

ROLE OF REGIONAL THERAPY (HIPEC/PIPAC/IP CHEMO)

FOR

GASTRIC CANCER PERITONEAL CARCINOMATOSIS



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Debbie's Dream Foundation Webinar
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Disclosures

FUNDING

DoD E01 Award W81XWH-19-1-0225 (PI, 2019-2021) & Clinical Trials Internal Funding Prioritization Committee Support

“Discovery of Immune Biomarkers That Predict Response to a Novel Chimeric Immuno-Oncolytic Virus Encoding Anti-PD-L1 in Gastric Cancer Peritoneal Carcinomatosis”

Stand Up 2 Cancer Gastric Cancer Interception Grant (Site PI, 2020-2023)

“Early Detection of Diffuse and Intestinal Gastric Cancer”

Department of Surgery Start Up (PI, 2015-2020)

“Molecular Staging of Gastric Cancer” and

“Preclinical studies in evaluation of the safety and efficacy of oncolytic viruses in GI cancers”

Medical Advisor

Hope for Stomach Cancer / Debbie’s Dream Foundation

CONSULTANT

Ethicon, Auris, Verb

Opportunities to Improve Survival in GC PC patients

- What is stomach cancer peritoneal carcinomatosis?
- What are the peritoneal carcinomatosis directed therapies in gastric cancer?
- How, when and who of IP /HIPEC/ PIPAC?
 - Intraperitoneal chemotherapy
 - Hyperthermic Intraperitoneal Chemotherapy
 - Pressurized Intraperitoneal Aerosolized Chemotherathy
- How do we select the right therapy for the right GC PC patients?
- How can we do more to achieve a cure for all GC patients?

No Life Should Be Lost to Stomach Cancer

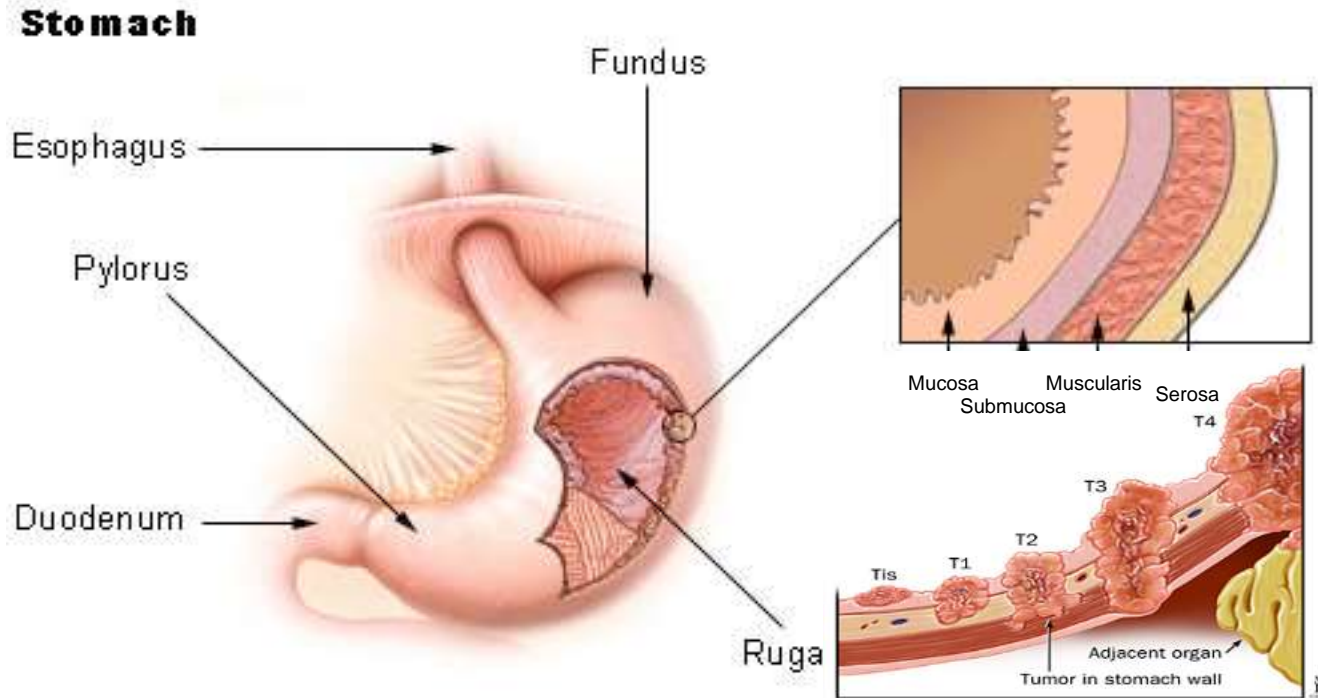


What is Gastric (Stomach) Cancer ?



