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Intraperitoneal Chemotherapy For The Treatment Of Malignant Peritoneal Mesothelioma

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Intraperitoneal Chemotherapy for the Treatment of Malignant Peritoneal Mesothelioma

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Our treatment protocol for malignant peritoneal mesothelioma (MPM) includes initial cytoreductive surgery with heated intraperitoneal chemotherapy (HIPEC), outpatient catheter-administered intraperitoneal chemotherapy (CAIPEC), and a second cytoreductive surgery with HIPEC. We hypothesized that even distribution of CAIPEC would correlate with better overall survival and fewer side effects; that the pharmacokinetics of HIPEC would be influenced by body surface area (BSA); and that tissue penetration of CAIPEC would exceed that of HIPEC due to the longer dwell time.

We analyzed CT peritoneograms from 38 MPM patients undergoing cisplatin CAIPEC for volume and surface area, and modeled overall survival and post-treatment glomerular filtration rate (GFR) with these as predictors. We collected intraoperative blood and peritoneal fluid samples from 10 patients undergoing oxaliplatin HIPEC, used mass spectrometry to determine fluid platinum levels and modeled these outcomes with BSA as a predictor. We collected intraoperative peritoneal tissue samples from 6 patients undergoing HIPEC and used x-ray fluorescence microscopy to characterize tissue platinum levels.

Decreased mortality was associated with larger surface areas ($p=0.02$) and smaller volumes of CAIPEC ($p=0.03$), controlling for age, sex, histologic subtype, and residual disease >0.5cm. Larger volumes were associated with higher post-treatment GFR, controlling for pre-treatment GFR, BSA, surface area and BSA-volume interaction ($p=0.02$). Higher BSA was associated with lower plasma oxaliplatin ($p=0.01$), and greater pharmacokinetic advantage ($p=0.02$). Tissue platinum was highest at second surgery post-HIPEC, lowest at first surgery post-HIPEC, and intermediate at second surgery pre-HIPEC.

CT peritoneography provides parameters associated with overall survival and post-treatment GFR in MPM patients undergoing CAIPEC. In HIPEC patients who receive a BSA-based oxaliplatin dose and carrier fluid volume titrated to achieve a desired flow rate, BSA is a predictor of systemic drug exposure. The direct tissue penetration depth of platinum attributable to multiple courses of CAIPEC is greater, and the tissue distribution of platinum more homogeneous, than that attributable to a single dose of HIPEC.

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Table of Contents

I. Introduction

Biodistribution of Intraperitoneal Chemotherapy……....1

Modalities of Intraperitoneal Chemotherapy Administration……..4

Indications for Intraperitoneal Chemotherapy…….7

Clinical Results of Intraperitoneal Chemotherapy for Malignant Peritoneal Mesothelioma……....10

II. Hypothesis and Aims…….……...15

III. Methods

Patients…….17

Plasma and Peritoneal Perfusate Platinum Content…….……18

Peritoneal Tissue Platinum Content…….……19

Peritoneaogram Imaging and Computer-Aided Volume and Surface Area Quantification…….20

Statistical Analysis……22

IV. Results

Quantitative CT Peritoneography…….……24

HIPEC Pharmacokinetics…….32

Tissue Penetration of Intraperitoneal Platinum Drugs…….39

V. Discussion

Quantiative CT Peritoneography……..46

HIPEC Pharmacokinetics…….49

Tissue Penetration of Intraperitoneal Platinum Drugs…….….51

VI. References…….……54

I. Introduction

Biodistribution of Intraperitoneal Chemotherapy

Intraperitoneal (IP) administration of chemotherapy has been used to treat peritoneal surface-spreading malignancies in order to maximize local concentrations while minimizing systemic toxicities. This rationale is supported by pharmacokinetic studies describing the "pharmacokinetic advantage" of IP administration of various drugs: the ratio of intraperitoneal to intravascular drug distribution, expressed either in peak concentration or area under the concentration-time curve (AUC).(1-13) The peak and AUC pharmacokinetic advantages of several commonly-used agents are listed in Table 1.

Intraperitoneal chemotherapy is instilled in a carrier fluid, which in most cases is normal saline or lactated Ringer's solution. The major exception is oxaliplatin, which, due to its instability in chloride-containing solutions, is frequently diluted in 5% dextrose. (14) As in intravenous chemotherapy, the dose of chemotherapy during IP chemotherapy is usually calculated based on body surface area (BSA).(15) Some institutions dilute the drug in a standard volume of carrier fluid, some calculate carrier fluid volume based on BSA, and some titrate carrier fluid volume to achieve a desired flow rate during hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC).(15-17) As a result, there is variability between patients in the concentration of oxaliplatin in the perfusate. Likewise, the duration of chemoperfusion has not been standardized; perfusion times range from 30 minutes to 2 hours.(15, 18)

Table 1. Pharmacokinetic advantage associated with intraperitoneal delivery of selected antineoplastic agents.

Drug	**Peak intraperitoneal to intravascular drug ratio**	**AUC intraperitoneal to intravascular drug ratio**
Carboplatin	---	18
Cisplatin	20	12
Cytarabine	664	474
Doxorubicin	474	---
5-fluorouracil	298	367
Floxuridin	---	1000
Melphalan	93	65
Methotrexate	92	---
Mitoxantrone	---	1400
Paclitaxel	1000	1000

AUC, Area under the concentration-time curve. Adapted from Markman 2007.(19)

Experimental measurements of tissue concentrations of locally-administered chemotherapy drugs compared to distance from tissue surface have been reported in tumor spheroids *in vitro*, and in IP-administration in mice and rats.(20-25) These have found the greatest drug accumulation at the tissue surface, with concentrations decreasing dramatically with distance from the tissue surface after drug dwell times ranging from 1 to 168 hours. A study of HIPEC, administered over 90 minutes to ovarian carcinoma patients, comparing antibody-based detection of DNA-cisplatin adducts in ovarian carcinoma tumor nodules versus buccal cells (as a control for systemic exposure), likewise found greater adduct formation in the tumor nodules only to a distance of 5mm from the peritoneal surface.(26)

A mathematical model estimated a direct tissue penetration distance on the order of 0.5mm for a one-time, limited-dwell IP administration of normothermic cisplatin; this distance increased to approximately 3-5mm with hyperthermic (43˚C) administration.(27) These values were based on an exponential decay of drug concentration within peritoneal tissues as a function of distance from the peritoneal surface, which is modeled to asymptotically approach the circulation drug concentration.

However, the previous studies and models concern IP administration with drug removal at a set end point, and may not be applicable to longer dwell-times, in which there is experimental evidence of greater tissue penetration and tumor drug concentration. The advantage in tumor cisplatin concentration of IP over IV administration in rats was only realized after 24 hours of dwell-time.(21) Tumor platinum concentration does not peak until at least 24 hours after IP instillation, and its ratio to plasma concentration increases

over at least the first 7 days, as drug remains in the peritoneal fluid for at least that long while it is cleared from the circulation.(22) Furthermore, for IP cisplatin and oxaliplatin after 24 hour dwell-times, platinum concentration does not appear to decay exponentially as a function of distance from the peritoneal surface, but to decrease linearly – suggesting that over longer dwell-times, the diffusion of drug from peritoneal fluid through peritoneal tissues to the systemic circulation may reach steady state.(28) Theoretically, at steady state, the concentration of drug may remain higher throughout the peritoneal tissue than the circulation, as the major obstacle to drug diffusion is the endothelial barrier.(29) For these reasons, it is important to distinguish between the biodistribution of limited-dwell versus indefinite-dwell IP chemotherapy.

Modalities of Intraperitoneal Chemotherapy Administration

Hyperthermic Intraoperative Intraperitoneal Chemotherapy (HIPEC)

Various protocols have been described for the administration of HIPEC. In general, chemotherapy is instilled intraoperatively after tumor debulking. The drug is heated to 40-43˚C and administered over 60-120 minutes, after which time it is removed from the peritoneal cavity.(30) Open, closed, and partially-closed techniques have been described, with different methods to maintain flow in order to preserve hyperthermia and to ensure even fluid distribution and maximal contact of the instilled drug with the peritoneal surfaces.(31-33) One study found dye distribution and temperature were most homogeneous using the open technique.(34) However, there is no evidence that different HIPEC techniques result in differences in survival.(35-37)

Intraoperative IP chemotherapy administration is thought to provide better fluid distribution than postoperative IP chemotherapy by avoiding postoperative adhesions and the development of preferential intraperitoneal pathways for perfusion fluid.(38) However, inflammation and vascular injury accompanying surgery may contribute to altered pharmacokinetics, and potentially decreased pharmacokinetic advantage, by increasing direct communication between the systemic circulation and the peritoneal fluid.(39, 40)

Several rationales have been advanced for hyperthermic drug administration. Hyperthermia has been shown *in vitro* to have direct cytotoxic effects, as well as to work synergistically with some chemotherapy drugs.(41-43) It has been suggested that hyperthermia contributes to greater tissue penetration of chemotherapy from the peritoneal surface.(44, 45) However, this claim appears to be based on two rat studies that are not entirely convincing. One study demonstrated higher diaphragm and tumor nodule drug concentrations with hyperthermic compared to normothermic cisplatin.(46) The other showed higher drug concentrations in some intra-abdominal organs, but not in diaphragm or abdominal wall with hyperthermic compared to normothermic doxorubicin.(47) Neither reported tissue drug concentrations compared to distance from the peritoneal surface.

