and extent of impairment in their quality of life will not usually be asked which will have direct effect on patient health, level of satisfaction with their treatment, their day-to-day activity level.

This study intends to screen patients with symptoms that require proper physician evaluation. It also tries to identify high risk patients who may develop radiotherapy related GI toxicity. By studying the prevalence of the symptoms and patients QoL, it will also alarm the physician to emphasize on listening to patient's concern, to discuss about the nature of symptoms and the treatment modalities applied. It will also shine light on the institution's adherence to QUANTEC GI dose-constraints and the performance of radiotherapy techniques that may suggests symptom development.

Nationwide, it will help to establish a channel of communication between Gastro-enterologists and oncologists and will open discussion on accessibility of treatment.

This research will also inform TASH, policy makers and Ministry of Health to avail different types of medication, to prompt inclusion of the issue in the medical curriculum and develop standard guideline to screen for symptoms, assess severity and impact on quality of life. As this is the first study on the issue in our center, it will provide a baseline data for the future re

2. LITERATURE REVIEW

Radiotherapy is frequently used in the treatment of pelvic cancers, including those of gynecologic origin. Radiotherapy for gynecologic cancers usually employs the use of sequential or interdigitated External beam radiotherapy and boost with Brachytherapy with or without chemotherapy is employed.

A 2017 Australian metanalysis of population benefit of radiotherapy showed that RT adds 5-year LC (local control) benefit of 10.4% and 5-year OS in 2.4% for all cancer types. Among gynecologic malignancies, the 5yr OS (overall survival) benefit for radiotherapy was 21%, and 6% for cervical and uterine cancers while their corresponding 5yr local control benefit was 37% and 6% (15)

Despite the Overall survival and local control benefit, radiotherapy is expectedly associated with treatment related side effect. As more people with pelvic tumors are treated with radiotherapy than any other anatomical site and as more people live longer with cancer or indeed survive it, the burden of radiation related GI side effect increases.(4)

An Ethiopian study in 2019 showed 14,260 new pelvic primary cancer diagnosed with an incremental trend as compared to 2010. The major pelvic primaries with incidence surpassing 1000 were cervical(6570), colorectal(3200), prostate(2570) and bladder cancer(1060).(3) The rise in cases could be because of the increasing population, the shifting to non-communicable disease and improving diagnostic.

Nationwide, there are only three LINAC machines currently functional and a third is on commission while there were none before 5 years. As more people are diagnosed with cervical and uterine cancers and with the improving utilization of Radiotherapy in the country, higher number of patients are expected to develop radiotherapy related GI side effect.

Radiotherapy related GI side effect is interchangeably termed radiation proctitis, colitis and enteritis, when not specified, and mostly classified under an umbrella term, radiation pelvic disease, encapsulating conditions including radiation enteritis, radiation proctitis and radiation cystitis.(4)

Radiotherapy related GI side effect has two clinical phases: Acute and chronic with the acute phase starting with radiation treatment and continuing up to 3 months after end of Radiotherapy while chronic phase starts after 3rd month post radiotherapy and extending up to decades after radiotherapy ended but typically present after a latency period of 6 months to 3 years.(16,17)

Acute Radiotherapy related GI symptoms are primarily a result of cell death in the rapidly proliferating crypt epithelium and a protracted acute inflammatory reaction in the lamina propria resulting in insufficient replacement of the villus epithelium, breakdown of the mucosal barrier, and mucosal inflammation.

Common symptoms in the acute phase include nausea, diarrhea, tenesmus, abdominal cramps, urgency, mucus discharge, fecal urgency, loss of appetite and bleeding.(4) Symptoms of early

bowel toxicity develop in 60-80% of patients during radiation therapy of tumors in the abdomen or pelvis. Nausea typically occurs relatively early, while diarrhea and abdominal pain usually become problematic 2-3 weeks into the course of radiation therapy.(17)

Such non-specific symptoms can overlap with differential diagnoses such as infection, which needs to be excluded. (4) Symptoms of acute PRD most commonly manifest in the second week postradiotherapy and peak in week four or five and resolve within two to six months.

Pathogenesis of chronic radiation related GI toxicity is complex and primarily involves atrophy of the mucosa, fibrosis of the intestinal wall, and microvascular sclerosis and is irreversible. (17)

Signs and symptoms of chronic RT related GI side effect can be related to bowel dysmotility such as urgency, altered transit of feces, malabsorption, fecal incontinence or bleeding.

Patients that experience long standing chronic RT related GI side effect can also experience surgical complications such as bowel obstruction due to stricture formation or adhesions; fissures and fistula formation or frank intestinal perforation. Corrective surgery is associated with high postoperative morbidity and mortality. Long term, the majority of patients have persistent or recurrent symptoms, and about 10% die as a direct result of radiation enteropathy.(17) Radiotherapy increases the risk of post operative, Surgeons should be alert to the fact that PRD may be the cause of acute or sub-acute small bowel obstruction(4)

2.1 Burden of Radiotherapy related GI symptoms

Incidence of patients adversely affected by PRD with symptoms of gastrointestinal disturbance eclipses the number of patients diagnosed with Crohn's disease.(8)

While there are questions regarding the proper screening questionnaires to be used for patient reported symptoms, earlier study by Andreyev showed that up to 80% of patients will develop symptoms related to acute GI toxicity most of which will settle in 3 months.(8)

Reports suggest that between 6% and 78% of long term survivors have gastrointestinal symptoms affecting quality of life'' with a reasonable estimate considering methodological and assessment tools being that 50% of patients will have chronic gastrointestinal side effects affecting quality of life(8)

In the acute setting, non-bloody diarrhea is the commonest complaint. Both in acute and chronic setting, only a third of patients have diarrhea due to proctitis while two-third of diarrhea cases are related conditions such as diverticular disease, bacterial overgrowth, IBD and relapse of primary. In the chronic setting rectal urgency and rectal bleeding after radiotherapy is said to occur in 29 - 51% of patients.

