Rev

A Phase II Study of Proton Beam Therapy in the Treatment of Esophageal Cancer

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Protocol Revision History

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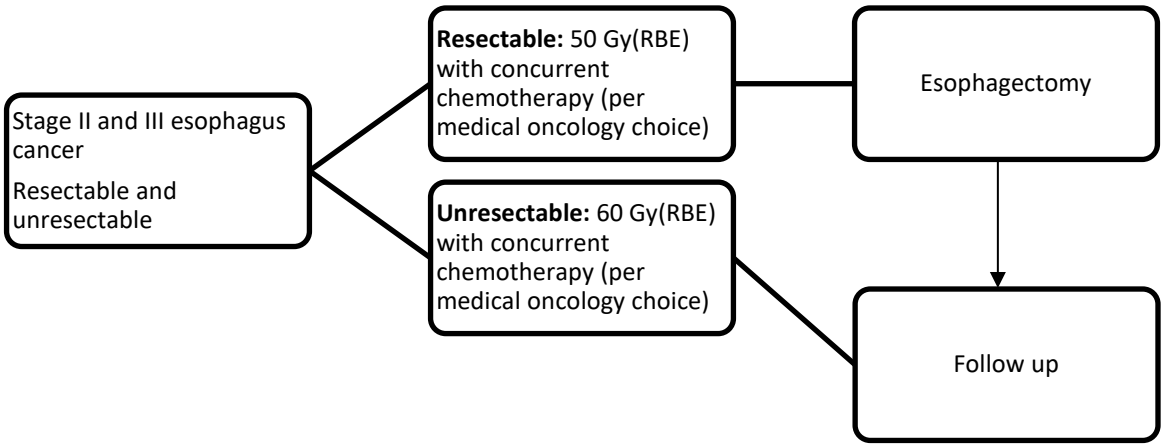
SCHEMA


Stage II and III esophagus cancer
Resectable and unresectable
Resectable: 50 Gy(RBE) with concurrent chemotherapy (per medical oncology choice)
Unresectable: 60 Gy(RBE) with concurrent chemotherapy (per medical oncology choice)
Esophagectomy
Follow up

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1.0 BACKGROUND AND RATIONALE

1.1 Esophageal Cancer

Esophageal cancer is a deadly disease that affects over 16,000 people per year in the United States. The majority of patients present with locally advanced disease (T2-4, or N1-3), and standard treatment in the United States for this group is definitive chemoradiotherapy or neoadjuvant chemoradiotherapy. Expected 5-year overall survival (OS) for either of these treatments ranges from 20% (definitive) to 35% (neoadjuvant). However, treatment with either bimodality or trimodality therapy is also associated with significant morbidity, both during the course of chemoradiation and in the months following completion of treatment, with late onset toxicities occurring up to one year after treatment. These toxicities may significantly impact patients' overall quality of life, and in patients consented for surgery, may hinder the ability to receive surgery or exacerbate postoperative complications. The radiotherapy portion of treatment is an important component of both the acute and late side effects associated with treatment, which is itself driven by variables such as dose, delivery technique (2D, 3D, IMRT), and potentially modality (photons, protons). Thus, altering one or more of these variables has the potential to improve toxicity, operability, and quality of life for patients undergoing this aggressive treatment.

1.2 Radiation Therapy in the Treatment of Esophageal Cancer

Radiation modality has advanced substantially over the past two decades. Photon therapy (such as higher energy X-rays) is the most common radiation modality used for cancer treatment. Since the esophagus is located between critical structures such as the heart anteriorly, the spinal cord posteriorly, and the lungs on either side, substantial doses are usually delivered to the normal organs in order to treat the tumor adequately. The current use of photon-based technology is called Intensity Modulated Radiation Therapy (IMRT), where each beam (typically 5-7) can be further modulated using computer-controlled multi-leaf collimators to dynamically block the path of the radiation while the beam is on, which effectively allows the dose to be "painted" with various intensities allowing greatest dose conformality to the tumor and dose avoidance to the normal structures. However, despite the advantages of IMRT, it is not considered a standard technique in routine clinical trials since it takes great expertise in the planning and quality assurance (QA) process. At Washington University, we have been using IMRT for treatment of esophageal cancer patients since 2006. Many of our patients receiving definitive chemoradiation therapy have been treated on our prospective clinical trial for locally-advanced esophagus cancer (HRPO# 201105449 / 06-1070). Our accrual to this trial was slow, mainly because most of our patients receive trimodality therapy (chemoradiation followed by surgery). Nevertheless, this form of photon therapy has been well-tolerated for this inoperable patient population.

There have been several trials evaluating the effectiveness and toxicity of photons in the management of esophagus cancer. A comprehensive review by Monjazeb and Blackstock summarizes toxicity risk for patients receiving chemoradiation alone or chemoradiation

followed by esophagectomy. (Monjazeb and Blackstock 2013) For patients receiving esophagectomy, the literature suggests a treatment mortality rate between 4%-10%. The rate of severe acute hematologic toxicity (≥ grade 3) varies between studies, but ranges from 3%-78% and is primarily attributed to chemotherapy. The common severe acute non-hematologic toxicities include esophagitis (16%-63%) and pain (3%-24%). As these studies used different radiation doses, chemotherapy agents, and toxicity definitions, the specifics of expected acute toxicity would be improved by incorporating patient-reported outcome instruments.

With respect to patient outcome measures from our experience at the Siteman Cancer Center, we completed an internal trial that used IMRT to a dose of 60 Gy with concurrent chemotherapy (HRPO# 201105449 / 06-1070). The 2-year progression-free survival (PFS) and overall survival (OS) rates from that experience are 25% (95% CI of 11-62%) and 36% (95% CI of 7-49%), respectively. These results are consistent with the literature. Overall, 60 Gy with concurrent chemotherapy has been well-tolerated. Many patients died of intercurrent illness due to associated comorbidities and/or advanced age.

