TITLE: Randomized Controlled Phase II Trial of Liver Resection Versus No Surgery in Patients with Liver and Unresectable Pulmonary Metastases from Colorectal Cancer

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1.0 Objectives

1.1 Primary objective

1.1.1 To estimate a survival benefit of liver resection in patients with resectable liver and unresectable low-volume pulmonary metastases from colorectal cancer.

1.2 Secondary objective

1.2.1 To identify biomarkers in blood and resected liver specimens that correlate with survival and development of extrahepatic and extrapulmonary metastases.

1.2.2 To assess patients' quality-of-life in each treatment arm with serial questionnaires.

2.0 Rationale

2.1 Introduction

Liver metastases occur in approximately 30% of all patients with colorectal cancer and account for at least two-thirds of colorectal cancer deaths.[1] Both hepatic and pulmonary metastases will develop in 5-10% of colorectal cancer patients.[2] Data supporting liver metastasectomy for stage IV colorectal cancer dates back to the 1970s, when 5-year overall survival of patients who underwent resection of solitary colorectal liver metastases (CLM) was reported to be 42%.[3] The survival benefit of liver resection was attributed to the unique tumor biology of an isolated liver metastasis from colorectal cancer. In 1995, Hellman and Weichselbaum coined the term "oligometastases," defined as metastases limited to a single or limited number of organs amenable to surgical resection as a curative therapeutic strategy.[4] They also described the potential for effective chemotherapy to convert patients with widespread polymetastatic disease to an oligometastatic state.

Multiple studies have established hepatic resection as the only potentially curative treatment for patients with CLM, resulting in a 5-year overall survival rate of 58%.[5] A study of nearly 2500 patients with stage IV colorectal cancer treated at MD Anderson and the Mayo Clinic demonstrated a median survival of 65.3 months in patients undergoing liver resection, compared to only 26.7 months with chemotherapy alone.[1] With the advent of effective chemotherapy that can downsize liver metastases, more patients are eligible for hepatic resection, regardless of tumor size, number, or distribution in the liver.

Resectability of liver metastases is defined as the ability to preserve two contiguous hepatic segments, preservation of adequate vascular inflow and outflow and biliary drainage, and the ability to preserve adequate future liver remnant.[6]

2.2 Extrahepatic metastases

In earlier studies, patients undergoing liver resection in the presence of extrahepatic disease had a particularly poor outcome, and the presence of extrahepatic disease was considered a

contraindication to liver resection. The presence of both hepatic and extrahepatic metastases was thought to represent systemic dissemination, or polymetastatic disease. However, more recently, studies have shown that carefully selected patients may have improved survival with complete resection of liver metastases and low-volume extrahepatic disease.[7] Among sites of extrahepatic disease, pulmonary metastases are associated with favorable survival.

Retrospective studies have shown that patients undergoing resection of both pulmonary and hepatic metastases have survival comparable to that of patients undergoing resection of isolated hepatic metastases.[8] In a report from MD Anderson of 41 patients undergoing both pulmonary and hepatic metastasectomy, the 5-year overall survival rate was 57%. In this study, patients had a mean number of 2.3 lung metastases, with a mean size of 1.5 cm, and 31% bilateral.

Most colorectal cancer patients with hepatic metastases and pulmonary nodules do not undergo lung biopsy. The diagnosis of pulmonary metastases is based on radiologic features and clinical suspicion when pulmonary nodules progress or regress with chemotherapy. A study from Memorial Sloan-Kettering Cancer Center evaluated patients with subcentimeter pulmonary nodules who underwent hepatic resection for metastatic colorectal cancer. After median follow-up of 31 months, factors associated with non-progression of pulmonary nodules included calcification and spiculated contours.[9]

Currently, there are no limits on number, size, or bilaterality for resection of pulmonary metastases from colorectal cancer.[10] The main determinant of irresectability of pulmonary metastases is inadequate pulmonary reserve to sustain a good performance status after the largest likely loss of pulmonary parenchyma.

