



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#: 10-011 A(4)

Rapid Gastric and Pancreas Cancer Staging Utilizing Peritoneal Lavage

MSKCC NON THERAPEUTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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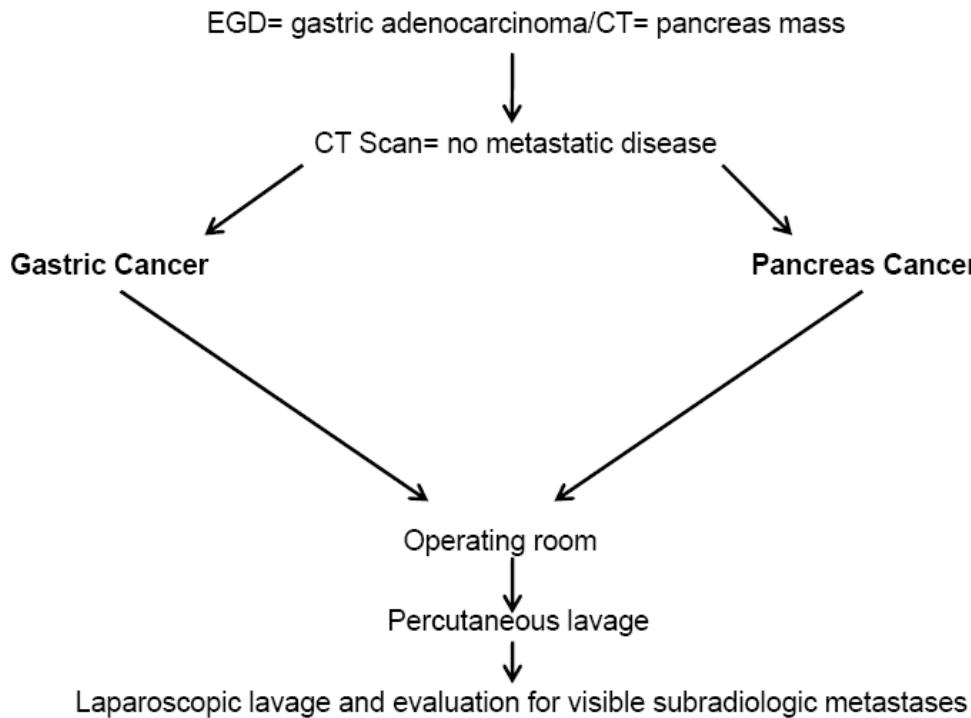
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a prospective study examining the utility of minimally invasive percutaneous peritoneal lavage for rapid gastric and pancreas cancer staging. The first aim of this study will be to evaluate whether results of percutaneous lavage are concordant with those of laparoscopically guided lavage. The secondary endpoint of this study will be to examine the safety of this technique.

Patient population: All patients with gastric or pancreatic cancer who currently undergo laparoscopic guided peritoneal lavage and cytology.

Design: Percutaneous lavage will be performed via a catheter placed over a wire prior to the standard laparoscopic lavage. The two techniques will be compared by evaluating peritoneal fluid cytology.

Time to completion: We will continue to enroll patients to meet two requirements: a total of at least 95 patients, and at least 10 gastric cancer patients with positive lavage (percutaneous or laparoscopic) and 10 pancreas cancer patients with positive lavage (percutaneous or laparoscopic) . This will likely take 18 months.



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Hypothesis: Percutaneous peritoneal lavage will yield results that are concordant with laparoscopically guided lavage.

Primary Objective: To determine if the cytology results from percutaneous peritoneal lavage are in concordance with the cytology from laparoscopically guided peritoneal lavage.

Secondary Objective: Percutaneous peritoneal lavage is a safe technique to utilize in place of laparoscopic lavage.