We previously published a retrospective analysis of 45 patients treated with chemoradiation followed by esophagectomy. (Trovo, Bradley et al. 2008) We do not expect proton therapy at preoperative doses (i.e., 50 Gy) to improve PFS (37%) or OS (63%), although there are limited published data for proton therapy in this setting.

1.3 Proton Beam Therapy in the Treatment of Esophageal Cancer

Radiation therapy for esophagus cancer has primarily employed photons. Literature review reveals only one recently published prospective experience with proton beam therapy (PBT). M.D. Anderson Cancer Center (MDACC) in Houston, TX tested proton beam radiation therapy in 62 patients receiving chemoradiotherapy. (Lin, Komaki et al. 2012) Patients received 50.4 Gy (RBE) in 1.8 Gy daily fractions using passively scattered protons and were followed for toxicity. All patients received concurrent chemotherapy, with drug choice left to the treating physician. Some patients received induction chemotherapy (42%). The median follow-up period for survivors was 20.1 months. The most common grade 2 to 3 adverse events were dysphagia (43.6%), esophagitis (46.8%), fatigue (43.6%), nausea (33.9%), anorexia (30.1%), and radiation dermatitis (16.1%). There was one case each of grade 2, 3, and 5 radiation pneumonitis. There were two total grade 5 events, one from radiation pneumonitis and one from ventricular tachycardia that occurred at a dose of 45 Gy during treatment. The investigators also reported survival outcome measures. The estimated 3-year overall survival was 51.7%. The 3-year relapse-free, distant metastasis-free, and local-regional control rates were 40.5%, 66.7%, and 56.5%, respectively. MDACC has an ongoing phase II randomized trial testing passively scattered proton beam radiation therapy versus IMRT, but there are no results reported yet (Lin et al. Personal communication). Other ongoing phase I trials at Loma Linda University and the University of Pennsylvania are also unreported to date.

Proton dosimetric studies appear favorable compared to x-rays, specifically with regard to adjacent normal tissue doses (Figure 1, Table 1). For example, Zhang et al. demonstrated

that in comparison to IMRT, PBT planning results in better sparing of the lung (improved mean lung dose of 2.9 Gy). (Zhang, Zhao et al. 2008) MDACC has also recently examined their experience in the first 50 PBT patients treated with surgery after chemoradiation compared to 165 patients treated with IMRT or 208 with 3D. They found that PBT significantly improved postoperative pulmonary complication rates compared to 3D (OR 0.26, 95%CI 0.09, 0.70). IMRT trended to worse postoperative complication rates compared to PBT (OR 1.74, 95%CI 0.66, 4.61). (Lin, Wang et al. 2012)

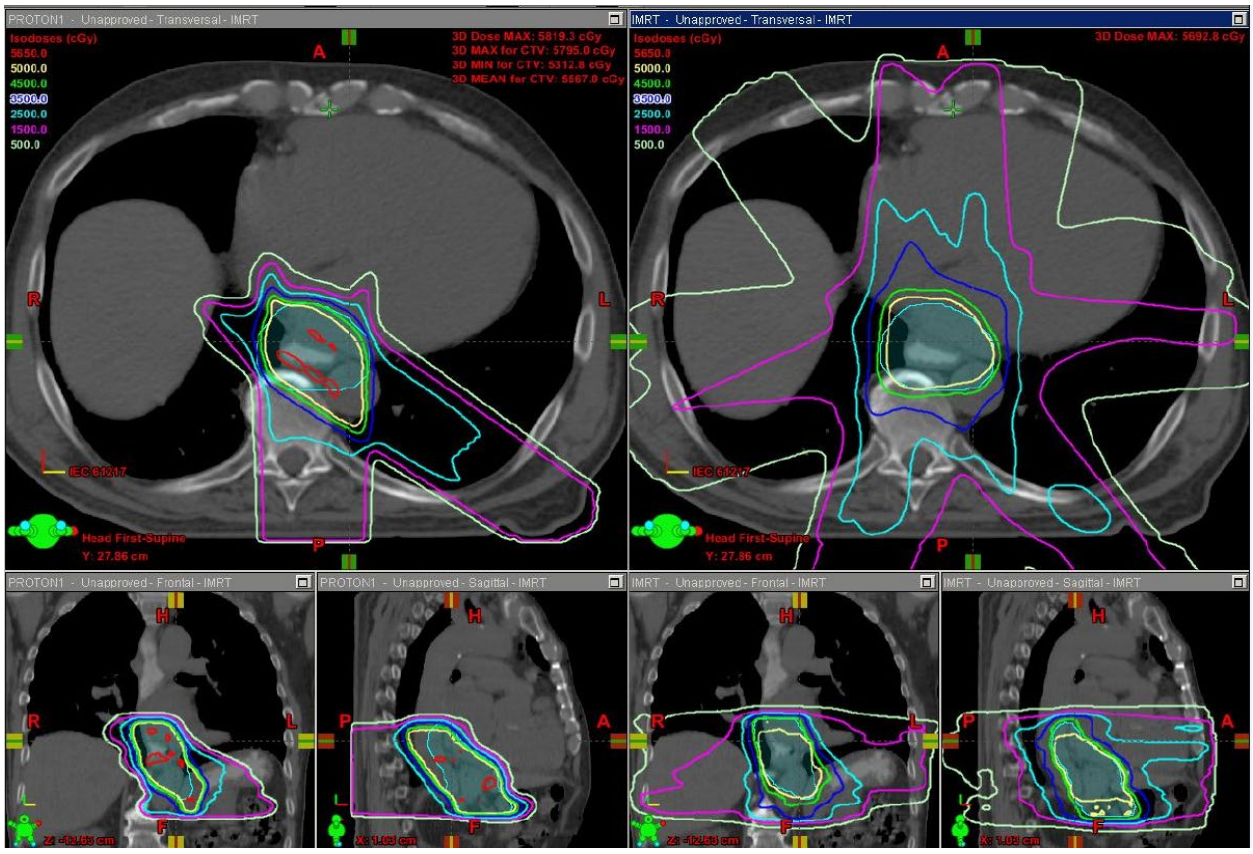

Figure 1. Comparison plan of proton beam therapy (PBT)(left side) versus intensity modulated radiation therapy (IMRT)(right side) in three image planes. The target doses to the esophagus are not different. However, the normal tissue doses to the adjacent normal tissues (lung, heart, spinal cord, and liver) are better with PBT.