Surgical complications such as stricture and small bower obstruction due to adhesion of the bowel to the irradiated field occurring particularly in those who had abdominal surgery before

radiotherapy occur in up to 5% of patients. Fistula formation especially after brachytherapy for gynecologic cancers and the development of secondary malignancy are also other complications needing consideration.(5) Generally, a third of patients with chronic radiotherapy related GI complication may end up having surgery.(18)

Of the chronic GI toxicity, fecal incontinence is underreported , possibly due to embarrassment and because there are insufficient prospective studies assessing fecal incontinence using adequate, validated and reproducible methodology(12) However, published data show 8–56% of patients have reduced quality of life as a result of fecal incontinence.(8)

Development of secondary neoplasm after pelvic radiotherapy is also considered as a delayed complication and Pooled analysis of 23 studies showed an increased risk of rectal cancer following radiotherapy (RR 1.43).Organ-specific meta-analysis showed an increased risk of rectal cancer after radiotherapy for cervical (RR 1.61) cancer. (19)

The symptoms related to chronic radiation GI toxicity have a significant impact on quality of life. Chronic radiation enteritis affects patient's physical, psychological and social aspects of their lives to the extent enforcing some to be virtually housebound.

2.2 Factors predicting radiotherapy related GI symptoms patients

Development of Radiotherapy related GI sideeffects are have multifactorial causation most of which are not yet known and predicting consequent risk of toxicity development and prevention are not entirely not possible. There appears to be a complex interaction of patient, genetic and treatment factors that contribute to incidence, severity and chronicity of symptoms.(20,21)

Patient related factors associated with development of radiotherapy related GI side effect include chronic illnesses such as hypertension, diabetes, HIV and inflammatory bowel diseases. (1,22) Fuccio et al reported that diabetes mellitus increases the risk 2 times while HIV and hypertension increase it by 1.4 times and 4 times respectively. Inflammatory bowel disease is associated with having significantly greater risk of developing loose stools than patients without IBD (hazard ratio, 2.31).

The association between hypertension and development of GI toxicity are not established with many researches showing no correlation. Prospective research to investigate the effect of HIV among cervical cancer patients didn't show a significant association with development of acute GI toxicity.(23)

Lifestyle factors such as reduced body mass index (BMI) and smoking also contribute to the severity of late effects of radiotherapy. Patients with BMIs less than 18.5 have 2- to 4-fold worse symptoms than patients with BMIs greater than 18.5kg/m^2 while the risk of late, rectal, and small-

bowel complications increased significantly among those who smoke 1pack/day compared with nonsmokers; the hazard ratio for rectal complications was 2.18 and for small-bowel toxicity was 3.97.(24)

Previous abdominal surgery increases the risk of acute and late GI toxicity by causing entrapment of the bowel. Patients treated with concurrent chemoradiotherapy have increased risk of acute bowel toxicity.(22)

Late consequential effect resulting from acute bowel toxicity is reported to suggest occurrence of late bowel toxicity.(25) A high rate of acute rectal toxicity is now recognized as associated with late RT proctopathy (18,21,22). In the Dutch randomized dose trial for localized prostate cancer, it was an independent significant predictor for late gastrointestinal (GI) toxicity (20,22). This raises the question as to whether early interventions that lessen acute toxicity might also reduce the risk of late complications, or whether greater-than expected acute toxicity might be an early indicator of patient hypersensitivity to RT.(26)

Radiotherapy related factors including the total and fractional dose of radiotherapy, volume of irradiated tissue ,radiotherapy delivery techniques, patient positioning and positioning devices used and implementation of different pharmacologic interventions were studied in different researches. (1,26,27)

QUANTEC dose-volume parameter significantly associated with increased risk of bleeding, overall late rectal toxicity is above 60 Gy with many studies suggesting non significance if total dose is below 45 Gy. QUANTEC suggests that for prescriptions up to 79.2 Gy, rectal dose constraints V50 < 50%, V60 < 35%, V65 < 25%, V70 < 20%, and V75 < 15% in 3D treatment planning utilizing standard fractionation of 1.8Gy-2Gy should limit probability of Grade 2 late rectal toxicity to <15% and the probability of Grade 3 late rectal toxicity to <10% standard 1.8- to 2-Gy fractions.(26)

QUANTEC reviews recommend dose-volume constraints for acute bowel toxicity based on peritoneal cavity and bowel loops as V15< 120 cc for individual bowel loops and V45<195 cc for the entire peritoneal cavity keep the risk of grade 3+ acute bowel toxicity below 10%. Despite no constraints are found for late toxicity and reviewers recommend using these same constraints for late bowel toxicity with a comment that this correlation is not established.(26,28)

Results are mixed for intermediate doses with researches suggesting significance only when the volume of irradiated tissue is significantly high.(26)

As the technique of pelvic radiotherapy is becoming more conformal, the bowel toxicity score is also reducing which has allowed for dose escalation.

A meta-analysis of radiotherapy techniques and GI toxicity has shown that in prostate and cervical cancer, IMRT was favorable over 3D conformal RT in reducing acute (RR) 0.48, and
late gastrointestinal toxicity grade 2+ (RR 0.37). This same research reported that Comparison of Conformal RT (3DCRT or IMRT) versus conventional RT showed reduced acute GI toxicity grade 2+ (RR 0.57) and trend to less late GI toxicity grade 2+ (RR 0.49). (1)

These outcomes are supported by postoperative RT studies for endometrial and cervical cancer as Time-c, which associated IMRT with less frequent diarrhea and antidiarrheal use in the acute setting, and in MSKCC study with less bowel obstruction at 5 years with IMRT.
(29,30). Another research of definitive Brachytherapy to post operative endometrial and cervical cancer associated reduced risk of bowel obstruction to the IMRT group 0.9% vs 9.3% for 3D RT.(29)

Definitive brachytherapy to early stage endometrial cancers shows reduced acute GI toxicity (grade 2+) (RR 0.02).(1)

A retrospective study by MSKCC on 61 patients treated with prostate only radiotherapy to dose of 81 Gy with either of 3D-CRT or IMRT showed a statistically significant reduced dose to rectal wall, decreased rate of combined G1 and G2 GI toxicity and risk of late G2 rectal bleeding(2% vs 10%) in favor of IMRT.(31)

Multiple dose escalation studies utilizing brachytherapy for cervical and endometrial cancer were associated with decreased risk of GI toxicity.

Portec-2 study of adjuvant radiotherapy for endometrial cancer showed that EBRT was associated with more diarrhea, fecal leakage, need to be close to toilet and impaired activity of daily living as compared to vaginal brachytherapy.(32)

In HDR-Brachythapy for gynecologic malignancy, multiple trials have shown inferiority of point based planning as compared to Image guided brachytherapy planning in terms of tumor control, Disease free survival and toxicity profile.(33–35) In RetroEMBRACE trial, the 5 year grade 3-5 GI toxicity rate was 7% while the French-STIC trial showed substantially lower grade 3-4 toxicity rate with image guided radiotherapy (2.6% vs 22.7%).

