A PROSPECTIVE PILOT STUDY TO EVALUATE THE FEASIBILITY OF INTENSITY MODULATED PROTON THERAPY IN REDUCING TOXICITY IN ANAL CANCER

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ABBREVIATION LIST

RCT	Randomized Controlled Trial
IMRT	Intensity Modulated Radiation Therapy
VMAT	Volumetric Modulated Arc Therapy
IMPT	Intensity Modulated Proton Therapy
IGRT	Image Guided Radiation Therapy

PROTOCOL SYNOPSIS

TITLE	**A PROSPECTIVE PILOT STUDY TO EVALUATE THE FEASIBILITY OF INTENSITY MODULATED PROTON THERAPY IN REDUCING TOXICITY IN ANAL CANCER**
STUDY PHASE/DESIGN	Prospective, non-randomized trial
INDICATION	Anal canal carcinoma
PRIMARY OBJECTIVE	To evaluate feasibility of intensity modulated proton therapy for anal cancer To estimate rates of acute (within 3 months of treatment) toxicity following fractionated chemoradiation using pencil beam proton radiotherapy. Toxicities of note include any grade 3 or greater hematologic, gastrointestinal, genitourinary, and dermatologic.
SECONDARY OBJECTIVES	To evaluate rates of late (> 3 months after treatment) hematologic, gastrointestinal, genitourinary, and dermatologic. To evaluate clinical complete response at 6 months, local progression free survival, locoregional progression free survival, colostomy free survival, distant metastases free survival, and overall survival after chemoradiation. To evaluate pre- and post- treatment patient reported quality of life (QOL) To develop and standardize adaptive proton planning for anal cancer and optimize the planning approach
TREATMENT	Patients will undergo standard chemoradiation using 5-FU, Mitomycin, with pencil beam proton radiotherapy instead of photon based therapy.

INCLUSION CRITERIA	• Age >18 years. • Karnofsky Performance Status >70% (see Appendix IV). • Patients with histologically documented squamous or basaloid carcinoma of the anal canal • American Joint Committee on Cancer clinical stage T1-4 disease with any N category • History/physical examination within 21 days before registration, anal and groin evaluation • Patients must have acceptable organ and marrow function (see section "Inclusion Criteria, page 17-18). • Women who are not post-menopausal (as defined in Appendix) should have a negative urine or serum pregnancy test. Women of childbearing potential must agree to use adequate contraception for the duration of study participation. • Ability to understand and the willingness to sign a written informed consent document.

EXCLUSION CRITERIA	• Presence of metastatic disease. • Unable to understand or unwilling to sign a written informed consent document.
PROCEDURES	None
STATISTICAL CONSIDERATIONS	See statistics section.

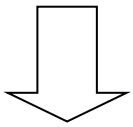
SCHEMA

Eligibility: Clinical stage T1-4 disease with any N category squamous cell carcinoma of the anal canal with appropriate PET Staging.

Study Entry

Day 1: Initiate Chemoradiation
5FU (1000 mg/m2/d as a 96-hour infusion) Days 1-5
Mitomycin (10mg/m2) Day 1
Radiation therapy begins Day 1

Day 29: 5FU (1000 mg/m2/d as a 96-hour infusion) Days 29-33, Mitomycin (10mg/m2) on Day 29



Clinical exam 2 weeks post treatment
Clinical exam 1 month
Clinical exam at 2 months
PET Imaging at 3 months
Anoscopic or Endoscopic exam at 6 months

I. OBJECTIVES

Primary Objective

- To evaluate the feasibility of Intensity Modulated Proton Therapy (IMPT) for the definitive treatment of anal cancer
- To estimate rates of acute (within 2 months of treatment) grade 2 or greater and grade 3 or greater hematologic, gastrointestinal, genitourinary, and dermatologic toxicity.

Secondary Objectives

- To evaluate rates of late (> 3 months after treatment) grade 3 or greater hematologic, gastrointestinal, genitourinary, and dermatologic toxicity
- Evaluate clinical complete response rate at 6 months
- To determine rates of local progression free survival, overall survival, and distant metastases free survival
- To evaluate patient quality of life before and after chemoradiation using Intensity Modulated Proton Therapy as assessed by the National Cancer Institute's Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE).

II. BACKGROUND

Natural History and Management of Anal Canal Cancer

There were an estimated 7,270 cases of anal canal cancer in 2015 with an estimated number of 1,010 deaths (SEER). Although uncommon, the relative incidence of anal cancer has been increasing over the last 20 years. The treatment of squamous cell carcinoma of the anal canal transitioned from abdominal perineal resection to definitive chemoradiation without surgical intervention with the publication of the Nigro regimen in the 1970's. Definitive treatment for anal cancer has been concurrent chemoradiation since that time using 5-Flourouracil and mitomycin chemotherapy. A variety of clinical trials have been conducted assessing variations of the standard backbone, but definitive chemoradiation with 5-Flourouracil and mitomycin chemotherapy remains the standard of care in 2016. [1–5]

RTOG 9811 was one of the largest clinical trials conducted in the United States for anal canal carcinoma. This trial evaluated whether induction chemotherapy in the form of cisplatin/5-Flourouracil followed by chemoradiation with concurrent cisplatin/5-Flourouracil compared to the standard mitomycin/5-Flourouracil regimen concurrent with radiation. Short term follow up showed an improved colostomy free survival and long term follow up revealed improved overall survival (78% vs 71%, p= 0.026) with standard chemoradiation using a mitomycin/5-Flourouracil backbone[5,6]. Criticisms of this trial cite the induction chemotherapy and prolonged duration of treatment as reasons for inferior outcome as oppose to direct inferiority of cisplatin compared to mitomycin.

