PROSPECTIVE EVALUATION OF LOW-DOSE IRINOTECAN AND CYBERKNIFE STEREOTACTIC BODY RADIOThERAPY IN THE TREATMENT OF PATIENTS WITH COLORECTAL CANCER AND LIMITED LIVER METASTASIS

PROTOCOL NUMBER:

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PROSPECTIVE EVALUATION OF LOW-DOSE IRINOTECAN AND CYBERKNIFE STEREOTACTIC BODY RADIOTHERAPY IN THE TREATMENT OF PATIENTS WITH COLORECTAL CANCER AND LIMITED LIVER METASTASIS

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the conduct of the study according to the protocol and in strict accordance with all applicable U.S. Food and Drug Administration ("FDA") regulations and guidelines applicable to the Study, including without limitation the regulations set forth in Parts 50, 54, 56 and 812 of 21 C.F.R., and all other applicable federal, state, or local laws, guidelines, rules, and regulations of any type.

__________________________
Clinical Site

__________________________  ______________
Signature, Principal Investigator               Date

__________________________
Printed Name, Principal Investigator

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PROSPECTIVE EVALUATION OF LOW-DOSE IRINOTECAN AND CYBERKNIFE STEREOTACTIC BODY RADIOThERAPY IN THE TREATMENT OF PATIENTS WITH COLORECTAL CANCER AND LIMITED LIVER METASTASIS

SCHEMA

<table>
<thead>
<tr>
<th>Ultrasound and Fiducial Placement</th>
<th>Planning CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan 40mg/m2 x 3 days</td>
<td>Cyberknife SBRT 18Gy x 3 (54Gy)*</td>
</tr>
</tbody>
</table>

3 treatments within 8 elapsed days

*Cyberknife SBRT to liver metastasis 18Gy x 3
*Per investigator decision and patient discussion, with consideration of age, performance status, medical co-morbidities.
Irinotecan will be administered on the same day, prior to SBRT

PATIENT POPULATION (see section 3.0 for complete eligibility)
Histologically-confirmed, colorectal cancer with liver metastasis
ECOG Performance Status 0-1
No prior liver radiation

Sample Size 41
### ELIGIBILITY CHECKLIST

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the patient above the age of 18 years?</td>
<td>(Y)</td>
</tr>
<tr>
<td>Is there histologically proven primary colorectal carcinoma?</td>
<td>(Y)</td>
</tr>
<tr>
<td>Is the patient a clinical stage IV? (AJCC 7th Edition)</td>
<td>(Y)</td>
</tr>
<tr>
<td>The patient exhibits 1-4 liver metastasis?</td>
<td>(Y)</td>
</tr>
<tr>
<td>Is the liver the only site of metastasis?</td>
<td>(Y)</td>
</tr>
<tr>
<td>Is there malignant ascites?</td>
<td>(N)</td>
</tr>
<tr>
<td>Chemotherapy was administered &gt;4 weeks prior to enrollment?</td>
<td>(Y)</td>
</tr>
<tr>
<td>Has the patient received prior liver radiation therapy?</td>
<td>(N)</td>
</tr>
<tr>
<td>ECOG performance status 0-1</td>
<td>(0-1)</td>
</tr>
<tr>
<td>Are the patient’s liver function tests (bilirubin, AST, ALT, alkaline phosphatase) &lt; 1.5 times the upper limit of normal (ULN)?</td>
<td>(Y)</td>
</tr>
<tr>
<td>Patient’s albumin level is &gt;3gm/dl</td>
<td>(&gt;3gm/dl)</td>
</tr>
<tr>
<td>Is the patient’s prothrombin time &lt; 1.5 time the upper limit of normal (ULN)?</td>
<td>(Y)</td>
</tr>
<tr>
<td>Does the patient have adequate hematologic function?</td>
<td>(Y)</td>
</tr>
<tr>
<td>Hgb&gt;10gm/dl</td>
<td></td>
</tr>
<tr>
<td>ANC&gt;1000/mm3</td>
<td></td>
</tr>
<tr>
<td>Platelets&gt;100,000/mm3</td>
<td></td>
</tr>
<tr>
<td>For women of childbearing potential, was a pregnancy test negative within 72 hours prior to study entry?</td>
<td>(Y)</td>
</tr>
<tr>
<td>Does the patient have inflammatory bowel disease?</td>
<td>(N)</td>
</tr>
<tr>
<td>Does the patient have hepato-renal syndrome?</td>
<td>(N)</td>
</tr>
</tbody>
</table>
1. BACKGROUND

1.1. Until recently, liver metastases were thought to represent an incurable state, warranting palliative care only. It is now recognized that selected patients with a small number of metastasis (oligometastasis), may have curative outcome, or delayed progression of disease with aggressive local therapy when combined with effective systemic therapy to address occult disease. Local treatment options for patients with liver oligometastasis include surgical resection, radiofrequency ablation, or stereotactic body radiosurgery. When possible, surgical resection is the standard of care for liver metastasis, with reported 5-year survival of 25-60%. Unfortunately, only 10-20% of patients are considered resectable on the basis of extent of disease, location of tumors, and medical comorbidities. Radiofrequency ablation, chemoembolization have shown promising local control results, but these techniques have limitations and variable high recurrence rates.

1.2. Conventional radiation therapy has a limited role in the treatment of patients with liver metastases because the radiation doses are limited by hepatic parenchyma toxicity. Recently, stereotactic body radiation therapy (SBRT) has been explored in the treatment of liver tumors. SBRT can deliver potentially ablative doses of radiation therapy to a tumor with great precision and thus cause less damage to normal tissues, while yielding a higher radiobiologic effect on the tumor.

1.3. The use of hypofractionated CyberKnife stereotactic therapeutic radiation entails a therapeutic radiation process that uses a more precise targeting methodology, allowing more focal treatment delivery to the tumor volume. This more effectively limits the volume of adjacent tissue receiving high dose radiation, which in turn allows the delivery of a much shorter series of treatments, employing a much larger dose of radiation per treatment. When so applied, the radiation becomes tissue ablative within the high dose zone, and as such, may be described as a form of radiosurgery.

