HIPEC

Hyperthermic Intraperitoneal Perfusion with Chemotherapy

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Hyperthermic

- Heat has a direct antitumor effect

Intraperitoneal

- The abdominal cavity. Works best on tumors that stay in this area and aren’t invasive.

Chemotherapy

- Apply directly to tumor. Use agents that work better with heat.
Background on HIPEC

- Standard of care in appendix tumors, mesothelioma, and ovarian cancer
- Controversial in colon cancer – is included in National Comprehensive Cancer Network Guidelines
- Very controversial for gastric cancer
- In theory makes sense – cut everything out, apply heat, apply chemo directly to tumor, use chemo that works better with heat
- There has never been a completed trial comparing HIPEC to standard of care chemo for gastric cancer
The Plan

- Review some of the older data
  - What is going on in Asia

- Cytoreduction vs Cytoreduction with HIPEC
  - China, France, Germany

- Cytoreduction with HIPEC vs Standard of care chemotherapy
  - Netherlands

- Current Options

*Cytoreduction = CRS = cut out all cancer*
Clinical trials that support theory

- Trials of [HIPEC & Gastrectomy] vs [Gastrectomy alone]

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<th>Author</th>
<th>Year</th>
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Randomized clinical trial of extensive intraoperative peritoneal lavage *versus* standard treatment for resectable advanced gastric cancer (CCOG 1102 trial)
Registry Data

- CYTO-CHIP
  - 19 Academic Centers in France
  - 25 year study ending in 2014
  - Cytoreduction & HIPEC vs Cytoreduction alone
  - Mortality 10% with 55% major morbidity
  - 20% 5 year Survival
  - Average of <1 patient per center per year

GI ASCO 2018, NCT03253939
Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy for Gastric Cancer With Peritoneal Metastases (CYTO-CHIP study): A Propensity Score Analysis

Pierre-Emmanuel Bonnot, MD1,2; Guillaume Piessen, MD, PhD1; Vahan Kepenekian, MD1,2; Evelyne Decullier, PhD1; Marc Pocard, MD, PhD1; Bernard Meunier, PhD1; Jean-Marc Bereder, MD3; Karine Abboud, MD1; Frédéric Marchal, MD, PhD1; François Quenet, MD1; Diane Goere, MD, PhD1; Simon Msika, MD, PhD1; Catherine Arvieux, MD, PhD1; Nicolas Pirro, MD, PhD1; Romuald Wermert, MD1; Patrick Rat, MD, PhD1; Johan Gagnière, MD, PhD1; Jérémie H. Lefèvre, MD, PhD1; Thomas Courvoisier, MD1; Reza Kianmanesh, MD, PhD2; Delphine Vaudoyer, MD1,2; Michel Rivière, MD, PhD2; Pierre Mees, MD1; Guillaume Passot, MD, PhD1; and Olivier Glehen, MD, PhD1,2; on behalf of the FREGAT and BIG-RENAPE Networks

![Graph showing OS (probability) over time (months) with different lines representing HIPEC and No HIPEC treatments, with unweighted P = .002 and IPTW-adjusted log-rank P = .005.]

- Isolated extraperitoneal recurrence
- Peritoneal and extraperitoneal recurrences
- Isolated peritoneal recurrence

Unweighted P = .002
IPTW-adjusted log-rank P = .005

No. at risk:
- HIPEC: 180 118 66 41 27 20
- CRSa: 97 47 23 10 5 5
Equipoise - counterbalance

101 Long-Term Survivors Who Had Metastatic Gastroesophageal Cancer and Received Local Consolidative Therapy

• 21% 5 year survival
• Duration of initial chemo important

Long-Term Survival in Patients With Metastatic Gastric and Gastroesophageal Cancer Treated With Surgery

13% 5 year Survival
RCTs that support HIPEC in gastric cancer

- Cytoreductive Surgery (N=34) vs CRS/HIPEC (N=34)
- Carcinomatosis
• Survival improved with addition of HIPEC to CRS
HIPEC in High Risk Resectable Gastric

• GASTRICCHIP - France
  – Big randomized controlled trial
  – Preoperative therapy allowed
  – Thick gastric tumors, can include positive cytology
  – Removing stomach vs removing stomach & HIPEC
  – Activated May 2013
  – Estimated completion May 2023
HIPEC vs. CRS Alone

• GASTRIPEC, Germany
  – Carcinomatosis
  – Everyone gets standard of care chemotherapy 1st
  – Removing stomach & cytoreduction vs same & HIPEC
  – Activated March 2014
  – Stopped early, but should be reporting soon
Clinical trials of HIPEC in gastric cancer

- PERISCOPE II, The Netherlands Cancer Institute
  - Relatively low volume peritoneal disease
  - Gastrectomy/CRS/HIPEC vs chemo alone
  - 106 patients
  - Activated October 2017
  - Estimated completion October 2022
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:
  - Cut out all the tumor
  - 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

- Everyone gets chemotherapy
- If HIPEC is going to work, make it work before cutting out stomach
- Can separate HIPEC from stomach removal
Laparoscopic HIPEC

- Insert camera and visualize disease
- Wash the peritoneum with saline
- Inflow 41-42°C
- 1 hour
- Mitomycin
- Cisplatin
- Thiosulfate – kidney protection
Patients enrolled (N=19)
- 100% (N=19) had received chemotherapy
- 26% (N=5) had received chemoradiotherapy

Laparoscopic HIPEC (≤5 procedures)
- 0% (N=0) received chemotherapy between planned procedures
- 47% (N=9) received chemoradiotherapy between planned procedures

Negative cytology, no carcinomatosis
- 37% (N=7)

Declined resection
- 11% (N=2)

Persistent positive washings or carcinomatosis
- 63% (N=12)

Resection
- 26% (N=5)
Did it work?

- 1, 2, 3 year OS rates 95%, 68%, and 44%
Recently Completed Phase II Trial

• Everyone gets chemotherapy

• 2-stage approach:
  • 1) Minimally Invasive HIPEC
  • 2) Combine Gastrectomy & HIPEC

NCT02891447
Is more aggressive better?

- 1, 2, and 3-year OS rates 90%, 49%, and 30%
NCI : CRS/HIPEC for Gastric Cancer

Phase II study of cytoreduction, gastrectomy and HIPEC for gastric cancer with limited peritoneal metastasis [NCT03092518]

Eligibility
• Adenocarcinoma of the stomach or GEJ (Siewert III)
• + Cytology and/or limited peritoneal metastasis (PCI < 10)

Primary endpoint: Overall Survival
Secondary endpoints: intra-peritoneal PFS, extra-peritoneal DFS, toxicity

Unpublished data, Jeremy L. Davis MD (jeremy.davis@nih.gov)
Peritoneal Options

- Importance of first line chemotherapy!

- Influence of markers and options for immunotherapy or targeted therapy
Current Status of HIPEC in Gastric

- The peritoneum is the best target to improve survival in gastric cancer

- HIPEC can play a role now
  - Clinical Trials!
Current Status of HIPEC in Gastric

- Currently offer 2 stage approach off protocol
- Trials to lower peritoneal disease prior to gastrectomy and HIPEC
International Gastric Cancer Congress
The Evolution of Gastric Cancer Science; The Future of Gastric Cancer Treatment

March 6-9, 2022  Marriott Marquis Houston  Houston, Texas