	TL Mean	Cord Max	Liver Mean	Heart Mean	Eso. Mean	PTV Mean	PTV %	PTV Max	CTV Mean	GTV Mean
IMRT (avg)	990	4012	1135	2104	2194	5285	95.9	5702	5323	5320
PBT (avg)	694	3217	296	1159	2251	5309	96	5744	5352	5360
difference	-296	-795	-839	-945	57	24	0	42	29	39
p-value	*0.0001*	*0.0001*	*0.0001*	*0.0001*	*0.13*	*0.17*	*0.96*	*0.12*	*0.75*	*0.81*

Table 1. *Average dose of PBT compared to IMRT to normal structures are significantly reduced without compromising tumor (Gross Tumor Volume (GTV), Clinical Target Volume (CTV), Planning Target Volume (PTV)) coverage. Units are in centigray. TL=Total Lung; Eso=Esophagus*

At the Kling Proton Therapy Center at the Siteman Cancer Center, we have an opportunity to study PBT for esophagus cancer patients. Protons differ substantially from photons in that protons are charged particles accelerated through a cyclotron to high energies (250 MeV) and released into the patient. By its interaction with various materials in its path and through the patient's tissue, the beam can be modulated to deliver a dose that covers the tumor volume. However, unlike photons, protons have a finite range and can be modulated to stop immediately past the tumor's edge. With very simple 2 to 3 beam arrangements, the entire tumor volume can be fully encompassed while maximally sparing the surrounding normal organs.

1.4 Patient-Reported Outcomes (PROs)

The Patient Reported Outcomes are symptom measures assessed using the MD Anderson Symptom Inventory (MDASI)-Plus module [4] (Appendix B) and the QOL questionnaire called the EuroQol (EQ-5D) (Appendix C), as well as the SF-12 (Appendix E), MOS Social Support Measure (Appendix F), and 4-item CES-D (Appendix G). We have chosen these instruments since all are validated tools that have been widely used to measure symptoms scoring and QOL measures. All of these surveys are administered to the patient by the clinical or research staff prior to starting therapy. PROs have not been reported for esophagus cancer. Thus, this trial would be one of the first to incorporate PRO measures using protons for the treatment of esophagus cancer.

1.4.1 MDASI-Plus

The MDASI-plus is a reliable, validated tool for assessing cancer-related symptoms regardless of therapy or specific cancer diagnosis. (Cleeland, Mendoza et al. 2000; Wang, Williams et al. 2010) Patients are asked to fill out a twenty-seven question inventory, ranking their symptoms on a 0 (no problems) to 10 (worst imaginable) scale before treatment, weekly during treatment, and in treatment follow-up.

1.4.2 EQ-5D

The EQ-5D is a standardized 2-part, patient-administered instrument used for direct and indirect assessment of health state utilities; it is cognitively simple, takes only a few minutes to complete, and yields a utilities index value for health status (Pickard 2007). The first part asks respondents to "check the ONE box [next to the appropriate statement] that best describes your health TODAY" for each of 5 health dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Johnson & Coons, 1998). The second part of the EQ-5D is a visual analogue scale (VAS) valuing current health state. Both the 5-item index score and the VAS score are transformed into a utility score between 0 "Worst health state" and 1 "Best health state." For this study, we will report both the health state classification instrument and the visual analog scale (VAS) utilities. The former is considered to satisfy the "community preferences" recommendation of the Panel on Cost Effectiveness, whereas the VAS is considered to satisfy the

Panel's "patient preferences" recommendation.(Gold 1996) Over 30 published studies provide evidence to support its validity and reliability in cancer.

1.4.3 SF-12

The 12-item SF-12 is a shorter, yet valid alternative to the SF-36 for measuring physical and mental functional status in the general population (Ware, Kosinski, Keller 1995) (Ware, Kosinski, Keller 1996). The SF-12 has well-established norms, has been extensively validated, is sensitive to changes over time, has established minimally clinically important changes, and has been used in cancer studies (Ramsey et al 2002) (Scarpa et al 2009) (Siassi et al 2009). We have experience using the SF-12 in our research (Lian, Jeffe, Schootman 2008). The SF-12 will be measured at each of 7 interviews, and mental and physical component scores will be calculated in addition to calculating the measure's eight individual subscales (physical functioning, social functioning, role limitations due to physical problems, body pain, general health, role limitations due to emotional problems general health, vitality, and mental health). Higher scores indicate better quality of life.

1.4.4 MOS Social Support

The 19-item Medical Outcomes Study (MOS) Social Support Survey was designed for use with patients with chronic diseases and measures how often different kinds of support are available, if needed (Sherbourne, Stewart 1991). Response choices range from "none of the time" (1) to "all of the time" (5). A mean social support score for all 19 items is computed with higher scores indicating a greater availability of social support. Social isolation and lack of social support are related to increased mortality from a number of causes (Berkman et al 1993; Berkman, Syme 1979; Orth-Gomer, Johnson 1987; Kaplan et al 1998) and social support has been associated with cancer patients' QOL in previous studies (Jeffe et al 2012; Waters et al 2013). We hypothesize that lower levels of perceived social support will be associated with poorer QOL.

1.4.5 4-Item CES-D

The Center for Epidemiological Studies Depression Scale (CES-D) is a 20-item measure which evaluates depressive symptoms. This trial will make use of the validated 4-item screening version in order to reduce participant burden (Melchior et al 1993). There will be a referral plan in place for psychosocial counseling services for depressed patients. Depression has been shown to be related to QOL in other cancer patient populations (Longman et al 1996; Jeffe et al 2012). We hypothesize that depressive symptoms will be associated with poorer QOL.