3.0 BACKGROUND AND RATIONALE

Peritoneal cytology has been shown to predict outcome in patients with gastric cancer in multiple studies.^{2,3,5} Although studies of outcomes in patients with pancreas cancer are not as convincing as in patients with gastric cancer, one review showed that 5% of pancreas cancer patients who were resected and had positive cytology had a significantly



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worse overall survival when compared to patients who were resected with negative

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cytology (8 months vs. 16 months $p<.001$).⁹ Currently, patients are diagnosed with gastric cancer by endoscopy and undergo endoscopic ultrasound at a subsequent visit. After ultrasound staging, patients undergo diagnostic laparoscopy with peritoneal lavage. If there is no gross disease and the lavage is negative, then patients undergo a gastrectomy (either before or after chemotherapy). Patients with pancreas cancer are diagnosed via CT scan and proceed to the operating room if the disease appears to be resectable or are offered participation in clinical trials of neoadjuvant therapy. Staging laparoscopy is frequently performed to rule out sub-radiologic metastatic disease. Given the need for improved operating room utilization, for decreased healthcare expenditure, and possibility of decreasing time to treatment, we hypothesize that rapid staging can be performed with percutaneous peritoneal lavage. This protocol will evaluate the equivalence of percutaneous and laparoscopically guided lavage. It will also determine the safety of using a percutaneous technique. The results from this study will serve as preliminary data to utilize percutaneous lavage at the time of EUS or in a monitored setting outside of the operating room. This could change standard practice patterns. In the future, patients with gastric or pancreas cancer could undergo percutaneous washings at the time of EUS. If the lavage is positive, those patients would avoid laparoscopy and could proceed directly to palliative treatment. If the lavage is negative, patients would go to the OR for laparoscopy and resection at the same setting if no gross disease is identified.

Background and Significance:

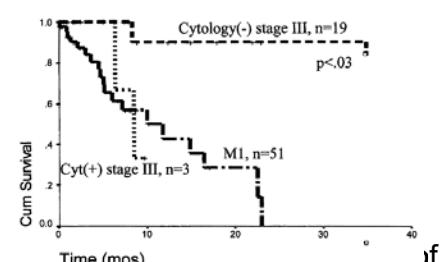
Gastric cancer

Locoregional recurrences are common following curative resection of gastric cancer. D'Angelica et al reported on patterns of recurrence among 1172 patients who underwent gastric resections⁸. Of the 42% patients who recurred, 26% recurred locoregionally; 16% were distant and locoregional, 14% were peritoneal only, and 9% were locoregional only. Since intraabdominal recurrence is a common site for metastatic spread of gastric cancer, peritoneal lavage has been utilized at the time of diagnostic laparoscopy to assist in identifying patients with microscopic peritoneal disease.

Several studies have shown that laparoscopy can be used to identify patients with gastric cancer who have

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radiographically occult metastatic disease. Brennan reported on 111 patients who were candidates for resection where 32/103 were found to have M1 disease at the time of laparoscopy; 72% of M1 disease involved the abdominal peritoneum³. Burke showed that 33/127 patients (26%) who were candidates for resection had positive cytology². Overall, 3 of the 33 resected patients who were stage III had positive cytology. In Burke's study, survival was significantly worse than those with cytology negative stage III disease. Of the 51 patients with M1 disease on laparoscopy 30 had positive cytology (59%). With macroscopic M1 disease, 73% of patients had positive cytology in all quadrants (Figure 1).

Badgwell looked at 381 patients with gastric or GE junction tumors that were thought to be resectable, who underwent diagnostic laparoscopy and lavage prior to neoadjuvant chemo. Survival was dramatically inferior in the patients with positive cytology. (Figure 2).¹ Twenty two percent of patients were found to have peritoneal mets on laparoscopy, 13% had positive lavage with no peritoneal disease, and 75% had negative lavage. There was no significant difference between median overall survival in patients with positive peritoneal cytology and no visible metastatic disease and patients with gross metastatic disease (11.6 months vs. 10. months, p=.06) (Figure 3).

