NCT02017704

Chemoradiation **OR** Brachytherapy for **RECT**al cancer

Protocol Number: J1360 (NA_00082167)

Coordinating Center: Johns Hopkins University

Protocol Chair: Amol Narang, M.D.
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University
Weinberg Building
401 N. Broadway, Suite 1440
Baltimore, MD 21231
Phone: 410-955-7390
Fax: 410-502-1419
Email: anarang2@jhmi.edu

Co-Investigators: Susan Gearhart, M.D., Johns Hopkins University
Laura D. Wood, M.D., Ph.D., Johns Hopkins University
Nilofer Azad, M.D., Johns Hopkins University
Luis Diaz, M.D., Johns Hopkins University
Elizabeth Wick, M.D., Johns Hopkins University
Sandy Fang, M.D., Johns Hopkins University
Susannah Ellsworth, M.D., Johns Hopkins University
Jonathan Efron, M.D., Johns Hopkins University
Jennifer Barsky Reese, Ph.D., Johns Hopkins University
Te Vuong, M.D., Segal Cancer Centre
William Blackstock, M.D., Wake Forest Cancer Center
Jerome Landry, M.D., Winship Cancer Institute, Emory University
Stephen Greco, M.D., Johns Hopkins University
Victoria Croog, M.D., Johns Hopkins University

Statistician: Hao Wang, PhD

Research Managers: Dana Kaplin
Terry Caldwell

Study Coordinators: James Huang
Zhi Cheng
Katie Lowe

Research Nurses: Jessica Leitzel, R.N.
Shirl DiPasquale, R.N.
Danielle Wendler, R.N.

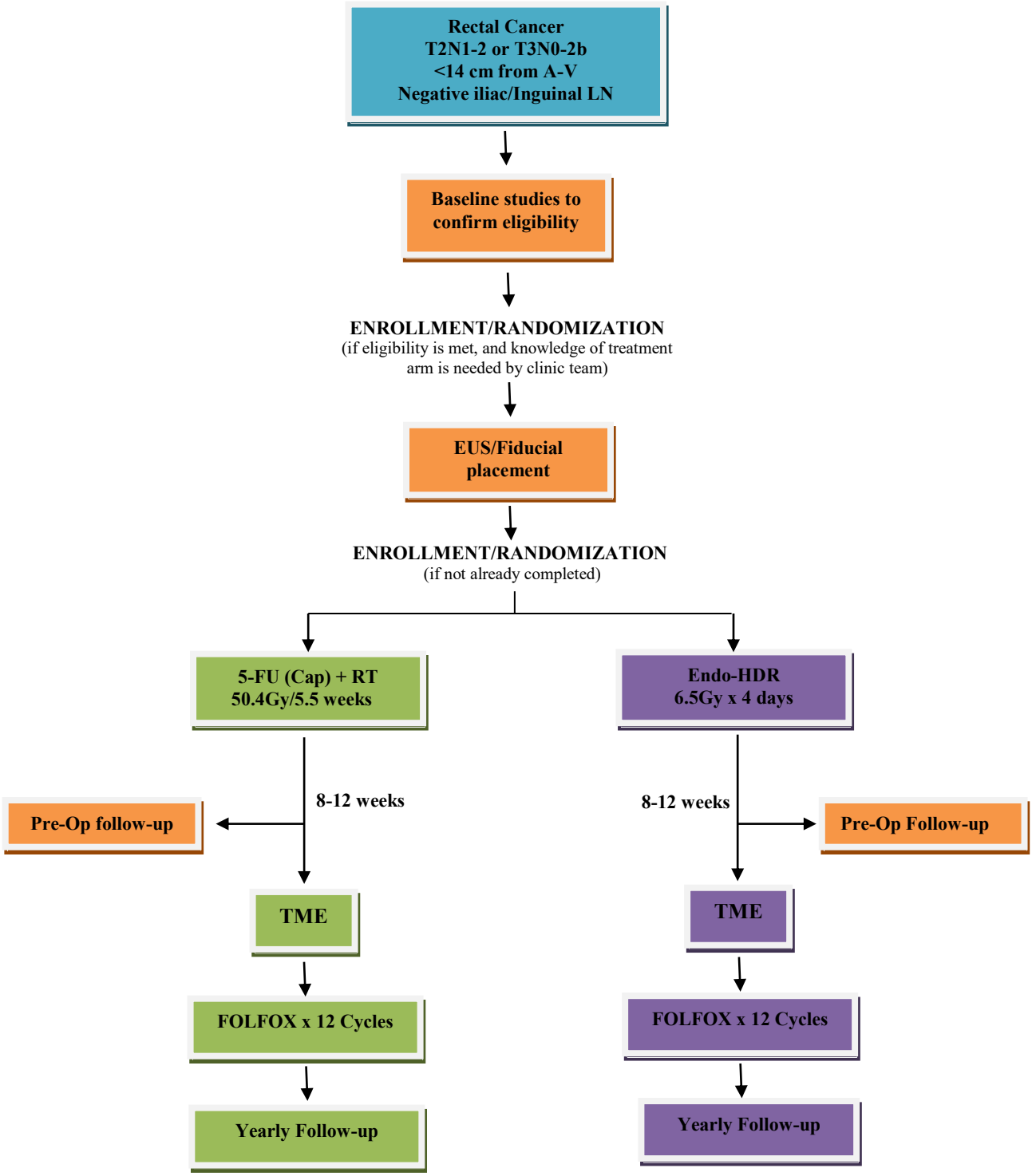
Sponsor: Nucletron

Table of Contents

Summary of Changes

Protocol Revision Date	Protocol Revision	Description of Change	Reason for Change
August 30, 2013	Version 1.0	Original version	Original release
August 27th, 2014	Version 2.0	Adjusting Site Info	Changing Gamma West PI
March 25th, 2015	Version 3.0	Eligibility/Parameters Revision	Accrual
January 21, 2016	Version 4.0	Study Calendar Revision/Enrollment process/Eligibility	Data Collection, scheduling, eligilbity clarification
July 13, 2016	Version 5.0	Study Team updates on the cover page	Changed Study Team
November 11, 2019	Version 6.0	Study Team updates on the cover page	Changed Study Team
May 19, 2020	Version 7.0	Study Team updates on the cover page	Changed Study Team

SCHEMA


Rectal Cancer
T2N1-2 or T3N0-2b
<14 cm from A-V
Negative iliac/Inguinal LN
Baseline studies to confirm eligibility
ENROLLMENT/RANDOMIZATION
(if eligibility is met, and knowledge of treatment arm is needed by clinic team)
EUS/Fiducial placement
ENROLLMENT/RANDOMIZATION
(if not already completed)
5-FU (Cap) + RT
50.4Gy/5.5 weeks
Endo-HDR
6.5Gy x 4 days
8-12 weeks
Pre-Op follow-up
8-12 weeks
Pre-Op Follow-up
TME
TME
FOLFOX x 12 Cycles
FOLFOX x 12 Cycles
Yearly Follow-up
Yearly Follow-up

1. HYPOTHESIS

Pathologic complete response (pCR) is associated with improved survival and lower risk for distant metastases. Neoadjuvant Endo-HDR will increase pCR rates compared to concurrent chemoradiation (RT + Capecitabine). We expect similar locoregional control, decreased treatment time (1 week as opposed to 6 weeks), improved sphincter preservation rates, and lower acute and chronic toxicity.

2. ELIGIBILITY

Patients with low rectal cancer who are candidates for endorectal brachytherapy (non-obstructing lesions which can be adequately treated with this technique will be eligible for the study). Distal rectal tumors at 14 cm or less from the anal verge or rectosigmoid junction are included. Patients with T4 and/or presumed pathologic iliac/inguinal lymphadenopathy on PET/CT or MRI (>1.5 cm in diameter or necrotic appearing) are excluded.

3. BACKGROUND

3.1 Rationale

Locally advanced rectal carcinoma continues to be a major oncologic problem in the United States with approximately 40,000 new cases diagnosed in 2012 For stage II/III rectal carcinoma, adjuvant chemoradiation (1-3) and total mesorectal excision (TME) (4, 5) represent the major treatment advances that have increased cure rates over the past 30 years.

In the setting of TME, a landmark phase III German trial of stage II/III rectal cancer patients established neoadjuvant 5FU-based chemoradiation (NCRT) as standard of care over the same regimen given post-operatively (6). The preoperative arm showed superior local control (6% vs. 13% p=0.006), a complete pathologic response of 8%, a higher rate of sphincter preservation and less grade 3 toxicity compared to post-operative treatment. However, disease-free and overall survival (76% versus 74%, respectively) were no different because of the high rate of distant metastasis occurring in over 1/3 of patients (5yr DM 36 vs 38%, p=0.84). Importantly, those attaining a pathologic complete response had a decreased rate of distant metastasis and improved disease-free survival. Drawbacks to the regimen include acute grade 3 or 4 toxicity in 27% of patients, low compliance rates with postoperative chemotherapy (27 – 50%), and an overall decline in anorectal function shown by long-term studies (6).

Given the excellent locoregional control reported in TME surgical series, several trials have investigated whether certain patients may be spared preoperative radiotherapy (7-9). Two large randomized trials by Dutch and British investigators showed that a short preoperative course of hypofractionated EBRT (25 Gy in 5 fractions) followed by TME surgery decreased locoregional recurrence by 2/3 as compared to patients treated with TME surgery alone. In the Dutch trial, patients with mid and distal rectal cancers were most likely to benefit from radiotherapy. In these patients, preoperative radiation was shown to decrease locoregional recurrence by 5-fold (10% to 2%); however, the

hypofractionated preoperative EBRT regimen was associated with a significant increase in acute and chronic morbidity. Indeed, the Dutch study revealed that irradiated patients, when compared to surgery alone, had more perineal wound healing problems after abdominoperineal resection (29% vs. 19%), worsening deterioration of anal sphincter dysfunction, and more severe long-term effects related to sexual functioning both in males ($p=0.004$) and females ($p<0.002$) (10-12). Additionally, colleagues have reported a consistent negative impact on bowel function in those patients undergoing sphincter preservation (13). In reviewing the long-term data of the Swedish short course preoperative EBRT rectal cancer trial, Birgisson also reported a higher incidence of secondary tumors (9.5%) in patients treated with preoperative radiation when compared to patients having surgery alone (4.3%) (14).

Modern approaches to address the risk of distant metastasis and poor compliance with adjuvant systemic chemotherapy (following NCRT) have incorporated newer effective chemotherapy agents earlier in the treatment protocol. For example, oxaliplatin has been one of the most widely studied agents as a result of its proven efficacy when combined with 5-fluorouracil and leucovorin (FOLFOX) both in the metastatic and adjuvant settings for colon cancer(15). Initial phase II studies with the addition of oxaliplatin to standard 5-FU based NCRT appeared to show improved pathologic complete response rates compared to standard NCRT. However, two phase III trials clearly show that the addition of oxaliplatin during 5FU-based NCRT does not significantly improve pathologic complete response, locoregional control, distant metastasis or survival but does increase acute grade 3-4 toxicity by two to three-fold (16, 17).

One approach to limit toxicity from external beam radiotherapy is the use of intensity modulated radiation therapy (IMRT). IMRT can limit radiation dose to normal rectum (above and below the tumor) and surrounding organs at risk (OARs) such as bladder and sexual organs. IMRT utilizes multiple beams of radiation to treat the rectal tumor plus a margin and limits dose to OARs. While IMRT decreases radiation dose to normal structures, it requires an additional 2-3 cm margin for microscopic extension (clinical treatment volume=CTV), set-up error, and rectal motion (planning treatment volume=PTV). Furthermore, IMRT still requires 5-6 weeks of radiation with concurrent chemotherapy, is substantially more expensive than conformal radiation, and is especially prohibitive in countries where access to technology necessary for IMRT is limited (20). Based on the preliminary results of RTOG 0822 and others, it still remains to be determined whether IMRT confers a statistically significant improvement in pCR, toxicity rates and QOL relative to standard NCRT.

A novel approach to limit radiation toxicity is the use of high dose rate endorectal brachytherapy (Endo-HDR) (21). Endo-HDR involves the placement of a silicon multicatheter applicator within the rectum to deliver large doses to the rectal tumor and mesorectum with rapid dose fall off to the surrounding organs. An Iridium 192 high dose rate brachytherapy source attached to a wire is inserted into each catheter to deliver a high dose of radiation therapy the tumor. High dose rate brachytherapy has been well established in various malignancies (prostate, uterine, sarcoma, head and neck) to escalate radiation dose to the tumor over a short period of time while sparing normal

tissue. Compared with NCRT and IMRT, Endo-HDR delivers treatment internally to the tumor without having to pass through surrounding normal tissue and organs. It requires smaller margins (CTV/PTV=~1 cm) on the tumor since the applicator is positioned under fiducial guidance over the tumor without need for a margin for organ motion allowing greater sparing of OARs (22). Furthermore, the area of the rectum exposed to high dose radiotherapy is surgically removed at the time of resection which further minimizes chronic toxicity. Important structures that may be spared include bone marrow, small bowel, bladder, the autonomic nerves, sexual organs, anal sphincter and skin. Considering that 1/3 of patients will develop metastases, limiting bone marrow toxicity may contribute to better compliance with systemic treatment and allow for a better treatment strategy to target systemic recurrence. Another distinct advantage of Endo-HDR is the shortened treatment time (1 versus 6 weeks). Endo-HDR therefore provides a major logistic advantage for patients who may benefit from neoadjuvant therapy but who are geographically distant from radiation centers, elderly, or medically infirmed.

At the McGill University Health Center (MUHC), Vuong reported a phase II trial using high dose rate brachytherapy without concurrent chemotherapy to treat 285 (260 T3 tumors, 7 T4 tumors, and 18 T2 tumors and 38% were N+) rectal cancer within 10 cm from the anal verge from 1998-2007. The median age was 69 years (range 42-90) (23). Patients received four fractions of 6.5 Gy (26 Gy total) HDR-BT treatments in one week followed by a 6-8 week period of downstaging prior to resection. Treatment planning was CT-based with MRI, ultrasound imaging and use of fiducial markers using radioopaque clips placed under direct endoscopic visualization with the tumor bed defined as any visible disease seen in at the primary site or mesorectal nodal deposits. Patients with node positive disease at the time of surgery received adjuvant chemotherapy and EBRT. At a median follow-up time of 54 months, the 5 year actuarial local recurrence rate is 5%, with a doubling of pathologic complete response compared to standard chemoradiation (27%), < 1% grade 3-4 acute toxicity and no apparent increased long-term toxicity when compared to patients treated with TME alone. The disease-free survival is 65%, and the overall survival rate is 68% (23). Those patients attaining a pathologic complete response had improved survival and fewer distant metastasis. Grade 1-2 proctitis was noted in all patients starting 7–10 days after therapy and continuing until resection. While one patient experienced grade 3 toxicity, none had grade 4 proctitis. Surgical complications were limited to an anastomic leak rate of 10% and a perineal wound infection rate of 12% comparable to standard surgical experiences alone. Importantly, Endo-HDR did not compromise the pelvic bone marrow function and was not associated with hematologic toxicity. Based on these promising results, a current NCI Canada trial randomizes rectal cancer patients treated with Endo-HDR followed by TME to either pre- vs. post-operative FOLFOX.

Although these are promising results supporting the use of Endo-HDR, a theoretical concern of using this treatment strategy to treat only the primary site and adjacent mesorectal nodes is the potential for increased pelvic nodal recurrence without elective treatment with external beam radiotherapy (24). Standard NCRT covers the internal iliac, perirectal lymph nodes, mesorectum, and primary tumor (25). Current radiation portals are derived largely from Gunderson and Sosin's detailed study of the pattern of

recurrence after bluntly dissected rectal cancers. However, modern surgical series in patients treated without external beam radiation have shown that the majority of pelvic failures occur locally in the anastomosis and presacral tumor bed and that the incidence of extramesorectal pelvic nodal failure is low both in overall incidence as well as an isolated source of failure (4, 26-28). Wiig, reporting on 100 cases of local recurrence after TME, concluded that all recurrences were within reach of the examining finger and at the tumor bed (26). In the same series, there was only one case of nodal recurrence in the lateral pelvic wall. In the Dutch TME referenced above, the rate of extramesorectal pelvic nodal failure was 1.6% in the TME alone arm versus 1.3% who received preoperative radiation therapy. Moreover, preoperative treatment of extramesorectal nodes with chemoradiation may not improve outcomes. In the MERCURY study, MRI-based assessment of tumor regression and circumferential margin were prognostic for survival after neoadjuvant chemoradiation (29). Importantly, the presence of MRI detected extramesorectal lymphadenopathy did negatively impact disease-free survival; however, the use of neoadjuvant treatment did not alter the negative outcomes of iliac node positivity (29).

3.2 Correlative Studies

3.2.1 FDG-PET

The motivation for HDR brachytherapy in the treatment of rectal cancer is that a localized high dose rate gradient will improve pathologic complete response rates when compared to the homogeneous dose delivery of IMRT. While the high dose rate aspect will enable a much higher biological effectiveness to the targeted region, it is important to note that according to the linear-quadratic model, normal organs are more sensitive to the effects of high dose rate than tumors. This makes the localization of the dose delivery an issue of concern.

In this situation, FDG-PET will be a valuable tool to monitor treatment effect on the primary tumor as it is believed to better correlate with tumor response than CT-based criteria (30). We will exploit this hypothesis by examining the relation between dose and response as measured by ^{18}F-FDG uptake in ^{192}Ir HDR brachytherapy of rectal cancer at the voxel level as well as for the whole tumor. This strategy exploits another emerging concept that a single mean absorbed dose value is rarely indicative of tumor response.

The following sequence of events will take place (the first four are patient procedures and the last is a theoretical exercise): 1) an initial 18F-FDG PET/CT scan (Figure 1a); 2) 4 treatments of HDR ^{192}Ir brachytherapy designed to deliver a minimum of 26 Gy total to every voxel of the defined tumor region (Figure 1b); 3) a second ^{18}F-FDG PET scan 8 weeks after treatment (Figure 1c); 4) resection of the tumor; 5) a comparison of pathologic tumor response with radiation dose distributions.

Consequently, the correlations we will be examining will be twofold: 1) the entire tumor and 2) the individual voxels. The whole tumor mean dose will be compared to the change in ^{18}F-FDG uptake in the tumor region both in absolute and in relative

change. A similar approach holds for the voxelized data; however, voxelized data represents a challenge in dosimetry: the uncertainty inherent in the individual voxel absorbed dose outweighs its value. However, when large number of voxels are considered, such as those that constitute an entire organ or a binned ensemble, significant results can be obtained. This is often exploited in the form of dose volume histograms (DVHs). We will use both DVHs and binned results in our analyses.

