City of Hope®

ISSPP

INTERNATIONAL SOCIETY FOR THE STUDY OF PLEURA AND PERITONEUM - 2018 -

WHY PIPAC?

Background

Richard L. Whelan, MD

System Chief, Colon & Rectal Surgery

Department of Surgery

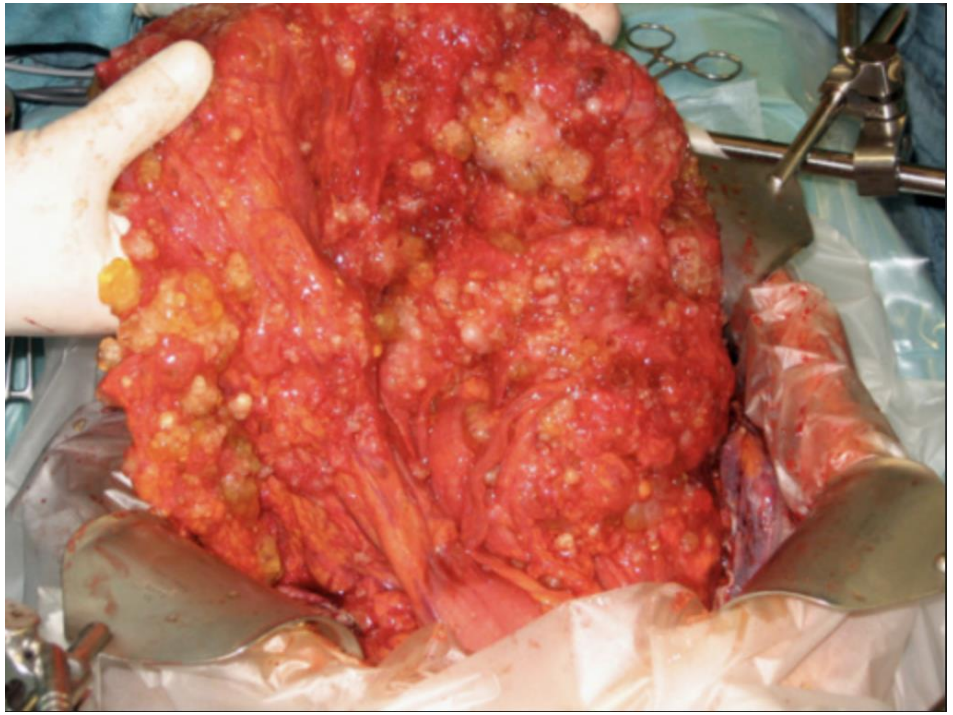