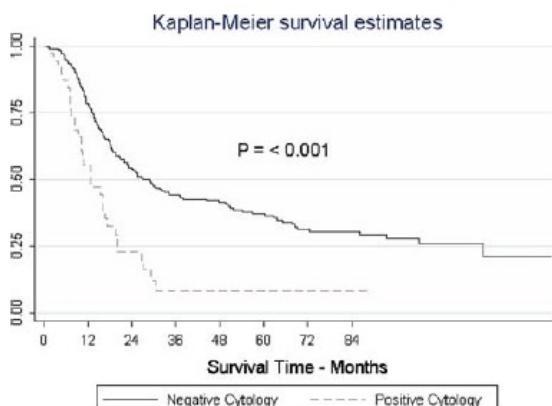


Figure 2

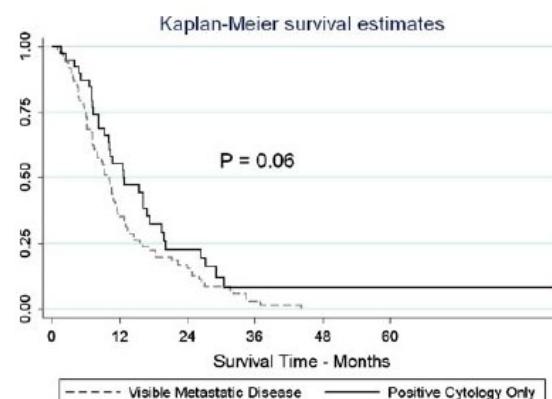


Figure 3

A third study examining the impact of peritoneal cytology on survival was by Bentrem. In this study of curatively resected patients, 19/181 with preoperative T3 or T4 disease had positive cytology without macroscopic M1 disease.³ Cytology status was the strongest independent preoperative predictor of survival with a 15 month median survival for patients with positive cytology compared to a 99 month median survival in patients with negative cytology.

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The importance of identifying patients with M1 disease is that these patients are treated with chemotherapy instead of resection. There are randomized trials that have shown response rates between 49 and 56% with the ECF regimen for patients with locally advanced gastric cancer.¹⁰ Cunningham reported the results of the MAGIC trial in the NEJM in 2006.⁷ They found that for patients with resectable gastric or GE junction adenocarcinoma neoadjuvant epirubicin, cisplatin, and fluorouracil improved survival. In both the MAGIC trial and INT 0116 trial, overall 5-year survival for all resected patients was less than 30%, despite improvements with neoadjuvant chemotherapy and radiation therapy.¹⁸ One way to improve surgical outcome is to operate on a more select population, which is where staging with peritoneal lavage is useful. Yonemura treated 61 patients with neoadjuvant intraperitoneal and systemic chemo in patients with peritoneal disease.²⁴ Of the 39 patients with positive cytology at the beginning of treatment, only 17 patients had positive lavage at the completion of treatment. Another regimen described by Brenner in a phase II trial is neoadjuvant cisplatin-5FU with postoperative IP floxuridine/leucovorin for T2N1 or T3-4 disease.⁴

Pancreatic cancer

Approximately 20-30% of patients with radiologically resectable disease pancreas cancer have M1 disease identified on laparoscopy.⁶ Ferrone looked at 462 patients who had radiographically resectable pancreas cancer and underwent diagnostic laparoscopy and cytology.⁹ Overall positive cytology rate was 17% and it was reported most frequently in the setting of macroscopic peritoneal disease. In pancreas cancer, the data correlating cytology results to survival are not as convincing as it is in gastric cancer, although current AJCC Staging characterizes patients with positive peritoneal cytology as Stage IV. Yamada examined 157 patients who had curative resections and found that in resected patients the median survival was equal between patients with positive and negative cytology (13.6 and 13.5 months).²³