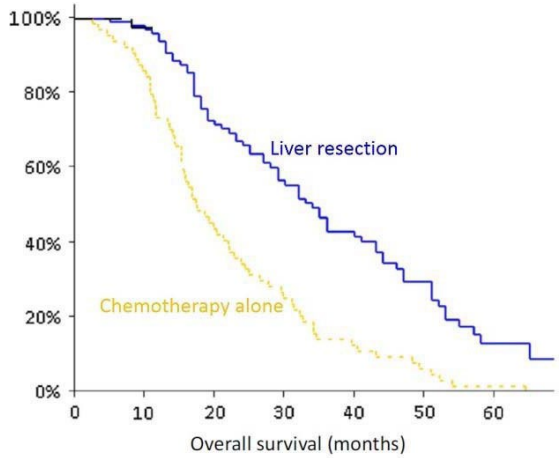
2.3 Preliminary data

The role of liver resection in the setting of unresectable extrahepatic metastases was not reported until our recent retrospective study of patients who underwent resection of liver metastases in the presence of unresectable pulmonary metastases.[8] This study was undertaken to clarify the impact of lung metastases, which are the most frequent form of extrahepatic colorectal cancer metastasis. With effective cytotoxic chemotherapy and biologic agents, long-term disease control can be expected in patients with unresectable lung metastases, which are often small-volume and have indolent tumor biology. In contrast, liver metastases typically represent a greater tumor burden and the primary determinant of patient survival.

For the retrospective study, 98 patients were identified who underwent hepatic resection for metastatic colorectal cancer with known pulmonary nodules that progressed after hepatectomy. In this study population, median number of lung nodules that progressed after hepatectomy was 3 (range, 1–14), all < 2 cm in size, and 60% bilateral.[8]

Independent predictors of poorer survival were *Kras* mutation and rectal primary tumor. The study population was matched with a group of patients (n=64) treated with chemotherapy only. The 3-year and 5-year overall survival rates were 43% and 13% for patients who underwent resection of their liver metastases, in contrast to 14% and 2% for those treated with chemotherapy only (P<0.01, figure 1). These nonrandomized analyses suggest that removal of the liver metastases may substantially prolong survival of patients with both hepatic and pulmonary metastases.

Figure 1. In patients with liver and unresectable, low-volume pulmonary metastases from colorectal cancer, retrospective analysis demonstrated improved survival with liver resection, compared to chemotherapy alone.[8]



2.4 Rationale for randomized trial

Current standard of care for patients with resectable liver and unresectable pulmonary metastases from colorectal cancer is chemotherapy. Our previous study of patients who underwent hepatic resection with unresected pulmonary metastases was limited by its retrospective design. A prospective, randomized trial is needed to support the use of liver resection over chemotherapy alone in this patient population. Furthermore, the proposed study is expected to identify surrogates of tumor biology to optimize selection of patients most likely to benefit from hepatectomy in the setting of unresectable pulmonary metastases.

2.5 Safety of liver surgery

Advances in imaging, anesthesia, perioperative care, and surgical technique have increased the safety of hepatic resection. Currently, the mortality and major morbidity rates after liver resection at MD Anderson are 2% and 14%, respectively.[11] The two most significant potential complications after liver resection are liver failure and bile leak. At MD Anderson, we precisely measure liver volumes, and if the volume of the liver remaining after surgery is insufficient, then we perform portal vein embolization to induce hypertrophy of the remnant liver. After portal vein embolization, we measure the kinetic growth rate (KGR), which is the growth rate of the remnant liver divided by the number of weeks since portal vein embolization. Previously, we showed that patients with KGR of ≥ 2% per week have a 0% risk of liver failure and liver- related mortality.[12] Furthermore, after major hepatectomy, we perform an intraoperative bile leak test by cannulating the bile duct and insufflating air to detect bile leaks, which are repaired intraoperatively. By using this technique, we have reduced the rate of postoperative bile leak to 1.9%.[13]

