Peritoneal Carcinomatosis

- *Rationale and Indications of Cytoreductive Surgery and Hyperthermic Intraperitonal Chemotherapy*

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December 13, 2019

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- No disclosures

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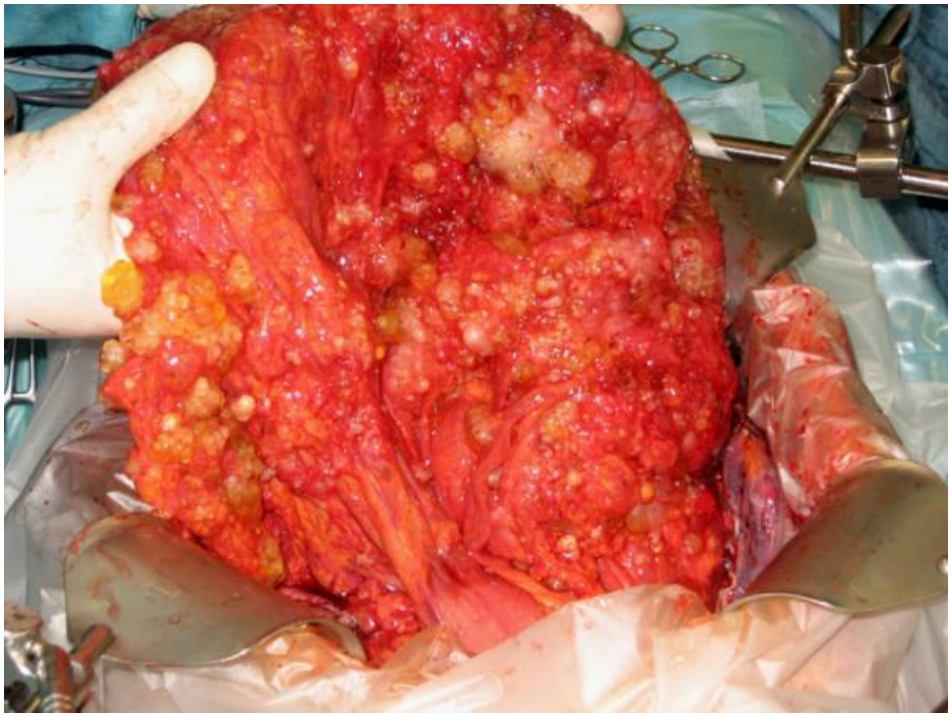
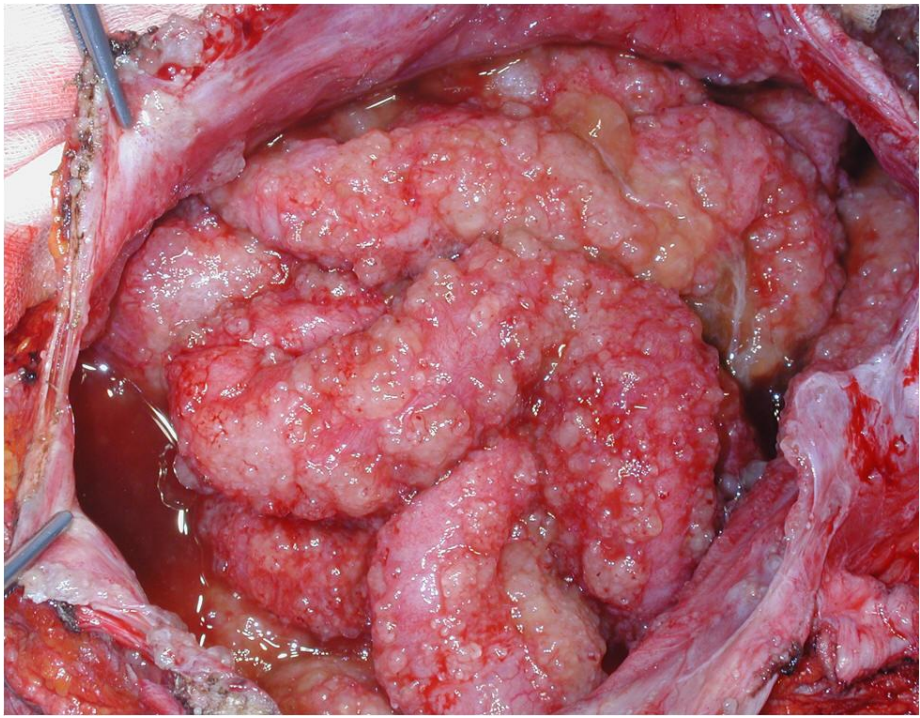
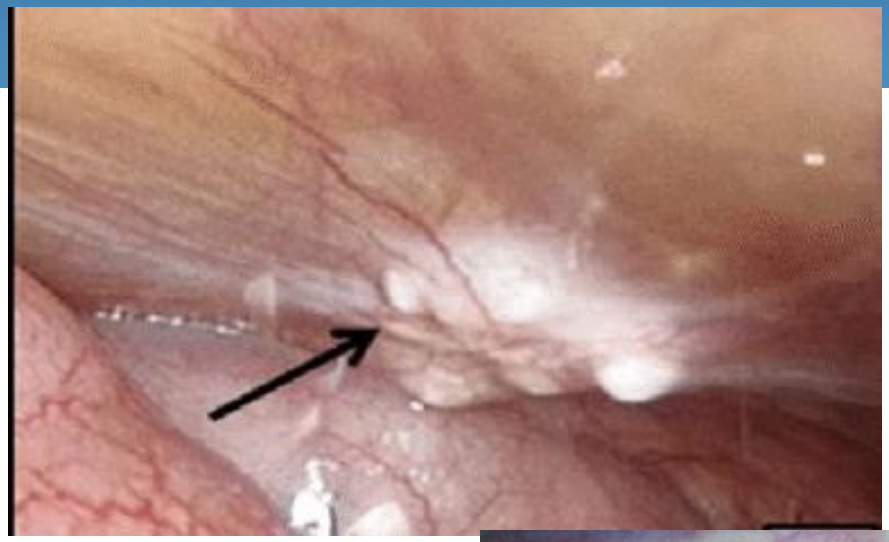
Peritoneal Carcinomatosis

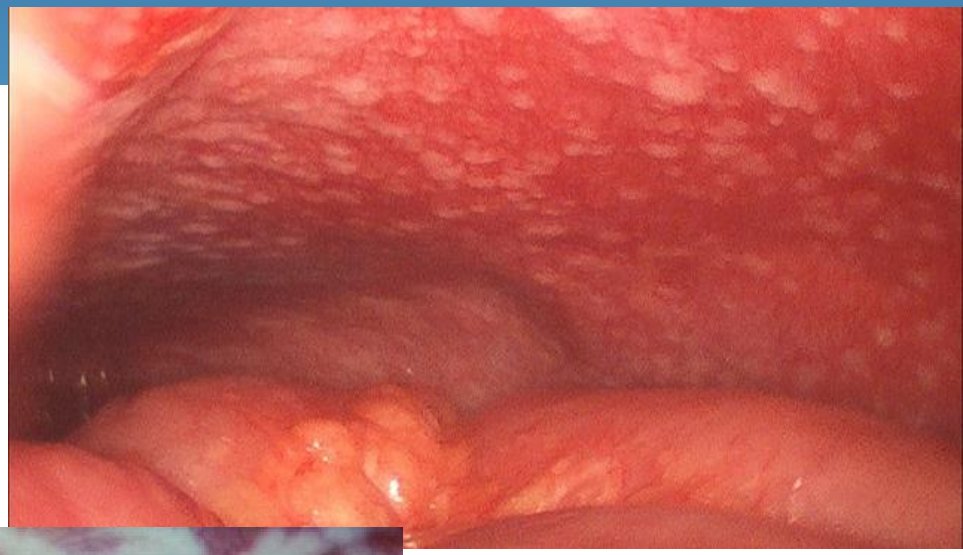
- Gastrointestinal and gynecologic malignancies
  - Colorectal, appendix, gastric, pancreatic, ovarian cancer
- Dissemination and growth in peritoneal cavity