Ferrone found that positive cytology did not significantly predict median survival in patients with locally advanced or distant metastatic disease. However, among patients undergoing pancreatic resection, the 5% of patients with positive cytology had a significantly worse overall survival when compared to patients who were resected with negative cytology (8 vs. 16

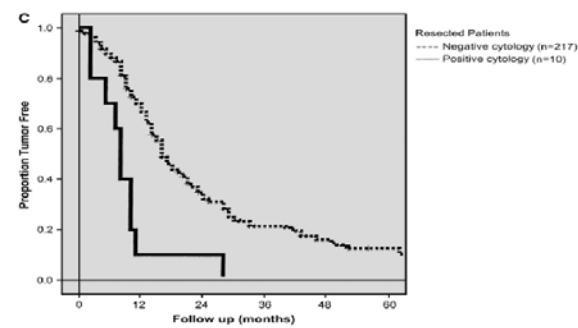


Figure 4



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months, $p < .001$). It is this group of patients that would benefit from earlier less invasive diagnosis of positive peritoneal cytology.

Percutaneous peritoneal lavage is well established in trauma

This protocol aims to assess the utility of percutaneous peritoneal lavage to obtain the specimens. Percutaneous peritoneal lavage has been performed for many years in the trauma setting. While originally done with a surgical cutdown to the fascia with direct insertion of the lavage catheter, percutaneous techniques have been validated. Saunders prospectively randomized 176 blunt trauma patients requiring diagnostic peritoneal lavage (DPL) to open vs. percutaneous DPL with Veress needles and a 9Fr catheter.¹⁹ He reported a shorter (2.73 minutes) procedure with the percutaneous procedure, no false-negatives, 1 false positive in each group, and 11% of percutaneous DPLs had <200mL return of the 1000mL instilled. Cue randomized 327 blunt trauma patient to open vs. percutaneous DPL and reported equal results between the two groups.²⁰ Hodgson performed a meta-analysis and found percutaneous and open had similar accuracy and complications.¹² Nagy reported a .8% complication rate, which was similar between the open and percutaneous group in a series with over 2500 DPLs.²²

Summary

Laparoscopy has proven to be a useful method of staging patients with gastric and pancreas cancer by identifying subradiologic M1 disease not apparent on preoperative imaging tests. Peritoneal lavage further increases the yield of clinically occult stage IV disease by identifying patients with clinically significant positive cytology^{2,3,5}. The majority of patients with gross peritoneal disease visualized by laparoscopy have positive cytology. In addition, there is a subset of patients with no visible disease who have positive lavage. Both populations behave in a similar fashion, consistent with M1 disease.

Our long-term goal is to make gastric and pancreas cancer staging more efficient. Currently, lavage is performed at the time of diagnostic laparoscopy or resection. If lavage is positive, patients are treated with chemotherapy and may be reevaluated for resection after completion of their treatment regimen. We hypothesize that peritoneal lavage using the diagnostic peritoneal lavage technique will be concordant to laparoscopically guided lavage. This technique has been studied intensively in evaluating trauma patients, and has been shown to be both safe and

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accurate. In the future, utilizing ambulatory lavage at the time of endoscopic ultrasound will assist in rapidly staging patients and avoiding unnecessary laparoscopy. If percutaneous lavage at the time of EUS is negative, patients will go to the operating room with the definitive plan of laparoscopy to rule out gross M1 disease and resection. Ten to 30% of these patients should have positive lavage. This is based on results from 3 papers:

- Burke⁵: 26% of all potentially resectable patients + cytology
- Bentrem³: 10% of T3/T4 patients without visible disease +cytology
- Badgwell²: 15% of potentially resectable patients with no visible M1 disease had + cytology; of the 22% with visible M1 disease, 50% of them had positive cytology

This project is innovative because it will adapt a procedure that has effectively been used in trauma surgery to detect gastric and pancreas cancer cells present in peritoneal lavages. This study fits into the overall research goals of the department of surgery at MSKCC because it will develop a diagnostic tool that is minimally invasive and can be used in the CIGI suite when it is established.