1.4. Although limited experience has been gained to date, the radiosurgical approach carries with it a number of potential advantages, including the possibility of lower morbidity due to the very small treatment margins, more rapid recovery from side effects due to the lack of a surgical resection or implanted radioactivity, convenience of a few day treatment course.

1.5. The main technical problem that prevents the application of radiosurgery for liver tumors is that the liver may move substantially during the treatment (intrafraction motion) and in between fractions (interfraction motion) even if rigid body immobilization is applied, due to the effect of organ motion and respiration. This motion effect necessarily leads to the application of a larger radiotherapy planning target volume to compensate, thereby exposing a greater
volume of normal tissues to radiation therapy, which may contribute to excessive toxicity.

1.6. The CyberKnife® is a unique noninvasive radiosurgical system, capable of treating any part of the body from any of approximately 1600 different targeting angles, creating a highly conformal three-dimensional radiosurgical treatment volume, guided by orthogonal X-ray-based targeting feedback, and delivering radiation by a highly collimated, robotically controlled linear accelerator. The CyberKnife® system targets implanted fiducial markers with sub-millimeter initial set-up accuracy, and continuously updates the planning target volume by obtaining multiple intrafractional orthogonal X-ray-images, producing an automated robotic adjustment after each X-ray feedback step, resulting in a real-time target volume tracking process that maintains millimeter accuracy throughout the radiosurgical treatment. Thus, the CyberKnife® device allows a reproducible method of radiosurgical treatment. Synchrony technology allows for realtime tracking of liver tumor motion by creating a correlation model between the patient’s breathing motion detected by the use of externally placed optical markers, with the internal movement of the fiducial markers.

1.7. There are several feasibility studies that have demonstrated high rates of local control and mild toxicity when SBRT has been used to treat liver tumors. Rusthoven et al. published a multi-institutional Phase I/II trial examining the efficacy and tolerability of high-dose SBRT for the treatment of patients with one to three hepatic metastasis. In-field local control at one and two years was 95% and 92% respectively, with a median survival of 20.5 months. A single patient (2%) experienced grade 3 or higher toxicity. Goodman et al. performed a single-fraction Phase I dose-escalation study for primary and metastatic tumors, escalating dose from 18 to 30Gy in 4 Gy increments. Grade I toxicity was observed in 9 patients, and acute Grade 2 toxicity in 1 patient, and late Grade 2 toxicity in 2 patients. Mendez Romero et al. utilized 12.5 Gy in 3 fractions or 5 Gy in 5 fractions for patients with primary and secondary liver lesions. One- and two-year local control rates were 94% and 82% for all patients and 100% and 86% for patients with metastases. Three instances of acute Grade 3 or higher toxicity were reported, including a patient with Childs B cirrhosis that died secondary to liver decompensation, esophageal bleeding and infection, 2 weeks post-radiosurgery. More recently, Hoyer et al. reported a phase II study in which patients with colorectal hepatic metastases were treated with 15 Gy in 3 fractions. They demonstrated a two-year local control rate of 86% and a 38% overall two-year survival rate. This treatment was well tolerated.
Table 1. SBRT for liver metastasis: Outcomes

<table>
<thead>
<tr>
<th>Dose</th>
<th>Institution</th>
<th># pts.</th>
<th>#lesions</th>
<th>F/U yrs</th>
<th>Local Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>10Gy x 3</td>
<td>Aarhus, Copenhagen 2006⁹</td>
<td>44</td>
<td>2</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>10-12.5Gy x 3</td>
<td>Erasmus, U Rotterdam ¹⁹</td>
<td>17</td>
<td>34</td>
<td>2</td>
<td>98%</td>
</tr>
<tr>
<td>12-20Gy x 3</td>
<td>Colorado, Multiinstitutional, 2009¹⁷</td>
<td>47</td>
<td>63</td>
<td>&lt;3cm 100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;3cm 71%</td>
<td></td>
</tr>
<tr>
<td>13-30Gy x 1</td>
<td>Stanford, 2010¹¹</td>
<td>19</td>
<td>33</td>
<td>1</td>
<td>77%</td>
</tr>
<tr>
<td>6Gy x 5</td>
<td>UT Southwest²¹</td>
<td>26</td>
<td>35</td>
<td>2</td>
<td>56%</td>
</tr>
<tr>
<td>10Gy x 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>89%</td>
</tr>
<tr>
<td>12Gy x 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

1.8. The topoisomerase I inhibitor irinotecan (Camptosar, CPT-11) has demonstrated activity in colorectal cancer and as radio sensitizer; however, the exact mechanism of radio sensitization is unknown. Irinotecan stabilizes DNA-topoisomerase 1 cleavable complex and that interaction between this complex and the replication machinery may lead to cell death.

1.9. Weekly irinotecan has been used in conjunction with conventional external beam radiation therapy to treat patients with unresected stage III non-small cell lung cancer with manageable toxicities.²⁵ The dose limiting toxicities were nausea, vomiting, and esophagitis; the recommended weekly dose was 40mg/m².²⁵ Systemic irinotecan has been successfully employed with Yttrium-90 resin microspheres in the treatment of patients with hepatic metastases from colorectal cancer. Dose limiting toxicities were anorexia, diarrhea, thrombocytopenia, obstructive jaundice, and leucopenia. The median progression free survival was 6.0 months. The recommended dose of irinotecan was 100mg/m² on days 1 and 8.²³

2.0 OBJECTIVES

2.1 The purpose of the current study is to explore the use of SBRT with the Cyberknife® in conjunction with irinotecan 40mg/m² for 3 days in patients with fewer than four hepatic metastases who are not candidates for hepatic resection with the following endpoints:

2.1.1 To determine the toxicities of concurrent SBRT with concurrent irinotecan in patients with colorectal cancer and fewer than 4 hepatic metastases

2.1.2 To assess the tumor response rate in these patients

2.1.3 To determine the progression-free survival

2.1.4 To determine overall survival

3.0 ELIGIBILITY

3.1 Age>18 years

3.2 Histologically confirmed primary colorectal cancer

3.3 Stage IV colorectal cancer with up to four liver metastases as determined by

3.3.1 CT scan orMRI of the abdomen with contrast, 30 days prior to enrollment
3.3.2 If patient is allergic to contrast, imaging without contrast is acceptable