2.6 Correlative studies

2.6.1 Biomarkers

Patient selection is critical to achieving favorable outcomes after liver resection in the setting of unresectable pulmonary metastases. In a study from Memorial Sloan-Kettering Cancer Center of patients undergoing resection of both hepatic and pulmonary metastases, 80% of patients developed disease recurrence.[14] Among the sites of disease recurrence, 9% involved extrahepatic and extrapulmonary sites, including the bone, brain, and adrenal, indicating a polymetastatic disease pattern. Recently, Uppal and colleagues analyzed resected lung metastases from various primary disease sites and found microRNAs encoded in the 14q32 microRNA cluster to mediate an oligometastatic phenotype.[15] Such biomarkers can serve as surrogates for favorable biology confined to the lung and liver to help select subsets of patients for hepatic resection.

2.6.2 Quality-of-Life

Prior quality-of-life studies after hepatectomy have shown severe deterioration of function in 30% of patients but functional recovery by 6 months.[16] In patients with hepatic and unresectable pulmonary metastases, whose median survival is reportedly less than 3 years, quality-of-life with hepatic resection or chemotherapy alone is important to evaluate.

3.0 Eligibility of Subjects

3.1 Inclusion criteria

3.1.1 Patients with synchronous or metachronous diagnosis of resectable liver metastases by computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen.

3.1.1a Patients requiring percutaneous or intraoperative ablation of liver metastases < 2 cm in size are eligible.

3.1.1b Patients who underwent prior liver resection or ablation for colorectal liver metastases are eligible.

3.1.2 Patients previously treated with systemic chemotherapy and/or biologic agents for colorectal cancer are eligible.

3.1.3 The primary tumor in the colon or rectum may be intact or resected.

3.1.4 Low-volume lung metastases are defined as solid pulmonary nodules < 2 cm with non-spiculated contours, no benign-appearing calcifications, and $\leq$ 14 in number, diagnosed by computed tomography of the chest or positron emission tomography (PET).

3.1.5 Lung metastases will be unresectable due to anatomic location, distribution, or patients' comorbidities, as determined by review of imaging by a faculty member in the Department of Thoracic & Cardiovascular Surgery.

3.1.6 Patients 18 years of age and older.

3.1.7 Patients must sign a study-specific consent form.

3.1.8 Patients will undergo CT imaging of the chest, abdomen, and pelvis to evaluate lung and liver metastases within 60 days of registration. For patients who cannot tolerate CT contrast or have hepatic steatosis that reduces the sensitivity of CT, MRI of the liver will be performed.

3.2 Exclusion criteria

3.2.1 Radiographic evidence of disease other than liver and lungs, with the exception of mediastinal lymph nodes < 2 cm and hepatoduodenal ligament lymphadenopathy, diagnosed by computed tomography, magnetic resonance imaging, or positron emission tomography.

3.2.2 Inadequate liver function, as evidenced by serum bilirubin $\geq$ 2 mg/dL and/or platelet count < 50,000/µL.

3.2.3 ECOG performance status of 3-4.

3.2.4 Patient refusal to participate in randomization.

3.2.5 Pregnant women are excluded from this study.

3.2.6 Planned stereotactic body radiation therapy (SBRT) for the pulmonary metastases.

3.2.7 Non-English-speaking patients are not eligible for participation.

4.0 Research Plan and Methods

4.1 Protocol schema

This is a randomized, non-blinded, controlled phase II trial of liver resection vs. no surgery in patients with liver and unresectable pulmonary metastases from colorectal cancer.

Standard resources needed for routine clinical care will be utilized for this protocol. The Institutional Tissue Bank (LAB03-0320 and PA14-0241) will be utilized for patients whose tissues are collected. Clinics of faculty in the Gastrointestinal Medical Oncology department are screened by designated study staff for potentially eligible patients.

