



THIRD ANNUAL
ISSPP
Congress 2022

*International Society
for the Study of Pleura
and Peritoneum*



GASTRIC CANCERS

Practice and Trials of Regional Therapy for Gastric Cancer in the U.S.

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Professor of Surgery

Section Chief - Gastric, Peritoneal, & Acute Care Surgical Oncology

MD Anderson Cancer Center

Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

The following CLC & IB components will be addressed in this presentation:

- Barriers and biases that impact cancer based on race
- Specific outcomes related to race

Racial Disparities in Preoperative Chemotherapy Use in Gastric Cancer Patients in the United States: Analysis of the National Cancer Data Base, 2006-2014

Naruhiko Ikoma, MD, MS^{1,2}; Janice N. Cormier, MD, MPH¹; Barry Feig, MD^{1,2}; Xianglin L. Du, MB, MS, PhD²; Jose-Miguel Yamal, PhD²; Wayne Hofstetter, MD⁴; Prajnan Das, MD⁵; Jaffer A. Ajani, MD^{1,6}; Christina L. Roland, MD, MS¹; Keith Fournier, MD¹; Richard Royal, MD¹; Paul Mansfield, MD¹; and Brian D. Badgwell, MD, MS¹

BACKGROUND: No studies have investigated whether race/ethnicity is associated with the recommended use of preoperative chemotherapy or subsequent outcomes in gastric cancer. To determine whether there is such an association, analyses of patients with gastric cancer in the National Cancer Data Base (NCDB) were performed. **METHODS:** Patients with clinical T2-4bNO-IMO gastric adenocarcinoma, as defined by the eighth edition of the American Joint Committee on Cancer staging manual, who underwent gastrectomy from 2006 to 2014 were identified from the NCDB. Multiple logistic regression was conducted to examine factors associated with preoperative chemotherapy use. **RESULTS:** This study identified 16,945 patients who met the criteria, and 8286 of these patients (49%) underwent preoperative chemotherapy. The use of preoperative chemotherapy remarkably increased over the study period, from 34% in 2006 to 65% in 2014. Preoperative chemotherapy was more commonly used for cardia tumors than noncardia tumors (83% vs 44% in 2014). In a multivariable analysis, races and ethnicities other than non-Hispanic (NH) white race were associated with less frequent use of preoperative chemotherapy in comparison with NH whites after adjustments for social, tumor, and hospital factors. The insurance status and the education level mediated an enhanced effect of racial/ethnic disparities in preoperative chemotherapy use. The use of preoperative chemotherapy and radiation therapy was associated with reduced racial/ethnic disparities in overall survival. **CONCLUSIONS:** Racial/ethnic disparities in the use of preoperative chemotherapy and in outcomes exist among patients with gastric cancer in the United States. Efforts to improve the access to high-quality cancer care in minority groups may reduce racial disparities in gastric cancer in the United States. *Cancer* 2018;124:998-1007. © 2018 American Cancer Society.

KEYWORDS: gastric cancer, insurance, preoperative therapy, public health, racial disparity, surgery.

Badgwell, JNCCN, Oct 2016

FLOT4 5-y OS
45% vs 36%

Table 1. Overall Survival Rates for Trials of Resectable Gastric Cancer From Western and Eastern Centers

Trial	Outcome	Surgery Alone	Chemotherapy	Chemoradiotherapy
Western centers				
Intergroup 0116 ¹⁸	3-y OS	41%		50%
MAGIC ¹²	5-y OS	23%	36%	
FNCLCC ¹³	5-y OS	24%	38%	
CROSS ²⁰	5-y OS	34%		47%
Eastern centers				
ACTS-GC ⁴¹	5-y OS	61%	72%	
CLASSIC ¹⁶	3-y OS	78%	83%	
ARTIST ¹⁷	5-y OS		73%	75%

Ann Surg Oncol (2017) 24:960–965
DOI 10.1245/s10434-016-5645-x

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Race Is a Risk for Lymph Node Metastasis in Patients With Gastric Cancer

Naruhiko Ikoma, MD¹, Mariela Blum, MD², Yi-Ju Chiang, MSPH¹, Jeannelyn S. Estrella, MD³, Sinchita Roy-Chowdhuri, MD³, Keith Fournier, MD¹, Paul Mansfield, MD¹, Jaffer Ajani, MD², and Brian D. Badgwell, MD, MS¹

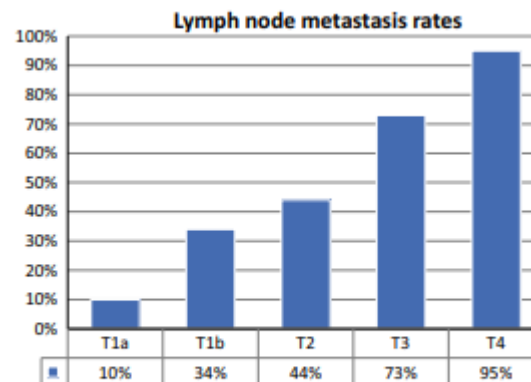


FIG. 1 Frequency of lymph node metastasis by T stage

Asked to address 2 questions:

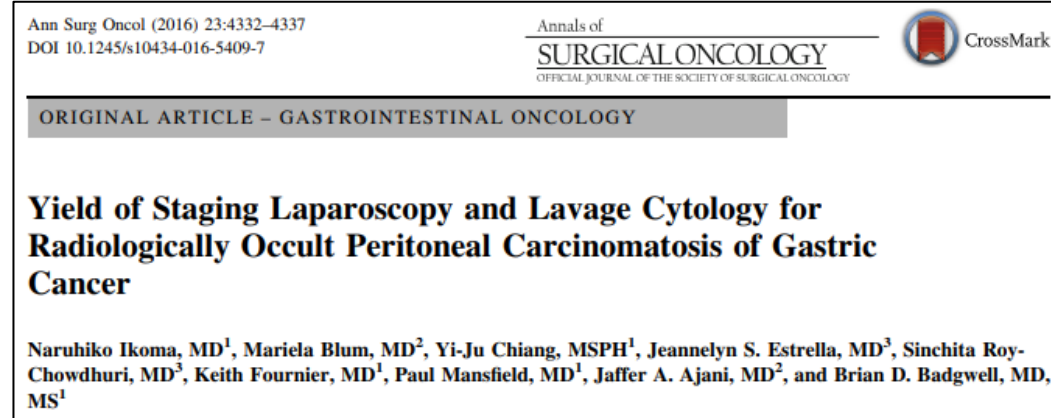
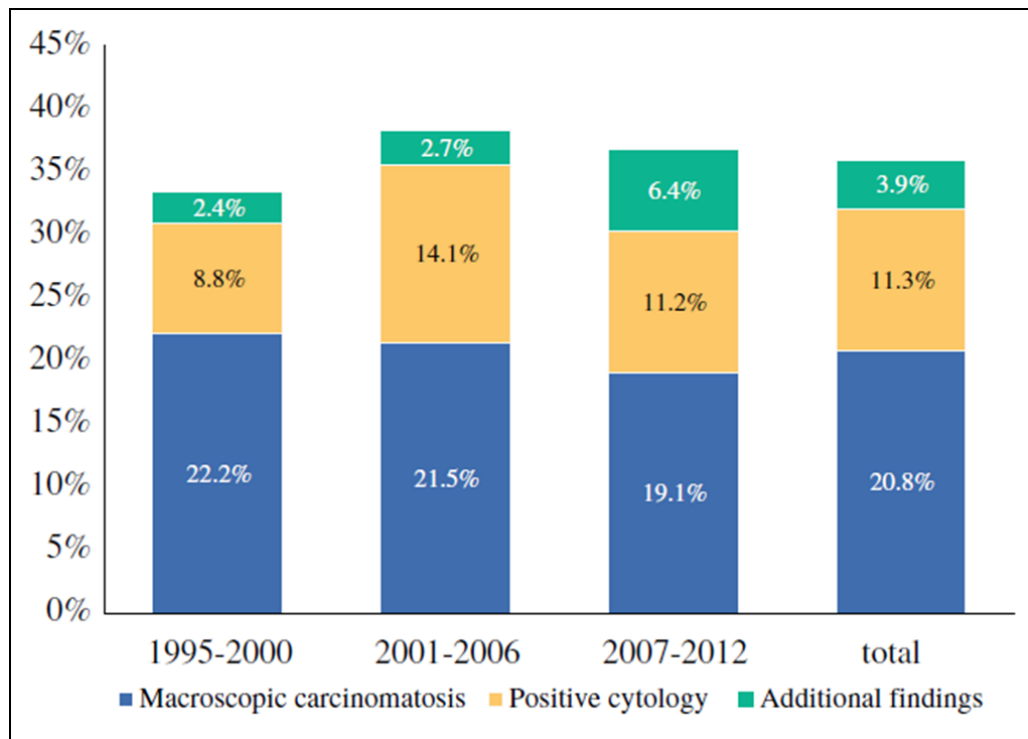
1. What evidence is needed to move peritoneal therapies forward?
2. Optimal timing for peritoneal directed therapies?