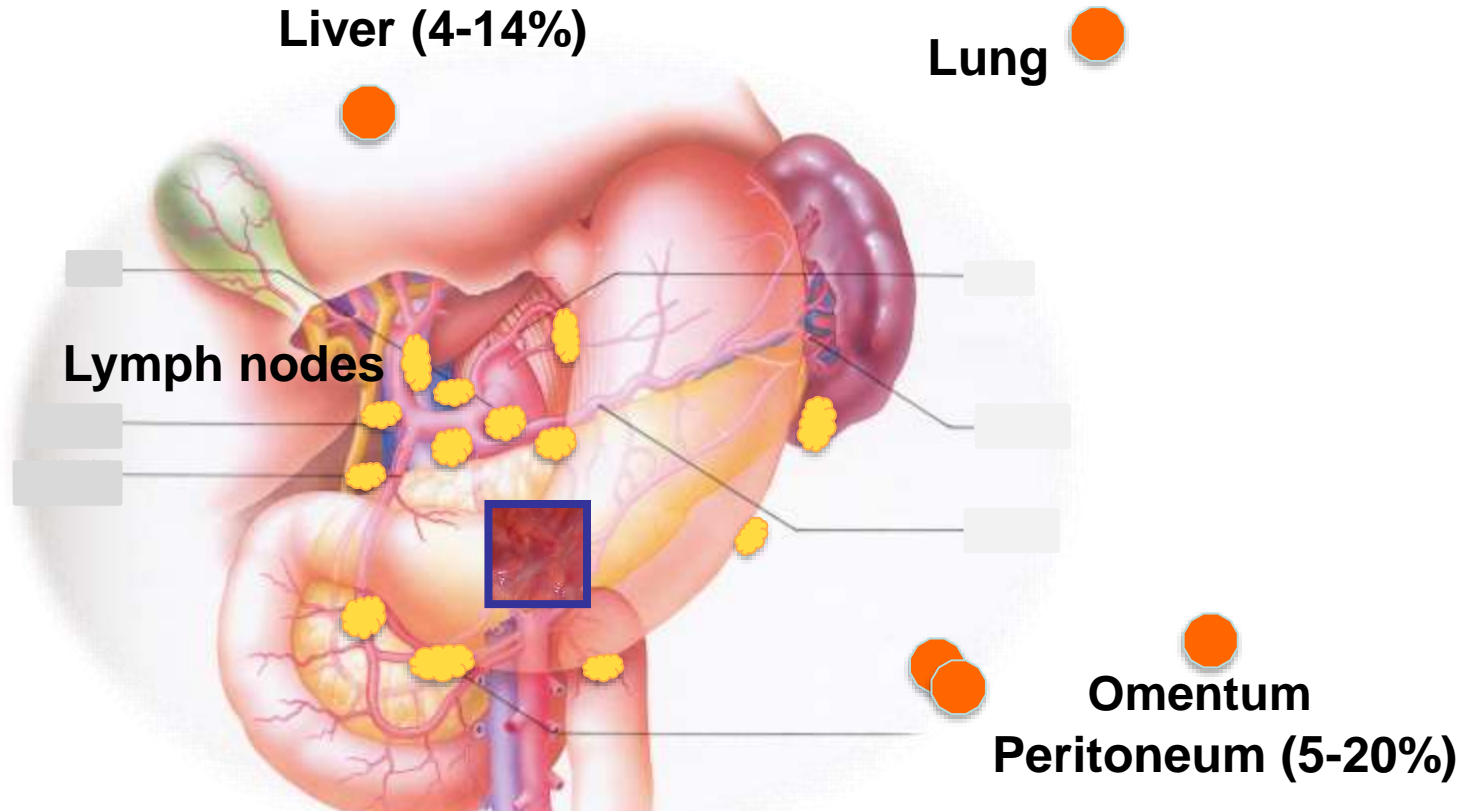
Malignant tumor that arises in the wall of the stomach anywhere from the junction of the esophagus and stomach the (EGJ) and the pylorus (the most distal portion of the stomach)

If Left Untreated Gastric Cancer Invades



Cancer cells invade the inner layers of the stomach outward

...and Spread to LNs and Other Organs



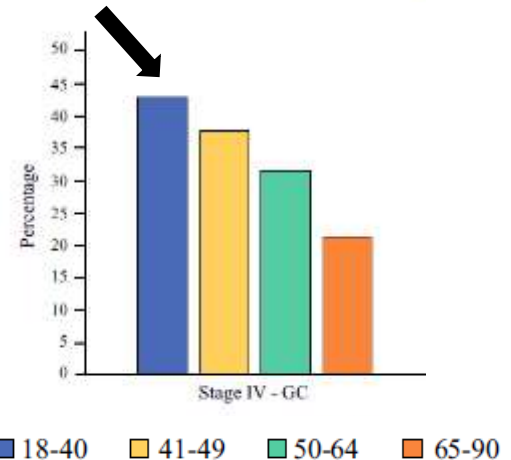
Peritoneal Carcinomatosis

- Tumors in the peritoneum are called peritoneal carcinomatosis (PC) and associated with many complications
 - Accumulation of malignant ascites
 - Development of bowel obstruction
 - Pain, malnutrition and cachexia
 - Can lead to deaths in weeks to months
- More than 40% of stomach cancer patients 18-40 yo present with Stage IV cancer
- YA are likely to present with PC at the time of initial stomach cancer diagnosis: 32.1% vs. 14.1%