Northwell Health Cancer Institute

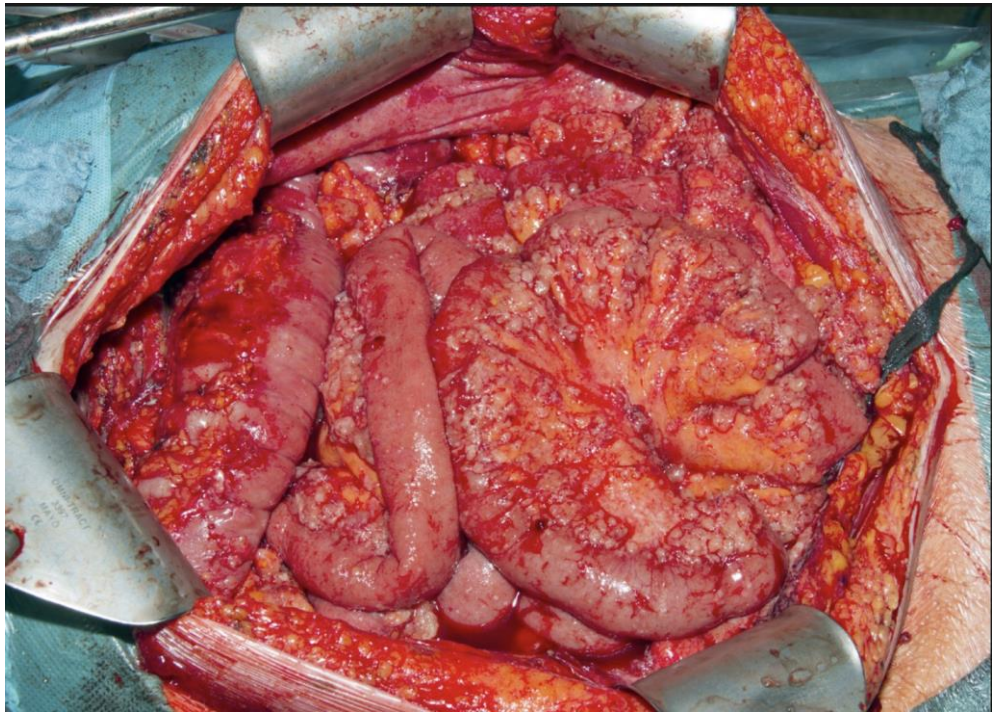
Disclosures

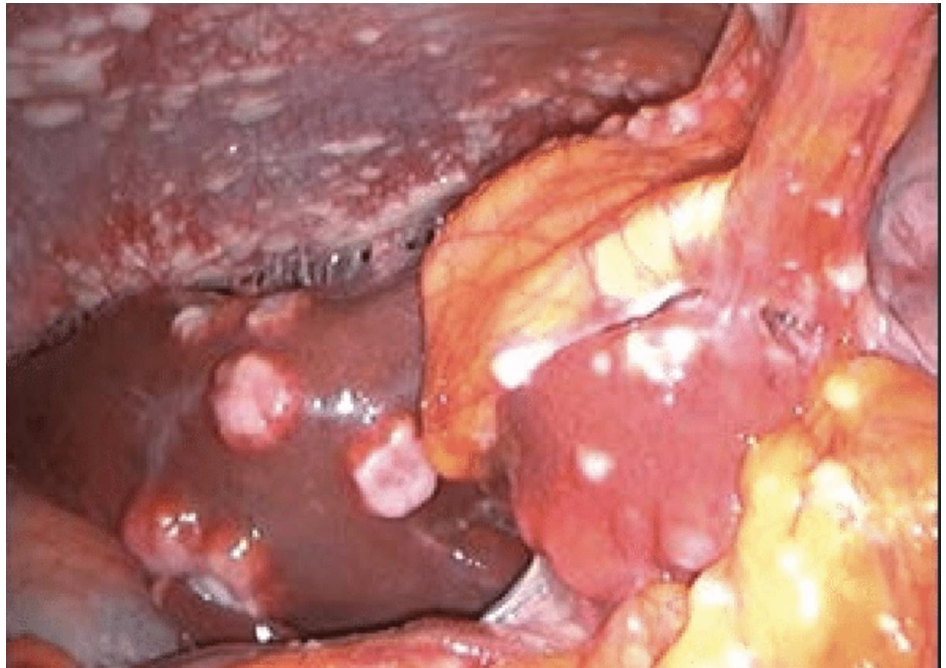
- I do not have relevant disclosures.

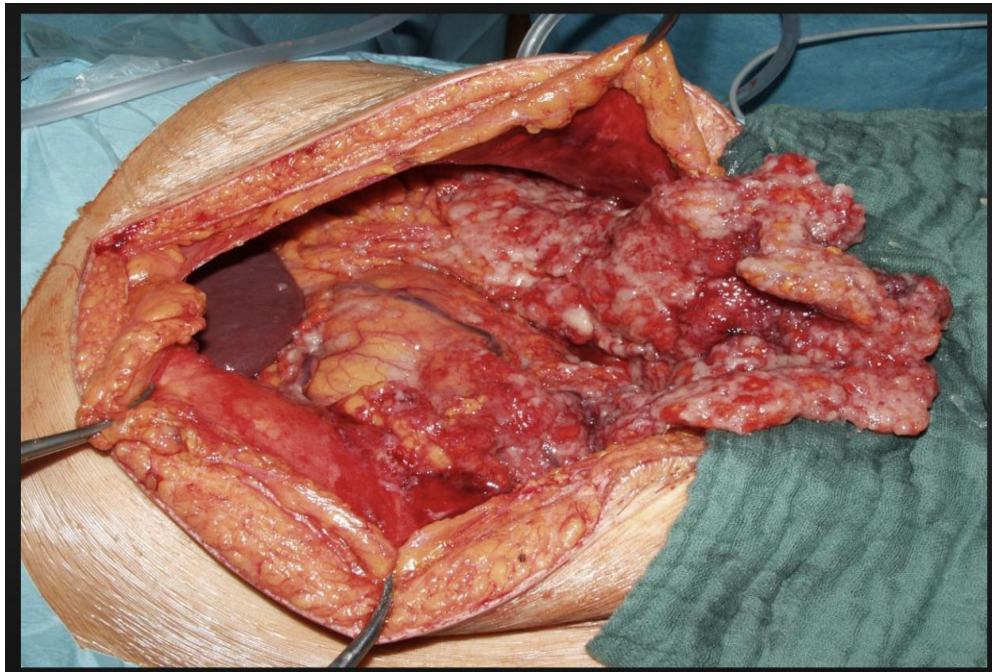
This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