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Yield of Staging Laparoscopy and Cytology for Patients with No Evidence of Metastatic Disease on Imaging



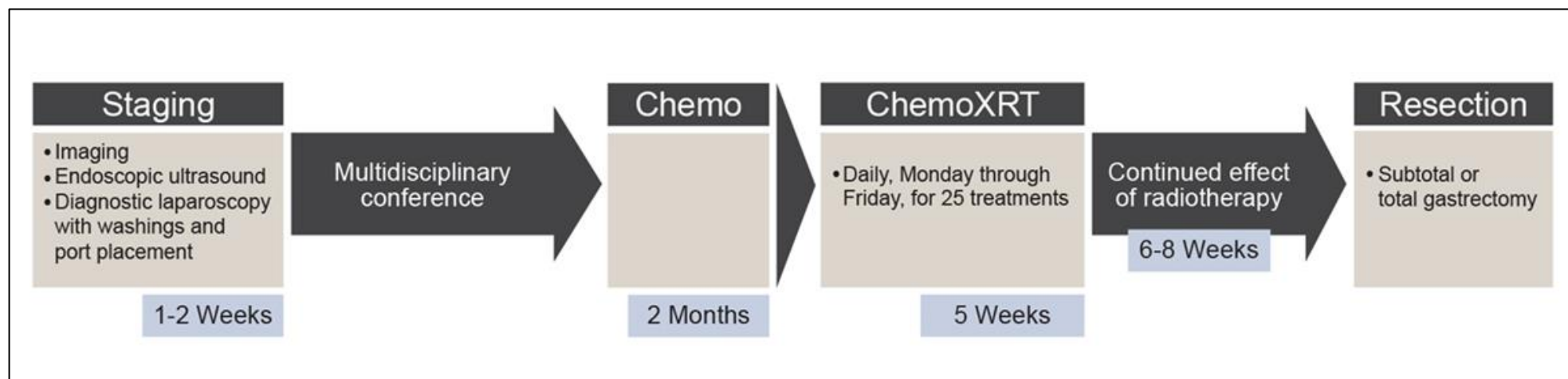
- Visible Carcinomatosis – 20%
- Positive Cytology Only – 10%

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Repeat staging laparoscopy for gastric cancer after preoperative therapy

Cornelius A. Thiels DO, MBA¹ | Naruhiko Ikoma MD, MS² |
Keith Fournier MD² | Prajnan Das MD³ | Mariela Blum MD⁴ |
Jeannelyn S. Estrella MD⁵ | Bruce D. Minsky MD³ | Jaffer Ajani MD⁴ |
Paul Mansfield MD² | Brian D. Badgwell MD, MS²

- 451 patients, negative laparoscopy
- Treated with chemo or chemoXRT
- 11% (N=48) had carcinomatosis



JSO.
2018;118:61-67

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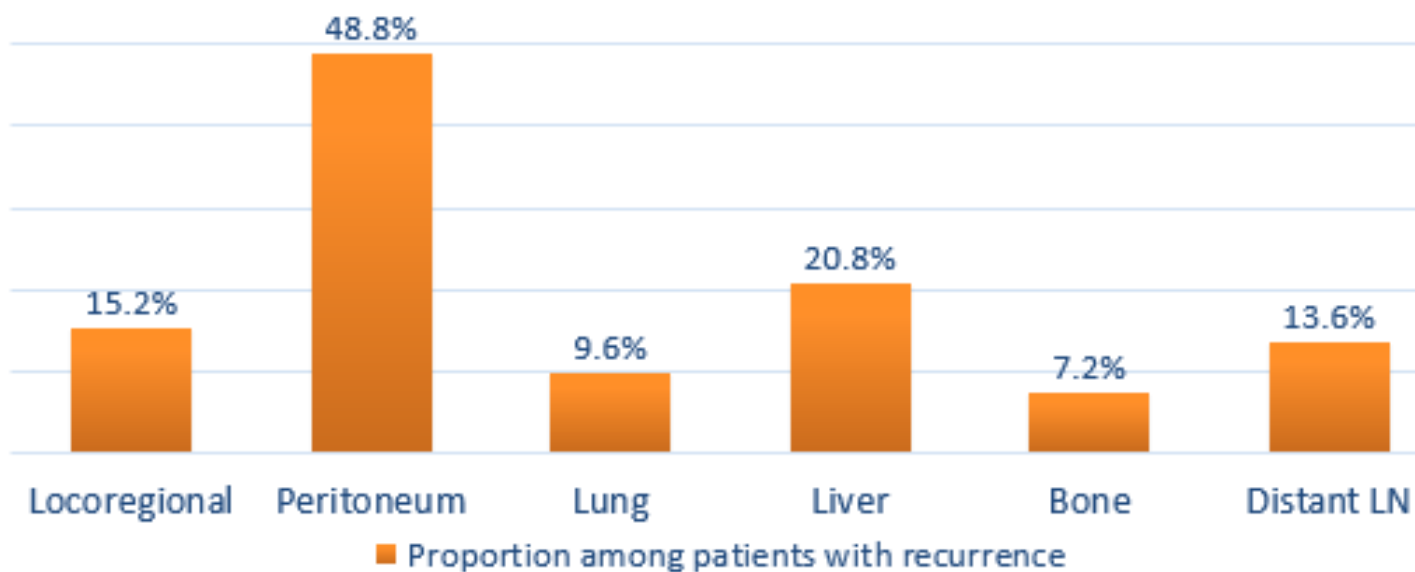


ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Patterns of Initial Recurrence in Gastric Adenocarcinoma in the Era of Preoperative Therapy

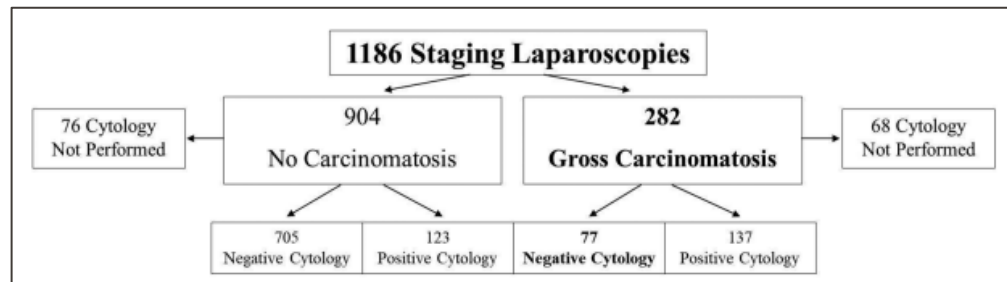
Naruhiko Ikoma, MD¹, Hsiang-Chun Chen, PhD², Xuemei Wang, MS², Mariela Blum, MD³, Jeannelyn S. Estrella, MD⁴, Keith Fournier, MD¹, Paul Mansfield, MD¹, Jaffer Ajani, MD³, and Brian D. Badgwell, MD, MS¹