3.3.4 Positron-Emission Tomography 3 weeks prior to enrollment

3.4 No additional sites of metastasis

3.5 No malignant ascites

3.6 At least 4 weeks from any chemotherapy

3.7 No prior liver radiation therapy

3.8 ECOG performance status 0-1

3.9 Life expectancy >3 months

3.10 Albumin >3.0 grams/dl

3.11 Liver function tests (bilirubin, AST, ALT, alkaline phosphatase) < 1.5 times the upper limit of normal (ULN)

3.12 Prothrombin time less than 1.5 ULN

3.13 Adequate hematologic function

3.13.1 Hemoglobin >10g/dl

3.13.2 ANC >1000/mm³

3.13.3 Platelets >100,000/mm³

3.14 Negative pregnancy test in women of child bearing potential within 72 hours prior to study entry

3.14.1 Women of child bearing potential must agree to use effective contraception while on study

3.15 No history of inflammatory bowel disease

3.16 No hepato-renal syndrome

4.0 DEVICE

Accuray, Inc. (Sunnyvale, CA), received FDA clearance in July 1999 to provide treatment planning and image-guided stereotactic radiosurgery and precision radiotherapy for lesions, tumors, and conditions of the brain, base of skull and cervico-thoracic spine, head and neck using the CyberKnife. On August 10, 2001, Accuray, Inc. received 510(k) FDA clearance (510(k) number K011024) to provide treatment planning and image-guided stereotactic radiosurgery and precision radiotherapy for lesions, tumors, and conditions anywhere in the body when radiation treatment is indicated.

5.0 PRETREATMENT EVALUATION

5.1 Complete history and physical examination within 30 days prior to enrollment

5.2 All patients will undergo abdominal CT or MRI with contrast 30 days prior to enrollment (if patient is allergic to contrast, imaging without contrast is acceptable)

5.3 All patients will undergo PET scan within 21 days of enrollment

5.4 CBC with differential, complete metabolic profile and liver function tests

6.0 CHEMOTHERAPY

6.1 Irinotecan hydrochloride is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as Mappia foetida and Campotheca acuminate.
6.2 Irinotecan is metabolized by carboxylesterase enzymes to its active metabolite SN-38. SN-38 is conjugated by the enzyme UDP glucuronosyl transferase 1A1 to form aglucuronide metabolite.

6.3 Toxicities

6.3.1 Diarrhea
6.3.2 Neutropenia
6.3.3 Hypersensitivity including severe anaphylactic reactions
6.3.4 Colitis/Ileus
6.3.5 Anemia
6.3.6 Thrombocytopenia
6.3.7 Dehydration
6.3.8 Fever
6.3.9 Asthenia
6.3.10 Abdominal Cramping/Pain
6.3.11 Flushing

6.4 Preparation of Irinotecan

6.4.1 Dilute with 0.9% NaCl or 5% Dextrose USP to a final concentration of 0.12 to 2.8mg/ml.
6.4.2 The prepared solution is stable for 24 hours at room temperature.

6.5 Dosage and Administration

6.5.1 Prior to the administration of Irinotecan, all patients will receive Atropine 0.25mg intravenously to attenuate diarrhea. Antiemetic and/or corticosteroid medications consistent with the institution’s standard of practice may be used.

6.5.2 Irinotecan 40mg/m² will be administered intravenously daily for 3 days (3 treatments within 8 elapsed days), and prior to radiation therapy.

Doses may be rounded per physician discretion.

Administer as an IV infusion over 90 minutes. Shorter infusions (30 minutes) are associated with a higher incidence of some adverse effects, including myelosuppression and cholinergic symptoms.

7.0 TREATMENT: CYBERKNIFE RADIOSURGERY

7.1 FIDUCIAL PLACEMENT: All patients will have fiducial markers placed in the liver at least 1 week prior to treatment planning. A minimum of three fiducial markers will be placed under CT-guidance. The physician will place seeds such that they are visible (and not superimposed) on CyberKnife orthogonal imaging, are not collinear, and ideally are separated by 2cm or more.

7.2 TREATMENT PLANNING IMAGING:

7.2.1 To allow fiducial stabilization and resolution of swelling, planning studies will be imaged >= 5 days after fiducial placement. Vac-Lock or a similar immobilization device will be used.

7.2.2 CT scans with or without contrast will be taken for treatment planning CT with contrast will be obtained in the arterial, venous and delayed phases. CT slices will be 1 – 1.5mm, with 250-512 slices taken centered at the liver. The imaging sets will be downloaded to the CyberKnife treatment planning system to develop the radiosurgery treatment plan.
7.2.3 MRI will be used at discretion of physician if it is thought to be helpful in defining liver metastasis location and contour.

7.3 CYBERKNIFE TREATMENT PLANNING

7.3.1 TREATMENT PLANNING PROCEDURES: Inverse planning using the CyberKnife planning system will be employed. The treatment plan used for each treatment will be based on an analysis of the volumetric dose including dose-volume histogram (DVH) analyses of the PTV and critical normal structures. Number of paths and beams used for each patient will vary and will be determined by the selected individual treatment plan. A priority will be placed on reducing overall treatment time, number of non-zero beams and total monitor units without compromising the dosimetric limits.

7.3.2 EVALUATED STRUCTURES

7.3.2.1 CTV: The Clinical Treatment Volume (CTV)
   7.3.2.1.1 The CTV is the preregistered contrast-enhanced CT or MRI liver metastasis volume.

7.3.2.2 PTV: The prescription dose shall be delivered to the Planning Tumor Volume (PTV).
   7.3.2.2.1 The PTV is an enlargement of the CTV. The CTV should be expanded to include a 5-10mm margin concentrically.

7.3.3 NORMAL TISSUES: CONTOURING REQUIRED: The structures listed below will be contoured and evaluated with DVH analysis.

