CRS & HIPEC: What is it and its role in cancer management?

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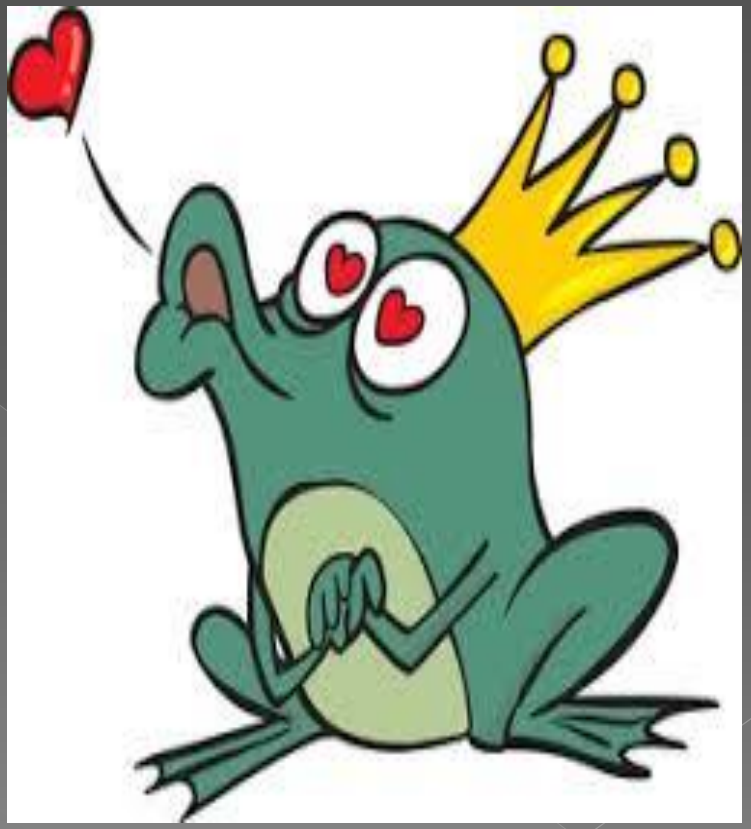
DISCLOSURE

- I LIKE TO K.I.S.S !
- KEEP IT SHORT AND SIMPLE!



HISTORY

- 1934: Miegs proposed removal of as much of tumor as possible in ovarian ca to increase the effect of post op chemo
- 1968 : Munnel published report of 235 cases of Ca Ovary. Noted significant improvement survival
- Omentectomy, appendicectomy,resection of localised peritoneal or intestinal metastasis in addition to TAH + BSO

- 1950-70 MSKCC reported inprovement in OS and DFS.
- Sugarbaker PH published landmark article in annals of surgery and standardised the technique for CRS including peritonectomy

Intraperitoneal chemotherapy & Hyperthermia

- Pretorius concluded from study of IV v/c IP Cisplatin in dog model, 50% of drug was excreted in urine on day 4
- D4 level of Cisplatin in peritoneal activity wes 2.5 x more then iv arm.
- Zimm et al in 1987 reported on IP arm of Ca Ovary with carcinomatosis survival >49 months with residual tumor less than 2cm

CRS + HIPEC

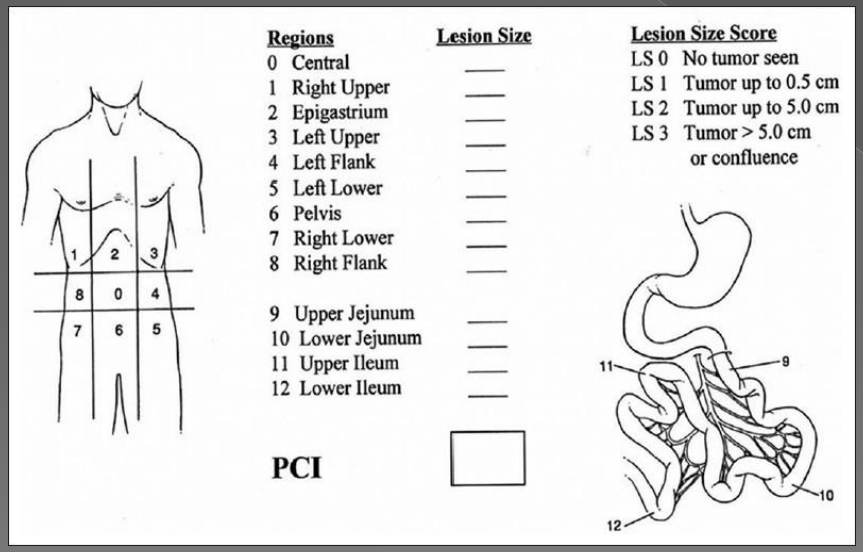
- **Principle:**
- **Malignant cells tend to implant at sites in the abdomen where there is less movement of bowel and intraabdominal structures.**