3.2.2 DNA Damage Response

The effect of radiation on tumor cells is to cause irreversible injury to essential components of the cell. A commonly affected pathway is the DNA damage response pathway. We wish to compare how Endo-HDR versus NCRT affects this pathway. To do this, we will examine well-described genetic alterations (VEGF/EFGR, p53, BRAF, KRAS, PIK3CA, γ-H2AX, and XRCC1). We will determine whether particular mutations predict for pCR rates status post treatment. We will also correlate our findings with overall and disease-free survival.

3.2.3 Cancer Genome Sequencing to Determine Genetic Predictors of Response to Endo-HDR and IMRT

Whole cancer exome analysis will be performed on a subset of cases of strong responders and non-responders in an unbiased manner. Twenty thousand genes will be interrogated using tumor samples and whole blood using the Agilent capture platform and the Illumina HiSeq2000. Samples will be sequenced at a depth of 100-200X and analysis of these results will take into account clinical response. Correlation with clinical and pathologic response to therapy, disease free survival and overall survival will be performed against all the somatic genetic alterations found in each subset (32).

3.2.5 The role of infectious and inflammatory processes in colon carcinogenesis is of intense interest since the colon is colonized with ~$10^{12\text{-}13}$ commensal bacteria with the potential to induce inflammatory processes if colonic epithelial homeostasis is disrupted. The importance of inflammation in CRC is demonstrated by the dramatic increase in incidence among individuals with Inflammatory Bowel Disease (IBD). Bacterial initiators and promoters of immunologically driven CRC have long been proposed. Supportive human epidemiologic data show that migrating populations adopt the cancer risk of the region to which they relocate. Over time, the investigative focus has been on either mutagen production by colonic bacteria or their conversion of dietary procarcinogens into DNA-damaging molecules. Despite considerable effort, no direct links between the metabolic activities of bacteria and sporadic CRC are established. To date, the strongest, yet limited, evidence suggesting that commensal microbiota contribute to CRC pathogenesis derive from select, usually immune, gene knockout murine models in which the incidence of colon tumors usually decreases under germ-free conditions. The idea that the microbiome structure confers disease potential is supported by data, for example, indicating that murine colitis or disease phenotypes are transmissible through the microbiome. In 2011, we initiated a project at Johns Hopkins in which primary, untreated CRC tumors along with flanking normal colon tissue from surgical specimens was

collected for microbial analysis. Microbial analysis included structural microbiology, classic anaerobic microbiology and deep sequencing of the tumor or normal tissue (mucosal)-associated microbiota. This project has yielded, to date a critical observations. In right CRCs examined to date, a marked biofilm is associated with the tumors and is also present on at least 40% of flanking normal tissues from the same patients. In contrast, no biofilms are detected on any left CRC tumors or on flanking normal colon tissues. These data suggest the microbial associations of right vs. left-sided CRC are distinct. Sequencing analyses have revealed trends to differences in specific microbial associations in right and left CRC. Left sided CRC analyzed to date have been from the descending and rectosigmoid region because most rectal cancer at JHH is treated before surgery with radiation and chemotherapy, both of which may modulate the microbiome, we have little information on microbial associations of rectal cancer. In conjunction with the endorectal brachytherapy trial for treatment of rectal cancer, we will collect 2 additional biopsies (tumor and normal) during the pre-treatment endoscopy (standard of care in current protocol). Biopsies are currently being collected for other correlative studies during this endoscopy and additional biopsies will not be taken if it interferes with patient care. Tissue will be snap frozen and used for microbial sequencing. Results will be analyzed in conjunction with ongoing CRC microbial studies (evaluations of right and left colon cancer) underway at JHH as well as correlative studies (tumor genetics) being conducted as part of the endorectal brachytherapy trial.

3.3 Preliminary Data

In order to accurately quantify the effects of a) dose rate and b) heterogeneity in the normal organs and tumors and consequently the relative merits and potential of HDR brachytherapy as an adjunct for rectal cancer treatment, we will use dose volume histograms (DVHs) for all sensitive normal organs as well as the tumors and compare the DVHs to the DVHs from the IMRT treatment plans (performed on patient diagnostic scans). In order to compare dose values from different modalities, brachytherapy and IMRT external beam therapy, a conversion based on radiobiological modeling and the linear-quadratic equation is used. The different voxel doses are converted to the biological effective dose (BED) (41, 42) and from there to equivalent 180-cGy fractions (43) used in the IMRT plan.

The formula for the biological equivalent dose (BED) is: $$BED = D\left(1+\frac{D/N}{\alpha/\beta}\right)$$

where D is the total absorbed dose, N is the number of fractions (4 for the HDR brachytherapy; 28 for the IMRT plan) and *alpha* and *beta* are the radiobiological parameters for the linear-quadratic model of cell kill.

The process of conversion to 180-cGy equivalent dose takes into account the higher dose rate in HDR. Accurate, detailed absorbed dose calculations are useful only to the extent that they are biologically relevant and easily interpretable. The uniformity (or lack thereof) of absorbed dose distributions and their biological implications has been examined intensively, primarily in animal studies (44-46). The equivalent uniform dose

(EUD) model converts the spatially varying absorbed dose distribution into an equivalent uniform absorbed dose value that would yield a biological response similar to the one expected from the original dose distribution. This provides a single value that may be used to compare different dose distributions (43, 47, 48) and may correlate to single tumor response values rather than the mean absorbed dose. This EUD value is another example of how voxelized data may be grouped to provide more biologically relevant information at a larger scale.

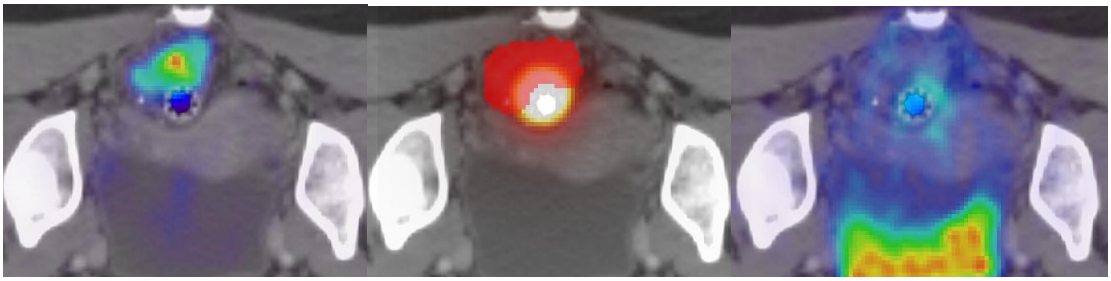


Figure 1a. Figure 1b. Figure 1c.

Figure 1. Illustration of dose-response as measured by ^{18}F-FDG uptake imaged using a PET scanner. Figure 1a shows the PET scan uptake prior to brachytherapy; Figure 1b shows the dose distribution (bright spot) as well as the tumor target volume (in red). Figure 1c is the post HDR therapy PET scan. All images are overlaid on the planning CT.

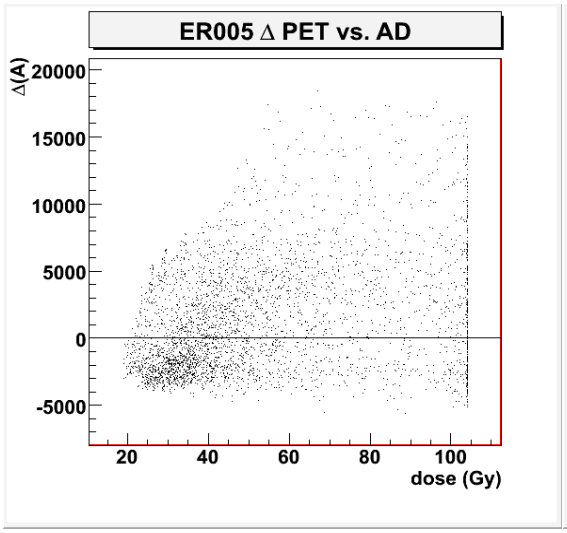


Figure 2a.

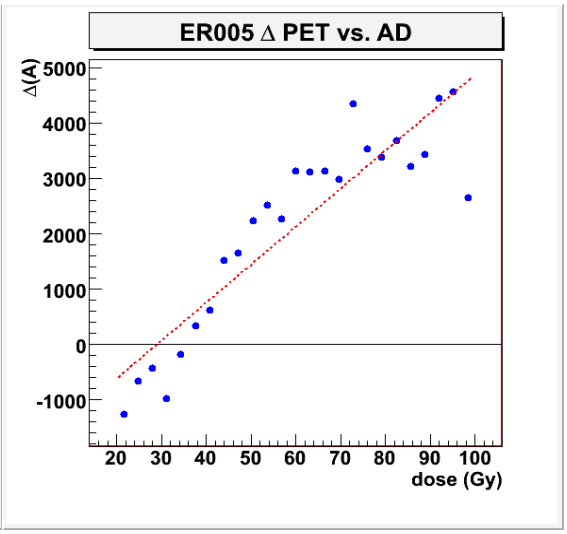


Figure 2b.

Figure 2. Dose and response results for the planning tumor volume for five patients. AD is the average absorbed dose value, AD_{eq} is the average in 180 cGy-fraction equivalent absorbed dose. EUD is the equivalent uniform dose. Change in PET is the total relative difference in PET uptake (absolute), while the R^2 is for the fit to the binned data (see Figure 1b).

Patient	AD (Gy)	AD_{eq} (Gy)	EUD (Gy)	Change in PET	R^2
ER001	41.0	86.5	34.8	71.9	0.82
ER003	51.6	125.1	44.7	26.5	0.18
ER004	51.1	124.6	32.7	43.7	0.89
ER005	51.0	126.7	30.4	20.3	0.82
ER006	49.7	121.4	25.3	45.8	0.70

Table 1. Dose and response results for the planning tumor volume for five patients. AD is the average absorbed dose value, ADeq is the average in 180 cGy-fraction equivalent absorbed dose. EUD is the equivalent uniform dose. Change in PET is the total relative difference in PET uptake (absolute), while the R2 is for the fit to the binned data (see Figure 1b).

In addition, patients will be evaluated by the PERCIST criteria as follows:
(PET Response Criteria in Solid Tumors)

Two key measurements performed in PERCIST 1.0 analyses are:

Baseline Lesion Threshold

It is calculated using the mean and standard deviation (in units of SUL-Standardized uptake value adjusted for lean body mass) of a 3cm diameter VOI placed in the right lobe of the liver.

Disease Threshold = (1.5 x Livermean) + (2 x Liversd)

Target Lesion Identification

It is defined as the hottest single tumor lesions (in SUL) of maximal 1cc volume VOI in tumor (SUL PEAK) greater than calculated threshold of lesion detectability.

For each study, the CAD system:

Measured normal reference hepatic tissue using an automated algorithm, recording the mean and standard deviation of a 3cm VOI placed within the imaging study volume, and calculating the disease threshold as defined by PERCIST 1.0.

Detected and statistically characterized lesion targets. Lesions targets were screened for false-positives and then ranked according to PEAK-SUL. The lesion with the hottest PEAK-SUL measurement was designated as the primary lesion.

3.3.1 Preliminary Clinicopathologic Comparison of Endo-HDR with Other Modalities

An initial 9 patients have been enrolled in our prospective Endo-HDR pilot study at Johns Hopkins University (ClinicalTrials.gov Identifier: NCT01226979). This is the first prospective study evaluating Endo-HDR in the U.S. All 8 evaluable patients had tumors <12 cm from the anal verge and no clinical/radiographic suspicious lymphadenopathy outside of the mesorectum (T2-T3, N0-N1). All patients had NCI CTCAE toxicity assessments, MRI, PET/CT, and CEA pre/post-Endo-HDR. RECIST/PERCIST criteria were used to assess response. Surgical specimens were reviewed by a single pathologist. All patients were margin negative and 8 had sphincter preserving surgery (one patient chose to have APR due to poor function prior to treatment). Three of 9 patients (33%) had a pCR of their primary tumors. Toxicity assessments showed only 1 patient with temporary grade 3 proctitis following Endo-HDR. All other toxicities were grade 2 or less, consisting of proctitis and pain managed conservatively.

We have compared surgical specimens of patients treated with endorectal versus chemoradiation with IMRT or 3-dimensional conformal therapy (49). Patients treated with endorectal brachytherapy showed greater treatment ulceration effect on the epithelium, greater hypertrophy of the submucosal rather than adventitial blood vessels and fewer serosal adhesions compared to external beam radiation techniques. See figures below.

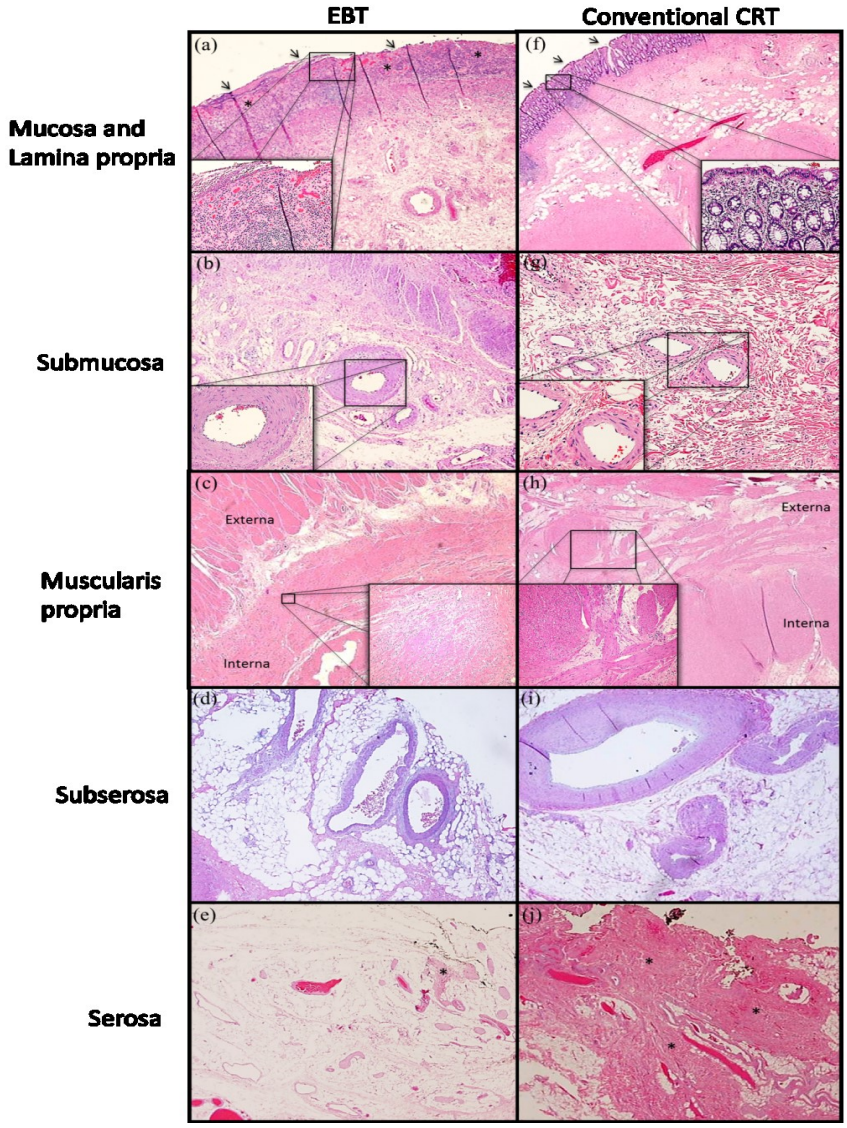


Figure 3. Representative H&E stained histopathologic sections at 4X magnification from patients who exhibited a complete pathologic response to Endo-HDR (a-e) and conventional external beam radiation (f-j). All images are taken from the region of the rectal wall where the tumor was located prior to neoadjuvant therapy. All insets are shown at 20X magnification. First Row – At the mucosa, extensive ulceration (solid arrows) is apparent after Endo-HDR (a), while the mucosa remains intact (solid arrows) after conventional CRT (f). Hyalinization of the lamina propria (asterisks) is also evident after Endo-HDR (a). Second Row – In the submucosa, marked hypertrophy and sclerosis of vessel walls can be seen following Endo-HDR (b), while only slight hypertrophy of vessel walls is seen after conventional CRT (g). Third Row – Within the muscularis propria, the more superficial interna layer can be seen to exhibit degeneration and atrophy after Endo-HDR while the externa layer remains largely intact (c); in a contrary fashion, following conventional CRT, it is the externa layer that exhibits more prominent degeneration compared to the interna (h). Fourth Row – At the level of the subserosa, vessel walls appear normal in patients treated with Endo-HDR (d), but distinctly hypertrophied in patients treated with conventional CRT (i). Fifth Row - The serosa demonstrates few adhesions (asterisk) after treatment with Endo-HDR (e), in contrast to the extensive adhesions (asterisks) present after treatment with conventional CRT (j).

We propose comparing Endo-HDR versus standard NCRT (IMRT) for stage II/III low rectal cancer (<14 cm from the anal verge). We have focused on patients with distal rectal carcinomas and include patients likely to undergo an APR as they are at highest risk for local failure after TME and most would be excluded in the current national PROSPECT trial. We have also incorporated staging FDG-PET/CT and MRI to exclude any patients with radiographic evidence of pathologic inguinal or iliac lymphadenopathy (defined as >1.5 cm, necrotic on MRI as detailed in the MERCURY study, or suspicious on PET/CT) (29).

4. OBJECTIVES

4.1 Primary Objective

Determine whether Endo-HDR improves pathologic complete response rates when compared to IMRT and capecitabine.

4.2 Secondary Objectives

- Test whether clinical response based on functional imaging (PET, MRI) pre/post radiation (Endo-HDR vs. CRT) predicts for pathologic complete response.
- Utilize preoperative imaging response rates and clinical exam to determine whether Endo-HDR results in improved sphincter preservation rates when compared to CRT.
- Determine whether tumor (VEGF/EGFR status) and blood predict for pathologic response following neoadjuvant Endo-HDR vs. CRT.
- Compare acute and long-term toxicity as well as quality of life for both Endo-HDR and CRT.
- Compare locoregional control, distant metastasis and overall survival for both Endo-HDR and CRT.