Future Directions

This protocol is important because if it proves that percutaneous lavage is a viable staging test, it may change how patients with gastric and pancreatic cancer are staged. It could enable patients to undergo more efficient complete staging in one-step with EGD/EUS and peritoneal evaluation. Although not part of the present proposal, it should allow the technique to be used in a monitored setting, with anesthesia personnel present and pre-procedure labs evaluated. The percutaneous lavage will be performed after the EUS, in order to avoid distorting the EUS imaging.

In gastric cancer, among patients felt to be resectable by noninvasive imaging, laparoscopy will identify 20-30% of patients with M1 disease. Of this 20-30% of patients, 75% will have positive cytology. If positive cytology is identified by lavage, then it would avoid laparoscopy in 15-22% of patients felt to be operable based on imaging. Similar to patients with gastric cancer, approximately 20-30% of patients with radiologically resectable pancreas cancer have M1 disease identified on laparoscopy. Of this 20-30%, 50% of these patients will have positive cytology, so 10-15% of patients felt to be operable based on imaging will have positive cytology

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and avoid laparoscopy. An algorithm as to how this procedure can change clinical practice in the future is:

EGD = adenocarcinoma of stomach

or CT scan suspicious for adenoca pancreas



Noninvasive imaging = no metastatic disease



Percutaneous Lavage +



Chemo

Percutaneous Lavage -



OR for diagnostic laparoscopy



Chemo



Chemo/Resection

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Patients with gastric cancer or pancreatic cancer who require diagnostic laparoscopy will be identified and offered enrollment in this trial. If they consent, they would undergo a percutaneous lavage for cytology in the OR, followed by immediate laparoscopy for cytology. The concordance



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rate between percutaneous lavage and laparoscopic lavage will be determined. The trial will continue until at least 95 patients and 20 patients with positive lavage are accrued. At least 10 patients with positive cytology from either gastric or pancreas cancer will be required so that there are enough data on each disease to show equivalence. It is highly unlikely that concordance will be disease specific, as theoretically there is no difference between sampling fluid with a laparoscopic suction device or a catheter inserted directly into the abdomen. The significance of positive cells may differ between the two diseases, but the technical diagnosis of cancer cells in peritoneal fluid is the same between the two diseases. Pancreas and gastric cancer patients are included together in this study, because it is testing a technique that is not cancer specific, and patients with both diseases potentially benefit from this technique in the future. It is estimated that approximately 50% of patients accrued for the study will have gastric cancer and 50% pancreas cancer. Ten to 30% of these patients should have positive lavage. Excess lavage fluid may be retained for potential future use under IRB #00-032.

The percutaneous lavage cytology results will be compared to those of traditional laparoscopically directed lavage. If the results of the percutaneous lavage are positive more often than laparoscopically guided, it is theoretically possible that the percutaneous lavage diluted the laparoscopic lavage or removed the only positive cells in the peritoneum. This event is extremely unlikely, as when one laparoscopic lavage is positive, generally all specimens are positive. For clinical decision making, it does not matter where the positive cells come from or by what method they are detected: any positive cells, from any quadrant or obtained with any method, represents a positive lavage. With this protocol, a finding of positive percutaneous lavage and negative laparoscopic lavage will be treated as a positive lavage for clinical decision making, and the patient will be referred for appropriate therapy. This provides patients with the appropriate clinical treatment, because positive cells obtained via percutaneous or laparoscopic lavage fluid all represent the same tumor biology, and it does not matter what method of introducing and extracting this fluid from the abdomen is used. For the purposes of experimental design in this study comparing percutaneous to laparoscopic lavage in this study, if the percutaneous method is positive and the laparoscopic lavage is negative, this will be treated as a "false positive." Thus, in the hypothetical situation, which we believe is a theoretical but unlikely possibility, where a patient who has a positive percutaneous lavage with a negative laparoscopic lavage:

1. Clinically, patients will be treated with whatever regimen is considered appropriate for a patient with a positive lavage



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2. Experimentally, for this study comparing percutaneous and laparoscopic lavage, this patient will be labelled as having a “false positive” test, as in this study attempting to prove equivalence between two techniques, laparoscopic lavage will be considered the true positive.