Primary	Syn	Recur	Autopsy
GC	15%	>50%	60%

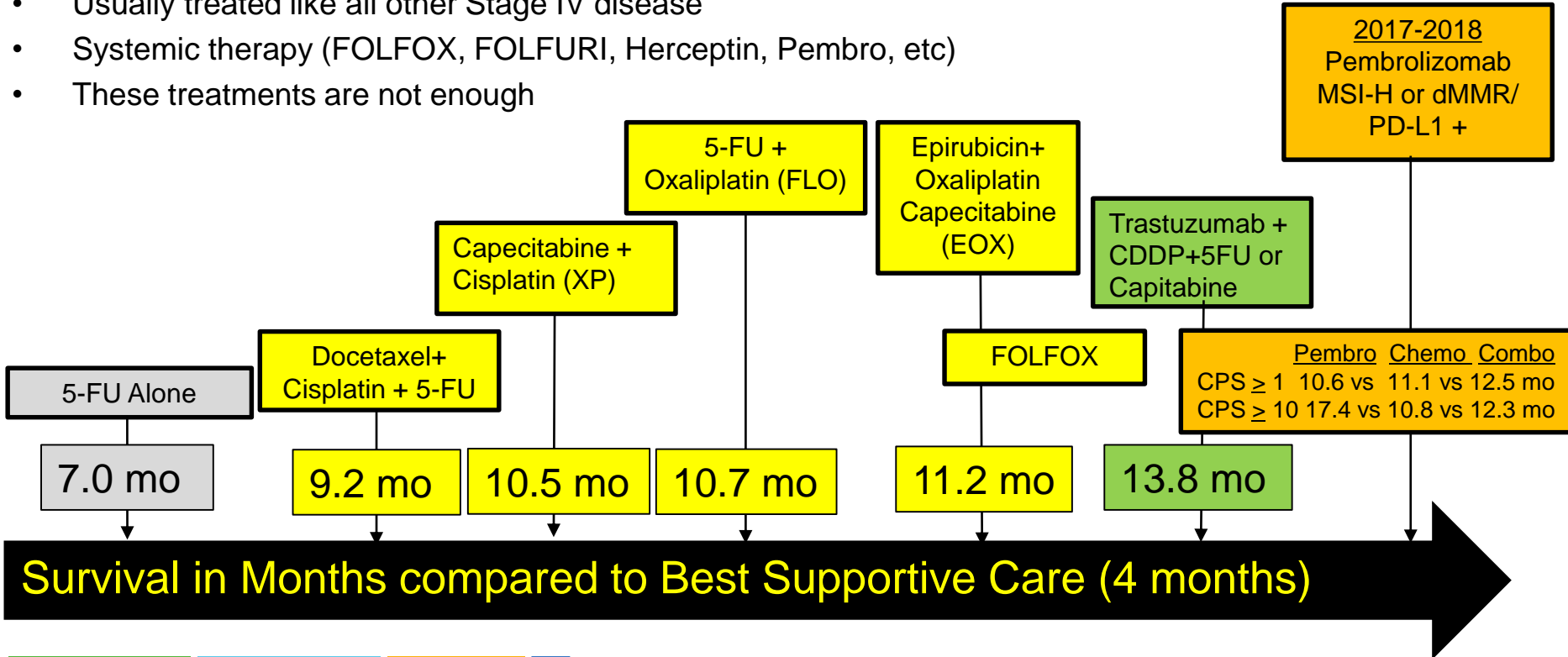
Disparate and Alarming Impact of Gastrointestinal Cancers in Young Adult Patients

Anir Khan, MD¹, Philip H. G. Isaacs, PhD², Mustafa Hasef, MD³, Ealah Melstrom, MD⁴, Baigong Li, PhD⁵, Yate-Ching Yuan, PhD⁶, Lily Lal, MD¹, Benjamin Paz, MD¹, Ajay Goel, PhD¹, Yuxun Feng, MD¹, and Yanghee Won, MD, FACS¹



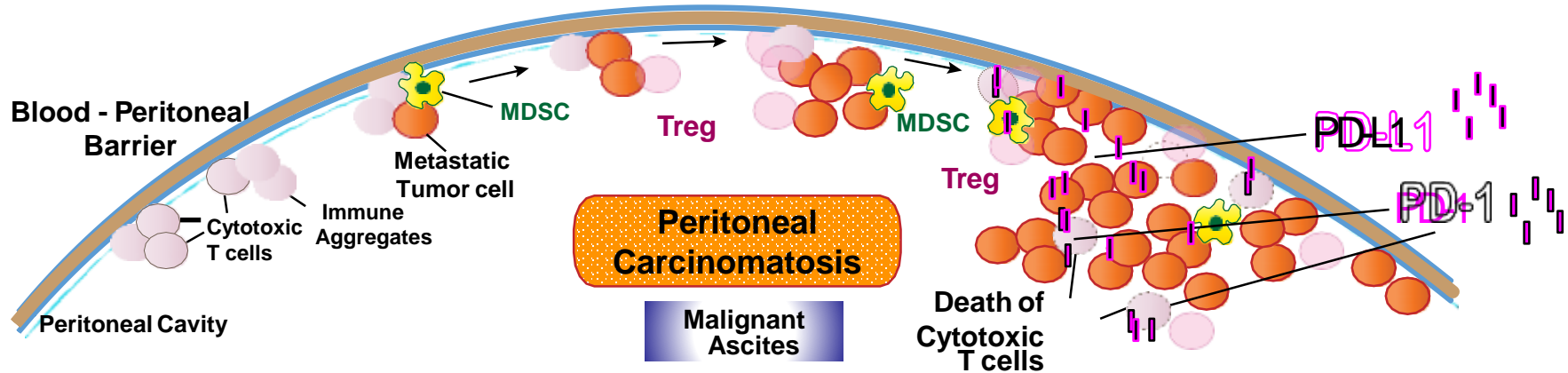
Treatment Strategies for Peritoneal Carcinomatosis