Figure 1. Sites of common recurrence and proportions



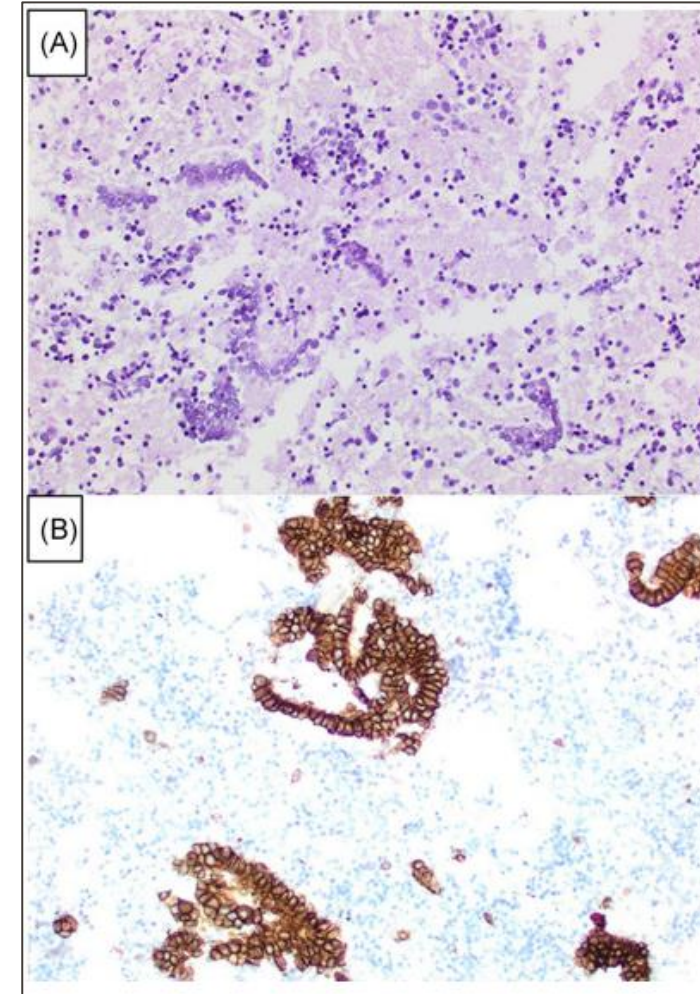
Yield of peritoneal cytology in staging patients with gastric and gastroesophageal cancer

Casey J. Allen MD¹ | Timothy E. Newhook MD¹ | Timothy J. Vreeland MD¹ |
Prajnan Das MD² | Bruce D. Minsky MD² | Mariela Blum MD³ | Shumei Song MD³ |
Jaffer Ajani MD³ | Naruhiko Ikoma MD | Paul F. Mansfield MD |
Sinchita Roy-Chowdhuri MD, PhD⁴ | Brian D. Badgwell MD



$$137 / (77 + 137) = 137 / 214$$

Sensitivity = 64%





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Impact of Maximal Cytoreductive Surgery Plus Regional Heated Intraperitoneal Chemotherapy (HIPEC) on Outcome of Patients With Peritoneal Carcinomatosis of Gastric Origin: Results of the GYMSSA Trial

NIH Study

- Powered for 136 (68 per arm)
- 9 patients underwent HIPEC, 8 systemic chemo only

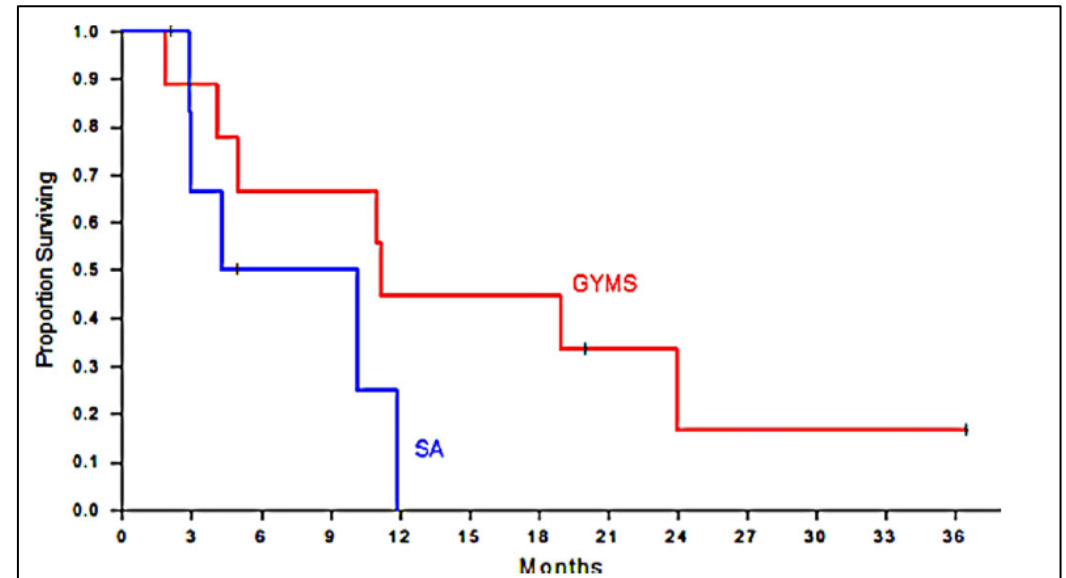


Fig. 3. Kaplan–Meier analysis of overall survival of patients randomized to multi-modality treatment including CRS and HIPEC (GYMS arm) versus patients receiving chemotherapy only (SA arm).



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MD Anderson Peritoneal Program

1. Laparoscopic HIPEC – if clear peritoneal disease – Gastrectomy alone
2. More aggressive study – 2 step approach:
 - a) Diagnostic laparoscopy with HIPEC
 - b) Combine Gastrectomy & HIPEC
3. Phase I trial to incorporate paclitaxel – triplet chemotherapy HIPEC
4. Now studying intraperitoneal paclitaxel (Ishigami type approach)





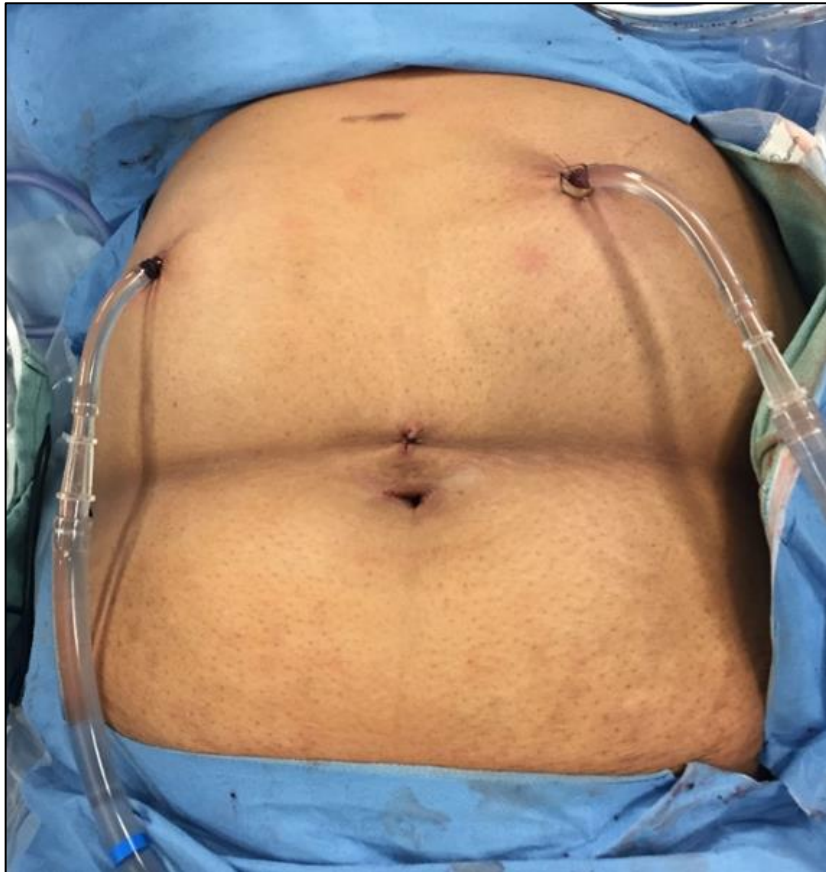
ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Phase II Trial of Laparoscopic Hyperthermic Intraperitoneal Chemoperfusion for Peritoneal Carcinomatosis or Positive Peritoneal Cytology in Patients with Gastric Adenocarcinoma

