CRS AND HIPEC FOR TRAINEES

CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY / HEATED INTRAOPERATIVE PERITONEAL CHEMOTHERAPY

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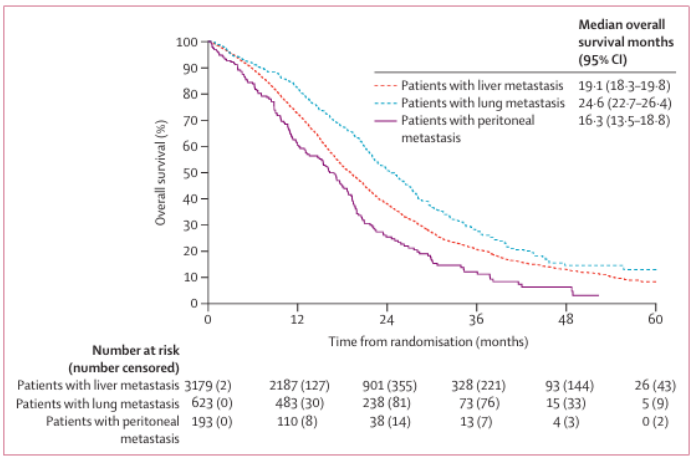
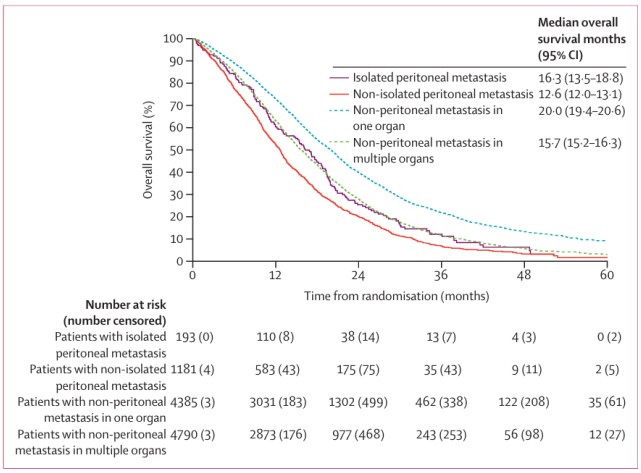
Introduction

Peritoneal carcinomatosis is a specific subgroup of **stage-IV** colorectal cancer (TxNxM1), characterized by **peritoneal spread** of tumour. Spread to the peritoneum is seen more often in cancers of the appendix, colon, rectum, stomach and in particular ovary. Metastasis to the peritoneum is much more common than a primary peritoneal malignancy.

Patients with peritoneal metastatic colorectal cancer have **reduced overall survival** compared to patients with metastatic colorectal cancer without peritoneal involvement e.g. isolated lung or liver metastasis. Whether this is the result of an increased number of metastatic sites that are also associated with peritoneal metastases or whether it is an inherent feature of peritoneal involvement is not clear. Mutations in **BRAF** are more common in patients with peritoneal metastases.





Overall survival (patients treated with chemotherapy) best for lung metastasis and worst for peritoneal metastasis and non-isolated peritoneal metastasis. (Franko et al)

Reminder of peritoneal anatomy:

*The peritoneum has two layers; the **parietal** peritoneum, which covers the inner surfaces of the abdominal and pelvic wall, and the **visceral** peritoneum, which covers the abdominal organs.*

*Spead across the peritoneal surfaces and towards other others is also known as the **transcoelomic mechanism***

Peritoneal carcinomatosis can develop in two different ways:

- *More commonly via **transversal growth (synchronous)***
    - *Transversal growth means tumour cells can exfoliate (detach) from the primary tumour into the peritoneal cavity, join to distant peritoneum and invade the subperitoneal space, this usually this occurs preoperatively*
- *Less commonly via **intraperitoneal spread (metachronous)***
    - *This can occur due to surgical trauma, where tumour cells get released unintentionally from transected lymph nodes or blood vessels or upon manipulation of the primary tumour during handling carcinomatosis.*

***Reminder**: Synchronous peritoneal metastases are when a patient is diagnosed with colorectal cancer and peritoneal metastases at the same time, while metachronous PM are when a patient is initially diagnosed with colorectal cancer, but later develops peritoneal metastases.*

General Statistics

- Peritoneal carcinomatosis is present in approx. 10% of all colorectal cancer patients
- Peritoneal metastatic colorectal cancer is associated with substantially shorter overall survival by 30–40% compared with non-peritoneal disease sites e.g. lung and liver metastasis
- Median survival without treatment is **6 months**, with ascites being a poor prognostic factor
- Median survival for patients with the most favourable features (low PCI, complete CRS) with CRS + HIPEC treatment is **50% at 5 years**
- Overall survival can reach up to **5 years (62 months)** if optimum cytoreduction is achieved (i.e. no tumour nodules left or nodules ≤2·5 mm in maximum dimension)

Reminder: R0 resection (no cancer cells seen microscopically at the primary tumour site) R1 (cancer cells present microscopically at the primary tumour site) R2 (Macroscopic residual tumour at primary cancer site or regional lymph nodes)

Patient Presentation

Peritoneal disease commonly causes intestinal stenosis and disturbed bowel motility, producing symptoms of early satiety, diet intolerance, bloating, nausea, and vomiting. Ultimately bowel obstruction is a common way for patients to present.