The presence of any positive cells will define a patient as positive, regardless of the number of positive cells.

Secondary objective:

The safety of using percutaneous lavage will be evaluated as a secondary objective. This will entail an examination and reporting of all potential complications related to using the percutaneous catheter.

The protocol will be suspended and reviewed if:

- Four serious adverse events occur (as described in 8.0).
- After the first 16 positive laparoscopic lavages, 13 or less of the percutaneous lavages are positive.

4.2 Intervention

Diagnostic peritoneal lavage will be performed at the time of laparoscopy utilizing a Veress needle/Seldinger technique to insert a peritoneal dialysis catheter. This is not a new technique. The Veress needle will be inserted in the abdominal wall, at a site to be left up to the individual surgeon. Caudal traction will be applied to the abdominal wall to provide a firm abdominal wall to insert the needle through, minimizing the peritoneum from tenting down closer to visceral structures. Intraperitoneal placement of the catheter will be confirmed by injection of saline into the needle with no resistance and with the saline in the hub of the needle falling into the peritoneal cavity spontaneously. Three passes with the needle will be allowed, after which an unconfirmed needle placement will cause cessation of the procedure. Patients who have a failed lavage will not be included in the 95 patients required for the study, but will be documented as a failed lavage, and this number will be reported with the final study results. A guide wire will be placed through the Veress and utilizing the Seldinger technique, a 9Fr peritoneal catheter will be placed.

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800cc of saline will be infused and 60ml will be extracted and sent to the cytopathology lab. When the laparoscope is inserted for laparoscopic guided lavage, no additional fluid will be instilled, unless there is no available fluid in the RUQ, LUQ, and pelvic locations that are currently sampled. Instead, the fluid already present from the percutaneous lavage will be utilized. In this protocol, several steps will be taken to avoid and identify potential complications. The percutaneous catheter will be left in place so that during laparoscopy the location of the catheter can be noted. A laparoscope will be inserted immediately after performance of the DPL, so any intraabdominal complication will be identified immediately at the time of the procedure.

5.0 CRITERIA FOR SUBJECT ELIGIBILITY

5.1 Subject Inclusion Criteria

- Men and women 18 years of age and older
- Informed consent in keeping with the policies of Memorial Sloan-Kettering Cancer Center
- Presentation of gastric or pancreatic cancer based on objective findings by either:
 - CT scan
 - Endoscopy
 - Pathologic examination
- Candidate for surgical treatment and are scheduled for laparoscopy with peritoneal lavage.

5.2 Subject Exclusion Criteria

- Under 18 years of age
- Inability to speak or read English, and an appropriate translator is not identifiable
- Unable or unwilling to give informed consent
- Patients with synchronous cancers of other abdominal organs
- Multiple prior surgical procedures on the abdomen where the surgeon feels that percutaneous lavage may be dangerous.



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6.0 RECRUITMENT PLAN

Subjects will be recruited by surgeons in the Gastric and Mixed Tumor or Hepatopancreatobiliary Services performing diagnostic laparoscopic lavage for gastric or pancreatic cancer. This will include women and minorities who are undergoing these procedures.

7.0 ASSESSMENT/EVALUATION PLAN

The pathology lab at MSKCC will perform cytology on both of the specimens.