Brian Badgwell, MD, MS¹, Mariela Blum, MD², Prajnan Das, MD³, Jeannelyn Estrella, MD⁴, Xuemei Wang, MS⁵, Linus Ho, MD², Keith Fournier, MD¹, Richard Royal, MD¹, Paul Mansfield, MD¹, and Jaffer Ajani, MD²

- Trial designed to be effective & safe:
 - CCR 0-1
 - Include systemic chemotherapy
 - Minimize complications

Trial Design



Single Arm, Phase 2

Positive peritoneal cytology or
peritoneal disease on laparoscopy or laparotomy



Systemic Chemotherapy



≥ 3 weeks

Laparoscopic HIPEC
Mitomycin C 30 mg
Cisplatin 200 mg

- May be repeated up to 5
- Chemoradiotherapy allowed

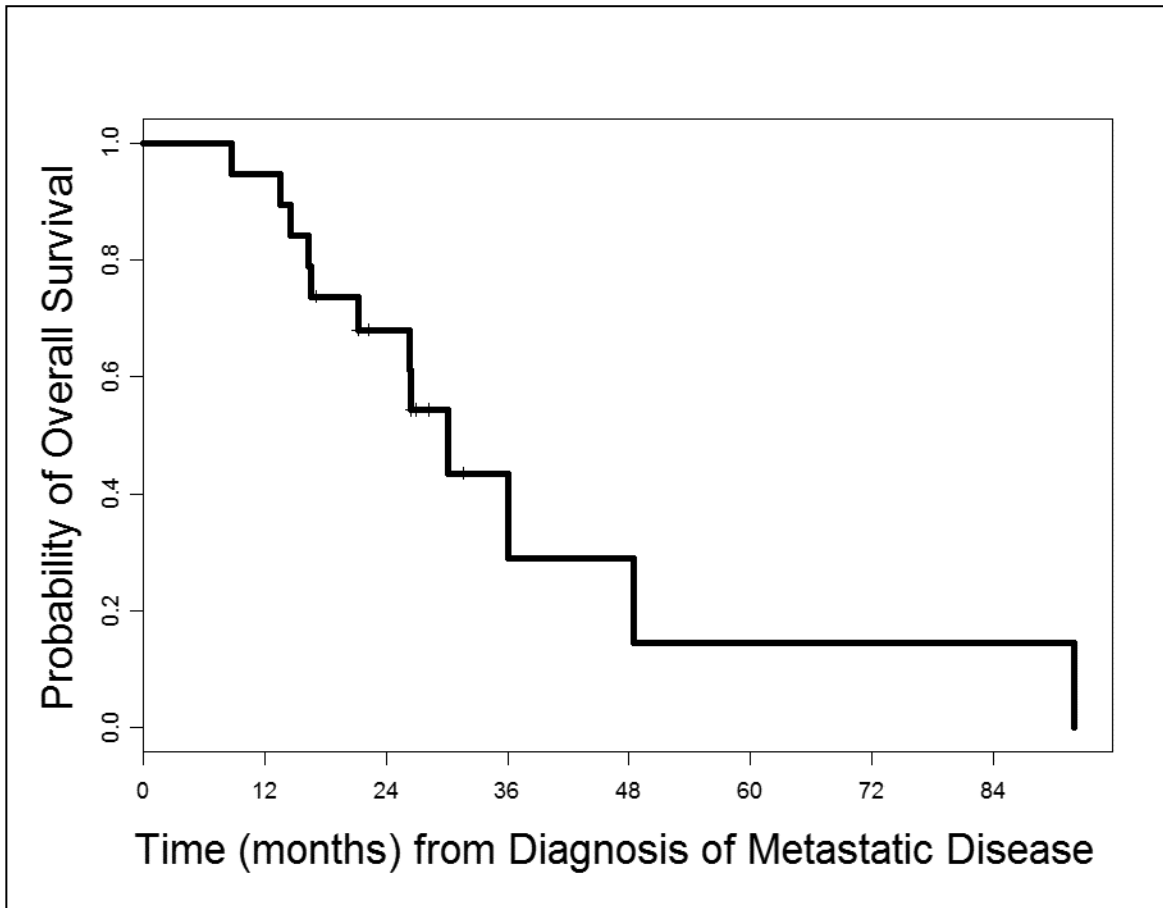


- Negative cytology
- No carcinomatosis
- No imaging metastases



≥ 2 weeks

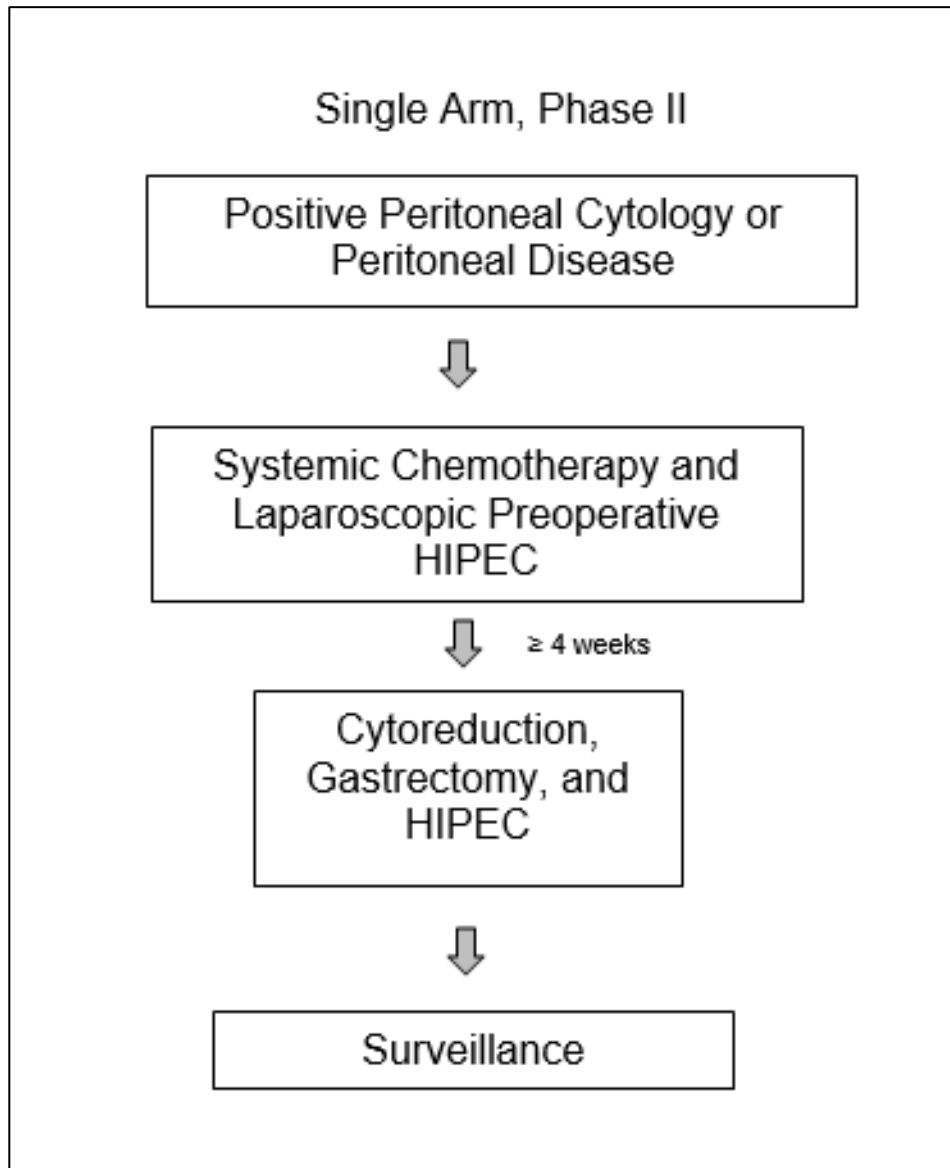
Exploratory laparotomy
and possible resection