It is plausible that hyperthermia causes increased tissue drug concentrations by increasing drug exposure via the circulation, rather than by increased direct tissue penetration. This mechanism is supported by preclinical and clinical data. Platinum concentrations in rat peritoneal tumors after carboplatin treatment at elevated temperatures were similar for the

IP and IV routes.(48) Patients who received IV 5-fluorouracil (5-FU) during intraoperative HIPEC with doxorubicin and mitomycin C had increased 5-FU concentrations in peritoneal fluid and tumor nodules compared to plasma, suggesting augmented communication with the circulation.(49) Inflammation and vascular injury accompanying surgery may also contribute to increased communication with the circulation as compared to non-intraoperative outpatient IP chemotherapy.(39, 40)

Catheter-Administered Intraperitoneal Chemotherapy (CAIPEC)

Outpatient administration of IP chemotherapy is accomplished through surgically-placed IP catheters. Catheter placement is usually done at the time of laparotomy for disease resection.(50) Interventional radiology and laparoscopic IP catheter placement techniques have also been described.(51, 52)

Following the placement of IP catheters, in the early post-operative and/or late post-operative period, room-temperature chemotherapy is infused through the IP catheters and allowed to dwell indefinitely in the peritoneal space. A comparison of the pharmacokinetics of HIPEC vs. CAIPEC in a small cohort of patients receiving both suggested that the total intraperitoneal drug exposure and the pharmacokinetic advantage over the course of perfusion was greater for CAIPEC than for HIPEC.(53) Furthermore, the indefinite dwell time, as compared to the removal of drug at the end of HIPEC, allows for even greater total intraperitoneal drug exposure. This may help explain why survival in a rat colon cancer model was increased with early post-operative CAIPEC compared to HIPEC.(54) To date, no human or animal studies have reported the peritoneal tissue

distribution of IP drug following multiple cycles of CAIPEC, such as is recommended for peritoneal carcinomatosis of ovarian origin.(55)

X-ray computed tomography (CT) peritoneography has previously been used in patients receiving catheter-administered IP chemotherapy to assess for catheter failure and infusate maldistribution.(56-60) However, no standard system has been established to assess infusate distribution, and outcomes data from patients assessed with CT peritoneography has not been reported. Radiologic response to IP chemotherapy was reported in a series of 11 ovarian carcinoma patients stratified into 3 categories by distribution of intraperitoneal Tc-99m, and was suggestive of better response in patients with free-flowing infusate than in those with loculation, but overall survival was not reported.(61)

Indications for Intraperitoneal Chemotherapy

Pseudomyxoma Peritonei

Pseudomyxoma Peritonei (PMP) is a rare disease characterized by mucinous ascites with peritoneal surface spread, most often of appendiceal mucinous neoplasms.(62) Historically, patients would often undergo repeated interval debulking surgeries and sometimes chemotherapy for symptomatic relief, as the disease and symptomatic ascites would invariable recur with transition to more aggressive histologic characterisitcs at repeat surgeries.(63, 64)

The current standard of care for PMP is cytoreductive surgery with HIPEC.(65) No randomized controlled trials or comparative studies have been performed to date to assess

the efficacy of cytoreductive surgery with HIPEC for PMP. However, a multicenter retrospective analysis showed marked improvement in survival and recurrence compared to historical controls.(66)

Peritoneal Carcinomatosis of Gastrointestinal Origin

Approximately 10% of colorectal cancer (CRC) patients present with peritoneal carcinomatosis (PC) at the time of diagnosis, and 25% of patients develop PC at recurrence; after liver recurrence, peritoneal surface spread is the most common site for tumor recurrence in CRC.(67, 68) Likewise, PC may be present in 5% to 20% of patients undergoing potentially curative resection of gastric cancer.(69) The prognosis in these cases is generally dismal, as median survival with 5-fluorouracil-based systemic chemotherapy is between 6 and 16 months.(67, 70, 71)

Several experienced groups now recommend HIPEC for PC of gastrointestinal origin.(72-75) These recommendations are supported by one randomized controlled study in CRC, one randomized controlled study in gastric cancer, and a number of case-control and single-arm studies.(76-79)

Advanced Ovarian Carcinoma

Ovarian carcinoma is the leading cause of death from gynecologic malignancies in the U.S.(80) The high rate of mortality is in part attributable to the large proportion of ovarian carcinomas, up to 89%, that are advanced (Stage III or Stage IV) at the time of diagnosis, including those that have spread over peritoneal surfaces.(81)

The strongest support for the use of CAIPEC is in the treatment of advanced ovarian carcinoma; meta-analysis in a recent Cochrane review showed increased overall and disease-free survival for patients treated with IP chemotherapy.(82) Despite this evidence, many advanced ovarian carcinoma patients who might benefit from IP chemotherapy are not offered it, largely depending on physician experience and preferences. Physician perceptions of IP chemotherapy are shaped in part by beliefs about biodistribution of IP chemotherapy, some of which are based on incomplete evidence. One article criticized IP chemotherapy for advanced ovarian cancer, stating, "It is well known that the higher tumor concentration observed with the i.p. administration of cisplatin only reaches to a depth of 1–2 mm."(83) This conjecture (which was unsupported in that manuscript by any references), may have been based on a study of HIPEC in humans, a study of IP cisplatin dwelling for 7 days in rats, and theoretical calculations.(21, 26, 27) None of these studies directly address the recommended regimen for advanced ovarian carcinoma, six 3-week cycles of platinum-based intraperitoneal chemotherapy.(55)

Less data is available to support the use of HIPEC in advanced ovarian carcinoma, although results from some non-randomized studies support its use, and it is a subject of ongoing investigation.(84-88)

Malignant Peritoneal Mesothelioma

Malignant mesothelioma is a rare, seldom-curable tumor of the pleura or the peritoneum whose origin has generally been linked to asbestos exposure.(89) Several experienced groups recommend HIPEC as part of the standard of care for malignant peritoneal mesothelioma (MPM).(30, 90-93) While no head-to-head trials have been performed,

overall and progression-free survival in reported HIPEC series compares favorably with those of systemic chemotherapy for MPM.(94-96)

Clinical Results of Intraperitoneal Chemotherapy for Malignant Peritoneal Mesothelioma

Three large series of MPM patients (two single-institution series and one multi-institution report, including patient series from 8 institutions, some of which had been previously reported) have been identified (Table 2). Several factors were noted to predict better progression-free and overall survival in these patients; these prognostic factors are summarized in Table 3.

Table 2. Intraperitoneal chemotherapy series for malignant peritoneal mesothelioma.

Investigator, year	**Institution**	**Chemotherapy Modality, drug, *n***	**Median Survival**	**1-year survival**	**3-year survival**	**5-year survival**
Alexander , 2003 (94)	NIH	Intraoperative HIPEC, Cisplatin, 49				
		Postoperative 5-FU and Paclitaxel, 35				
		Total, 49	92 months	86%	59%	59%

Sugarbaker, 2009 (96)	Multiple	Intraoperative HIPEC, Cisplatin and Doxorubicin, 311				
		Intraoperative HIPEC, Cisplatin and Mitomycin C, 14				
		Intraoperative HIPEC, Cisplatin, 19				
		Intraoperative HIPEC, Mitomycin C, 26				
		Intraoperative HIPEC, Other, 2				
		Postoperative, Cisplatin and Doxorubicin, 16				
		Postoperative, Paclitaxel, 77				
		Postoperative, Other, 1				
		Total, 405	53 months	81%	60%	47%

Chabot (95)	Columbia University	Outpatient Gemcitabine, Cisplatin, Doxorubicin, Interferon				
		Outpatient Cisplatin, Doxorubicin, Interferon				
		Intraoperative HIPEC, Cisplatin and Mitomycin, 39				
		Total, 39	55 months	80.9%	61.7%	48.9%

Table 3. Statistically-significant prognostic factors.

Investigator	**Prognostic Factor**	**Analysis**	**P-value**
Alexander (94)	Age ≤ 60	Cox: Overall survival	0.034
Sugarbaker (96)	Age ≤ 50	Univariate: Overall survival	0.003
Sugarbaker (96)	Female sex	Univariate: Overall survival	<0.001
Alexander (94)	No deep invasion	Cox: Overall survival Cox: Progression-free survival	0.041 0.003
Alexander (94)	Residual disease <1 cm	Cox: Overall survival	0.032
Sugarbaker (96)	Cytoreduction score	Univariate: Overall survival	<0.001
Sugarbaker (96)	Epithelioid histology	Univariate: Overall survival	0.003
Chabot (95)	Epithelioid histology	Univariate: Overall survival	<0.001
Sugarbaker (96)	No lymph node metastasis	Univariate: Overall survival	0.008
Sugarbaker (96)	No extra-abdominal metastasis	Univariate: Overall survival	0.013

Our protocol for the treatment of MPM includes initial debulking surgery with HIPEC (41°C over 1 hour, after which drug is removed), then 6 cycles of CAIPEC (room temperature, indefinite dwell-time), and a second debulking surgery with HIPEC (Dr. Robert Taub, personal communication). This allowed us to obtain tissue samples from patients during the initial surgery immediately after their first HIPEC, and during the second surgery before HIPEC (but after 6 cycles of CAIPEC) and immediately after HIPEC.

Initial debulking surgery prior to IP chemotherapy is performed with a goal of removing all tumor nodules greater than 0.5 cm in depth or plaques greater than 0.5 cm in diameter, as residual disease greater than 0.5 cm has been associated with adverse outcomes, in peritoneal carcinomatosis in general and MPM in particular.(94, 96, 97) As a standard assessment of catheter function and infusate distribution, many of these patients underwent CT peritoneography.(98)

II. Hypothesis and Aims

Our overall goals were to better characterize the sequence of events that are theorized to lead from the pharmacokinetic advantage associated with intraperitoneal chemotherapy (i.e. high local drug concentrations with lower systemic concentrations), to improved local cytotoxicity with decreased systemic side effects, to better disease control and therefore better survival. We used pharmacokinetic, radiologic and clinical parameters to measure these purported effects.

In a previous study, the absorption of oxaliplatin during HIPEC was associated with body mass index (BMI).(16) We sought to confirm or disconfirm and extend these results in order to determine whether the dosing of intraperitoneal chemotherapy on the basis of BSA, as is standard in most institutions, resulted in equivalent or predictably disparate pharmacokinetic parameters for patients of various sizes, as measured by BMI or BSA. We investigated this question in patients undergoing HIPEC with oxaliplatin for MPM and other diseases.

The direct tissue penetration of platinum-based chemotherapy drugs has previously been reported in *in vitro* and animal models, with treatment durations up to 1 week.(20-23, 25, 81) A study of tissue penetration of cisplatin in patients undergoing HIPEC used antibody-detection of cisplatin-DNA adducts rather than direct imaging of the drug.(26) None of these adequately address the tissue penetration of multiple cycles of CAIPEC over the course of several months, as is used clinically. We sought to compare the depth of direct tissue penetration of platinum-based chemotherapy drugs in HIPEC versus CAIPEC in patients treated with both for MPM using direct imaging of tissue platinum.

Finally, we sought to determine whether distribution of CAIPEC, as measured by quantitative CT peritoneograms, were associated with overall survival and/or complications as manifested by post-treatment GFR in patients treated with cisplatin-based IP chemotherapy, a regimen known for its side effect profile including nephrotoxicity.

III. Methods

Patients

Retrospective chart review identified 38 patients who underwent CT peritoneography while receiving IP chemotherapy between February 2000 and August 2011. Baseline characteristics of the 38 patients are reported in Table 4.

Table 4. Baseline characteristics of peritoneogram cohort.