5. PARTICIPANT SELECTION

5.1 Inclusion Criteria

5.1.1 Histologically confirmed adenocarcinoma of the rectum

5.1.2 T2N1-2 or T3N0-2b tumors at ≤ 14 cm from the A-V margin (below the peritoneal reflection) or the rectosigmoid junction.

5.1.3 Tumors with a lumen sufficient to allow the positioning of the rectal applicator (standard probe/scope) confirmed by the treating physician.

5.1.4 Tumors of less than 4 cm thickness from the rectal mucosa documented at the time of staging images

5.1.5 Patients should be suitable candidates for surgery and chemotherapy

5.1.6 ECOG/WHO performance status 0-1

5.1.7 Patients must be 18 years or older

5.1.8 No previous history of pelvic radiation

5.1.9 Patients must have acceptable organ and marrow function as defined below:

- Absolute Neutrophil Count ≥ 1.5 x 10^9/L
- Platelets ≥ 100 x 10^9/L.
- Serum creatinine ≤ 1.5 x ULN
- Bilirubin ≤ 1.5 x ULN
- ALT or AST ≤ 2.5 x ULN

5.1.10 Non pregnant, non-breast feeding females under active contraception

5.1.11 Ability to understand and willingness to sign a written informed consent document.

5.2 Exclusion Criteria

5.2.1 Evidence of signet ring involvement on histology

5.2.2 Evidence of necrotic or > 1.5 cm in diameter pelvic (iliac/inguinal) nodes

5.2.3 Evidence of distant metastatic disease

5.2.4 Evidence of sphincter invasion on MRI

5.2.5 Prior history of radiation to the pelvis

5.2.6 Prior malignancy except for adequately treated basal cell or squamous cell skin cancer, cervical carcinoma in situ, DCIS, or other cancer from which the patient has been disease free for at least 3 years

5.2.7 Presence of multiple small bowel loops trapped within the immediate tumor bed (post hysterectomy or prostatectomy).

5.2.8 Use of any investigational agent within the 4 weeks preceding enrollment

5.2.9 Previous exposure to chemotherapy for rectal cancer

5.2.10 Uncontrolled intercurrent illness including but not limited to, ongoing or active infections (or infections requiring systemic treatment), symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

5.2.11 Pregnant and breastfeeding women are excluded, as well as 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. Should a woman become pregnant or suspect she is pregnant while participating in this study she should inform her treating physician immediately.

5.2.12 Women who are not post-menopausal and have a positive urine or serum pregnancy test or refuse to take a pregnancy test.

5.2.13 Contraindication for safe MRI, implants, or other conditions that interfere with imaging required for the study (e.g., pacemaker or non-MRI compatible hip prostheses). Note: Subjects with bilateral hip implants are not eligible for the study. Subjects with a unilateral hip implant may be eligible assuming the implant is MRI compatible and does not present artifact on MRI in the areas of interest.

5.2.14 Subject is pacemaker dependent.

5.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

6. REGISTRATION PROCEDURES AND RANDOMIZATION

6.1 Informed Consent

All subjects considered from enrollment in the study must complete an IRB approved informed consent prior to any study-specific procedures being performed (Section 13.2).

6.2 Screening/Baseline Assessments and Procedures

The following procedures and assessments will be performed within 6 weeks prior to the initiation of radiation therapy.

- Demographic information
- Medical history and physical examination
- Performance status
- Concomitant medications
- Fiducial marker placement (within 3 weeks of start)
- Research biopsies of tumor and adjacent normal tissue and blood samples (optional)
- FDG-PET/CT
- Pelvic MRI
- CBC w/ diff, CMP, CEA, and testosterone for male participants
- Quality of life assessments
- Assessment of baseline symptoms
- Pregnancy test for women of child-bearing potential

6.3 Fiducial Placement

Endoscopic evaluation will be performed by the surgical team to assess the tumor, ensure adequate lumen for probe placement, and to mark the tumor with MRI compatible gold fiducials (markers) for guidance during **Endo-HDR and CRT** treatment planning. Fiducials should be placed above and below the tumor and the **tumor margins should also be marked with tattoo**. The recommended fiducials to be used are Visicoil™ (0.75mm x 1cm) image markers. When possible, dye should be placed during EUS in the mucosa to demarcate the superior, inferior, and lateral aspects of the tumor.

At the time of endoscopic assessment, tissue biopsies of the tumor may be obtained for correlative studies. After completion of clinical and radiological evaluations under direct rectoscopy, radio-opaque markers are placed to identify the proximal and distal margins of the tumor for subsequent positioning quality control of simulation and treatment applications.

6.4 Registration Procedures

Eligible patients will be entered on study centrally at the Johns Hopkins Hospital by the Study Coordinator.

To register a patient, the following documents should be completed by the research nurse or data manager and sent to the Study Coordinator.

- Source documentation verifying eligibility
- Eligibility checklist
- Signed patient consent form

If the patient is deemed eligible for the study, the Study Coordinator will register the patient and assign a study number.

6.5 Randomization

Eligible subjects will be randomly assigned in a 2:1 ratio to receive either endorectal brachytherapy or IMRT using the method of randomly permuted blocks in strata defined by study site. The patient may be enrolled and randomized before the endoscopic ultrasound and fiducial placement if all eleiglibility requirements are met. A master list of randomization assignments will be made by the protocol statistician, and will be delivered to the lead site by email or facsimile report.

7. TREATMENT PLAN AND DELIVERY

7.1 Quality Assurance

Tumor volumes and radiation plans for Endo-HDR, 3D-conformal radiation, and IMRT will be reviewed. Dr. Vuong and Dr. Narang will review the first 5 endorectal plans at each institution. The first 3 3D-conformal and/or IMRT plans from each institution will be reviewed by either Dr. Narang, Dr. Hu, or Dr. Biagioli. All plans (Endo-HDR and IMRT) will be centrally reviewed by Dr. Narang, Dr. Hu, or Dr. Biagioli after completion of the study.

7.2 Endorectal Brachytherapy Radiation Therapy

7.2.1 Endorectal Brachytherapy Radiation Therapy

At the initial assessment, the surgeon will be asked to determine the likelihood of sphincter preservation. Endo-HDR is an outpatient procedure.

Patients will be treated with a daily dose of 6.5 Gy over four consecutive days for a total of 26 Gy. To administer Endo-HDR, patients will be placed in the lateral decubitus position to insert the endorectal applicator and then maneuvered into the supine position. Once in place, the applicator is secured to the plate/holder and an anal BB is placed at the anal verge. Dummy wires are inserted into the applicator and the patient is scanned using CT (2 mm slices). The radio-opaque (MRI safe-optimal) markers will guide application of the endorectal probe and assist with tumor delineation during IMRT treatment. For Endo-HDR, RT dose will be prescribed to the tumor radial margins or mesorectal node, whichever is greater not to exceed 3.5 cm from the mucosal surface. Prescribed dose will include a 1 cm CTV/PTV proximal and distal expansion excluding anal sphincter distally. However, when the GTV is close to the sphincter, the CTV should not be expanded distally into the

sphincter (treat GTV only). The endorectal applicator is flexible, with nine-channels using a high dose-rate remote after-loading system. Standard radiation procedures will be followed during Endo-HDR as outlined in the protocol. QOL will be assessed throughout the treatment process (see calendar). Endoscopic endorectal ultrasound (EUS) is obtained for tumor staging and magnetic resonance imaging (MRI) of the pelvis is used for tumor measurements (length and bulk evaluation).

7.2.2 Endorectal Brachytherapy Equipment

The treatment is delivered using a recognized endorectal applicator (Oncosmart, Nucletron) consisting of a central flexible tube with 8 catheters arranged around the circumference of a central tube. Treatment planning is performed using CT simulation. A hydraulic locking clamp mounted on a Plexiglas plate is manufactured for immobilization during the CT simulation. High dose rate brachytherapy is delivered using a Nucletron microselectron HDR (iridium-192 source).

7.2.3 Endorectal Brachytherapy Simulation

The 3D treatment planning process is carried out as follows. Prior to CT simulation, an initial anterio-posterior (AP) scout view of the patient lying in supine position is done in order to visualize the endorectal radio-opaque markers. The endorectal applicator is introduced using lubrication with the patient lying in the lateral decubitus position. The patient is then repositioned in the supine position and a Plexiglas plate with the mounted hydraulic locking clamp is slid under the patient's pelvis and the Oncosmart intracavitary mold is latched onto the hydraulic locking clamp. Repeated AP and lateral scout views are then taken and examined. When necessary, adjustments are made to the cephalic orientations of the applicator relative to the radio-opaque marker locations. The tip of the applicator will be positioned at least 2 cm beyond the proximal extent of tumor. With the applicator in the optimal position, CT scanning is performed using a slice thickness and separation of 2.5 to 5 mm to scan the area, which extends from the upper third thigh to a few cm above the tip of the endorectal applicator. Following the CT, the acquired images are sent a dedicated virtual simulation image processing workstation. Contoured tumor, catheters and endorectal markers are incorporated into digitally reconstructed radiographs (DRRs) or digitally composite radiographs (DCRs) to enhance selectively visualization and use as references for daily treatment.

7.2.4 Endorectal Brachytherapy 3D Treatment Planning

The tumor volume is defined as the (gross tumor volume=GTV). The GTV plus additional intramesorectal extension is defined as the clinical target volume=CTV) (Figure 4). Adjacent normal tissues will also be contoured. The normal rectal volume is the volume confined to within 5 mm of the perimeter of the balloon that did not extend beyond 1 cm of the superior and inferior margins of the target. When a balloon is not used, the normal rectum volume will be confined to the normal rectum (non-CTV) within 5 mm of the applicator. The percentage of the CTV covered by 100% and 150% of Dref (V100 and V150), and the minimum dose received by 90% of the CTV (D90) will be calculated. The mean dose (Dmean) to normal tissues, inclusive of bladder, femoral heads, bone marrow, uterus, vagina,

prostate, penile bulb will also be calculated and included in the dose volume histogram. Bone marrow will be defined by contouring all osseous structures from the L4/L5 interspace through the sacrum, pelvis, and proximal femurs to the inferior aspect of the inferior pubic rami. The other normal structures will be defined in accordance with the RTOG male and female atlas guidelines (see Section 7.2.9). In addition, the minimum dose to the hotest 1, 2, and 5 cm^3 (D1cc, D2cc, and D5cc) of the normal structures will be calculated to examine anatomic heterogeneity effects. The doses are expressed as a percentage of Dref. We will confirm that 100% of the CTV volume is covered by the 95% isodose line. Any visible perirectal lymph nodes seen on imaging will be included in the treatment volume however other mesorectal lymph nodes are not always included as it is assumed these will be removed by the TME. As a general rule, any lymph node deposits located within 0.5 and 1 cm from the target CTV will receive 75% and 50% of the prescribed dose. Endorectal markers as well as the first dwell position are incorporated into digitally reconstructed radiographs for use as a reference for the daily treatments. The digitally reconstructed radiographs will be created with the reconstruction plane set at the level of the applicator so that the ruler can be used for distance measurements between radio-opaque markers and the first dwell position of the applicator. Dwell positions are determined with respect to the extent of the contoured target. Catheters are loaded in a differential manner so that only those in close proximity with the tumor contain active source dwell positions. After the source position determination, CT-aided brachytherapy treatment planning is carried out to fully conform the dose distribution to the target, and to limit dose as much as possible to immediately adjacent tissues beyond the rectal wall.

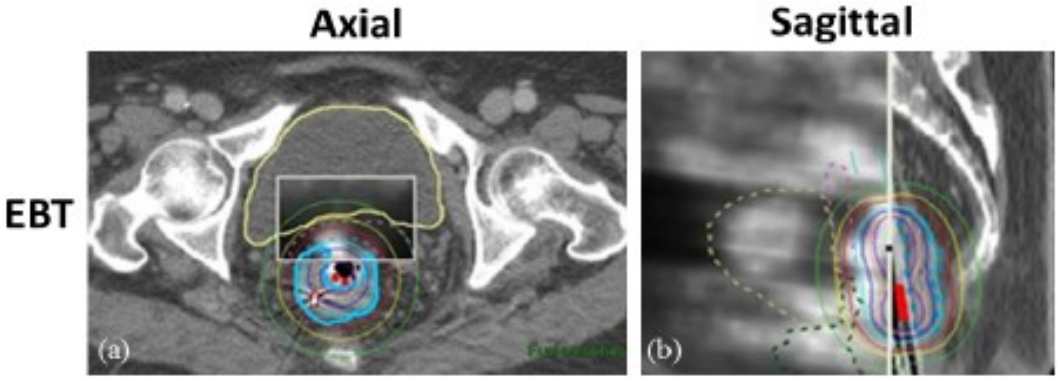


Figure 4. Fusion of Endo-HDR CT simulation with a) MRI and b) PET/CT imaging.

7.2.5 The Differential Source Positioning Technique

Source positions for brachytherapy are determined with respect to the contoured tumor. Catheters are loaded in a differential manner so that only those in direct contact with the tumor contain active source dwell positions. Following the source position determination, CT-aided brachytherapy treatment planning is carried out so as to optimize fully the dose to the tumor, while limiting the dose to immediate adjacent tissues beyond the rectal wall. Isodose distributions were generated by Oncentra software (Nucletron USA), see dose distribution above (Figure 4b).

7.2.6 Treatment Delivery

With the patient in lithotomy position, individually marked tungsten dummies are inserted into selected channels. Prior to each treatment, AP and lateral daily check films are obtained and compared to either AP and lateral scout films or treatment planning DRRs to visualize the endorectal applicator position and orientation according to the radio-opaque endorectal markers and bony landmarks. These pre-treatment check films aid in determining both the depth and rotation of the endorectal applicator with respect to the intended position, as determined from the CT-simulation. The channel orientation is determined by the position of the dummies on check films. In the event that plain films are not available prior to a brachytherapy fraction, it is permissible to evaluate the brachytherapy applicator and plan on CT.

7.2.7 Dose Prescription

A total dose of 26 Gy in 4 daily fractions of 6.5 Gy will be prescribed at the CTV, defined as the GTV and intramesorectal deposits seen on the pre-staging MRI. The dose will be delivered with a differential channel loading of the endorectal applicator.

7.2.8 Dose Modifications

Every effort will be made to administer the entire radiation treatment to participants. Every effort will be made to limit the dose to the bladder, femoral heads, small bowel, vagina, uterus, and/or penile bulb.

7.2.9 Organs at Risk (OAR)

The following normal tissues of interest will be contoured and the dose to each recorded according to the RTOG male and female atlas guidelines:
http://www.rtog.org/CoreLab/ContouringAtlases/MaleRTOGNormalPelvisAtlas.aspx
http://www.rtog.org/CoreLab/ContouringAtlases/FemaleRTOGNormalPelvisAtlas.aspx

No part of these normal structures will be permitted to receive more than the prescription dose of 26 Gy (6.5 Gy x 4 fractions).

- All patients:
  - Small bowel, large bowel, sigmoid colon
  - Bladder
  - Femoral Heads
  - Anal sphincter
- Female patients:
  - Vagina
  - Uterus
- Male patients:
  - Prostate
  - Seminal Vesicles
  - Penile bulb

Structure	0.1 cc	2 cc
Anus*	6.5 Gy	4.8 Gy
Penile Bulb	5.9 Gy	4.8 Gy
Bladder	7.0 Gy	
Sigmoid	6.5 Gy	

Table 2. Dose Constraints for Endorectal Brachytherapy Treatment
*When the tumor approaches but does not involve the anal sphincters the dose to the anus may exceed the above constraints. Every effort should be made to limit this dose as much as possible.

7.3 Intensity Modulated Radiation Therapy and Capecitabine

7.3.1 IMRT Planning

External radiotherapy will be based on contouring guidelines from the RTOG atlas and Radiation Therapy Oncology Group (RTOG 0822) with modifications described below.

Patients will undergo CT (required) and MRI simulation (optional) in the supine position with concurrent administration of IV and oral contrast. (IV contrast may be omitted for patients with contrast allergy or another contraindication.) The bladder should be full. A custom immobilization device such as a vac-loc bag or alpha cradle should be used to ensure consistent setup. An anal BB marker should also be placed at the time of simulation.

7.3.1.1 Gross Tumor Evaluation for IMRT Treatment Planning

- GTV Primary Tumor
- Increased SUV on PET/CT will define inferior and superior aspect of tumor. Use bony anatomy to help with orientation if PET cannot be fused to planning CT.
- Use MRI to better define the anterior and posterior borders of the tumor. Again use Bony landmarks to help with orientation.
- GTV Involved Nodes
- Contour GTV for mesorectal lymph nodes which are >1cm and adjacent to the tumor (<1 cm), show enhancement on PET or MRI and/or have anatomic abnormalities suspicious for tumor involvement (based on MERCURY study).
- CTV for gross disease (per RTOG 0822)
- Primary tumor CTV = Primary Tumor GTV +1.5cm radially and 2.5cm craniocaudally
- Involved Node CTV = Involved Node GTV + 1.5cm symmetrical expansion

7.3.1.2 Clinical Treat. Vol. (CTV) & Planning Treat. Vol. (PTV) for IMRT

The RTOG Anorectal Contouring Guidelines will be used to guide treatment planning for patients in the IMRT arm of this study (50). Two PTVs will be created according to these guidelines. PTV-Initial will consist of CTVA plus margin,

including pelvic lymph nodes, the mesorectum, and the primary tumor plus margin and will receive 45 Gy in 25 1.8-Gy fractions. PTV-Conedown will include the rectal primary tumor plus margin and will receive 5.4 Gy in 3 1.8-Gy fractions. The RTOG contouring guidelines for creating target volumes are summarized below.

PTV-Initial
CTVA consists of the following areas that must always be treated in rectal cancer and will be uniformly expanded by 0.5 cm to create PTV-Initial. This volume will receive 45 Gy (1.8 Gy x 25).

- Superior border: The recommended superior extent of the peri-rectal component of CTVA was at whichever is more cephalad: the rectosigmoid junction or 2 cm proximal to the superior extent of macroscopic disease in the rectum/peri-rectal nodes. This defines how much of the distal large bowel should be within CTVA. The most cephalad extent of CTVA will be higher than the peri-rectal component, in order to properly cover the internal iliac and pre-sacral regions. The most cephalad aspect of CTVA should be where the common iliac vessels bifurcate into external/internal iliacs (approximate boney landmark: sacral promontory).