For centers utilizing the point-based planning, D2cc rectum/rectovaginal point < 65-75 Gy EQD2 is recommended.

2.4 Tools to measure Quality of life in radiotherapy related GI symptoms

For patients experiencing PRD to receive appropriate treatment, they must first be identified. For symptomatic evaluation and toxicity scoring/grading, studies used different criteria which has caused decreased comparability in meta-analyses due to the wide variety of toxicity scores in use.

Many studies use their own toxicity scores, as investigators have found the above to be inadequate and in addition, in the developing world, patient-based questionnaires are not appropriate, due to language and literacy constraints. In summation, the recording of late toxicity is very unsatisfactory

The difference in the symptoms included from trial to trial emanates from the goal of the questionnaire and also because

Researches used Inflammatory Bowel Disease Questionnaire-bowel function dimension (IBDQ-BD), Gastrointestinal Symptom Rating Scale (GSRS) or any other questionnaire along with Common Terminology Criteria for Adverse Events (CTCAE), European Organization for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG) scoring system for symptom grading.(1,13,36)

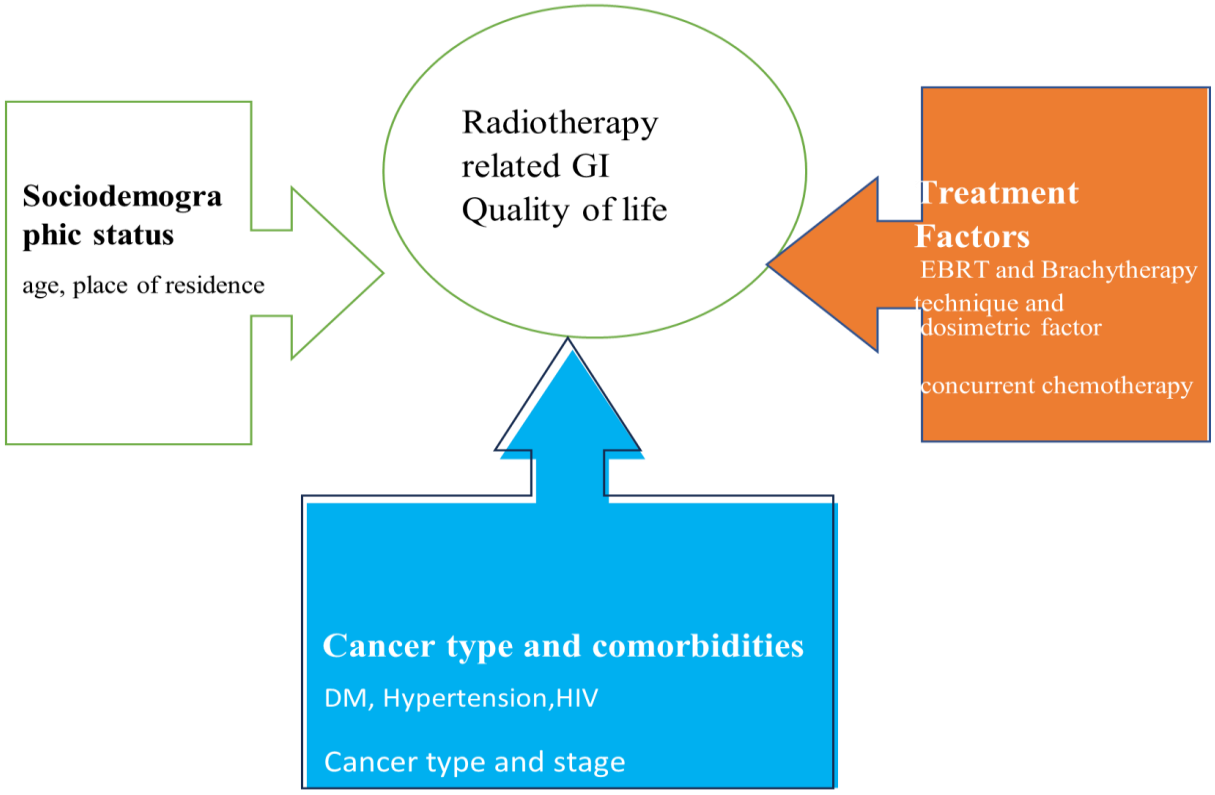
Gastrointestinal Rating Scale (GSRS) with 15 questions is criticized for being to long for routine symptom screening and the IBD-Q was even longer with thirty-two questions. Another assessment tool, the Vaizey incontinence questionnaire, focused on only fecal incontinence and would therefore not provide detailed information on other symptoms.(37)LENT SOMA is the most extensive but entirely unsuited for day-to-day use in the busy clinic setting.

Therefore, Taylor et al (2016a) developed a validated three question symptom screening tool for routine clinical use after pelvic radiotherapy, entitled ALERT-B (Assessment of Late Effects of Radiotherapy- Bowel) consisting of three major questions related to bowel control, blood in stool and any bowel symptom affecting mood, activity of daily living.(36)

There are different radiotherapy related GI symptom QoL assessment tools used depending on the site of primary cancer yet the recently validated EORTC radiation proctitis questionnaire QLQ-PRT20 is a global tool recommended to assess QoL and follow for new symptom development.(13)

The revised version, the QLQ-PRT20 comprising of 20 questions intended to assess five dimensions: Bowel Control; Bloating and Gas; Emotional Function/Lifestyle; Pain; and Leakage. Three additional items are included to gain specific clinical information relevant to patient comfort and future treatment.(13)

2.5 Conceptual frame work



OBJECTIVES

3.1 General objective:

- ✓ To assess the prevalence of radiation related GI toxicity and quality of life among cervical and endometrial cancer patients who received curative intent radiotherapy at Black Lion Specialized Hospital, Addis Ababa, Ethiopia

3.2 Specific objectives:

- ✓ To assess the prevalence of radiation related GI toxicity among cervical and endometrial cancer patients who received curative intent radiotherapy at Black Lion Specialized Hospital, Addis Ababa, Ethiopia, 2023
- ✓ To identify associated factors of GI quality of life among cervical and endometrial cancer patients who received curative intent radiotherapy at Black Lion Specialized Hospital, Addis Ababa, Ethiopia,2023
- ✓ To assess the magnitude of quality of life among cervical and endometrial cancer patients who received curative intent received radiotherapy at Black Lion Specialized Hospital, Addis Ababa, Ethiopia, 2023

4. METHODS AND MATERIALS

4.1 Study Area and Period

The study was conducted at the Oncology unit of Tikur Anbessa specialized hospital (TASH), Addis Ababa Ethiopia. TASH is a tertiary-level hospital equipped with cancer diagnostic and treatment facilities. It is one of the three cancer treatment centers in Ethiopia. Cervical and endometrial cancer patients who took curative radiotherapy for cervical and endometrial cancer at the center between June 2023 and November 2023 were enrolled for the study.when was data collection done

4.2 Study Design

Hospital based cross sectional study was conducted.