1.5 Study Rationale

We plan to include both operable and inoperable patients with esophagus cancer in this

prospective trial. Since both proton and photon treatments are biologically equivalent, we do not expect a difference in tumor control compared to IMRT. We have a prospective experience of physician-reported toxicity and patient outcome using IMRT for patients with inoperable esophagus cancer that will serve as a comparison group. For the resectable patients receiving trimodality therapy (chemoradiation followed by surgery), we will carefully track toxicity and patient outcomes prospectively. Our central hypothesis is that the biologic efficacy for tumor control should be similar between protons and photons, and therefore survival measures should be similar between the two groups, but that the main difference lies in the total severe toxicities experienced by the patients undergoing therapy.

2.0 OBJECTIVES

2.1 Primary Objectives

1. To assess patient-reported outcomes of proton beam therapy (PBT) for esophageal cancer at 6 months following chemoradiation.

2. To assess physician-reported toxicity of PBT for esophageal cancer.

3. To assess patient-reported outcomes of PBT for esophageal cancer at 12 months following chemoradiation.

2.2 Secondary Objectives

1. To assess progression-free survival (PFS) of PBT for patients with resectable vs. unresectable esophageal cancer.

2. To assess overall survival (OS) of PBT for patients with resectable vs. unresectable esophageal cancer.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically or cytologically documented adenocarcinoma or squamous cell carcinoma of the cervical or thoracic esophagus or gastroesophageal junction or cardia of stomach.

2. Staged by PET/CT and esophagogastroduodenoscopy (EGD) or endoscopic ultrasound (EUS) **OR** CT w/contrast and EGD to have stage II or III disease per AJCC 7th edition guidelines.

3. Prior endoscopic mucosal resection (EMR) with a diagnosis of stage II or III esophageal cancer (AJCC 7th edition) is eligible, irrespective of margin status.

4. Induction chemotherapy prior to concurrent chemoradiation is allowed.

5. Prior thoracic radiation is allowable if degree of overlap with the esophageal radiotherapy treatment is deemed to be safe by the treating radiation oncologist.

6. At least 18 years of age.

7. ECOG performance status $\leq$ 2 (Karnofsky $\geq$ 60%, see Appendix A)

8. Normal bone marrow and organ function as defined below:
   a. WBC > 2,500/mcL
   b. Platelets $\geq$ 75,000/mcl
   c. Total bilirubin $\leq$ 1.5 x IULN
   d. AST(SGOT)/ALT(SGPT) $\leq$ 3.0 x IULN
   e. Creatinine $\leq$ 1.5 x IULN
      OR
      Creatinine clearance $\geq$ 50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

9. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

10. Ability to understand and willingness to sign an IRB approved written informed consent document.

11. English speaker.

12. Financial coverage for proton therapy.

3.2 Exclusion Criteria

1. Planned treatment with radiation therapy alone without concurrent chemotherapy or chemotherapy alone.

2. Previous or concomitant cancers within the past 3 years other than curatively treated carcinoma in situ of the cervix, basal cell carcinoma of the skin, curative treatment for transitional cell carcinoma of the bladder, and low risk prostate cancer. Except for prostate cancer (which can be observed if low risk), other cancers listed must have been treated in the past 3 years without evidence of recurrence at the time of registration.

3. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac

arrhythmia not controlled by pacer device, myocardial infarction within 3 months of registration, or psychiatric illness/social situations that would limit compliance with study requirements

4. Pregnant and/or breastfeeding. Patient must have a negative pregnancy test within 7 days of the start of treatment.

3.3 Inclusion of Women and Minorities

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

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

5.1 Chemotherapy

Since this is a radiation modality trial, all patients suitable for concurrent chemotherapy with or without experimental therapies on clinical trials or for induction chemotherapy prior to neoadjuvant concurrent chemoradiation and patients receiving definitive concurrent chemotherapy and radiation are eligible for this study. This study will not mandate use of any one regimen but will defer to the treating oncologist's recommendations.

Dose adjustments for all chemotherapy agents may be made per physician discretion/preference. It is not a protocol violation for changes in a chemotherapy regimen during treatment if that is the deemed necessary by the treating medical oncologist. All chemotherapies will be prepared and administered in accordance with the prescribing information approved by the Food and Drug Administration (FDA) or other regulatory agencies.

Typically, neoadjuvant chemotherapy is completed at the time of the completion of concurrent radiation therapy. Patients receiving definitive therapy typically receive an additional 4 to 8 weeks of chemotherapy after radiation therapy has been completed.

All chemotherapy labs and procedures will be collected and performed following the standard of care process and timeline.

5.2 Radiation Therapy

3-D CT based planning must be used for all patients. Passive scattering proton beam will be employed. The Mevion S-250 Proton Radiation Beam Therapy System will be used.

5.2.1 Dose Specifications

The daily prescription dose will be 1.8 or 2 Gy RBE ("Relative Biologic Equivalence"), at the discretion of the treating radiation oncologist, to be delivered to the periphery of the planning target volume (PTV). The isodose line (generally 93-98%) chosen will encompass at least 95% of the PTV.

The maximum point dose, minimum point dose, and mean dose to PTV will also be reported.

a.) **For patients with unresectable esophagus cancer, the total dose will be 60 Gy (RBE) (at 2 Gy/Fx/day) or 59.4 Gy (RBE) (at 1.8 Gy/Fx/day) to PTV2.** All doses will be prescribed to the periphery of PTV2. PTV1 will receive 50.4 Gy (RBE) (at 1.8 Gy/Fx/day) or 50 Gy (RBE) (at 2 Gy/Fx/day). PTV1 will encompass volumes that are not apparently involved based on PET/CT and/or EUS, but where pathological involvement risk is >20%.

b.) For patients with resectable esophagus cancer, the total dose will be 50 Gy (RBE) (at 2 Gy/Fx/day) or 50.4 Gy (RBE) at (1.8 Gy/Fx/day) **to PTV1.** All doses will be prescribed to the periphery of the PTV.