- Inferior border: Minimum 2 cm caudal to gross disease including coverage of entire mesorectum to the pelvic floor. Unless radiographic evidence of extension to ischiorectal fossa, CTVA need not extend through the levator muscles. For very advanced anal or rectal cancers, extending through the mesorectum or the levators, the group's recommendation is to add ~1-2 cm margin up to bone wherever the cancer extends beyond the usual compartments. An MRI and/or PET/CT scan is strongly recommended in such cases.

CTVA will also include the following structures:
  - Iliac Lymphatic CTV= Internal iliac vessels + 1.0 cm symmetrical expansion.
  - Presacral Lymphatic CTV = 8mm anterior to anterior border of sacral bone (extending from S1-S5)
  - Mesorectal and perirectal lymphatic CTV
  - Posterior border: anterior border of the sacrum and gluteus maximus
  - Lateral border: Ileum, piriformis and obturator muscles
  - Anterior border should overlap 1cm into the bladder, vagina or prostate.
  - In the mid pelvis, this volume should include at least the posterior portion of the internal obturator vessels (which lie between the external and internal iliacs in the mid pelvis).

PTV-Conedown
CTV-B consists of the following structures that require a boost dose of radiation. A 0.5 cm uniform margin will be placed around the following structures to create PTV-Conedown. This volume will receive 5.4 Gy (1.8 Gy x 3).
  - Primary tumor GTV

- Involved nodal GTV (if present)
- Presacral CTV (see above)

References:
RTOG Anorectal Contouring Atlas
http://www.rtog.org/LinkClick.aspx?fileticket=DgflROvKQ6w%3d&tabid=231
RTOG 0822 Protocol, Section 6 (Radiation Therapy)
http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=4663

7.3.1.3 Planning Constraints for IMRT Plans

7.3.1.3.1 Normal Tissue Dose Constraints

The following normal structures must be contoured for each IMRT treatment plan:

- Small bowel, large bowel, sigmoid colon (contour up to 1cm above PTV)
  - ≤ 180 cc above 35 Gy
  - ≤ 100 cc above 40 Gy
  - ≤ 65 cc above 45 Gy
  - No small bowel volume should reach 50 Gy
- Bladder
  - ≤ 40% above 40 Gy
  - ≤ 15% above 45 Gy
  - No bladder volume should reach 50 Gy
- Femoral Heads
  - ≤ 40% above 40 Gy
- Contour and Limit Dose as much as possible to the following structures:
  - Anal Sphincter
  - Female:
    - Uterus
    - Vagina
  - Male:
    - Prostate
    - Seminal Vesicles

7.3.1.3.2 PTV Planning Dose-Volume Constraints

- ≥ 98% of PTV receives at least 93% of planned dose
- ≤ 10% of PTV receives ≥ 105% of prescribed dose
- ≤ 5% of PTV receives ≥ 110% of prescribed dose
- None of the PTV is to receive ≥ 115% of prescribed dose

7.3.2 Image Guided Radiation Therapy (IGRT) for IMRT Plans

IGRT is optional in this trial. If used, IGRT should consist of daily CBCT or MVCT to bony pelvis with shifts made on kV port films to ensure that rectal markers and pelvis lymph nodes are covered with an adequate margin.

7.3.3 3-D Conformal Radiation Therapy (3-D CRT)

3-D CRT and/or tomotherapy 3-D plans will be permitted on this protocol for patients who have difficulty obtaining insurance coverage or have other issues that preclude the use of IMRT, although IMRT is preferred.

For designing 3-D fields, CTV, PTV, and OARs will be the same as those specified in the IMRT planning section (51). CTV and PTV must be delineated. Normal tissue dose constraints will also be the same. We recommend the following field borders for 3-D fields:

AP-PA field
Superior: L5-S1 interspace
Inferior: Ischial tuberosity
Lateral: 1-cm exterior to pelvic brim

Lateral field
Superior: L5-S1 interspace
Inferior: match to AP-PA fields
Anterior: Pubic symphysis; bowel may be excluded as long as there is a 1.5 cm margin around the PTV to ensure adequate coverage of this volume
Posterior: follow posterior curve of the sacrum to ensure complete coverage of the presacral space

Boost volumes
A 2-cm margin should be placed circumferentially on the primary GTV, involved nodal GTV, and presacral CTV to create the boost PTV. The field arrangement used to treat this target may be at the discretion of the treating radiation oncologist.

7.3.4 Treatment Break Outline

Pursuant with RTOG 0822: "Treatment interruptions are discouraged; however, they may be necessitated by uncontrolled diarrhea or other acute complications. The reason for and length of any such interruption must be documented. If the sum total of such interruptions exceeds 5 normally scheduled treatment days, this would constitute a major treatment violation. A minimum of 4 daily radiation therapy treatments are required in any given week. Any missed radiation treatments will be made up at the end of the treatment schedule, such that the total number of delivered 1.8 Gy fractions remains 28. If chemotherapy is held, radiation therapy will continue."

Toxicity	XRT Dose
Grade 2 thrombocytopenia	Continue at current dose.
Grade 3 thrombocytopenia	Hold until recovery to grade ≤1, then resume.
Grade 4 thrombocytopenia	Hold until recovery to grade ≤1 (platelets ≥ 75 x109/L), then resume.
Grade 3 neutropenia	Hold until recovery to grade ≤1 , then resume.
Grade 4 neutropenia	Hold until recovery to grade ≤1, then resume.
Grade ≥3 febrile neutropenia	Hold until resolution of fever and neutropenia to grade ≤ 1. Hold until the ANC ≥ 1,500/mm3 and fever has resolved. Then resume treatment.

References:
RTOG 0822 Protocol, Section 6 (Radiation Therapy)
http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=4663

7.3.5 Capecitabine (Xeloda)

Capecitabine shall be delivered at 825mg/m^2 BID during IMRT radiotherapy. Dose modification shall occur as follows:

- If ANC < 1000/mm^3 capecitabine will be held until the blood counts recover above these values and the patient can resume full dosing
- If platelet count < 100,000/mm^3, capecitabine will be held until the blood counts recover above these values and the patient can resume full dosing

Event Name	**Hand-Foot Skin Reaction**
Grade of Event	**Management/Next Dose for Capecitabine**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. For the first appearance resume at 100% of the dose. For the second appearance, dose reduce to 650 mg/m^2 For the third appearance, dose reduce to 500 mg/m^2 For the fourth appearance, discontinue.
Grade 3	Hold until ≤ Grade 1. For the first appearance, dose reduce to 650 mg/m^2 For the second appearance, dose reduce to 500 mg/m^2 For the third appearance, discontinue.
Grade 4	Hold until ≤ Grade 1. For the first appearance, dose reduce to 500 mg/m^2 For the second appearance, discontinue.

Event Name	**Diarrhea**
Grade of Event	**Management/Next Dose for Capecitabine**
≤ Grade 1	No change in dose
Grade 2	For the first appearance, dose reduce to 650 mg/m^2 For the second appearance, dose reduce to 500 mg/m^2 For the third appearance, discontinue.[1]
Grade 3	For the first appearance, dose reduce to 650 mg/m^2 For the second appearance, dose reduce to 500 mg/m^2 For the third appearance, discontinue.[1]
[1]Capecitabine may be discontinued at the discretion of the investigator	

7.4 Surgery

7.4.1 Patient Assessment

After the patient has been identified as a candidate for the trial, the surgeon will assess the patient and will determine:

1. Exact height and location of tumor with regards to the anal margin as measured by a rigid or flexible proctoscope and/or digital exam.
2. Mobility of tumor as assessed if possible by rectal exam
3. Type of surgical procedure: Abdomino-perineal resection vs. sphincter saving procedures, which will include colo-anal with mucosectomy vs. stapled anastomosis.

7.4.2 Patient Preparation

Routine pre-operative assessment will be undertaken as standard care. Efforts will be made for the patient to be seen by a stomatherapist pre-operatively in order to mark the future site of either temporary ileostomy or permanent colostomy. Bowel preparation, perioperative antibiotics, and venothromboembolic prophylaxis will be encouraged and administered at the discretion of the treating facilities. Skin preparation, glucose monitoring, and temperature regulation will be at the discretion of the treating surgeon and facility.

7.4.3 Tumor Assessment

The following items will be assessed at the time of surgery either before the procedure begins or once the specimen has been removed.

1. Macroscopic response to brachytherapy (complete vs. partial vs. non response)
2. Height between tumor bed and anal margin, to assess feasibility of either colo-anal anastomosis vs. stapled anastomosis vs. abdomino-perineal resection (APR).
3. Location of the tumor on the bowel wall (anterior/posterior).

The pathologist should be orientated to the position of the tumor and should open the lumen of the specimen so that the response can be directly observed. We follow the criteria outlined by Mandard et al. with tumor regression grade (TRG) 1-2 demonstrating a good response to therapy (52).

7.4.4 Surgical Technique

Surgery should occur between 8 and 12 weeks from the completion of neoadjuvant therapy.

Patients will be positioned in lithotomy. The use of ureteral stents will be at the discretion of the treating surgeon. Open and minimally invasive techniques are allowed. If preservation of the anal sphincter muscles is planned, a standard laparotomy will be undertaken. An assessment of the liver, peritoneum, pelvic organs (uterus/ovaries) should be performed. The objective of the operation is a curative

procedure with full total mesentery excision (TME) of the rectum. It will be expected that all attempts to perform a high ligation of the IMA will occur and that the nodes within this portion of the mesentery will be carefully examined. The plane between the fascia propria of the rectum and the presacral fascia will be entered in the midline posteriorly. Every attempt will be made to identify the hypogastric nerves along the pelvic side wall and the findings will be recorded as injured or preserved (See Appendix VI). It is expected that all tumors located in the mid and lower rectum will be removed with a complete TME. All attempts will be made to achieve at least a 3-cm margin on the mesorectum and a 1-cm mucosal margin. If the margin is in question, additional margin should be taken. A frozen section may be performed at the discretion of the treating surgeon. The surgeon will record their assessment of the TME as either complete, nearly complete, or incomplete recording difficulty encountered. It will be at the discretion of the surgeon to perform either a straight end-to-end or side-to-end anastomosis with or without a colonic pouch or coloplasty. Evaluation of the anastomosis will be performed from the abdominal side, i.e., tension-free anastomosis and from the perineal side, i.e., complete ring of the anastomosis and negative air test. All patients undergoing a resection with re-anastomosis will have a diverting loop ileostomy performed. If an APR is performed, the perineum will be removed in an oncological fashion with preservation of the radial margin either at the start of the procedure of at the end of the procedure. The perineum will be closed in a method which is at the discretion of the treating surgeon and the patient will be given a permanent stoma.

Abdominal or perineal drainage will be left to the discretion of the surgeon.

7.4.5 Post-Operative Assessment

Standard post-operative care will be undertaken. Length of stay, transfusion requirements, surgical site infections (including clinical and sub-clinical anastomotic leaks), and venothrombolic events as captured by the National Safety Quality Improvement Project (NSQIP) will be recorded. Any hospital mortality with cause of death will be recorded. Any other intraoperative findings such as perineal wound infection (for patients undergoing APR), anastamotic leak (managed with IR drainage vs. requiring return to OR), or intraabdominal abscesses will be recorded.

7.4.6 Follow-Up Evaluation

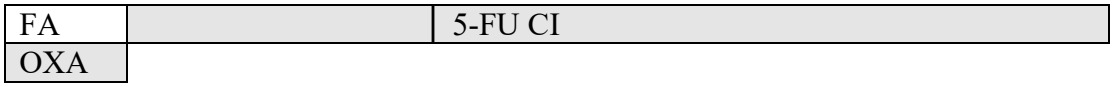
Patient will be considered for stoma closure 2 to 3 months after surgery or following additional chemotherapy. Prior to stoma closure, patient will have anastomosis evaluation by either standard contrast radiography direct in the rectum and or by rectal exam with sigmoidoscopy. Any abnormal finding will be recorded and may delay stoma closure.

7.4.7 Postoperative Adjuvant Chemotherapy

Per standard of care and at the discretion of the treating physician, approximately 6-10 weeks after surgery, patients will receive modified FOLFOX6 adjuvantly after resection for 6 months (12 cycles). Below is a recommended regimen but final plan is at the discretion of treating physician.

FOLFOX6:

Day 1
Oxa infusion (2h)
FA infusion (2h)
5-FU bolus
↓



Day 1:

Oxaliplatin: 85 mg/m² in 500ml glucose 5% solution, 2-h infusion
Folinic acid (FA) 400mg/m² in 250ml glucose 5% solution, 2-h infusion simultaneously with the oxaliplatin infusion
5-Fluorouracil (5-FU) bolus 400mg/m² following the oxaliplatin/FA infusions
5-FU continuous infusion 2400 mg/m², 46-h infusion following the 5-FU bolus

Cycle length: 14 days (2 weeks)

Duration of treatment: 12 cycles

7.5 Follow-Up Assessments

Patients will be followed per standard of care. For study purposes. an initial follow-up will occur post-operatively and then annually by PI and/or study team members. Every effort made to collect any SAE's or hospitilizations that occurred in the year prior. QOL will in collected per the study calender In the event this cannot be completed in person or online, it will be mailed out.

7.5 Supportive Care

The following supportive care is recommended. However, it is ultimately at the discretion of the treating physician.

7.5.1 Patients receiving Endo-HDR

Proctitis and rectal pain are the main side effects reported among patients receiving Endo-HDR. These symptoms are currently managed as follows:

- Cortifoam enema (all patients)
- Naproxen 375 – 500 mg (all patients; twice daily; discontinue 3 weeks before surgery)
- Acetaminophen with codeine 300/30 mg (patients experiencing mild to moderate pain; take 3 – 4 times daily as needed)
- Hydromorphone 2 mg (patients with severe pain only; take 3 – 4 times per day as needed)

7.5.2 Patients receiving External Beam Radiotherapy

Diarrhea, skin irritation, fatigue, urinary tract irritation, and decreased blood counts are the main side effects experienced during concurrent chemotherapy and pelvic radiation therapy. Standard supportive care measures may be used at the treating physician's discretion throughout the course of therapy, including antidiarrheal agents (loperamide, etc.), skin creams, and phenazopyridine (Pyridium). Specific guidelines for dose-reducing capecitabine as needed are given in Section 7.3.5.

7.6 Subject Withdrawal/Removal

Patients will be removed from the study for the following reasons:

- Unacceptable toxicity from therapy. Toxicity must be appropriately documented.
- Development of intercurrent, non-cancer related illness that prevents either continuation of therapy or regular follow-up
- The patient decides to discontinue enrollment in the protocol at any time and for any reason
- Continuation of participation could be harmful
- Pregnancy
- The patient needs treatment not allowed in the study

All reasons for discontinuation of treatment must be documented.

- Patients who prematurely discontinue radiation treatment but undergo surgical exploration will be followed per the prescribed protocol schedule.
- Patients who prematurely discontinue radiation treatment and do not undergo surgical exploration will be followed for survival for five years.
- Patients who complete radiation treatment and do not undergo surgical exploration will be followed for survival for five years.

7.7 Costs

Patients and/or their insurance companies will be responsible for the cost of all procedures and treatments under this protocol.

8. COORDINATING CENTER

8.1 Responsibilities

Johns Hopkins Hospital will serve as the coordinating center for this study. Coordinating Center functions will include:

1. Coordination of all data collection and analyses
2. On site monitoring/auditing of patient study charts and source documents at regular intervals that will be dictated by the rate of enrollment and treatment
3. Coordinating among the sites and reporting to a data monitoring committee. Each site will be expected to provide information on adverse events to their IRB as per each institution's procedures.

A complete discussion of the roles and responsibilities of the Coordinating Center and Participating Sites can be found in Appendix II.

9. STUDY CALENDAR

Evaluation	Baseline[1]	RADIATION TREATMENT[7]	Pre-Op[8]	SURGERY[9]	Post-Op[10]	CHEMOTHERAPY[12]	Post Surgical Follow-Up[13]				
							1Y	2 Y	3Y	4Y	5Y
Informed Consent	X										
H&P	X		X		X		X	X	X	X	X
Performance Status	X		X		X		X	X	X	X	X
Pregnancy Test[2]	X										
Concomitant Medications[3]	X						X	X	X	X	X
Endoscopic Ultrasound[4]	X										
Marker Placement[5]	X										
Research Biopsy[5] (optional)	X										
FDG-PET/CT	X		X								
Pelvic MRI	X		X								
CT C/A/P							X	X	X	X	X
CBC w/ Diff, CMP	X		X		X		X	X	X	X	X
CEA	X		X		X		X	X	X	X	X
Testosterone[6]	X		X				X	X	X	X	X
Biomarkers (optional, lead site only)	X		X		X		X	X	X	X	X
TME Evaluation					X[11]						
Toxicity Evaluation	X		X		X		X	X	X	X	X
QOL Surveys[14]	X		X		X		X	X	X	X	X

1 Must be conducted within 6 weeks of RT initiation

2 Required for premenopausal women who have not been surgically sterilized within 1 month of RT initiation. All women of child-bearing potential must have negative pregnancy test (urine or serum).