The UK ACTII trial addressed this issue with a direct substitution of cisplatin for mitomycin without an induction arm[3]. This trial showed no improvement in outcomes with cisplatin and therefore mitomycin/5-Flourouracil based chemoradiation remains the standard of care for localized squamous cell carcinoma of the anal canal.

Use of IMRT for Treatment of Anal Canal Cancer

The early trials that established mitomycin/5-Flourouracil based chemoradiation as the standard of care used a 3D-Conformal radiation therapy technique [3,5]. Treatment is associated with significant acute toxicity including dermatologic, gastrointestinal, genitourinary, and hematologic. In RTOG 9811, the rate of acute non-hematologic toxicity grade 3 or grade 4 was 74% in both the mitomycin and cisplatin groups. The rate of grade 3 or grade 4 hematologic toxicity was 61% in the standard arm which used concurrent mitomycin/5-Flourouracil[5]. In the UK ACT II trial rates of grade 3 or grade 4 non-hematologic toxicity were 62% in the mitomycin/5-Flourouracil arm. Rates of grade 3 or grade 4 hematologic toxicity was 26%[3].

RTOG 0529 was a phase II, multicenter trial assessing the use of Intensity Modulated Radiation Therapy (IMRT) in patients with squamous cell carcinoma of the anal canal[7]. The rationale for this trial was to evaluate whether a more conformal radiation technique that results in sparing of the organs at risk in the pelvis would result in a reduction in acute toxicity. The primary end point of the study was grade 2 or higher gastrointestinal (GI) or genitourinary (GU) events as compared to historical controls on the standard arm of RTOG 9811. A total of 52 patients were enrolled on the trial. Compared to the historical controls on RTOG 9811, there were no differences in grade 2 or higher GI/GU events (77% vs 77%, p= 0.50). In the IMRT treated patients, there was a significant reduction in combined grade 3 or higher GI/GU events (37% vs 21%, p= 0.0052) and grade 3 or higher dermatologic events (49% vs 21%, p= 0.0052). In addition, treatment breaks due to toxicity were needed in 49% of IMRT treated patients compared with 62% on 9811 (p=.09). IMRT treated patients required less days off during treatment and completed treatment in fewer days compared to RTOG 9811[7]. Prolonged treatment package time in squamous cell carcinoma of the anal canal has been associated with inferior disease outcome[8].

III. RATIONALE

Rationale for Pencil Beam Proton Therapy for Treatment of Anal Canal Cancer

Despite improved rates of acute toxicity with IMRT as compared to previously treated patients with 3D Conformal radiation therapy, therapy with IMRT continues to result in significant acute toxicity. During radiation planning coverage of the target volume is often prioritized over organs at risk such as bowel, bladder, or bone marrow. Intensity Modulated Proton Therapy (IMPT) offers unique physical characteristics during delivery that may allow reduced dose to the organs at risk with preservation of dose to the target volumes.

Previous Dosimetric Studies

Dosimetric planning studies have been performed assessing IMPT compared to IMRT in the ability to spare organs at risk. One study compared 8 patients who were planned using the standard target volumes and dose prescriptions as outlined in RTOG 0529[9]. This study showed greater than 50 % dose reduction in dose to small bowel and bone marrow in the proton therapy plans compared to IMRT plans.