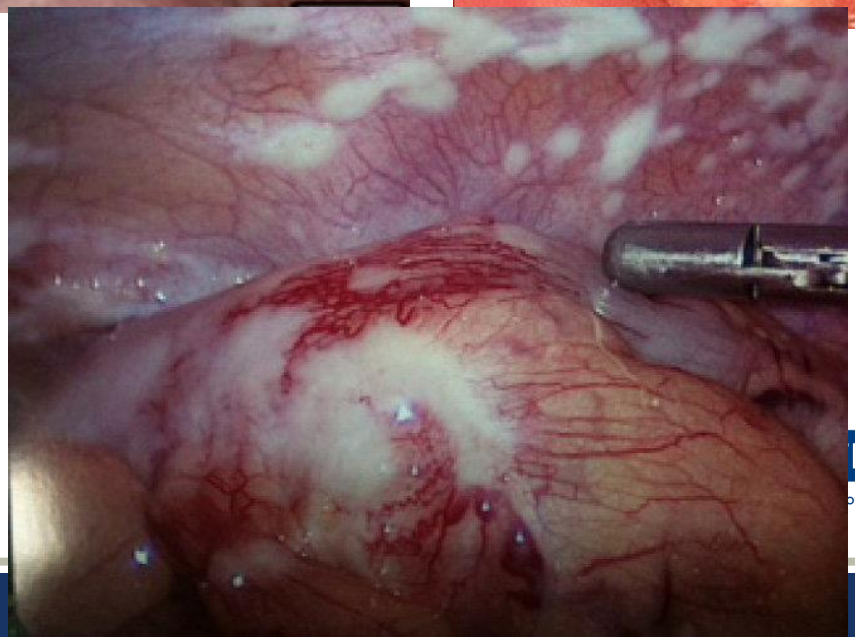




Peritoneal Carcinomatosis







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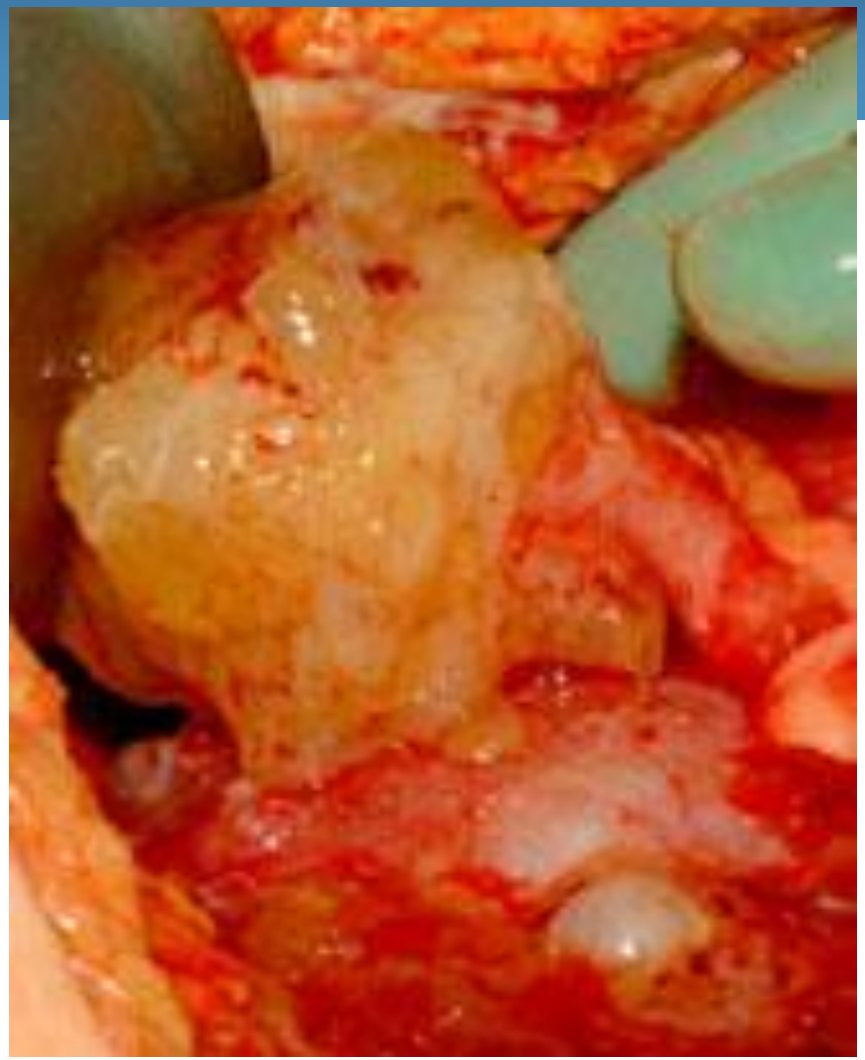

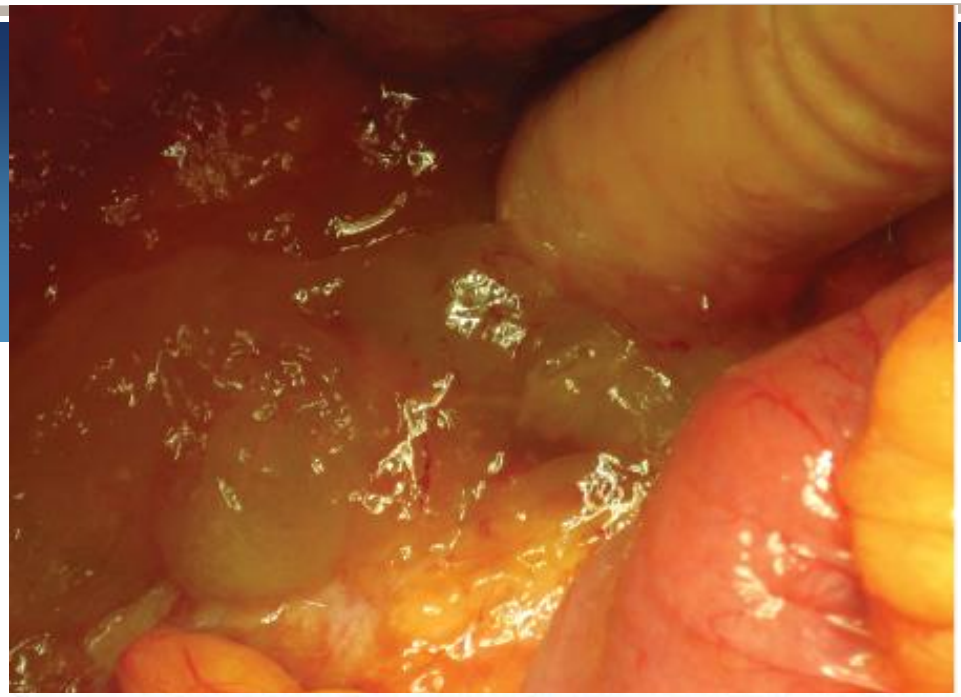

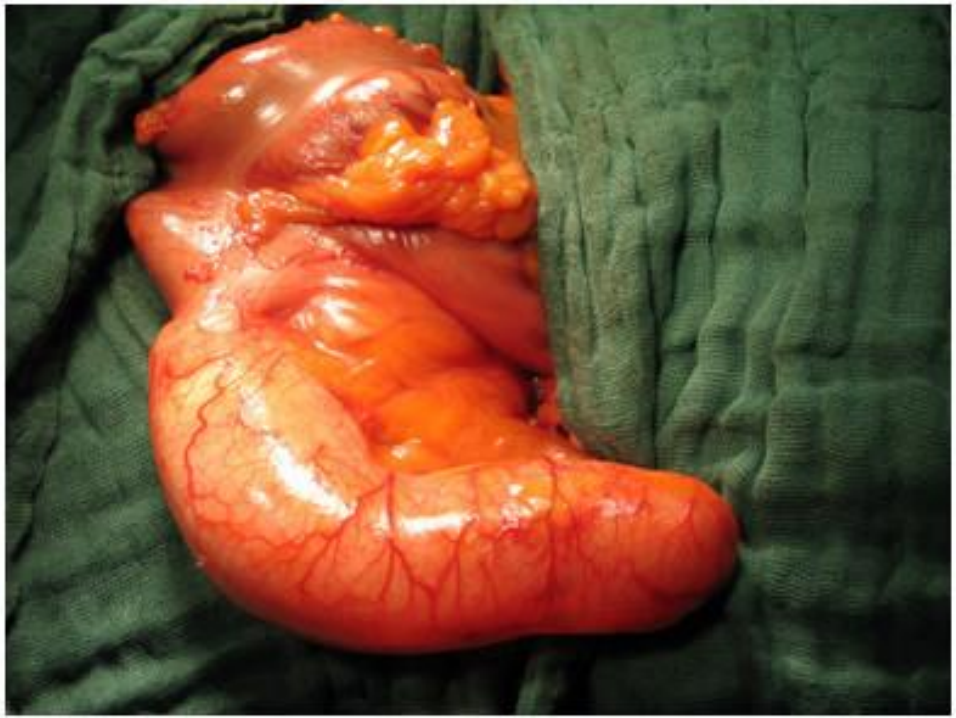

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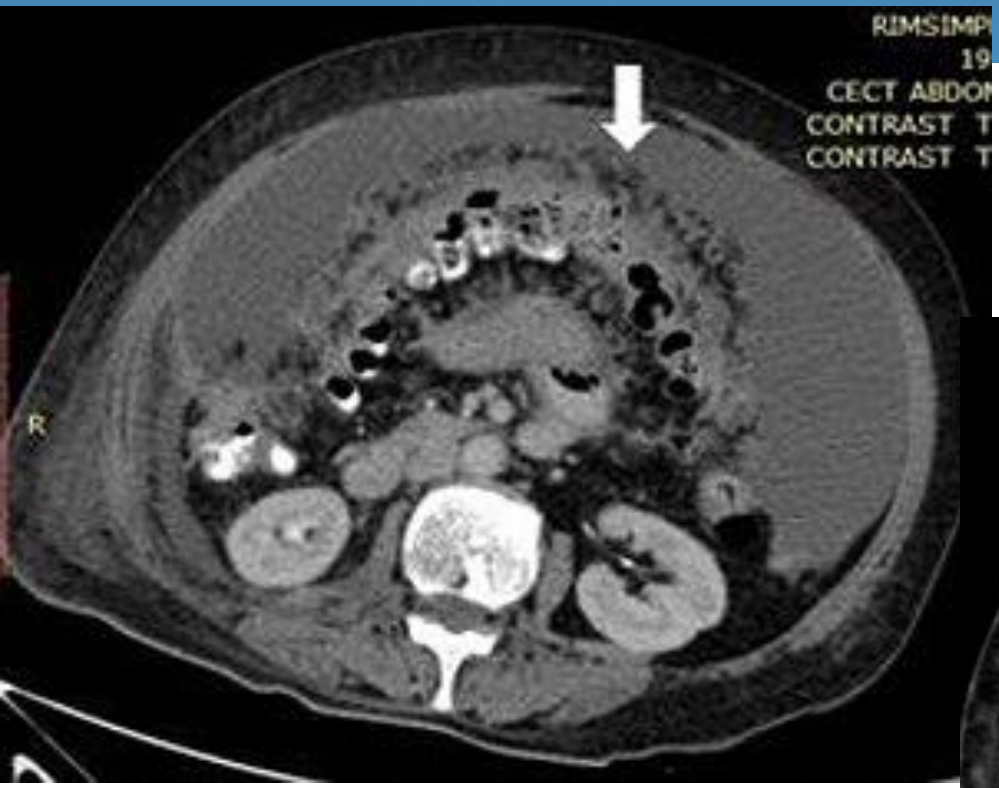