Abdominal pain, distension and ascites are common, ascites can be sent for cytology to reveal organ origin and confirm malignancy. Disease progression causes cachexia, loss of performance (i.e. as assessed by loss of strength, nutrition, and diminished resilience), and death.

Presentation may be synchronous or metachronous and can also be accidental finding during surgical exploration for primary tumour resection or other elective procedures.

Treatment options for peritoneal disease

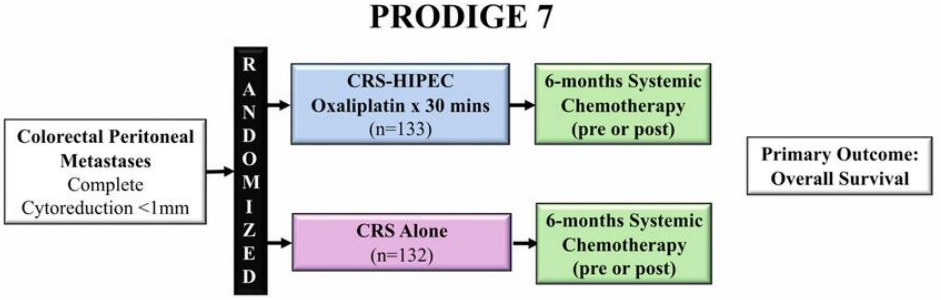
Historically peritoneal disease was considered incurable, and these patients received palliative care, but advancements in care and attitudes encouraged the aggressive treatment of peritoneal disease whenever feasible. **Dr. Sugarbaker** changed the perception from a terminal cancer to a loco-regional disease and recommended an aggressive surgical approach with **cytoreductive surgery**.

Complete resection of peritoneal metastases can be achieved by peritoneal **cytoreductive surgery (CRS)** a treatment often combined with **intraperitoneal (HIPEC)** and **systemic chemotherapy**. Despite support from key trials, CRS +/- HIPEC is not entirely without controversy. ESMO guidelines do currently support resection of peritoneal disease, although the benefits of HIPEC are less clear. The idea behind cytoreductive surgery is to remove any **macroscopic** lesions completely, and the simultaneous use of HIPEC is to hopefully remove **microscopic** cancer lesions. Systemic chemotherapy is thought to have a limited affect for peritoneal tumours due to the poor tumour blood supply and poor penetration.

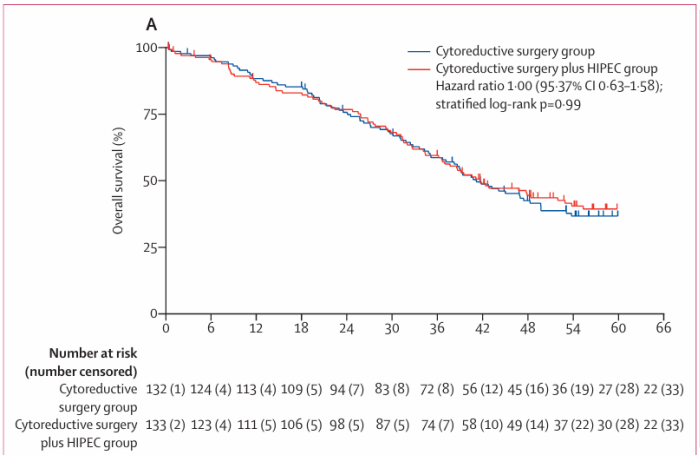
Key trials:

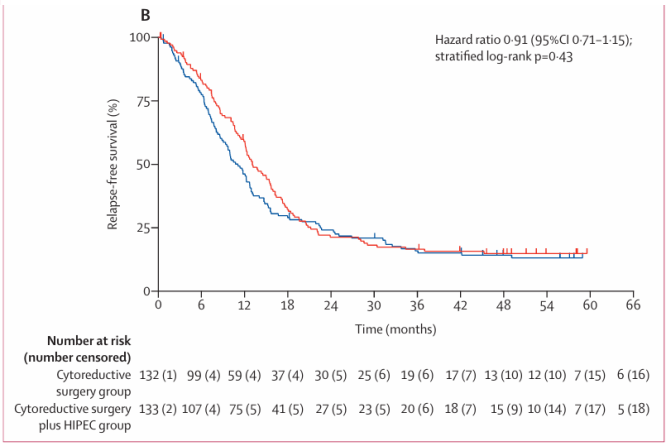
CRS + HIPEC vs. systemic chemotherapy alone (Verwaal et al), Median survival: 22.3 vs. 12.6 months, P = 0.032

This study emphasized that achievement of complete cytoreduction is an important determinant given that the 5-year survival with an R1 resection was 45%.