7.3.3.1 LIVER: Entire liver
7.3.3.2 SMALL BOWEL: Small bowel within 2cm of PTV
7.3.3.3 LARGE BOWEL: Large bowel within 2cm of PTV
7.3.3.4 KIDNEYS: Entire bilateral kidneys
7.3.3.5 CHEST WALL: Chest wall abutting liver within 2cm of PTV
7.3.3.6 BLOOD VESSELS to include portal vein, inferior vena cava and aorta within 2cm of PTV.
7.3.3.7 SPINAL CORD: Spinal cord 2cm above and below the PTV.

7.3.4 DOSE SPECIFICATIONS:

7.3.4.1 Prescription dose of 54Gy in 3 fractions to be delivered in <= 8 days, with >95% PTV encompassed within the prescription isodose volume.

7.3.4.2 The following table will define the normal tissue dose-volume constraints:

<table>
<thead>
<tr>
<th>Structure</th>
<th>Volume (cc)</th>
<th>Threshold Dose</th>
<th>Dose/Fx (Gy)</th>
<th>Max Point Dose (Gy)</th>
<th>Max Point Dose/Fx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>&gt;700cc</td>
<td>17.1Gy</td>
<td>5.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. kidney</td>
<td>&gt;200cc</td>
<td>14.4</td>
<td>4.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. kidney</td>
<td>&gt;200cc</td>
<td>14.4</td>
<td>4.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;5</td>
<td>17.7</td>
<td>5.9</td>
<td>25.2</td>
<td>8.4</td>
</tr>
<tr>
<td>Large bowel</td>
<td>&lt;20</td>
<td>24</td>
<td>8</td>
<td>28.2</td>
<td>6.7</td>
</tr>
<tr>
<td>Duodenum</td>
<td>&lt;5</td>
<td>16.5</td>
<td>5.5</td>
<td>22.2</td>
<td>7.4</td>
</tr>
<tr>
<td>Duodenum</td>
<td>&lt;10</td>
<td>11.4</td>
<td>3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;10</td>
<td>16.5</td>
<td>5.5</td>
<td>22.2</td>
<td>7.4</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>&lt;0.35</td>
<td>18</td>
<td>6</td>
<td>21.9</td>
<td>7.3</td>
</tr>
</tbody>
</table>
Major vessels | <10 39 13 45 15
Chest wall     | <30 30

### 8.0 POST-TREATMENT ASSESSMENT

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Pre-entry</th>
<th>Last Day SBRT</th>
<th>Follow-up interval: weeks post therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>X</td>
<td>X X X X X X X X X</td>
<td>3 6 9 13 17 21 25 37 49</td>
</tr>
<tr>
<td>Physical exam</td>
<td>X</td>
<td>X X X X X X X X</td>
<td>3 6 9 13 17 21 25 37 49</td>
</tr>
<tr>
<td>ECOG Performance Scale</td>
<td>X</td>
<td>X X X X X X X X</td>
<td>3 6 9 13 17 21 25 37 49</td>
</tr>
<tr>
<td>Number and size (volume) of liver metastasis</td>
<td>X</td>
<td>X X</td>
<td>3 6 9 13 17 21 25 37 49</td>
</tr>
<tr>
<td>CT or MRI abdomen</td>
<td>X</td>
<td>X</td>
<td>3 6 9 13 17 21 25 37 49</td>
</tr>
<tr>
<td>PET-scan</td>
<td>X</td>
<td>X X X X X X X X</td>
<td>3 6 9 13 17 21 25 37 49</td>
</tr>
<tr>
<td>CBC with differential, CMP &amp; LFTs</td>
<td>X</td>
<td>X X X</td>
<td>3 6 9 13 17 21 25 37 49</td>
</tr>
<tr>
<td>Pregnancy test for women of childbearing potential</td>
<td>X</td>
<td>X X X X X X X X X</td>
<td>3 6 9 13 17 21 25 37 49</td>
</tr>
<tr>
<td>Toxicity evaluation</td>
<td>X</td>
<td>X X X X X X X X X</td>
<td>3 6 9 13 17 21 25 37 49</td>
</tr>
</tbody>
</table>

### 9.0 TOXICITIES

9.1 Toxicities will be assessed during treatment, at the completion of treatment and during patient follow-up per the schedule documented in 8.1.
9.2 The NCI Common Toxicity Criteria for Adverse Events (CTCAE) V4.0 will be utilized (see Appendix IV).

### 10. DATA COLLECTION

10.1. Specific data entry fields will be collected at initial enrollment, and at all follow-up visits, and will be entered into a database.
10.2. Please see Appendix III for data collection forms.

### 11. ASSESSMENT OF THERAPEUTIC RESPONSE

11.1. Response to overall therapy will be based on the combined imaging studies of abdominal MRI/CT and PET scans.
11.2. The Common Response Criteria will be used in assessing response. See Appendix III.
11.3. Time to progression is calculated as number of days (months) between day 1 of combined SBRT and irinotecan until date of new disease in ANY location and is thus calculated.
11.4. Survival is calculated as the number of days (months) between day 1 of combined SBRT and irinotecan until date of death.
11.5. Local failure is calculated as the number of days (months) between day 1 of combined SBRT and irinotecan until the appearance of both CT and PET progression of the individual treated lesions.
11.6. Regional failure is calculated as the number of days (months) between day 1 of combined SBRT and irinotecan until the appearance of new lesions in the liver.

### 12. STATISTICAL CONSIDERATIONS
12.1 One objective of this study is to define the “response rate” which we predict will be greater than 60%.

12.2 According the first 14 patients accrued will be assessed for response which we define as CR+PR+SD. If only 1/20 patients achieve a response the study will be terminated. If more than 1 of the first 14 patients achieve a “response” accrual will continue to a maximum of 41 patients.

12.3 A second objective is to define toxicities. In the event, Grade 3 or 4 toxicities exceed 50% among the first 20 patients, the study will terminate.

12.4 Investigators expect that 60% ± 0.15 with a confidence level of 95% of patients will have a “response” defined as CR+PR+SD, therefore a required sample size of 41 is necessary (Hully SB, Cummings SR, Designing Clinical Research. Williams and Walkins, Baltimore, MD 1988. Table 13.E. pg 220).