8.0 TOXICITIES/SIDE EFFECTS

Serious adverse events with using a Veress needle include bowel injury, major omental injury, and major abdominal vessel or anterior abdominal wall vessel injury. In a Cochrane review of laparoscopic entry techniques, incidence of bowel perforation with all types of laparoscopic entry techniques was 1.8/1,000 cases, and abdominal bleeding episodes were reported at .9/1,000 cases.¹ These rates reflect injuries that are caused generally by periumbilical entry. There were no significant differences in rate of injury between Veress needle entry or the direct cut-down technique. In this protocol, several steps will be taken to avoid and identify potential complications. Caudal traction on the abdominal wall helps prevent the peritoneum from collapsing near visceral organs. In addition, a laparoscope will be inserted immediately after performance of the DPL, so any intraabdominal complication will be identified immediately at the time of the procedure. Failed entry will also be documented as part of the second aim of the protocol, but is not considered an adverse event unless there is morbidity associated with it (e.g. bowel injury).

9.0 PRIMARY OUTCOMES

The pathology lab at MSKCC will perform cytology to compare percutaneous and laparoscopic lavage results.

10.0 CRITERIA FOR REMOVAL FROM STUDY

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- Patients will be removed from the study upon the patient's request, or if the patient is found to be ineligible for the protocol as designated in the section on criteria for subject eligibility.
- In addition, patients can be removed from the study if there are unexpected complications from the percutaneous lavage.

11.0 BIOSTATISTICS

The primary objective is to determine if percutaneous lavage and laparoscopically guided lavage are concordant in terms of diagnosing intraperitoneal metastases. The outcome of the lavage tests examined for each patient will be binary: positive or negative (suspicious cytology will be treated as positive, consistent with current practice). We will test the null hypothesis that the concordance is at least 80% using a two-stage design distinguishing between 80% and 90% with Type I and Type II errors of 10%. 80% was chosen as a reasonable percentage, because in the future, the percutaneous lavage will be used at the time of endoscopy, and if it is falsely negative, patients will proceed to laparoscopy as is the current practice, and will be afforded all appropriate treatment options. We will enroll 37 patients at the first stage and stop the trial if in 30 or less patients the percutaneous and laparoscopically guided lavage are concordant. Given the small sample size, there will be no requisite number of positive patients in this interim analysis group. If at least 31 concordances are observed out of the 37 patients in the first stage, we will enroll 58 more patients (for a total of 95). We will continue to enroll patients to meet two requirements: a total of at least 95 patients, and at least 10 patients with positive lavage and gastric cancer and 10 patients with positive lavage and pancreas cancer. If the two tests agree in 80 or more patients out of 95, we will recommend percutaneous lavage for further study.

	Laparoscopic Positive	Laparoscopic Negative
Percutaneous Positive	A	C
Percutaneous Negative	D	B

A+B (concordant tests) must be greater than 80% of total number of patients.

A+B+C concordance must be >90%

D must be <10%

The protocol will be suspended if:

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- After the first 16 positive laparoscopic lavages, 13 or less of the percutaneous lavages are positive.

Cytology is the key test, as that is the test that is utilized for clinical decisions, and equivalence will be defined as similar cytological results between the percutaneous and laparoscopic lavage groups.

The secondary objective is to determine the safety of the patients undergoing percutaneous lavage. This will be reported with a 95% confidence interval. Safety will be measured as number of bowel injury, major omental injury, or major abdominal vessel or anterior abdominal wall vessel injury.

Limitations:

There is a very small risk that instilling fluid percutaneously prior to conventional laparoscopically guided lavage will dilute the laparoscopic lavage and artificially improve the results of percutaneous lavage. Given that 800cc will be instilled and less than 60cc will be withdrawn for the percutaneous portion, any residual fluid in the LUQ will be utilized for the LUQ laparoscopic lavage. It is likely that no additional fluid will have to be instilled into the abdomen, but if there is not enough fluid left over from the percutaneous lavage, then additional fluid will be instilled laparoscopically. If the laparoscopic lavage is negative and the percutaneous lavage is positive, it is possible this discrepancy is due to a dilutional effect, and this will be treated as a "false positive" result. Clinically, this indicates that percutaneous lavage can identify disease when present, and the positive result will be used to initiate appropriate systemic treatment. This is the same as having lavage positive in one quadrant and all other quadrants negative. It does not matter where the positive cells come from or by what method they are detected. Any positive cells, from any quadrant or obtained with any method, represent positive lavage clinically.