Inclusion Criteria: (a) Synchronous or metachronous localized CRC PM (confirmed histologically); (b) complete cytoreduction (<1mm); (c) Age 18-70; (d) Eligible for 6 months of systemic chemotherapy; (e) PCI < 25; (f) Able to tolerate HIPEC; (g) medical eligibility





CRS + HIPEC vs. CRS alone (PRODIGE 7 TRIAL, Quénet et al), Similar overall survival and disease free survival. Median overall survival was 41.7 months in the CRS + HIPEC group and 41.2 months in the CRS alone group. Notably the HIPEC protocol was different to what we use at Imperial / in the UK, thus it is still felt that CRS + HIPEC is superior to CRS alone.

One multicentre Dutch randomized controlled trial showed significant improvement in survival in patients treated with CRS+HIPEC compared to the CRS alone for advanced ovarian disease (Van Driel et al).

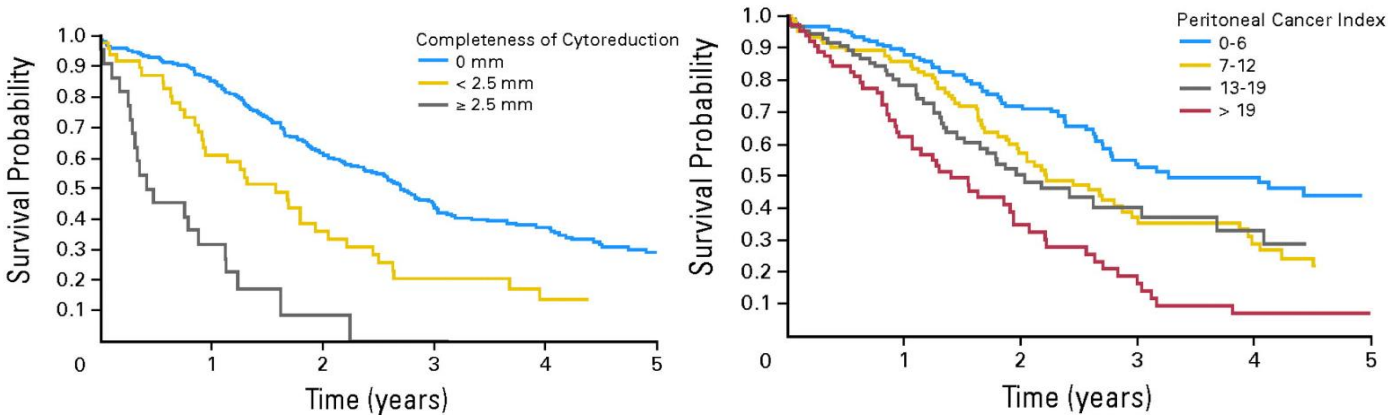
Prognosis

The prognosis of patients with peritoneal carcinomatosis depends on the following:

- Histology
    - Disease from an unknown primary tumour has a poor prognosis
    - Favourable prognostic factors:
        - Low grade tumours
        - Absence of signet ring cells
        - Absence of mucinous component
        - Presence of microsatellite sequences instability
- The extent of carcinomatosis
    - Through imaging (CT, MRI, PET)
    - Gilly staging
    - PCI scoring system
    - Other scoring systems: Staging by the Japanese cancer society for gastric cancer,
    - Dutch simplified peritoneal carcinomatosis index (SPCI)
- Completeness of cytoreduction (CC)

PCI score and CC score are the most crucial prognostic factors

A low pre op PCI score and complete cytoreduction give the best outcomes



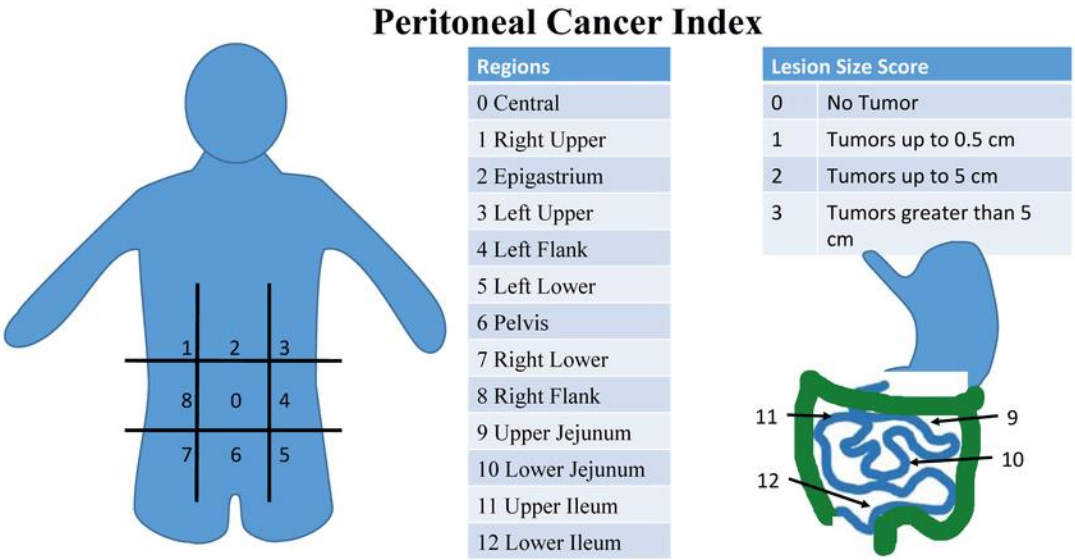
The effect of completeness of CRS on survival outcome and the pre op PCI score on survival outcome (Elias et al)