- **Particularly where the bowel is fixed to the retroperitoneum and sites if absorption of peritoneal fluid including rectosigmoid , IC junction, antrum of stomach, lesser sac, greater and lesser omentum and right diaphragm.**

HIPEC + EPIC

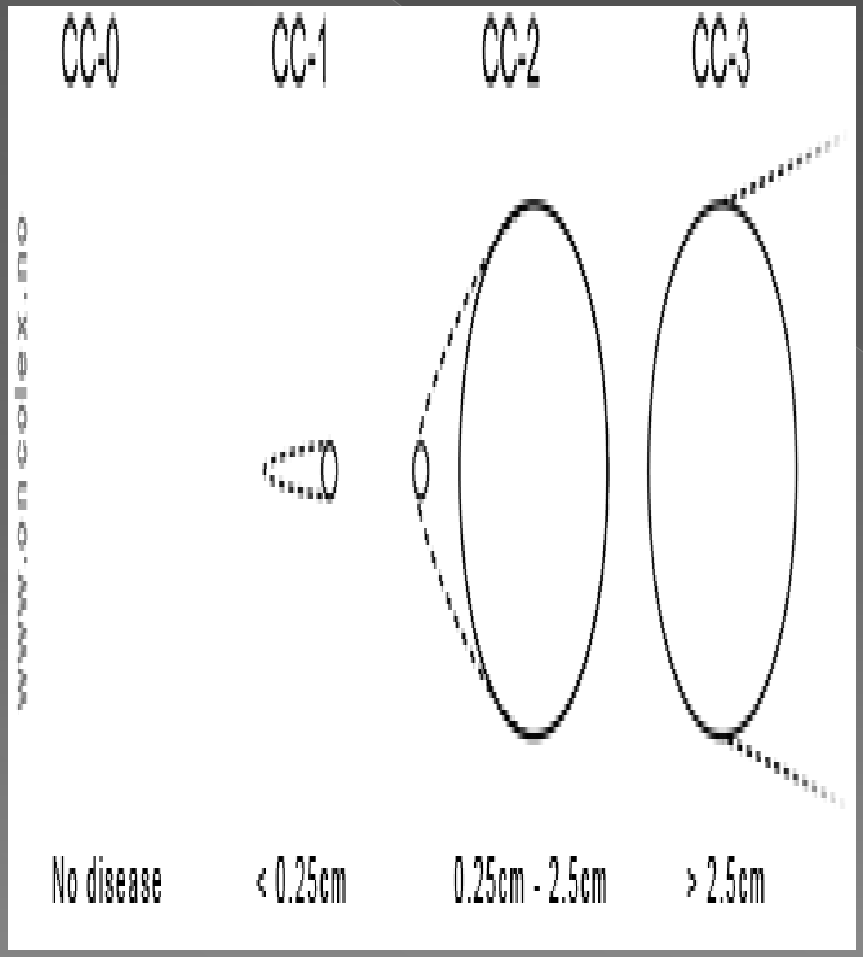
- CRC with peritoneal dissemination
- Carcinoma Ovary
- Primary Peritoneal malignancies
- Carcinoma Stomach
- Peritoneal mesothelioma

PERITONEAL CANCER INDEX (PCI)



