COLUMBIA PRESBYTERIAN CANCER CENTER PROTOCOL

Revision Date:	February 5, 2008
Current Amendment:	**Amendment 4**
Administrative Change:	1
Cooperative group number:	None
NCI number:	None
Pharmaceutical sponsor:	None
Rascal IRB number:	AAAB9658
Protocol name:	**A Randomized, Phase II, Lung-Sparing Combined Modality Protocol for the Treatment of Malignant Pleural Mesothelioma: The Columbia Protocol.**
Short form:	Trimodal Lung-Sparing treatment for Pleural Mesothelioma
Phase of study:	II (Feasibility, efficacy)
Randomized?	Yes
Principal Investigator:	Robert Taub MD PhD (Medical Oncology)
Other investigators:	Joshua Sonnett, MD (Surgery) Mark Ginsburg, MD (Thoracic Surgery) Lyall Gorenstein, MD (Thoracic Surgery) Rashid Fawwaz, MD (Nuclear Medicine) Zhezhen Jin, PhD (Biostatistics)
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Outside sites:	NYPH (Columbia Campus only)

Check all that apply:

Institutional Participants:	
CPMC inpatient	**x**
CPMC outpatients	**x**
Approved for outreach use?	**no**
List other Institutions:	**none**
Target Population:	
Adults	**x**
Pediatrics	
Non-cancer patients	
Modalities:	
Surgery	**x**
Radiation Therapy	**x**
Marrow transplant	
Chemotherapy	**x**

Drugs: cisplatin, doxorubicin, pemetrexed

Radioactive Agents: Chromic Phosphate P-32 and Tc-99m sulfur colloid.

A phase II trial of trimodal treatment (pleurectomy, intrapleural chemotherapy, and conformational radiotherapy) for stage I-II resectable pleural mesothelioma.

Patient Eligibility:

See section 3.0 for details
Evaluation at the CPMC prior to study entry
Histologically confirmed malignant mesothelioma, < 20% sarcomatoid type
SWOG Performance Status 0-2
ONE PRIOR REGIMEN OF IV CHEMOTHERAPY ALLOWED
No prior pleural radiation allowed
No other active malignancy
No other serious medical/psychiatric illness
Informed consent; IRB Approval
SGOT or SGPT< 1.5 x normal
White cell count > 3,000/ul
Platelet count > 100,000/ul
BUN < 1.1 x normal
Creatinine clearance ≥ 45 ml/min
Bilirubin < 2 x normal

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1.0 INTRODUCTION

1.1 Background on Tumor

Malignant pleural mesothelioma (MPM) is a rare tumor generally associated with asbestos exposure. The annual incidence of malignant mesothelioma in the United States is approximately 3000 cases per year, of which **approximately 85% are pleural mesotheliomas**. Mesothelioma most commonly develops in the fifth to seventh decade. The incidence appears to be increasing, due to the long latency period (40 years) and the prevalence of occupational exposure to asbestos in the mid-20th century (1, 2).

The disease course is characterized by pleural effusion and tumor consolidation in the space between the visceral and parietal pleura forming a hardened, fibrotic "rind", compressing the ipsilateral lung, which, if inadequately controlled, leads to respiratory failure, pneumonia, and death (3).

1.2 Background and Rationale for New Treatment

Malignant mesothelioma is very difficult to treat. The median survival of treated patients is 9 to 18 months depending on the histology (1). Neither surgery nor radiotherapy results in increased survival; those with sarcomatous features fare worse (4).

Surgical removal of the involved pleura is the most commonly used treatment. Extrapleural pneumonectomy (EPP) is promoted as a means of achieving the most complete resection possible. EPP involves en bloc removal of the pleura (parietal and visceral), the entire ipsilateral lung, and portions of the pericardium and diaphragm. EPP carries a high operative and in-hospital mortality risk (on the order of 15%-20%). In specialized centers, the perioperative mortality rates have been reported to be less than 5% (5, 6, 7). Another surgical approach utilized is a radical pleurectomy with decortication (P/D) in which only the diseased pleura is removed while the ipsilateral lung is spared. In P/D, the parietal pleura is dissected from the endothoracic fascia and an incision is made to allow exposure and decortication of the visceral pleura. Portions of the diaphragm and pericardium are also resected with reconstruction as needed. Although this approach is technically difficult, it is better tolerated than EPP, with perioperative mortality rates less than 5% (3, 8). As a single modality, the results of aggressive surgical resections, either EPP or P/D have been disappointing, with median survivals of less than 1 year in most series (3, 5, 6, 8).