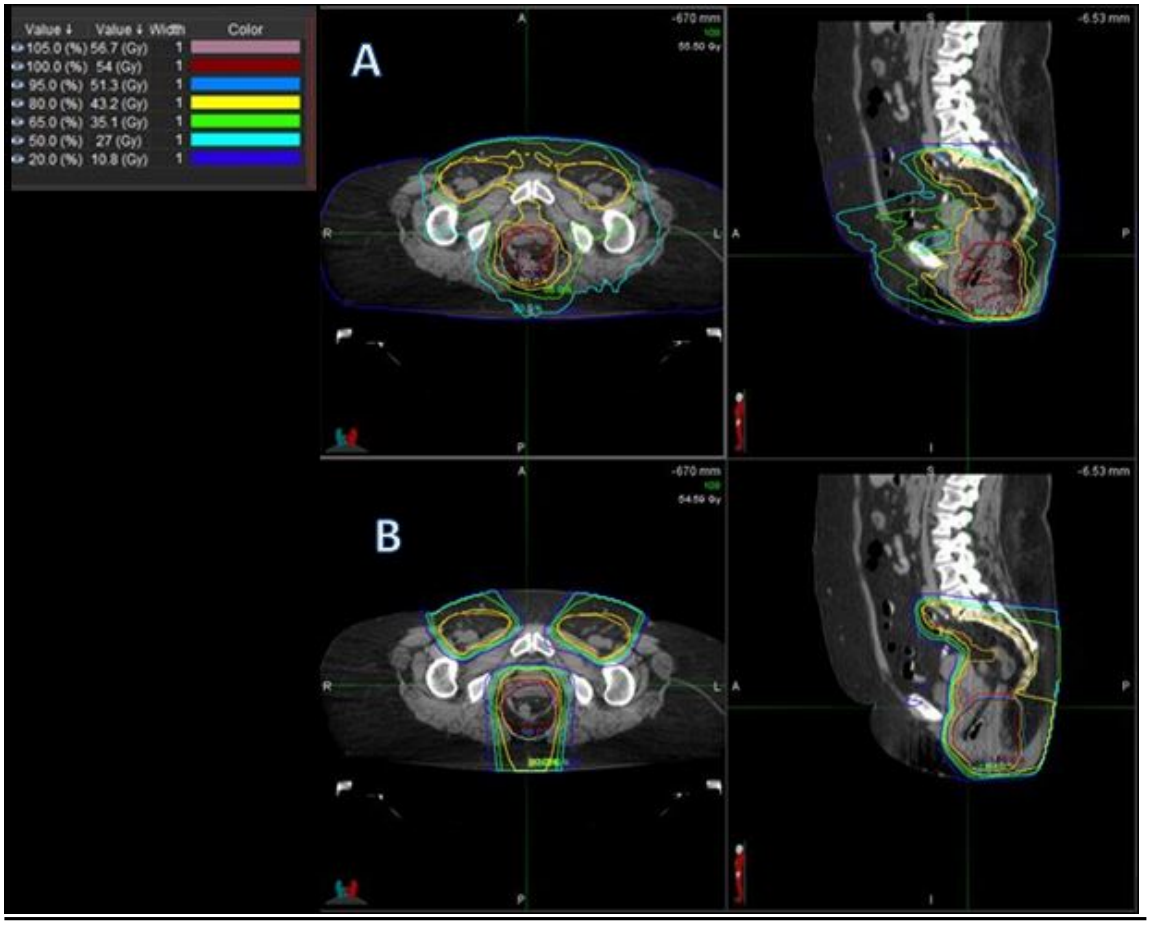
We have performed a similar study at our institution (unpublished data). CT datasets of 9 patients with anal cancer previously treated with IMRT using Volumetric Arc Therapy (VMAT) at our institution were used for comparison. Both VMAT and IMPT plans were created for each patient. The IMPT plans were created using a Multi-Field Optimized (MFO), split-target technique.

Planning constraints for RTOG 0529 as well as bone marrow (mean <22 Gy, V10 <90%, and V40 <37%) were used for treatment planning. The dose to OARs including the bone marrow, bladder, small bowel, large bowel, femoral heads, and genitalia were compared with a paired t-test. IMPT provided similar planning target volumes (PTV) coverage as VMAT plans (99% vs 98%, p =0.0381). The mean bone marrow dose with IMPT and VMAT plans was 17.42 Gy and 30.76 Gy respectively (P<0.0001). Based on the NTCP modeling for bone marrow toxicity IMPT may reduce the rate of grade III or higher hematologic events from 40% to <20%[10]. IMPT also showed significant sparing of other organs at risk including the small and large bowel, femoral heads and genitalia. Mean results of the OARs are included in the table 1. A representative comparison of an IMPT plan compared to a VMAT plan is shown in Figure 1.

Table 1. Dose Comparison of IMPT Compared to VMAT/IMRT Plans

	IMPT	VMAT	P-value
Bone Marrow V10<90%	48.97%	92.56%	<0.0001
Bone Marrow V40<37%	23.67%	20.82%	0.3460
Bladder V40<35%	38.9%	52.35%	0.1243
Small Bowel V30<200cc	176.64cc	400cc	0.0009
Small Bowel V35<150cc	151.12cc	291.91cc	0.0051
Large Bowel V35<150cc	70.37cc	114.23cc	0.0136
Femoral Heads V40<35%	2.80%	21.94%	0.0160
Genitalia V20<50%	2.55%	63.68%	0.0006
Genitalia V30<35%	1.24%	41.67%	0.0164

Figure 1. Representative Comparison of Intensity Modulated Radiation Plan (A) and Intensity Modulated Proton Therapy Plan (B)



IV. METHODS

REGISTRATION PROCEDURES

General Guidelines

Subjects will be identified per the recommendation of Surgeons, Medical Oncologists, Radiation Oncologists or GI Combined Modality Tumor Board or equivalent combined modality assessment. Subjects will be recruited through self-referral and the advice of their attending physician. Patients will be enrolled prior to start of chemoradiation.