Characteristic	**Patients (*N*=38)**
Female sex – number [%]	19 [50%]
Age in years – median [range]	61 [21-83]
Body Surface Area in m^2 – mean [SD]	1.92 [0.25]
Histologic subtype – number [%]	
Epithelioid	34 [89%]
Biphasic	4 [11%]
Residual disease >0.5 cm – number [%]	10 [26%]

On an IRB approved protocol and with informed consent, peritoneal fluid and blood samples were collected during closed-technique HIPEC in 10 patients receiving oxaliplatin for pseudomyxoma peritonei (n=5), malignant peritoneal mesothelioma (n=4), or peritoneal carcinomatosis from colon cancer (n=1), and 7 patients receiving cisplatin

for malignant peritoneal mesothelioma. Patients received a BSA-based oxaliplatin dose of 250 mg/m^2 in 5% dextrose carrier fluid or cisplatin dose of 100 mg/m^2 in 0.9% saline, titrated to achieve a flow rate of 1 L/min over a 60-minute chemoperfusion. Blood glucose was recorded for 24 hours following HIPEC for patients receiving oxaliplatin. Peritoneal cancer index (PCI) and completeness of cytoreduction (CC) scores were determined for all patients.(99, 100)

On an IRB-approved protocol, we collected peritoneal tissue and contemporaneous blood samples from 6 MPM patients receiving cisplatin or oxaliplatin HIPEC at first (n=2; both cisplatin) or second surgery (n=4; 2 cisplatin and 2 oxaliplatin). All second surgery patients had received intraperitoneal cisplatin as outpatients. The median age of the patients was 63 years (range 39-79). Four were male and 2 were female. Five patients had epithelioid disease and one had biphasic disease.

Plasma and Peritoneal Perfusate Platinum Content

Blood samples were collected and centrifuged, and blood plasma isolated by Joshua Leinwand and delivered to the Graziano lab for spectrophotometric analysis. Peritoneal perfusate samples were collected and centrifuged, and the supernatant isolated by Joshua Leinwand and delivered to the Graziano lab for spectrophotometric analysis. In the Graziano lab, diluted plasma and peritoneal perfusate samples (in 2% HNO_3, 1% Methanol, 0.2% Triton 100-X) were analyzed for Pt concentrations using a Perkin-Elmer Elan DRC II (Perkin Elmer, Shelton, CT) Inductively Coupled Plasma Spectrophotometer (ICP-MS) equipped with an AS 93+ autosampler. The platinum concentration of calibration standards was chosen to cover the expected range of

platinum concentrations in the diluted plasma samples: 1, 5, and 10ug/L. Matrix-induced interferences were corrected using an iridium internal standard to match the mass and ionization properties of the platinum. Stock internal standard spiking solution was prepared and added to all calibrators and samples in the same concentration, 50 ng Ir per tube. After the initial instrument calibration, quality control samples (QC-plasma spiked in our laboratory and serum samples of known Pt concentration provided by Institut de Sante Publique du Quebec) were run. To control instrument drift over the period of running hours, we ran QC samples every 10-15 samples, and recalibrated if QCs didn't meet quality control criteria (± 10% of target values).

Peritoneal Tissue Platinum Content

Peritoneal tissue samples were collected intraoperatively and stored at -70˚C in frozen tissue matrix by Joshua Leinwand, and then delivered to the Borczuk lab for sectioning. In the Borczuk lab, 20-micron-thick sections of each peritoneal tissue sample were cryosectioned and deposited on Ultralene windows for x-ray fluorescence microscopy. These sections were delivered to the Miller lab. In the Miller lab, the platinum contents of the samples were imaged using x-ray fluorescence microscopy at beamline X27A at the National Synchrotron Light Source. X-ray fluorescence spectra were collected using an x-ray excitation energy of 12 keV using a Si(111) channel-cut monochromotor. The monochromatic beam was then collimated to 350 μm × 350 μm and then focused to approximately 6 μm × 10 μm using Rh-coated silicon mirrors in a Kirkpatrick-Baez (KB) geometry. The sample was placed at a 45° angle to the incident x-ray beam and x-ray fluorescence was detected with an energy dispersive, 9 element germanium array detector

(Canberra, Meriden, CT) oriented at 90° to the incident beam. The sample was approximately 6 cm from the detector. A light microscope objective (Mitutoyo, M Plan Apo 5X) was coupled to a digital CCD camera for sample viewing. Energy dispersive spectra were collected by raster scanning the sample through the x-ray beam using a dwell time of 30 s/pixel and a step size of 4 μm to provide oversampling. The intensity for platinum was quantified by integrating the area under the curve for the peak in the x-ray fluorescence spectrum (Kα = 66832.9 eV).

A semi-automated computer program developed at the National Synchrotron Light Source identified regions-of-interest (ROIs) at the area of highest x-ray fluorescence intensity at the peritoneal surface. The average platinum concentrations in these ROIs were compared to the average platinum concentrations in the entire samples. Plots of x-ray fluorescence intensity versus distance from the peritoneal surface were produced by drawing a region-of-interest polygon around each tissue sample and then summing fluorescence counts for each horizontal section as a function of vertical distance. We defined the depth of tissue penetration as the distance from the peritoneal surface at which the average tissue platinum concentration fell below the contemporaneous plasma platinum concentration.

Peritoneogram Imaging and Computer-Aided Volume and Surface Area Quantification

After injection of between 100cc and 500cc of diluted iohexol contrast into IP catheters with patients in supine or semi-Fowler position, patients underwent standard abdominopelvic CT scans. Smaller volumes of contrast were used in patients who experienced pain or pressure with injection. CT scans were performed with patients in the

supine position. Contrast-filled compartments are identifiable based on higher density than surrounding structures on CT images. An in-house segmentation algorithm was developed by the Schwartz lab in the Matlab programming language and applied to assist in calculating volumes and surface areas of the compartments in this work (Dr. Lawrence Schwartz, personal communication).

Joshua Leinwand manually selected a region-of-interest (ROI) enclosing all contrast-filled compartments on a single image. Localization followed by segmentation of each of the compartments inside the ROI were then carried out automatically by the developed algorithm. Once the segmentation was completed on an image, the result was propagated to neighboring images, with automatic segmentation of the contrast-filled compartments. This process continued iteratively until all compartments were segmented. To ensure correct results, computer-generated compartment contours were superimposed on the original images for inspection and modification as needed by Joshua Leinwand. These images were reviewed by radiologists Dr. Lawrence Schwartz and/or Dr. Saravanan Krishnamoorthy.

Once the segmentation was finalized, volumes and surface areas of the compartments were automatically calculated. The compartment volume was calculated by multiplying the total number of all compartments' voxels and the image resolutions along x- (in-plane), y- (in-plane) and z- (axial) directions. The compartment surface area was defined as the sum of the interface areas of all compartment voxel sides facing non-compartment voxels, where the area of a voxel side is calculated by multiplying the image resolutions along the two directions spanning the plane at which the voxel side resides.

The computer algorithms and a number of manual interaction functions such as selection of ROI and modification of suboptimal computer results were integrated into a user-friendly image viewing system developed with the Matlab computer language by the research group.

Statistical Analysis

For the 60 minute duration of HIPEC (samples at 10, 30 and 60 minutes) and 24 hour blood glucose levels, area under concentration-time curve (AUC) was calculated by Trapezoidal Rule, BSA determined by DuBois & Dubois formula, and pharmacokinetic advantage by (AUC[peritoneal fluid]/AUC[plasma]).(101)

All statistical analysis was performed by Joshua Leinwand using SAS Version 9.2. The LIFETEST procedure was used to produce the Kaplan-Meier survival estimates for all patients and to compare survival by volume of residual disease (>0.5cm vs. <0.5cm). In order to determine whether the presence of bulky disease was independent of peritoneogram parameters and GFR, the TTEST procedure was used to test for differences in mean surface area and volume of the contrast-filled compartment as well as pre- and post-treatment GFR between patients with residual disease >0.5cm vs. those with residual disease <0.5cm after initial tumor debulking surgery. Univariate Cox models were conducted using the PHREG procedure for survival. In addition to the surface area and volume of the contrast-filled compartment, any covariate with a *P*-value < 0.1 in the univariate analysis was selected for multivariate analysis. Overall survival was measured from IP catheter placement.

Linear regression analyses with post-treatment GFR as the outcome measure were conducted using the REG procedure. The regression models included pre-treatment GFR, BSA (since cisplatin is dosed based on BSA), the surface area and volume of the contrast-filled compartment, and two-way interactions between BSA, surface area or volume, with only statistically significant ($p<0.05$) two-way interaction terms retained in the final model. Pre- and post-treatment GFR were calculated from, respectively, the last serum creatinine measured before IP catheter placement and the first serum creatinine measured after IP catheter removal, by Cockgroft-Gault formula.(102) BSA was calculated from the height and weight at the time of IP catheter placement by Mosteller formula.(103)

Three patients underwent CT peritoneography twice. For these patients, we used the mean surface area and volume of the contrast-filled compartment from the two CT peritoneograms.

For HIPEC pharmacokinetic data, linear regression with cisplatin plasma AUC as the outcome measure and BSA as the independent variable was conducted using the REG procedure.

IV. Results

Quantitative CT Peritoneography

Examples of computer-aided peritoneogram analysis images are presented in Figure 1. Median overall survival by Kaplan-Meier analysis, pre-treatment and post-treatment GFR and computer-aided peritoneogram volume and surface area data are presented in Table 5. There were no statistically-significant differences in volume or surface area parameters between patients with residual disease >0.5cm versus those with residual disease <0.5cm after initial debulking. We therefore considered the peritoneogram parameters independent of the volume of residual disease.

We used univariate Cox models to determine which covariates to include with volume and surface area in the multivariate Cox model of overall survival. Four variables (age, sex, histologic subtype and residual disease >0.5cm) had $p<0.1$ and were included in the multivariate model. We found that, controlling for age, sex, histologic subtype and residual disease, the surface area of the contrast-filled compartment had a positive relationship with overall survival ($p=0.0201$) and the volume of the contrast-filled compartment had a negative relationship with overall survival ($p=0.0341$, Table 6). In terms of proportional hazards, controlling for the above covariates, a 1-standard-deviation increase in surface area is predicted to result in a hazard ratio of 0.222 (95% CI: 0.063 – 0.790) and a 1-standard-deviation increase in volume is predicted to result in a hazard ratio of 3.165 (95% CI: 1.090 – 9.193).

We used linear regression with post-treatment GFR as the outcome, and included pre-treatment GFR and BSA, along with volume and surface area as covariates, as well as the two-way interaction between volume and BSA (the only two-way interaction to reach statistical significance). We found that, controlling for pre-treatment GFR, BSA, surface area and the interaction between volume and BSA, the volume of the contrast-filled compartment had a statistically-significant positive relationship with post-treatment GFR ($p=0.0167$, Table 7). The interaction between volume and BSA is illustrated in Figure 2.

Table 5. Overall survival, GFR and CT peritoneography parameters.