- Usually treated like all other Stage IV disease
- Systemic therapy (FOLFOX, FOLFURI, Herceptin, Pembro, etc)
- These treatments are not enough



Rationale for Peritoneum Directed Therapy

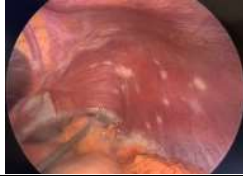
- PC poses distinct therapeutic challenges
 - Tumor protective **blood-peritoneal barrier** and an **immunosuppressive environment** that prevent effective drug delivery and promote **drug resistance**
 - Diffuse nature of PC makes complete surgical resection ineffective, if not harmful
 - **Disease often not measurable → Patients do not qualify for clinical trials**



Rationale and Goals of Peritoneum Directed Therapy

- Goals of care
 - Decrease tumor burden and improve symptoms from complications such as malignant ascites
 - Complete eradication of tumor in the peritoneum to improve survival (combination of therapies)
- Rationale:
 - To bypass or penetrate the blood-peritoneal barrier: Intraperitoneal chemotherapy can achieve higher concentrations in the peritoneal tumor
 - Heated chemotherapy can penetrate tumor better
 - Repeated dosing is possible and more effective
 - Cytoreductive surgery can have high risk of complications – reserved for those with chance of complete clearance of all tumors
 - Treatment approaches: systemic, intraperitoneal, normal versus heated versus pressurized, cytoreductive surgery or no surgery, what are the best combinations?

Peritoneal Directed Therapy: Lessons from Past Trials



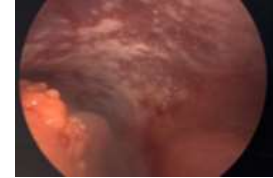
IP Intraperitoneal Chemotherapy

Phase III Trial Comparing Intraperitoneal and Intravenous Paclitaxel Plus S-1 Versus Cisplatin Plus S-1 in Patients With Gastric Cancer With Peritoneal Metastasis: PHOENIX-03 GC Trial

- Trials have failed to demonstrate clear survival benefit IP + IV versus IV alone
- However, responses were encouraging in patients with MA
- **Suggested improved survival with IP in high ascites patients**

Goals of Care Palliative Preventative Curative ?

- Combination of IV plus IP maybe better
- Earlier treatment of PC is better
- Heated has advantages
- Better strategies are needed



HIPEC + CRS Heated IP Chemotherapy

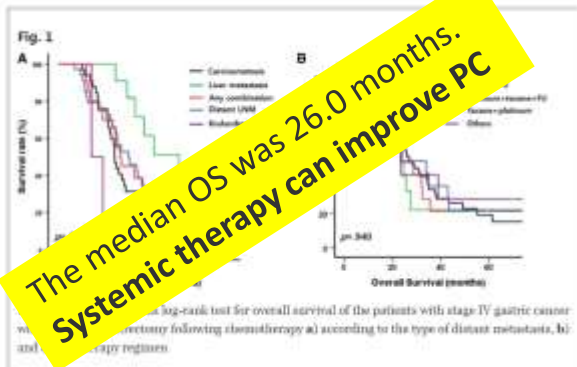
- 30 years of clinical trials failed to achieve survival benefit for single dose HIPEC in most
- Chemo agents, dosing, timing is varied across the trials
- **Benefits patients with occult disease and for improvement of 4 months**

Lessons from Practice-based on Trials

Systemic chemo plus CRS

Multidisciplinary treatment for patients with stage IV gastric cancer: the role of conversion surgery following chemotherapy

Seung-Hoon Beom^{1,2}, Yoon Young Cho^{1,2}, Sang-In Park¹, Shuang Ji Li³, Joon Seok Lim⁴, Taek Seon Hwang^{5,6,7}, Jae-Ho Cheong⁸, Woo-Jin Hwang⁹, Seung-Ho Cho¹⁰, Minhye Jung¹¹, Hyeon Seung Kim¹², Hee-Chul Jung¹³, Hyun Chul Chung¹⁴, Sun-Young Huh¹⁵ and Sang-Hoon Noh¹⁶

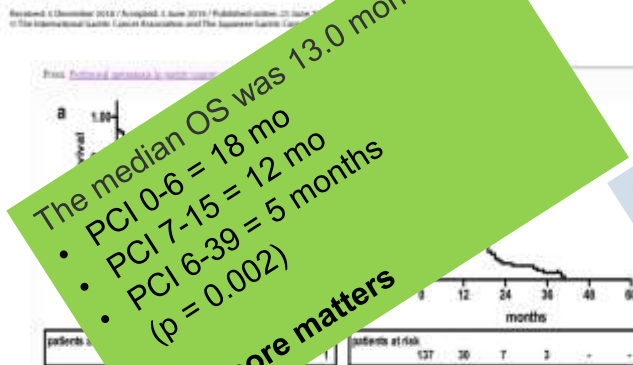


Beom, SH et al. BMC Cancer, 2018
South Korea

Systemic chemo plus One HIPEC (one or two chemo agents) plus CRS

Peritoneal metastasis in gastric cancer: results from the German database

Beate Rau¹, Andreas Brandt², Pompilio Pitti³, Jörg Pütz⁴, Peter Busch⁵, Gerd Dierks⁶, Hans-Jürgen Schmoll⁷, Marc Rothmar⁸, Jürgen Tapscott⁹, Udo Sulkowski¹⁰, Falk Unger¹¹, Rüdiger Hübner¹², Michael Strohlein¹³, Stefan Becker¹⁴, Ingrid Kögler¹⁵, for the Peritoneal Surface Oncology Group and members of the IuDoQ (Peritoneal Surface Oncology Society for General and Visceral Surgery (IGAS))



The median OS was 13.0 months.