Single-modality radiation therapy has also been used for the treatment of MPM. However, because of the amount of tumor that is often present at the time of diagnosis, it is extremely difficult to deliver a tumoricidal dose of beamed radiation to the volume at risk (i.e., the entire ipsilateral pleural surface) without damaging a significant volume of the underlying lung. The results of radiation therapy alone have been disappointing and it is now used mainly for symptom palliation (9, 10).

Single-modality chemotherapy has been tried with limited success while mutli-modality chemotherapy regimens such as platinum containing regimens, doxorubicin-containing regimens, and combinations of both of these agents were tried but have shown limited response rates of 20% to 30% (11, 12). More recent studies combining raltitrexed/oxaliplatin (13),

gemcitabine/cisplatin (14), and cisplatin/pemetrexed (15) showed objective responses of up to 41%. These studies laid the groundwork for a later Phase II/III studies with cisplatin/pemetrexed. Although the median survival times reported for the initial Phase II study (i.e. 12.1 months for pemetrexed/cisplatin and 9.3 months for cisplatin alone) in chemotherapy naive patients was striking (16), this same response could not be reproduced in a larger Phase III expanded access study conducted at the Dana Farber Cancer Institute (17).

Combinations therapies, including surgical intervention (EPP or radical P/D) with intraoperative brachytherapy, intrapleural chemotherapy, postoperative radiation therapy, and/or systemic chemotherapy, have been tried to improve survival over single-modality treatment (7, 18-24). At the Dana-Farber Cancer Institute, patients with pleural mesothelioma are treated with EPP followed by postoperative chemo-radiation. With this treatment modality, this group recently reported a median survival of 19 months, with even better outcomes in certain subgroups of patients. In particular, node-negative patients with epithelial histological characteristics who had complete resection have achieved median survivals of 51 months. However, because the DFCI series only included patients capable of tolerating EPP, a built-in selection bias might be present. Moreover, unlike some other groups, the Dana-Farber staging system has been retrospective, i.e., those patients found at surgery to have incompletely resected disease are excluded from their analysis. A recent review of extant clinical trials in mesothelioma notes that there is no firm data supporting the use of either EPP or radical P/D to improve patient survival (25).

At the University of California, San Francisco (UCSF), radical P/D with adjuvant radiation therapy has been used to allow patients with a less favorable cardiopulmonary status to undergo tumor resection. In their selected series of 26 analyzed patients, 24 received intraoperative radiotherapy to mitigate the possibility of radiation pneumonitis. External beam radiation therapy was generally started 1 to 2 months after resection and delivered by means of 3-dimensional conformal radiation therapy, or with inverse treatment planning intensity-modulated radiation therapy (IMRT). When given, chemotherapy consisted of 2 to 3 cycles of cyclophosphamide, doxorubicin (Adriamycin), and cisplatin initiated 1 to 2 months after completion of radiation. At the time of data analysis, 5 of 26 patients were alive. The median follow-up was 9.7 months (range, 2-67.6 months). The median overall survival and progression-free interval from the time of the operation were 18.1 and 12.2 months, respectively. The Kaplan-Meier estimates of overall survival and freedom from progression at 1 year were 64% and 50%, respectively. The sites of failure were mostly locoregional. However, there were 4 abdominal failures and 1 contralateral lung failure (18). Because of the different techniques for staging patients, it is doubtful that EPP offers a significant survival advantage over pleurectomy/decortication.