The off-label or investigational use of Cisplatin, Doxorubicin, Oxaliplatin, Mitomycin C may be discussed.









Peritoneal Metastasis (PM): How big a problem in the U.S. ?

Cancer type*	Number of patients/year
Ovarian cancer	14,000
Colorectal cancer	12,000
Gastric cancer	5,000
Appendiceal	800
Mesothelioma	500
Total	**32,300 /year**

* PC may also develop from pancreatic, hepatobiliary, and other cancers

Peritoneal Metastases (PM) / Carcinomatosis

- Poor prognosis
- Treatment options:
  - Cytoreductive surgery (CRS) alone
  - **Surgery + systemic chemotherapy**
  - Surgery + intraperitoneal (IP) liquid chemotherapy (+ IV chemo)
  - **CRS + HIPEC (heated intraperitoneal chemotherapy)**
  - **Chemotherapy alone**

IV chemotherapy for PM: Problems

- Peritoneal lesions are poorly vascularized
- High blood levels are required to get effective levels in the PM lesions
- Considerable associated systemic toxicity (CTCAE Grade 3,4,5 events)
- Impact in the abdomen limited
- Results: modest improvement in survival vs surgery alone
- Limited number of evidence based regimens

Systemic chemotherapy regimens for PM

- Colorectal/appendiceal:
  - FOLFOX, FOLFIRI +/- avastin
  - Regorafenib or lonsurf
  - Immunotherapy where appropriate
- Ovarian:
  - Carboplatin and paclitaxel, +/- avastin
  - Carboplatin and doxorubicin
  - Platin + PARP inhibitor
- Gastric:
  - Oxaliplatin, 5 FU, +/- leucovorin (metastatic dx)
  - Trastuzumab (HER2-NEU +) (metastatic dx)
  - Oxaliplatin, leucovorin, 5FU, docetaxel (preop)
  - Cisplatin, 5 FU (or capecitabine (preop)

Current alternatives to systemic chemotherapy?

- Normothermic IP liquid chemo treatment
- ***Cytoreductive surgery + hyperthermic intraperitoneal chemotherapy***

CRS HIPEC improves survival and is curative in a small subset of patients

- Sugarbaker was early champion:
  - In subset of PC patients near complete debulking was possible
  - After cytoreduction the abdomen is filled with heated liquid chemotherapy
  - HIPEC penetrates the peritoneum a short distance and eradicates tumor
- CRS HIPEC is now used for wide variety of PM patients
  - ***Single administration of chemo***
- Limited & contradictory phase 3 study results vs CRS only (ovary, colorectal)
- Remains controversial but is commonly employed
- Small percentage of patients are cured
- Great majority recur

Eligibility Criteria for CRS HIPEC

- Reasonable burden of disease (PCI score)
  - Ability to adequately cytoreduce such that HIPEC can eradicate the residual disease.
  - Heated chemotherapy penetrates peritoneum a finite distance
  - Contraindication: Diffuse invasion of small bowel, mesentery & unresectable lesions
- Absence of intra-abdominal parenchymal metastases (liver, nodal disease) and extra-abdominal metastases
- Acceptable performance status (Karnofsky score) & co-morbidity assessment
- The minority of PM patients are accepted for CRS HIPEC
- **The majority are not candidates and, instead, get IV chemotherapy**

CRS HIPEC: No walk in the park

- Multiple bowel resections in some patients are needed
- Extent of feasible cytoreduction varies
- Grade 3-4 adverse events/complications: 22-34%
- Morbidity 30-70% reported
- Mortality (30-60 day):
  - 0.8-4.1 % - for CRC, Pseudomyxoma peritonei, malignant mesothelioma
  - 3.9-6.5% - for gastric cancer patients
- Lengthy hospitalization is common
- **Majority of CRS HIPEC patients will develop recurrences**
- **Moderate to severe adhesions commonly develop**