Eligible patients will be randomized in a 1:1 allocation ratio to the treatment group of liver resection or control group of no liver resection. The randomization will be conducted by the Clinical Oncology Research System (CORe) after consent and registration. Randomization will occur when patients are being considered for liver surgery.

Patients whose pulmonary metastases become resectable with chemotherapy will be considered for pulmonary metastasectomy. A patient who changes treatment plan (surgery or chemotherapy), per patient or physician discretion, will continue to be followed on the study for the primary endpoint of overall survival, and analysis will be performed in an intent-to-treat fashion.

Potential benefits for the patient are being evaluated by a hepatobiliary surgeon for possible liver resection, which may or may not be associated with longer recurrence-free survival. Potential risks are complications of liver surgery for patients randomized to the surgery arm. If participants suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to their insurance provider or the participant in the ordinary manner. The participant will not be reimbursed for expenses or compensated financially by MD Anderson for this injury. We do not anticipate any economic burdens beyond those that the patient would experience with standard of care treatment. Patients who withdraw from the study will continue to receive care under the discretion of their treating physician(s).

4.2 Treatment scheme

4.2.1 Liver resection

Laboratory studies, imaging, and correlative studies will be performed at time-points shown in Table 1. All hepatectomies will be performed at MD Anderson by one of four dedicated liver surgeons, using either a laparoscopic or open approach. Postoperative chemotherapy may be deferred in patients suffering from major postoperative complications.

All postoperative complications will be assessed by the attending surgeon and graded by a well-established classification system by Dindo et al. and managed as part of routine standard of care, including percutaneous drain placement for symptomatic fluid collections.[17]