- Median follow-up 18.9 months
- 1, 2, 3 year OS rates 95%, 68%, and 44%
- Median OS 30.2 months

Variable	N	%
Morbidity rate	4	11
<ul style="list-style-type: none"> - Intraoperative arrhythmia - Elevation in Cr (1.3) - Deep venous thrombosis - Pneumothorax 	<u>Grade</u> I I IId III	
Mortality	0	0
Median hospital length of stay, range	3 (2-6)	

Recently Completed Phase II Trial combining CRS/Gastrectomy/HIPEC



Ann Surg Oncol
<https://doi.org/10.1245/s10434-020-08739-5>

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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

A Phase II Trial of Cytoreduction, Gastrectomy, and Hyperthermic Intraperitoneal Perfusion with Chemotherapy for Patients with Gastric Cancer and Carcinomatosis or Positive Cytology

Brian Badgwell, MD, MS¹, Naruhiko Ikoma, MD, MS¹, Mariela Blum Murphy, MD², Xuemei Wang, MS³, Jeannelyn Estrella, MD⁴, Sinchita Roy-Chowdhuri, MD, PhD⁴, Prajnan Das, MD⁵, Bruce D. Minsky, MD⁵, Elizabeth Lano, MD⁶, Shumei Song, PhD², Paul Mansfield, MD¹, and Jaffer Ajani, MD²

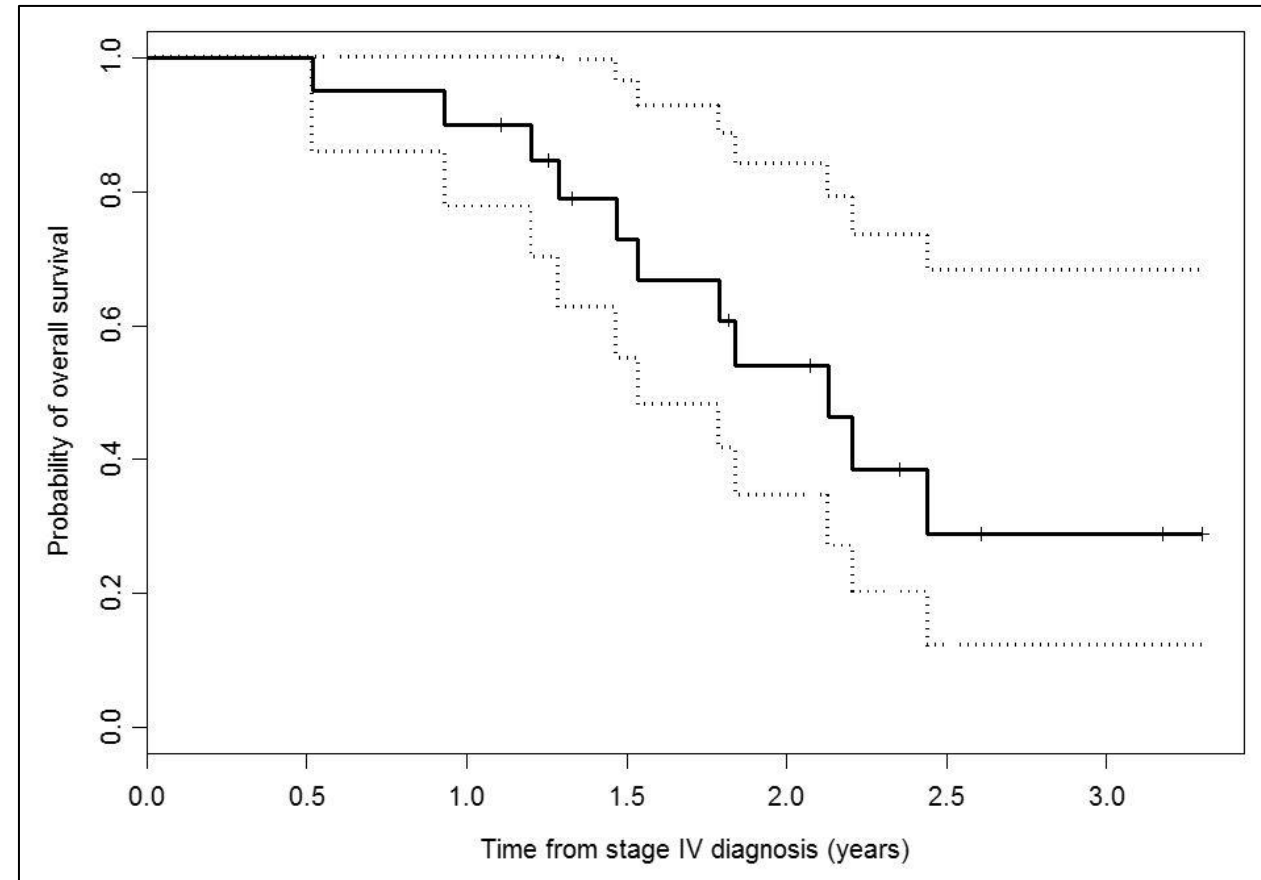
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Overall Survival – median follow-up 2.8 years

- 1, 2, and 3-year OS rates 90%, 49%, and 30%
- Median OS 1.8 years



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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Phase I Trial of Hyperthermic Intraperitoneal Chemoperfusion (HIPEC) with Cisplatin, Mitomycin, and Paclitaxel in Patients with Gastric Adenocarcinoma and Associated Carcinomatosis or Positive Cytology

Mariela Blum Murphy, MD¹, Naruhiko Ikoma, MD, MS², Xuemei Wang, MS³, Jeannelyn Estrella, MD⁴, Sinchita Roy-Chowdhuri, MD, PhD⁴, Prajnan Das, MD⁵, Bruce D. Minsky, MD⁵, Shumei Song, PhD¹, Paul Mansfield, MD², Jaffer Ajani, MD¹, and Brian Badgwell, MD, MS²

- Triplet chemotherapy for laparoscopic HIPEC
- Mitomycin 30 mg, Cisplatin 200 mg, Paclitaxel 60 mg/m²