4.2.1 Source Population

All pelvic patients who took curative cervical and endometrial cancer patients with curative intent at the radiotherapy unit of Tikur Anbessa hospital during the study period.

4.2.2 Study Population

All cervical, endometrial, cancer patients who took curative intent radiotherapy at the radiotherapy unit of Tikur Anbessa hospital during the study period and fulfill the inclusion criteria.

4.3 Sample Size and Sampling Procedure

Sample size was be calculated based on a single population proportion formula for the 1st objective

Sample size (n) $= 0.2 \cdot 0.8 \cdot (\frac{1.96}{0.05})^2 \approx 247$

Where: n = the desired sample size

$Z_{\alpha/2}$ = Z-value for a 95% confidence level which is 1.96

d = the marginal error tolerated degree of confidence (5%=0.05)

P =Proportion of gynecologic cancer patients who developed chronic radiation proctitis based on previous study reported by Andreyev et.al

Based on the above assumptions a total of 247 patients will be required for the study.

Since the total number of patients who took curative intent radiotherapy for cervical and endometrial cancer at TASH in the specified time is less than 10,000 then

$$nf = \frac{no}{1 + \frac{no}{N}} = 87 \quad \text{Where}$$

n_f = final sample size

n_o = initial sample size which is 247

N = total population which is 123

With population correction formula the final sample size(n_f) will be **83 .**

Taking a 10% contingency (non-response rate), the final sample became **92**.

But since there are no 92 patients who were treated at the center with curative intent radiotherapy for cervical or endometrial cancer at the specified period, we have used census method.

4.4 Sampling technique

Due to few numbers of patients who were treated at the center with curative intent radiotherapy for cervical or endometrial cancer as seen from EBRT Treatment planning records and HDR Gynesourse treatment system, all patients that fulfill the inclusion criteria were included for the survey during the data collection period.

4.5 Study Variables

4.5.1 Dependent Variable

- Symptom scores based on PRT-20

4.5.2 Independent Variables

- Age, comorbidity (HIV, Diabetes, IBD, Hypertension), site of primary tumor (cervical or endometrial), pre-RT surgery and/or chemotherapy and intent, bladder volume, rectal

diameter, External beam radiotherapy type, radiotherapy dose/s and fractionations, brachytherapy dosimetry (Point A and rectal dose). and applicators, table to applicator clamp site time of radiotherapy completion, EBRT DVH for peritoneal cavity/bowel bag V45Gy and rectum (V50Gy, V60Gy and V65Gy)

4.6 Inclusion and Exclusion criteria

4.6.1 Inclusion Criteria

All cervical and endometrial cancer patients who completed radical dose curative gynecologic radiotherapy with minimum tumor EQD2 of 4500cGy at TASH radiotherapy center during the study period.

4.6.2 Exclusion Criteria

Patients who are not alive or not reachable on phone or are critically ill.
Patients who had documented rectal/anal invasion (due to risk of symptom overlap)
Patients who took part of their radiotherapy at other centers like Jimma or Haremaya university medical center (incomplete radiotherapy data)
Difficulty communicating

4.7 Operational Definitions

Gynecologic malignancies referred in this research are uterine and cervical cancers.

Criteria for diagnosis of radiotherapy related GI side effect is based on symptomatic evaluation as presented in the Inflammatory Bowel Disease Questionnaire-bowel function dimension IBDQ-BD), Gastrointestinal Symptom Rating Scale (GSRS). Yet Since there is significant overlap between these and the recently developed EORTC QLQ – PRT20 – Proctitis Module, we'll use the later.

Quality of life

For evaluation of quality of life of patients EORTC QLQ – PRT20 – Proctitis Module was used. Raw data were generated and converted to symptom score grouped into 5 as per module.(13) (see annex)

Severity of radiotherapy related GI symptoms

Patients with symptoms suggestive of radiotherapy related GI symptoms was staged for severity based on the Common terminology criteria for adverse effects 5.0. (38) Symptoms chosen for CTCAE reporting are fecal Incontinence, rectal hemorrhage and diarrhea.

Dosimetric parameters

a Vx refers to the volume of the target volume receiving x% of the dose (i.e., V100 refers to the volume receiving 100.0% of the prescription dose)

-VxGy refers to the volume of the target volume receiving x Gy (i.e., V5Gy refers to the volume of the organ at risk receiving 5 Gy).

- Dx% refers dose received by x% of target volume (i.e., D98% refers to the dose received 100.0% of the prescription dose)
- EQD2 was calculated with the equation $EQD2 = D \times [(d + \alpha/\beta)/(2 + \alpha/\beta)]$, as derived from the linear-quadratic model; D = total dose, d = dose per fraction, α = linear (first-order dose-dependent) component of cell killing, β = quadratic (second-order dose dependent) component of cell killing, α/β ratio = the dose at which both components are equal.

Linear Transformation**:** To obtain the Score S, standardize the raw score (ITEM SUM for symptom group) to a 0 – 100 range following the transformation:

$$\text{Symptom scale}=\left(\frac{\boldsymbol{raw\ score-1}}{\mathbf{3}}\right) * \mathbf{100}$$

4.8 Data collection procedure

All patients who fulfill the inclusion criteria and are treated between Jun and Nov 2023 were enrolled. Radiotherapy related data was collected from VARIAN RT PLANNING SOFTWARE DATABASE and Brachytherapy planning DATABASE by the principal investigator of the study.