Registration Process

A member of the research team (most likely the research coordinator) will enroll the patient into the trial. Consent will be obtained after a clear and thorough discussion between the patient and the principal investigator or any of the co-investigators in clinic. Any patients that are deemed by the principal investigator or co-investigators to be mentally or physically incapable of consent will not be included in the study.

RADIATION TREATMENT PLANNING

Pre-Treatment Tests, Procedures, and Planning

The following will be completed prior to chemoradiation:

- Signed informed consent document.
- Documentation of performance status
- Medical history and clinical examination.
- CBC/Diff with differential, Chemistry Panel within 2 weeks of initiation of chemoradiation
- PET scan within 42 days from initiation of chemoradiation
- Pathologic confirmation of malignancy.
- Baseline collection of symptoms using the National Cancer Institute Patient Reported Outcomes- Common Terminology Criteria for Adverse Events (PRO-CTCAE).

Simulation:
Typically, patients will be positioned supine, in the frog leg position using vac-fix or equivalent immobilization device that will be custom-made for each patient. Oral contrast may be used to visualize the small bowel. Slice thickness will be < 5mm

Treatment Planning:
All patients will be planned using a multi-field optimization, split-target technique using intensity modulated proton therapy. The treatment plan will be created as a Simultaneous Integrated Boost (SIB), except where the physician and/or physicist perceive a benefit to a sequential boosting schema. It is expected that the typical field arrangement will include two anterior oblique fields to cover the inguinal nodal planning target volume and upper pelvic lymph node volume. A posterior beam will be used to cover the anal primary planning target volume, the mesorectum, and posterior pelvic lymph node volumes as per the judgment of the dosimetrist and radiation physicist. In the case of utilizing robust optimization techniques, a standard 3% CT uncertainty and 5mm setup uncertainty criteria is implemented.

Target Contours:
All patients will be treated with a simultaneous integrated boost approach. Contours and planning target volumes will be based on the pretreatment clinical stage.

The contouring atlas anal cancer from Ng et al should be used as reference for definition of GTV, CTV, and PTV [11].

Primary Tumor:
GTV Primary: The GTV should be delineated as a separate structure based on all available clinical and imaging information.

CTV Primary: This volume must encompass (1) the GTV, (2) the entire anal canal from the ano-rectal junction to the anal verge, and (3) the internal and external anal sphincters. A further 20-mm isotropic margin should be added to items (1), (2), and (3) above, to account for microscopic disease, while respecting anatomical boundaries. Attention must be given, especially for anal

verge and perianal lesions, that a 20-mm radial and caudal margin is used to ensure coverage of perianal skin

Involved Nodes:
GTV LN: Lymph nodes considered positive clinically or by radiographic imaging will be called GTV LN and will receive higher dose than elective lymph node coverage.

CTV Lymph Node: The involved node(s) or nodal region(s) with a 10- to 20 mm margin, respecting anatomical boundaries.

Planning Target Volume:
An isotropic expansion of 5-10 mm will be used for all PTV. In the case of utilizing robust optimization techniques, the PTV will be used as a PTVeval only.

Organ at Risk:
Organs at risk will be delineated as per RTOG 0529[7] and will include small bowel (defined as loops), genitalia, bladder, large bowel, and bone marrow. Bone marrow will be defined as defined on the planning CT as the volume of bone encompassing the pelvic bones, proximal femoral heads, and the vertebral bodies from L4 to the coccyx.

Treatment Planning Goals:
Small Bowel:
No more than 200 cc above 30 CGE
No more than 150 cc above 35 CGE
No more than 20 cc above 45 CGE
None above 50 CGE

Femoral heads:
No more than 50% above 30 CGE
No more than 35% above 40 CGE
No more than 5% above 44 CGE

External genitalia:
No more than 50% above 20 CGE
No more than 35% above 30 CGE
No more than 5% above 40 CGE
Bladder:
No more than 50% above 35 CGE
No more than 35% above 40 CGE
No more than 5% above 50 CGE

Large bowel:
No more than 200 cc above 30 CGE
No more than 150 cc above 35 CGE
No more than 20 cc above 45 CGE

PTV Prescription:

T1-2N0

Primary PTV will receive 50.4 CGEin 28 fractions at 1.8 CGEper fraction
Elective nodal PTVs will receive 42 CGEin 28 fractions at 1.5 CGEper fraction.

T3-4 N0-3

Primary PTV will receive 54 CGEin 30 fractions at 1.8 CGEper fraction
Gross nodal PTV for lymph nodes **less than 3 cm** will receive 50.4 CGEin 30 fractions at 1.68 CGEper fraction
Gross nodal PTV **greater than 3 cm** in size will receive 54 CGEin 30 fractions at 1.8 CGEper fraction
Elective nodal PTVs received 45 CGEin 30 daily fractions at 1.5 CGE

PTV Coverage:

No more than 5% of any PTV will receive < 90% of the prescription dose.
No more than 2% of any PTV will receive < 80% of the prescription dose.
No more than 2% of the primary PTV will receive > 115% of the prescription dose.

GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Anti-diarrheals and Anti-emetics

For symptoms of diarrhea and/or abdominal cramping, patients will be instructed to take anti-diarrheals. Additional antidiarrheal and anti-emetic measures may be used at the discretion of the treating physician. Patients should be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea. For symptoms of nausea and vomiting, anti-emetics will be given 30 minutes prior to radiation

Other Concomitant Medications

Therapies considered necessary for the patient's well being may be given at the discretion of the investigator or medical oncologist as according to standards of care for concurrent mitomycin/5-Flourouracil based chemoradiation.

Supportive Care Guidelines

All commonly accepted supportive care guidelines will be used.

Use of Radioisotopes/Rad Machines

Radiation therapy will be given at the Cincinnati Children's/ UC Health Proton Therapy center commissioned for clinical use. The radiation treatment plan will be designed to use multiple beams of radiation to concentrate radiation within the tumor target volume and at risk regional lymphatics. The proton machines are equipped with cone beam CT imaging and daily KV imaging that can be used to deliver image-guided radiation therapy (IGRT). IGRT allows delivery of highly accurate radiation treatment.

V. STUDY POPULATION

PATIENT SELECTION

Inclusion Criteria

- Age >18 years.
- Karnofsky Performance Status >70% (see Appendix IV).
- Patients with histologically documented squamous or basaloid carcinoma of the anal canal
- American Joint Committee on Cancer clinical stage T1-4 disease with any N category
- History/physical examination within 21 days before registration, anal and groin evaluation
- Patients must have acceptable organ and marrow function (see section "Inclusion Criteria, page 17-18).
- Women who are not post-menopausal (as defined in Appendix V) should have a negative urine or serum pregnancy test. Women of childbearing potential must agree to use adequate contraception for the duration of study participation.
- Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria

- Children (< 18 years) are excluded because pancreatic tumors rarely occur in this age group. Furthermore, treatment requires a great deal of patient cooperation including the ability to lie still for several hours in an isolated room.
- Psychiatric illness/social situations that would limit compliance with study requirements.
- Pregnant and breastfeeding women are excluded as are women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control (hormonal or barrier method of birth control; abstinence) to avoid pregnancy for the duration of the study treatment. Should a woman become pregnant or suspect she is pregnant while undergoing radiotherapy in this study, she should inform her treating physician immediately.
- Women who are not post-menopausal (as defined in Appendix) and have a positive urine or serum pregnancy test or refuse to take a pregnancy test.
- Patients with a life expectancy of < 3 months.

VI. RISK / BENEFIT

Risk Information

The treatment outlined in this protocol includes standard of care chemotherapy (5-Flourouracil/Mitomycin) concurrent with radiation therapy with IMPT. The risks and side effect profile associated with this therapy would be expected to be no greater than standard concurrent chemoradiation.

Toxicities commonly associated with standard treatment includes nausea, vomiting, fatigue, anorexia and weight loss, skin dequamation, dysuria and urinary frequency, bowel irritability, diarrhea, fecal urgency. Hematologic toxicities include neutropenia, febrile neutropenia, thrombocytopenia, and anemia. Severe side effects such as gastrointestinal (GI) obstruction, perforation, and fistula are uncommon complications, occurring in <5% of patients undergoing standard radiation therapy for anal cancer. Hepatic and renal toxicity is not anticipated given the expectation of limited incidental irradiation of these organs. Complications, if any, will be graded according to the CTCAE, National Cancer Institute, version 4.0. Toxicity will also be measured using the NCI Patient Reported CTCAE for relevant items.

Duration of Study
It is anticipated that this study will last approximately 60 months (48 months of accrual and 12 months while cohort matures)

Duration of Follow Up
Patients will remain on study for a maximum of 8 years.

Criteria for Removal from Study
Patients will be removed from the study for any of the following reasons: death or patient withdrawal. The protocol director may also withdraw a patient from the study for one or more of the following reasons: failure of the patient to follow the instructions of the protocol study staff, the protocol director decides that continuing participation could be harmful to the patient, pregnancy (if applicable), the patient needs treatment not allowed in the study, the study is cancelled, other administrative reasons, or unanticipated circumstances. Patients that have been removed from or discontinue the study will be followed for survival information until death.

Alternatives
Alternative therapies include standard chemoradiation with standard photon based radiation therapy as oppose to proton therapy. The risks of photon based chemoradiation are the same as outlined for proton based treatment.

VII. COMPENSATION

Subjects will not be paid to participate in the study.