What is the fate of CRS HIPEC patients that recur

- Repeat CRS/HIPEC is a consideration in a select subpopulation of patients with isolated peritoneal recurrence.
  - In one study 7% of patients underwent repeat CRS/HIPEC*
  - Complete cytoreduction (CC) was not possible in 33 % of colorectal cancer patients undergoing a 2nd CRS HIPEC**
  - Majority will recur again
- **IV chemotherapy is given to most patients with recurrent disease**

*Mogal et al. J Gastrointest Oncol. 2016 Feb; 7(1): 129–142.

**Vassos et al. World J Surg Oncol. 2016; 14: 42. PMCID: PMC4765140, PMID: 26912149.

What type of treatment would augment our current treatment approaches

A treatment that:

- Delivers chemo directly into abdomen
- Is a minimally invasive procedure
- Is well tolerated and has short LOS & complication rate
- Can be repeated

Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) *

- Palliative treatment that can be repeated
- Aerosol: colloidal suspension of particles in gas
- Laparoscopic procedure: 1 ten mm & 1-2 five mm ports
- Multiple peritoneal biopsies taken, PCI determined, ascites sampled
- Thirty minute administration period
- **Currently, no cytoreduction or LOA carried out**
- Drugs in use: oxaliplatin; cis-platinum, doxorubicin, mitomycin C, and others
- Usually 3 PIPAC's/patient given at 6 week intervals (up to 15 Rx's)

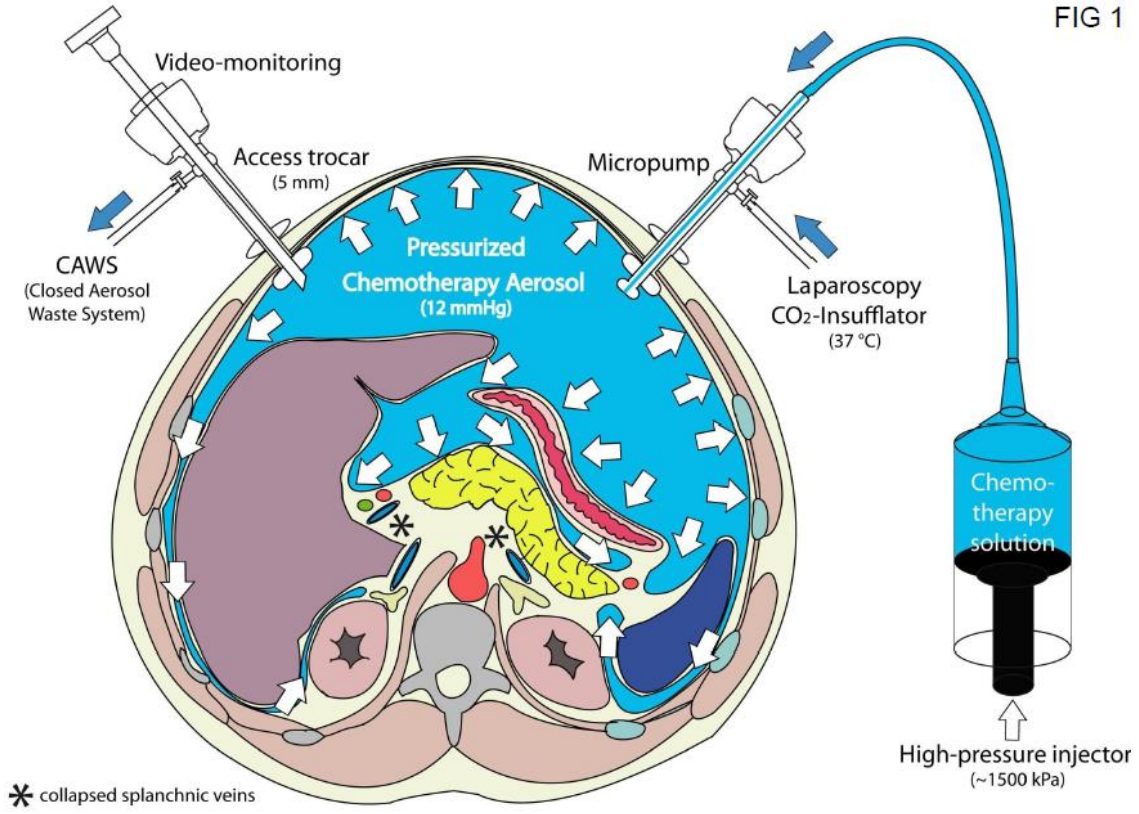
* Inventor and early investigator: Marc Reymond, University of Tuebingen