Peritoneal carcinomatosis index (PCI) score

The PCI scoring system proposed by Sugarbaker provides a useful tool for better patient selection for surgery and a better understanding of prognosis and outcome. The score represents deposit **size** and **distribution** by dividing the abdomen into **9 areas** and the small bowel into **4 areas = Total 13 areas**. The number of nodules is not scored, only the size of the largest nodule is considered. The sum of lesion size score in each of the 13 abdominopelvic region is the PCI for that patient. Thus, a minimum score of 1 and a maximum of 39 (3 × 13) is possible.

The PCI is calculated by imaging (CT, MRI, PET) or surgical examination i.e. diagnostic laparoscopy. Surgical PCI staging at laparoscopy would be performed if there is suspicion of small bowel involvement or suspicion that the PCI staging by imaging may not be accurate, or if the score is very high such as ≥15. Imaging is notoriously weak at assessment of small bowel involvement.

Generally, a low score is considered 0-6, a medium score 7-12 and a high score is 13-19. Many surgeons use a **cut of off ≥15** to decide whether CRS + HIPEC should be attempted although there is no specific guideline and patients are considered case by case.

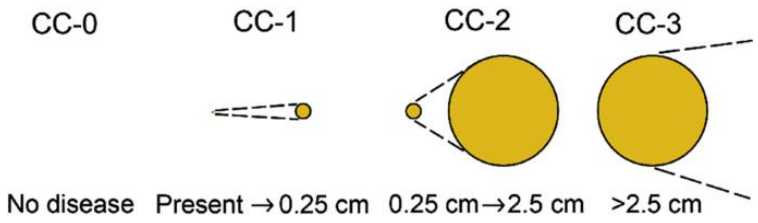


Completeness of Cytoreduction (CC) score

The Completeness of Cytoreduction (CC) score is used to assess surgical resection. The levels 0-3 describe the presence of carcinomatous lesions in any abdominal quadrant. CC 0 and CC 1 scores suggest better survival outcomes. The goal is to achieve complete cytoreduction whenever possible.

CC 0 and CC 1 scores are considered complete cytoreduction. CC 2 and CC3 are considered incomplete

- CC 0 - no disease
- CC 1 - present - <2.5mm *Key cut off size for penetration by intracavity chemotherapy, hence still complete CRS
- CC 2 – 2.5mm to 2.5 cm
- CC 3 - greater than 2.5 cm



Pre-operative work up

Patient selection is extremely important. Factors to consider:

- Performance status <3 and fitness for surgery
    - Review by HIPEC surgeon
    - Review by HIPEC anaesthetist
    - Review by physician (e.g. at Imperial surgical liaison)
- Clinical symptoms
    - Ascites
    - Episodes of bowel obstruction
- Prognosis of disease as discussed above
    - Histology and primary cancer diagnosis
    - PCI score
        - Generally low volume, low grade, without systemic spread is optimal
        - <17-15 for colorectal cancer
        - <12 for gastric cancer

A Peritoneal Surface Disease Severity Score (PSDSS) can be employed to aid decision making

Clinical symptoms	PCI	Histopathological features
No symptoms=0 point	PCI <10=1 point	Well or moderately differentiated and N0=1 point
Mild symptoms=1 point	10< PCI <20=3 points	Moderately differentiated and N1/N2=3 points
Severe symptoms=6 points	PCI >20=7 points	Poorly differentiated or signet ring cell tumor=9 points

PSDSS is graded according to the total score of these three components

PSDSS score	PSDSS Group
2-3	1
4-7	2
8-10	3
>10	4

PSDSS: Peritoneal Surface Disease Severity score, PCI: Peritoneal cancer index, N: Node
Mild symptoms: <10% weight loss, mild abdominal symptoms, asymptomatic ascites,
Severe symptoms: >10% weight loss, unremitting pain, bowel obstruction, symptomatic ascites

Contraindications can include:

- High PCI ≥15
- Extensive small bowel involvement
- Massive sub-hepatic disease
- Biliary and ureteral obstruction
- Multiple bowel obstructions
- Massive pelvic/retroperitoneal nodal involvement
- Moderate to severe ascites
- Extra-peritoneal disease

For patients with **liver metastasis** we could consider surgery appropriate if:

- There are up to 3 liver metastasis
- Liver disease is localised peripherally
- Liver disease is resectable
- PCI score is limited