Parameter	**Overall**	**Residual Disease <0.5 cm**	**Residual Disease >0.5 cm**	***P*-value**
Overall survival (months) – median [95% CI]	48 [11-76]	62 [47-94]	5 [1-22]	<0.0001
Pre-treatment GFR (cc/min) – mean [SD]	96.0 [35.5]	101.9 [38.5]	79.5 [17.9]	0.0872
Post-treatment GFR (cc/min) – mean [SD]	90.1 [42.6]	96.2 [46.4]	73.1 [24.1]	0.1444
Contrast-filled compartment volume (cm^3) – mean [SD]	558.4 [532.0]	582.5 [458.4]	491.0 [725.6]	0.6468
Contrast-filled compartment surface area (cm^2) – mean [SD]	1261.7 [1158.5]	1405.0 [1216.8]	860.4 [912.7]	0.2062

Patient outcomes following intraperitoneal chemotherapy and algorithm-derived peritoneogram values. GFR, glomerular filtration rate; CT, computed tomography; CI, confidence interval; SD, standard deviation.

Table 6. Univariate and Cox models with overall survival as outcome.

Covariate (Univariate model)	**Hazard Ratio**	**95% CI**	***P*-value**
Age (years)	1.038	0.998 – 1.079	0.0628
Sex (female vs. male)	0.319	0.119 – 0.858	0.0235
Body surface area (m^2)	1.160	0.179 – 7.539	0.8764
Histologic subtype (biphasic vs. epithelioid)	20.798	4.419 – 97.890	0.0001
Residual disease (>0.5cm vs. <0.5cm)	11.685	3.785 – 36.074	<0.0001
Contrast-filled compartment volume (cm^3)	1.000	0.999 – 1.001	0.3551
Contrast-filled compartment surface area (cm^2)	1.000	0.999 – 1.000	0.0907

Covariate (Multivariate model)	**Hazard Ratio**	**95% CI**	***P*-value**
Age (years)	1.060	1.002 – 1.120	0.0424
Sex (female vs. male)	1.188	0.347 – 4.066	0.7835
Histologic subtype (biphasic vs. epithelioid)	4.502	0.810 – 25.026	0.0856
Residual disease (>0.5cm vs. <0.5cm)	7.657	1.991 – 29.456	0.0031
Contrast-filled compartment volume (cm^3)	1.002	1.000 – 1.004	0.0341
Contrast-filled compartment surface area (cm^2)	0.999	0.998 – 1.000	0.0201
Overall model	---	---	<0.0001

All variables with $p<0.1$ in the univariate analysis were included in the multivariate model. Overall survival was measured from the time of intraperitoneal catheter placement. CI, confidence interval.

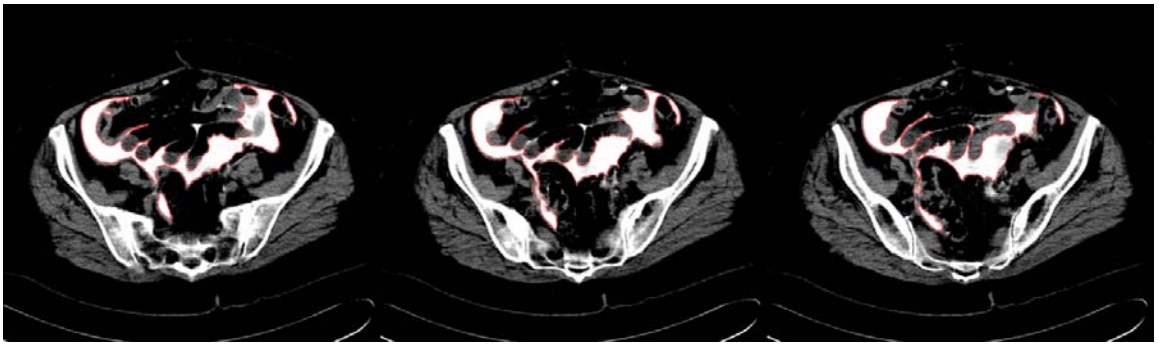
Table 7. Multiple linear regression with post-treatment GFR as outcome measure.

Covariate (Linear Regression Model)	**Estimated Regression Coefficient**	***P*-value**
Pre-treatment GFR (cc/min)	0.802	<0.0001
Body Surface Area (m^2)	69.969	0.0182
Contrast-filled compartment volume (cm^3)	0.154	0.0167
Contrast-filled compartment surface area (cm^2)	-0.003	0.5893
Interaction between volume and body surface area	-0.070	0.0260
Overall model	---	<0.0001

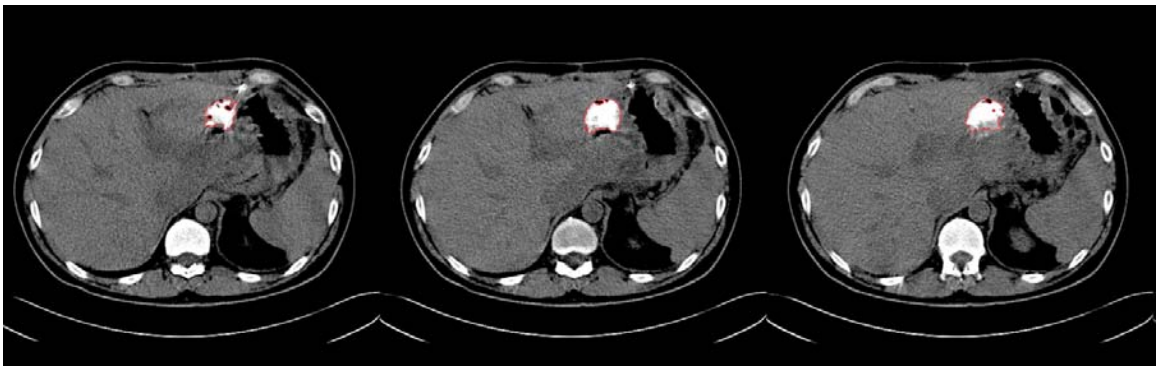
Multivariate linear regression model, including only those 2-way interactions with $p<0.05$. GFR, glomerular filtration rate.

Figure 1. Computer-aided quantitative peritoneogram images.

(a)

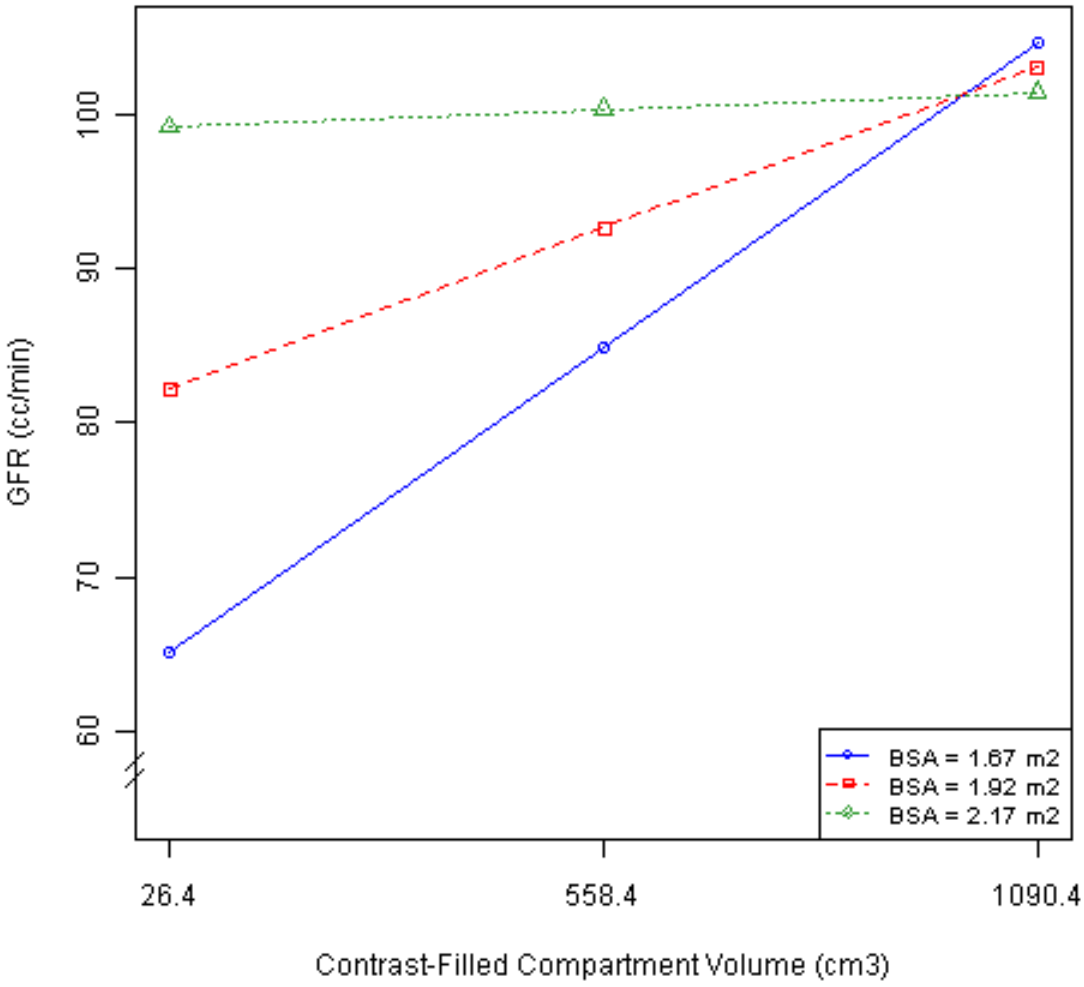


(b)



The contrast-filled compartments are outlined in red for (a) well-distributed and (b) loculated intraperitoneal contrast.

Figure 2. Predicted post-treatment glomerular filtration rate.



For a patient with a pre-treatment GFR of 100cc/min and a contrast-filled compartment surface area set at the sample mean (1262 cm^2), comparing body surface area set at the sample mean $\pm$ one standard deviation (Low, Average and High BSA) and contrast-filled compartment volume set at the sample mean $\pm$ one standard deviation (Low, Average and High Volume).

HIPEC Pharmacokinetics

Cisplatin

To validate whether the effect of BSA on post-treatment GFR was related to systemic cisplatin levels, we analyzed the relationship between BSA and cisplatin plasma AUC in 7 patients undergoing HIPEC using linear regression. We found that higher BSA was associated with lower plasma AUC during HIPEC (estimated regression coefficient = -89.7 mg•min/L/m^2, p=0.0381).

Oxaliplatin

Baseline characteristics of all patients, peritoneal cancer index and completeness of cytoreduction scores are listed in Table 8. One patient had a PCI score of 0, as he had previously undergone cytoreduction without any gross disease recurrence, and HIPEC only was performed, without any resection.