5.2.2 Treatment Planning Imaging and Localization Requirements

A volumetric treatment planning CT study will be required to define gross tumor volumes (GTV) and planning target volume (PTV). For this study, the local regional nodes (whether clinically positive or negative) will be included in the clinical target volume (CTV). Each patient will be positioned in an individualized immobilization device in the treatment position on a flat table. Contiguous CT slices, 3-5 mm thickness of the regions harboring gross tumor and 8-10 mm thickness of the remaining regions, are to be obtained starting from the level of the cricoid cartilage and extending inferiorly through the liver. The GTV and PTV and normal organs will be outlined on all appropriate CT slices and displayed using beam's eye view. Normal tissues to be contoured include lungs, skin, heart, spinal cord, esophagus, and liver. A measurement scale for the CT image shall be included.

Optimal immobilization is critical for this protocol. Alpha cradle or approved alternative immobilization system is required. Patients may be placed on the supine or prone position.

5.2.3 Volume and ICRU Reference Point Definitions

The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

Gross Tumor Volume (GTV) is defined as all known gross disease as defined by the planning CT and clinical information. Gross tumor includes the primary (GTV-P) only.

Clinical Target Volume (CTV) is defined as the area of subclinical involvement around the GTV. For this protocol, we have chosen to define the CTV as minimum of 4 cm proximal and distal and 1 cm lateral beyond the GTV delineated by CT scan and /or endoscopy (endoscopy is preferable). However, final CTV may be larger to make sure that nodal regions at $\geq$ 20% risk of involvement are included at the discretion of the radiation oncologist. For example, for upper esophagus primaries (defined as tumors above the carina), the bilateral supraclavicular nodes should be included. For mid-esophageal primaries (at or below the carina), the paresophageal nodes should be included—not the supraclavicular or celiac. For distal/gastroesophageal primaries, the field should include the celiac nodes and left gastric nodes. The final CTV must respect anatomic boundaries of potential microscopic disease spread.

Planning Target Volume (PTV) will provide margin around the CTV to compensate for variability in treatment set up, breathing, or motion during treatment. The PTV will be generated by the dosimetrist, as each beam will need its own PTV delineation due to the effect of differing tissue inhomogeneities and distal and lateral penumbra as it relates to dose coverage of the CTV.

The *ICRU Reference Point* is to be located in the central part of the PTV. Typically this point should be located on the beam axis or at the intersection of the beam axis (isocenter).

5.2.4 Radiation Treatment Planning

The normal tissues in the table below are to be contoured in their entirety.

The following organs and doses are guidelines for the radiation treatment plan (see Table 4: Normal Tissue Volume and Tolerance). Physician/Dosimetrist should make every effort not to exceed these tolerance levels. All normal tissues assume treatment at 1.8 or2 Gy RBE/Fx

Table 4: Normal Tissue Volume and Tolerance

Tolerance Dose			
Organ	**Volume**	**TD 5/5**	**End Point**
Lung	*Mean lung dose <21 Gy*	*V20 ≤35%*	Clinical Pneumonitis
Spinal Cord	5 cm 10 cm 20 cm	50 Gy 50 Gy 47 Gy	Myelitis Myelitis Myelitis
Heart	1/3 2/3 3/3	50 Gy 45 Gy 40 Gy	Clinical Pericarditis Clinical Pericarditis Clinical Pericarditis
Liver	1/2 2/2	35 Gy 30 Gy	Clinical Hepatitis Clinical Hepatitis

It is expected that the dose to the lungs, heart, spinal cord, and liver will be the primary dose-limiting structures. Every effort should be made to keep the total lung dose to a minimum.

When planning the beam arrangement to the PTV, the lungs, heart, spinal cord, and liver should be excluded from the radiation field to the greatest extent possible. The dose per fraction to the lungs, heart, and spinal cord should be maintained at 2 Gy or less per fraction to the greatest extent possible. If tolerance dose to any of the normal organs is exceeded, alternate beam arrangement should be used.

5.3 Surgery

Once patients are deemed eligible for surgical resection, surgery should ideally be performed no later than 8 to 10 weeks after completing chemoradiation. In the post-operative period for patients who undergo surgery, postoperative complications will be scored by the surgeons and/or nursing/research staff at the post-op visit with the surgeon and will be recorded.

5.4 Patient-Reported Outcomes Measures (PROs)

Treatment-related symptom scores and QOL will be assessed by a research coordinator at the following time points:

- prior to the start of therapy
- at the end of chemoradiation (day of EOT or up to 1 week after)
- 2 months (+/- 2 weeks) following the end of chemoradiation; this should be just prior to surgery for those patients undergoing surgery who have received CRT but not definitive chemotherapy
- 4 months (+/- 2 weeks) following the end of chemoradiation; this should be just prior to surgery for those patients undergoing surgery who have received CRT + definitive chemotherapy and should be approximately 2 months following surgery for those patients undergoing surgery who have received CRT but not definitive chemotherapy
- 6 months (+/- 2 weeks) following the end of chemoradiation; this should be approximately 2 months following surgery for those patients undergoing surgery who have received CRT + definitive chemotherapy
- 9 months following the end of chemoradiation
- 12 months following the end of chemoradiation

The QOL and other PRO assessments will be conducted using a computer-assisted interview program, and may be done in person before/after a routine office visit or over the phone at the preference of the study participant.

Regardless of whether the patient had surgery, clinical outcomes and treatment-related toxicity will continue to be captured at each follow-up visit after Month 12 along with standard clinical assessments. Follow-up visits are typically are done at intervals of 3-4 months for the first 2 years after completion of last treatment procedure, and every 6 months for the 3 years thereafter.

5.5 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test within 7 days prior to study entry.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study.

If a patient is suspected to be pregnant, study treatment should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 3 months after the last study treatment, the investigator must be notified in order to facilitate outcome follow-up.

5.6 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, PBT may continue for 6 weeks and QOL assessments for one year after the end of CRT or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol (if the patient is noncompliant with their recommended treatment, rendering his/her QOL data not usable)
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

5.7 Duration of Follow-up

Follow-up visits are typically done at intervals of 3-4 months for the first 2 years after completion of last treatment procedure, and every 4-6 months thereafter for the next 3 years.