There is general agreement that the local failure rate among patients undergoing pleurectomy/decortication needs to be addressed by more vigorous local adjuvant therapies. After pleurectomy, the entire ipsilateral lung and pleural surfaces, and often the interlobar fissures, remain at risk for involvement by persistent microscopic mesothelioma. Up until now, the entire ipsilateral hemithorax has conventionally been targeted for radiation. The dose-limiting thoracic structures are the spinal cord (45Gy), heart (45Gy), and lung (conventionally 20 Gy or less, possibly no more 8cGy total dose soon after systemic chemotherapy). If radiation therapy is used as adjuvant therapy after debulking, it would be necessary to deliver 50-54 cGy to effectively treat areas of disease. In the past, however, this

could not be accomplished without critical damage to surrounding structures. Gupta et al. evaluated pleurectomy/decortication (P/D) and adjuvant radiotherapy (RT) in the treatment of MPM in a retrospective review of 123 patients at Memorial Sloan Kettering hospital from 1974 to 2003. (26) When indicated, patients received intraoperative brachytherapy to residual tumor. All 123 patients received external beam RT (median dose, 42.5 Gy; range, 7.2-67.8 Gy) to the ipsilateral hemithorax postoperatively. Fifty-four patients underwent brachytherapy (matched peripheral dose, 160 Gy). The median and 2-year overall survival for all patients was 13.5 months (range, 1-199 months) and 23%, respectively. One-year actuarial local control for all patients was 42%. Multivariate analysis for overall survival revealed radiation dose <40 Gy ($p = 0.001$), non-epithelioid histology ($p = 0.002$), left-sided disease ($p = 0.01$), and the use of an implant ($p = 0.02$) to be unfavorable. Two patients (1.6%) died from Grade 4 toxicity within 1 month of treatment. They concluded that pleurectomy/decortication with adjuvant radiotherapy is not an effective treatment option for patients with MPM. These results imply that residual disease cannot be eradicated with external RT, with or without brachytherapy, and that more extensive surgery followed by external RT might be required to improve local control and overall survival. Thus, by default, extrapleural pneumonectomy has been the procedure of choice if multimodality treatment is given because it allows high (>5000 rads) doses of radiation to be administered to the remaining parietal pleura after a large component of potentially neoplastic tissue (visceral pleura, diaphragmatic surface, interlobar pulmonary fissures) has been removed. Recent advances in IMRT make it theoretically possible to selectively, and reproducibly, irradiate the entire pleural surface of a single hemi-thorax, albeit at a suboptimal dose. Although this maneuver partially addresses this problem, in practice the local failure rate remains high (20) and this method cannot be used if an ipsilateral lung is in place.

The above considerations have prompted us to reexamine the possibility of administering radiation in combination with intrapleural chemotherapy so as to achieve tumoricidal adjuvant treatment doses, while sparing the ipsilateral and contralateral lung parenchyma and adjacent critical organs. One possible technique for selectively irradiating pleural surfaces uses intrapleural colloidal P32 chromic phosphate, a beta-emitter with an average and maximum effective tissue penetration of 1.4 to 3 mm and 8mm, respectively (27). This technique has been used in children in combination with external beam whole lung radiation, to successfully sterilize the pleura after spillage of sarcoma cells into the pleural cavity during resection (22). The treatment was tolerated without side effects, other than a layer of stable fibrosis which developed around the entire pleural surface over the ensuing months. We recently used this technique to irradiate a patient with mesothelioma who wished a lung-sparing operation, but who desired intense combined chemotherapy/radiation full-dose adjuvant treatment. No unanticipated untoward effects were observed.

Single modality systemic adjuvant chemotherapy given perioperatively to patients with malignant mesothelioma has been disappointing. Intrapleural chemotherapy or biotherapy (28) offers the possibility of exposing tumor tissue to very high concentrations of active agents, with less systemic toxicity, with possible improvement in results.