We examined perfusate volume, BSA and BMI as independent variables; of these, only perfusate volume and BSA were significantly correlated. Overall pharmacokinetic parameters and Pearson correlation coefficients with perfusate volume, BSA and BMI and as independent variables are listed in Table 9. Higher perfusate volume was associated with lower plasma oxaliplatin AUC (β = -30.7 mg•min/L^2, p=0.0170). Higher BSA was associated with lower plasma oxaliplatin AUC (β = -153.2 mg/m^2•min/L, p=0.0075), and with a greater pharmacokinetic advantage (β = 28.7 m^{-2}, p=0.0198) over the 60-minute duration of HIPEC. There were no statistically significant relationships between perfusate volume and peritoneal fluid oxaliplatin AUC or pharmacokinetic

advantage; or between BSA and peritoneal fluid oxaliplatin AUC; or between BMI and any of the pharmacokinetic parameters. The relationships between BSA and oxaliplatin pharmacokinetic parameters are depicted in Figure 3. There did not appear to be differences in pharmacokinetics based on diagnosis, extent of peritonectomy or between patients with greater or lesser burdens of disease, as measured by PCI with a cut-off of 7.

There were no statistically significant relationships between perfusate volume, BSA or BMI and 24-hour glycemia or peak intra-operative blood glucose.

Table 8. Baseline characteristics, extent of disease and surgical treatment.

ID	**Diagnosis**	**Age (years)**	**Sex**	**PCI**	**CC**	**Extent of Peritonectomy**	**Resections**	**Prior Resections**
1	Peritoneal Mesothelioma	79	M	3	0	Right diaphragm	None	Omentectomy
2	Pseudomyxoma Peritonei	65	F	5	0	Pelvis	Omentectomy, TAH-BSO	None
3	Pseudomyxoma Peritonei	57	F	4	0	Bilateral paracolic gutters	Omentectomy, TAH-BSO	None
4	Pseudomyxoma Peritonei	48	F	2	0	None	Right hemicolectomy	TAH-BSO
5	Colon Cancer	61	F	12	0	None	Right hemicolectomy, TAH-BSO	None

6	Peritoneal Mesothelioma	63	F	2	0	None	Omentectomy	None
7	Peritoneal Mesothelioma	65	M	15	0	Right paracolic gutter, Left diaphragm	Omentectomy, splenectomy	None
8	Pseudomyxoma Peritonei	25	F	6	0	Bilateral diaphragms, Bilateral paracolic gutters	None	Omentectomy, Appendectomy, Right salpingo-oophorectomy
9	Pseudomyxoma Peritonei	63	F	15	0	Bilateral diaphragms	Omentectomy, splenectomy, appendectomy, TAH-BSO	None
10	Peritoneal Mesothelioma	68	M	0	0	None	None	Omentectomy

F, Female; M, Male; PCI, Peritoneal Cancer Index score; CC, Completeness of Cytoreduction score; TAH-BSO, total abdominal hysterectomy – bilateral salpingo-oophorectomy.

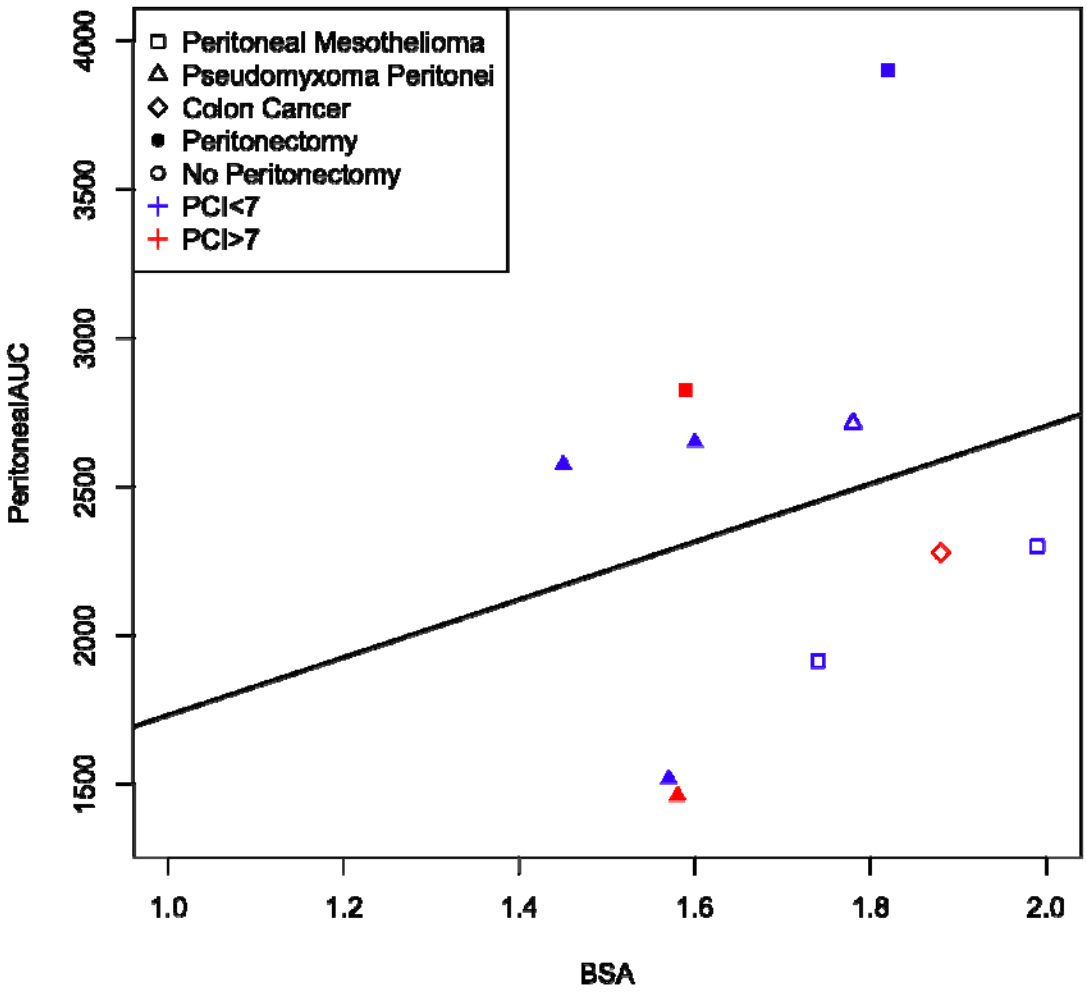
Table 9. Pharmacokinetic parameters and Pearson correlation coefficents.

	Mean [SD]	**Correlation with Perfusate Volume [P-value]**	**Correlation with BSA [P-value]**	**Correlation with BMI [P-value]**
Perfusate Volume (L)	2.7 [0.8]	---	0.788 [0.0068]	0.130 [0.7205]
BSA (m^2)	1.70 [0.17]	---	---	0.095 [0.7935]
BMI (kg/m^2)	25.8 [4.6]	---	---	---
Plasma AUC (mg•min/L)	138.1 [33.1]	-0.728 [0.0170]	-0.782 [0.0075]	-0.054 [0.8820]
Peritoneal fluid AUC (mg•min/L)	2412.9 [711.4]	0.112 [0.7590]	0.227 [0.5273]	-0.402 [0.2496]
Pharmacokinetic Advantage	18.6 [6.8]	0.587 [0.0744]	0.716 [0.0198]	-0.334 [0.3453]

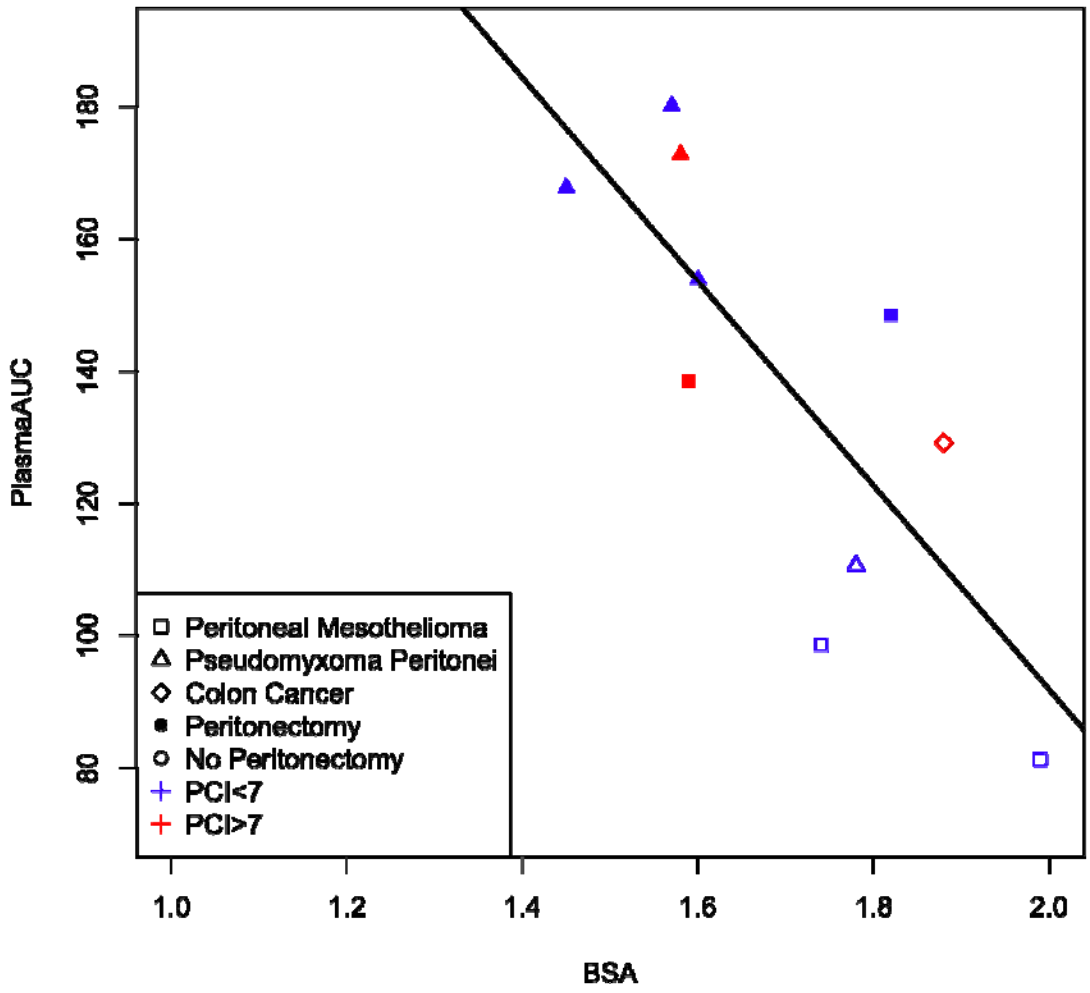
BSA, body surface area; BMI, body mass index; AUC, area under the concentration-time curve; β, estimated correlation coefficient.

Figure 3. Linear regression plots of body surface area vs. oxaliplatin pharmacokinetic parameters.