- MINIMUM PCI SCORE 0
- MAXIMUM PCI SCORE 39
- Acceptable
- PCI < 20 for CRC
- PCI <10 For Gastric Ca
- PCI < 7 For Ca Ovary

Completeness of CRS Score (CC score)



- CC-0 & CC-1 is considered as "optimal"
- CC-2 & CC-3 are considered sub optimal for CRS-HIPEC

PREVENTION OF PERITONEAL CARCINOMATOSIS IN INDIVIDUAL CANCER

ColoRectalCancer (CRC)

Table 1: High risk group of colorectal cancer patients (For peritoneal recurrence)

Sl No	High risk groups
1	Visible evidence of peritoneal carcinomatosis
2	Synchronous Ovarian metastasis
3	Perforated cancer
4	Positive lateral margins of excision
5	Obstructed cancer
6	Positive cytologic results either before or after cancer resection
7	T3 mucinous cancer/signet cell
8	T4 cancer or a positive "touch prep" of primary cancer
9	Cancer mass ruptured during resection/colonoscopy
10	Adjacent organ involvement or cancer-induced fistula
11	Lymph nodes positive at margin

- IN group 1-4 there is 50-100% incidence of locl-regional recurrence / and or peritoneal mets in absense of CRS
- Samartino found significant improvement on DFS, OS & RR after CRS/HIPEC (T3/T4,any N, M0, mucinous & signet cell

Ann Surg Oncol 2011;18:396-404

OVARIAN CANCER

- Standard for advance EOC >> CRS followed by adj CT
- FIGO Stage III 5 year survival < 30%
- 60-80% complete remission rates with median survival of 35 months
- Inspite of good response most patients come with recurrence limited to peritoneum

Lancet 2009 Oct 17;374; 1371-82

OVARIAN CANCER

- HUO & Colleagues showed a strong rationale for use of HIPEC + CRS & CT in primary FIGO STAGE III and recurrent EOC compared to CRS & alone

- OS 33.9 months (CRS + CT) v/s **45.7 months** (CRS+HIPEC+CT)

- Recurrence free survival 10.7 months (CRS + CT) v/s **14.2 months** (CRS+HIPEC+CT)

Eur J Surg Oncol Eur Soc Surg Oncol Br Assoc Surg Oncol 2015;41:1578-89

GASTRIC AND PANCREATIC CANCER

- In Gastric CA, peritoneal recurrence develop in 20-50% patients with curative gastrectomy
- Increases to 80% for pt with positive peritoneal cytology
- Prophylactic HIPEC indicated in high risk group (serosa invasion or nodal metastasis)

Ann Surg Oncol 2012 :19: 1568-74

GASTRIC AND PANCREATIC CANCER

- Pancreas cancer pt resected for cure who have narrow or positive margins of resection are at high risk for loco-regional recurrence with or without peritoneal mets
- 50 % of these gastric or pancreas ca will manifest with peritoneal mets
- Adjuvant treatment with HIPEC

Am J Surg 1999 Sep;178(3):256-62

APPENDICEAL CANCERS

- LAMN (low grade appendiceal mucinous neoplasm)
- LAMN II (mucin and/or neoplastic epithelium in the appendiceal submucosa, wall/or periappendiceal tissue with or without perforation
- High risk for peritoneal disemmination
- Risk reducing second look CRS+HIPEC is beneficial

Br J Surg 2012, Jul;99(7);987-92

CRS

- ASSESSMENT PHASE
- CYTOREDUCTION PHASE
- HIPEC PHASE

ASSESSMENT PHASE

- PCI SCORE (incision)
- PREDICTED CC SCORE
- Rule out extaperitoneal mets 1. massive retroperitoneal nodes and >3 liver mets
- Other factor like involvement of root of mesentry, porta hepatis and the pancreatectomy

CYTOREDUCTION PHASE

- Parietal Peritonectomy
- Visceral perltonectomy

PARIETAL PERITONECTOMY

Peritonectomy procedures	Resections
Anterior parietal peritonectomy	Old abdominal incisions, umbilicus, epigastric fat pad
Left upper quadrant peritonectomy	Greater omentum and spleen
Right upper quadrant peritonectomy	Glissons capsule deposits
Pelvic peritonectomy	Uterus, ovaries and rectosigmoid colon
Omentalbursectomy	Gall bladder and lesser omentum