Clinical and demographic data was collected from patients records (institutional computer data base and medical chart) and corroborated with the patient during telephone questionnaire. Radiotherapy related GI symptoms and QoL Data was collected by telephone interview using closed ended questionaries after clearly explaining the purpose and taking verbal consent from patients that fulfill inclusion criteria. Three health professionals who were trained did the r data collection under close supervision and facilitation by the principal investigator. Questionnaires were formed by electronic form using Kobo Toolbox mobile application and the link were sent to data collectors. Each day, the collected data were checked for accuracy and completeness. Data collection were done by kobo toolbox application using mobile devices

Data collection were conducted after receiving ethical clearance from the TASH oncology department ethical review committee.

4.9 Data Quality Control

Questionnaire were translated into Amharic, were checked for completeness before entry into the ODK application and data collection. The questionnaire were pre-tested on 5% of sample size on randomly selected individuals from the research area and these individuals were not included in the main study. During the pre-test, the questionnaire was assessed for its clarity of the questions, accuracy of responses, estimate of time required, any difficulties, proper functioning of the application and modifications were made on the basis of the findings. When the ODK questionnaires were prepared, those mandatory questions had asterixis in which one cannot proceed to the other question without answering it. Daily collected data will be sent to the investigator who will check for completeness of the data daily

4.10 Data Analysis

After collecting questionaries, completeness was checked, cleaned and coded and exported to SPSS version 26 for further analysis. For symptom severity assessment was made based on the CTCAE as attached below. For quality of life evaluation, EORTC PRT-20 scores as no, small, moderate and very large effect on patient's life and grouped into 5 groups and analyzed based on EORTC PRT-20. Descriptive statistics such as mean and standard deviation for continuous and frequencies for categorical variables were calculated.

To determine the factors linked to poor quality of life, inferential statistics was done. First inferential analysis, .using pearsons and independent T test with consequent linear regression was planned but due to failure of assumption tests the non-parametric tests ,Mann Whitney U and Spearman's correlation test were used for analysis Statistical significance on the link of the predictor variables to quality of life was determined at P-value < 0.05.

4.11 Ethical consideration

To respect patients' rights, and the regulation of the hospital where the study was conducted, ethical considerations was taken into account. A written formal letter was obtained from the oncology department at black lion hospital before commencing the data collection process.

For the questionnaire verbal consent was be taken from each participant after explaining the importance of the study and the benefits and risks of the study

The right of respondents to withdraw from the study or not to participate at all was explained and respected. The information collected from the study participants will be kept confidential and will be used only for the study purpose. This study will not inflict harm on or expose the patients to unnecessary risk. All patients will continue to receive care and treatment irrespective of their decision in participation of the study.

4.12 Dissemination of result

The result of the study will be submitted to TASH clinical oncology department, public health department, ministry of health, national and international oncology associations and stakeholders. Attempts will be made to present it in scientific conferences and publish it in a journal.

5. Result

5.1 Descriptive statistics

From brachytherapy planning system, a total of 123 patients who took brachytherapy at TASH Radiotherapy center were identified and 68 of the patients were eligible be included in the study.

The median age of participants is 52.8 years (range 30-78 years). As seen in the table below 78% of participants were from urban areas.

The study population included 64 cervical cancer and 4 endometrial cancer patients. Most frequent cervical cancer stage is FIGO stage 2B (48.5%) and the least frequent is stage 2A2(2.2%). There are also 4 cases of Recurrent cervical cancer after surgical management and 4 cases of endometrial cancer.

Table 1

Cervical Cancer	Frequency	Percent
Recurrence	4	5.9
Stage 2A2	2	2.9
Stage 2B	33	48.5
Stage 3A	6	8.8
Stage 3B	4	5.9
Stage 3C1	8	11.8
Stage 3C2	3	4.4
Stage 4A	4	5.9
Total	68	100.0

The number of patients with comorbidities is 3 diabetes, 6 Hypertension and 12 participants had RVI.

Regarding abdominal surgeries, 8 patients had hysterectomy done while 2 patients underwent exploration.

52 patients (81% of cervical cancer cases) received concurrent chemotherapy with a mean chemotherapy cycle number of 2.9. The commonest symptom reported during radiotherapy was

diarrhea (n=19) while vomiting, nause, rectal bleeding, and abdominal pain were reported by 15,10,2 and 2 patients.

Mean bladder volume during scanning was 1332.0 cc ranging between 357 cc and 2936 cc. The mean rectal diameter during simulation for EBRT was found to be 5.33 cm with range between 1.33 and 20 cm.

Frequently used planning brachytherapy applicator ring size is 42-2 (n=42). Tandem size 42-7(n=31) and tandem size 42-8(n=14) are also used in conjunction. The median time of EBRT completion IS 24 days while the mean Radiotherapy completion time is 77 days.

Mainly utilized Phase 1 EBRT dose and fractionation were 36 Gy in 12# (50% of the patients) and 40 Gy in 15# (36%) of the patients. EBRT mean EQD2 to tumor, rectum and the bowel bag(peritoneal cavity) were 42.20 Gy, 34.89 Gy and 33.79 Gy respectively. Average EQD2 rectal point dose from Brachytherapy was 9.52Gy which makes the assumed total rectal dose from the combined radiation 42.0Gy.

As per the EORTC QLQ 30 Module and the classification of the symptoms into 5 symptom score classes of the EORTC, Participants response to the EORTC PRT- 20 proctitis questionnaire is transformed into five symptom scores each out of 100.(see annex)

Table 2

Outcome variables	Range	Minimum	Maximum	Mean ±Std. Deviation
Symptom score-Bowel and Gas	88.89	11.11	100.00	32.02± 23.70
Symptom score-Leakage	66.67	.00	66.67	3.43±12.73
Symptom score-bowel control	58.33	.00	58.33	6.84±12.21
Symptom score-PAIN	44.44	.00	44.44	8.00±13.27
Symptom score-Emotion	80.00	.00	80.00	13.82±18.47