Figure 2. Study schema

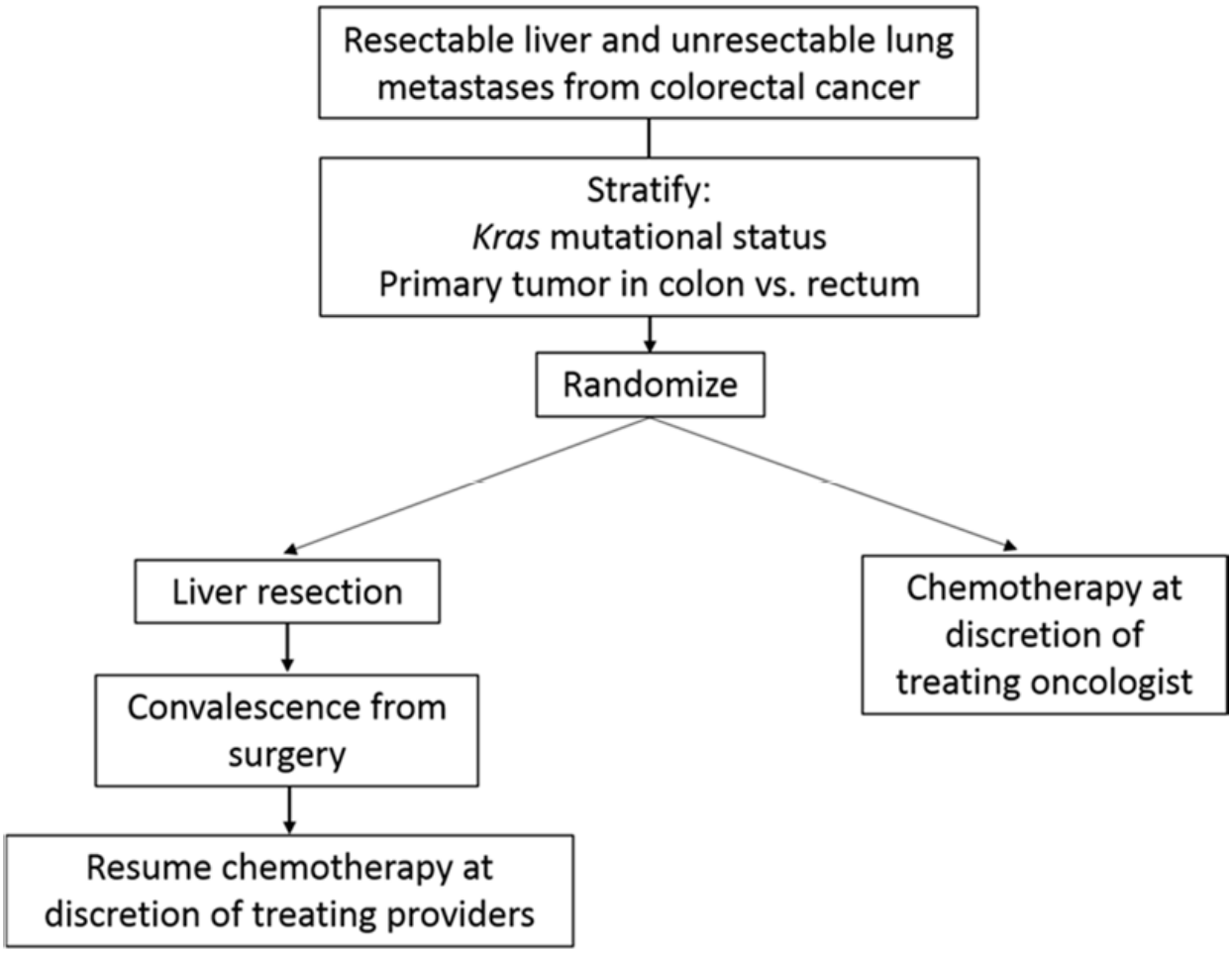


Table 1. Schedule of events

	At registration	Restaging Appointments**	Liver resection*	Restaging appointments	Post-treatment follow-up**
Tests & Observations					
History and Physical Examination	x	x		x	x
Performance Status	x	x		x	x
Staging					
Chest x-ray or chest CT	x	x		x	x
Abdominal/pelvic imaging (CT, MRI, or PET scan)	x	x		x	x
Companion Studies					
Quality-of-life survey**	x	x		x	x
Tumor block			x		
Plasma, when available	x	x		x	x
Primary tumor block, when available	x				

* For patients randomized to surgery.
** Every 3-6 months until 3 years after randomization or until death. Patients may or may not continue on chemotherapy during this time period. For patients who do not return to MD Anderson, attempts will be made to obtain outside medical records for determination of the primary endpoint.

Residual tumor and non-tumorous liver tissue will be collected from surgical resection specimens. All samples will be residual samples removed as part of the planned surgical procedure. Prior to surgery, a research study assistant will communicate with the surgeon regarding a consented patient.

For patients who consent to tissue collection, residual tissue samples will be snap-frozen in liquid nitrogen, including a portion embedded in optimum cutting temperature (OCT) compound. Each sample will be assigned a unique identifier code and stored in the laboratory of Dr. Scott Kopetz. Future studies on this tissue may include examining tumor DNA and protein.

4.2.2 Chemotherapy alone

Patients randomized to chemotherapy alone will receive chemotherapy at the discretion of the treating oncologist as routine standard ofcare.

4.3 Blood collection

Blood collection will occur at time-points specified in Table 1 and will be coordinated with each patient's standard of care blood draw to minimize additional venipuncture. Specimens will be labeled with a unique identifier code. A research study assistant will collect and transport the blood to the laboratory of Dr. Scott Kopetz as detailed in Table 2. Plasma samples will be stored in -80ºC freezers.

Table 2. Blood collection, processing, and storage

Sample type	BD vacutainer color	Volume collected	Transport conditions	Centrifuge	Transfer and aliquot
Plasma	Lavender	9 ml	Invert 10 times after collection. Then transport on ice.	2500 rpm (1160xG) x 10 min at 4ºC	Transfer plasma layer into 500 µl cryovials

4.4 Assessment of stratification factors

The following stratification factors, shown to be significant in the prior retrospective study, shall be observed throughout the enrollment period of the study:

- Tumor RAS mutational status
- Site of primary tumor, colon vs. rectum[8]

4.5 Follow-up

Patients will be followed for quality-of-life and survival as shown in Table 1.