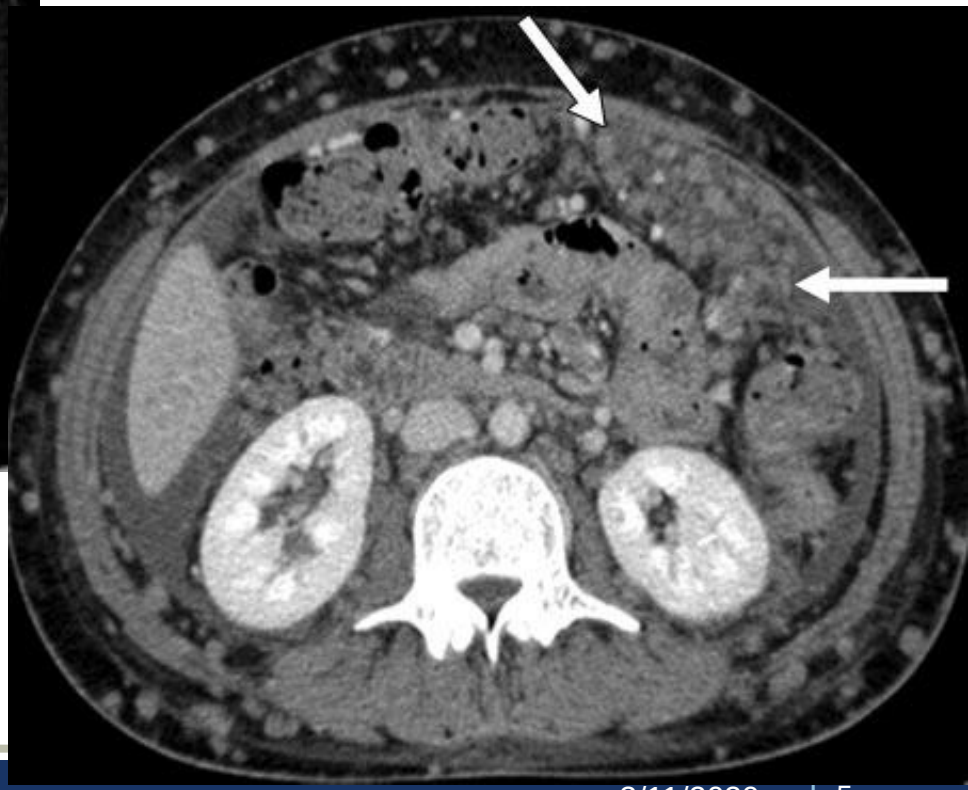

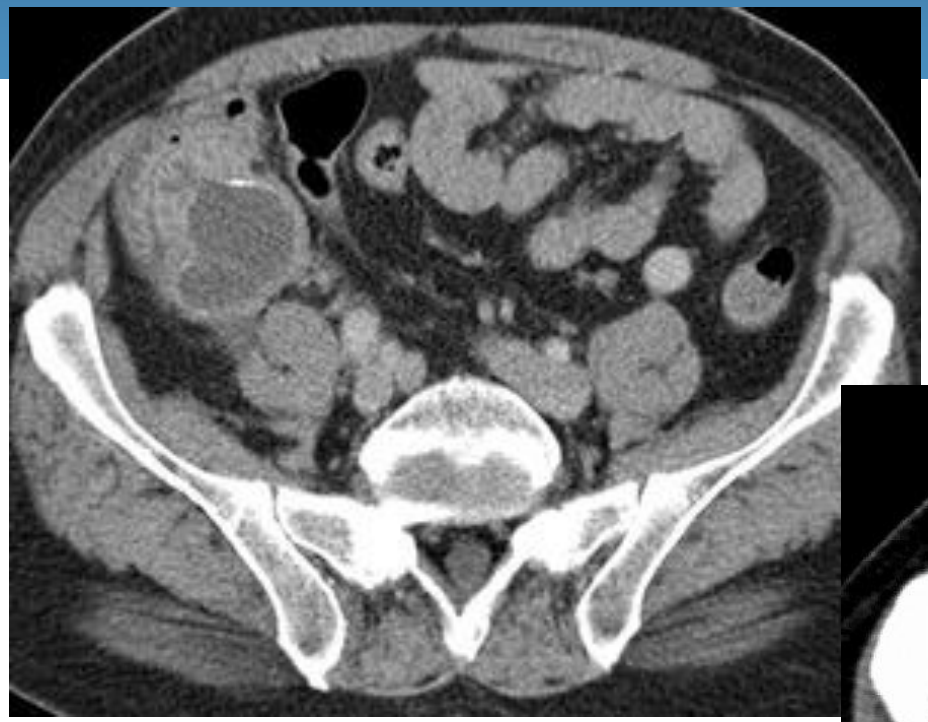

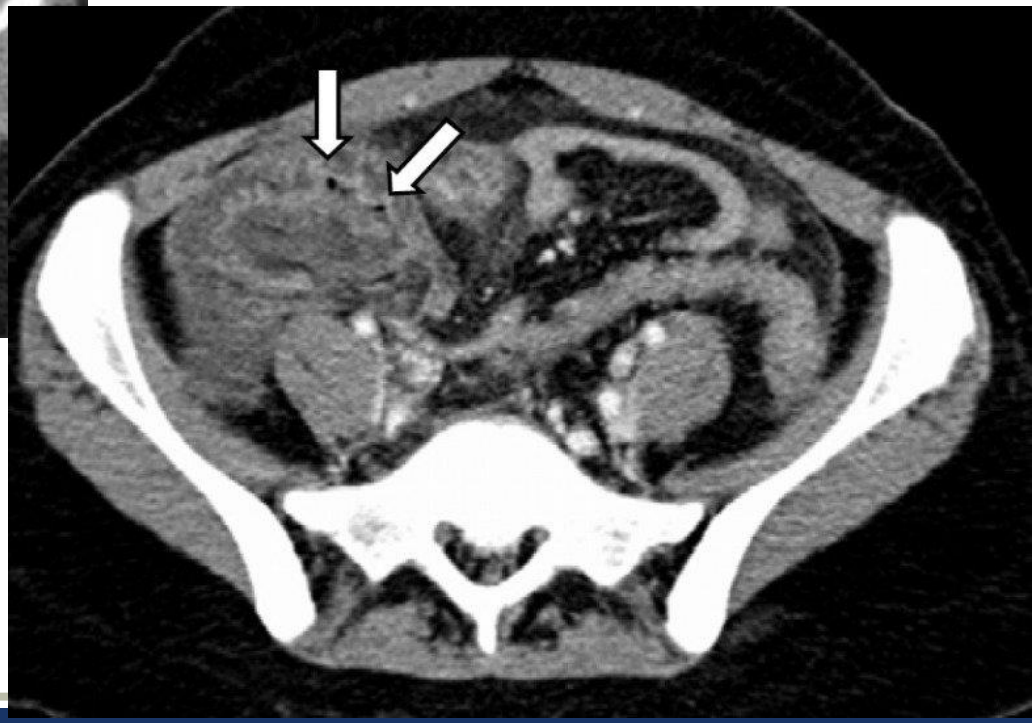

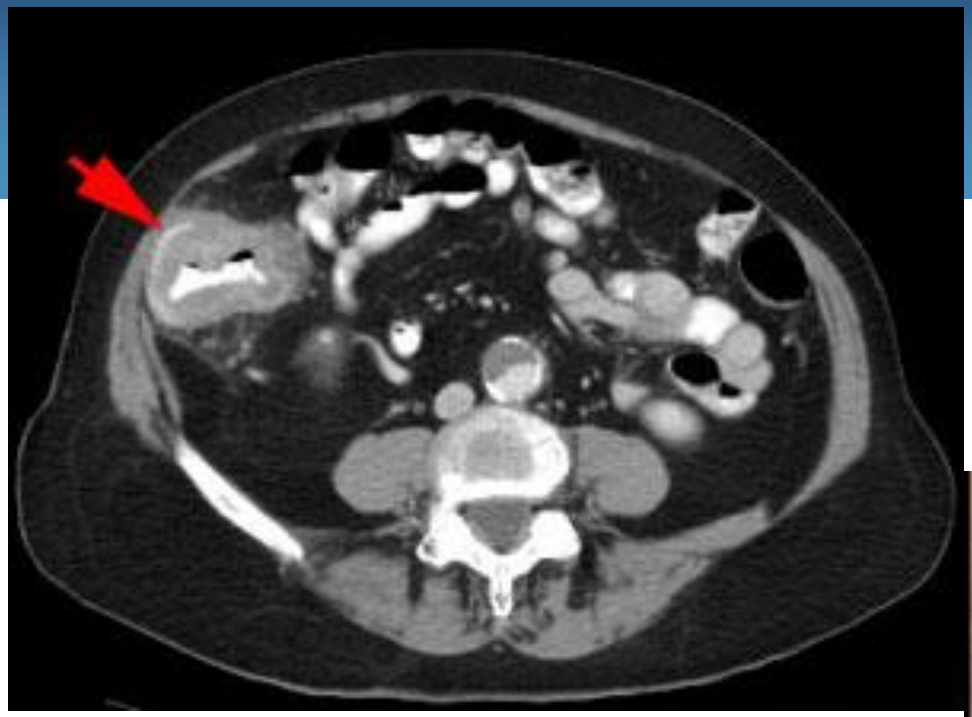

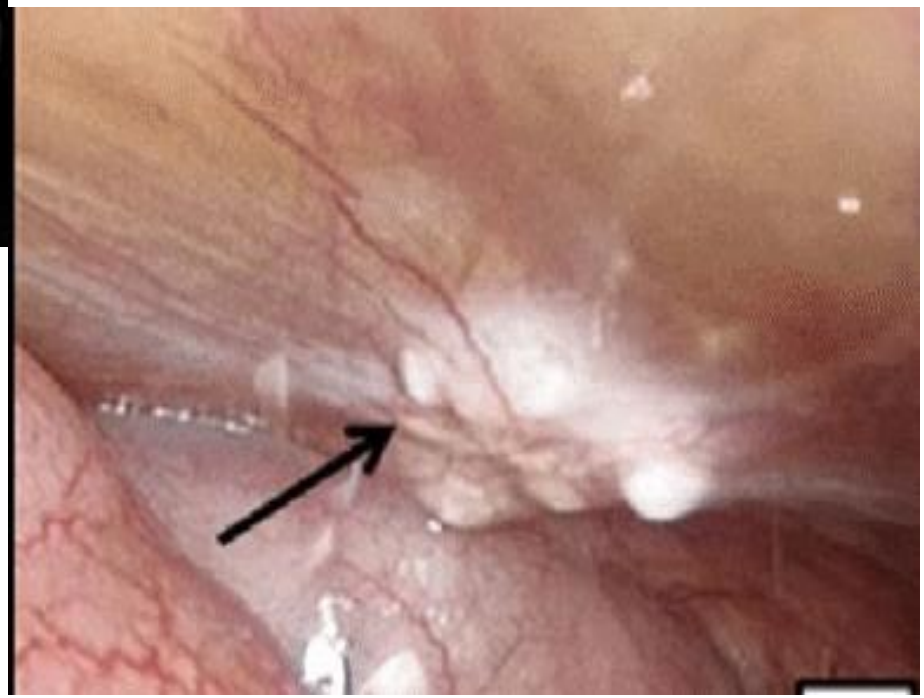

Peritoneal Carcinomatosis

- Associated with disease progression and poor prognosis
- Systemic chemotherapy is generally ineffective − peritoneum restricts the diffusion of systemic drugs into the peritoneal space.