- PCI 0-6 = 18 mo
- PCI 7-15 = 12 mo
- PCI 16-39 = 5 months (p = 0.002)

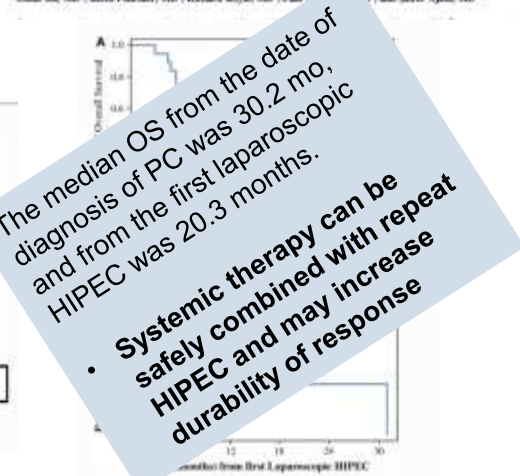
PCI score matters

Rau, B et al. Gastric Cancer, 2019
Germany

Systemic chemo plus repeat HIPEC (two chemo agents) 5 of 19 CRS

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

Brian Badgwell, MD, MS¹, Marjela Khan, MD², Pranjay Das, MD³, Joseph Entoffa, MD⁴, Xuesi Wang, MD⁵, Lina He, MD⁶, Keith Forsgren, MD⁷, Richard Ryski, MD⁸, Paul S. Fung, MD⁹, and Jeffrey Ajani, MD¹⁰



The median OS from the date of diagnosis of PC was 30.2 mo, and from the first laparoscopic HIPEC was 20.3 months.

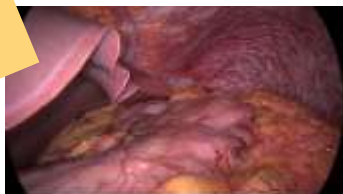
- Systemic therapy can be safely combined with repeat HIPEC and may increase durability of response

Badgwell, B et al. ASO, 2020

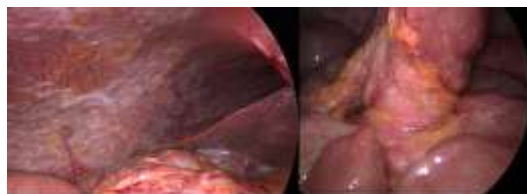
Have We Optimized Our PC Treatment Strategy

Poorly Diff, diffuse,
SRC, HER2 (2+);
PD-L1 CPS 5

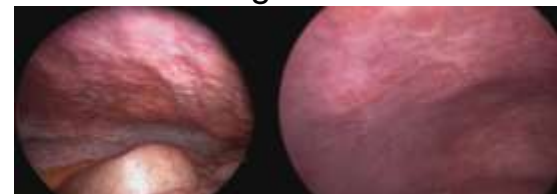
PreTreatment
Jan 2020



FOLFOX/Herceptin/Pembro
May 2020



Systemic Plus HIPEC#2
August 2020



Systemic Plus HIPEC#3
October 2020



FOLFIRI / Herceptin / Pembro;
November 2020



No HIPEC for 3 months



Evidence for PIPAC from International Experts



	Number of PIPAC patients	Pleural/Peritoneal tumor burden improvement	Assessment of response				Survival
			Stable disease	Regression	CR/CR1	Other	
Overall							
Stomach							
PIPAC ¹	64	40/22 (50%)	33/4 (75%)	27/21 (50%)	1/1 (100%)	11/22 (50%)	10/22 (45%)
Stomach and colleagues ²	22	16/2 (73%)	14/10 (70%)	1/1 (100%)	0/0	1/1 (100%)	14/22 (64%)
Stomach and colleagues ³	12	10/2 (83%)	10/10 (100%)	0/0	0/0	0/0	10/12 (83%)
Stomach and colleagues ⁴	10	8/2 (80%)	8/8 (100%)	0/0	0/0	0/0	8/10 (80%)
Stomach and colleagues ⁵	10	8/2 (80%)	8/8 (100%)	0/0	0/0	0/0	8/10 (80%)
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- 42 Clinical Trials
 - Over 800 total patients
 - ~200 stomach cancer
 - Safe and feasible
 - 79% stable disease or decreased ascites
 - 10-20 months survival
 - May prolong survival
 - On-going trials in Europe and Singapore
- ❖ Phase I Device Registry trial open at COH (T. Dellinger, PI)

PIPAC for Gastric Cancer Peritoneal Carcinomatosis

- Exactly, what is PIPAC?
 - **P**ressurized **I**ntra**P**eritoneal **A**erosolized **C**hemotherapy
 - A laparoscopic approach of delivering chemotherapy (or other anti-cancer agents) to destroy cancer cells in the peritoneum
 - Uses a high-pressure drug delivery system **CapnoPen** that is **NOT YET FDA approved in U.S.**
- What is role of PIPAC in the treatment of stomach cancer patients in the U.S.?
 - In its **INVESTIGATIONAL PHASE**
 - Currently undergoing Phase I clinical trial