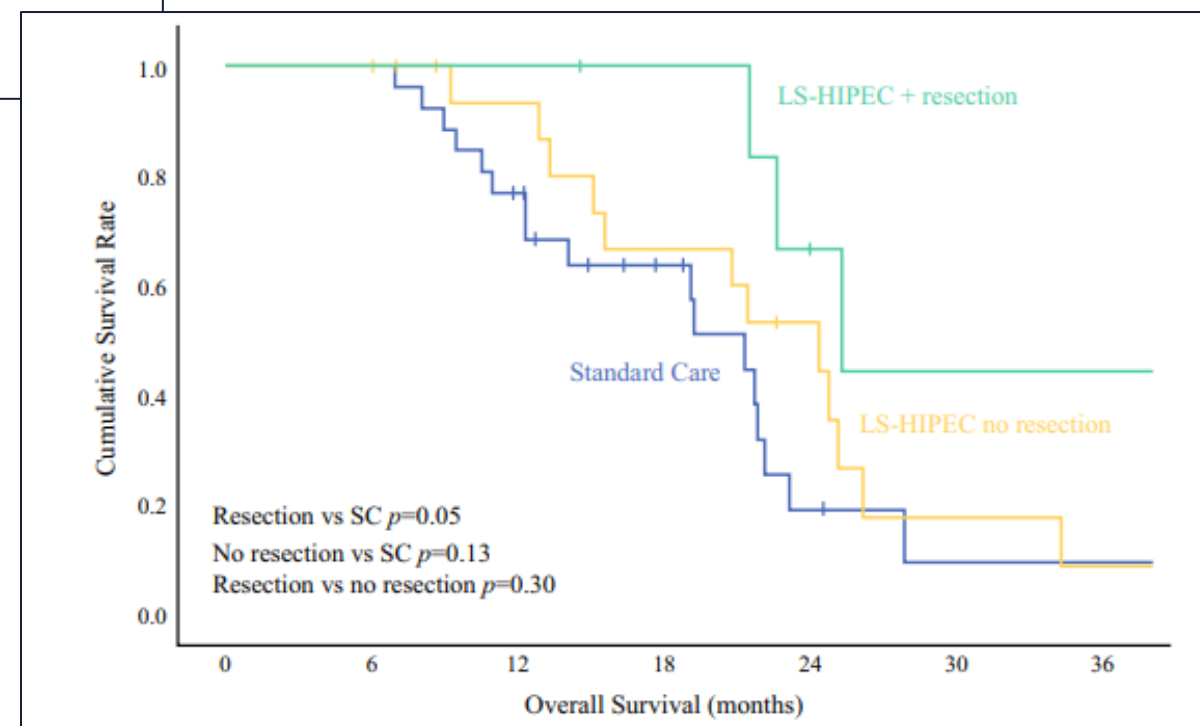
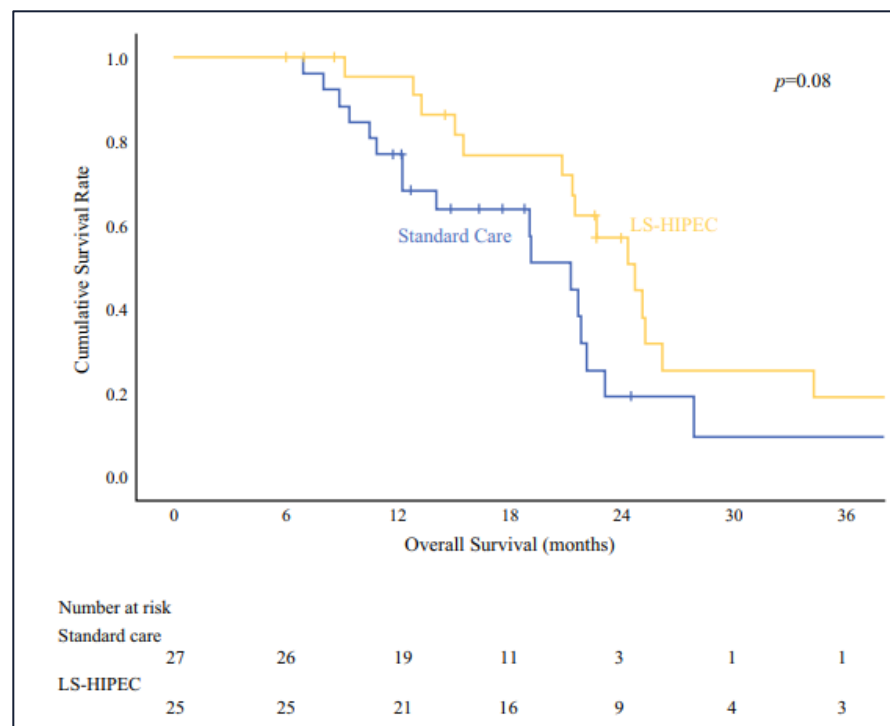
- PMID 32277764, Br J Surg 2020
- Periscope I Dutch Trial – PhI/II trial:
Oxaliplatin 460 mg/m² & docetaxel 50 mg/m²



ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Laparoscopic HIPEC for Low-Volume Peritoneal Metastasis in Gastric and Gastroesophageal Adenocarcinoma

Alisa N. Blumenthaler, MD¹, Casey J. Allen, MD¹, Naruhiko Ikoma, MD¹, Mariela Blum, MD², Prajnan Das, MD³, Bruce D. Minsky, MD³, Paul F. Mansfield, MD¹, Jaffer A. Ajani, MD², and Brian D. Badgwell, MD, MS¹

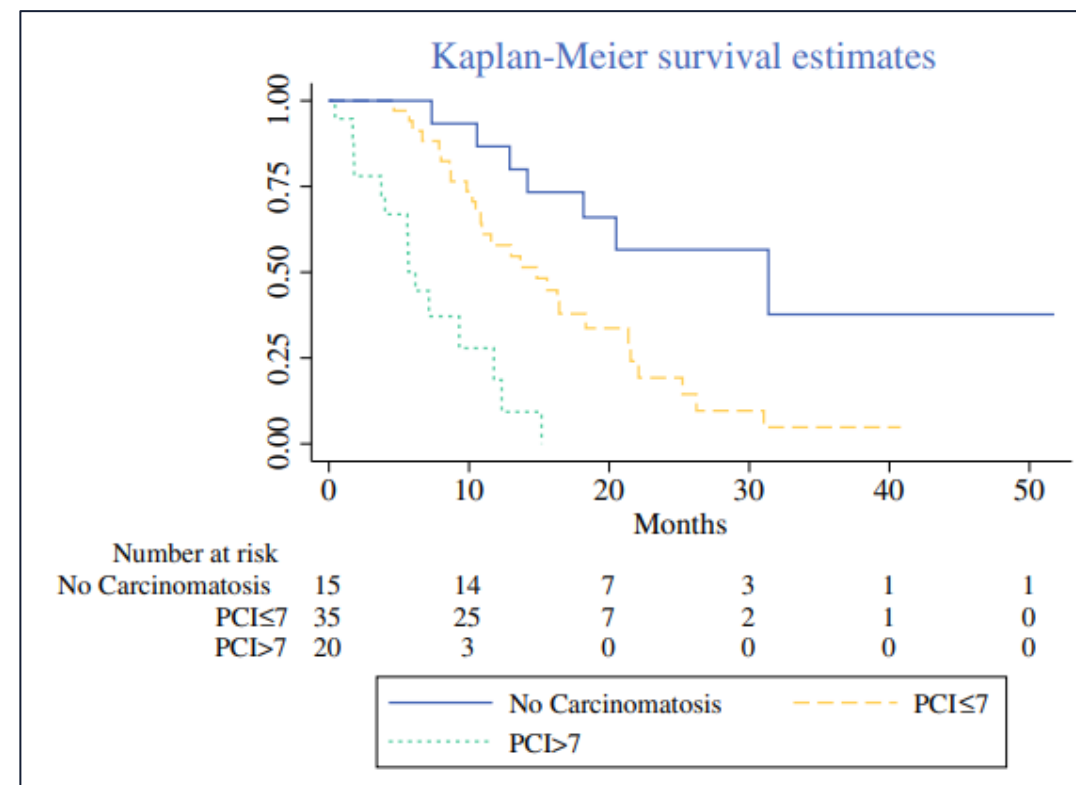
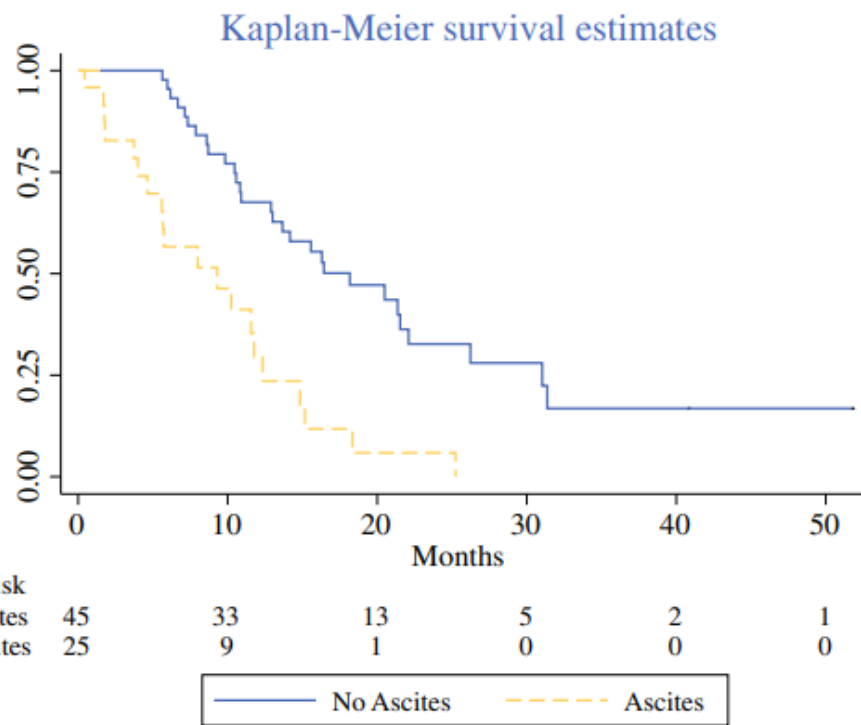




ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Factors Associated with Resection and Survival After Laparoscopic HIPEC for Peritoneal Gastric Cancer Metastasis

Michael G. White, MD, MSc¹, Anai Kothari, MD, MSc¹, Naruhiko Ikoma, MD¹, Mariela Blum Murphy, MD², Shumei Song, MD², Jaffer Ajani, MD², Paul Mansfield, MD¹, and Brian Badgwell, MD, MS¹





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2. History of Trials in the U.S.
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CYTOREDUCTION AND HIPEC FOR GASTRIC CARCINOMATOSIS: MULTI-INSTITUTIONAL INTERIM ANALYSIS OF TWO PHASE II CLINICAL TRIALS

Benjamin L. Green¹

Alisa N. Blumenthaler², Lauren A. Gamble¹, James D. McDonald¹, Kristen Robinson², Andrew M. Blakely¹, Jonathan M. Hernandez¹, Brian D. Badgwell², and Jeremy L. Davis¹

¹ Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

² Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX



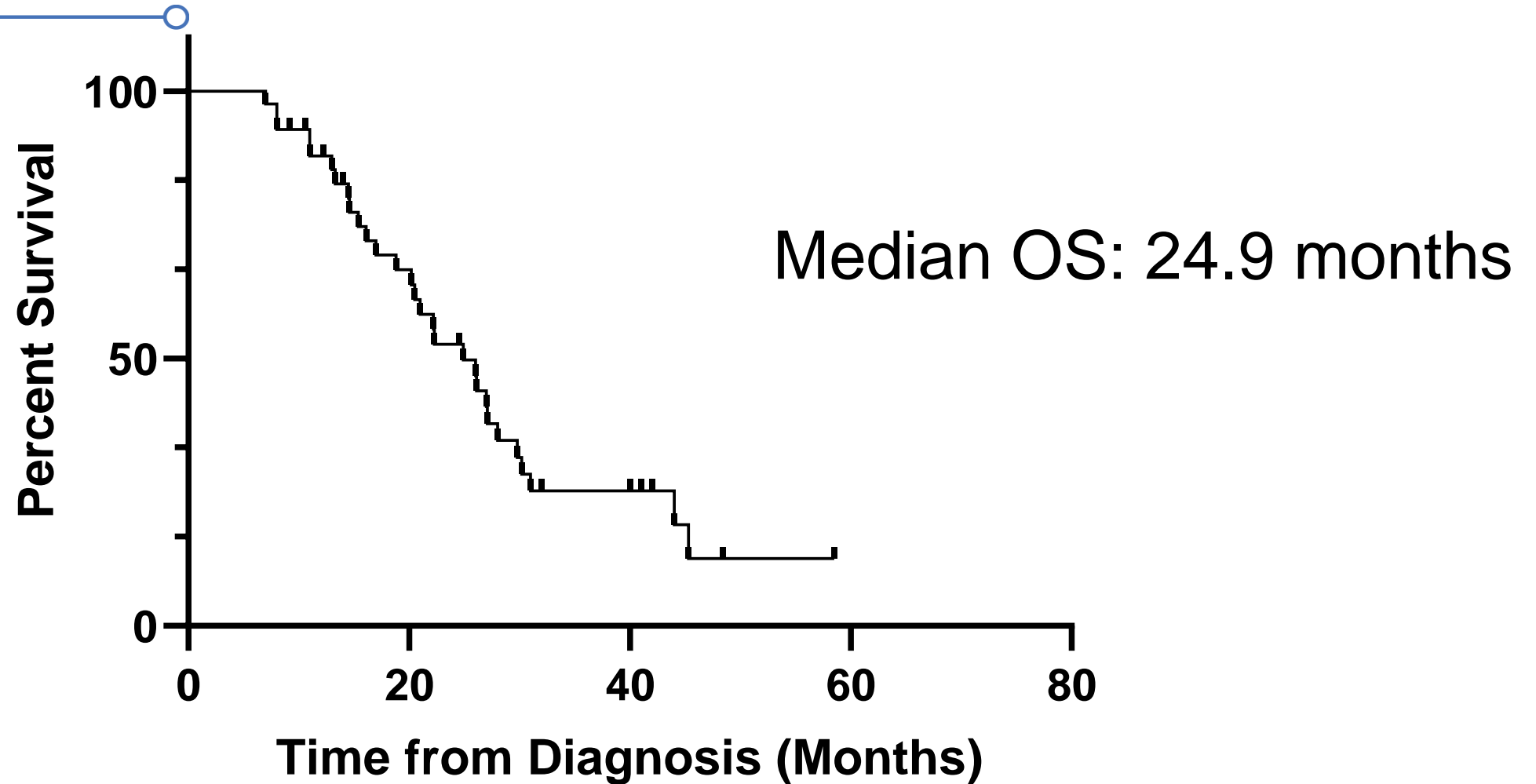
Surgical Oncology Research Fellowship



OPERATIVE CHARACTERISTICS

Characteristic	Patients (n = 42)	
Multivisceral resection, n (%)	14	33%
PCI, mean \pm SD (range)	4.1 \pm 4.7	0 - 19
CC score, n (%)		
0	40	96%
1	1	2%
2	1	2%
Extent of gastrectomy, n (%)		
Total	30	71%
Subtotal	12	29%
Location of primary tumor, n (%)		
Antrum	12	28%
Total	11	26%
Body	8	19%
GEJ	2	5%
Fundus	7	17%
Incisura	2	5%

POST-DIAGNOSIS OVERALL SURVIVAL



PREDICTORS OF POSTOPERATIVE OS

Variable	Univariate	Multivariate
Age	ns	-
Sex	ns	-
Race	ns	-
Differentiation	ns	-
LVI	ns	-
PCI	p = 0.014	ns
CCR	p = 0.003	ns
PNI	p = 0.043	ns
Lymph nodes (LN)	p < 0.001	p=0.032
Margin	ns	-
Grade	ns	-
ypT	ns	-
ypN	p < 0.001	ns
ypM	ns	-
FLOT NAC	ns	-
Triplet NAC	ns	-
NAC agents	ns	-
PDL1	ns	-
Her2	p = 0.018	ns
MMR	ns	-
p53	ns	-