Both normothermic and heated cisplatin (29) and oxaliplatin (30) have been given intraperitoneally, and both have shown significant antitumor activity and acceptable safety profiles. Furthermore, these drugs are demonstrably tumoricidal. Intraperitoneal cisplatin, alternating with intraperitoneal doxorubicin and interferon, followed in selected cases by whole

abdominal radiation, has been the cornerstone of our program of multimodality treatment of peritoneal mesothelioma over a seven year period. In our first such prospective group of twenty seven patients, we reported a median survival of 78 months and complete pathologic responses verified by second-look laparotomy in 10 patients (31).

Encouraged by these results, and with the knowledge that normothermic or heated platinum compounds are now being used for intrapleural treatment of mesothelioma elsewhere, we would like to test the feasibility and effectiveness of a randomized, intensive multimodal treatment plan in selected patients with locally treatable mesothelioma. One of the questions we wish to answer in this randomized trial is whether the addition of systemic chemotherapy will lengthen the progression free survival rate and impact the overall survival of patients with malignant mesothelioma. This regimen would employ two treatment arms. Patients entered into arm A and B will all undergo: thoracoscopic placement of intrapleural catheters/ports with intraoperative chemotherapy immediately following port placement; repeated intrapleural chemotherapy with doxorubicin and cisplatin (weeks 1, 2, 4, 5, 7, and 8); intrapleural P32 radiotherapy (when feasible); and repeat intraoperative chemotherapy at the time of catheter removal. In addition, those patients enrolled in arm A will receive three additional systemic chemotherapy treatments with Cisplatin and Alimta (pemetrexed) during weeks 3, 6, and 9. At this time, all patients may elect to undergo additional surgery (extrapleural pneumonectomy or radical pleurectomy/decortication) with or without intensity-modulated external beam radiotherapy (for EPP patients only). Following completion of surgery or radiation therapy, patients will initiate a course of systemic Cisplatin and Alimta (pemetrexed) chemotherapy in the out-patient treatment center. Each patient's subsequent treatment will build upon concepts which have proven successful in treating our peritoneal mesothelioma patients.

2.0 OBJECTIVES

2.1 Primary Objective:

2.1.1 The primary objective of the study is to determine the overall 1-year survival rate of the two combined arms.

2.2 Secondary Objectives:

2.2.1 To assess the overall toxicity of neoadjuvant multimodal therapy

2.2.2 To compare documented toxicities with or without the addition of systemic chemotherapy (weeks 3, 6 & 9).

2.2.3 To determine if the addition of systemic chemotherapy to a neoadjuvant muti-modal regimen will have any impact on the 8 or 12 month progression free survival rate and overall survival among patients with pleural mesothelioma

3.0 ELIGIBILITY CRITERIA

Patients must fulfill the following criteria:

3.1 *Histologically confirmed* malignant mesothelioma, < 20% sarcomatoid type

3.2 No radiographic or other imaging evidence of Stage IV (cardiac, mediastinal, peritoneal, other distant) disease.

3.3 Ineligible for other high priority national or institutional study.

3.4 Age >18 years [to physiologic 75 years].

3.5 Life expectancy > 3 months.

3.6 Performance status, PS 0-2 [Karnofsky Performance Status, KPS=70-100 %].

3.7 Prior therapy allowed (one prior systemic regimen) meeting the following parameters.
3.7.1 No prior chest radiation therapy within 6 weeks of treatment
3.7.2. No prior chemotherapy regimens within four weeks of treatment
3.7.3 No prior pemetrexed.

3.8 Non pregnant, non-lactating. (serum HCG test will be performed in patients in whom there is a possibility of pregnancy.)

3.9 Required initial laboratory data/clinical parameters (see also Sec. 8.0)
White cell count: >3000/ul.
Platelet count: >100,000/ul.
Creatinine clearance: ≥ 45 ml/min
Bilirubin: < 2 x ULN
SGOT or SGPT: < 2 x ULN

3.10 *Informed Consent:* Each patient must be completely aware of the nature of his/her disease process and must willingly give consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts.

3.11 No prior malignancy within last 5 years (other than curatively treated carcinoma in-situ of the cervix or skin cancer) the measurable lesion must be histologically proven mesothelioma.