4.6 Data collection

Data collection will include the following:

- Patient age and gender
- Dates of diagnosis and treatment
- Number, size, and distribution of liver and pulmonary metastases
- Primary tumor TNM stage, lymphovascular and perineural invasion
- Blood CEA levels
- Quality-of-life surveys
- Perioperative morbidity and mortality
- New lung metastases
- New liver metastases
- Development of tumors outside the liver and lung
- Blood loss and transfusions associated with hepatectomy
- Molecular testing, including tumor RAS mutational status

- Surgical margins
- Site of primary tumor (colon vs. rectum)
- Extent of liver resection required (major vs. minor hepatectomy)
- Interval since primary resection

5.0 Endpoints

5.1 Primary endpoint

The primary endpoint is overall survival.

5.2 Secondary endpoints

5.2.1 Time to development of extrahepatic, extrapulmonic metastases.

5.2.2 Quality-of-life
Patients will be asked to complete the Functional Assessment of Cancer Therapy-General 7 (FACT-G7) quality-of-life survey at specified time-points listed in Table 1.[18]

5.2.3 Intrahepatic recurrence among patients randomized to surgery.

5.2.4 Associations between biomarkers and survival.

6.0 Statistics and Justification of Sample Size

This is a single-center, non-blinded, randomized controlled phase II trial of liver resection or no surgery in patients with hepatic and unresectable pulmonary metastases from colorectal cancer. Patients will be 1:1 randomized to the surgery arm and non-surgery arm. The primary objective is to compare overall survival between the two arms. The overall survival time is defined as the time period from the date of randomization to the date of death or the date of last follow-up if the patients are alive at the time of last follow-up. 80 patients were planned to be randomized with 40 patients per arm, and the randomization was planned to be stratified by tumor *Kras* mutational status and site of primary tumor (colon versus rectum). We are now revising the protocol to randomize 40 patients with 20 patients per arm.

Sample size and power

A group sequential design with one interim analysis was initially implemented for the study. The primary endpoint is overall survival. A retrospective study showed that the median overall survival was 17 months for patients without surgery and 34 months with surgery. A sample size of 80 with 55 deaths was calculated to have 80% power to detect a difference of 17 months and 34 months using a log-rank test at a one-sided significant level of 0.05. Assuming accrual rate is 2 patients per

month, the accrual time will be 40 months, and the maximum study duration will be approximately 60 months.

Due to slower accrual than expected, the trial objectives and statistical analysis plan have undergone redesign to account for a smaller sample size.

The study is now targeting an accrual rate of 0.53 patients per month, for a total of 21 patients in the next 40 months. Thus, there are expected to be 40 patients in the entire study by the end of April 2024.

Due to the lower sample size, no hypothesis testing will be performed. With only 40 subjects, we calculate that the originally-planned log-rank test will only have 55% power to detect the assumed difference between treatment and control groups. The interim analysis will also be removed due to the smaller sample size, although we will continue monitoring for early death.

The primary objective of the adjusted study will be to estimate the survival benefit of liver resection in patients with resectable liver and unresectable low-volume pulmonary metastases from colorectal cancer. Secondary objectives will remain unchanged. We will accomplish the primary objective by calculating the median survival times and restricted mean survival times in both treatment and control arms. We will also calculate the differences in median survival and restricted mean survival. This information will offer suggestive evidence of the benefit or lack of benefit of liver resection and may possibly lead to future trials with a larger sample size.