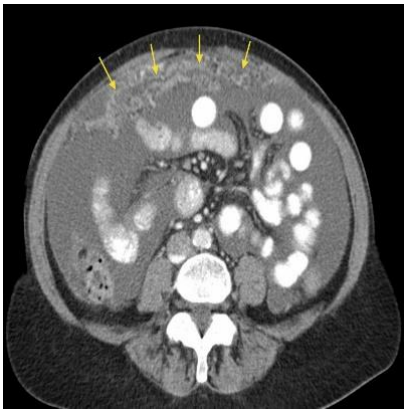
Investigations

- Colonoscopy
- Biopsy of primary tumour
- Cytology of ascites

Imaging

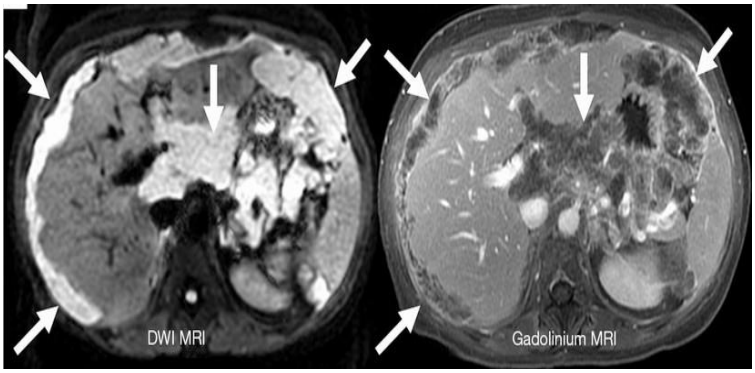
- Classically, peritoneal metastases and their volume and distribution are notoriously difficult to detect on imaging compared to direct surgical visualisation. Although cross-sectional imaging has improved in the past 20 years, the following scans should be performed in the work up:

- **CT CAP**
    - Peritoneal disease can be visible on CT as focal or diffuse thickening of the peritoneum and 'omental caking'
    - CT probably underestimates the extent of carcinomatosis
    - Ascites can be seen
    - Nodules on the liver or spleen or small bowel mesentery can be seen
    - The sensitivity is low (25%) for lesions <5cm and for assessment of the small bowel



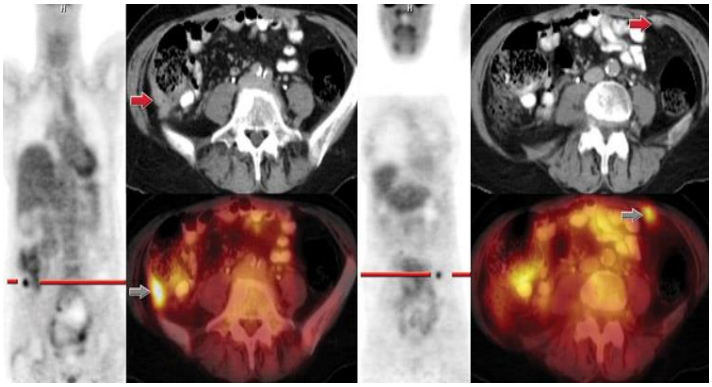
Peritoneal disease seen on CT scan

- **MRI**
    - MRI does not add a huge amount to CT but the combination of CT and MRI is superior
    - Whole-body diffuse weighted imagine-MRI is significantly better in the prediction of inoperability for peritoneal carcinomatosis with sensitivity of 90.6%, specificity of 100%



Peritoneal disease seen on MRI scan

- **FDG PET CT**
    - This is the preferred imaging that works by detecting the presence of cancer lesions based on the cells glucose uptake
    - PET-CT provides better accuracy and negative predictive value than MRI in identifying the exact location and area of the peritoneal metastasis



- Diagnostic surgery
    - Diagnostic laparoscopic surgery can be used to assess PCI score before undergoing a CRS laparotomy
    - This approach is useful in patients whose previous imaging studies are insufficient in providing adequate information about the extent of disease involvement, particularly small bowel
    - Caution is required with trocar insertion and there is a risk of port-site tumour seeding and recurrence
    - Hence *all ports are placed in the midline* so that the scar can be excised at the time of CRS

Jobs for the registrar

Pre-op jobs for colorectal registrar

- Review notes as soon as you know the case is scheduled
    - Look for key medications that might need to be held e.g. anticoagulants
    - Check bowel prep is prescribed if colorectal resection if happening for patient to collect
    - Check for any investigations incomplete from anaesthetic pre op assessment e.g. patient needs echo
    - Check for rare blood type / antibodies which may require additional time to prepare blood

- Ensure there is up to date imaging
    - At least up to date CT CAP in the **last 2 weeks**, check with the consultant they are happy with the last imaging date and if more up to date scans are required
    - This is very important as you do not want to find on the day of surgery that the disease is more advanced than anticipated
- Assist consultant with liaison with oncology
    - Plan date of surgery
    - Ensure HIPEC counselling and consent is completed by oncology
- Consenting the patient
    - Use concentric which has an option for cytoreductive surgery
    - Oncology will consent separately for HIPEC
    - Add on individual components
        - E.g. omentectomy, diaphgragmectomy
    - Know the relevant risks to discuss with the patient (discussed later)
    - Take the details of the patients NOK on the day of surgery and ask them if they are happy to be phoned at all times of the night if the operation finished very late