- For some cancers, PC may be locoregional disease
- PC alone without other systemic disease - locoregional control improves overall survival

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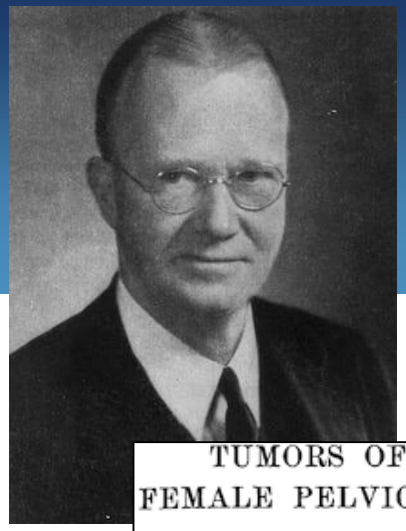
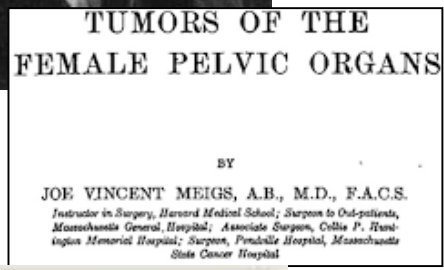
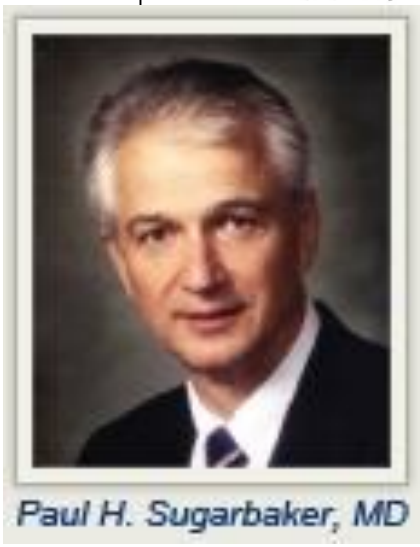
History

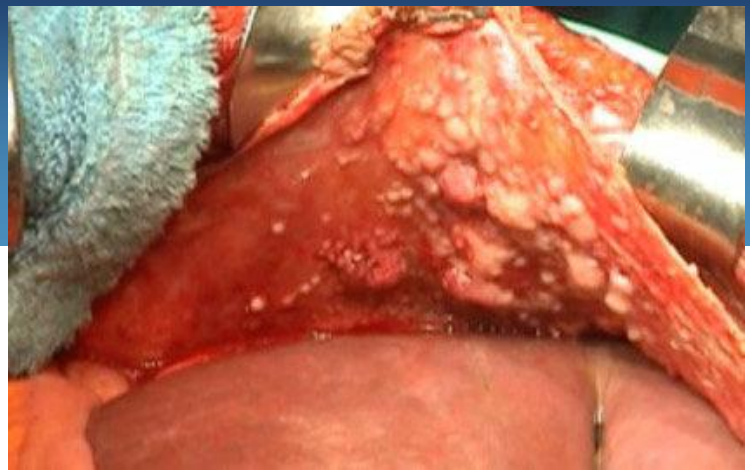




- 1930s − J.V. Meigs:. Demonstrated improved survival in patients with ovarian cancer and peritoneal metastasis with aggressive debulking
- 1960s: applied to pseudomyxoma peritonei
- 1990s: Paul Sugarbaker optimized technique of peritonectomy
- 1980-1990s:
  - Spatt − heated infusion of intraperitoneal chemotherapy
  - Palta − IP therapy infiltration system

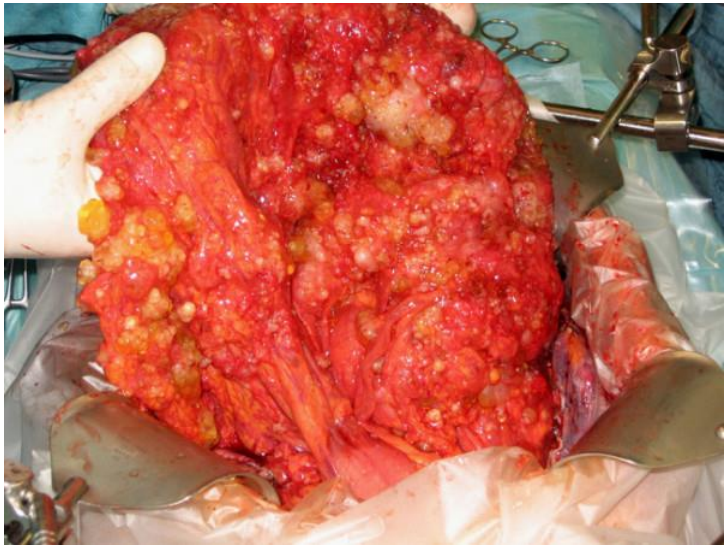


Cytoreductive Surgery



Goal – removal of all visible peritoneal carcinomatosis

- Parietal peritonectomy
- Omentectomy
- Right and left diaphragm peritonectomy
- Pelvic Peritonectomy
- Lesser omentectomy
- Liver capsule (Glisson's capsulectomy) as needed
- Splenectomy, cholecystectomy and oophorectomy is considered
- Resection of small bowel, colon, stomach as needed



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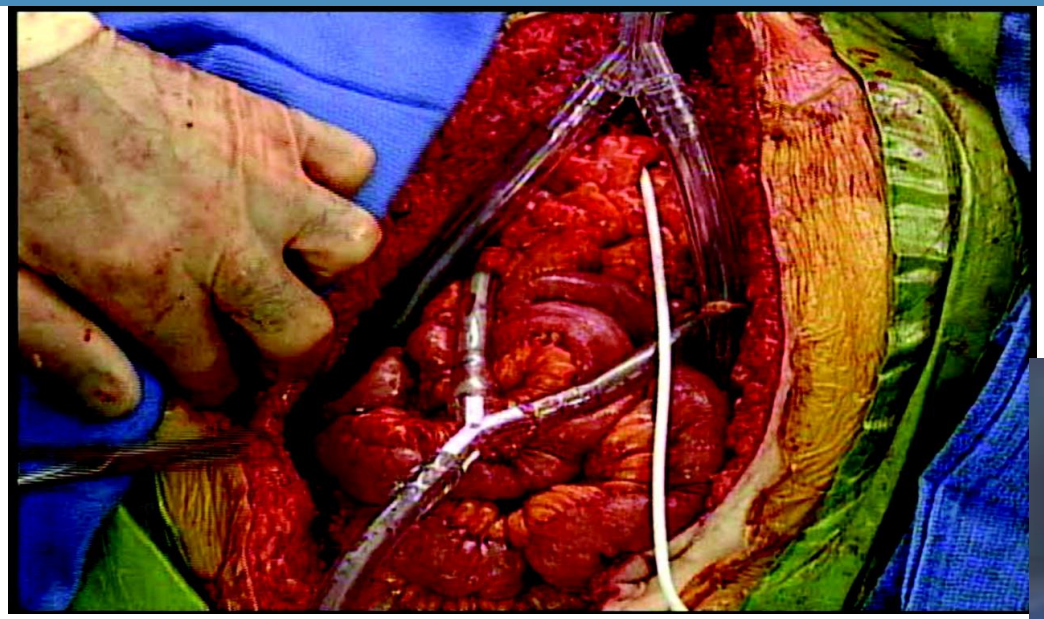
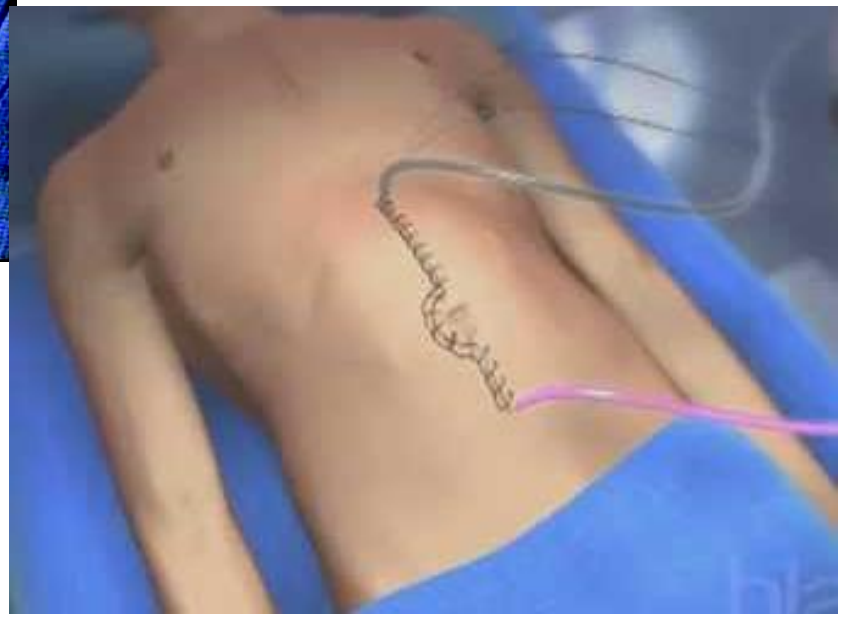
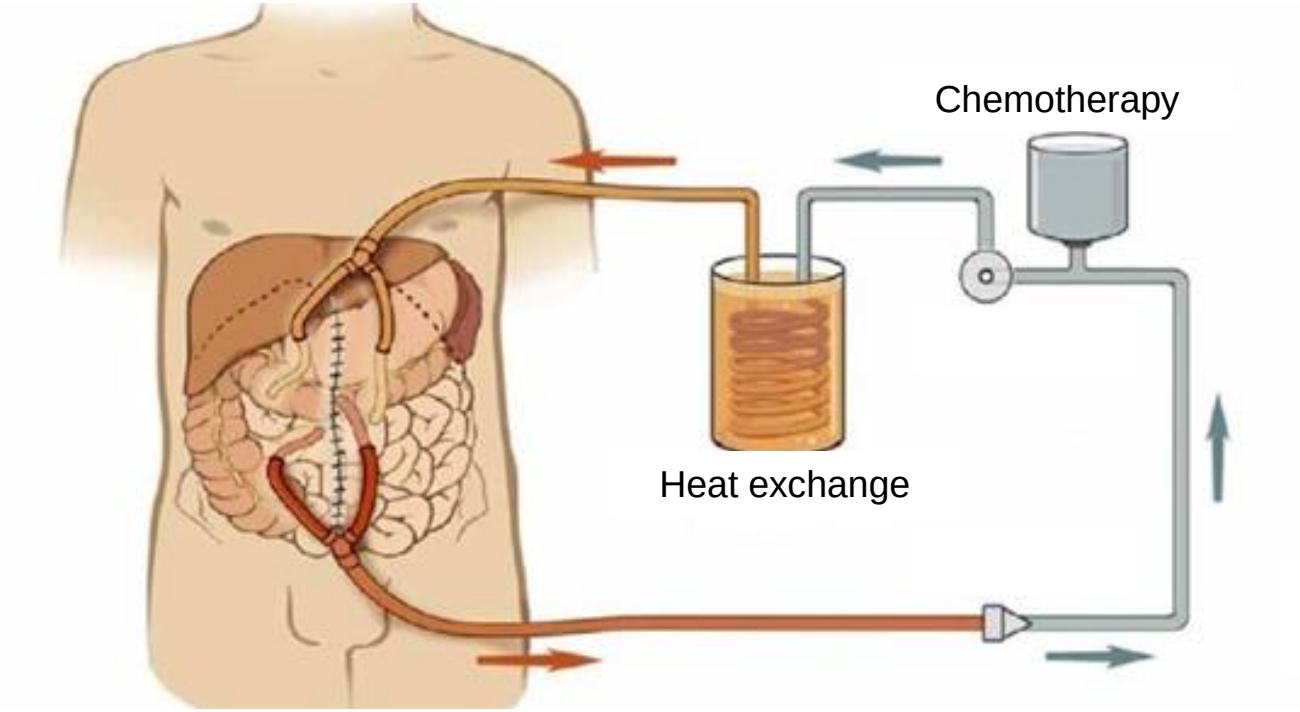
Hyperthermic Intraperitoneal Chemotherapy