3.10 *No serious medical or psychiatric illness* preventing informed consent or intensive treatment (e.g., serious infection, congestive heart failure, angina pectoris, cardiac arrhythmia(s), or uncontrolled hypertension). HIV status or other severe illnesses will be assessed using medical records.

4.0 PATIENT ENTRY AND RANDOMIZATION

4.1 **Referrals:** Referral from the consultation service may take place only with the agreement of the responsible attending physician.
4.2 **Staging:** Evaluate all areas of original disease.
4.3 **Informed Consent and Eligibility Assessment:** document in patient's medical record informed consent discussion and any specific information regarding eligibility.
4.3 **Randomization:** upon documentation of patient eligibility, prior to scheduling surgery.
4.4 **Clinical Research Management Office:** provide patient information to Cancer Center by registering patient in *Velos*.

5.0 STUDY PROCEDURES/TREATMENT PLAN (ARMS A AND B)

5.1 Thoracoscopic Placement of Intrapleural Catheters and Intraoperative Perfusion of Normothermic Chemotherapy.

Enrolled, eligible patients will undergo thoracoscopy at which time two adjacent subcutaneous Mediport® access chambers will be implanted over the ipsilateral rib cage leading to anterior and posterior 12 French intrapleural drainage catheters. The anterior Mediport®//catheter is aligned vertically along pleuro-pericardial border and the posterior Mediport®/catheter is aligned horizontally along the posterior diaphragmatic border. The catheters will be placed in order to allow flow of chemotherapy throughout the pleural space and diaphragmatic sulci.

Following placement of two intrapleural catheters, the surgeon will initiate perfusion of normothermic cisplatin (20 mg) in a total volume of 200-500 ml Icodextrin (Baxter) dialysis solution.

5.2 Intrapleural Chemotherapy (Arms A + B) and Systemic Chemotherapy (Arm A).

Intrapleural chemotherapy will be administered within two weeks after surgery, if feasible, according to the schema below**.** Individual doses and intervals may be changed if deemed necessary in the judgment of the principal investigator.

CHEMOTHERAPY EVALUATION DURING TREATMENT:

CBC with differential count and platelets, as well as comprehensive metabolic panel will be done weekly; drug doses will be adjusted as necessary, as per details in dose-adjustment section.

Creatinine Clearance: The standard Cockcroft and Gault formula or the measured glomerular filtration rate (GFR) using the appropriate radiolabeled method (51-CrEDTA or Tc99m-DTPA) must be used to calculate CrCl for enrollment or dosing. The same method used at baseline should be used throughout the study. No dosage adjustment is needed in patients with creatinine clearance $\geq$ 45 mL/min. To date, an insufficient number of patients have been studied with creatinine clearance < 45 mL/min to give a dose recommendation. Therefore, cisplatin should not be administered to patients whose creatinine clearance is <45 mL/min.

CONCOMITANT MEDICATIONS:

Vitamin Supplementation: In order to assure that the addition of folic acid and vitamin B-12 does not interfere with the overall evaluation of response, all patients will receive the following dietary supplementation:

Folic Acid: 350-1,000 micrograms PO/PEG 5-7 days prior to the first dose of pemetrexed, daily during therapy, and continuing for 21 days after last pemetrexed dose.

Vitamin B12: 1000 micrograms IM 1 week prior to the 1st dose of pemetrexed & every 3 cycles (9 weeks) thereafter.

WEEK 1: First intrapleural dose (day 1-4 after initial thoracoscopy)

The pleural space will first be imaged by CT scan after intrapleural injection of 50-100 ml of Omnipaque™ (as tolerated) into each mediport catheter (at the physician's discretion). Following this injection, the patient will be pronated, supinated, and stood upright repeatedly. After verification that the flow pattern allows for distribution of chemotherapy to cover the ipsilateral diaphragmatic surface, the posterior sulcus, and significant portion of the remaining pleural space, cisplatin (50 mg fixed dose) mixed with doxorubicin (20 mg fixed dose) in 100-200 ml of saline followed by a 10 ml saline flush will be injected into the port(s) (depending upon fluid volume remaining in the pleural space).