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General tips for beginners talking about CRS surgery:

This is a major >6 hour operation with 3 days in ITU, 2 weeks in hospital and 3 months until you are back to a reasonably normal life. There is a <5% mortality but 30% morbidity with complications of some kind expected

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- Book a critical care bed
    - Ideally do this as soon as you find out the operation is scheduled
    - This can be done on cerner 'critical care bed request'
    - Fill in the date of the operation

- Warn the lab in advance regarding any blood products you might need
    - You can telephone or email the lab in advance to warn them that a major case is scheduled with likelihood of needing blood, FFP, platelets, cryoprecipitate

imperial.cxh.btlab@nhs.net

- Blood tests
    - On the day a fresh group and save will be required
    - Phone the lab to ensure products are available

Post-op jobs for colorectal registrar

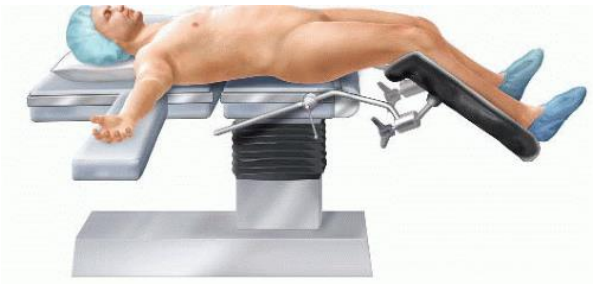
- Call family post op (remember to take number down at the start)
- Histology – usually multiple pots, ensure accurate description, send as urgent
- Make sure patient is on MDT (imperial.lgi.mdt@nhs.net)
- Write operation note (example op note included at the end). Please write *COMPLEX CANCER SURGERY* at the top of the operation note as this affects coding and funding.
- Make sure medication instructions are clear e.g. continue antibiotics, hold heparin as patient is going to ITU drug chart can only be done by then
- Post op ward rounds

Cytoreductive Surgery

Aims to remove all *macroscopic* tumor

KEY FACTS:

- Laparotomy from xiphoid to pubis (often excising umbilicus and old scars from previous surgery)
- >6 hour surgery
- Positioning: Lloyd-Davies
- Careful theatre and patient preparation is done at the start to prepare for HIPEC part.
    - Only the abdomen exposed and dressings/inco-pads cover the rest of the skin for protection
- Ioban is placed over the abdomen



Surgical technique

An initial through exploration is performed to look for any contraindications to CRS and no bowel should be resected till the surgical plan is finalized.

Peritonectomy of involved entire involved wall is performed by stripping the peritoneum en-bloc of all visible disease. Normal peritoneum is not excised, only that which is affected is removed (Sugarbaker 2015) i.e. if the left sided peritoneum does not have any disease then this side does not need resection. If the right sided peritoneum has disease then this entire side needs to be stripped.

Constant traction on the abdominal wall and the specimen is important to expose the correct planes so that the abdominal wall is not excised and only the peritoneum is stripped.

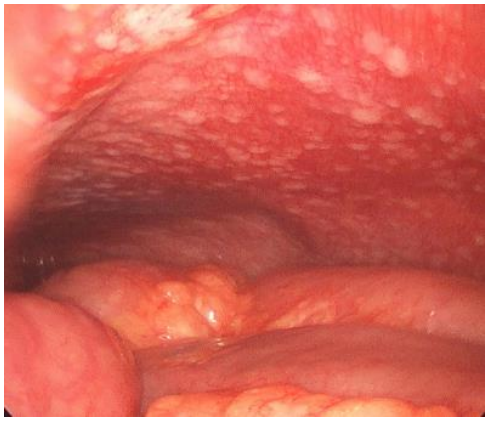
Intraperitoneal chemotherapy is not effective in eradicating tumour nodules larger than 2.5 mm in size which is why all visible disease should be removed.

Peritonectomy procedures and associated resections:

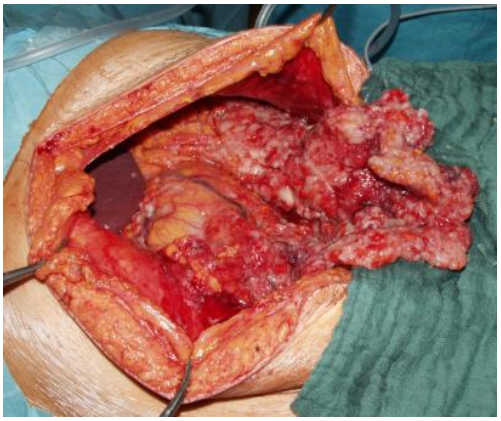
- Omentectomy should also be performed for all patients
- Hysterectomy with bilateral salping-oophorectomy should be performed for all female patients
- Other resections that may be performed due to disease nearby:
    - Abdominal midline incision and umbilicus
    - Splenectomy
    - Partial gastrectomy
    - Cholecystectomy
    - Bowel (right, sigmoid, total colectomy, rectum)
    - Appendix
- Resection close to the diaphragm or of a part of the diaphragm itself may be performed. The diaphragm is then closed primarily with sutures. Caution of pneumothorax when operating in this area.