Sugarbaker . Ann Surg 1995;221:29e42

VISCERAL PERITONECTOMY

- Organs involved and is completed by omentectomy and resection of involved mesentery
- Falciform ligament, gallbladder, appendix, greater and lesser omentum
- Major limitation are small bowel deposits
- Spleenectomy +/-

VISCERAL RESECTIONS

- Subtotal/ total gastrectomy
- Colectomy
- Distal pancreatectomy +/- splenectomy
- Hepatic Resection:synchronous solitary liver mets in Ca Ovary

Ann Surg 263 (2): 369-75

Rationale for HIPEC

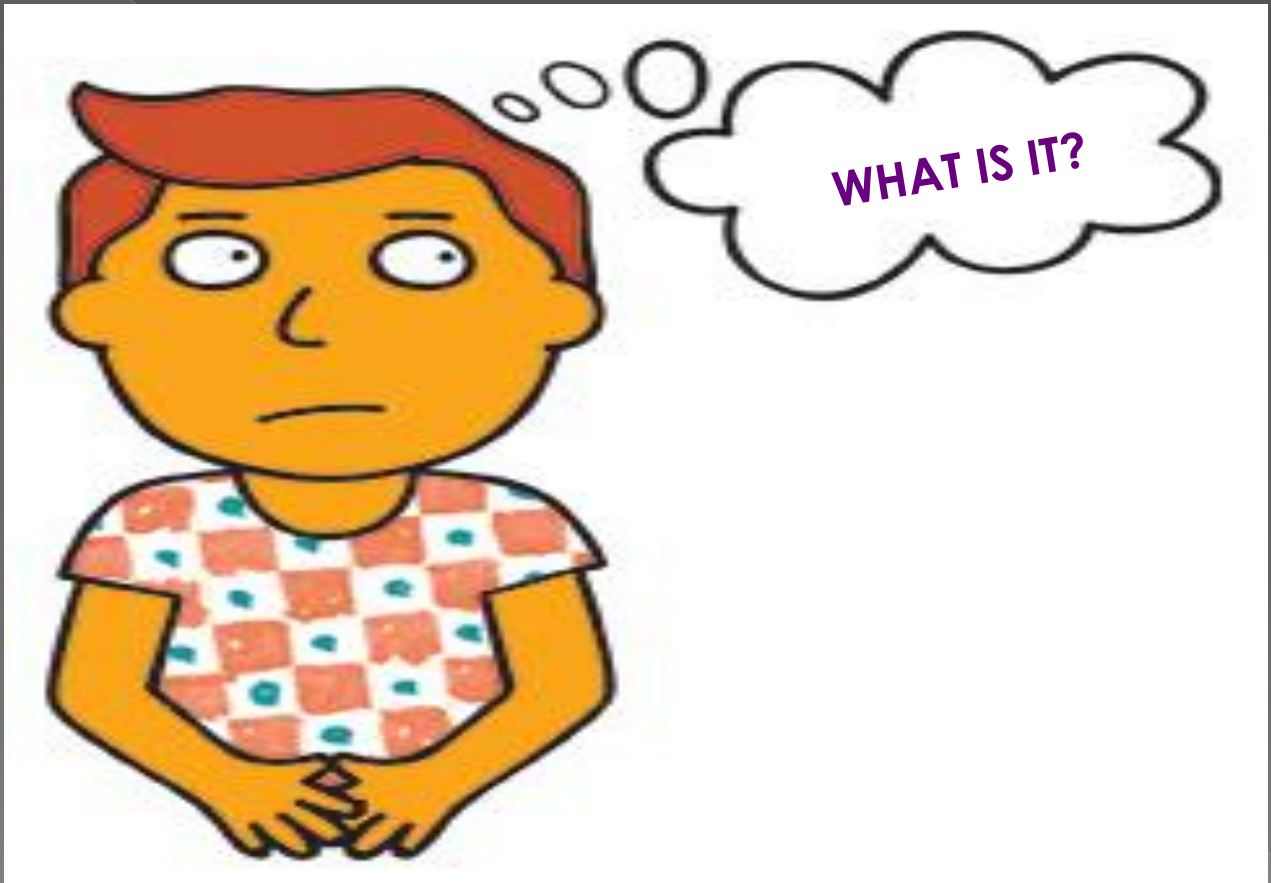
- Early exposure to drug immediately after debulking before formation of adhesion.
- Peritoneal chemotherapy max action on cancerous cells<<< systemic absorption
- Synergestic action of hyperthermia 45 c anti tumour action – augmenting cytotoxicity secondary to failure of DNA REPAIR.