Cox Proportional Hazards Model
 Significant: p<0.05; ns: not significant

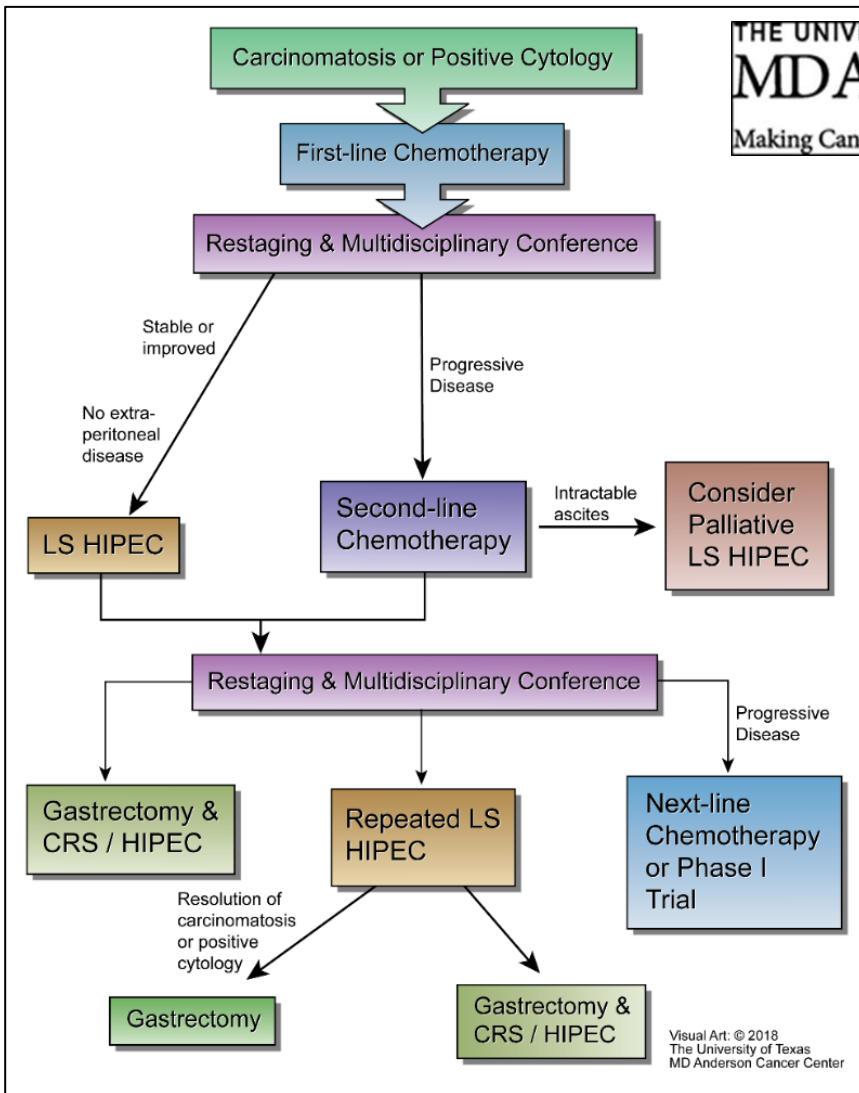


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2018 Chicago Consensus

on Peritoneal Surface Malignancies



Newhook et al, ASONC, 2019, PMID: 30680477

- Lists options for synchronous peritoneal gastric mets
- Standard chemotherapy
 - CRS/HIPEC
 - Neoadjuvant intraperitoneal & systemic (NIPS)
 - LS HIPEC
 - Trial options

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Gastric Cancer

Version 2.2022 — January 11, 2022

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients

- Therapeutic alternative, carefully selected patients, clinical trial setting



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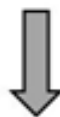
Prior to gastrectomy & HIPEC

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Single Arm, Phase I

Positive Peritoneal Cytology or Peritoneal Disease

Systemic Chemotherapy



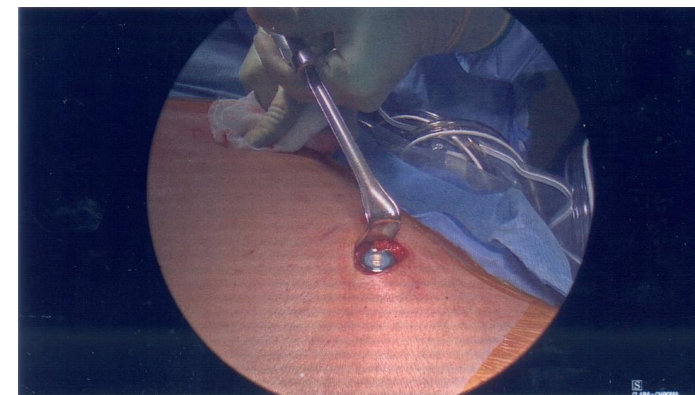
Diagnostic Laparoscopy and Intraperitoneal Port Placement



IP Paclitaxel
X 8 weeks (weekly treatment x 3 weeks, one week off)





NCT04220827

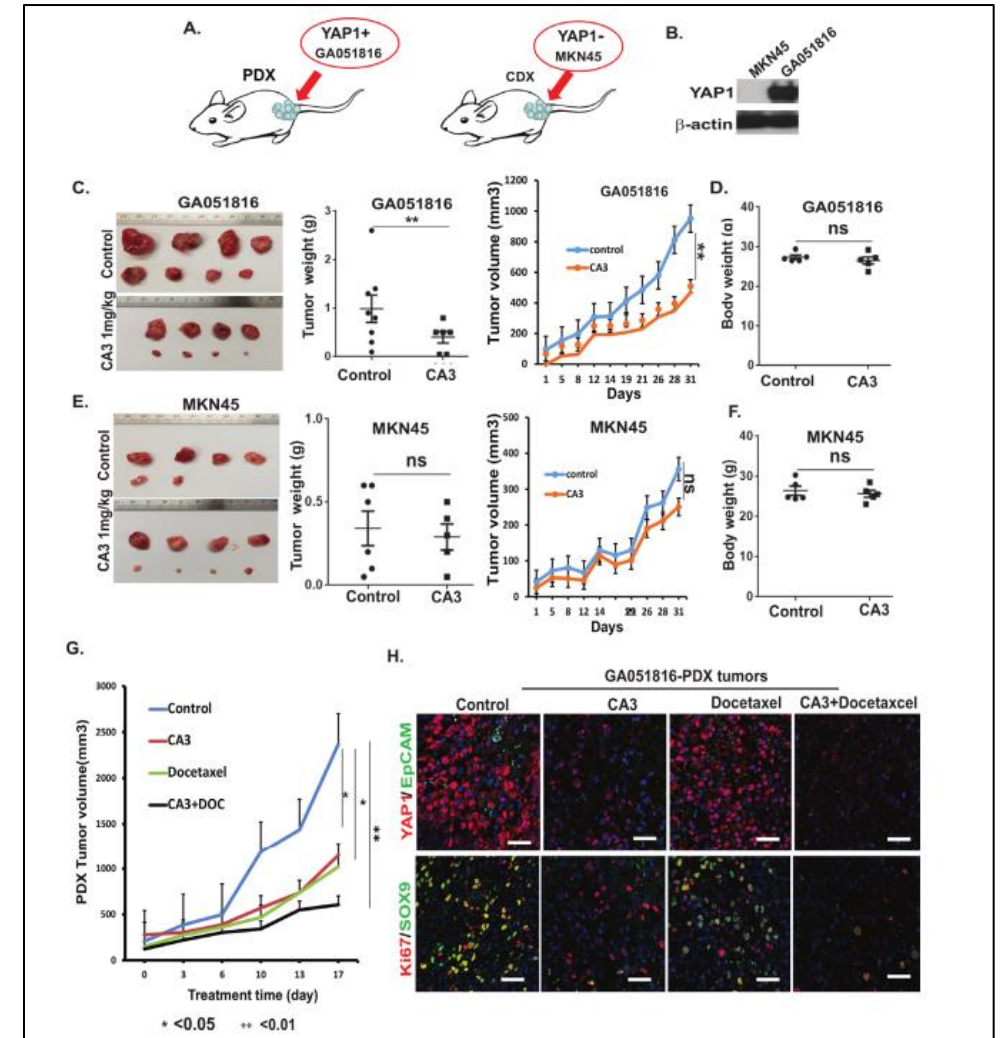
Proud to be
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New targets from basic scientists?

YAP1 mediates gastric adenocarcinoma peritoneal metastases that are attenuated by YAP1 inhibition

Jaffer A Ajani ¹, Yan Xu,^{1,2} Longfei Huo,¹ Ruiping Wang,³ Yuan Li,^{1,2} Ying Wang,¹ Melissa Pool Pizzi,¹ Ailing Scott,¹ Kazuto Harada,⁴ Lang Ma,¹ Xiaodan Yao,¹ Jiankang Jin,¹ Wei Zhao,⁵ Xiaochuan Dong,⁶ Brian D Badgwell,⁷ Namita Shanbhag,¹ Ghia Tatlonghari,¹ Jeannelyn Santiano Estrella,⁸ Sinchita Roy-Chowdhuri,⁸ Makoto Kobayashi,⁹ Jody V Vykoukal,⁹ Samir M Hanash,⁹ George Adrian Calin ¹⁰, Guang Peng,⁹ Ju-Seog Lee,¹¹ Randy L Johnson,¹² Zhenning Wang,² Linghua Wang ³, Shumei Song ¹



Asked to address 2 questions:

1. What evidence is needed to move peritoneal therapies forward?

Comparison to Standard of Care

1. Optimal timing for peritoneal directed therapies?

Importance of Response to Systemic Therapy

CONCLUSIONS

- **Have established phase I & II dosing regimens**
- **Correlative studies to identify new targets will be crucial**
- **Incorporation into new standards of care – immunotherapy**
- **Revisit role of surgery for each incremental improvement in systemic therapy**

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Thank You!