*Cytoreductive surgery is performed followed by HIPEC followed by reconstruction of areas e.g. suture repair, anastomosis.

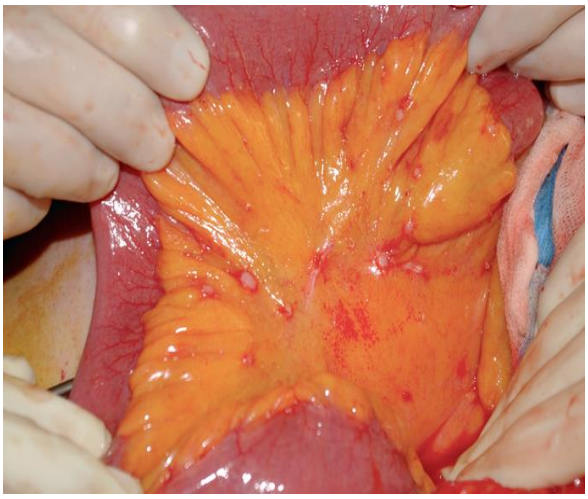
Intraoperative Images



Peritoneal disease lining anterior abdominal wall



Omental caking



Disease on the small bowel mesentery

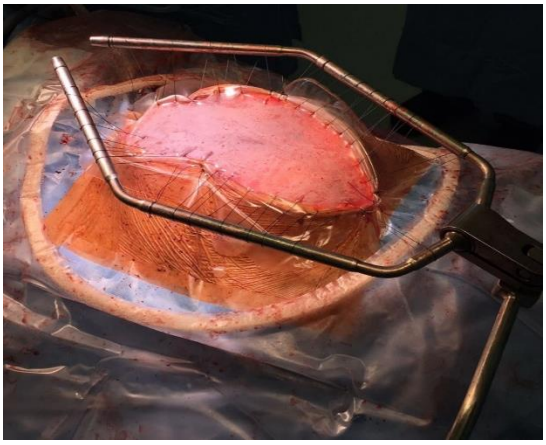
HIPEC

Hyperthermic intraperitoneal chemotherapy / Heated intraoperative peritoneal chemotherapy

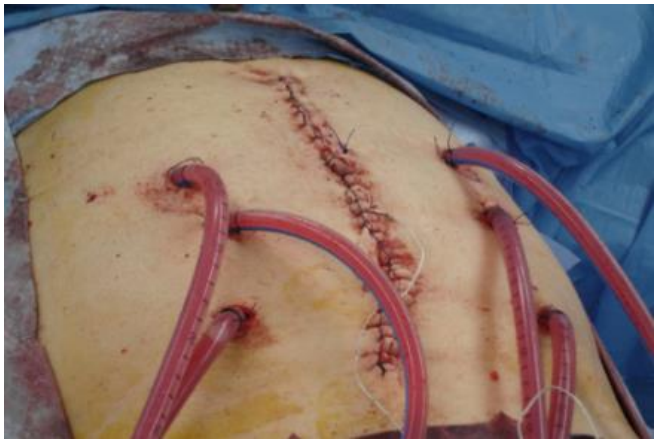
Aims to eliminate all residual microscopic tumour

KEY FACTS

- The abdominal wall can be open or closed
- At Imperial the Open technique is used

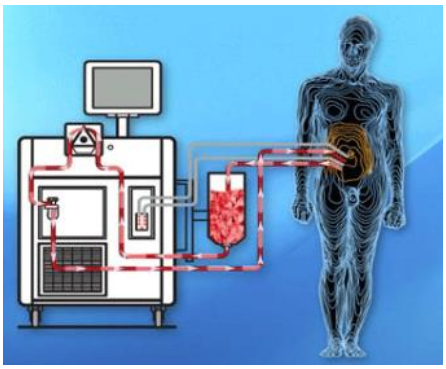


Open “Colosseum” technique



Closed technique

- A roller pump is used to perfuse the chemotherapy drug solution throughout the peritoneal cavity



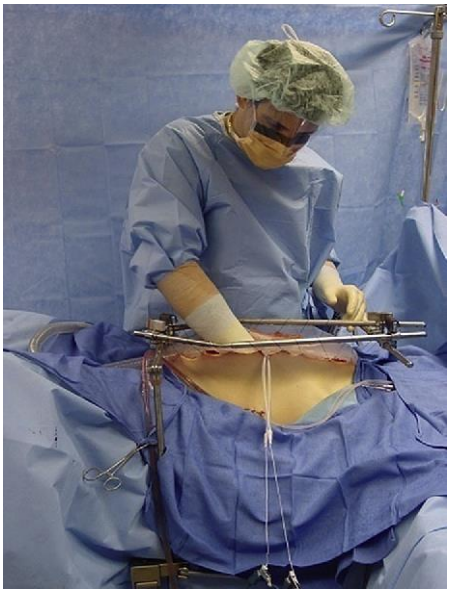
- 60 minutes duration at Imperial
- Intra-abdominal temperature 40°C to 42°C
- Two main chemotherapeutic agents
    - **Mitomycin C** → preferred agent at Imperial
    - Oxaliplatin
    - They are alkylating agents, non-cell cycle-dependent, with enhanced cytotoxicity under hyperthermia and maximal tissue penetration up to 2.5 mm.
- Hyperthermia adds a direct **cytotoxic advantage**:
    - DNA repair impairment
    - Protein denaturation
    - Oxidative metabolism inhibition
    - Increased apoptosis
    - Increases the efficacy and penetration of chemotherapeutic agents