Rationale for HIPEC

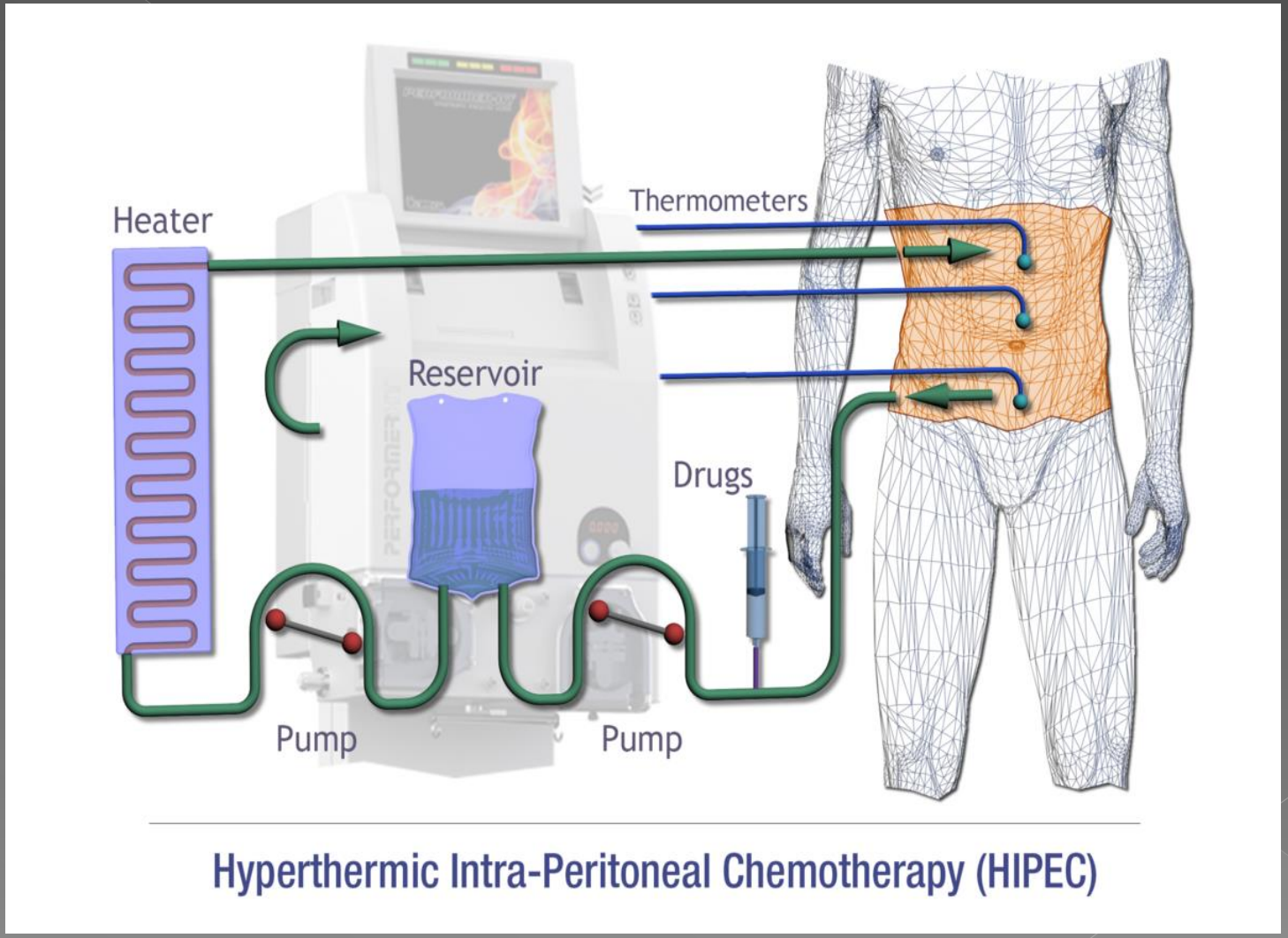
- Hyperthermia reverses platinum resistance
- Selectively induces cytotoxicity due to