Table 3

Assessment of Radiotherapy	Minimum	Maximum	Mean Std. Deviation
Table Top	12.0	20.5	17.27±1.61
maximum rectal diameter	1.34	20.00	5.34± 3.41
Bladder volume	35.70	2936.00	1332.01±668.02
BOWEL BAG mean dose in cGy	1509.00	3373.90	2047.37±744.64
BOWEL BAG V4500.0 cGY	0.00	1323.00	2.95±7.82
Rectal dose V5000.0 cGy	0.00	0.00	0.00
Rectal dose V6000.0 cGy	0.00	0.00	0.00
Rectal dose V6500.0 cGy	0.00	0.00	0.00
EBRT Rectal dose %	26.61	98.00	49.83 ± 11.99
EBRT PHASE 1 in Gy	30.00	42.00	38.28 ± 3.30
Fraction of phase 1 EBRT	10.00	25.00	13.84 ± 2.78
EBRT Boost Total	0.00	16.00	1.462 ± 3.93
Boost fraction	0	8	0.72 ± 1.954
Tumor EQD2 phase 1	32.50	55.19	40.83 ± 2.98
EBRT PHASE 2 Tumor EQD2	0.00	16.00	1.44 ± 3.90
Total Tumor EBRT dose EQD2	32.50	65.19	42.28 ±5.55
BRACHY TUMOR EQD2(cGy)	12.00	36.00	34.58 ± .41
Total tumor dose in EQD2(cGy)	51	98	76.8±6.81
Mean EBRT rectal dose in percentage	0.00	137.27	79.59 ±26.02
EBRT Rectal dose in EQD2 (cGy)	39.00	5902.70	3480.53 ±754.09
Brachytherapy Rectal dose in EQD2(cGy)	0.00	3900.00	952.42 ±598.63
Assumed Total rectal dose in EQD2(cGy)	538	7817	4200.21 ±1308.06
EBRT Completion time(days)	12	137	24.8 ±18.8
Radiotherapy Completion time(days)	25	239	68.63 ±37.22

5.2 Inferential statistics

For one-to-one comparison of independent variables against dependent variables (symptom scores) with Anova, independent T-test and Bivariate analysis with Pearson correlation was planned yet test for fulfillment of assumption failed. Thus, after testing fulfillment of assumption for non-parametric analysis, Mann-whitney U test and spearman tests were done and the result is as shown below.

Table 4

Maximum rectal diameter vs bowel and gas symptom score			maximum rectal diameter	Bowel and Gas score
Spearman's rho	maximum rectal diameter	Correlation Coefficient	1.000	-.282*
		Sig. (2-tailed)	.	**.021**
		N	67	67
	Bowel and Gas score	Correlation Coefficient	-.282*	1.000
		Sig. (2-tailed)	**.021**	.
		N	67	68

Table 5

Bowel control score vs Assumed rectal EQD2			**Bowel control score**	total rectal EQD2
Spearman's rho	Symptom score-BOWEL CONTROL	Correlation Coefficient	1.000	.299*
		Sig. (2-tailed)	**.**	**.014**
		N	67	67
	total rectal EQD2	Correlation Coefficient	.299*	1.000
		Sig. (2-tailed)	**.014**	**.**
		N	67	68

Table 6

Pain score vs number of concurrent chemotherapy cycles			Pain score	number of concurrent chemotherapy cycles
Spearman's rho	Symptom score-PAIN	Correlation Coefficient	1.000	.249*
		Sig. (2-tailed)	.	.046
		N	68	65
	number of concurrent chemotherapy cycles	Correlation Coefficient	.249*	1.000
		Sig. (2-tailed)	.046	.
		N	65	65

Table 7

Pain score vs bladder volume			Pain score	Bladder volume
Spearman's rho	Pain score	Correlation Coefficient	1.000	-.296*
		Sig. (2-tailed)	.	**.016**
		N	68	66
	Bladder volume	Correlation Coefficient	-.296*	1.000
		Sig. (2-tailed)	**.016**	.
		N	66	66

Table 8 and Table 9

Time since RT completion (less than 90 days vs more than 90 days	Pain score
Mann-Whitney U	309.500
Wilcoxon W	660.500
Z	**-2.110**
Asymp. Sig. (2-tailed)	.035

Radical Hysterectomy	Emotion/Life style score
Mann-Whitney U	152.500
Wilcoxon W	197.500
Z	**-2.189**
Asymp. Sig. (2-tailed)	.029

6. Discussion

In conclusion, combined EBRT and intracavitary brachytherapy with concurrent administration of chemotherapy has improved the survival and locoregional control control. But various factors are being considered to contribute for the development of bowel toxicity and until present time there is no consistently demonstrated predictor of development of radiation GI toxicity other than the radiation dose

This study was conducted to assess the GI related quality of life and associated factors in the of cervical and endometrial cancer patients who were treated with definitive dose radiotherapy with combined EBRT and intracavitary brachytherapy.

Fourty eight(70%) of the study participants have at least one GI symptom they attributed to come since radiotherapy which is similar to earlier studies(5,12)

This study also has shown that while patients receive an average of 2.9 cycles of chemotherapy, the number of concurrent chemotherapy is positively related with the development of higher Pain score with a significant positive correlation which is consistent with previous studies.(1)

Due to the few natures of diabetic and hypertensive patients there was no association seen.

While researches suggest that the development of acute toxicity implies late consequential effect as a predictor of a late GI toxicity, however in this small sample study, no association was demonstrated in this study.(26,28)

Patients who had hysterectomy are associated with a higher emotion score as seen on mann whitney U test consistent with previously established knowledge.(1)

While QUANTEC suggests that for prescriptions up to 79.2 Gy, rectal dose constraints V50 < 50%, V60 < 35%, V65 < 25%, V70 < 20%, and V75 < 15% in 3D treatment planning to limit clinically significant bowel toxicity, the assumed mean rectal EQD2 is around 55Gy, but as one is 2D and the other volumetric, summation is misleading. But this assumption may still be a better estimate of the true rectal dose as is seen in our study population where total rectal EQD2 was directly related with high bowel control symptom score.

Reaffirming the previously held knowledge that the bladder volume is negatively related to development of sideeffects and quality of life, a significant yet a negative correlation is found on spearman test.

Exploration for any association between used applicator type and the table top (table to clamp site distance) didn't show any significance likely due to the limited number of the sample size and the secondary nature of the variables.

7. Conclusion and recommendation

7.1 conclusion

In conclusion, the rectal point EQD2 of 9.52 Gy and mean and the QUANTEC rectal and bowel doses are within recommended range but the rectal diameter of 5.33 cm during simulation are out of the recommended reproducible empty rectum. This research has also described a 70% probability of any GI bother symptom among patients.