12.5 Descriptive statistics (means, SDs) will be reported for all continuous variables and frequencies (%) for all categorical variables. One group Kaplan-Maier analysis will be performed to show 12 month cumulative probability of tumor response and progression free survival. Toxicity outcomes will be reported descriptively for the sample.

13. COSTS

The patient or patient’s health plan/ insurance company will be responsible for treatment costs, including the cost of managing the side effects of therapy. Patients are responsible for checking with their health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost the patient’s insurance company more than the cost of getting regular cancer treatment. The patient will be responsible for paying any deductibles, coinsurance, and co-payments as required under the terms of their insurance plan(s). Patients will not be paid for taking part in this study. The study doctors will not be paid for the patient’s participation in this study.
14. REFERENCES

15. APPENDICES
Appendix I: Sample Patient Consent Form

Informed Consent

PROSPECTIVE EVALUATION OF LOW-DOSE IRINOTECAN AND CYBERKNIFE STEREOTACTIC BODY RADIOThERAPY IN THE TREATMENT OF PATIENTS WITH COLORECTAL CANCER AND LIMITED LIVER METASTASIS

Date: _____ / _____ / _____

MM DD YY

Are you participating in any other research studies? _____ yes _____ no

Why have I been asked to take part in this research study?
You are invited to participate in a clinical evaluation of a highly focused radiation treatment in combination with chemotherapy for limited liver metastasis from colorectal cancer.

Who is conducting the study?

[PLEASE ADD INSTITUTION HERE]

Why is this research study being done?
The purpose of this study is to determine the effects of CyberKnife radiosurgery in combination with irinotecan chemotherapy in patients with colon or rectal cancer that has spread to the liver. The CyberKnife system is a type of radiation machine that uses a special system to precisely focus large doses of x-rays on the tumor. The device is designed to concentrate large doses of radiation onto the tumor so that injury from radiation to the nearby normal tissue will be minimal. The purpose of this evaluation is to see if this treatment will help patients with your condition and to understand the potential side effects of treatment.

The CyberKnife system previously has been used in the lung, brain, head and neck as well as other areas of the body. The results of treating tumors in the brain are similar to an operation in which the tumor is removed. The CyberKnife system has market clearance from the U.S. Food and Drug Administration to treat tumors, lesions and conditions anywhere in the body when radiation therapy is required. While the device is no longer classified as “investigational”, the best treatment dose and times still are being evaluated.

The feasibility of using highly focused radiation therapy for treating liver metastasis has been reported by a number of investigators. The results of these studies suggest that this type of radiation therapy delivered without chemotherapy can result in control rates to the
site of treatment of 80-95%, depending upon the size of the tumors, and the doses of radiation therapy utilized. Chemotherapy delivered with radiation therapy can increase the effectiveness of treatment, and may allow for a lower dose of radiation therapy to be utilized, thereby limiting the negative side effects.

What will happen if I take part in this research study?
If you agree to participate in this study, you will receive Cyberknife radiosurgery directed to your liver metastasis for 3 treatments, given every other day. Irinotecan chemotherapy infusion will be given before radiation therapy (on the same day), for a total of 3 treatments.

Before you begin the study:
You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated.

- History and physical exam within the last 30 days
- Blood Tests (including a CBC with differential, complete metabolic profile and liver function tests) within the last 30 days
- A pregnancy test for women of childbearing potential within 72 hours before starting treatment
- Abdominal CT/MRI scan within the last 30 days
- PET-CT scan of the body within the last 30 days

Preparation for CyberKnife treatment to the liver:
You will have a physical examination and a procedure to place 3-4 small gold seeds into the liver. These markers will be used to determine the location of the liver lesions during the CyberKnife treatment.
Within 5-10 days after placement of the gold seeds, you will be asked to have a planning CT scan of the liver with and without contrast. This is a regular CT scan and is standard procedure for patients receiving external beam irradiation. The images obtained during the scan will be used to plan the CyberKnife treatments. You may also have an MRI scan of the abdomen to further define the liver metastasis, unless medically contraindicated (for example if you have a pacemaker) which will be used for treatment planning purposes.

CyberKnife treatment to the liver:
The CyberKnife treatment will usually be started a few days after the CT scan of the abdomen. Your course of radiation will consist of three separate CyberKnife treatments delivered every other day. Each treatment session will take approximately 1.5-2.5 hours. You will lie on the treatment table and breathe normally while you receive your radiation treatment.

Irinotecan chemotherapy treatment:
Prior to the irinotecan chemotherapy, you will be given medication (atropine and ondanestron) to prevent side effects, such as nausea and vomiting. Irinotecan chemotherapy infusion will be given on days 1, 2 and 3 before radiation therapy.

Following completion of treatment:
- Physical exams
• 3, 6, 9, 13, 17, 21, 25 weeks following treatment
• and then every 3 months for another 3 years while you are on the study.

• Blood Tests:
  • Same schedule as Physical Examination

• CT scan of liver (if patient is allergic to contrast, abdominal CT without contrast is acceptable).
  • 6 weeks after treatment
  • Every three months for the first year
  • Every four months for the second year
  • Every six months for the third year.

• PET scan
  • Weeks 13, 25, 49 and every 6 months for 2 years unless there is a clinical indication to perform it sooner.

How long will I be in the study?
After you are finished with the radiation treatments, the study doctor will ask you to visit the office for follow-up exams and laboratory tests for at 3 years.

Can I stop being in the study?
You may decide to stop and withdraw from the study at any time.

What side effects or risks can I expect from being in the study?
You may have side effects while on this study. Most of these are listed here, but there may be other side effects that we cannot predict. Side effects will vary from person to person. Everyone taking part in the study will be carefully watched for any side effects. However, doctors do not know all the side effects that may happen. Side effects may be mild or very serious. Your physician may prescribe medications to help lessen some of the side effects. Many side effects go away soon after your radiation therapy. In some cases, side effects may be very serious, long-lasting, or may never go away. You should talk with your study doctor about any side effects that you may have while taking part in the study.
The administration of radiation itself is painless and the only discomfort is expected to be from your having to lie very still during the treatment.