3Specifically: phosphodiesterase inhibitors, bi- and tri-mix injections, testosterone therapy, vaginal estrogen cream, and hormone replacement therapy

4 Must be conducted within 3 months of RT initiation

5 Must be conducted within 3 weeks of RT initiation; biopsy should include tumor and normal tissue sample (see Section 10.4.4)

6 Total and free testosterone level for male participants only

7 Patients will be monitored for toxicity weekly during RT

8 Within 4-8 weeks pre-surgery

9 Patients will undergo surgery 8-12 weeks from RT completion

10 Within 4-12 weeks post-surgery

11 Documentation must be complete within 1 week post-surgery

12 Adjuvant chemotherapy is standard and will not be monitored/tracked by the Principal Investigator or the study team

13 Annual follow-up appointments will be based on the date of surgery and have a tolerance window of +/- 30 days

14 See 9.1 for quality of life survey calendar

9.1 Quality of Life Survey Calendar

Measure	Baseline	Pre-op	Post-Op	Post-Surgical Follow-Up				
				Y1	Y2	Y3	Y4	Y5
Marital/Partnered Status	X			X	X	X	X	X
Sexual Relationship Screener/ Sexual Activity Items	X	X	X	X	X	X	X	X
EORTC QLQ C30	X	X	X	X	X	X	X	X
EORTC CR38	X	X	X	X	X	X	X	X
CRF 21	X	X	X	X	X	X	X	X
FSFI/IIEF	X	X	X	X	X	X	X	X
Sexual Aids for Women/Men	X	X	X	X	X	X	X	X
Treatment-Related Stress Items		X	X					
Perceived Stress Scale	X	X	X					

10. MEASUREMENT OF EFFECT

10.1 Central Imaging Review and Determining Response

Initial imaging including rectal protocol MRI and FDG-PET/CT scan will be performed within 6 weeks of initiating RT. At 4-8 weeks following RT repeat MR imaging with DWI and CE-MR and FDG-PET/CT will be performed. Scans will be assessed using criteria outlined in the Mercury study. PERCIST and RECIST will be centrally determined on PET/CT and MRI images as outlined in Appendix VII at the completion of the study. We will integrate FDG-PET/CT into Endo-HDR treatment planning to improve our ability to accurately delineate tumor boundaries. We will co-register FDG-PET images with the MRI planning scan using the CT component of the PET/CT. To control for the effects of PET window/level, we will contour the tumor boundary at a threshold of 40% of the maximum SUV value as validated in previous studies. We have previously shown that FDG-PET/CT is an important investigative tool in the initial evaluation of primary rectal cancer and that it can accurately predict response to NCRT (53). Our initial data demonstrated that PET/CT is more accurate at initial staging of rectal cancer than conventional CT imaging. More recently, we have shown that FDG-PET/CT is an effective method of monitoring the response of tumors to NCRT (54). Serial FDG-PET/CT scans demonstrated that changes in the visual response score (VRS) and SUV were able to predict tumor downstaging on final pathology. To better evaluate tumor response, a newer method to examine the relation between dose and response as measured by ^{18}F-FDG uptake in ^{192}Ir HDR brachytherapy and IMRT treated rectal cancer will be utilized at the voxel level as well as for the whole tumor. Furthermore, newer modalities in MR may provide additional information to assess tumor response. Specifically, functional MR imaging can essentially provide in vivo physiologic and metabolic information via spectroscopy, diffusion, and perfusion techniques (55). Functional MRI has been evaluated at our institution in the management of metastatic colorectal disease to the liver (56). Data regarding the use of functional MRI in the assessment of response in adenocarcinoma of the rectum is limited; however, the ability to perform physiologic evaluation of tumors may help predict for pCR following Endo-HDR and IMRT.

10.2 Pathologic Evaluation of Total Mesorectal Specimen

10.2.1 Gross Specimen

Pathology report shall include the T and N staging according to the 2002 AJCC 6th Addition Guidelines as well as histologic type, depth of invasion, tumor grade, presence of lymph-vascular or perineural invasion and the surgical margin status. Resection margin shall be designated as R0, no residual disease; R1, microscopic residual disease or R2, gross residual disease.

- Pathologic stage evaluation using the TNM staging system of the AJCC/UICC
- Uniform reporting of all additional stage-independent, prognostically significant histological parameters
- Pathologic evaluation of the specimen

10.2.2 Macroscopic Examination

The completeness of the mesorectum is scored as follows:

- Incomplete (#1)
  Little bulk to the mesorectum. Defects in the mesorectum down to the muscularis propria. (After transverse sectioning [see below] – very irregular circumferential margin)
- Nearly Complete (#2)
  Moderate bulk to the mesorectum. Irregularity of the mesorectal surface with defects greater than 5mm but none extending to the muscularis propria. No areas of visibility of the muscularis propria except at the insertion site of the levator ani muscles.
- Complete (#3)
  Intact bulky mesorectum with a smooth surface. Only minor irregularities of the mesorectal surface. No surface defects greater than 5 mm in depth. No coning towards the distal margin of the specimen. (After transverse sectioning– smooth circumferential margin)

10.3 Quality of Life Toxicity Comparison

10.3.1 EORTC

The current literature regarding health-related QOL for rectal cancer patients treated with pelvic radiotherapy is sparse and suffers from several limitations, including retrospective, cross-sectional study designs, use of QOL instruments that have not been validated, and a lack of emphasis on the effects of non-surgical treatment modalities on QOL. In order to help bridge this gap, we have recently completed a phase II multi-institutional (University of Michigan and Johns Hopkins Hospital) study evaluating QOL in patients receiving conventional neoadjuvant 5-FU based CRT as measured by the EORTC QLQ-C30, QLQ-CR38 and CR29 instruments (59, 60). The frequency and severity of disease- and treatment-related symptoms before, during, and following CRT were obtained. Eligible patients included rectal cancer patients who received NCRT (45-54 Gy) using a standard 3-field technique. The results of this study (N=50) were presented at the ASCO/ASTRO GI 2011 meeting and the manuscript was recently published (Herman et al. 2013). During NCRT, patients had a statistically and clinically significant decline in global QOL, which normalized following completion of NCRT. During NCRT, patients also experienced a significant increase in GI symptoms (21 to 27, p=0.028), urinary symptoms (16 to 30, $p < 0.0001$), male sexual dysfunction (23 to 34, p=0.013), and chemotherapy related side effects (8 to 20, $p = 0.0001$). Interestingly, while these measures returned to baseline 1 month post-CRT, overall sexual function and sexual enjoyment remained persistently low after treatment end compared to pretreatment levels. Those patients who experienced grade 3 toxicity during treatment showed markedly decreased global QOL.

Given its potential to improve the side effect profile of radiation delivery for rectal cancer, we will attempt to capture potential enhancements in QOL with Endo-HDR

through prospective (pre/post) short and long term (5 years) QOL assessment with validated questionnaires. The EORTC QLQ-CR38 is an internationally validated, colorectal cancer-specific quality of life index, and the EORTC QLQ-30 is an internationally validated questionnaire assessing general quality of life. Patients will be asked to complete both of these assessments.

10.3.2 Stress Evaluation

Cancer treatments can cause significant stress for cancer patients (61) because they lead to physical and psychological side effects and disruptions in daily life and social activities. Stress levels tend to differ according to the stage in treatment for cancer patients, with the highest levels occurring around diagnosis and treatment, and often declining over time (62). Presumably, cancer treatments could have differing effects on patients' stress levels and impact in their daily life depending on the severity of side effects and their length of course. Comparisons between Endo-HDR, the newer radiation therapy under examination in the current trial, and 5-FU (Cap) + RT on their impact on patients' stress levels have not been conducted. By limiting the dose and length of treatment, it is hypothesized that Endo-HDR may be perceived as less stressful and having less of a negative impact on daily life compared with 5-FU (Cap) + RT. To compare the trajectory of patient stress in the two treatment conditions, study patients will complete 7 items assessing impact on daily life, which were developed for this study or assessed previously in colorectal cancer studies (63), and the Perceived Stress Scale (64), a widely used 10-item scale that measures global life stress over the past month.

10.3.3 Sexual Function

Increasing research finds that long-term sexual function is impacted by radiation therapy for rectal cancer patients (65, 66). In a prior research study by our team (67), we examined changes in patient-reported QOL during and after neoadjuvant chemoradiation in 50 patients with locally advanced rectal cancer to establish a baseline for future research. Findings revealed that at 1 post-CRT, most physical symptoms returned to pre-CRT levels, but sexual enjoyment and sexual function remained persistently diminished. While suggestive, our ability to demonstrate a potential impact on sexual outcomes would be strengthened by the use of comprehensive validated questionnaires specifically designed to measure multiple dimensions of sexual function. Given the reduced spread to nearby organs, we hypothesize that the impact of newer radiotherapy techniques on sexual function will be reduced when compared to older techniques with greater spread. In order to test this hypothesis, patients will complete gold-standard, comprehensive sexual function measures (68, 69), the Female Sexual Function Index (70) and the International Index of Erectile Function (71) at all study time points. In addition, because use of therapeutic aids (e.g., phosphodieterase inhibitors such as Viagra, vaginal lubricants) can impact self-reported sexual function, we will assess patients' use of therapeutic aids through 8 items assessing use of such aids over the past month (4 for women; 4 for men). These items are selected from the Therapeutic Aids domain of the PROMIS Sexual Function and Satisfaction measure, which has been extensively validated in cancer populations (72).

The complete texts of these assessments are listed in Appendix VI. It is hypothesized that Endo-HDR will limit the dose to sexual organs as well as the anal sphincter in patients who do not have direct sphincter invasion with tumor. By doing so, Endo-HDR may result in long term preservation of sexual and anorectal function resulting in an improved toxicity profile and QOL.

10.4 Molecular Biology Correlative Studies

10.4.1 DNA Damage Response

With regard to biomarkers, we will compare how Endo-HDR versus NCRT affects DNA damage response pathway and correlate with pathologic complete response. We will determine whether particular mutations predict for pCR rates (VEGF/EFGR) and evaluate whether circulating tumor DNA levels and DNA damage response pathways predict for pCR following Endo-HDR. Immunohistochemical detection of activated DNA damage signaling in human tumors will be evaluated on pre-treatment tumor biopsies and correlated with pCR rates following Endo-HDR.

10.4.2 VEGF-/EGFR+ Status, Hypoxia Markers

Dr. Vuong's group found that tumors with VEGF-/EGFR+ status were more likely to respond to Endo-HDR (pCR). This is contrary to what has been reported in patients receiving standard neoadjuvant CRT. Furthermore, we will prospectively evaluate whether circulating levels of tumor DNA correlate with staging (lymph node status), pCR rates, and other outcomes (survival, patterns of recurrence). In addition to VEGF and EGFR, other well-described genetic alterations (p53, BRAF, KRAS, PIK3CA, γ-H2AX, and XRCC1) and hypoxia related markers will be evaluated and may predict for response to Endo-HDR versus IMRT following FOLFOX chemotherapy.

10.4.3 Microbial Associations of Rectal Cancer

We will collect a tumor and normal tissue biopsy sample at the time of initial sigmoidoscopy. The sample will be snap frozen and later analyzed using microbial sequencing techniques to define the microbial associations of rectal cancer. The results will be analyzed in conjunction with microbial studies of colon cancer already underway.

10.4.4 Cancer Genome Sequencing to Determine Genetic Predictors of Response to Endo-HDR and IMRT

Whole cancer exome analysis will be performed on a subset of cases of strong responders and non-responders in an unbiased manner. Twenty thousand genes will be interrogated using tumor samples and whole blood using the Agilent capture platform and the Illumina HiSeq2000. Samples will be sequenced at a depth of 100-200X and analysis of these results will take into account clinical response. Correlation with clinical and pathologic response to therapy, disease free survival and overall survival will be performed against all the somatic genetic alterations found in each subset.

10.4.5 Specimen Processing, Storage, and Shipping

All participating institutions must ask patients for consent to participate in correlative science studies, although patient participation is optional.

Blood samples for research purposes will be drawn prior to radiation treatment, pre-operatively, post-operatively and at each follow-up along with the patient's regular labs. For each collection, up to 8mL will be drawn. Immediately, after collection, blood will be centrifuged at 3000 RPM for 10 minutes and plasma collected. The supernatant will be aliquoted for storage at -80°C into 10 separate tubes. The pellet will also be stored in a separate tube at -80°C.

Biopsy samples for research purposes will be divided in half. One half will be flash frozen with liquid nitrogen. The other half will be fixed into a paraffin embedded sample.

All specimens must be labeled with the protocol number, site number, subject number, patient's initials, collection date and type of specimen collected (e.g., serum, whole blood). For tissue specimens the labeling should include institutional surgical pathology case number and block number.

All samples will be stored at participating institutions until completion of the trial. Batch shipments should be addressed to:

Dr. Amol Narang
Attn: Joyce Schanne
401 N. Broadway
Suite 1440
Baltimore, MD 21231
(410) 502-3823

Upon shipment, participating institutions must notify coordinating center Research Program Coordinator with delivery information.

Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary. Samples should be shipped Monday-Thursday by overnight service. DO NOT SHIP SPECIMENS ON FRIDAYS OR SATURDAYS.

11. ADVERSE EVENT REPORTING

11.1 General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v 4.0) that is available at http://ctep.cancer.gov/reporting//ctc.html.

Adverse events not listed in the NCI Common Terminology Criteria for Adverse Events will be evaluated using the following criteria:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

11.2 Definitions

11.2.1 Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition during or following an exposure to a treatment, whether or not considered causally related to the treatment. An undesirable medical condition may be symptoms (headache, nausea), signs (tachycardia, enlarged liver), or abnormal results of an investigation (MRI, laboratory finding).

11.2.2 Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- Results in death.
- Is immediately life threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Is a congenital abnormality or birth defect
- Unexpected event that cause harm or place person at a greater risk of harm than was previously known or recognized, and which was possibly related to the research. Unexpected means that the event was not described in the consent form or the event exceeded the expected severity.
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

11.2.3 Expectedness

- Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.
- Unexpected: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk

11.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Not Related: The adverse event is clearly related to other factors such as the subject's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the subject.
- Not likely: There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.
- Possible: The adverse event follows a reasonable temporal sequence from administration of the study drug, and/or follows a known response pattern to the study drug, but could readily have been produced by the subject's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the subject.
- Probable: The adverse event follows a reasonable temporal sequence from administration of the study drug and follows a known response pattern to the study drug, and cannot readily have been produced by the subject's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the subject.
- Definite: There is a reasonable causal relationship between the investigational product and the AE. The event responds to withdrawal of investigational product (dechallenge), and recurs with rechallenge when clinically feasible.

11.3 Potential Adverse Events

Signs and symptoms of disease progression are not considered AEs. The development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study.

Because patients are receiving standard treatments, which are not part of this study, their treating physician will be counseling them on the risk of their treatments, including the risk of surgery, radiation therapy, and/or chemotherapy, whichever is appropriate for the type and the stage of their cancer.

Phlebotomy can cause pain, bleeding, and rare needle site infection. PET imaging results in low dose radiation exposure, which has an extremely small risk of causing a secondary cancer.

11.4 Endoscopy & Marker Implantation

The use of endoscopy to initially assess and follow-up rectal cancer following neoadjuvant treatment is routine. For the purposes of this study it is necessary prior to therapy to place endoscopic markers to mark the tumor for guidance to place the endoluminal catheter. The risk of flexible sigmoidoscopy and marker placement are minimal and include bleeding in less than 1 in 100 patients and perforation in less than 1 in 1,000 patients. Generally, this procedure is done without sedation but sedation will be provided if the patient requests the use of it. The risks of sedation include heart arrhythmias, hypotension, respiratory distress, and confusion. All endoscopic procedures are performed in a monitored setting with a nurse to minimize this risk.

11.5 Endorectal Brachytherapy Radiation Therapy

- Rectal bleeding: The risk of minimal bleeding after catheter placement is common and nearly all patients will have bleeding from their tumor. The risk of major bleeding from this procedure is similar to endoscopic evaluation and is <1%.
- Rectal perforation: This risk of perforation from insertion of the endoluminal probe is less than 1% and is similar to endoscopic procedure. The catheter is placed using direct image guidance.
- Rectal discomfort: Rectal discomfort from the application of the brachy probe will be common to all patients. To minimize the risk of this, routine endoscopic assessment of rectal luminal size prior to port placement will be performed and local anesthetic gel will be used if necessary.
- Poor catheter placement with inadequate treatment dose administration: All patients prior to treatment will have endoscopic radiopaque markers placed to outline the tumor to guide in catheter placement. All patients prior to HDRBT treatment will undergo simulation planning to assure full tumor treatment. The catheter is guided intraluminally using real time imaging (C-arm CT scan).

Toxicity for HDRBT is reportedly limited to grade 1-2 proctitis with less than 1% of patients experiencing a grade three toxicity. Rare systemic side effects of radiation have occurred and are listed below.

Expected Adverse Events from HDRBT

More Frequent (>10%)

Dermatologic/Skin

- Rash
- Radiation Dermatitis
- Puritis/Itching
- Dry Skin

Gastrointestinal

- Proctitis
- Diarrhea
- Rectal Pain
- Rectal Bleeding

Renal

- Urinary Frequency

Less Frequent (< 5%)

Dermatologic/Skin

- Moist Desquamation

Gastrointestinal

- Ulcer
- Obstruction (small bowel NOS) Secondary Malignancy

Renal

- Renal Failure

Blood/Bone Marrow

- Anemia
- Pancytopenia

Since we are just learning about treating cancers of the distal bowel with this type of radiation, there may also be side effects and discomforts that are not yet known.

11.6 Intensity Modulated Radiation Therapy

All radiation related adverse events will be recorded on the local toxicity case report forms. Neoadjvuant intensity modulated radiation therapy (IMRT) and capecitabine chemotherapy is considered standard of care treatment for localized rectal cancer.

In accordance RTOG 0822, "side effects expected from radiation therapy include fatigue, rectal frequency, diarrhea, urinary frequency, dysuria, loss of pubic hair, hyperpigmentation of the skin in the treatment field, lower blood counts. Rare but possible side effects include small bowel obstruction, fistula, small bowel ulceration, wet desquamation, infection, and urethral obstruction."

The following are common potential short term reactions/ risks that are associated with external beam radiation therapy:
Increased urinary frequency, urgency, pain, mild to moderate increase in frequency and looseness of bowel movements, fatigue, diarrhea, decreased blood cell count, temporary hair loss in area treated, skin redness and irritation in area treated, vaginal inflammation and bladder inflammation.

The following are uncommon potential short term reactions/ risks associated with external beam radiation therapy:
Nausea or vomiting, darkened skin and dryness in area treated, blood in the urine or stool, nausea or vomiting, painful bowel movements, hemorrhoidal bleeding, increased flatulence (gas), urine or stool leakage, severe difficulty with urination or bowel movements requiring a treatment break, such as for an obstruction requiring surgery.

The following are common potential long term reactions/ risks associated with external beam radiation therapy:
Increased tendency to develop flatulence or diarrhea, more frequent urination and the urine cannot be held as long as normal, impotence or sterility/infertility, temporary bleeding in the gastrointestinal tract or genitourinary tract (bladder, prostate, urethra), subsequent surgery in the treated area may be more difficult, early menopause/sterility, and decreased vaginal secretions.

The following are uncommon long term reactions/ risks associated with external beam radiation therapy:
Occasional small amount of bleeding from the bladder or rectum, chronic diarrhea, urinary frequency, narrowing of the vaginal cavity, severe scarring in the vagina resulting in pain during intercourse, rectal stricture, urethral stricture (narrowing of the urinary channel that could require surgery), discomfort in the prostate area or perineum, leakage of urine or stool, injury to organs which may require major surgery, such as removal or the bladder or bowel, and swelling of the legs or genitalia.

The following are rare potential long term reactions/ risks associated with external beam radiation therapy:
Injury to the hips or bones which may require surgery, bowel complications requiring surgical procedure, urinary complications requiring surgical procedure, osteopenia, and femoral head fracture.