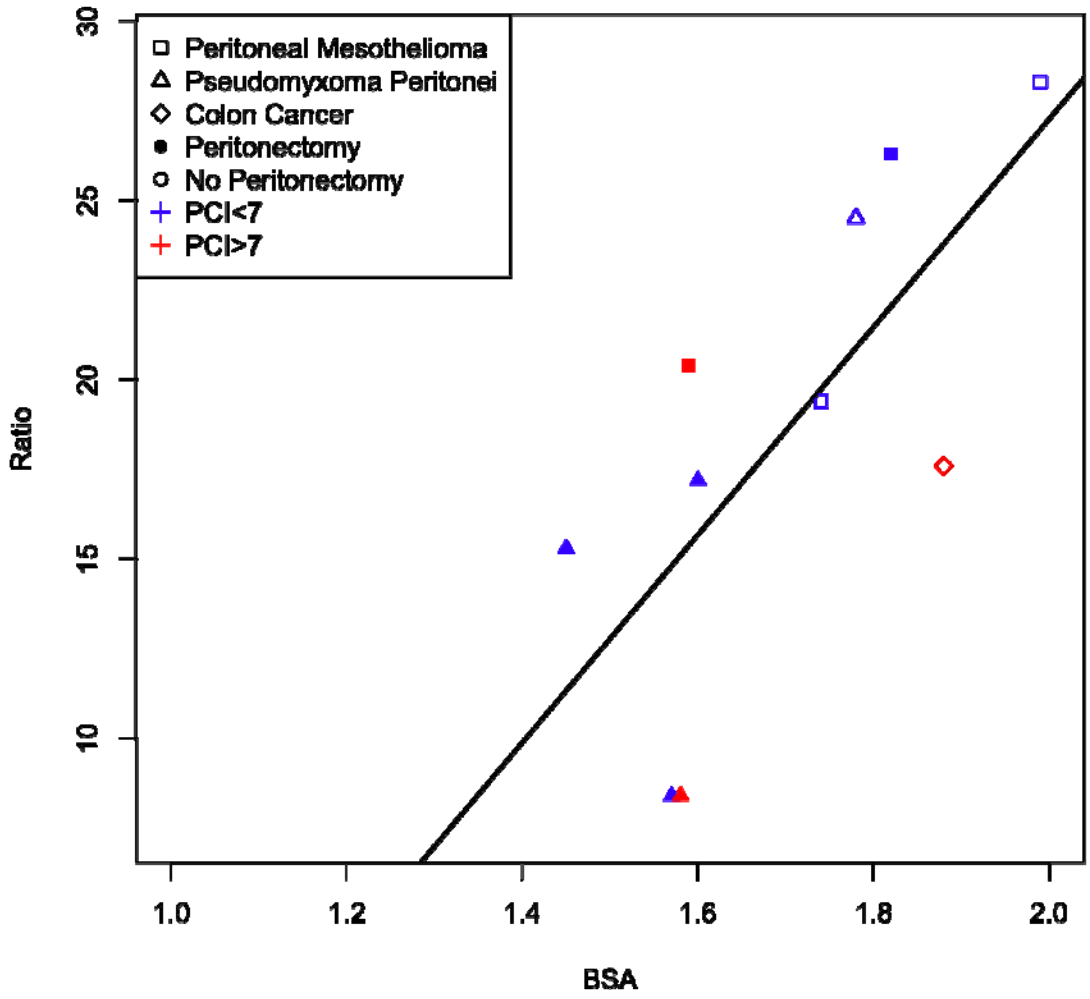
(a)



(b)


PlasmaAUC
180
160
140
120
100
80
1.0
1.2
1.4
1.6
1.8
2.0
BSA
Peritoneal Mesothelioma
Pseudomyxoma Peritonei
Colon Cancer
Peritonectomy
No Peritonectomy
PCI<7
PCI>7

(c)



BSA (m^2) vs. (a) peritoneal fluid AUC (mg•min/L) [p=0.5273], (b) plasma AUC (mg•min/L) [p=0.0075], and (c) pharmacokinetic advantage [p=0.0198].

Tissue Penetration of Intraperitoneal Platinum Drugs

Peritoneal tissue without macroscopic evidence of tumor involvement was collected from 6 patients. One patient had remaining macroscopic disease during HIPEC at first surgery; we collected post-HIPEC tissue samples of both macroscopically normal and tumor tissue from that patient. The depths of platinum penetration in those samples were similar: 1.056 mm in normal tissue versus 1.060 mm in tumor tissue. The parameters from that patient's normal tissue were used in the following analysis.

Examples of the x-ray fluorescence microscopy images obtained from one patient's samples at second surgery, both pre-HIPEC and post-HIPEC, are shown in Figure 4. Examples of the tissue and contemporaneous plasma platinum plots from that patient's second surgery, both pre-HIPEC and post-HIPEC, are shown in Figure 5. Measured overall and peritoneal surface ROI tissue platinum concentrations are shown in Table 10. Measured tissue sampling depths and platinum penetration depths are shown in Table 11.

Tissue platinum was highest from second surgeries post-HIPEC, lowest from first surgeries post-HIPEC, and intermediate from second surgeries pre-HIPEC. Every sample had higher platinum at the peritoneal surface; these were also highest from second surgeries post-HIPEC, lowest from initial surgeries post-HIPEC, and intermediate from second surgeries pre-HIPEC. The ratio of platinum concentrations in the peritoneal surface ROI versus the overall sample was lowest from second surgeries pre-HIPEC, and was similar from first surgery post-HIPEC and second surgery post-HIPEC.

The median sampling depth of peritoneal tissue was 1.55 mm (range 1.04 – 2.36). The platinum penetration depths were not reached in 7 of 10 samples, including all 4 of the second surgery pre-HIPEC samples. Both of the first surgery cisplatin post-HIPEC samples had measurable platinum penetration depths (of 0.26 mm and 1.06 mm), as did one second surgery oxaliplatin post-HIPEC sample (1.63 mm).

Table 10. Overall and peritoneal surface platinum concentrations from all enrolled patients (n=6).

Sample Time Point	**Median Pt (ppm) [range] – Entire Sample**	**Median Pt (ppm) [range] – Peritoneal Surface**	**Median Ratio [range] – Peritoneal Surface: Entire Sample**
First surgery, post-HIPEC (n=2)	5.2 [4.7 – 5.8]	11.3 [8.4 – 14.2]	2.1 [1.8 – 2.5]
Second surgery, pre-HIPEC (n=4)	16.0 [5.6 – 21.8]	25.9 [8.4 – 29.9]	1.6 [1.1 – 2.0]
Second surgery, post-HIPEC (n=4)	26.1 [2.2 – 113.4]	40.4 [4.4 – 219.7]	2.0 [1.1 – 2.5]

Pt, platinum; HIPEC, hyperthermic intraoperative intraperitoneal chemotherapy; ppm, parts per million.

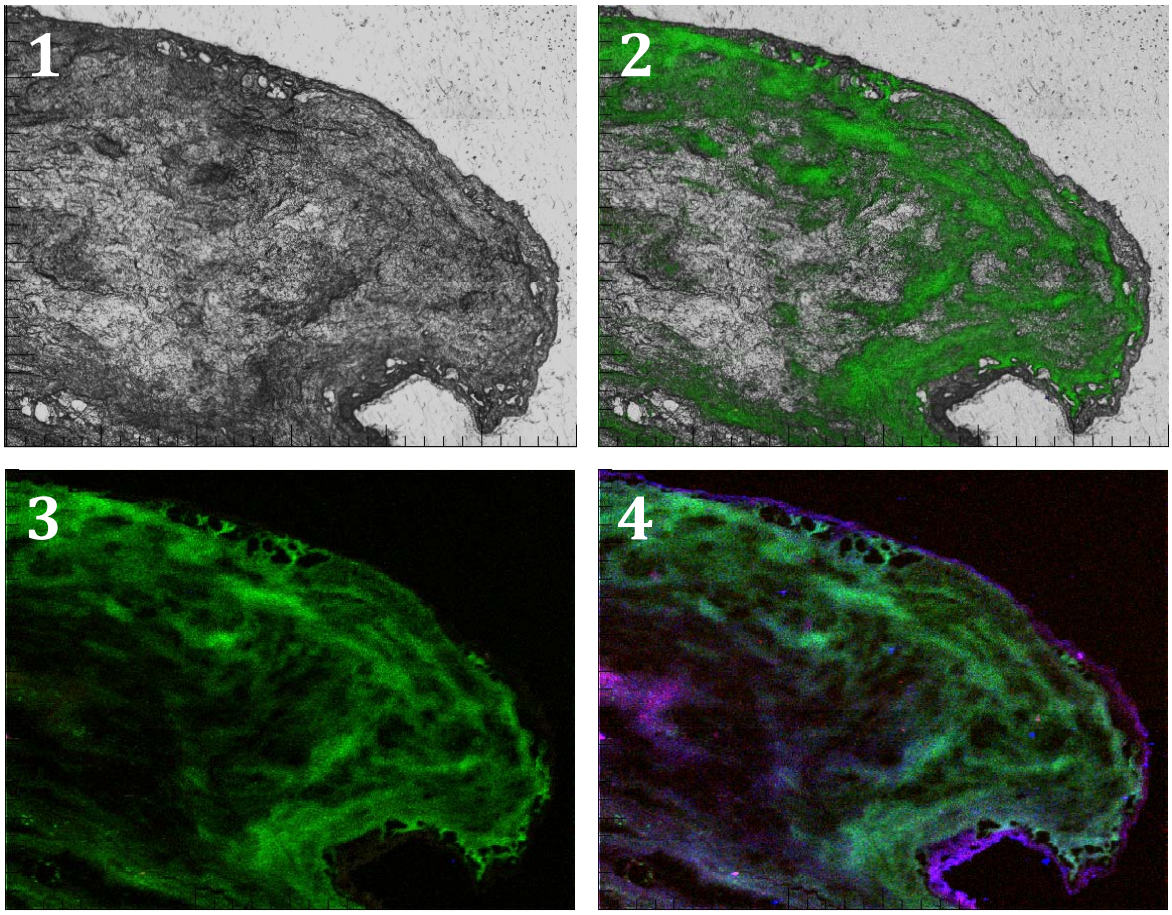
Table 11. Peritoneal tissue sampling depth and depth of platinum penetration.