Rationale for PIPAC

- Aerosol distribution in abdomen more homogenous than liquid IP Rx
- Pneumoperitoneum generates pressure gradient that increases penetration
- Higher tissue drug concentration attained (vs IV or IP liquid chemotherapy).
- Less drug needed (10%-20% systemic dose, notably less than HIPEC dose)
- Well tolerated
- **Ambulatory or 1 day LOS**
- **Can be repeated at 5-6 week intervals**
- Avoidance of IV chemotherapy infusion-related complications

Reymond et al Surg Endosc 1999, Esquis P et al, Ann Surg 2006, Facy O et al, Ann Surg 2012
Solass et al, Ann Surg Oncol 2014, Khosrawipour et al 2017, Blanco et al, Ann Surg Oncol 2014, Robella et al, World J Surg Oncol 2016

PIPAC: pressurized intraperitoneal aerosol drug delivery



Not a specific therapy but a drug delivery method !

Utilization options for PIPAC

- As stand alone palliative treatment for patients who have failed or poorly tolerated the evidence based systemic chemotherapy regimens
  - Vs IV chemo, fewer adverse events
  - More time out of hospital, better QOL
- As part of “bidirectional” treatment (PIPAC + systemic chemotherapy) for:
  - Non operative candidates
  - Borderline candidates for CRS/HIPEC in hopes of downstaging their disease → CRS/HIPEC

Palliative Use: Case report

- 61 yo male with appendiceal LAMN
- Underwent CRS HIPEC at Wake Forest (colon, stomach, spleen,GB)
- Node + disease → FOLFOX x 6 months
- Recurred 4 months later.
- Enrolled US PIPAC study → 3 PIPAC (oxaliplatin) & same day bolus 5 FU (400 mg/m2)
  - CEA dropped from 29 to 6.4
  - Ascites from 300 ml → 50 ml
  - PCI 29 → 24, gross impression at 2nd and 3rd laparoscopy notably fewer lesions
- Additional PIPAC x 5 given on compassionate use basis at 6-10 week intervals)
- Total of 8 PIPAC Rx given over 1 year. Stopped due to encroaching anterior adhesions.
- 1 brief partial SBO that resolved in 3 days and has not recurred. No other hospital admissions
- QOL excellent (multiple vacations, ski trips, wedding, etc)

Bidirectional treatment: PIPAC + systemic chemotherapy

- Attacks tumors both from the bloodstream and directly via the peritoneal cavity
- If 6 week cycle contains 2 chemo and 1 PIPAC Rx (2 weeks between) then patients:
  - Get less systemic chemo overall and
  - Have a 4 week period between chemo cycles. That should translate into fewer systemic chemo related AE's
- Notably greater toxicity and AE's than for PIPAC alone.

Of note …

- Responses to PIPAC have been noted using chemo agents that patients were resistant to when given systemically
- Suggests that delivery via aerosol results in higher drug levels in the lesion (vs IV administration)
- Also, 5-15% of patients who were not CRS/HIPEC candidates pre PIPAC have successfully undergone CRS HIPEC after multiple PIPAC treatments

Challenges to PM treatments:

- Evaluating disease burden and response to treatment:
  - Limited ability to detect small lesions and accurately assess extent of PM
  - RECIST criteria are the gold standard
  - PCI (limited or no access to some zones/regions of abdomen)
  - Ascites analysis ?
  - ? PRGS or other histologic evaluation
- PM case incidence for most primaries is limited
- Multitude of treatment approaches for some cancers (ovarian)
- Early PIPAC literature concerns mixtures of different tumors

Summary

- Current Rx options for PM have improved survival rates in PM patients, however …
- PM patients reach a point where the only options are experimental drugs/regimens with very low response rates
- A new approach with reasonable response rates and low morbidity that can be repeated is desired
- PIPAC is an attractive chemo delivery option that merits investigation
- Preliminary results are promising
- Phase 2 and 3 study data are needed