1. impaired DNA repair
2. Protein denaturation
3. Inhibition oxidative metabolism to malignant cells >>>> increased apoptosis & inhibition of angiogenesis

HIPEC

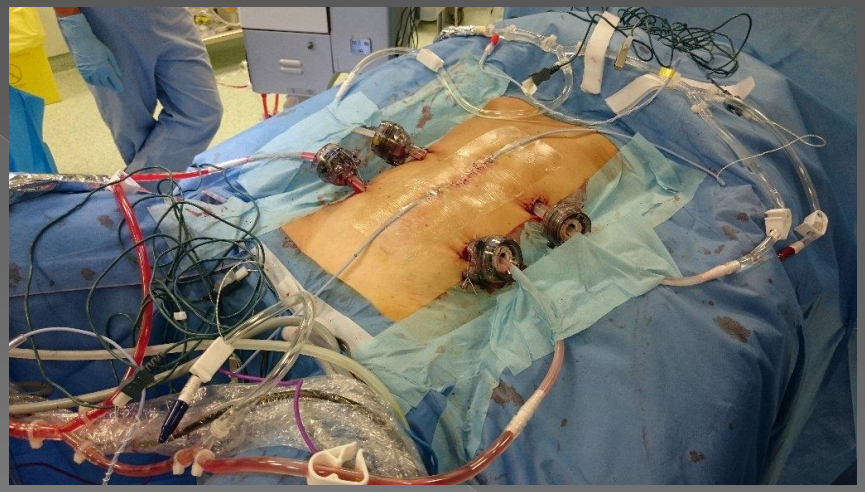


HIPEC



Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC)

HIPEC



HIPEC

- Drugs
- Drug dosage
- Carrier solution
- Duration of perfusion
- Temparature of perfusate
- Perfusion method

DRUGS

- Have nonspecific cytotoxic action with heat synergistic activity
- Intraperitoneal to plasma concerntration should be high
- Penetration of drugs delivered is estimated to be max 3-5mm(2.5mm residual tumor is considered adequate)

Neoplasia 2004; 6:117-27

DRUGS

- **Mitomycin c (AUC ratio 23.5)**

a) CRC & APPENDICULAR NEOPLASM & MESOTHLIOMA

b) 12.5-35 mg/m^2 over 90 mins

- **CISPLATIN (AUC ratio 7.8)**

a) Mesothelioma, EOC, Gastric Ca

b) Associated with nephrotoxity in 5-15% patients

c) saline diuresis with urine output of 1mL/kg/hr

- **Oxaliplatin (AUC ratio 16 to 25)**

a) Crc & appendicular adenocarinoma

b) Administered in a 5%D

c) Hypercalcaemia & hyponatremia common

CARRIER SOLUTION AND VOLUME OF PERFUSATE

- Enhanced exposure of the peritoneal surface
- Prolonged high concerntration
- Slow clearance from the peritoneal cavity
- Absence of adverse effects to the peritoneal cavity

CARRIER SOLUTION AND VOLUME OF PERFUSATE

- Perfusuate volume 1.5- 2l/m^{2*}
- Females have 10% larger peritoneal surface
- Carrier solution 1.5% D isotonic peritoneal dialysis solution or 5% D depending on type of chemotherapy agent