Risks and side effects related to radiation therapy include those which are:

**Likely (>20%)**
- Redness, dryness, or itching of the skin within the treatment area.
- Hair loss in the treatment area, which may be permanent.
- Fatigue
- Nausea,
- Loss of appetite and weight loss,
- Diarrhea,
• Indigestion-type pain during treatment, which disappears after radiation treatment has ended.

**Less Likely (<20)**

• Low blood counts which can increase the risk of infection or bleeding
• Change in liver function blood tests that may indicate problems with your liver. This would usually not give any symptoms but could cause jaundice (the skin to become yellow).

**Rare but Serious (<3%)**

• Inflammation of the liver which may cause fever, swelling of the abdomen and in some cases death.
• Intestinal blockage requiring surgery.
• Change in kidney function

**Risks and side effects related to irinotecan include those which are:**

**Likely (>20%)**

• Delayed diarrhea (occurring within hours of receiving study drug and lasting up to 5-7 days)
• Abdominal cramping, including delayed abdominal cramping (stomach pain that can last for 5-7 days)
• Nausea and vomiting
• Lack of appetite
• Sweating
• Flushing
• Runny nose
• Teary eyes
• Hair loss
• Weakness
• Decrease in blood cells (due to the drug preventing your body from making and keeping new blood cells)
• Sudden urge to have a bowel movement occurring shortly after the irinotecan infusion (*Note: Dehydration has occurred as a consequence of diarrhea, particularly when associated with severe vomiting. Diarrhea that occurs at a time when the white blood cell count is low can be especially dangerous, which can make you more susceptible to severe infections that could be life-threatening. Should you experience a fever or other sign of infection when your white blood cell count is very low, you may need to be admitted to the hospital for precautionary measures and receive intravenous antibiotics until your blood cell counts rise to safe levels. Diarrhea has been the most frequent severe side effect associated with receiving irinotecan. When severe diarrhea has occurred, some patients have had to be admitted to the hospital to receive intravenous fluids until*
the diarrhea resolved (usually in 5-7 days). With early recognition and proper treatment, the likelihood of severe diarrhea may be decreased. In order to minimize the severity of the diarrhea, you are advised to follow these directions:

1. Be aware of your bowel movements. If they become softer than usual or if you have any increase in the number of bowel movements over what is normal for you, begin taking loperamide tablets right away.
2. Take two loperamide (Imodium) tablets immediately after the onset of diarrhea or increased frequency of bowel movements, and then take one tablet every two hours until you have been without a bowel movement for 12 hours straight. At night, you may take two tablets every four hours so that you won't have to wake up so often. Make sure that you drink plenty of fluids (soups, juices, etc.) to replace the fluids lost in the bowel movements. If your soft bowel movements or diarrhea do not stop within 36 hours, call your doctor. Should you become weak, lightheaded, or feel faint, call your doctor immediately. Don't take loperamide tablets unless you have loose or frequent stools or diarrhea.

**Less likely (<20)**

- Mouth sores
- Frequent bowel movements (sometimes with blood noted in your bowel movements)
- Redness or irritation of your skin at infusion sites

**Rare but Serious (<3%)**

- Lung problems with symptoms shortness of breath, nonproductive (dry) cough, and abnormal chest x-ray
- Abnormal blood, kidney and liver lab results, which could indicate serious blood, kidney, or liver problems

**Reproductive risks**

The treatment in this study can affect an unborn baby. You should not become pregnant or father a baby while on this study because the radiation and chemotherapy in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Women of childbearing potential must have a must have a pregnancy test within 72 hours before participating in this study.

For more information about risks and side effects, ask your study doctor.

**Are there benefits to taking part in the study?**
CyberKnife treatment to the liver is done with the delivery of large doses of highly focused radiation. The three important possible benefits to CyberKnife therapy are that the higher doses of radiation may be: 1) more damaging to the tumor and, therefore, lengthen the time to tumor progression 2) have a greater chance of prolonging your life, 3) less damaging to surrounding tissue 3) more convenient than treatments being given daily over seven to nine weeks 4) a minimally invasive procedure performed on an outpatient basis. The addition of chemotherapy may improve upon the results expected from Cyberknife treatment alone.

The information which is obtained from this clinical evaluation will be used to see how helpful this treatment is to patients with liver metastasis. This information also may be helpful to others with your condition.

We cannot and do not guarantee or promise that you will receive any benefits from taking part in this study. You will be told if any new information is learned which may affect your condition or influence your willingness to continue participation in this evaluation.

While participating in this clinical evaluation, you should not take part in any other research project without approval from all of the investigators. This is to protect you from possible injury resulting from such things as extra blood drawing, extra x-rays, interaction of research drugs, or similar hazards.

**What other options are there?**
There are alternatives to CyberKnife radiation for treatment of liver metastasis. These include:

- Getting radiation treatment or care for your cancer without being in a study
- Chemotherapy
- Surgery
- Other treatments to eliminate the tumor by applying cold (cryotherapy) or heat (radiofrequency ablation).
- Taking part in another study
- Getting no treatment

These options may or may not be appropriate for you. You should discuss them with your physicians prior to your agreement to participate in this research protocol.

**Costs**
There is no cost for participating in this evaluation. You and/or your health plan/insurance company will be responsible for the entire cost of treating your cancer in this study, including the cost of managing the side effects of therapy and subsequent evaluation. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. You will be responsible for paying any deductibles, coinsurance, and co-payments as required under the terms of your insurance plan(s). Ask the study staff for help in determining your insurance coverage.

Your doctor will discuss these with you.
For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at
http://cancer.gov/clinicaltrials/understanding/insurancecoverage
You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

Compensation
You will not be paid for taking part in this study. The study doctors will not be paid for your participation in this study.

Research Related Injury
You will get medical treatment if you are injured as a result of taking part in this study but you and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

It is important that you inform the principal investigator, Arica Hirsch, MD, or your study doctor, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him or her at 847-723-8030.