Another limitation is that visual disease will not be identified. Currently, patients undergo staging laparoscopy and lavage, so both visual and microscopic disease is identified. In this protocol, since percutaneous and laparoscopic lavage are both performed at the same setting, this remains unchanged. If this protocol proves that percutaneous and laparoscopic lavage are equivalent with regard to cytology status, and the next study examines utilizing percutaneous lavage at the time of EUS, visible disease would be missed in cases with positive peritoneal cytology. As discussed in the background data, this is the point of peritoneal cytology – positive cytology is equivalent to

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M1 disease; those patients with positive cytology by percutaneous lavage proceed to palliative chemotherapy without the need for laparoscopy. Those patients with negative cytology will undergo routine staging laparoscopy to rule out visible sub-radiologic disease, and either proceed to immediate resection, or go on to appropriate neoadjuvant therapy. In the presence of negative cytology but visible sub-radiologic disease, appropriate palliative treatment will be offered. Finally, patients who have a failed lavage will not be included in the 95 patients required for the study, but will be documented as a failed lavage, and this number will be reported with the final study results.

12.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

12.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

12.2 Randomization

This study does not involve randomization.

13.0 DATA MANAGEMENT ISSUES

All data will be collected by an RSA. A CRDB database will be created on a password locked server at MSKCC for access to the data limited to the study coordinators. It is estimated that this study will accrue approximately 95 to 115 patients over an 18 month period.

13.1 Quality Assurance

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Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

13.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: <http://cancertrials.nci.nih.gov/researchers/dsm/index.html>. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:

http://mskweb5.mskcc.org/intranet/_assets/_tables/content/359709/DSMPlans07.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be



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addressed and the monitoring procedures will be established at the time of protocol activation.

14.0 PROTECTION OF HUMAN SUBJECTS

The study is voluntary, and there are no benefits to the individual patient, other than possibly advancing the level of knowledge about future rapid staging tests. Privacy and confidentiality will be ensured by utilizing a password protected database on a secure server at MSKCC. All patient data will be protected by HIPAA regulations. There is no cost to the patient for participation in this study. It will take place at the same time that the patient is already undergoing the diagnostic exam with the scope. The patient will not be paid for taking part in this study.

The possible complications include:

Likely

- Mild discomfort at the needle insertion site. The tube used is similar in size to a large intravenous line like the one that gets placed in veins in the arm.

Less Likely

- There is a chance that putting fluid in with this study will dilute the traditional laparoscopic lavage and falsely make the laparoscopic lavage negative. If this happens, a positive result from the percutaneous test will be considered overall positive.

Rare but serious

- Bowel injury. We know from large research studies that the risk of injuring the bowels is about 0.18%.
- Major abdominal vessel or abdominal wall vessel injury. We know from large research studies that the risk of these injuries is about 0.09%
- If there is a serious bowel injury or major abdominal vessel injury that is not recognized, or that can not be repaired, there also is a very small risk of death.

Protection of human subjects from the above complications will include preoperative evaluation by anesthesia, preoperative laboratories, placement of the percutaneous catheter into a site to be selected by the operating surgeon to minimize visceral injury, caudal traction on the skin to increase abdominal wall tension to minimize underlying visceral injury, and laparoscopy

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immediately after percutaneous lavage to check the location of the catheter and for the presence of any underlying visceral injury. All patients will be monitored after the procedure in the PACU for possible complications.

14.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

14.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org containing the following information:

:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
 - A explanation of how the AE was handled

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- A description of the subject's condition
- Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

14.2.1

None applicable.

15.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

16.0 REFERENCES

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17.0 APPENDICES

None

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