	Pre-HIPEC		**Post-HIPEC**	
Drug, Surgery	**Sample Depth (mm)**	**Pt Penetration (mm)**	**Sample Depth (mm)**	**Pt Penetration (mm)**
Cisplatin, 1st	---	---	1.170	0.258
Cisplatin, 1st	---	---	1.520	1.060
Cisplatin, 2nd	1.368	Not Reached	1.038	Not Reached
Cisplatin, 2nd	1.668	Not Reached	1.572	Not Reached
Oxaliplatin, 2nd	1.818	Not Reached	1.224	Not Reached
Oxaliplatin, 2nd	2.214	Not Reached	2.358	1.632

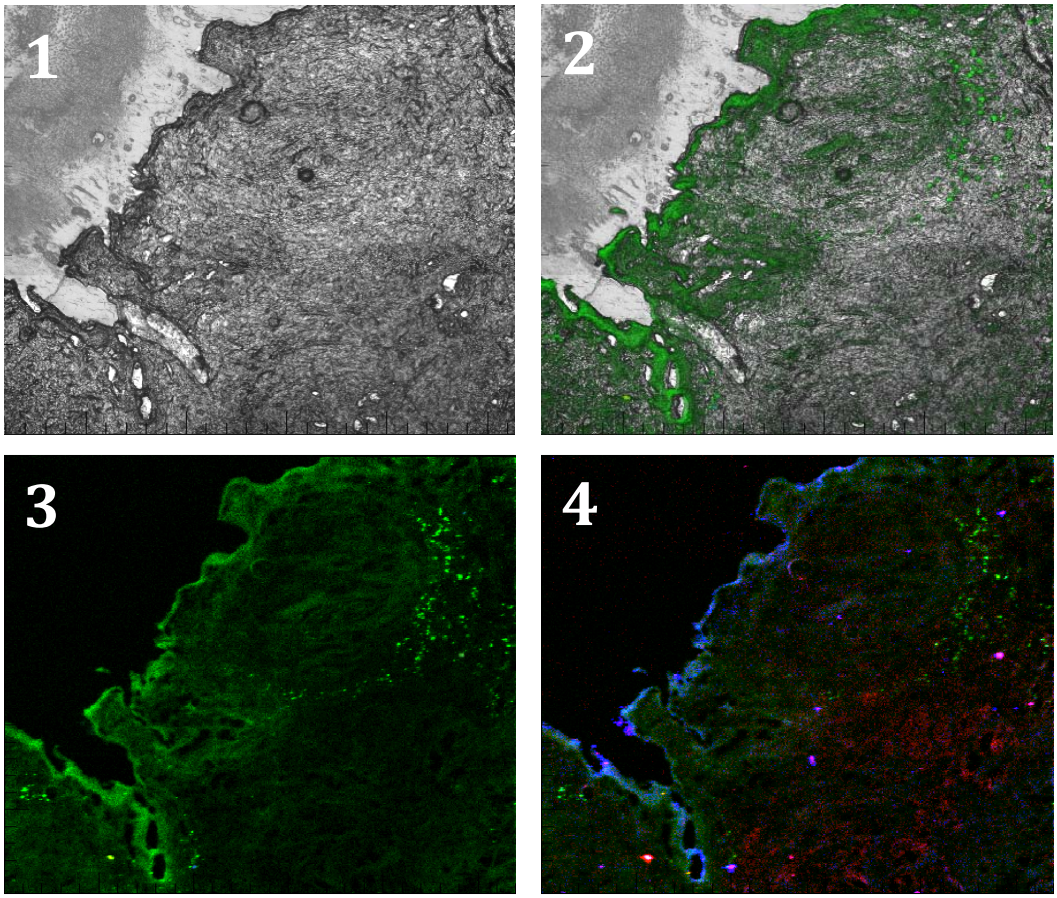
Pt, platinum; HIPEC, hyperthermic intraoperative intraperitoneal chemotherapy

Figure 4. X-ray fluorescence microscopy images.

(a)



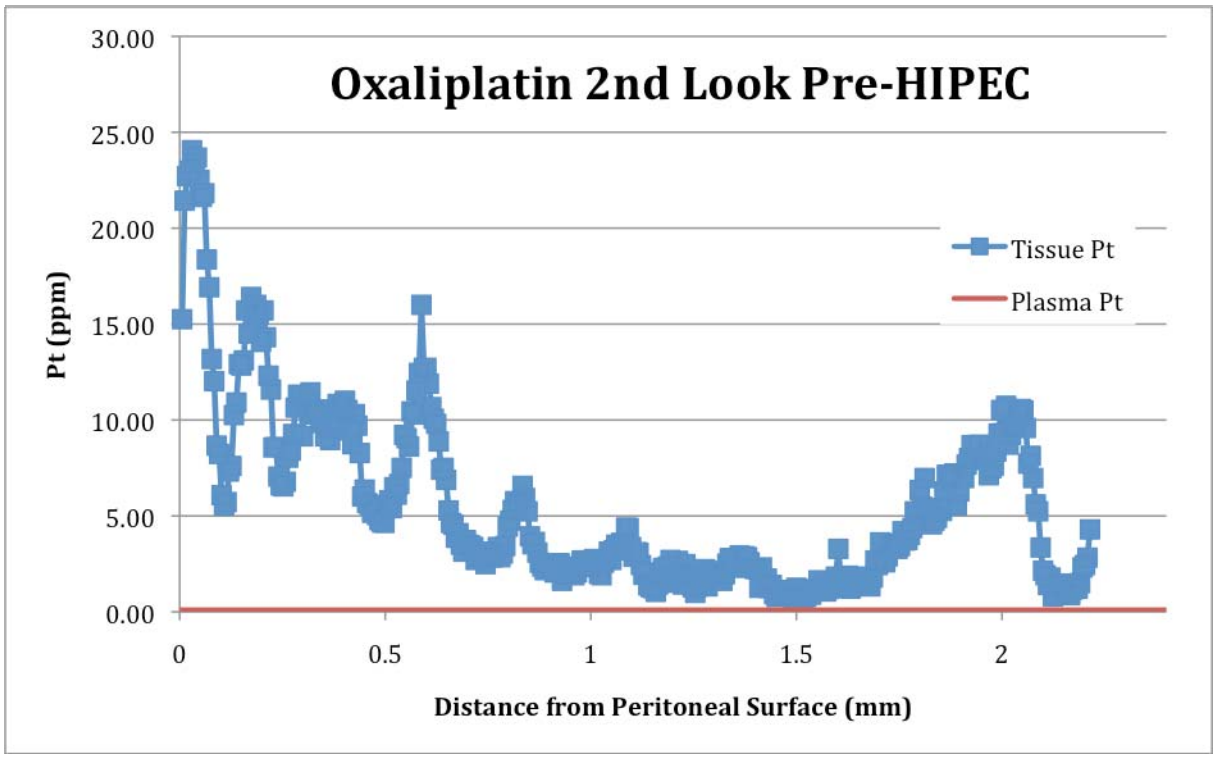
(b)



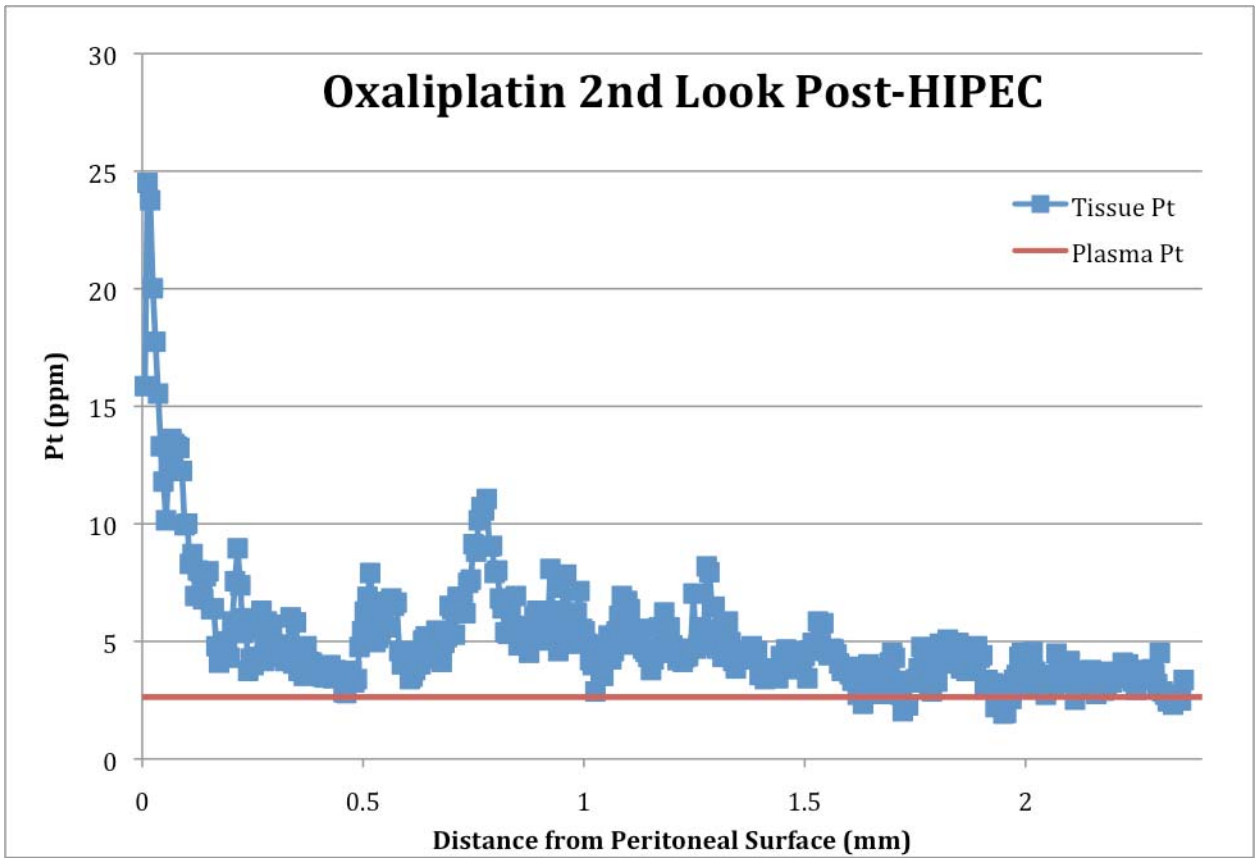
Obtained from one patient at second surgery, both pre-HIPEC (a) and post-HIPEC (b). Panel 1, visible light microscopy; Panel 2, Pt imaging in green; Panel 3, Pt imaging in green with visible light subtracted; Panel 4, Pt imaging in green, Zn imaging in red, Ca imaging in blue with visible light subtracted.

Figure 5. Oxaliplatin concentration plots.

(a)



(b)



Tissue and contemporaneous plasma platinum concentration plots obtained from one patient at second surgery, both pre-HIPEC (a) and post-HIPEC (b).

V. Discussion

Quantitative CT Peritoneography

Our data suggest that larger surface areas of the compartment available to chemotherapy administered by IP catheters are associated with improved overall survival in MPM patients. This is consistent with the rationale for IP treatment of peritoneal surface-spreading malignancies – direct drug contact with a larger peritoneal surface area means that more drug is directly delivered to potential areas of tumor spread.(104) Controlling for surface area, larger volumes were associated with decreased survival, suggesting that a high surface area-to-volume ratio of the contrast-filled compartment is optimal. This is consistent with the observation that loculated intraperitoneal compartments are more spherical, while free-flowing intraperitoneal compartments have irregular edges corresponding to the peritoneal organs, notably the small bowel. In addition, a higher surface area-to-volume ratio ensures that a larger proportion of the infused chemotherapy is in close proximity to peritoneal surfaces.