VIII. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse Events and Potential Risks List
Toxicities commonly associated with standard treatment includes nausea, vomiting, fatigue, anorexia and weight loss, skin dequamation, dysuria and urinary frequency, bowel irritability, diarrhea, fecal urgency. Hematologic toxicities include neutropenia, febrile neutropenia, thrombocytopenia, and anemia. Long term effects can include sterility in men and women, vaginal stenosis, erectile dysfunction, anal canal fibrosis, hip fractures. Severe side effects such as gastrointestinal (GI) obstruction, perforation, and fistula are uncommon complications, occurring in <5% of patients undergoing standard radiation therapy for anal cancer. Hepatic and renal toxicity is not anticipated given the expectation of limited incidental irradiation of these organs. Complications, if any, will be graded according to the CTCAE, National Cancer Institute, version 4.0.
For this protocol we are concerned with tracking both acute/late adverse events. Some RT effects that are high grade events may not manifest for months to years following RT. For example, fistula/rectal bleeding/urinary bleeding due to telangectasias/vaginal stenosis. To reduce the potential for long-term collection of late AEs which are unlikely to be at least possibly related to RT, once the 90 day post treatment collection of all AEs is reached the following sub-set of AEs as described below must be collected by the study team and evaluated by a qualified investigator for attribution. If a study team member is ever unsure whether an AE should be collected during the follow up period, they should collect/record the AE for evaluation.

The description of the following potential sub-set of AE's for collection only during follow up is intentionally broad (vs a specific listing of CTCAE Terms/Categories to collect) as some AEs may be unexpected within the treatment field.

- AEs that may be reasonably related to the organ systems within the study treatment field (such as the GI/GU/Vaginal/Skin/pelvic bone organ systems) must be collected regardless of potential attribution to protocol treatment. Adverse events clearly occurring outside of the treatment field organ systems (For example, pulmonary, cardiac, or neurological events) should not be collected.
- All serious adverse events (e.g., hospitalizations, death) should also be collected during this long term follow-up time-frame if they also may be reasonably related to the organ systems within the study treatment field (such as the GI/GU/Vaginal/Skin/pelvic bone organ systems) must be collected regardless of potential attribution to protocol treatment.

Reporting of Serious of Unexpected Adverse Events

All fatal events, both anticipated and unanticipated, must be reported to the UC IRB within a time period as specified by current institutional guidelines after the PI learns of the event, whether or not the PI believes the event to be related to the study. All other events, which are both serious and unanticipated, must be reported to the UC IRB within a time period as specified by current institutional guidelines after the PI learns of the event. Events which are serious, but anticipated, should be reported as part of the continuing review application. If any of these Serious Adverse Events requires a change to the protocol or consent form, the PI must make those changes promptly and submit the revised documents to the UC IRB. Important Adverse Events that are unanticipated must be reported to the UC IRB within a time period as specified by current institutional guidelines. If the Important Adverse Event requires changes to the protocol or consent form, the PI must make those changes promptly and submit the revised documents to the UC IRB. All other unanticipated Adverse Events or changes to the protocol and consent form must be reported to the UC IRB, within a time period as specified by current institutional guidelines.

IX. STATISTICAL CONSIDERATIONS

Study Overview

This pilot study is designed to assess the feasibility of giving proton based chemoradiation for anal canal carcinoma. The feasibility demonstration will establish the infrastructure for future randomized phase II clinical trials in a single or multi-center setting and to evaluate the baseline toxicity rates with proton based chemoradiation. At least fifteen patients with anal cancer, confirmed by multi-disciplinary radiologic review, will be enrolled and treated. The decision regarding whether this study demonstrates sufficient feasibility to support a phase II study testing novel regimens in this disease population will be based on three key considerations:

- Estimated toxicity rates assessed by 95% confidence intervals are similar or improved compared to RTOG 0529 IMRT based chemoradiation.
- The completion rate of treatment and total treatment duration is similar or less than IMRT based chemoradiation.

Sample Size

The goal for accrual will be 15 patients or maximum of 20 patients if accrual if this is performed

within 5 years of study activation.

Accrual time
The anticipated monthly accrual rate is approximately 3-4 patients per year. The trial is expected to accrue in approximately 60 months.

Statistical Design for Primary Endpoints

Primary Endpoints
To evaluate rates of acute (within 3 months of treatment) toxicity following fractionated chemoradiation using pencil beam proton radiotherapy. Toxicities of note include any grade 2 or higher and grade 3 or greater hematologic, gastrointestinal, genitourinary, and dermatologic.

Secondary Endpoints
To evaluate rates of late (> 3 months after treatment) hematologic, gastrointestinal, genitourinary, and dermatologic.

To evaluate clinical complete response at 6 months, local progression free survival, locoregional progression free survival, colostomy free survival, distant metastases free survival, and overall survival after chemoradiation.

To evaluate pre- and post- treatment patient reported quality of life (QOL)

Study Design and Decision Rules
The purpose of this study is to demonstrate the feasibility of conducting a study assessing the proposed regimen. The sample size of fifteen patients with squamous cell carcinoma of the anal canal is selected based on financial and logistic considerations. If, at the conclusion of the trial, none of the following stopping rules has been crossed, we will conclude that the proposed regimen and trial design warrants further phase II study for proton based chemoradiation for anal cancer.