Hyperthermic Intraperitoneal Chemotherapy

- Mitomycin C – 40mg, 42° C, 90 minutes
- Others - Cisplatin, Oxaliplatin, Doxorubicin, etc



What does NOT need to be considered when offering cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC)?

a) Original cancer type
b) History of systemic chemotherapy
c) Tumor burden (amount of tumor)
d) Ability to completely remove tumor
e) Functional status
f) None of the above

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Treatment of Peritoneal Carcinomatosis

- In the world of surgical oncology, **biology is King**; **selection of cases is Queen**, and the **technical details of surgical procedure are princes and princesses** of the realm who frequently try to overthrown the powerful forces of King and Queen, usually to no long-term avail, although some temporary apparent victories."

  - Blake Cady, MD 1997

Cady, "Basic Principles in Surgical Oncology", Arch Surg 1997: 132: 338

Patient Selection

- Functional Performance Status: ECOG <=2
- Comorbidities
- Age
- Nutrition − Albumin
- Sarcopenia

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Surgical Outcomes

ACS-NSQIP 2005-2011, 694 cases

- Overall Morbidity: 32%
  - Transfusion: 17%
  - Sepsis/septic shock: 16%
  - Wound disruption 2%, pneumonia 5%, ventilator >48 hrs 5%, renal insufficiency 4%, DVT 2%, PE 1.3%, MI 0.3%
- 30-day Mortality: 2.3%
- Return to OR within 30d: 9.8%
- Readmission: 11.4%
- Length of stay: 13 days (SD 16 days)

Jafari M, et al. Surgical Outcomes of HIPEC in NSQIP. JAMA Surgery 2014

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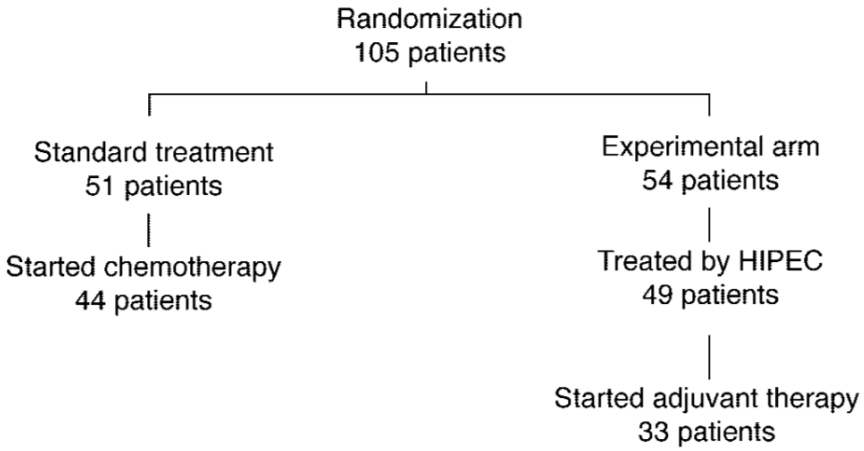
Hyperthermic Intraperitoneal Chemotherapy - Randomized Control Trial

- Peritoneal metastatsis of colorectal adenocarcinoma
- No other sites of distant mets (liver, lung)
- Age <71, fit for surgery
- Sites: Appendix (18), Colon (75), rectum (17)

5FU + Leucovorin vs.

Cytoreductive surgery

+ Mitomycin C (90 min, 42° C)



Verwaal VJ, et al. RTC of CRC/HIPEC vs Systemic Chemo. JCO 2003
Verwaal VJ, et al. 8 year follow up. Ann Surg Onc 2008

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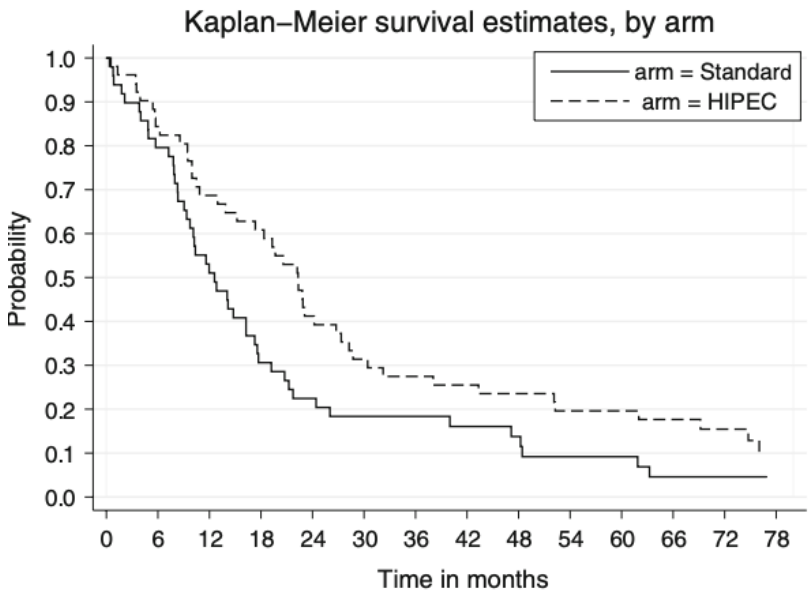
Hyperthermic Intraperitoneal Chemotherapy - RCT

Median Survival

- 12.6m vs. 22.4m

HR 0.55, p=0.032

5 year survival: 10% vs 20%



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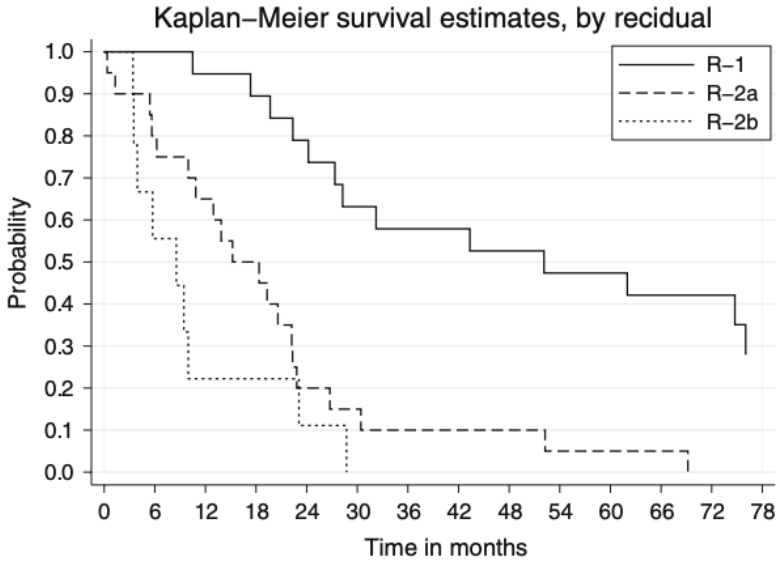
Hyperthermic Intraperitoneal Chemotherapy - RCT

Residual disease is important

- Main impact factor on survival was completeness of cytoreduction

5 year survival

- Complete: 45%
- Incomplete: <5%



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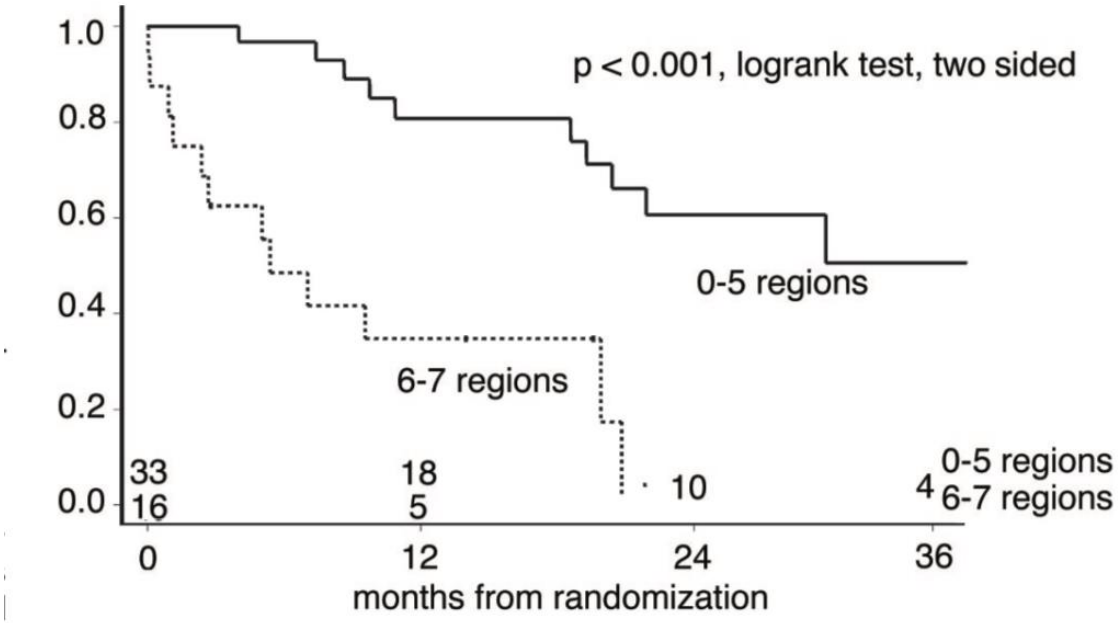
Hyperthermic Intraperitoneal Chemotherapy - RCT