Cancer Chemother Pharmacol 2001;47:269-76

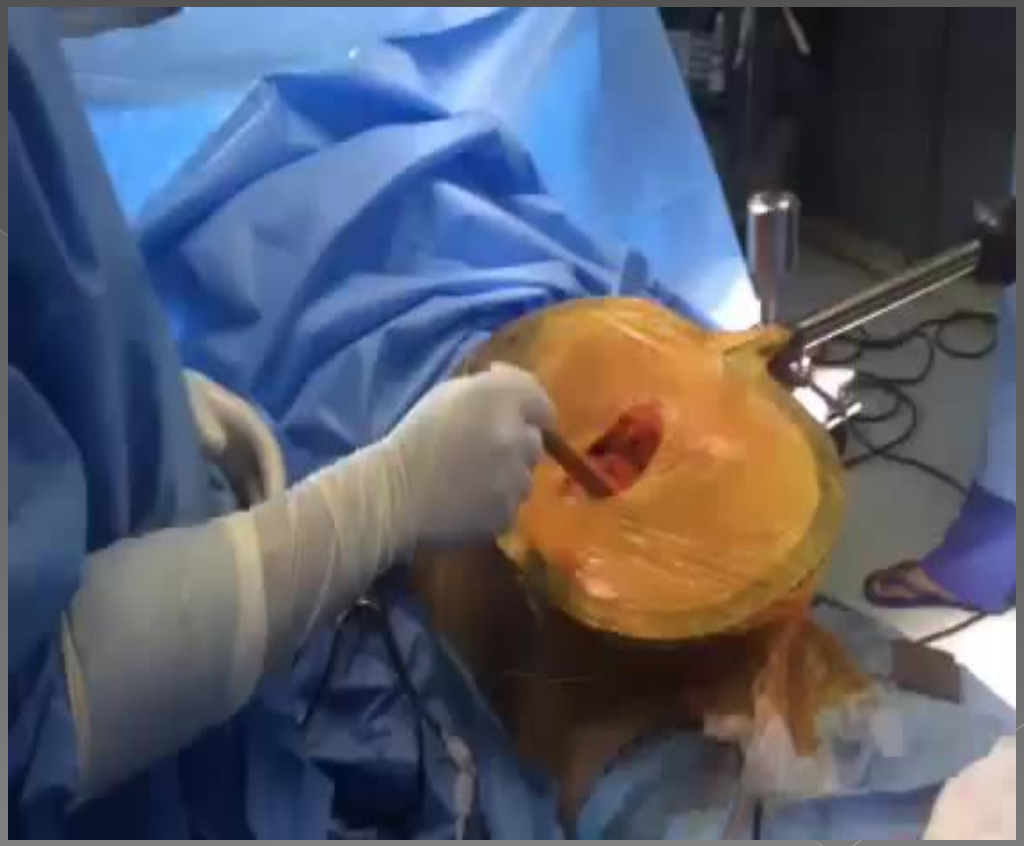
DURATION OF PERFUSION

- Most chemotherapeutic agents have interperitoneal halflife of 90 mins or less
- Time should be dependant on systemic and bone marrow toxicity
- Most data demonstrate safety @ temp of 41 c during 90 mins and 43 c for 30-40 min
- Synergism of cytotoxic drug starts at 39 c and 45 c

Br J Surg 2001;88:458-63

PERFUSION METHOD

- OPEN METHOD
- CLOSED METHOD
- COLISEUM TECHNIQUE (SEMI OPEN)
- ALL ARE EQUAL IN TERMS OF OUTCOME



SELECTION CRITERIA (patient)

- ECOG 0/1
- Age

I. < 70 year
II. < 65 with limited co morbidity
III. > 6 without co morbidity with low PCI and low garde malignancy

- BMI< 35 (PREFERABLE)
- Pre op Sr Albumin > 3g/dl
- Prior systemic chemo

i. Drug : platinum , dose modificatio
ii. Duration
iii. Response :stable/ eary recurrence(< 6months)/progression (poor predictor)

SELECTION CRITERIA (Disease)