No funds have been set aside by Advocate Health Care or Radiation Oncologist Consultants for injury or for any associated costs. You do not waive any of your legal rights by signing this form.

What are my rights if I take part in this study?
Participation in this study is entirely voluntary. You are free to withdraw your consent to participate in this treatment program at any time without prejudice to you or your medical care. Refusal to participate will involve no penalty or loss of benefits. You are free to seek care from a physician of your choice at any time. If you do not take part in or withdraw from this clinical evaluation, you will continue to receive care.

The decision may be made to take subjects out of this clinical evaluation due to unanticipated circumstances. Some possible reasons for withdrawing a subject from the evaluation are:
- failure to follow instructions
- the investigator decides that continuation could be harmful to you
- you need treatment not allowed in this clinical evaluation
- the evaluation is canceled
- other administrative reason

Who can answer my questions about the study?
If you have any questions, you will be expected to ask them of the doctor and/or his study coordinator. If you have any additional questions later, please contact:
What happens if I am injured because I took part in this study?
All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this evaluation. If such complications occur, the doctors will assist you in obtaining appropriate medical treatment but this evaluation does not provide financial assistance for additional medical or other costs. There will be no payment for treatment of pre-existing conditions or for any treatment of conditions arising after the evaluation. No funds have been set aside to compensate you for wages associated for lost time at your workplace.

Signatures

I have been given a copy of this form. I have read the consent form or it has been read to me. This information was explained to me and my questions were answered.

I agree to take part in this research study.

<table>
<thead>
<tr>
<th>Date</th>
<th>Patient’s Signature</th>
<th>Printed Name</th>
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<table>
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<tr>
<th>Date</th>
<th>Signature of person conducting the informed consent discussion</th>
<th>Printed Name</th>
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<tr>
<th>Date</th>
<th>Investigator’s Signature</th>
<th>Printed Name</th>
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In the event that an interpreter is needed:

I have accurately and completely read the foregoing document to: ________________________
(patient or legal representative’s name)

in ______________________ the patient’s (or legal representative’s) primary language.
(Identify language used)

He/She understands all terminology/conditions, acknowledges his/her agreement by signing the document in my presence.

______________________________ Date
Signature of Interpreter
AUTHORIZATION FOR USE OF PROTECTED HEALTH INFORMATION FOR RESEARCH PURPOSES

USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION

Protected Health Information is any personal health information through which you can be identified. A decision to participate in this research means that you agree to the use of your health information for the purposes explained in this consent form. By signing this form, you are authorizing the use and disclosure of your health information collected in connection with your participation in this research study. Your information will only be used in accordance with the provisions of this consent form and applicable law.

Your health information related to this study, including, blood and other tissue samples and related records, physical examinations, past medical history, x-rays, CT scans, consulting specialist’s reports, operative reports, and pathology reports may be used or disclosed in connection with this research study. Study records that identify you will be kept confidential as required by law. Except when required by law, you will not be identified by name, Social Security #, address, phone #, or any other direct personal identifier in study records disclosed.
Appendix II: Performance Status Scales

ECOG PERFORMANCE SCALE
0 Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
Appendix III: Data Collection Documents
MEDICAL HISTORY
NO Personal History of:
☐ Malignant ascites
☐ Additional sites of metastasis
☐ Prior liver radiation therapy
☐ Inflammatory bowel disease
☐ Hepato-renal syndrome
☐ Inflammatory bowel disease

PHYSICAL EXAM
Clinical Staging Clinical Staging:  T___ N___ M___
Primary Tumor (T) TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraepithelial or invasion of lamina propria
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through the muscularis propria into pericolorectal tissues
T4a Tumor penetrates to the surface of the visceral peritoneum
T4b Tumor directly invades or is adherent to other organs or structures

Regional Lymph Nodes (N)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1–3 regional lymph nodes
N1a Metastasis in one regional lymph node
N1b Metastasis in 2–3 regional lymph nodes
N1c Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2 Metastasis in 4 or more regional lymph nodes
N2a Metastasis in 4–6 regional lymph nodes
N2b Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis
M1a Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
M1b Metastases in more than one organ/site or the peritoneum

Assessment of Performance Status (0-1 only acceptable for baseline)
ECOG Performance Scale
☐ 0 Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
☐ 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
☐ 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
☐ 3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
☐ 4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

CT / MRI
☐ Yes
☐ No

PET Scan
☐ Yes
☐ No

CBC, platelets, CMP and LFT all within normal institutional limits
☐ No
☐ Yes

Pregnancy test for women of child bearing potential
☐ Negative
☐ Positive
☐ Not Applicable
# Toxicity Evaluation

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>GRADE</th>
<th>If AE &gt; 0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
</tr>
<tr>
<td>Flushing</td>
<td>none</td>
<td>Intervention no indicated</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>none</td>
<td>Limited to one site (palms, soles, or axillae); self care interventions</td>
</tr>
<tr>
<td>Fatigue</td>
<td>none</td>
<td>Fatigue relieved by rest</td>
</tr>
<tr>
<td>Alopecia</td>
<td>none</td>
<td>Hair loss of &lt;50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage</td>
</tr>
<tr>
<td>Pain - SITE</td>
<td>none</td>
<td>Mild pain not interfering with function</td>
</tr>
<tr>
<td>Nausea</td>
<td>none</td>
<td>Loss of appetite without alteration in eating habits</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>none</td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
</tr>
<tr>
<td>OTHER, specify:</td>
<td>none</td>
<td>-</td>
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</tbody>
</table>
Radiation - CyberKnife 54Gy (18Gy x 4) Gy

Radiation Therapy Start Date: ________-______-______
Radiation Therapy End Date: ________-______-______
Elapsed Days: ________

Treatment Interruptions

☐ No
☐ Yes
Number of Days* RT interrupted Due to Toxicity: ________
Number of Days* RT Interrupted Due to Other Reasons: ________
* Weekends not included