Initial tumor burden is important



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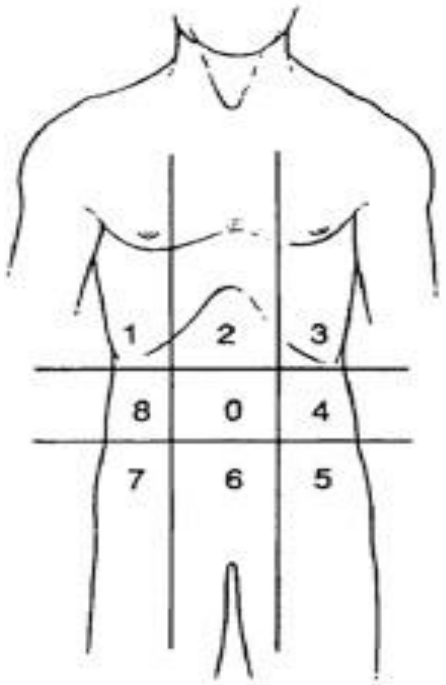
Degree of Tumor Burden
- Peritoneal Carcinomatosis Index (PCI)

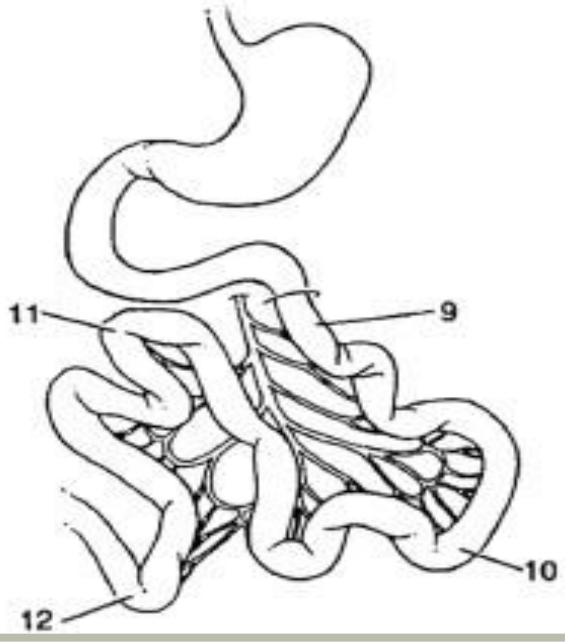


Regions		Lesion Size
0	Central	____
1	Right Upper	____
2	Epigastrium	____
3	Left Upper	____
4	Left Flank	____
5	Left Lower	____
6	Pelvis	____
7	Right Lower	____
8	Right Flank	____
9	Upper Jejunum	____
10	Lower Jejunum	____
11	Upper Ileum	____
12	Lower Ileum	____

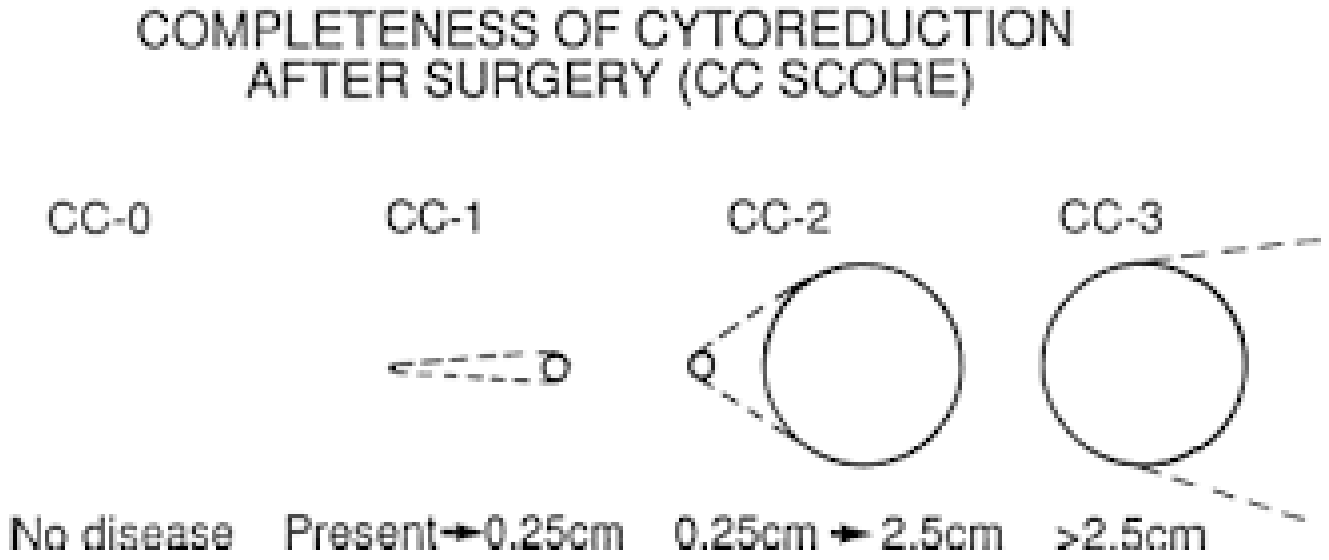
PCI ☐

Lesion Size Score

LS 0 No tumor seen
LS 1 Tumor up to 0.5 cm
LS 2 Tumor up to 5.0 cm
LS 3 Tumor > 5.0 cm or confluence



Completeness of Cytoreduction - CC Score



Which is an appropriate indication for first-line therapy with CRS/HIPEC?

a) Massive abdominal distention with pseudomyxoma peritonei

b) Appendix cancer, high grade, with low volume peritoneal metastasis

c) Colorectal cancer, low grade, with metastasis to peritoneum and liver (resectable)

d) Gastric cancer, with cytology only peritoneal mets

e) All of the above

f) None of the above

Appendectomy is planned for appendiceal mass. During surgery some mucin pools are seen. Pathology from appendectomy shows low grade mucinous neoplasm (LAMN) without adenocarcinoma, negative margins, 1 negative lymph node.

What is next step?

a) No further treatment necessary.

b) Right colectomy

c) Right colectomy and referral for CRS/HIPEC

d) Referral for CRS/HIPEC

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INDICATIONS for CRS/HIPEC

- Pseudomyxoma Peritonei (well differentiated mucinous appendiceal neoplasm/adenoca)
- Appendiceal Cancer (moderate or high grade)
- Colorectal Cancer
- Gastric Cancer
- Mesothelioma
- Ovarian Cancer

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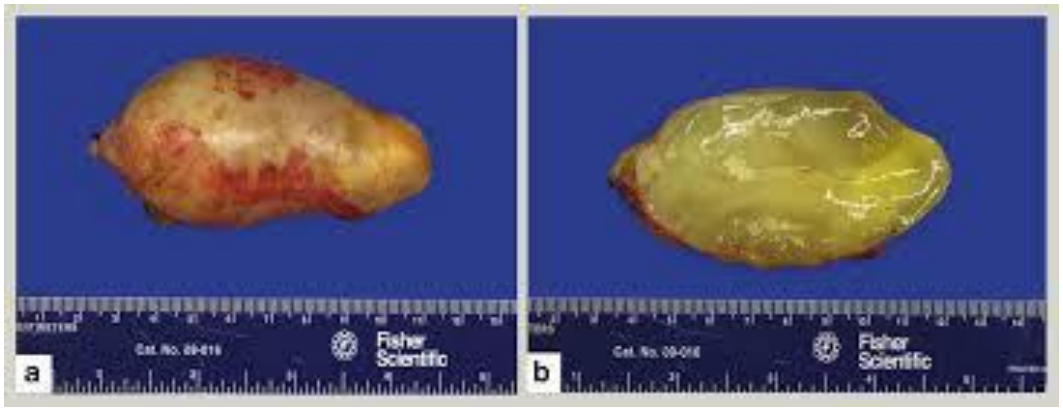
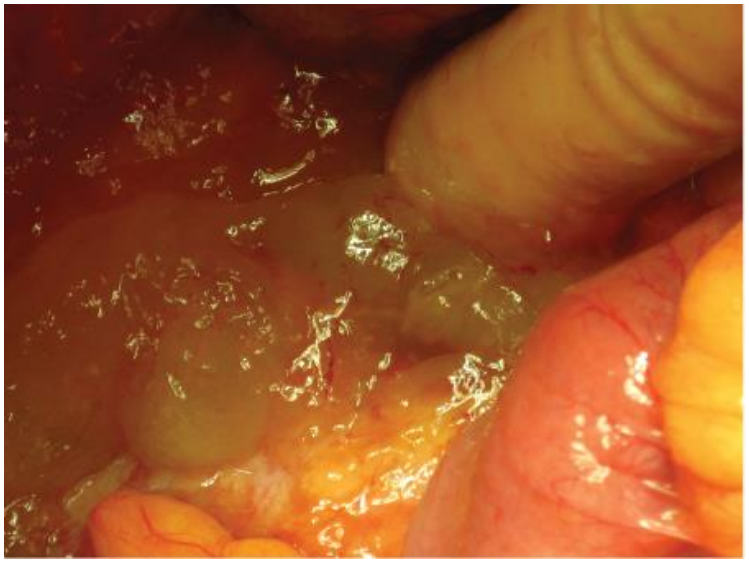
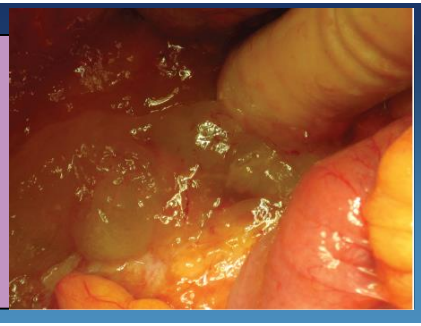
Well-differentiated Mucinous Appendiceal Neoplasm/Adenoca

- Abundance of mucin
- Paucity of epithelial cells
- Attaches to viscera, but does not invade beyond peritoneum
- Often can be completely resected with peritonectomy
- LN met <5%