The varying trial results currently published in terms of HIPEC benefits are likely due to differences in:

- the type of chemotherapeutic drug used, its concentration, carrier solution, the volume of the perfusate, temp of the perfusate, treatment duration, delivery technique, and patient selection
- delivery technique (open vs. closed) and perfusate temperature (varied 41 to 43 C)

HIPEC Safety Precautions:

Appropriate theatre protection with gown, theatre shoes and covers, double gloved with long gloves, with tape around the wrists, mask with visor or goggles.



(González-Moreno et al)

Pregnant or breast feeding women should be excluded from scrubbing for this procedure.

Overall the risk of cytotoxic exposure to staff is low. The abdomen is drained for chemotherapy agents before 6L water washout of the abdominal cavity.

Post operatively gloves, gown and mask with eye protection should be worn by staff seeing the patient for 72 hours.

Complications

- Morbidity (Grade III-IV complications) 34%
- 30-day mortality of 4%

General

•Pain
•Bleeding including major haemorrage
•Infection (abdominal collection, wound infection, pneumonia)
•VTE / PE
•Mortality

Gastrointestinal

•Peritonitis
•Bowel obstruction
•Fistulation including enteroperineal fistula
•Stoma dehiscence / retraction / ischaemia / parastomal hernia
• Anastomotic leak

HIPEC

•Acidosis
•Hyperglycaemia
•Electrolyte imbalance
•Renal toxicity
•Coagulopathy
•Neutropenia
•GI side effects

Post-operative management

- Patients will be kept on ITU for approximately 3 days
- 1-3 week hospital stay
- Usually back to reasonable function within 3 weeks
- Post op plans:
    - Heparin usually held that evening
    - Sips water
    - NG tube
    - Continue antibiotics
    - TPN often required
    - Drain to stay usually until discharge

CRS +/- HIPEC Protocol Checklist

Courtesy of Anne Moutadjer

	Task
Patient referrals received:	Treating hospital/team GP
Peritoneal MDT:	Review of scans If PCI <15 and stable on chemotherapy then suitable for surgery
Outpatient appointment at Imperial:	Email/Telephone contact details (CNS) Patient information sheet Staging Laparoscopy if PCI more than 15 or suspicion of small bowel involvement to assess suitability
Patient agreed to surgery:	Pre assessment Bowel prep prescription (If required) Iron infusion (If required)
Agreed date for surgery:	Oncology team - If having HIPEC/fit for systemic anti cancer therapy (SACT) Inform the aseptic pharmacy team Inform bookings team HDU/ITU bed CTTAP (within two weeks of surgery) Peritoneal MDT Stoma Nurses (Bilateral stoma siting/1 hour clinic appointment) Pre op HIPEC clinic (with the CNS/1 hour clinic appointment) Physiological support Email/Telephone contact (CNS) Blood test 48 hours prior to surgery
Post-Operative:	72-hour HIPEC precautions (If having HIPEC) High dependency care Parental feeding Post-op catheters Wound drains Stoma nurses visit (If applicable) Clips to remain for 21 days Weekly ward rounds (CNS/if allowed) Physiological support Family/Carer support Email/Telephone contact (CNS) Peritoneal MDT (histology/follow up)
After discharge:	Email/Telephone contact (CNS) Clip removal clinic appointment (If required) Complex wound clinic appointment (If required) Clinic review two weeks post discharge Follow up (Locally/Imperial) Oncology appointment (If required) Referral back to the local team

Follow Up Protocol

- Patients are followed up for a minimum of 5 years
- These patients are not suitable for OAFU (open access follow up) which is where patients simply attend investigations as an outpatient and they are chased virtually
- Usually patients are referred back to their local team for follow up and the peritoneal CNS will be informed of their scan results. If there is any recurrence they will be redicussed at the peritoneal MDT

    - **Year 1-2**
        - 6 montlhly clinic appointment for history and examination
        - 6 monthly CEA + Ca 19-9 + Ca 125
        - 6 monthly CT CAP
    - **Year 2-5**
        - Annual clinic appointment for history and examination
        - Annual CEA + Ca 19-9 + Ca 125
        - Annual CT CAP
        - At year 3 a COLONOSCOPY

Example Operation Note

COMPLEX CANCER SURGERY

Insert operation note

Useful resources and references

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