Reason Treatment Ended

☐ Completed per protocol criteria
☐ Disease progression, relapse during active treatment
☐ Adverse event / side effects / complications
☐ Death on study
☐ Withdrawal / refusal after beginning protocol therapy
☐ Withdrawal / refusal prior to beginning protocol therapy
☐ Alternative therapy, specify___________
☐ Patient off (protocol) treatment for other complicating disease
☐ Other reason, specify_______________

Chemotherapy - Irinotecan 40mg/m2 x 3 days

Date ________-______-______ dose ___________ mg/m2
Date ________-______-______ dose ___________ mg/m2
Date ________-______-______ dose ___________ mg/m2

Assessment of Performance Status

ECOG Performance Scale

0 Fully active, able to carry on all predisease activities without restriction (*Karnofsky 90-100).
1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (*Karnofsky 70-80).
2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (*Karnofsky 50-60).
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# Toxicity Evaluation

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>GRADE</th>
<th>If AE &gt; 0</th>
<th>Indicate Attribution to Protocol Tx</th>
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<tr>
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<td>2</td>
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</table>

<table>
<thead>
<tr>
<th>Flushing</th>
<th>none</th>
<th>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</th>
<th>Moderate symptoms; medical intervention indicated; limiting instrumental ADL</th>
<th>Symptomatic, associated with hypotension and/or tachycardia; limiting self care ADL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperhidrosis</td>
<td>none</td>
<td>Limited to one site (palms, soles, or axillae); self care interventions</td>
<td>Involving &gt;1 site; patient seeks medical intervention; associated with psychosocial impact</td>
<td>Generalized involving sites other than palms, soles, or axillae; associated with electrolyte/hemodynamic imbalance</td>
</tr>
<tr>
<td>Watering eyes</td>
<td>none</td>
<td>Intervention not indicated</td>
<td>Intervention indicated</td>
<td>Operative intervention indicated</td>
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<tr>
<td>Fatigue</td>
<td>none</td>
<td>Fatigue relieved by rest</td>
<td>Fatigue not relieved by rest; limiting instrumental ADL</td>
<td>Fatigue not relieved by rest, limiting self care ADL</td>
</tr>
<tr>
<td>Alopecia</td>
<td>none</td>
<td>Hair loss of &lt;50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss, but it does not require a wig or hair piece to camouflage</td>
<td>Hair loss of &gt;=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact</td>
<td></td>
</tr>
<tr>
<td>Pain - SITE</td>
<td>none</td>
<td>Mild pain not interfering with function</td>
<td>Moderate pain; pain or analgesics interfering with function, but not interfering with ADL</td>
<td>Severe pain; pain or analgesics severely interfering with ADL</td>
</tr>
<tr>
<td>Nausea</td>
<td>none</td>
<td>Loss of appetite without alteration in eating habits</td>
<td>Oral intake decreased without significant weight loss, dehydration or malnutrition</td>
<td>Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>none</td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline</td>
<td>Increase of &gt;=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL</td>
</tr>
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**OTHER, specify:** none

Physician's signature ____________________________ Date ___________________________
FOLLOW-UP

<table>
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<td>☐ 27</td>
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<td>☐ 33</td>
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</tbody>
</table>

CASE ID: _________

Vital Status  □ Alive  □ Dead

Date of Last Contact or Death: ___-___-_______

Primary Cause of Death
□ Not applicable
□ Due to this disease
□ Due to protocol treatment
□ Due to other cause, specify ____________
□ Unknown

Documented Clinical Assessment for this Cancer (since last follow-up)
□ Unknown
□ No
□ Yes

Date ___-___-_______

Assessment of Performance Status
ECOG Performance Scale
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4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

CBC, platelets, CMP and LFT all within normal institutional limits
(required at week 3, 6, 9, 17, 25, 49 and months: 15, 18, 21, 24, 27, 30, 33 and 36)
□ Yes
□ No

CT / MRI (required at week 6 and months: 3, 6, 9, 12, 16, 20, 24, 30 and 36)
□ Yes
□ No

PET scan (required at week 13, 25, 49 and months: 18, 24, 30 and 36)
□ Yes
□ No

First Local Recurrence (since last follow-up)
□ Unknown
□ No
□ Yes

Date: _____ / _____ / ______

Method of Evaluation (Local Progression)
□ Physical exam
□ Pathologic
□ Other, specify ____________

Site(s) of Progression (First distant): ________________________________

New Primary Cancer or MDS (since last follow-up)
□ Unknown
□ No
□ Yes

Date: _____ / _____ / ______

Site(s) of Progression (First distant): ________________________________
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**First Distant Progression** (since last follow-up)

- Unknown
- No
- Yes

**Date:** ____ / ____ / ____

**Method of Evaluation (Distant Progression)**

- Physical exam
- Pathologic
- Radiographic
- MRI (NMR)
- Other, specify_____________________

**Toxicity Evaluation**

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**Physician's signature ____________________________                                 Date ___________________________**
Appendix IV: NCI Common toxicity criteria/RTOG/EORTC:
Refer to:
Appendix V: Abbreviation List

ALT  Alanine Aminotransferase
AST  Aspartate Aminotransferase
AJCC American Joint Committee on Cancer
CA  California
CBC  Complete blood count
CT  computed tomography
cc  Cubic centimeter
CFR  Code of federal Regulations
cm  centimeter
CMP  Complete metabolic panel
CR  Complete remission
CTCAE  Common Terminology Criteria for Adverse Events
dl  deciliter
DVH  dose-volume histogram
ECOG  Eastern Cooperative Oncology Group
EORTC  European Organisation for Research and Treatment of Cancer
et al. et alia
FDA  Food and drug administration
gm  grams
Gy  Gray
LFT  Liver Function Test
mm³  Cubic millimeter
mg  milligram
ml  Milliliter
MRI  Magnetic Resonance Imaging
NaCl  Sodium Chloride
NCI  National Cancer Institute
PET  Positron Emission Tomography
PR  Partial remission
PTV  Planning Tumor Volume
RTOG  Radiation Therapy Oncology Group
SBRT  Stereotactic Body Radiation Therapy
SD  Stable Disease
UDP  Uridine Diphosphate
ULN  Upper limit of Normal
USP  United States Pharmacopeia
UT  University of Texas