WEEK 2: Second Intrapleural Dose (day 8-11 after initial thoracoscopy)

A PA and lateral CXR will be obtained to assess pleural fluid. Cisplatin (50 mg fixed dose) mixed with doxorubicin (20 mg fixed dose) in 100-200 ml of saline followed by a 10 ml saline flush will be injected into the port(s) (depending upon fluid volume remaining in the pleural space).

WEEK 3: Systemic Chemotherapy (Arm A) or Rest Week (Arm B)

Arm A (systemic chemotherapy): patients will receive intravenous cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) unless otherwise contraindicated. Systemic chemotherapy treatments will not be delayed more than 1 week but can be omitted at the discretion of the investigator (without protocol violation) due to treatment related toxicities noted.

Arm B (rest period): a routine office visit with assessment of signs and symptoms.

WEEK 4: Third Intrapleural Dose (day 22-25 after initial thoracoscopy)

The pleural space will first be imaged by CT scan after intrapleural injection of 50-100 ml of Omnipaque™ (as tolerated) into each mediport catheter (at the physician's discretion). After verification that the their is uniform distribution of chemotherapy to cover the ipsilateral diaphragmatic surface, the posterior sulcus, and significant portion of the remaining pleural space, cisplatin (50 mg fixed dose) mixed with doxorubicin (20 mg fixed dose) in 100-200 ml of saline followed by a 10 ml saline flush will be injected into the port(s) (depending upon fluid volume remaining in the pleural space).

WEEK 5: Fourth Intrapleural Dose (day 29-32 after initial thoracoscopy)

A PA and lateral CXR will be obtained to assess pleural fluid. Cisplatin (50 mg fixed dose) mixed with doxorubicin (20 mg fixed dose) in 100-200 ml of saline followed by a 10 ml saline flush will be injected into the port(s) (depending upon fluid volume remaining in the pleural space).

WEEK 6: Systemic Chemotherapy (Arm A) or Rest Week (Arm B)

Arm A (systemic chemotherapy): patients will receive intravenous cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) unless otherwise contraindicated. Systemic chemotherapy treatments will not be delayed more than 1 week but can be omitted at the discretion of the investigator (without protocol violation) due to treatment related toxicities.

Arm B (rest period): a routine office visit with assessment of signs and symptoms.

WEEK 7: Fifth Intrapleural Dose (day 42-45 after initial thoracoscopy)

The pleural space will first be imaged by CT scan after intrapleural injection of 50-100 ml of Omnipaque™ (as tolerated) into each mediport catheter (at the physician's discretion). After verification that there is uniform distribution of chemotherapy to cover the ipsilateral diaphragmatic surface, the posterior sulcus, and significant portion of the remaining pleural space, cisplatin (50 mg fixed dose) mixed with doxorubicin (20 mg fixed dose) in 100-200 ml of saline followed by a 10 ml saline flush will be injected into the port(s) (depending upon fluid volume remaining in the pleural space).

WEEK 8: Sixth Intrapleural Dose (day 49-52 after initial thoracoscopy)

A PA and lateral CXR will be obtained to assess pleural fluid. Cisplatin (50 mg fixed dose) mixed with doxorubicin (20 mg fixed dose) in 100-200 ml of saline followed by a 10 ml saline flush will be injected into the port(s) (depending upon fluid volume remaining in the pleural space).

WEEK 9: Systemic Chemotherapy (Arm A) or Rest Week (Arm B)

Arm A (systemic chemotherapy): patients will receive intravenous cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) unless otherwise contraindicated. Systemic chemotherapy treatments will not be delayed more than 1 week but can be omitted at the discretion of the investigator (without protocol violation) due to treatment related toxicities.

Arm B (rest period): a routine office visit with assessment of signs and symptoms

5.3 Intrapleural Radiation Therapy

Following a 3 week rest period, after completion of their last dose of chemotherapy, all patients will undergo CT scanning to assess both the pleural space and the extent of any pleural thickening in order to determine if intrapleural radiation with P-32 is feasible.