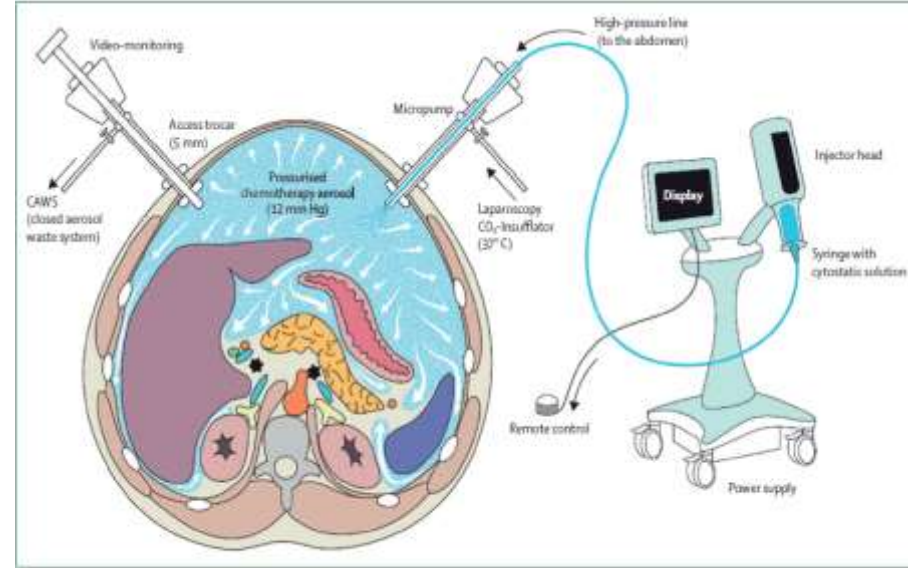


Figure 2: Schematic of PIPAC set-up

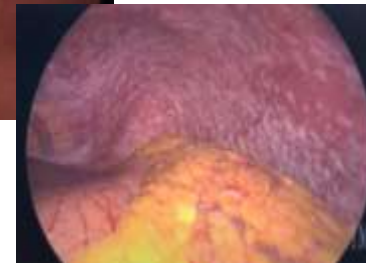
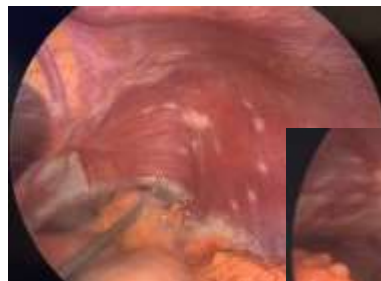
A hermetically sealed 10–12-mm trocar and a 5-mm balloon trocar are inserted. The liquid chemotherapy regimen is vaporised using a standard injector connected to a nebuliser. Reprinted from Hübner and colleagues²⁶ with permission from Médecine et Hygiène. PIPAC—pressurised intraperitoneal aerosol chemotherapy.

Phase I Trial In U.S. – PIPAC Device Registry

- *To evaluate the safety of the PIPAC device and the method of intraperitoneal delivery of combination chemotherapies by PIPAC*
- Indications:
 - Patients with PC from stomach, ovarian, colon and appendiceal cancers
 - High burden of peritoneal disease
 - Progressed on systemic therapy
- Laparoscopic procedure
- Short hospital stay ~24 hr
- Repeat 3 times

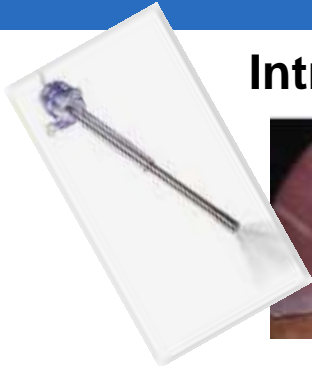


Cisplatin
Doxorubicin

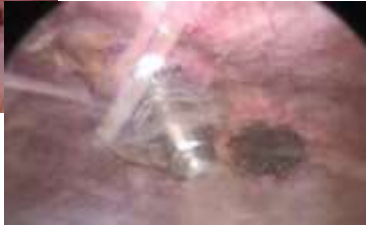


Peritoneal Carcinomatosis
Index (PCI) Score: 0 to 39

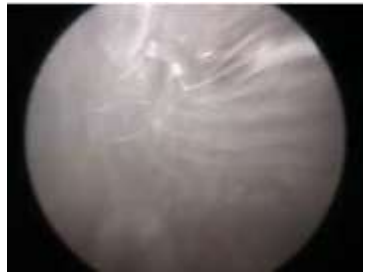
Minimally Invasive and Short Operative Time