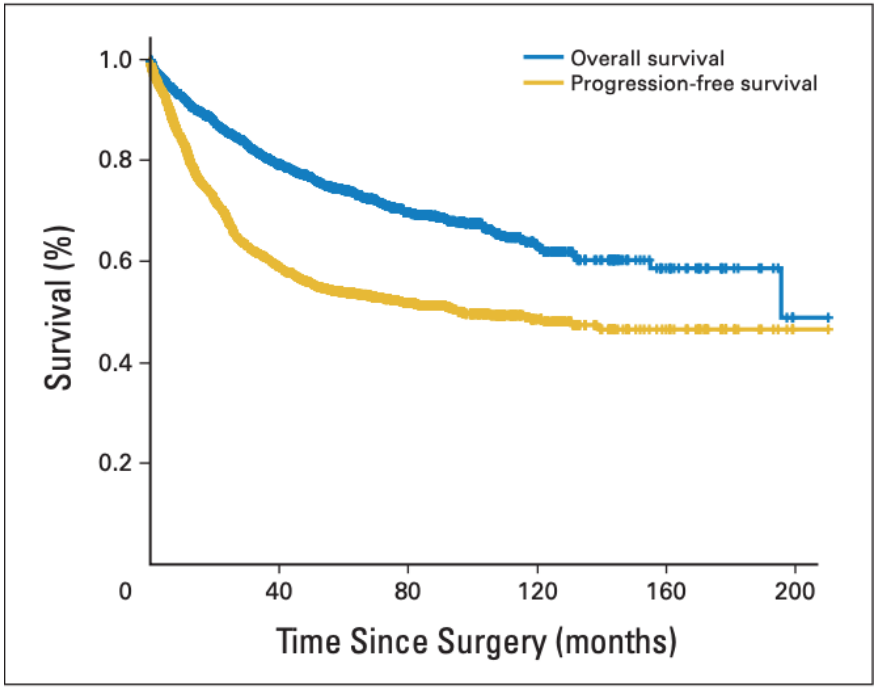




Well-differentiated Mucinous Appendiceal Neoplasm/Adenoca

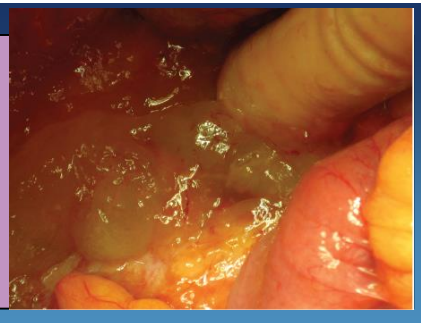


- Median Survival: 16.3 years
- Median Progression Free survival 8.2 years

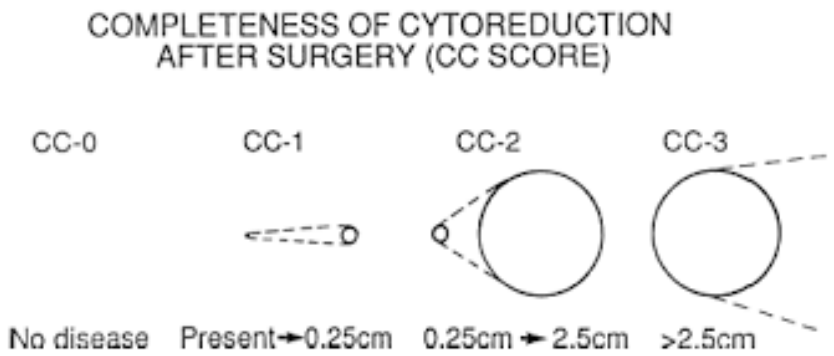


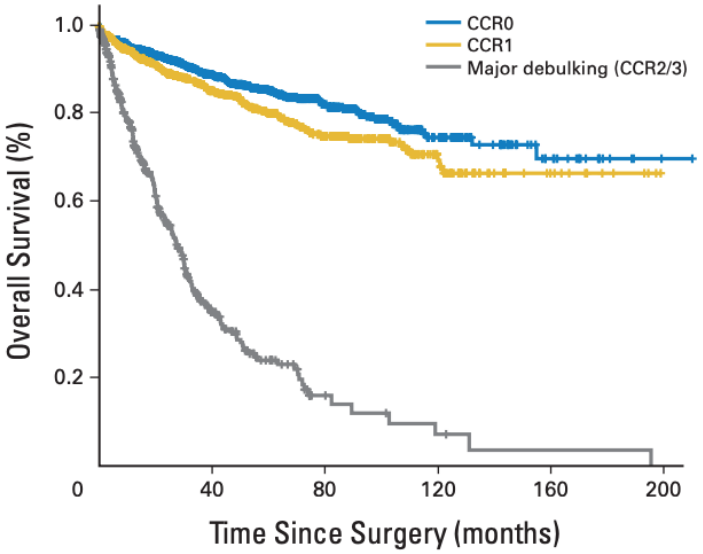
Chua TC et al. HIPEC for Pseudomyxoma Peritonei. JCO 2012

Well-differentiated Mucinous Appendiceal Neoplasm/Adenoca



- Completeness of cytoreduction (CCR) is most important predictor of outcome





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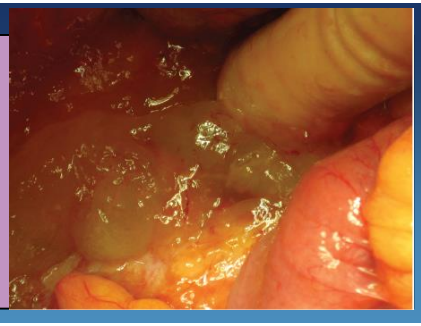
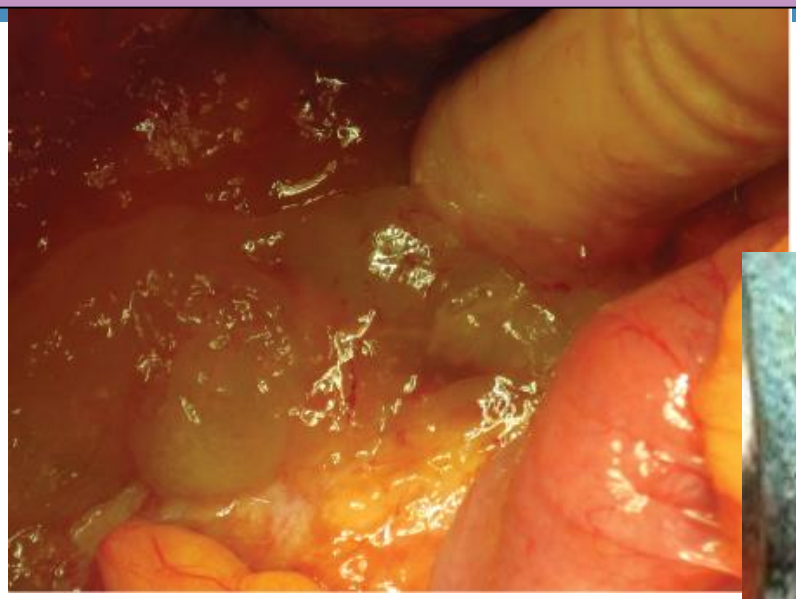
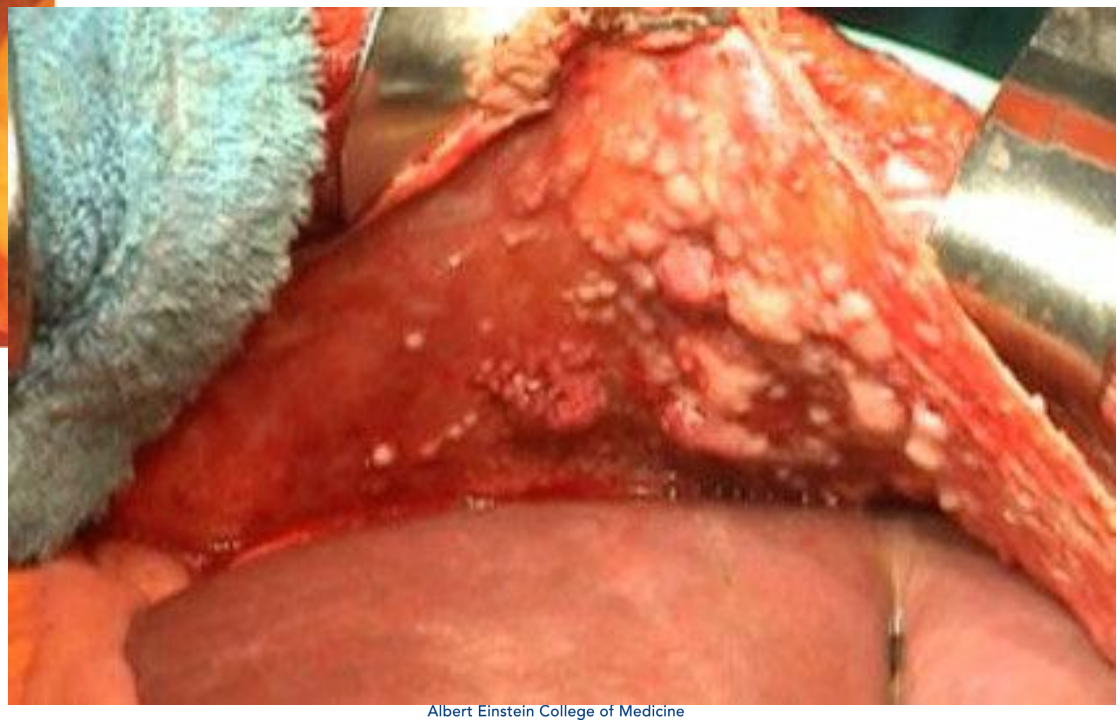
Well-differentiated Mucinous Appendiceal Neoplasm/Adenoca







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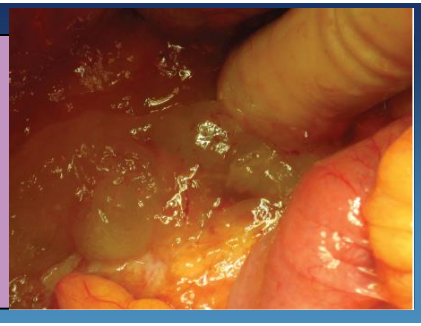
Well-differentiated Mucinous Appendiceal Neoplasm/Adenoca



Characteristics

- Systemic chemotherapy does not work well, and surgery is main stay of treatment
- Right colectomy is not needed - Local excision of positive margin should be performed (wedge resection or cecectomy)
- If peritoneal spread (mucin, tumor spillage) − need to go back for reevaluation and CRC/HIPEC
- Large volume tumor is **NOT** contra-indication - High PCI (30-39): 5 year survival: 73%, 10 year survival: 68%. HIPEC with incomplete tumor resection controls 90% of ascites

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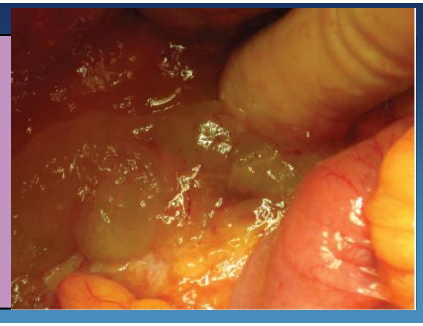
Well-differentiated Mucinous Appendiceal Neoplasm/Adenoca



Treatment

- Appendectomy (neg margin), no peritoneal spread − surveillance
- Appendectomy (positive margin), no peritoneal spread − Local excision of positive margin should be performed (wedge resection or cecectomy)