Monitoring for early death

Death within 30 days from surgery will be monitored. Denote the probability of early death rate by $T_{deathD30}$. We assume T_{LE} ~ beta (0.05, 0.95). We will stop the enrollment if at any point $Pr(T_{deathD30} > 0.05 \mid data) > 0.9$. That is, we will stop the trial if, at any time during the study, we determine that there is more than 90% chance that the rate of death within 30 days is more than 5%. This toxicity monitoring rule will be applied after the first 10 patients have been enrolled. The corresponding stopping boundaries are to stop the trial if (number of patients died in 30 days from surgery / number of patients) ≥2/10-11, 3/12-19, The operating characteristics are listed in table 3.

Table 3: Operating Characteristics (OCs) for early death monitoring

True Prob(death in 30 days from surgery)	Pr(stop)	Average # Pts treated
0.01	0.006	19.94
0.03	0.048	19.57
0.05	0.124	18.93
0.08	0.276	17.67
0.10	0.386	16.74
0.15	0.637	14.54

Multc Lean V2.1 software developed in the Department of Biostatistics, UT MDACC was used for design of monitoring early death.

Analysis method

The primary analysis will be performed in an intention-to-treat data set. No hypothesis testing will be performed. We will calculate the median survival time in both the treatment and control arm, as well as the difference in median survival across arms. Additionally, we will calculate the restricted mean survival time up to four years in both arms, as well as the difference across arms.

The hazards ratio of overall survival for the surgery arm compared to the non- surgery arm will be estimated by fitting Cox proportional hazards regression models, adjusting for the effects of covariates including stratification factors.

Adverse events will be tabulated by frequency and percentages, by grade, and by their relations to surgical treatment. For secondary analyses, the Kaplan-Meier method will be used to estimate time to extrahepatic and extrapulmonary metastases, as well as time to time to intrahepatic recurrence among patients randomized to surgery. Univariate and multivariate Cox proportional hazards models will be fitted to evaluate the association between biomarkers in blood and resected liver specimens and time to event outcomes, including overall survival development of extrahepatic and extrapulmonary metastases, and time to intrahepatic recurrence among patients randomized to surgery. Univariate and multivariate logistic regression will be used to assess the association between biomarkers and response to chemotherapy.

Descriptive statistics including mean, standard deviation, median, and range will be used to summarize scores of the FACT-G7 questionnaire for each item. Summation of item GP1, GP4, GP2, and GE6 (higher score indicates worse condition) and summation of GF5, GF3 and GF7 (higher score indicates better condition) will be calculated for each patient. Two sample t-tests will be used to compare scores of each item or summations between the two treatment arms, and also to compare their changes after treatment. Linear mixed models will be fitted to compare each item between two treatment arms.

7.0 Informed Consent/Authorization Procedures

Patients will be identified primarily from medical oncology and surgical oncology clinics and will require signed consent for participation in this protocol. Patients will be approached by a member of the research team in the clinic to request consent.

The investigator must obtain documentation of consent from each potential subject prior to participating in a clinical trial. Informed Consent will be conducted in compliance with the Clinical Research Administration SOP 4.0 and Institutional Informed Consent Policy 44.0.

The protocol and informed consent documentation for this study must conform to institutional regulations and local and national laws and regulations. As soon as a potential subject is considered for this study and prior to any other study procedures, each prospective subject will be given a full explanation of the purpose of the study, the procedures to be carried out and the potential hazards. Once this essential information is provided to the subject and once the Investigator believes that the subject understands the implications of participating in the study, the subjects will be asked to provide written informed consent and authorization to access medical records needed for study documentation. Subjects will be required to read, sign, and date a properly executed written Informed Consent Form prior to enrollment and will be assured that they may withdraw from the study at any time without jeopardizing their medical care. They will be given a copy of their Informed Consent Form.

Patients will either be consented in person, via phone, or through an Institutionally-approved teleconferencing system (i.e., Zoom). For patients who are identified as eligible but not available to approach and consent in person, a letter will be sent via MyChart to introduce the study prior to attempts to contact (see Appendices D and E). These patients will be contacted by phone or approved teleconferencing system to assess interest and complete the consent process through Institutionally-approved remote-consenting procedures. The same process and language used for in-person consenting will be used when remote-consenting participants.