Intra-abdominal view



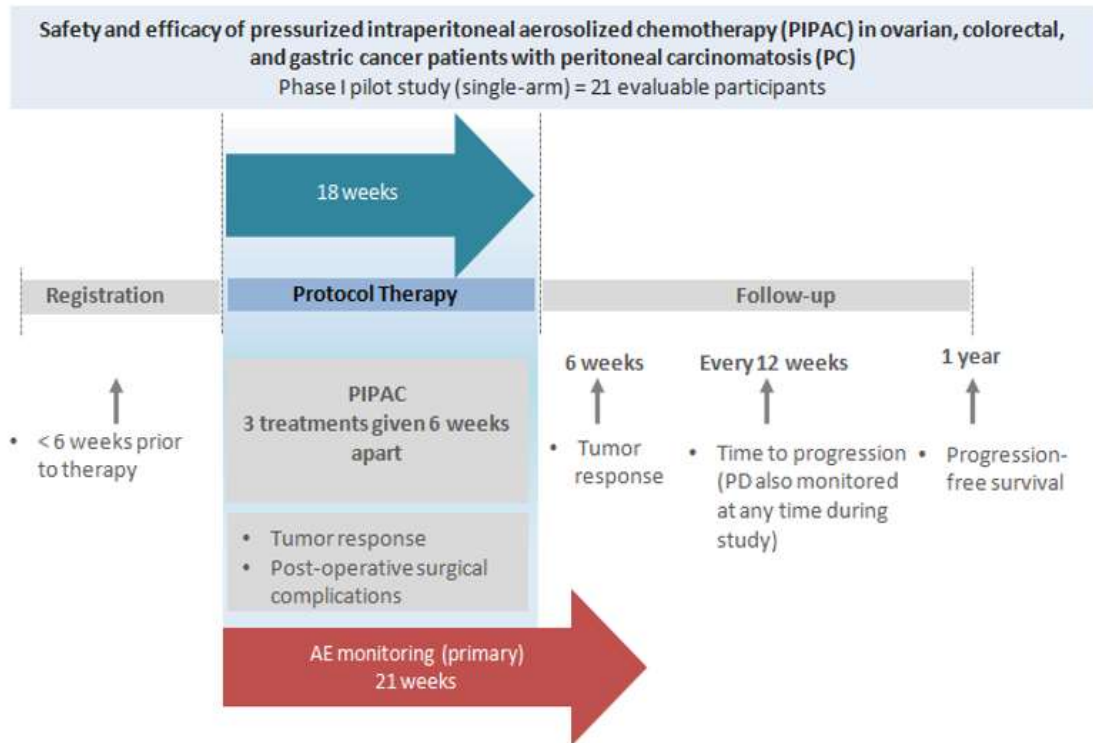
OR Setup



Extra-abdominal view

Phase I PIPAC Trial: Experimental Design

Experimental Design Schema



Potential Role for Regional Therapy in GC PC

At Time of Initial Presentation Comprehensive Multi-Disiplinary Treatment Strategy

Diagnostic laparoscopy when safe and able: assess extent of disease, obtain tissue biopsy

High Risk
Cytology +

Minimal Disease
PCI Score <6

Moderate Disease
PCI Score 6-12

High Burden of Disease
PCI Score >12

Standard of Care Guideline-Based 1st Line Treatment Strategy

Second Line / Clinical Trials / No measurable disease by RECIST

- TRIAL: Bidirectional Therapeutic Strategies**
- Method of Delivery (HIPEC, PIPAC)
 - Agents (chemotherapeutics, immunotherapeutics)
 - Mode & Frequency of reassessment

PIPAC Phase I
Device Registry

Outcome: Safety and efficacy
Goal: palliation or curative (improve QoL and prolong survival)

Let's Summarize the Clinical Realm of GC PC

- Every patient with GC PC should be evaluated by a multidisciplinary team for potential regional treatment option
- Patient-tailored, tumor specific treatment strategy should be developed
- Standard of care is not enough
- Clinical trials of novel therapies and strategies should be considered based on patient's tumor specific molecular profiles
- Regional therapy with IP, HIPEC, or PIPAC can be considered on clinical trial or on an individualized patient bases (expert centers, experienced surgeons)
 - HIPEC for stomach cancer in clinical trials; and used in clinical practice in select settings
 - PIPAC is INVESTIGATIONAL and undergoing safety evaluation in the United States
 - Phase II trials of efficacy of regional therapy for stomach cancer is planned at COH
- We are striving to bring novel and more effective treatments for GC PC patients

Precision Oncology for GC PC Patient-Tailored Treatment

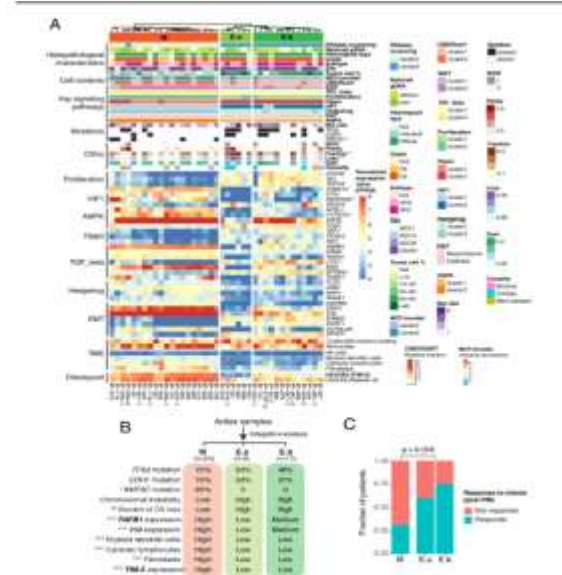
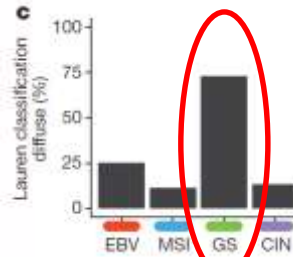