Accrual stopping rules
If, 15 months following the date IRB approval is obtained, no patients have been accrued, we will conclude the study does not demonstrate sufficient feasibility. Thereafter, the accrual rate will be monitored monthly. If at any evaluation time point, the accrual rate is less than or equal to 1 per year, we will conclude the study does not demonstrate sufficient feasibility.

Completion of Therapy Stopping Rules
The completion of therapy stopping rules are specified as the following:

- If 5 patients among the 10 evaluable patients fail to complete radiation therapy, we will conclude that the study does not demonstrate sufficient feasibility.

Analysis Plan
All acute AE (within 3 months after treatment) and the maximum grade for each type of adverse events (including all adverse events and those that are possibly, probably or definitely related to

study treatments) will be recorded for each patient. The frequency tables will be reviewed to determine the patterns. Point estimate and confidence interval will be reported for binary endpoints.

Toxicity Endpoints
The toxicity feasibility stopping rules are specified as the following:

- Upon completion of the trial, the rate of grade 3 or higher Hematologic toxicity using IMPT will be estimated with 95% confidence interval and compared to the previously published rate using IMRT. The multicenter IMRT based photon trial demonstrated a combined grade 3 or higher Hematologic toxicity event rate of 58%.[7]

- Upon completion of the trial, the rate of grade 3 GU/GI toxicity using IMPT will be estimated with 95% confidence interval and compared to the previously published rate using IMRT. The multicenter IMRT based photon trial demonstrated a combined grade 3 or higher GI/GU event rate of 37%[7]

- The proportion of patients requiring a treatment break and the 95% confidence interval for this rate will be assessed upon completion and compared to the IMRT based photon trial resulted in 49% of patients requiring a treatment break.[7]

Supplementary Analysis Plans (Secondary Endpoints)
All late AE and the maximum grade for each type of adverse events (including all adverse events and those that are possibly, probably or definitely related to study treatments) will be recorded for each patient. The frequency tables will be reviewed to determine the patterns. Point estimate and confidence interval will be reported. All patients meeting the eligibility criteria and confirmed by central review who have signed a consent form and have begun any dose of treatment will be evaluable for the following secondary endpoints, unless otherwise specified.

- Grade 2 or higher and grade 3 or higher hematologic toxicity, genitourinary, gastrointestinal, and dermatologic acute toxicity
- Total treatment time and treatment breaks required
- Clinical complete response rate at 6 months
- Time to locoregional recurrence is defined as time from the date of registration to the date of the first documented locoregional recurrence. The Kaplan-Meier methods will be used to estimate the median time, and event-free rate at specific time points (6 month, 12 month, etc.).
- Time to distant recurrence is defined as time from the date of registration to the date of the first documented distant recurrence. The Kaplan-Meier methods will be used to estimate the median time, and event-free rate at specific time points (6 month, 12 month, etc.).
- Overall survival is defined as time from the date of registration to the date of the death due to all causes. The Kaplan-Meier methods will be used to estimate the median time, and event-free rate at specific time points (6 month, 12 month, etc.).
- Quality of life outcomes will be assessed using the NCI Patient Reported- Common Terminology Criteria for Adverse Events (see additional documents)

Safety Stopping Rules

In addition to toxicity feasibility stopping rules, accrual will be temporarily suspended to the study, if at any time, we observe events considered at least possibly related to study treatment an adverse event with attribute specified as ("possible," "probably," or "definite") that meet the following:

- The rate of treatment-related deaths during treatment, or within the first 60 days following completion of treatment, is 2 or more in the first 10 patients, or after 10 patients, 20% or more of all treated patients.
- We will also review grade IV and V adverse events deemed "unrelated" or "unlikely to be related" to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event
- All adverse events will be reviewed by the primary investigator and will be presented at the Data Safety Monitoring Board.
- If there are unexpected adverse effects directly related to protocol treatment, the study will be placed on hold or permanently closed at the discretion of the primary investigator or the Data Safety Monitoring Board.

X. DATA REPORTING / REGULATORY CONSIDERATIONS

Study Monitoring
This study will be monitored by the University of Cincinnati DSMB and IRB. The PI will be responsible for maintaining the clinical protocol and subjects' study charts, reporting adverse events, assuring that consent is obtained and documented, and reporting the status of the trial in continuing renewals submitted to their IRB and trail monitoring group(s) as per UC protocol. There will be password-protected limited access to the database in order to maintain privacy (See Confidentiality below).

Monitoring Plan
UCCI DSMB will conduct study audits after enrollment of each 5 patients to review subjects' timely and complete enrollment, registration into the electronic database, and follow-up per study calendar. More frequent monitoring will take place as needed. Trial monitoring with subject chart and trial binder reviews will be done by the UCCI Clinical Trials office.