7.2 Recommendation and limitation

Considering the significant proportion of cervical and uterine cancer patiets who develop symptoms related to pelvic radiotherapy with a compromise in their quality of life, better patient followup and linkage to gastroenterology care shall be made routine.

While this research shines light on the prevalence of bowel bother among patients, its limitations are the method of data collection which is telephone based and the lack of any previously validated Amharic version of EORTC QLQ PRT-20 Questionnaire.

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Annex 1 Data collection tool

Data collection tool - Radiotherapy related GI Side-effects

Code ---------- I-Care Number _____ Phone Number_____

Demographic data

Age _____*Region* _____ *Residence Urban/rural*

Lifestyle and comorbidity

Smoking *History? Yes/no If yes before/during/after radiation? Pack year* _____

BMI(kg/m^2) at time of Radiotherapy _____

Comorbidity?

Hypertension Diabetes IBD_crohns disease/ulcerative colitis RVI

If yes*, describe duration since diagnosis/treatment/If RVI,CD4 (latest)*

_____

_____

*Any known GI condition like Dyspepsia before Radiotherapy? Yes/No Specify*_____

Treatment related data

Diagnosis - Cervical ca/ Endometrial cancer

TNM _____ Group stage _____ Histology

Any abdominal/pelvic surgical History (yes/no)

Describe when/why and Type of surgery

_____

_____

Any chemotherapy received? Yes/no If yes, before/during/after radiotherapy

Describe number/ type/Last cycle of chemotherapy regimen _____

Any GI related Symptom during Radiation? YES/NO CTCAE Grade? _____

Management _____

Radiotherapy related Data

Radiotherapy intent (Definitive/Adjuvant) **Date of start of EBRT** _____

If adjuvant, describe indication _____

EBRT

Scanned with contrast? Yes/no Prescribed dose (Gy) and fraction _____Received dose (Gy) _____

If full dose not received, describe reason _____

EBRT Techenique used -3D-CRT /IMRT/VMAT

PTV volume (in cm^3) _____

Dose to PTV (Gy) _____

Bladder volume (in cm^3) _____

Rectum size (maximum diameter in cm) _____

Rectal constraint V50 _____ V60 <_____V65_____

Bowel definition (contoured in loops/bowel bag)

Individual bowel loops constraints V15_____Peritoneal cavity constraints V45_____

BRACHYTHERAPY

Prescribed dose(Gy) and fractionation _____ Received fractions _____

sum total EQD2 received(Gy) _____

If full dose not received, describe reason _____Date of last Brachytherapy____

Type of applicator_____ Size of applicator _____

Table top _____ Gauze used during scanning? Yes/no _____

Gauze used During brachytherapy treatment? circle fractions_ 1st 2nd 3rd 4th

Rectal/Rectovaginal dose (as percentage of prescribed dose) _____EQD2 received(Gy) _____

Annex 2 EORTC QLQ PRT-20 Questionnaire English form

The aim of this questionnaire is to measure how much your GI problem has affected your life.

Numbered as given by EORTC-PRT-20-QLQ format.

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you					
During the past week		Not at all	A little	Quite a bit	Very much
31.	Have you had a **bloated feeling in your abdomen**?	1	2	3	4
32.	Were you **troubled by passing wind / gas / flatulence**?	1	2	3	4
33.	Have you had **excessive gurgling noise** from your abdomen?	1	2	3	4
34.	Have you had any **unintentional release (leakage) of wind** or mucous?	1	2	3	4
35.	Have you had any unintentional **release (leakage) of liquid stools?**	1	2	3	4
36.	Have you needed to get up at night to open your bowels?	1	2	3	4
37.	Have you had abdominal pain or **cramping** not related to a bowel movement?	1	2	3	4
38.	Have you had pain or **cramping in your rectum** (deep inside the back passage)?	1	2	3	4
39.	Have you **had pain /discomfort** around your anal opening (back passage)?	1	2	3	4
40.	Have you had **bright blood** in your stools?	1	2	3	4
41.	Have you been unable to **wait 15 minutes** to open your bowels?	1	2	3	4
42.	Have you had the feeling of being unable to **completely empty your bowels?**	1	2	3	4
43.	Does **passing water** cause your bowels to act immediately?	1	2	3	4
44.	Have you had **difficulty going out of the house**, because you needed to be close to a toilet, because of bowel problems?	1	2	3	4
45.	Did your **treatment restrict the types of food** you can eat due to your bowel problems?	1	2	3	4

46.	Did you **worry** about your bowel problem?	1	2	3	4
47.	Did you feel **embarrassed** by your bowel problem?	1	2	3	4
48.	How **unhappy** would you feel if you lived the rest of your life with your bowel habit as it is now?	1	2	3	4
49.	Have you needed to take medication to control diarrhea?	1	2		
50.	What was the **highest number of times** you had to open your bowels in any 24 hours period? Please indicate number in box?				
51.	Would you like more **assistance** to manage your bowel problem? (optional question)	Yes	No		

OVER THE LAST WEEK. Please tick (□) one box for each question

Thank you for your participation.

Annex 4-EORTC PRT -20 QLQ Scoring Principle

EORTC QLQ-PRT20 Scoring Manual

The EORTC Proctitis Module (QLQ-PRT20) is a supplementary questionnaire module to be employed in conjunction with the QLQ-C30. The QLQ-PRT20 incorporates 5 multi-item scales to assess proctitis symptoms following cancer treatment to the pelvis. In addition, 2 single item assess whether the patient has needed to take medication to control diarrhoea (yes/no) and whether the patient would like more assistance to manage their bowel problem (optional question - yes/no). A third additional question asks patients to identify the highest number of times they have needed to open their bowels in any 24 hour period (number).

The scoring approach for the QLQ-PRT20 is identical in principle to that for the symptom scales of the QLQ-C30. All scoring information specific to the QLQ-PRT20 is presented in Table 1.

Interpretation:
All of the scales and single item measures range in score from 1 to 4. A high score for the items represents a high level of symptomatology or problems.

Table 1. Scoring the QLQ-PRT20

	Scale	Number of items (n)	Item range*	QLQ-PRT20 item numbers ($I_1, I_2, \ldots, I_n$)
Multi item scales				
Bloating and Gas	BG	4	3	31-33, 37
Leakage	LK	2	3	34, 35
Bowel Control	BC	4	3	36, 41-43
Pain	PA	3	3	38-40
Emotional Function / Lifestyle	EFL	5	3	44-48

* "Item range" is the difference between the possible maximum and the minimum response to individual items. All items are scored 1 to 4, giving range = 3.