- **Organ**

a) primary peritoneal tumor (carcinamatosis, mesothelioma)

b) PC of CRC, appendix, Ca Ovary

c) less promising gastric/ HPB cancers

- **volume & extent**

a) extrabdominal is CI for CRS

b) High volume invasive disease

SELECTION CRITERIA (Disease)

- CECT : Predictor of poor outcome

a. Tumour nodules more than 5 cm in small bowel mesentry or bowel serosal surface
b. Involvement of root of mesentry or porta hepatis
c. > 3 parenchymal liver mets

ABSOLUTE CONTRADICTION FOR (CRS AND HIPEC)

- Extra abdominal disease
- Significant extraperitoneal disease, > 3 liver mets
- Large extraperitoneal lymph nodes
- Infiltrative tumor deposits at root of mesentry
- Unknown primary

RELATIVE CONTRAINDICATIONS

- Grade 3 adenocarcinoma (signet-ring cells & PMCA)
- Short interval between primary adeno ca and peritoneal carcinomatosis (synchronous or < 6months)
- Frozen pelvis secondary to rectal cancer recurrence.

COMPLICATIONS

- Similar to other supramajor surgeries
- More related to surgical techniques
- Mortality 0.8-1% (GI>>Ovarian Ca)
- More due to multivisceral resections
- Throboembolis 5%

Eur J Surg Oncol 2013; 39:1435-43

CRS + HIPEC IN Ca OVARY

- 80% Stage III & IV
- Optimal CRS Stage IIIC onwards followed by CT
- Despite efforts >75% have recurrence with 36-39 months survival
- CRS+HIPEC survival 45-49months and DFS 14.2 months

N Engl J Med 2018;378(3)230-40

CRS+HIPEC in PSEUDOMYXOMA PERITONEI & APPENDICULAR TUMOR

- DPAM (Disseminated peritoneal adenomucosis)
- PMCA (Peritoneal mucinous carcinomatosis)
- Not aggressive or metastasise
- Fatal as abdomen gets filled with mucin and require multiple surgery
- CRS HIPEC median survival 6year in 53-75%*

Ann Surg 1994 ;219: 112-9

CRS+HIPEC for peritoneal mets in CRC

- 5-10% at time of primary presentation
- 15-30% in patient with recurrent disease
- Systemic CT +/- targetted therapy survival 12months
- CRS + HIPEC median survival reported varies from 12-62 months*

BMC Cancer 2015, Indian J Surg Oncol 2016;7:177

HIPEC IN Gastric Cancer

- 5 year survival 24.5% in Europe , 40-60% in Asia
- Gastric Ca with macroscopic peritoneal carcinomatosis have median overall survival 3-6 months
- **Parenchymal mets or non regional mets** managed with CT/BSC/Palliative resections

HIPEC IN Gastric Cancer

Table 1:

Group	Features	Management
Group 1	Parenchymal metastasis or non-regional nodal metastasis	Chemotherapy, Best supportive care, palliative resecti on, rarely curative resection
Group 2	Surface deposits on bowel, mesentery and omentum without parenchymal metastasis	Primary surgery +/- Neo/adjuvant therapy +/- HIPEC Or Palliative Therapy
Group 3	Cytologically positive malignant cells in ascites or peritoneal lavage	Primary surgery +/ - Neo/adjuvant therapy +/- HIPEC
Group 4	T3/T4 primary lesion, without above features	Primary surgery +/ - Neo/adjuvant therapy +/- HIPEC

HIPEC IN Gastric Cancer

- Meta-analysis show improved 5year survival in HIPEC+CRS group
- GASTROCHIP study will give definitive answer.

BMC Cancer 2014 ;14: 183

- BIOLOGY IS THE **KING**
- SELECTION IS THE **QUEEN**
- TECHNICAL MANOUVERS are the **Prince** and **Princess.**

- Occasionally the prince and princess try to overthrow the powerful forces of the king and queen, sometimes with temporary apparent victories, but usually to no long term avail.

WHAT WE BELIEVE?

- Patient selection is the queen behind the success of the King (SURGEON)!!!

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