8.0 Data Safety and Monitoring Board

This study will be monitored by The Data Safety and Monitoring Board (DSMB), through routine reviews and/or institutional audits. The DSMB reports to the President, or his designee, as the on-campus representative of The University of Texas Board of Regents. It oversees the data and patient safety issues for randomized clinical trials that originate at MD Anderson; that are coordinated or analyzed by MD Anderson and are not being monitored by any other DSMB; or has been designated as the DSMB for any trial at the request of the IRB, the CRC, or institution. The primary objectives of the DSMB are to ensure that patients' rights pertaining to participation in a research study are protected, and that patients' interests are prioritized over the interests of the scientific investigation. Responsibilities include:

(a) Review interim analyses of outcome data;

(b) Determine whether, and to whom, outcome results should be released prior to the reporting of study results;

(c) Review interim toxicity data and efficacy of treatment;

(d) Review major research modifications proposed by the investigator or appropriate study committee prior to implementation (e.g., termination, dropping an arm based on toxicity results from the study or results of other studies, increasing target sample size).

The DSMB consists of not more than 15 members (including the Chair) as recommended by the President, or his designee, for each fiscal year. The committee includes physicians, statisticians and lay member(s), and will be selected based on their experience, reputation for objectivity, absence of conflicts of interest (or the appearance of the same), and knowledge of good clinical trial methodology. The committee meets 5 times per year, and may schedule additional meetings if needed.

9.0 Data Confidentiality:

Data will be available to the Principal Investigator (PI) and people directly involved with the collection and analysis of data related to this project. IRB approval will be obtained for any exchange of data within and outside of MD Anderson.

Collection of Identifiers: Identifiers (name, medical record number and dates) will be collected.

Name and MRN will be replaced by study numbers in the analytic file. The key linking these numbers will be retained in a locked file by the investigator's designated personnel. Dates will be retained as a limited data set. Data will not be shared with any party outside of MD Anderson and will not be retained or disseminated for other research without prior IRB approval.

Training of Personnel: Only MD Anderson personnel designated by the Principal Investigator will have access to study records. These personnel will be fully trained to maintain the patient health information confidentially. Training will be documented as required by institutional policy.

Data Storage: The PI and research staff will attempt to minimize risk through only storing information containing subject identifiers in locked file storage, on password-protected computers, on encrypted servers behind an institutional firewall and according to current institutional and federal data security requirements. In addition, access to patient identifiers will be limited to the minimum number of necessary research personnel, and only to those research personnel directly involved with obtaining patient information and assigning random study identifiers. Keys containing information linking study subjects to personal identifiers will be maintained in locked storage for paper records or behind institutionally-approved firewall and electronic security measures for electronic keys, and available ONLY to the PI and research personnel directly involved in creating random study identifiers. Information containing subject personal identifiers will not be removed from MD Anderson Cancer Center without IRB approval and will not be shared in publications or reports concerning this research study.

Data Sharing: Study data will not be shared with any individuals or entities that are not involved in the study without IRB approval. No identifying information will be shared with outside collaborating sites or outside collaborating research staff without prior IRB approval and a data use or material transfer agreement has been implemented. If approval is obtained, sharing of data would be done after approval of the PI and only by secure mechanisms, as approved by MD Anderson Information Security.

Final Disposition of Study Records: These data will be used for this research study. Data that is in hard-copy form will be retained on site until the study is terminated, and may be stored indefinitely, per institutional standards, in long-term off-site storage with an MD Anderson approved, secured contract site. Electronic data will be retained indefinitely on MD Anderson servers behind the institutional firewall. Data will not be shared with any party outside of MD Anderson without IRB approval and will not be retained or disseminated for other research without prior IRB approval. Study data and paper records will not be destroyed but will be retained permanently.

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