The following is an extremely rare potential reaction/ risk associated with external beam radiation therapy:
Tumors caused by radiation.

References:
RTOG 0822 Protocol, Section 6 (Radiation Therapy)
http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=4663

11.7 Surgery

All patients in this study will have a temporary ileostomy (diversion of the bowel into a bag) at the time of surgery unless they are having an APR, in which case they will have a permanent colostomy. This is done to decrease the risk of a leak or complication following surgery. In most cases this ileostomy is temporary, however, depending on the location of the tumor, it may be permanent.

Expected Adverse Events for Surgery

More Frequent (>10%)

- Infection of wound
- Intra-abdominal abscess
- Urinary retention
- Urinary tract infection
- Ileus
- Stoma irritation
- Pain/Rectum
- Anastomotic suture separation/leak – 10% in HDRBT literature
- Dehydration

Less Frequent (<1%)

- Thrombosis/Embolism
- Pneumonia
- Cardiac Ischemia/Infarction
- Fistula – rectovaginal/rectourethral/perineal
- Fecal incontinence
- Stricture at suture line

11.8 Chemotherapy

Chemotherapy is considered standard of care. Only grade 3 or greater side effects thought to be related to chemotherapy will be recorded. Since this is standard of care treatment, adjustments made to the chemotherapy regimen are left to the discretion of the treating oncologists.

The following are very common potential side effects of capecitabine (occurring in more than 50 out of 100 people):
Anemia hand-and-foot syndrome.

The following are common potential side effects of capecitabine (occurring in 20 to 50 people out of 100):
Fatigue or weakness, vomiting, abdominal pain, loss of appetite, neutropenia, risk of infection, mouth sores, unusual burning or tingling sensations in hands or feet.

The following are less common potential side effects associated with capecitabine (Occurring in 5 to 20 people out of 100):
Constipation, eye irritation, vision changes, or conjunctivitis, difficulty breathing, pain (including back pain, muscle pain, or joint pain), lethargy, headaches, indigestion or heartburn, dizziness, insomnia dehydration, coughing, hair loss, taste changes and mood changes.

The following are even less common potential side effects of capecitabine (occurring in less than 5 people out of 100):
Nosebleeds, sore throat, stomach ulcers, nail problems, increased sweating, sensitivity to the sun, hot flashes, drowsiness, shakiness, weight gain, weight loss, high triglycerides, coughing, asthma, pneumonia, hypotension, hypertension, and vertigo.

Serious side effects we will be looking for very closely will be:
Depression, signs of blood clots, blood in the stool, very severe constipation, nausea, vomiting, or mouth sores, severe redness of the hands or feet, an increase in tumor size or appearance of new tumors, a fever or signs of infection, signs of liver problems and signs of allergic reaction.

11.9 Risks of Blood Draws

About 8ml (1 ½ teaspoons) of blood may be drawn before radiation, after radiation, before surgery, and during follow-up for research purposes. Whenever possible, these samples will be obtained at the same time as other routine laboratory studies. Although trained phlebotomists will be obtaining the blood samples, there are minimal risks associated with this procedure. Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, and there is a small risk of infection. In rare cases, blood drawing may result in fainting.

11.10 Risks of Radiographic Imaging

Imaging studies (MRI, FDG-PET/CT) are part of standard clinical care. Patients will be given a clinical consent form for each imaging procedure that explains the risks of the procedures.

11.11 Risks of completing the study questionnaires

Patients may get tired or bored when they answering questions or completing questionnaires.

11.12 Reporting Procedures

11.12.1 General

Adverse events will be recorded at each visit. If an adverse event requiring medical attention occurs between visits, this will be recorded as well. The variables to be recorded for each adverse event include, but are not limited to, onset, resolution, intensity, action taken, outcome, causality rating and whether or not it constitutes an SAE. The intensity of the adverse event should be captured using CTCAE criteria, version 4.0, when possible.

Pregnancy should be excluded before enrollment. Pregnancy in itself is not reported as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

All adverse events will be captured on the appropriate study-specific case report forms (CRFs).

11.12.2 Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification to the study protocol, these modifications will be provided to the IRB as soon as is possible.

11.12.3 SAE Guidelines for Johns Hopkins Hospital

All SAEs, with the exception of death, must be reported to the Johns Hopkins Medicine Institutional Review Board (JHM-IRB) within 10 working days of the Principal Investigator learning of the event. Reporting for the death of a patient which was unexpected (i.e.: not related to a risk of participation that was listed in the protocol or the consent document, and was more likely than not to be caused by the research procedure/intervention) must be reported to the JHM-IRB within 3 working days of when the Principal Investigator receives the report of the death. Reporting for death of a participant that was expected due to the nature of the patient's underlying disease or condition, or identified as caused by a possible risk of the study procedure/intervention as described in this protocol or consent form, must be reported to the JHM-IRB within 10 working days from the time the Principal Investigator learns of the event. If death occurs 30 days after the participant has stopped or completed their study treatment, the Principal Investigator does not have to report the death until the time of continuing review.

12. DATA AND SAFETY MONITORING PLAN

This is a DSMP Level I study under the SKCCC Monitoring Plan (see Appendix I). A Level I study requires both internal and external data monitoring. The Principal Investigator is responsible for internal monitoring for both safety and data quality. External data monitoring will be performed by the SKCCC at Johns Hopkins Clinical Research Office Quality Assurance Program (CRO QA).

Data and safety monitoring oversight will be conducted by the SKCCC at Johns Hopkins Safety Monitoring Committee. Per the SKCCC at Johns Hopkins Safety Monitoring plan, the CRO QA will forward summaries of all monitoring reports to the Safety Monitoring Committee for review. All reportable anticipated and unanticipated protocol events/problems and amendments that are submitted to the IRB will also be reviewed by the Safety Monitoring Committee Chair (or designee) and QA manager.

12.1 Data Recording

Data will be collected on Case Report Forms (CRFs). These CRFs will be completed by the Study Coordinator. The CRFs for each subject will be kept in a separate research binder. Along with each completed CRF there will be corresponding source documentation filed for verification. The Principal Investigator, Research Study Nurse, and Study Coordinator will informally meet on a regular basis to make sure that the trial is progressing as mandated by the protocol. The CRO will audit this trial per their

standards to ensure and verify that the protocol is being carried out according to specifications as well as to verify that data included on subject CRFs are accurate. Exit reports generated as a result of these CRO audits will be forwarded to both the Safety Monitoring Committee as well as to the IRB of record for review.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards.

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB prior to implementation.

13.2 Informed Consent

The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.3 Ethics and GCP

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

14. STATISTICAL CONSIDERATIONS

14.1 Endpoints

14.1.1 Study Design

This is a multi-institutional, randomized, two-arm, phase II trial of endorectal brachytherapy alone (Endo-HDR) versus intensity modulated external beam radiotherapy (IMRT) or 3-D conformal radiation therapy with capectitabine in patients with stage II/III rectal distal adenocarcinoma. Patients enrolled in the study will be randomized (2:1 ratio) to either Endo-HDR or standard external beam chemoradiation.

14.2 Sample Size/Accrual Rate

14.2.1 Sample Size and Power

We will screen a total of 165 patients for the trial. Based on our phase II single arm endorectal brachytherapy study, we expect approximately 20% of candidates will drop out because of unexpected findings on PET/CT (i.e. metastases) or MRI (i.e. iliac/inguinal lymph nodes). Therefore, we expect to randomize 138 patients in 2:1 ratio into two treatment arms (92 in the Endo-HDR arm and 46 in the control arm). Using a one-sided Fisher's exact test at significance level 0.1, we will have 80% power to detect a 17% increase of pathologic complete response rate from the 13% in the control treatment arm to 30% pCR in the Endo-HDR arm. After randomization, we expect <5% drop-out rate.

One interim analysis for early assessment of futility is planned after 69 patients (half of the total planned sample size) have had their pCR evaluation. The trial will be terminated early if the ratio of the pCR rate in the Endo-HDR arm vs. control arm is 1 or less, i.e., the Endo-HDR treatment appears the same or worse than the control treatment by any amount. This leads to minimal loss of power compared to an analysis without intermediate look.

14.2.2 Accrual Rate

Each center will enroll approximately 1 patient per month or 10-12 patients per year per site or approximately 60 patients total per year with six centers. With the appeal of a shorter treatment course and potential for decreased toxicity from radiotherapy, we are confident that we will accrue actively to meet our target goals. However, if we do not enroll 30 patients after 6 months, we will add additional sites.

14.3 Early Stopping Guidelines

One interim analysis for early assessment of futility is planned after 69 patients (half of the total planned sample size) have had their pCR evaluation. The trial will be terminated early if the pCR rate in the Endo-HDR arm is less than the control group (standard chemoradiation). If the pCR rate is the same or better with endorectal brachytherapy, the trial will continue. This leads to minimal loss of power compared to an analysis without an intermediate look.

14.4 Analysis of Primary Endpoint

The primary endpoint is pathologic complete response rate, which will be estimated for both arms as the proportion of patients who achieve pathologic complete response after the treatment. The corresponding 95% confidence intervals will be calculated. The comparison of pCR between the two arms will be performed using Chi-square test. The primary analysis of the pCR endpoint will be based on the intent-to-treat population which includes all randomized patients where patients are classified according to the randomized treatment assignment regardless of what treatment was received.

14.5 Analysis of Secondary Endpoints

Secondary endpoints of this phase II trial include toxicity, quality of life, locoregional control/distant metastasis, overall survival, and correlative analyses of biomarkers and functional imaging changes.

The acute and chronic toxicity and adverse events will be summarized in frequency tables by type and grade for each arm and will be compared between arms using Fisher's exact tests.

Qualify of life will be assessed via EORTC QLQ-C30 (v3.0) questionnaires as mentioned above. Scoring will be based on procedures outlined by the EORTC. For our study population of rectal cancer patients, the analysis will be focused on general and colorectal model regarding urinary/bowel toxicity, sphincter function, and sexual dysfunction. For each module, summary statistics of the scores will be reported at baseline and each follow-up time. After confirming that there are no baseline differences in quality of life across the two treatment arms using independent samples t-test, changes in quality of life scores from pre- to post-treatment will be computed, and the difference between these change scores will be evaluated by paired-sample t-tests. We will compare the quality of life scores at each endpoint as well as the differences between the two arms using two-sample t-test. Given the plurality of comparisons, p-values <0.01 will be considered statistically significant. In addition, mixed effect models will be used for assessing the quality of life change over time and comparing the two treatment arms. For instance, mixed effects models will be used to assess changes in QOL over time first in all study patients and then to compare the effects of the two treatment arms on change in QOL over time. Need for sexual aids will be compared in a descriptive fashion between the two cohorts.

Overall survival, distant metastases free survival, progression free survival, and local recurrence will be measured from the date of randomization to the date of death due to any causes. Patients last known to be alive are censored at date of last contact. Kaplan-Meier curves will be used to characterize overall survival in each arm and log rank test will be used for the comparison.

The analysis of correlative endpoints of imaging and biomarkers will be exploratory.

For all patients in both study arms, the presence of VEGF/EGFR status will be assessed using pre-treatment tumor biopsies prior to the start of radiation therapy. The result will be expressed as a binary variable indicating the presence of expression (positive/negative). Its association with pCR will be assessed using Fisher's exact test. We will also examine the role of VEGF/EGFR and other hypoxia related biomarkers as a predictive marker for tumor response following Endo-HDR treatment by testing the interaction of the treatment group and VEGF/EGFR status using a logistic regression model where pCR is the dependent variable.

For those treated with Endo-HDR, we anticipate the pCR rate to be 40% among patients with favorable VEGF/EGFR and/or hypoxia marker signature compared to 10% pCR in the group with unfavorable signature. If we observe 40% patients with unfavorable profile, with 92 patients in the Endo-HDR arm, the test will have 89% power.

Prevalence of unfavorable signatures	Power
25%	0.77
40%	0.89
50%	0.90
75%	0.85

Table 3. Power to detect a 30% difference under various observed prevalence of unfavorable VEGF/EGFR and/or hypoxia marker signatures using a two-sided Fisher's exact test at significance level 0.05.

To assess the correlation of functional PET/MR and treatment response, we will compare the change of SUV pre- and post-treatment between responders and non-responders using a two-sample t-test. Non-parametric Wilcoxon test will be considered when the data are not normally distributed. For a binary response outcome, the predictive ability of the PET/MR marker will be evaluated using an ROC curve based on a logistic regression model in which the imaging marker will be entered as an independent variable.

REFERENCES:

1. Prolongation of the disease-free interval in surgically treated rectal carcinoma. gastrointestinal tumor study group. *N Engl J Med.* 1985 Jun 6; 312(23): 1465-1472.

2. Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, Kubista TP, Poon MA, Meyers WC, Mailliard JA. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med.* 1991 Mar 14; 324(11): 709-715.

3. O'Connell MJ, Martenson JA, Wieand HS, Krook JE, Macdonald JS, Haller DG, Mayer RJ, Gunderson LL, Rich TA. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med.* 1994 Aug 25; 331(8): 502-507.

4. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet.* 1986 Jun 28; 1(8496): 1479-1482.

5. Enker WE, Thaler HT, Cranor ML, Polyak T. Total mesorectal excision in the operative treatment of carcinoma of the rectum. *J Am Coll Surg.* 1995 Oct; 181(4): 335-346.

6. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R, German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med.* 2004 Oct 21; 351(17): 1731-1740.

7. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW, van de Velde CJ, Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med.* 2001 Aug 30; 345(9): 638-646.

8. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, Quirke P, Couture J, de Metz C, Myint AS, Bessell E, Griffiths G, Thompson LC, Parmar M. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): A multicentre, randomised trial. *Lancet.* 2009 Mar 7; 373(9666): 811-820. PMCID: PMC2668947.

9. Improved survival with preoperative radiotherapy in resectable rectal cancer. swedish rectal cancer trial. *N Engl J Med.* 1997 Apr 3; 336(14): 980-987.

10. Marijnen CA, van de Velde CJ, Putter H, van den Brink M, Maas CP, Martijn H, Rutten HJ, Wiggers T, Kranenbarg EK, Leer JW, Stiggelbout AM. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: Report of a multicenter randomized trial. *J Clin Oncol.* 2005 Mar 20; 23(9): 1847-1858.

11. Peeters KC, van de Velde CJ, Leer JW, Martijn H, Junggeburt JM, Kranenbarg EK, Steup WH, Wiggers T, Rutten HJ, Marijnen CA. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: Increased bowel dysfunction in irradiated patients--a dutch colorectal cancer group study. *J Clin Oncol.* 2005 Sep 1; 23(25): 6199-6206.

12. Marijnen CA, Kapiteijn E, van de Velde CJ, Martijn H, Steup WH, Wiggers T, Kranenbarg EK, Leer JW, Cooperative Investigators of the Dutch Colorectal Cancer Group. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: Report of a multicenter randomized trial. *J Clin Oncol.* 2002 Feb 1; 20(3): 817-825.

13. Birgisson, H, Pahlman, L, Gunnarson U and Glimelius. Adverse effects of preoperative radiotherapy for rectal cancer: Long-term follow up of the swedish rectal cancer trial. *J Clin Oncol.* 2006; 23: 8697-8705.

14. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Late adverse effects of radiation therapy for rectal cancer - a systematic overview. *Acta Oncol.* 2007; 46(4): 504-516.

15. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A, Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med.* 2004 Jun 3; 350(23): 2343-2351.

16. Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, Vendrely V, Francois E, de La Roche G, Bouche O, Mirabel X, Denis B, Mineur L, Berdah JF, Mahe MA, Becouarn Y, Dupuis O, Lledo G, Montoto-Grillot C, Conroy T. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: Results of the phase III trial ACCORD 12/0405-prodige 2. *J Clin Oncol.* 2010 Apr 1; 28(10): 1638-1644.

17. Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, Artale S, Tagliagambe A, Ambrosini G, Rosetti P, Bonetti A, Negru ME, Tronconi MC, Luppi G, Silvano G, Corsi DC, Bochicchio AM, Chiaulon G, Gallo M, Boni L. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: Pathologic results of the STAR-01 randomized phase III trial. *J Clin Oncol.* 2011 Jul 10; 29(20): 2773-2780.

18. Glynne-Jones R, Sebag-Montefiore D. Role of neoadjuvant chemotherapy in rectal cancer: Interpretation of the EXPERT study. *J Clin Oncol.* 2006 Oct 1; 24(28): 4664-5; author reply 4665-6.

19. Gollub MJ, Gultekin DH, Akin O, Do RK, Fuqua JL,3rd, Gonen M, Kuk D, Weiser M, Saltz L, Schrag D, Goodman K, Paty P, Guillem J, Nash GM, Temple L, Shia J, Schwartz LH. Dynamic contrast enhanced-MRI for the detection of pathological complete response to neoadjuvant chemotherapy for locally advanced rectal cancer. *Eur Radiol.* 2012 Apr; 22(4): 821-831.

20. Brezovich IA. IMRT may be used to excess because of its higher reimbursement from medicare. against the proposition. *Med Phys.* 2004 Jan; 31(1): 2-3.

21. Vuong T, Belliveau PJ, Michel RP, Moftah BA, Parent J, Trudel JL, Reinhold C, Souhami L. Conformal preoperative endorectal brachytherapy treatment for locally advanced rectal cancer: Early results of a phase I/II study. *Dis Colon Rectum.* 2002 Nov; 45(11): 1486-93; discussion 1493-5.

22. Vuong T, Devic S, Moftah B, Evans M, Podgorsak EB. High-dose-rate endorectal brachytherapy in the treatment of locally advanced rectal carcinoma: Technical aspects. *Brachytherapy.* 2005; 4(3): 230-235.

23. Vuong T, Devic S, Podgorsak E. High dose rate endorectal brachytherapy as a neoadjuvant treatment for patients with resectable rectal cancer. *Clin Oncol (R Coll Radiol).* 2007 Nov; 19(9): 701-705.

24. Gunderson LL, Sosin H. Areas of failure found at reoperation (second or symptomatic look) following "curative surgery" for adenocarcinoma of the rectum. clinicopathologic correlation and implications for adjuvant therapy. *Cancer.* 1974 Oct; 34(4): 1278-1292.

25. Gunderson LL, Russell AH, Llewellyn HJ, Doppke KP, Tepper JE. Treatment planning for colorectal cancer: Radiation and surgical techniques and value of small-bowel films. *Int J Radiat Oncol Biol Phys.* 1985 Jul; 11(7): 1379-1393.