6.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 6.2.

6.1 Definitions

6.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

6.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

6.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

6.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

6.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

6.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

6.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

6.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

6.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

6.4 Timeframe for Reporting Required Events

Only AE's grade 3 or greater which are at least possibly related to the proton beam radiation therapy and listed in Appendix D, will be tracked Grade 3 or higher AE's possibly related to PBRT and found in Appendix D will be documented in clinical notes and the relatedness will be assessed in a timely fashion for the first year. After 12 months, the AE's will be reviewed at the 5 year follow-up time point through chart review and they will be assessed at that time. Please review Appendix D for a list of reportable adverse events. SAEs will be reported for 30 days after the end of concurrent chemoradiation regardless of the attribution. Thereafter, SAEs, which are possibly, probably, or definitely related will be reported for up to one year after the end of concurrent chemoradiation.

7.0 STUDY CALENDAR

	Screening / Baseline	On-treatment RT visits	End of CRT	First post-CRT visit (8 wks after end of CRT)[2]	4 mos after end of CRT[2]	6 mos after end of CRT[2]	9 mos after end of CRT[2]	12 mos after end of CRT[2]	Follow-up[3]
Informed consent	X								
ACE-27 comorbidity index[4]	X								
History and physical, vitals	X[1]	X		X					
Performance status	X[1]	X		X					
Proton beam therapy approval	X								
CBC w/diff	X[1]								
BMP[9]	X[1]								
LFTs[10]	X[1]								
CT chest/abdomen or PET/CT	X[8]			X[6]					
EGD/EUS +/- biopsy	X			X					
Adverse events collection (MD-reported CTCAE v 4.0)	X[1]	X		X	X	X	X	X	X[7]
MDASI-plus	X[1]		X	X	X	X	X	X	
EQ-5D	X[1]		X	X	X	X	X	X	
SF-12	X[1]		X	X	X	X	X	X	
MOS Social Support Survey	X[1]		X	X	X	X	X	X	
4-item CES-D	X[1]		X	X	X	X	X	X	
Post-op complication eval[5]									

1. At the time of initial Radiation Oncology consultation (within 4 weeks prior to start of protocol therapy), recognizing that some of these patients will go on to receive induction therapy prior to enrollment in the trial
2. +/- 2 weeks
3. Typically every 3-4 months for the first 2 years and every 6 months for the next 3 years; patients will be tracked for toxicity for the first year and for survival for the remaining 4 years
4. From tumor board; need not be available for data capture at baseline, but comorbidity index must be derived from patient status prior to initiation of CRT
5. Assessed at 4-6 weeks after surgery (which will be at different time points dependent on receipt of definitive chemotherapy)
6. Must be PET/CT
7. Grade 3 events or higher, at least possibly related to PBRT and found in Appendix D, for the first year only
8. Within 8 weeks of start of protocol therapy
9. BMP = Na^+, K^+, Cl^-, CO_2, BUN, creatinine, glucose
10. LFTs = bili, AST, ALT, ALP

8.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form	Prior to starting treatment
Chemotherapy Form Radiation Form	End of CRT
EQ-5D* MDASI-plus* SF-12* MOS Social Support Survey* 4 item CES-D*	Baseline End of CRT 8 weeks after end of CRT 4 months after end of CRT 6 months after end of CRT 9 months after end of CRT 12 months after end of CRT
Adverse Events Form**	Baseline At each on-treatment RT visit End of CRT Every 3-4 months during Year 1
Post-Op Form	4-6 weeks post-op
Follow Up Form	Every 3-4 months during Years 1-2 Every 6 months during Years 3-5

* The QOL forms will be entered via a computer-assisted interview program and will be stored on the computer's hard drive. The data will then be transferred via encrypted email, Dropbox, or encrypted flash drive and dumped into a password-protected database for data accumulation and merging. The other forms will be entered directly into the study REDCap database.
** MD-reported AE's will be obtained from clinical note and chart review.

9.0 MEASUREMENT OF EFFECT

9.1 Toxicity

Toxicities related to radiation therapy, both acute (< 90 days from RT start) and late (> 90 days from RT start) will be documented and graded according to the NCI CTCAE v 4.0

9.2 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

10.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

11.0 STATISTICAL CONSIDERATIONS

This is a single arm clinical trial to evaluate proton beam radiation therapy (PBT) for treatment of stage II/III esophageal cancer in two clinical settings; a.) definitive chemoradiation and b.) neoadjuvant chemoradiation followed by esophagectomy. While we will report and provide descriptive statistics between the two clinical settings, analyzing the differences is not our main concern. The main endpoints are to determine the patient-reported outcomes and physician-reported toxicities of proton beam therapy for esophagus cancer at 6 months. Additional endpoints in the setting of definitive chemoradiation are to assess the progression-free and overall survival

rates at 2 and 5 years.

11.1 Sample Size

Due to the novel nature of this study, standard sample size and power calculations are not possible. Therefore, we plan to enroll 20 patients to both the operative and non-operative treatment arms (40 patients total) because we believe that we have the ability to accrue this number of patients in a timely and clinically relevant manner. This is NOT a randomized trial between these two therapy strategies. This number of patients is intended to obtain preliminary data upon which to base subsequent studies.

11.2 Toxicity Analysis

Although this is not a randomized trial where the number of patients on each treatment arm is controlled, we will capture that information and hope that these two groups will be relatively the same size. Early stopping rules would cease accrual to the trial if ≥Grade 4 CTCAEv4 gastrointestinal or pulmonary toxicity rates exceed 10% (2), or if ≥ grade 3 CTCAEv4 gastrointestinal or pulmonary toxicity rates exceed 30% (6) for the first 20 patients enrolled. In order to assess the overall toxicity of this treatment method we will compare the proportion of ≥Grade 3 gastrointestinal or pulmonary toxicity events against historical controls utilizing Binomial tests for proportion.