Arm A 77-80 days after initial thoracoscopy
or,
Arm B 70-73 days post initial thoracoscopy

WEEK 11/12: Intrapleural Radiotherapy with P-32 will be given 3 weeks after last dose of chemotherapy and 11 to 12 weeks after initial thoracoscopy

Imaging with Technetium sulfur colloid (Day -1). Prior to P-32 radiation therapy, the pleural space will be imaged by nuclear scanning (gamma camera) after intrapleural injection of a total dose of 15 mCi of technetium sulfur colloid (Tc-99m colloid) divided equally into 2 mediport catheters in order to determine the pattern of localization within the pleural cavity. During this procedure, the patient will be repeatedly pronated, supinated, and stood upright to verify that the flow pattern would allows for a layered and even distribution of an inoculate over the ipsilateral diaphragmatic surface, the posterior sulcus, and a significant portion of the remaining pleural space.

Radioactive Therapy with Chromic Phosphate P-32 (Day 1). the following day, the patient will be re-imaged by both CT and nuclear scanning prior to initiating intrapleural radiation therapy. P-32 treatment will be administered utilizing 10-12 mCi of intrapleural radioactive chromic phosphate P-32 in <10 ml solution followed by a 10 ml saline flush. The aim will be to deliver a calculated dose of 6,000 rads to the exposed pleural surfaces to a tissue depth of 7-8 mm. Inability to carry out this step will not, however, remove the patient from the study.

Only one pleural cavity will be treated with P-32.

5.4 Thoracoscopic Removal of Intrapleural Catheters

Intrapleural catheters and mediports will be removed by the surgeon via thoracoscopy. Following removal of intrapleural catheters, the surgeon will initiate perfusion of normothermic cisplatin (20 mg final dose) in a total volume of 200-500 ml Icodextrin (Baxter) dialysis solution.

Following completion of the above course of intrapleural chemotherapy/P32 treatment, patients can be taken off study and followed as set forth below.

6.0 ADDITIONAL (OFF-STUDY) SURGICAL, RADIOTHERAPY, AND SYSTEMIC CHEMOTHERAPY

Eligible patients may elect to receive additional surgical treatment, external beam radiotherapy, systemic chemotherapy or a combination of these as deemed necessary or feasible by the principal investigator(s). All patients will have the option of receiving additional (systemic) chemotherapy consisting of 6 cycles of cisplatin and Alimta (pemetrexed).

6.1 Surgery (Lung Sparing Pleurectomy/Decortication)

Patients and the attending surgeon may elect to perform extrapleural pneumonectomy (EPP) with or without external beam radiation, or Lung Sparing Pleurectomy/Decortication (P/D) according to generally accepted current practice. If P/D is performed, no external beam radiation (IMRT) will be given.

6.2 Systemic Chemotherapy (cisplatin and Alimta® (pemetrexed))

Three weeks post surgical resection or radiation therapy (in the case of patients undergoing EPP) all patients may elect to initiate a course of up to six doses of conventional systemic chemotherapy consisting of intravenous cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) given in an out-patient setting every 21 days (3 weeks). Prior to initiating treatment, patients will need to be re-assessed by CT scan according to routine, standard-of-care practices.

6.3 30-day Follow-up, and Survival Assessments

Approximately 30 days post last dose of chemotherapy (+/- 14 days), the patient should be reassessed for resolution of any treatment-related toxicity which may have occurred during the course of study participation. At the physician's discretion, repeat scans may be ordered if they have not been performed or if the patient's condition has worsened.

Assessments for survival will be performed every 3 months (+/- 1 month) for the first 2 years, and then every 6 months (+/- 2 months) for the next 3 years (5 year survival endpoint for study). The coordinator will be required to review and document any additional treatments or therapies the patient may have initiated during the interval time period and the investigator's overall assessment of the patient's current disease status and overall response to each new therapeutic intervention.

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8.0 APPENDIX I: STUDY DIAGRAM