In the final multivariate Cox model, in addition to larger surface area and smaller volume, younger age and residual disease <0.5cm were associated with improved overall survival, consistent with previous studies.(94-96, 105, 106) In this analysis, histology and sex were not statistically-significant predictors of overall survival, which may be attributable to the fact that in our cohort all of the females had epithelioid disease and 18 of 19 females had no residual disease >0.5cm, while all 4 patients with biphasic disease also had residual disease >0.5cm.

Statistical analysis showed no differences in measured peritoneogram volume or surface area between patients with residual disease >0.5cm vs. <0.5cm, making it likely that the peritoneogram parameters were independent of observed tumor volume. We therefore included both groups of patients in the survival analysis. Indeed, the final multivariate Cox model showed that the volume and surface area of the contrast-filled compartments, and the presence of residual disease >0.5cm were all statistically-significant independent predictors of overall survival. However, the relatively small number of patients with residual disease >0.5cm limits our ability to draw conclusions about this subgroup.

Our data suggest that larger volumes of the compartment available to IP catheter-administered chemotherapy are associated with higher post-treatment GFR in MPM patients, which is consistent with the physiology of the peritoneal diffusion barrier. Elevated intra-abdominal pressure is associated with increased fluid transfer from the peritoneal space; the major diffusion barrier is the blood vessel wall and surrounding interstitium, rather than the anatomic peritoneum.(29) Although we have not directly measured intra-abdominal pressures, it is possible that increased compartment volume are associated with lower compartmental pressures, resulting in lower intravascular drug levels and less cisplatin nephrotoxicity.

In the final multiple linear regression model, larger BSA was associated with higher post-treatment GFR, possibly because of lower systemic drug exposure. This is consistent with our HIPEC pharmacokinetic data (in which free flow is assured, as chemoperfusion occurs during surgery, before adhesions can form), which showed that higher BSA was associated with lower cisplatin plasma AUC.

The strongest clinical evidence for improved survival with cathether-administered IP chemotherapy is in advanced ovarian carcinoma, including a large meta-analysis suggesting improved overall and disease-free survival for patients who receive IP chemotherapy.(82) The landmark GOG-172 trial for ovarian carcinoma reported a significant difference in overall survival for patients receiving intraperitoneal chemotherapy vs. intravenous chemotherapy (median overall survival 65.6 vs. 49.7 months, p=0.03 by intention to treat analysis); however, only 42% of those assigned to intraperitoneal chemotherapy completed all 6 cycles, due chiefly to catheter-related complications, as well as renal/metabolic toxicities, neuropathy and nausea/vomiting/dehydration.(107, 108) Prognostic factors, not only of overall survival but of potential chemotherapy-related toxicities, are needed to optimally plan IP chemotherapy, given the high rate of discontinuation due to adverse events. For example, patients at risk for cisplatin nephrotoxicity may be treated with less nephrotoxic drugs.

Our retrospective data suggest that quantitative CT peritoneography provides parameters associated with overall survival (compartment surface area and volume) and post-treatment GFR (compartment volume) in MPM patients undergoing IP chemotherapy. It is possible that these data reflect a selection bias in which patients might have been chosen to undergo CT peritoneography because of clinical suspicion of catheter-related complications. In addition, patients who experienced pain or pressure with injection received lower volumes of contrast. It is likely that these symptoms indicated that the volume available to intraperitoneal contrast was filled, but use of a standardized volume for all patients would provide added validity. Finally, standard prone-position CT scans were used; however, they may not have reflected the physiologic distribution of

intraperitoneal chemotherapy for different body positions. Prospective studies should be undertaken, using a standardized contrast volume with patients in multiple positions, possibly undergoing low-dose CT, to confirm the prognostic value of CT peritoneography, and to extend our findings to other diseases including advanced ovarian carcinoma.

HIPEC Pharmacokinetics

BSA is an imperfect but useful proxy to calculate drug doses, because of its association with circulating blood volume.(109) Likewise, BSA has been used to estimate peritoneal volumes for peritoneal dialysis.(110) BSA has been shown to be a predictor of outcomes following cardio-pulmonary bypass, likely because of the association between low BSA and hemodilutional anemia in that setting.(111) We hypothesized that the pharmacokinetics of HIPEC with oxaliplatin would be associated with BSA, due to its known association with circulating blood volume and peritoneal volume.

Our results suggest that in patients who receive a BSA-based oxaliplatin dose and carrier fluid volume titrated to achieve a desired flow rate, BSA is a predictor of systemic drug exposure and pharmacokinetic advantage. This is partially explained by the inverse relationship observed between perfusate volumes and systemic oxaliplatin levels, as perfusate volume was found to correlate with BSA. Patients with higher BSA had lower plasma oxaliplatin AUC over the 60-minute duration of HIPEC, and thus greater pharmacokinetic advantage, possibly because they also had larger circulating blood volumes with inadequate time for equilibration between the peritoneal and circulating blood compartments. Further studies should examine whether these relationships hold for

patients who receive a set volume of carrier fluid, or a BSA-based volume of carrier fluid. We did not find that BMI was a significant predictor of pharmacokinetic parameters. The present study differed from a previous study showing such a relationship in terms of the patients' diagnoses, the duration and technique of HIPEC, and surgical procedures and technique.(16) We did not find obvious differences in pharmacokinetics on the basis of diagnosis, disease burden, or extent of peritonectomy, consistent with previous reports.(112)

We did not find statistically significant relationships between BSA or BMI and glycemia in our 10 patients, but hyperglycemia was observed in all patients. Given the relatively small amount of oxaliplatin degradation in sodium chloride solution over the usual duration of HIPEC, use of normal saline in the perfusion circuit (after oxaliplatin reconstitution in 5% dextrose), as has previously been described, may be considered.(14, 18)

The present study shows that BSA can be used to predict the pharmacokinetics of HIPEC with oxaliplatin, likely due to the effects of circulating blood volume with inadequate time for drug equilibration. With the exception of metabolic derangements due to hyperglycemia, oxaliplatin HIPEC was well-tolerated by all patients, suggesting that the range of systemic drug levels they experienced is safe. Patients with larger BSA, who had lower systemic drug levels, should therefore be able to tolerate higher total doses of oxaliplatin. This was a small cohort, however, and we did not prospectively analyze toxicity or efficacy, making it difficult to make clinical recommendations on the basis of our data alone. We therefore recommend further study of HIPEC dosing modified to

achieve a desired intraperitoneal drug concentration for all patients, rather than a BSA-based total dose. For example, a system like ours, which titrates carrier fluid to achieve a minimum flow rate (which results in an variability in intraperitoneal drug concentrations) could be modified to use oxaliplatin at a set concentration, with the volume (and therefore the total dose) titrated to achieve the desired flow rate (which would result in equal intraperitoneal drug concentrations for all patients). Patients with larger BSA would then receive a higher total dose of drug, but, based on our data, the greater pharmacokinetic advantage in these patients would ensure that their systemic drug levels would remain tolerable. This method of dosing is more consistent with the observation that intraperitoneal oxaliplatin concentration, rather than total dose, is the chief determinant of HIPEC pharmacokinetics.(113, 114)

These data do not address the most important biodistribution endpoint, namely intratumoral drug concentrations, but instead uses peritoneal fluid concentration as a proxy. Few tissue analysis studies have been undertaken, and more are needed to optimize HIPEC administration and dosing in order to achieve the highest possible drug levels in tumor cells.(115) Our measurements of tissue drug concentrations are discussed below.

Tissue Penetration of Intraperitoneal Platinum Drugs

Our protocol for the treatment of MPM, with sampling of peritoneal tissues at first surgery post-HIPEC and at second surgery pre-HIPEC and post-HIPEC, allowed us to investigate the roles of HIPEC versus CAIPEC in peritoneal tissue platinum distribution. In particular, the second surgery pre-HIPEC time point can be considered to primarily

represent the contribution of CAIPEC to tissue platinum distribution, while the post-HIPEC time point at first surgery represents the contribution of HIPEC alone, with the post-HIPEC time point at second surgery representing the contributions of both to some extent. This inference is supported by our findings, that the ratio of peritoneal surface platinum to whole sample platinum was similar in both post-HIPEC time points while lower in the second surgery pre-HIPEC samples, and that the depth of direct tissue platinum penetration was reached only in post-HIPEC samples (both of those from first surgery, and one of four from second surgery).

On the basis of these findings, we conclude that the direct tissue penetration depth of platinum attributable to multiple courses of CAIPEC is greater, and the tissue distribution of platinum more homogeneous, than that attributable to a single dose of HIPEC. Among the factors that likely contribute to these differences are the differences in dwell time (indefinitely for CAIPEC versus 60 minutes for HIPEC), which allows for more equilibration of drug between the peritoneal fluid, peritoneal tissue and systemic compartments in CAIPEC; and the vascular injury and inflammation that accompany surgery in HIPEC but not CAIPEC, resulting in greater direct communication between the peritoneal fluid and systemic circulation (potentially bypassing absorption in peritoneal tissues).

The samples obtained from all patients were from macroscopically normal tissue, because the removal of macroscopic disease before HIPEC has been shown to improve survival in PC patients.(97) In one patient who could not be debulked of all macroscopic disease at first surgery, depth of platinum penetration was nearly identical in tumor tissue and

normal tissue, suggesting that our findings may be applicable to tumor tissue as well. However, aberrant tumor tissue architecture and vasculature may in fact contribute to different tissue drug distributions in some patients.(116, 117)

Our findings demonstrate more homogeneous peritoneal tissue distribution and greater depth of tissue penetration of platinum-containing chemotherapy drugs in multiple courses of CAIPEC (such as is recommended for the treatment of advanced ovarian carcinoma) compared to single-dose HIPEC (such as is becoming more common for the treatment of PC of GI origin). Therefore, the use of biodistribution data from HIPEC studies should not be assumed to apply to CAIPEC, or vice versa.

Furthermore our results suggest that in patients who may benefit from HIPEC (such as patients with MPM or PC of colorectal or gastric origin), a pharmacokinetic rationale exists for even greater benefit from CAIPEC, since many failures of IP chemotherapy are due to insufficient tissue penetration.(118) For MPM, which is not routinely cured by HIPEC alone, and which is unlikely to be subject to a successful clinical trial due to its rarity, CAIPEC should therefore be offered following debulking surgery with HIPEC. For PC of colorectal or gastric origin, clinical trials should include a CAIPEC arm to determine if there is a survival benefit of CAIPEC compared to systemic chemotherapy following HIPEC.

VI. References

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