11.3 Progression-Free Survival and Overall Survival Rates

PFS and OS will be assessed using the Kaplan-Meier estimate. Since we don't have enough patients on either arm for a firm comparison to the literature, we plan to simply provide descriptive statistics and projected 2-year and 5-year PFS and OS estimates for the following two arms:

A. Definitive chemoradiation – We completed an internal Phase II trial that used intensity-modulated radiation therapy (IMRT) to a dose of 60 Gy with concurrent chemotherapy. The 2-year PFS and overall survival rates (OS) from that experience are 25% (95% CI of 11 - 62%) and 36% (95% CI of 7 - 49%), respectively. These results are consistent with the literature.
B. Neoadjuvant chemoradiation followed by esophagectomy – The two-year PFS and OS rates for patients with adenocarcinoma of the esophagus or gastroesophageal junction treated with neoadjuvant chemoradiation followed by esophagectomy on CALGB 9781 was 60% and 70%, respectively (taken from PFS and OS curves). (Tepper, Krasna, Mayer et al. 2008: 26:1086)

11.4 Patient Reported Outcomes

We will calculate descriptive statistics (mean, standard deviation, etc.) for all QOL data (EQ-5D, SF-12) in addition to other PROs (depressive symptoms, social support) at each evaluation period. Univariate tests will explore the associations among QOL and PROs using analysis of variance (ANOVA) and Fisher's exact test for correlation. Changes over time in QOL and PROs will be analyzed utilizing repeated-measures modeling techniques

(repeated measures analysis of covariance).

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: MD Anderson Symptom Inventory (MDASI)-Plus

14032

Date: ___ / ___ / ___
(month) (day) (year)

Participant Initials: ___

Participant #: ___

PLEASE USE BLACK INK

Data collection to Assess Acute and Late Normal Tissue Sequelae in Proton Therapy for Adults
Protocol: PCR05-0207
PI: James D. Cox, MD
Revision: 05/25/2010

Assessment Visits: ___ Week

M. D. Anderson Symptom Inventory - Plus

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	NOT PRESENT 0	1	2	3	4	5	6	7	8	9	AS BAD AS YOU CAN IMAGINE 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your difficulty **swallowing** at its Worst?	○	○	○	○	○	○	○	○	○	○	○
15. Your **coughing** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

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	NOT PRESENT 0	1	2	3	4	5	6	7	8	9	AS BAD AS YOU CAN IMAGINE 10
16. Your **skin pain/burning/rash** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your **constipation** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your **diarrhea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your problem with **tasting food** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your **mouth or throat sores** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your **pain in swallowing** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
22. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
23. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
24. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
25. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
26. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
27. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

APPENDIX C: EuroQol (EQ-5D)

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems with self-care ❑

I have SLIGHT problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES (*e.g., work, study, housework, family or leisure activities)*

I have no problems doing my my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN/DISCOMFORT

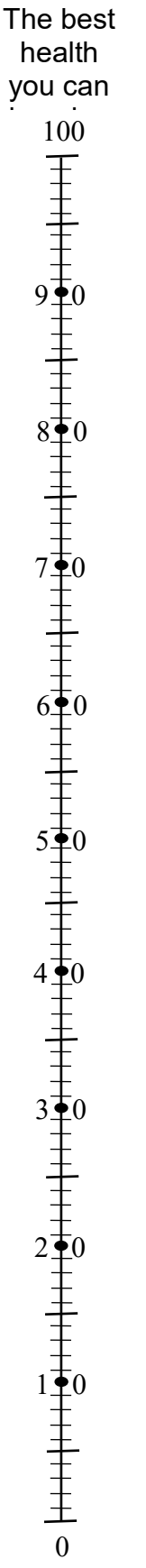
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

- We would like to know how good or bad your health is TODAY
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below

YOUR HEALTH TODAY = ☐



APPENDIX D: Reportable Adverse Events from CTCAE version 4.03

Cardiac AEs

Adverse Event	1	2	3	4	5
Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death
Definition: A disorder characterized by gross necrosis of the myocardium; this is due to an interruption of blood supply to the area.					
Myocarditis	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by inflammation of the muscle tissue of the heart.					
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Definition: A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of the heart.					
Paroxysmal atrial tachycardia	Asymptomatic, intervention not indicated	Symptomatic; medical management indicated	IV medication indicated	Life-threatening consequences; incompletely controlled medically; cardioversion indicated	Death
Definition: A disorder characterized by a dysrhythmia with abrupt onset and sudden termination of atrial contractions with a rate of 150-250 beats per minute. The rhythm disturbance originates in the atria.					
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation.					
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium.					
Pericarditis	Asymptomatic, ECG or physical findings (e.g., rub) consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irritation to the layers of the pericardium (the protective sac around the heart).					

Gastrointestinal AEs

Adverse Event	1	2	3	4	5
Duodenal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the duodenum and another organ or anatomic site.					
Duodenal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the duodenum.					
Duodenal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization or elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of stomach contents through the duodenum.					
Duodenal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the duodenal wall.					
Duodenal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the duodenum.					
Duodenal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the duodenal wall.					
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting.					
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by difficulty in swallowing.					
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the small and large intestines.					
Enterovesical fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; noninvasive intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine.					
Esophageal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site.					
Esophageal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the esophagus.					

Esophageal necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the esophageal wall.					
Esophageal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents in the esophagus.					
Esophageal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the esophageal region.					
Esophageal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the esophagus.					
Esophageal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the esophagus.					
Esophageal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the esophageal wall.					
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the esophageal wall.					
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by inability to control the escape of stool from the rectum.					
Flatulence	Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	-
Definition: A disorder characterized by a state of excessive gas in the alimentary canal.					
Gastric fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the stomach and another organ or anatomic site.					
Gastric hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the gastric wall.					
Gastric necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gastric wall.					

Gastric perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the stomach wall.					
Gastric stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the stomach.					
Gastric ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the stomach.					
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the stomach.					
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter, and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion.					
Gastrointestinal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between any part of the gastrointestinal system and another organ or anatomic site.					
Gastrointestinal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gastrointestinal region.					
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Definition: A disorder characterized by a queasy sensation and/or the urge to vomit.					
Upper gastrointestinal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, esophagus, and stomach).					
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.					
Gastrointestinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Metabolism and Nutrition AEs

Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a loss of appetite.					
Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis.					