Figure 7. Integrative clustering of clinical, genomic, and expression features of post-PC gastroesophageal (GC) cancers defines three molecular phenotypes that correlated with post-PC chemotherapy response. (A) Heatmap of histopathological and molecular features of three defined clusters: top-trunk molecular phenotype (M), mesenchymal-like phenotype (P), epithelial-like phenotype (E). (B) Heatmap showing normalized expression values in 100 GCs for 100 available differentially expressed genes (DEGs) selected from 3 top signaling pathways. The asterisk indicates statistically significant differences between M and E phenotypes ($p < 0.05$, $**p < 0.01$, $***p < 0.001$). Fisher's exact test and non-parametric Mann-Whitney U test were used to calculate a p-value. (C) Intensity and enrichment characteristics of three molecular subtypes. CTR: chromosome instability; CR: copy number; exp: expression; CI: correlation of defined molecular phenotypes with post-PC chemotherapy response. Compared with the epithelial phenotype (E) and E-M, the mesenchymal phenotype is less likely to respond to chemotherapy. P value was calculated by the non-parametric Mann-Whitney U test. Data: bioRxiv, bioRxiv.

Current Clinical Trials Open to Accrual at COH

Protocol No.	Allows RECIST Non-measurable disease?	Most Novel Therapeutic Agents being tested IMMUNOTHERAPIES	PI Name	Sponsor	Line of Therapy
20244	No	A Phase 2a, Multicenter, Open-Label Study of DKN-01 in Combination with Tislelizumab ± Chemotherapy as First-Line or Second-Line Therapy in Adult Patients with Inoperable, Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma	J. Chao	Leap Therapeutics	1L and 2L cohorts
19311	Yes (during dose escalation)	A Global Phase I Study: Bispecific T-cell Engager AMG199 in Subjects with MUC17-positive GC	J. Chao	AMGEN	≥ 3L
20052	Yes (during dose escalation)	A Global Phase I Study: Bispecific T-cell Engager AMG910 in Subjects with CLDN18.2-positive GC	J. Chao	Amgen	≥ 3L
18289	Yes	A Phase 3, Global Multi-center, Double Blind, Randomized Efficacy Study of IMAB362 Plus mFOLFOX6 compared with Placebo plus mFOLFOX6 as First Line Treatment of subjects with Claudin (CLDN)18.2+, HER2-, locally advanced unresectable or mGC or mGEJ AdenoCa	J Chao	Astellas Pharm	1L
19572	No	A Phase 2/3 Trial to Evaluate Margetuximab in combo with INCMGA00012 and Chemo or MGD013 and chemo in patients with mGC or locally adv, treatment-naïve HER2+ GC or GEJ AdenoCA	J. Chao	Macrogenics	1L
17450	No	PHII-162, NCI#10066: A Phase ½ Study of Olaparib in combo with ramucirumab in mGC and GEJ AdenoCa	J. Chao	ETCTN / NCI	≥ 2L
18069	Yes	A Phase 1b/2 Trial of the IRX-2 Regimen and Pembro in AGC and Adv GEJ adenoCA	J. Chao	COH	≥ 3L

Future of Novel GC PC Therapies

Translation of new drugs / strategies

- Numerous novel agents for cancer are under investigation
- Direct these novel discoveries for stomach cancer patient treatment
- Evaluate these novel agents for stomach cancer peritoneal carcinomatosis in preclinical setting (our laboratories)
- Conduct clinical trials for stomach cancer patients
- Development of better treatment strategies

Improve Stomach Cancer Outcome

Awareness

Advocacy

Funding

Awareness

Advocacy

Funding

Regional Therapy

Immunotherapy

Oncolytic
Viruses

CAR-T Therapy

Liquid biopsy

Plan: Bring best of science and technology to cure stomach cancer patients

Gastric Cancer Workgroup at City of Hope

The GCWG at COH is a multidisciplinary team of experts in GC / GEJ.
We strive to provide the best quality of life and long-term survival for our patients.
Our goal is to eliminate deaths due to stomach cancer nationally and worldwide.

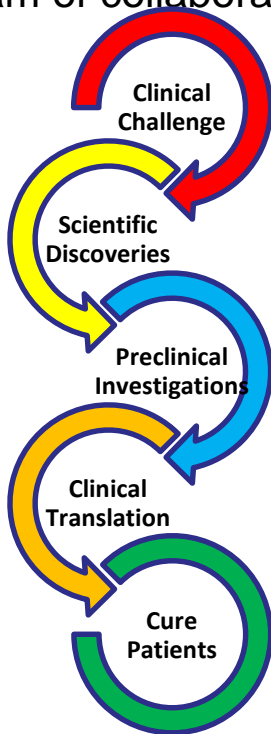


Teaming up to cure stomach cancer

- It takes vision, dedication and a team of collaborators to find a cure for stomach cancer



DoD Award Team



SU2C team



Alicia Smith (@AliciaStoCAN)

We are committed

- *To eliminate deaths due to stomach cancer (gastric cancer, GC)*
- *To bring the best of science and technology to improve quality of life and long-term survival for patients with GC*
- *To develop more effective diagnostic and therapeutic strategies for gastric cancer peritoneal carcinomatosis (GC PC)*

Thank you for your dedication and advocacy!

PATIENTS & ADVOCATES



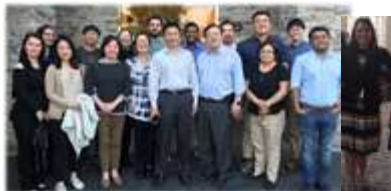
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