26. Wiig JN, Wolff PA, Tveit KM, Giercksky KE. Location of pelvic recurrence after 'curative' low anterior resection for rectal cancer. *Eur J Surg Oncol.* 1999 Dec; 25(6): 590-594.

27. Arbman G, Nilsson E, Hallbook O, Sjodahl R. Local recurrence following total mesorectal excision for rectal cancer. *Br J Surg.* 1996 Mar; 83(3): 375-379.

28. Cecil TD, Sexton R, Moran BJ, Heald RJ. Total mesorectal excision results in low local recurrence rates in lymph node-positive rectal cancer. *Dis Colon Rectum.* 2004 Jul; 47(7): 1145-9; discussion 1149-50.

29. MERCURY Study Group, Shihab OC, Taylor F, Bees N, Blake H, Jeyadevan N, Bleehen R, Blomqvist L, Creagh M, George C, Guthrie A, Massouh H, Peppercorn D, Moran BJ, Heald RJ, Quirke P, Tekkis P, Brown G. Relevance of magnetic resonance imaging-detected pelvic sidewall lymph node involvement in rectal cancer. *Br J Surg.* 2011 Dec; 98(12): 1798-1804.

30. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. *J Nucl Med.* 2009 May; 50 Suppl 1: 122S-50S. PMCID: PMC2755245.

31. Li M, Chen WD, Papadopoulos N, Goodman SN, Bjerregaard NC, Laurberg S, Levin B, Juhl H, Arber N, Moinova H, Durkee K, Schmidt K, He Y, Diehl F, Velculescu VE, Zhou S, Diaz LA,Jr, Kinzler KW, Markowitz SD, Vogelstein B. Sensitive digital quantification of DNA

methylation in clinical samples. *Nat Biotechnol.* 2009 Sep; 27(9): 858-863. PMCID: PMC2847606.

32. Diehl F, Diaz LA,Jr. Digital quantification of mutant DNA in cancer patients. *Curr Opin Oncol.* 2007 Jan; 19(1): 36-42.

33. Ljungvist AS, Bussink J, Kaanders JHAM, Van Der Kogel AJ. Dynamics of tumor hypoxia measured with bioreductive hypoxic cell markers. *Radiat Res.* 2007; 167(2): 127-145.

34. Trotter MJ, Chaplin DJ, Durand RE, Olive PL. The use of fluorescent probes to identify regions of transient perfusion in murine tumors. *Int J Radiat Oncol Biol Phys.* 1989; 16(4): 931-934.

35. Milosevic M, Fyles A, Hedley D, Hill R. The human tumor microenvironment: Invasive (needle) measurement of oxygen and interstitial fluid pressure. *Semin Radiat Oncol.* 2004; 14(3): 249-258.

36. Kavanagh MC, Sun A, Hu Q, Hill RP. Comparing techniques of measuring tumor hypoxia in different murine tumors: Eppendorf pO2 histograph, [3H]misonidazole binding and paired survival assay. *Radiat Res.* 1996; 145(4): 491-500.

37. Raleigh JA, Chou SC, Arteel GE, Horsman MR. Comparisons among pimonidazole binding, oxygen electrode measurements, and radiation response in C3H mouse tumors. *Radiat Res.* 1999; 151(5): 580-589.

38. Jenkins WT, Evans SM, Koch CJ. Hypoxia and necrosis in rat 9L glioma and morris 7777 hepatoma tumors: Comparative measurements using EF5 binding and the eppendorf needle electrode. *Int J Radiat Oncol Biol Phys.* 2000; 46(4): 1005-1017.

39. Gerstner ER, Sorensen AG, Jain RK, Batchelor TT. Advances in neuroimaging techniques for the evaluation of tumor growth, vascular permeability, and angiogenesis in gliomas. *Curr Opin Neurol.* 2008; 21(6): 728-735.

40. Lee-Kong SA, Ruby JA, Chessin DB, Pucciarelli S, Shia J, Riedel ER, Nitti D, Guillem JG. Hypoxia-related proteins in patients with rectal cancer undergoing neoadjuvant combined modality therapy. *Dis Colon Rectum.* 2012; 55(9): 990-995.

41. Dale RG. Dose-rate effects in targeted radiotherapy. *Phys Med Biol.* 1996 Oct; 41(10): 1871-1884.

42. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br J Radiol.* 1985 Jun; 58(690): 515-528.

43. Hobbs RF, Baechler S, Fu DX, Esaias C, Pomper MG, Ambinder RF, Sgouros G. A model of cellular dosimetry for macroscopic tumors in radiopharmaceutical therapy. *Med Phys.* 2011 Jun; 38(6): 2892-2903. PMCID: PMC3117894.

44. Humm JL, Cobb LM. Nonuniformity of tumor dose in radioimmunotherapy. *J Nucl Med.* 1990 Jan; 31(1): 75-83.

45. Flynn AA, Pedley RB, Green AJ, Boxer GM, Boden R, Begent RH. Optimizing radioimmunotherapy by matching dose distribution with tumor structure using 3D reconstructions of serial images. *Cancer Biother Radiopharm.* 2001 Oct; 16(5): 391-400.

46. Niemierko A. Reporting and analyzing dose distributions: A concept of equivalent uniform dose. *Med Phys.* 1997 Jan; 24(1): 103-110.

47. Dewaraja YK, Schipper MJ, Roberson PL, Wilderman SJ, Amro H, Regan DD, Koral KF, Kaminski MS, Avram AM. 131I-tositumomab radioimmunotherapy: Initial tumor dose-response results using 3-dimensional dosimetry including radiobiologic modeling. *J Nucl Med.* 2010 Jul; 51(7): 1155-1162. PMCID: PMC3302158.

48. Hobbs RF, McNutt T, Baechler S, He B, Esaias CE, Frey EC, Loeb DM, Wahl RL, Shokek O, Sgouros G. A treatment planning method for sequentially combining radiopharmaceutical therapy and external radiation therapy. *Int J Radiat Oncol Biol Phys.* 2011 Jul 15; 80(4): 1256-1262. PMCID: PMC3090537.

49. Smith JA, Wild AT, Singhi A, Raman SP, Qiu H, Kumar R, Hacker-Prietz A, Hruban RH, Kamel IR, Efron J, Wick EC, Azad NS, Diaz LA,Jr, Le Y, Armour EP, Gearhart SL, Herman JM. Clinicopathologic comparison of high-dose-rate endorectal brachytherapy versus conventional chemoradiotherapy in the neoadjuvant setting for resectable stages II and III low rectal cancer. *Int J Surg Oncol.* 2012; 2012: 406568. PMCID: PMC3399366.

50. Myerson RJ, Garofalo MC, El Naqa I, Abrams RA, Apte A, Bosch WR, Das P, Gunderson LL, Hong TS, Kim JJ, Willett CG, Kachnic LA. Elective clinical target volumes for conformal therapy in anorectal cancer: A radiation therapy oncology group consensus panel contouring atlas. *Int J Radiat Oncol Biol Phys.* 2009 Jul 1; 74(3): 824-830. PMCID: PMC2709288.

51. Jones WE,3rd, Thomas CR,Jr, Herman JM, Abdel-Wahab M, Azad N, Blackstock AW,Jr, DAS P, Goodman KA, Hong TS, Jabbour SK, Konski AA, Koong AC, Rodriguez-Bigas M, Small W,Jr, Zook J, Suh WW. ACR appropriateness criteria(R) resectable rectal cancer. *Radiat Oncol.* 2012 Sep 24; 7(1): 161.

52. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, Roussel A, Jacob JH, Segol P, Samama G. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. clinicopathologic correlations. *Cancer.* 1994 Jun 1; 73(11): 2680-2686.

53. Gearhart SL, Frassica D, Rosen R, Choti M, Schulick R, Wahl R. Improved staging with pretreatment positron emission tomography/computed tomography in low rectal cancer. *Ann Surg Oncol.* 2006 Mar; 13(3): 397-404.

54. Melton GB, Lavely WC, Jacene HA, Schulick RD, Choti MA, Wahl RL, Gearhart SL. Efficacy of preoperative combined 18-fluorodeoxyglucose positron emission tomography and computed tomography for assessing primary rectal cancer response to neoadjuvant therapy. *J Gastrointest Surg.* 2007 Aug; 11(8): 961-9; discussion 969.

55. Padhani AR. Dynamic contrast-enhanced MRI in clinical oncology: Current status and future directions. *J Magn Reson Imaging.* 2002 Oct; 16(4): 407-422.

56. Assumpcao L, Choti M, Pawlik TM, Gecshwind JF, Kamel IR. Functional MR imaging as a new paradigm for image guidance. *Abdom Imaging.* 2009 Dec 2; 34: 675-685.

57. Compton CC. Pathologic prognostic factors in the recurrence of rectal cancer. *Clin Colorectal Cancer.* 2002 Nov; 2(3): 149-160.

58. Nagtegaal ID, Marijnen CA, Kranenbarg EK, Mulder-Stapel A, Hermans J, van de Velde CJ, van Krieken JH, Pathology Review Committee. Short-term preoperative radiotherapy interferes with the determination of pathological parameters in rectal cancer. *J Pathol.* 2002 May; 197(1): 20-27.

59. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC. The european organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993 Mar 3; 85(5): 365-376.

60. Whistance RN, Conroy T, Chie W, Costantini A, Sezer O, Koller M, Johnson CD, Pilkington SA, Arraras J, Ben-Josef E, Pullyblank AM, Fayers P, Blazeby JM, European Organisation for the Research and Treatment of Cancer Quality of Life Group. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. *Eur J Cancer.* 2009 Nov; 45(17): 3017-3026.

61. Carey MP, Burish TG: Etiology and treatment of the psychological side effects associated with cancer chemotherapy: A critical review and discussion. Psychological Bulletin 104:307-325, 1988

62. Andersen BL, Kiecolt-Glaser JK, Glaser R: A biobehavioral model of cancer stress and disease course. Am Psychol 49:389-404, 1994

63. Kojima M, Wakai K, Tokudome S, et al: Perceived Psychologic Stress and Colorectal Cancer Mortality: Findings From the Japan Collaborative Cohort Study. Psychosomatic Medicine 67:72-77, 2005

64. Cohen S, Kamarck T, Mermelstein R: A global measure of perceived stress. J Health Soc Behav 24:385-96, 1983

65. Stephens RJ, Thompson LC, Quirke P, et al: Impact of Short-Course Preoperative Radiotherapy for Rectal Cancer on Patients' Quality of Life: Data From the Medical Research

Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 Randomized Clinical Trial. Journal of Clinical Oncology 28:4233-4239, 2010

66. Traa MJ, De Vries J, Roukema JA, et al: Sexual (dys)function and the quality of sexual life in patients with colorectal cancer: a systematic review. Annals of Oncology 23:19-27, 2012

67. Herman JM, Narang AK, Griffith KA, et al: The Quality-of-Life Effects of Neoadjuvant Chemoradiation in Locally Advanced Rectal Cancer. International Journal of Radiation Oncology*Biology*Physics 85:e15-e19, 2013

68. Rosen RC, Cappelleri JC, Gendrano N, 3rd: The International Index of Erectile Function (IIEF): a state-of-the-science review. Int J Impot Res 14:226-44, 2002

69. Sand M, Rosen R, Meston C, et al: The female sexual function index (FSFI): a potential "gold standard" measure for assessing therapeutically-induced change in female sexual function. Fertility and Sterility 92:S129-S129, 2009

70. Rosen R, Brown C, Heiman J, et al: The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 26:191-208, 2000

71. Rosen RC, Riley A, Wagner G, et al: The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 49:822-30, 1997

72. Flynn KE, Lin L, Cyranowski JM, et al. Development of the NIH PROMIS® Sexual Function and Satisfaction Measures in Patients with Cancer. Journal of Sexual Medicine. 2013;10: 43-52).

APPENDIX I: SKCCC DSMP I

This is a DSMP Level I study under the SKCCC Monitoring Plan. A Level I study requires both internal and external data monitoring. The Principal Investigator is responsible for internal monitoring for both safety and data quality. External data monitoring will be performed by the SKCCC at Johns Hopkins Clinical Research Office Quality Assurance Program (CRO QA).

Data and safety monitoring oversight will be conducted by the SKCCC at Johns Hopkins Safety Monitoring Committee. Per the SKCCC at Johns Hopkins Safety Monitoring plan, the CRO QA will forward summaries of all monitoring reports to the Safety Monitoring Committee for review. All reportable anticipated and unanticipated protocol events/problems and amendments that are submitted to the IRB will also be reviewed by the Safety Monitoring Committee Chair (or designee) and QA manager.

APPENDIX II: PARTICIPATING SITE GUIDELINES

This study will be conducted in accordance with the Sidney Kimmel Comprehensive Cancer Center's Coordinating Center Protocol.

Patient Registration

Prior to protocol enrollment and initiation of treatment, subjects must sign and date an IRB approved consent form. All patients must be registered centrally at the Sidney Kimmel Comprehensive Cancer Center.

To register a patient, the following documents must be completed and faxed (443-287-8354) or e-mailed to the Coordinating Center:

- Signed patient consent form
- Registration Form
- Copies of pertinent lab results, pathology reports, etc. (*please specify what source documents are required to confirm eligibility, if applicable*)

The Coordinating Center will review the documents to confirm eligibility. To complete the registration process, the Coordinating Center will:

- assign a patient study number
- register the patient on the study with the Sidney Kimmel Comprehensive Cancer Center's Clinical Research Office
- fax or e-mail the patient study number to the participating site.

Multicenter Guidelines

Protocol Chair

The Protocol Chair is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE)
- Reviewing data from all sites.

Coordinating Center

The Coordinating Center is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration.
- Collecting and compiling data from each site.

- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Registering all patients with the Coordinating Center by submitting patient registration form, and signed informed consent promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

Quality Assurance

This is a Level I study under the SKCCC Data Safety Monitoring Plan. Data Monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored internally at SKCCC by Dr. Amol Narang weekly and externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee at SKCCC.

Authorized representatives of the Coordinating Center may visit participating sites to perform audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

Data Submission

Data and/or completed case report forms must be transmitted by facsimile report, email, or internet database to the Coordinating Center monthly. Case report forms will be provided to participating sites by the Coordinating Center.

Adverse Event Reporting

Definition of Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical trials, from the time of signing an informed

consent, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no trial treatment has been administered.

Definition of Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any trial phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Protocol Chair

The Protocol Chair is ultimately responsible for the required reporting of all adverse events.

Coordinating Center

The Coordinating Center is the central location for the collection and maintenance of documentation of adverse events and is responsible for submitting adverse event reports to the Protocol Chair promptly. The Coordinating Center will maintain documentation of all adverse event reports for each participating site. Adverse event reports submitted to the Coordinating Center must be signed and dated by the participating site's Principal Investigator. The Coordinating Center will provide appropriate forms to be used by all participating sites for reporting adverse events. Information to be provided must include:

- Subject ID number, and initials
- Date of the event
- Description of the event
- Description of site's response to the event
- Assessment of the subject's condition
- Subject's status on the study (on study, off study, etc.)
- Attribution of event to study drug

Participating Sites

Participating sites are responsible for reporting adverse events to their IRB according to its specific requirements and to the Coordinating Center as follows:

Fatal Events whether anticipated or unanticipated, and whether or not related to the study must be reported to the Coordinating Center within **24 hours** of the participating site Principal Investigator's learning of the event.

Serious and Unanticipated Adverse Events as defined above must be reported to the Coordinating Center within **24 hours** of the participating site Principal Investigator's learning of the event.

Other Serious Adverse Events which may result in a change to the protocol, informed consent, or risk to subjects as specified in the protocol must be reported within **three (3) working days** of the participating site Principal Investigator's learning of the event.

Adverse Events which result in no change to protocol, informed consent, or risk to subjects must be reported to the Coordinating Center on a monthly basis.

Adverse event reports are to be faxed to the Coordinating Center at 443-287-1889. Follow-up reports are faxed, mailed, or sent electronically to the Coordinating Center as necessary.

The investigator must also report follow-up information about SAEs within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided within the same time frames described above.

All SAEs must be collected whether or not they are considered causally related to the investigational product. Investigators and other site personnel are responsible for reporting all casually related SAEs to their IRB and the Protocol Chair.

APPENDIX III: Neoadjuvant Endo-HDR Quality Criteria

Major Violation Criteria

1. Geographic miss of the tumor bed
2. Loading error during the treatment
3. Inability to reproduce the planning position of the catheter during the treatment
4. Rectal perforation

Minor violation Criteria

1. Tight or generous tumor margins
2. Minor deviation (less than 1cm) in the daily loading prescription

Medical Physicist

1. Inappropriate assignment of the first dwell position on the planning CT data set (more than 2 x slice thickness)
2. More than 5% of the target volume outside from the prescription isodose cloud
3. Inadvertent use of the step size during the treatment as compared to the planning (example: plan performed with 2.5 mm step size and treatment delivered with 5.0 mm step size)
4. Loading the daily treatment in the opposite direction with respect to the daily prescription (example: daily Rx is to load 1 cm above and the treatment is loaded 1 cm below the reference dose distribution)
5. Improper channel assignment during a daily treatment
6. Inappropriate assignment of the channel rotational position (more than $\pm 5^{o}$, or more than 1.5 mm misalignment between x-ray markers in channels 1 and 5 as seen on a daily radiograph)

APPENDIX IV: Tumor Regression Definition

Grade 0: no regression
Grade 1: minor regression (dominant tumor mass with obvious fibrosis in 25% or less of the tumor mass)
Grade 2: moderate regression (dominant tumor mass with obvious fibrosis in 26 to 50% of the tumor mass)
Grade 3: Good regression (dominant fibrosis outgrowing the tumor mass; i.e., more than 50% tumor regression)
Grade 4: Total regression (no viable tumor cells, only fibrotic mass).

Ref: Rodel C. Prognostic Significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. Journal of Clinical Oncology. 2005,23 8688-8696

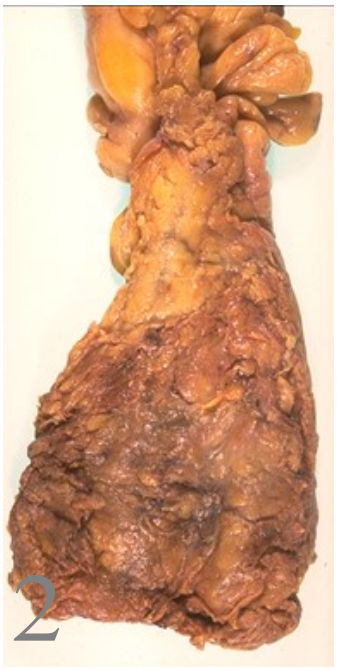
Versus

Grade 1: No fibrosis with extensive residual cancer or single cells or small groups of cancer cells
Grade 2. Residual cancer outgrown by fibrosis
Grade 3. No viable cancer cells or single cells or small groups of cancer cells.