Respiratory, Thoracic and Mediastinal AEs

Bronchial fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
Definition: A disorder characterized by an abnormal communication between the bronchus and another organ or anatomic site.					
Bronchial obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., mild wheezing); endoscopic evaluation indicated; radiographic evidence of atelectasis/lobar collapse; medical management indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by blockage of a bronchus passage, most often by bronchial secretions and exudates.					
Bronchial stricture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the bronchial tube.					
Bronchopleural fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
Definition: A disorder characterized by an abnormal communication between a bronchus and the pleural cavity.					
Bronchopulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the bronchial wall and/or lung parenchyma.					
Mediastinal hemorrhage	Radiologic evidence only; minimal symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the mediastinum.					
Pleural effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., diuretics or limited therapeutic thoracentesis)	Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pleurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort.					
Pleural hemorrhage	Asymptomatic; mild hemorrhage confirmed by thoracentesis	Symptomatic or associated with pneumothorax; chest tube drainage indicated	>1000 ml of blood evacuated; persistent bleeding (150-200 ml/hr for 2 - 4 hr); persistent transfusion indicated; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pleural cavity.					
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pleura.					
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					

Pulmonary fibrosis	Mild hypoxemia; radiologic pulmonary fibrosis <25% of lung volume	Moderate hypoxemia; evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25 - 50%	Severe hypoxemia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50 - 75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing	Death
Definition: A disorder characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnea, respiratory failure or right heart failure.					
Pulmonary fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Limiting self care ADL; endoscopic stenting or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Tracheal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder characterized by an abnormal communication between the trachea and another organ or anatomic site.					
Tracheal mucositis	Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the trachea.					
Tracheal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Stridor or respiratory distress limiting self care ADL; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the trachea.					

Skin and Subcutaneous AEs

Adverse Event	1	2	3	4	5
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-
Definition: A disorder characterized by an intense itching sensation.					
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by darkening of the skin due to excessive melanin deposition.					
Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by loss of skin pigment.					
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by an area of hardness in the skin.					
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss	Death
Definition: A disorder characterized by circumscribed, inflammatory and necrotic erosive lesion on the skin.					
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by local dilatation of small vessels resulting in red discoloration of the skin or mucous membranes.					

APPENDIX E: SF-12

Date _____

Instructions: This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Please answer every question by marking one box. If you are unsure about how to answer, please give the best answer you can.

1. In general would you say your health is:

☐	☐	☐	☐	☐
Excellent	Very good	Good	Fair	Poor

The following items are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
2.	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	☐	☐	☐
3.	Climbing **several** flights of stairs	☐	☐	☐

During the <u>past 4 weeks</u>, have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

		YES	NO
4.	**Accomplished less** than you would like	☐	☐
5.	Were limited in the **kind** of work or other activities	☐	☐

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		YES	NO
6.	**Accomplished less** than you would like	☐	☐
7.	Didn't do work or other activities as **carefully** as usual	☐	☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

☐	☐	☐	☐	☐
Not at all	A little bit	Moderately	Quite a bit	Extremely

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

		All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9.	Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
10.	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
11.	Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relative, etc.)?

☐	☐	☐	☐	☐
All of the time	Most of the time	Some of the time	A little of the time	None of the time

APPENDIX F: MOS Social Support Survey

MOS Social Support Survey

People sometimes look to others for companionship, assistance, or other types of support. How often is each of the following kinds of support available to you if you need it? Circle one number on each line.

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
Emotional/informational support					
Someone you can count on to listen to you when you need to talk	1	2	3	4	5
Someone to give you information to help you understand a situation	1	2	3	4	5
Someone to give you good advice about a crisis	1	2	3	4	5
Someone to confide in or talk to about yourself or your problems	1	2	3	4	5
Some whose advice you really want	1	2	3	4	5
Someone to share your most private worries and fears with	1	2	3	4	5
Someone to turn to for suggestions about how to deal with a personal problem	1	2	3	4	5
Someone who understands your problems	1	2	3	4	5
Tangible support					
Someone to help you if you were confined to bed	1	2	3	4	5
Someone to take you to the doctor if you needed it	1	2	3	4	5
Someone to prepare your meals if you were unable to do it yourself	1	2	3	4	5
Someone to help with daily chores if you were sick	1	2	3	4	5
Affectionate support					
Someone who shows you love and affection	1	2	3	4	5
Someone to love and make you feel wanted	1	2	3	4	5
Someone who hugs you	1	2	3	4	5

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
Positive social interaction					
Someone to have a good time with	1	2	3	4	5
Someone to get together with for relaxation	1	2	3	4	5
Someone to do something enjoyable with	1	2	3	4	5
Additional item					
Someone to do things with to help you get your mind off things	1	2	3	4	5

APPENDIX G: 4-Item CES-D

Date: _____

Instructions: Darken the circle next to each statement which best describes how often you felt or behaved this way—DURING THE PAST WEEK.

1. I felt depressed	○ Rarely or none of the time (less than 1 day) ○ Some or a little of the time (1-2 days) ○ Occasionally or a moderate amount of the time (3-4 days) ○ Most or all of the time (5-7 days)
2. I felt lonely	○ Rarely or none of the time (less than 1 day) ○ Some or a little of the time (1-2 days) ○ Occasionally or a moderate amount of the time (3-4 days) ○ Most or all of the time (5-7 days)
3. I had crying spells.	○ Rarely or none of the time (less than 1 day) ○ Some or a little of the time (1-2 days) ○ Occasionally or a moderate amount of the time (3-4 days) ○ Most or all of the time (5-7 days)
4. I felt sad.	○ Rarely or none of the time (less than 1 day) ○ Some or a little of the time (1-2 days) ○ Occasionally or a moderate amount of the time (3-4 days) ○ Most or all of the time (5-7 days)