Principle for scoring

1) **Raw score**
For each multi-item scale, calculate the average of the corresponding items.

$$Raw\ Score = RS = \left\{\frac{(I_1 + I_2 + \ldots + I_n)}{n}\right\}$$

2) **Linear Transformation**
To obtain the Score S, standardize the raw score to a 0 – 100 range following the transformation:

Symptom scales: $S = \left\{\frac{(RS-1)}{range}\right\} \times 100$

For directions on Missing Data or for more detailed information on the Interpretation of Scores, we redirect to the EORTC QLQ-C30 Scoring Manual (2001).

Further questions or remarks regarding the scoring algorithms for the QLQ-PRT can be directed to the QOL Specialist at the Quality of Life Department of the EORTC.

Reference papers

Halkett, G. K. B., Wigley, C. A., Aoun, S. M., Portaluri, M., Tramacere, F., Livi, L., Detti, B., Arcangeli, S., Lund, J, Kristensen, A., McFadden, N., Grun, A., Bydder, S., Sackerer, I., Reimel, E., Spry, N on behalf of the EORTC Quality of Life Group. (2018). International validation of the EORTC QLQ-PRT20 module for assessment of quality of life symptoms relating to radiation proctitis: a phase IV study. Radiat Oncol, 13(1), 162. doi:10.1186/s13014-018-1107-x

Halkett, G., Aoun, S., Hayne, D., Lund, J. A., Gruen, A., Villa, J., Livi, L., Arcangeli, S., Velikova, G., Spry, N., on behalf of the EORTC Quality of Life Group (2010). EORTC radiation proctitis-specific quality of life module - pretesting in four European countries. Radiother Oncol, 97(2), 294-300. doi:10.1016/j.radonc.2010.04.001

Spry, N., Halkett, G., Aoun, S., Spry, J., & Yeoh, E. (2008). Development of a European organization for research and treatment of cancer module to assess the quality of life of patients with proctitis after pelvic radiotherapy for malignancy. International Journal of Radiation Oncology, Biology, Physics, 72(2), 522-528. doi:10.1016/j.ijrobp.2007.12.062

Annex 5 Common Terminology Criteria for Adverse Events (CTCAE) v5.0 relevant to radiation proctitis(39)

Adverse event	Definition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Proctitis	A disorder characterized by inflammation of the rectum	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Diarrhea	A disorder characterized by frequent and watery bowel movements	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
fecal incontinence	A disorder characterized by inability to control the escape of stool from the rectum	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated		

Rectal hemorrhage	A disorder characterized by bleeding from the rectal wall and discharge from the anus	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated, invasive intervention indicated; hospitalization	Life threatening consequences; urgent intervention indicated	Death

ANNEX 6 – EORTC PRT 20 Questionnaire response- frequency table

		Frequency	Percent
bloating	Not at all	40	58.8
	A little	15	22.1
	Quite a bit	13	19.1
	Total	68	100.0
		Frequency	Percent
wind / gas / flatulence?	Not at all	54	79.4
	A little	7	10.3
	Quite a bit	7	10.3
	Total	68	100.0
		Frequency	Percent
excessive gurgling noise	Not at all	41	60.3
	A little	13	19.1
	Quite a bit	14	20.6
	Total	68	100.0
		Frequency	Percent
unintentional release (leakage) of wind or mucous?	Not at all	63	92.6
	A little	3	4.4
	Quite a bit	2	2.9
	Total	68	100.0
		Frequency	Percent
Have you had any unintentional release (leakage) of liquid stools?	Not at all	63	92.6
	A little	3	4.4
	Quite a bit	2	2.9
	Total	68	100.0
		Frequency	Percent
Have you needed to get up at night to open your bowels?		1	1.5
	Not at all	62	91.2
	A little	3	4.4
	Quite a bit	1	1.5
	very much	1	1.5
	Total	68	100.0
		Frequency	Percent
Have you had abdominal pain or cramping not related to a bowel movement?	Not at all	48	70.6
	A little	15	22.1
	Quite a bit	5	7.4
	Total	68	100.0

		Frequency	Percent
Have you had pain or cramping in your rectum (deep inside the back passage)?	Not at all	48	70.6
	A little	20	29.4
	Total	68	100.0
		Frequency	Percent
Have you had pain /discomfort around your anal opening (back passage)?	Not at all	58	85.3
	A little	9	13.2
	Quite a bit	1	1.5
	Total	68	100.0
		Frequency	Percent
Have you had bright blood in your stools?	Not at all	57	83.8
	A little	5	7.4
	Quite a bit	5	7.4
	very much	1	1.5
	Total	68	100.0
		Frequency	Percent
Have you been unable to wait 15 minutes to open your bowels?	Not at all	52	76.5
	A little	12	17.6
	Quite a bit	4	5.9
	Total	68	100.0
		Frequency	Percent
Have you had the feeling of being unable to completely empty your bowels?	Not at all	53	77.9
	A little	11	16.2
	Quite a bit	4	5.9
	Total	68	100.0
		Frequency	Percent
Does passing water cause your bowels to act immediately?	Not at all	60	88.2
	A little	6	8.8
	Quite a bit	2	2.9
	Total	68	100.0
		Frequency	Percent
Have you had difficulty going out of the house, because you needed to be close to a toilet, because of bowel problems?	Not at all	61	89.7
	A little	4	5.9
	Quite a bit	3	4.4
	Total	68	100.0
		Frequency	Percent
Did your treatment restrict the types of food you can eat due to your bowel problems?	Not at all	46	67.6
	A little	17	25.0

	Quite a bit	5	7.4
	Total	68	100.0
		Frequency	Percent
Did you worry about your bowel problem?	Not at all	39	57.4
	A little	14	20.6
	Quite a bit	14	20.6
	very much	1	1.5
	Total	68	100.0
		Frequency	Percent
Did you feel embarrassed by your bowel problem?	Not at all	52	76.5
	A little	11	16.2
	Quite a bit	4	5.9
	very much	1	1.5
	Total	68	100.0
		Frequency	Percent
How unhappy would you feel if you lived the rest of your life with your bowel habit as it is now?	Not at all	41	60.3
	A little	18	26.5
	Quite a bit	8	11.8
	very much	1	1.5
	Total	68	100.0