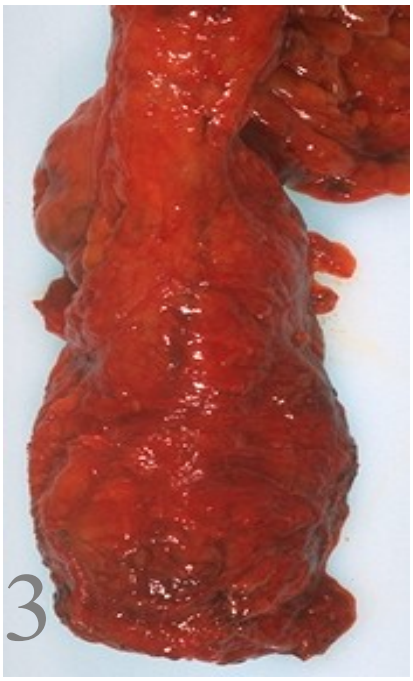
Ref: R. Ryan. Pathological response following long course neoadjuvant chemoradio-therapy for locally advanced rectal cancer. Histopathology 2005.47,141-146.

APPENDIX V: Quality of TME

Poor surgery
little mesorectum



Average surgery with incomplete removal of mesorectum



Excellent surgery with complete mesorectal excision

APPENDIX VI: Intra-Operative Data Collection

Intra-Operative Data Collection: Autonomic Nerve Preservation

1. Name_____ 2. JHH#_____

3. **Procedure** performed: _____

4. Surgical technique: **Open** **Laparoscopic**

5. Did you think you were going to preserve sphincter function in this patient on initial evaluation?

Yes (>50% likely) **No (<50% likely)**

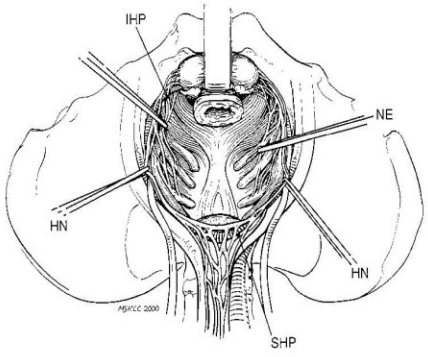
6. Please grade the clinical response of the tumor to neoadjuvant therapy.

CR (complete response) **PR** (partial ≥50% response) **NR** (<50% response)

5. Did you **totally** preserve the **pelvic autonomic nerves**? ____Yes ____No

If "**no**," which **nerves did you affect** and what **percent** of the nerve was **preserved**?

Nerve:	**Location:**
Superior hypogastric plexus[1] (SHP)	**near aortic bifurcation**
Hypogastric nerve (HN)	**along pelvic side walls**
Inferior hypgastric plexus (IHP)	**between pelvic viscera and pelvic wall**
Nervi erigentes[2] (NE)	**Denonvilliers' fascia**
Pudendal nerve (PN)	**Levator ani muscle**



[1] **Superior hypogastric plexus** also known as **presacral nerve**
[2] **Nervi erigentes** also known as **pelvic splanchnics**

APPENDIX VI: Quality of Life Assessments

Marital/Partnered Status

a. Marital status: What is your current marital status?
    i. Married
    ii. Living with partner, not married
    iii. In a significant relationship but not living together
    iv. Widowed and not currently in a relationship
    v. Divorced and not currently in a relationship
    vi. Single, never married

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _ _ _ _

Your birthdate (Day, Month, Year): _ _ / _ _ / _ _

Today's date (Day, Month, Year): 31 _ _ / _ _ / _ _

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ – CR38

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. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Did you have pain when you urinated?	1	2	3	4
34. Did you have a bloated feeling in your abdomen?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks?	1	2	3	4
37. Were you bothered by gas (flatulence)?	1	2	3	4
38. Did you belch?	1	2	3	4
39. Have you lost weight?	1	2	3	4
40. Did you have a dry mouth?	1	2	3	4
41. Have you had thin or lifeless hair as a result of your disease or treatment?	1	2	3	4
42. Did food and drink taste different from usual?	1	2	3	4
43. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
44. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
45. Have you been dissatisfied with your body?	1	2	3	4
46. Were you worried about your health in the future?	1	2	3	4

During the past <u>four</u> weeks:	Not at All	A Little	Quite a Bit	Very Much
47. To what extent were you interested in sex?	1	2	3	4
48. To what extent were you sexually active (with or without intercourse)?	1	2	3	4
49. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

ENGLISH

During the <u>past</u> four weeks:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
<u>For men only:</u>				
50. Did you have difficulty getting or maintaining an erection?	1	2	3	4
51. Did you have problems with ejaculation (e.g., so-callled "dry ejaculation")?	1	2	3	4
<u>Only for women who have had intercourse:</u>				
52. Did you have a dry vagina during intercourse?	1	2	3	4
53. Did you have pain during intercourse?	1	2	3	4

54. Do you have a stoma (colostomy bag)?	**No**	**Please answer questions 55 to 61**
(Please circle No or Yes)	**Yes**	**Please skip questions 55 to 61 and answer questions 62 to 68**

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
<u>Only for patients WITHOUT a stoma (colostomy bag):</u>				
55. Did you have frequent bowel movements during the day?	1	2	3	4
56. Did you have frequent bowel movements during the night?	1	2	3	4
57. Did you feel the urge to move your bowels without actually producing any stools?	1	2	3	4
58. Have you had any unintentional release of stools?	1	2	3	4
59. Have you had blood with your stools?	1	2	3	4
60. Have you had difficulty in moving your bowels?	1	2	3	4
61. Have your bowel movements been painful?	1	2	3	4
<u>Only for patients WITH a stoma (colostomy bag):</u>				
62. Were you afraid that other people would be able to hear your stoma?	1	2	3	4
63. Were you afraid that other people would be able to smell your stools?	1	2	3	4
64. Were you worried about possible leakage from the stoma bag?	1	2	3	4
65. Did you have problems with caring for your stoma?	1	2	3	4
66. Was your skin around the stoma irritated?	1	2	3	4
67. Did you feel embarassed because of your stoma?	1	2	3	4
68. Did you feel less complete because of your stoma?	1	2	3	4

Treatment-Related Stress

A. Individual items assessing treatment-related stress and impact on daily life.

1. In the last month, how many days of work have you missed because of your cancer treatment? [0 days; 1-2 days; 3-4 days; 4-6 days; a week or more; not applicable because wasn't working]

2. Overall, how much has your cancer treatment interfered with your daily life? [0=Not at all; 1=A little bit; 2=Somewhat; 3=Much; 4= Very much]

3. Overall, how much has your cancer treatment caused you stress (e.g., hassles)? [0=Not at all; 1=A little bit; 2=Somewhat; 3=Much; 4= Very much]

4. In the last month, how much has your cancer treatment interfered with your ability to do your work (including work at home)? [0=Not at all; 1=A little bit; 2=Somewhat; 3=Much; 4= Very much]

5. In the last month, how much has your cancer treatment interfered with your ability to participate in social activities (e.g., go to church; spend time with friends or family)? [0=Not at all; 1=A little bit; 2=Somewhat; 3=Much; 4= Very much]

6. In the last month, how much has your cancer treatment interfered with your ability to engage in enjoyable activities with your spouse/partner or friends? (e.g., go out to dinner) [0=Not at all; 1=A little bit; 2=Somewhat; 3=Much; 4= Very much]

7. Overall, do you feel stress during your daily life? [1=Little or none; 2=Moderate; 3=High; 4=Extreme]

B. *The Perceived Stress Scale**

*Scoring for each item is given below.

STRESS					
Perceived Stress Scale					
The questions in this scale ask you about your feelings and thoughts **during the last month**. In each case, you will be asked to indicate by circling *how often* you felt or thought a certain way.	Never	Almost Never	Sometimes	Fairly Often	Very Often
1. In the last month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2. In the last month, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3. In the last month, how often have you felt nervous and "stressed"?	0	1	2	3	4
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	4	3	2	1	0
5. In the last month, how often have you felt that things were going your way?	4	3	2	1	0
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7. In the last month, how often have you been able to control irritations in your life?	4	3	2	1	0
8. In the last month, how often have you felt that you were on top of things?	4	3	2	1	0
9. In the last month, how often have you been angered because of things that were outside of your control?	0	1	2	3	4
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

Female Sexual Function Index (FSFI) ©

Subject Identifier _____ Date _____

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

   ☐ Very high
   ☐ High
   ☐ Moderate
   ☐ Low
   ☐ Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Very high
   ☐ High
   ☐ Moderate
   ☐ Low
   ☐ Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Very high confidence
   ☐ High confidence
   ☐ Moderate confidence
   ☐ Low confidence
   ☐ Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Extremely difficult or impossible
   - ☐ Very difficult
   - ☐ Difficult
   - ☐ Slightly difficult
   - ☐ Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

   - ☐ No sexual activity
   - ☐ Almost always or always
   - ☐ Most times (more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (less than half the time)
   - ☐ Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

    - ☐ No sexual activity
    - ☐ Extremely difficult or impossible
    - ☐ Very difficult
    - ☐ Difficult
    - ☐ Slightly difficult
    - ☐ Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain <u>during</u> vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain <u>following</u> vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

Thank you for completing this questionnaire

APPENDIX

Individual items of International Index of Erectile Function Questionnaire and response options (US version)

Question*	Response Options
Q1: How often were you able to get an erection during sexual activity? **Q2:** When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q3: When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner? **Q4:** During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q5: During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	0 = Did not attempt intercourse 1 = Extremely difficult 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
Q6: How many times have you attempted sexual intercourse?	0 = No attempts 1 = One to two attempts 2 = Three to four attempts 3 = Five to six attempts 4 = Seven to ten attempts 5 = Eleven+ attempts
Q7: When you attempted sexual intercourse, how often was it satisfactory for you?	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always

Q8: How much have you enjoyed sexual intercourse?	0 = No intercourse 1 = No enjoyment 2 = Not very enjoyable 3 = Fairly enjoyable 4 = Highly enjoyable 5 = Very highly enjoyable
Q9: When you had sexual stimulation or intercourse, how often did you ejaculate? **Q10:** When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?	0 = No sexual stimulation/intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q11: How often have you felt sexual desire?	1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q12: How would you rate your level of sexual desire?	1 = Very low/none at all 2 = Low 3 = Moderate 4 = High 5 = Very high
Q13: How satisfied have you been with your overall sex life? **Q14:** How satisfied have you been with your sexual relationship with your partner?	1 = Very dissatisfied 2 = Moderately dissatisfied 3 = About equally satisfied and dissatisfied 4 = Moderately satisfied 5 = Very satisfied
Q15: How do you rate your confidence that you could get and keep an erection?	1 = Very low 2 = Low 3 = Moderate 4 = High 5 = Very high

* *All questions are preceded by the phrase "Over the past 4 weeks."*

Sexual Relationship Screener

Are you in a relationship that could involve sexual activity?

☐ No

☐ Yes

In the past 30 days
Have you had any type of sexual activity with another person (including your partner)

☐ No

☐ Yes

Are you…

☐ Male

☐ Female

☐ Other

Sexual Activity Items

PROMIS Item Number	Item Wording	Response Options
Items for Women In the past 30 days		
SFAID101	How often have you used personal lubricants (such as KY Jelly or Astroglide) for sexual activity?	0=Have not had any sexual activity in the past 30 days 1=Never 2=Rarely 3=Sometimes 4=Often 5=Always
SFAID102	How often have you used vaginal moisturizers (such as Replens)?	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always
SFAID103	Have you used hormones (for example, estrogen, testosterone, or progesterone) for sexual activity either as a patch on your skin, or a cream, tablet, or ring inserted into your vagina?	1=No 2=Yes 0=I don't know
SFAID104	Have you used a vaginal dilator?	1=No 2=Yes 0=I am not sure what a vaginal dilator is
Items for Men In the past 30 days		
SFAID105	How often have you taken a pill such as Viagra, Cialis, or Levitra for sexual activity?	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always
SFAID106	Have you taken testosterone for sexual activity?	1=No 2=Yes 0=I don't know
SFAID107	How often have you used an injection into your penis to get an erection?	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always
SFAID108	How often have you used a vacuum pump (penis pump) to get an erection?	1=Never 2=Rarely 3=Sometimes 4=Often 5=Always

APPENDIX VII: Imaging Techniques/Central Image Review

MRI Imaging Guidelines

1) **All imaging will be electronically transferred according to the IRAT guidelines. See appendix for specific information.** All MRS and MRI sequences will be performed on the same scanner when possible (3.0T field strength) to ensure high repeatability and minimal variability between MR scans. Dedicated research MR technicians will be trained specifically for our protocol and MR parameters will be standardized for this study to minimize variability further. During the course of the trial, a quality assurance phantom will be scanned bi-weekly to ensure that the MR unit is functioning properly for the acquisition of reproducible data. An MRI will be performed before and 8 weeks following Endo-HDR. T2-weighted images, diffusion-weighted images, dynamic perfusion images and subtracted dynamic images will be interpreted side by side to facilitate anatomic localization. For diffusion weighted imaging the apparent diffusion coefficient values (ADC) will be calculated from the low and high b-value images according to the formula; ADC = [ln (Sh/Sl)]/(bh-bl), where Sh and Sl are signal intensities in the region/volume of interest obtained with low and high b values, respectively.

At baseline and 8 weeks following Endo-HDR we will perform a subjective local tumor and nodal staging. A confidence level scoring system will be used for T-staging and nodal morphology, and heterogenicity will be used for N-staging. The confidence levels will be set at: tumor definitely absent (complete intact muscular layer)=CR, probably absent (partial disruption of the muscular layer without extension of tumor beyond the contour of the rectal wall), probably present (complete disruption of the muscular rectal wall with mild bulging tumor margin) and definitely present (complete disruption of the muscular rectal wall with tumor invasion of the perirectal fat). Tumors will be classified as T1 when they are confined to the submucosa, T2 when it invades, but does not penetrate the muscularis propria, T3 when it penetrates the muscularis propria and T4 when it invades adjacent organs including the pelvic wall or visceral peritoneum. For nodal status, morphology and heterogenicity will be used for differentiating malignant and non-malignant lymph nodes (LN). Nodes with a smooth, well-defined margin and homogeneous intensity will be grouped as nonmalignant LN. Nodes with an irregular or spiculated contour, indistinct margin and mottled heterogeneous intensity will be grouped as malignant LN. The TNM classification system will be used for nodal staging as follows: N0, no malignant nodes; N1, 1-3 malignant nodes; or N2, >4 malignant nodes. All MRI data analysis will be performed by Dr. Kamel, a clinical gastrointestinal radiologist with vast experience, who will be blinded to other clinical or histopathological information. MR measurements after neoadjuvant treatment will be performed mirroring the baseline analysis. Baseline MR images and scoring will be co-registered to post-treatment images to obtain voxelwise comparison of the MR measurements. Should it not be possible to co-register the tumors, due to extreme size change or deformation, post-treatment and baseline images will be analyzed side by side to ensure that comparable volumes of interest are being analyzed at each time point. Further imaging of the participant will be at the discretion of the treating physician.

2) As part of the MRI acquisition and to gain data from the use of functional aspects of the MRI, the tumor will be segmented on dynamic perfusion images to create a volume of interest.

Diameter and volume of the tumor will be measured. The volume of interest will be analyzed on all sequences to provide the various multiparametric MR measurements (e.g. ADC, % perfusion).

3) Spectral data will be processed on a dedicated workstation, aligned with the corresponding MR images by using voxel-shifting and baseline phase-correcting tools available with the point-resolved spectroscopy sequence package and archived as an array of spectral data (including automated estimates of the choline plus creatine-to-citrate ratio and the choline-to-creatine ratio) with the corresponding MR images in Digital Imaging and Communications in Medicine format. Peak area ratios will be calculated by means of integration of the metabolite peak over a fixed frequency range defined in a peak file containing peak positions and widths. With use of an MR spectroscopic imaging overlay sheet and pre-established criteria for the probability of malignancy based on the choline plus creatine-to-citrate ratio and the choline-to-creatine ratio, the location and size of areas suspicious for cancer will be determined and the type and total number of abnormal voxels will be recorded for each lesion depicted at MR spectroscopic imaging at baseline and during post-treatment assessment. Spectral data will be obtained from Johns Hopkins patients only.

PET-CT Imaging Guidelines

Participants will undergo a FDG-PET/CT (diagnostic CT) before and 8 weeks after Endo-HDR using standard JHU protocols. Specifically, a 4-hour fast will be required prior to the examination, although water intake is allowed. A blood glucose level will be checked in patients, and the study will not be performed if the blood glucose exceeds 150 mg/dL. Participants are initially injected with 15 to 20 mCi of FDG intravenously and then instructed to drink oral CT contrast lacking glucose with a 13% barium concentration. Imaging will take place in the supine position from the skull base to the mid thigh with the GE Discovery LSFDG- PET/CT system (GE Medical Systems, Milwaukee, WI, or similar machines at participating subsites). Simultaneous diagnostic IV/oral contrast CT images will be obtained generally at 140 kV, 80 mA, and 0.8 seconds per CT rotation, with a pitch of 6 and a table speed of 22.5 mm/second.

APPENDIX VII: Performance Status

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX IX: AJCC Staging

A. Primary Tumor

pTX Primary tumor cannot be assessed
pT0 No evidence of primary tumor
pTis Carcinoma in situ and intramucosal carcinoma (high grade dysplasia)
pT1 Tumor invades submucosa
pT2 Tumor invades muscularis propria
pT3 Tumor invades through the muscularis propria into subserosa or into nonperitonealized pericolic or perirectal tissue
pT4a Tumor invades other organs or structures
pT4b Tumor perforates the visceral peritoneum

B. Regional Lymph Nodes

pNX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis in 1 to 3 regional lymph nodes
pN2 Metastasis in 4 or more regional lymph nodes

C. Distant Metastasis

pMX Cannot be assessed
pM0 No distant metastasis
pM1 Distant metastasis

Reference:

AJCC Cancer Staging Manual. Lippincott-Raven Press, 6th edition, 2002.