Data Entry and Compilation
Subject data will be documented and stored in the electronic database Oncore, the software and infrastructure being supplied by UCCI clinical trials office. Research Staff (Coordinators, Nurse, or Co-Investigators) will enter/scan subject data into Oncore, which will include:

- Eligibility or Inclusion/Exclusion Criteria
- Patient Demographics
- Pre-Study Evaluation including H & P, Allergies, and Review of Systems
- Surgical Procedures, with dates and findings (including biopsy)
- Scan dates
- Radiation treatment start and end dates
- Total treatment time
- Treatment breaks required (yes/no) and total treatment days missed.
- Pre-Study Labs including hematology, chemistry

- Pre-study chemotherapy records including drugs, doses, and schedules
- Surgery records including pathology reports (pathologic staging, margin status, histology), length of hospitalization and postop complications according to Appendix VI.
- Toxicity documentation and grade
- Follow-up Evaluations including H&P, Review of Systems, and toxicities
- Follow-up labs and dates
- Completion of QOL questionnaires
- Subject study withdrawal, date, and reason

Confidentiality
Study data will be maintained in password protected computer files. Only research personnel listed on this protocol will have access to this information. Only the patients unique IDN will be used. The patient's name or other public identifiers will not be included in any information shared with other investigators. The study data with identifiers will be kept at in Oncore.

XII. MEASUREMENT OF EFFECT AND RESPONSE CRITERIA

Anti-tumor Effect
Patients will be evaluated for anti-tumor effect by clinical exam, anoscopic exam, and/or PET-CT imaging) as outlined above. Patients will be evaluable for toxicity and evaluable for objective response at the follow-up intervals specified above.

Disease Parameters
Measurement of Local Tumor
Patients should be evaluated for response at 8 weeks after, 3 months, and 6 months after completing treatment. It is expected the tumor will regress with time following completion of chemoradiation. Complete response will be determined by digital rectal exam and proctosigmoidoscopy supplemented with pelvic axial imaging. Complete response will be the absence of all disease based on these evaluations. Any measurable disease at 6 months from the completion of chemoradiation therapy will be considered a treatment failure (local failure) as per the UK ACT II trial.[3] Any tumor recurrence in the anus in patients who initially have a complete response will also be considered local recurrence and locoregional control will be censored at the time local recurrence.

Regional Failure: Regional failure is defined as follows: a) For patients with no disease in pelvic and/or groin nodes, the appearance of disease in pelvic or groin nodes; b) For patients with disease in pelvic and/or groin nodes at study entry, nodal recurrence following clearance or persistent nodal disease for more than 12 weeks after completion of treatment.

Distant Metastases Failure: The appearance of distant metastases

Colostomy Failure: For patients entering the study without a diverting colostomy, failure is a colostomy for any reason. For patients entering the study with a diverting colostomy, failure is defined as one of the following: a) If the colostomy is reversed within 1 year from study entry, failure is a subsequent colostomy for any reason; b) If the colostomy is not reversed

within 1 year, then it will be considered a colostomy failure at that time.

Overall Survival:
Overall survival will be determined from the date of diagnosis to death or date of last follow up.

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APPENDIX

STUDY CALENDAR

	Pre-Study	Pre-treatment[8]	Chemoradiation [1,2,3]	Follow-Up (Post-Radiation Treatment)						
				2 weeks	4 weeks	8 weeks	3 mos	6 mos	12 mos	Yrs 2-5 Q 3-6
Initial Consult	X									
Demographics	X									
History / Physical Exam	X			X	X		X	X	X	X
Informed consent	X									
Biopsy (confirmed carcinoma)	X									

Labs: CBC/Diff, CMP,		X		X	X		X	X	X	X
Tumor Measurement						X	X	X		
Negative Pregnancy Test		X								
PET scan		X					X			
Anoscopy eval								X		
Simulation Scan		X								
Radiologic Evaluation (PET)		X					X			
PRO-CTCAE Forms[1]		X		X	X		X	X	X	X
CTCAE Evaluation[2]	X			X	X		X	X	X	

1. PRO-CTCAE Forms will be completed at each weekly on treatment visit
2. CTCAE events will also be graded at the time of completion of chemoradiation
3. Lab collection at Weeks 1, 3 and last week of RT (5-6)

APPENDIX

Karnofsky Performance Status

Score	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.

APPENDIX

Definition of Menopausal Status

Menopausal status will be defined according to the following criteria:

Post-menopausal:

- Woman 60 years of age or older
- Woman aged 45-59 years with spontaneous cessation of menses for at least 12 months prior to registration
- Woman aged 45-59 years with cessation of menses for less than 12 months prior to
- registration AND an FSH level in the postmenopausal range (or >34.4 IU/L if institutional range is not available)
- Woman aged 45-59 years on hormone replacement therapy who have discontinued hormone replacement therapy at diagnosis of breast carcinoma and have an FSH level in the postmenopausal range according to institutional/laboratory standards (or 34.4IU/L if the institutional range is not available)
- Prior bilateral oophorectomy
- Woman younger than 60 years of age who have had a prior hysterectomy (without bilateral oophorectomy) AND who have an FSH level in the postmenopausal range (or >34.4 IU/L if institutional range is not available)

Pre- or peri-menopausal:

Not meeting definition for postmenopausal as outlined above.