- Peritoneal spread (mucin, tumor spillage) during surgery − biopsy followed by CRS/HIPEC
- Pseudomyxoma on imaging – investigate for origin, CRS/HIPEC (no systemic chemotherapy)

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- Pseudomyxoma Peritonei (well differentiated mucinous appendiceal neoplasm/adenoca)

- **Appendiceal Cancer (moderate or high grade)**
- **Colorectal Cancer**
- **Gastric Cancer**
- **Mesothelioma**
- Ovarian Cancer

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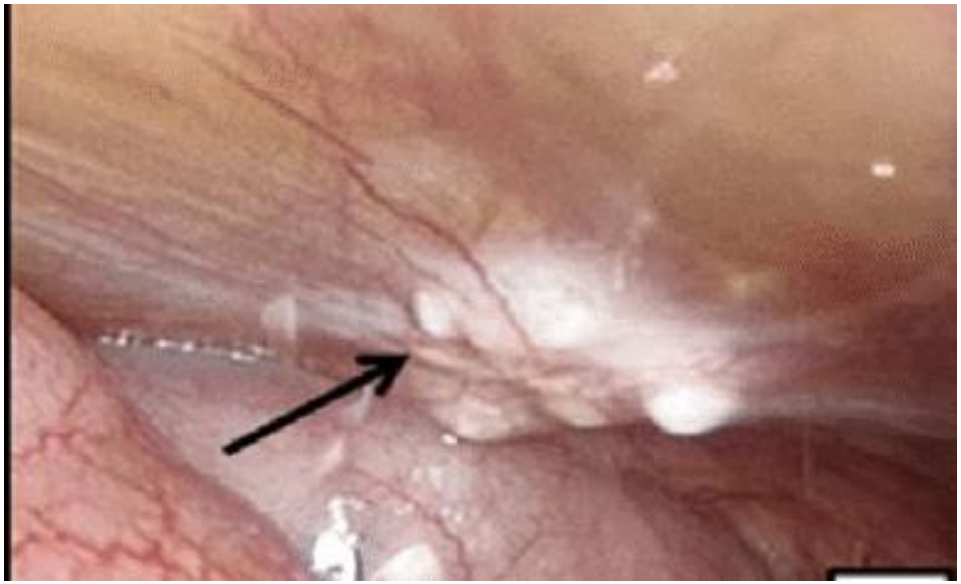
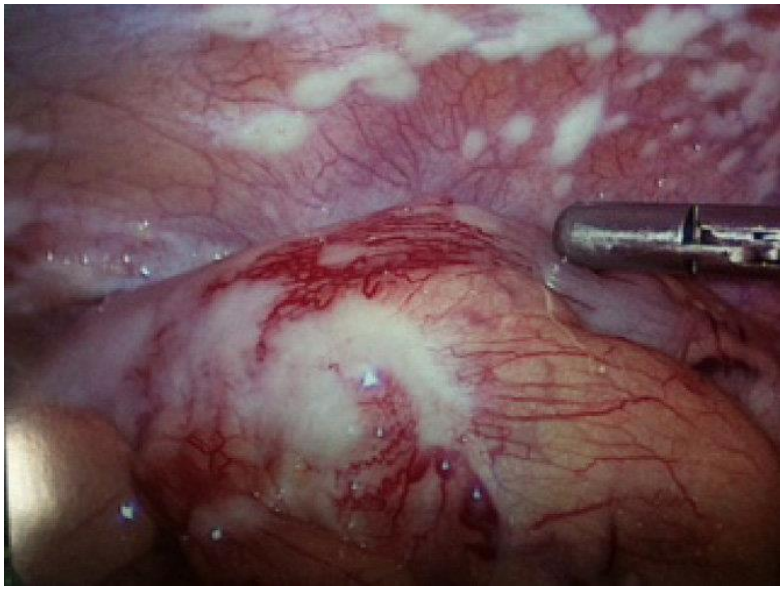
Other Cancers

- **Tumor biology** and **patient selection** are critically important.





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Other Cancers

Factors to assess **tumor biology** and **patient selection**

- Tumor burden − PCI score
- Ability to achieve complete cytoreduction
  - Extensive involvement of small bowel mesentery
  - Extensive porta hepatis involvment
  - Extensive pelvic floor disease necessitating exenterative procedure
- Tumor histology/type
- Response to systemic therapy
- Disease free interval

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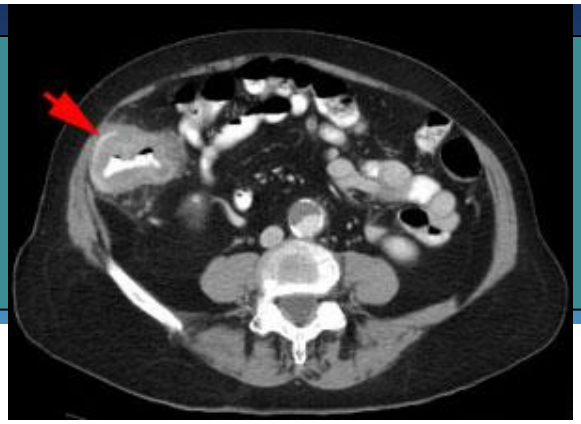
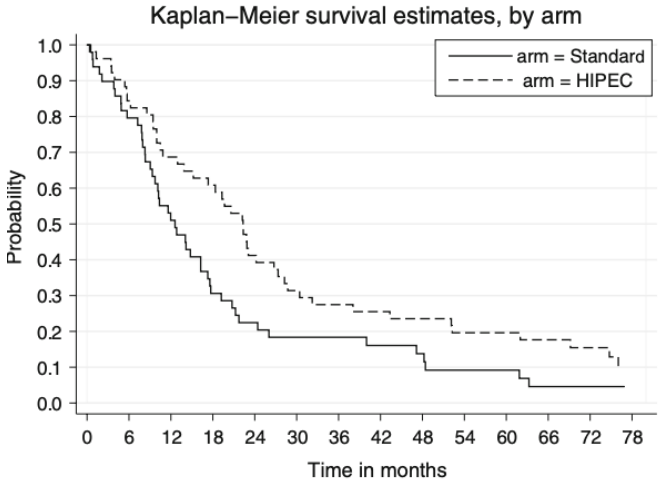
Colorectal Cancer



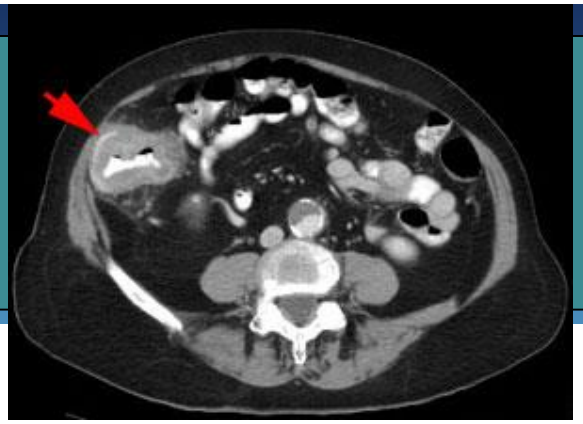
- Colorectal Cancer
  - 10% of stage IV will have disease limited to peritoneum
  - 15% of stage II-III cancer will develop peritoneal disease
  - Metachronous, 10-35% is limited to peritoneal cavity

- Stage IV colorectal cancer
  - 5 year survival: 14% (national)
  - Chemo alone: 10%
  - With CRS/HIPEC: 20%



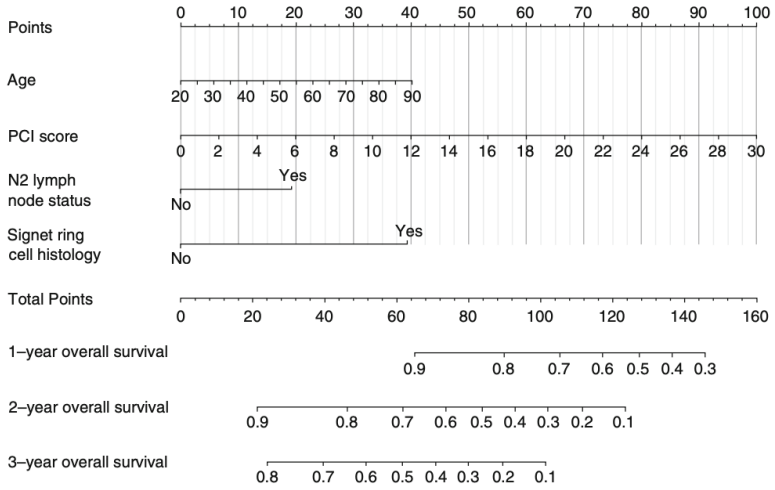
Verwaal VJ, et al. RTC of CRC/HIPEC vs Systemic Chemo. JCO 2003

Colorectal Cancer



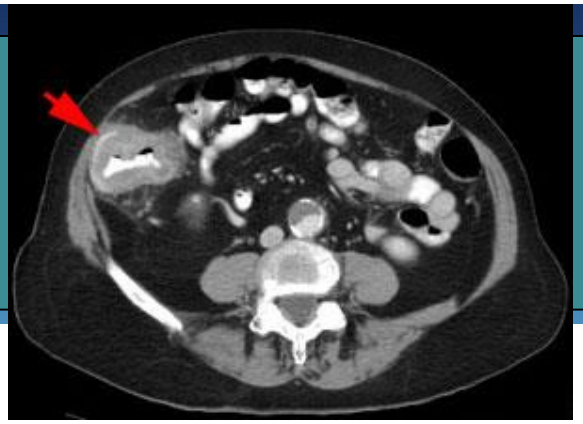
- Disease Severity Scores
  - > **PSDSS** – scoring system
    - Symptoms (none, mild, severe)
    - PCI (<10, 10-20, >20)
    - Histology (differentiation, signet ring cell, LN+)
  - > **COMPASS** - nomogram
    - Includes age

Clinical	CT- PCI	Histology
No symptoms **0**	PCI < 10 (Low) **1**	G1 G2 N- L- V- **1**
Mild symptoms **1**	PCI 10-20 (Medium) **3**	G2 N+ and/or L+ and/or V+ **3**
Severe symptoms **6**	PCI > 20 (High) **7**	G3 Signet Ring **9**



Eequivel J et al. Peritoneal Disease Severity Scoring System. Ann Surg Onc 2014
Simkens F, et al. Nomogram for Colorectal Cytoreductive Surgery and HIPEC. Ann Surg Onc 2016

Colorectal Cancer



PSDSS – scoring system

Clinical	CT- PCI	Histology
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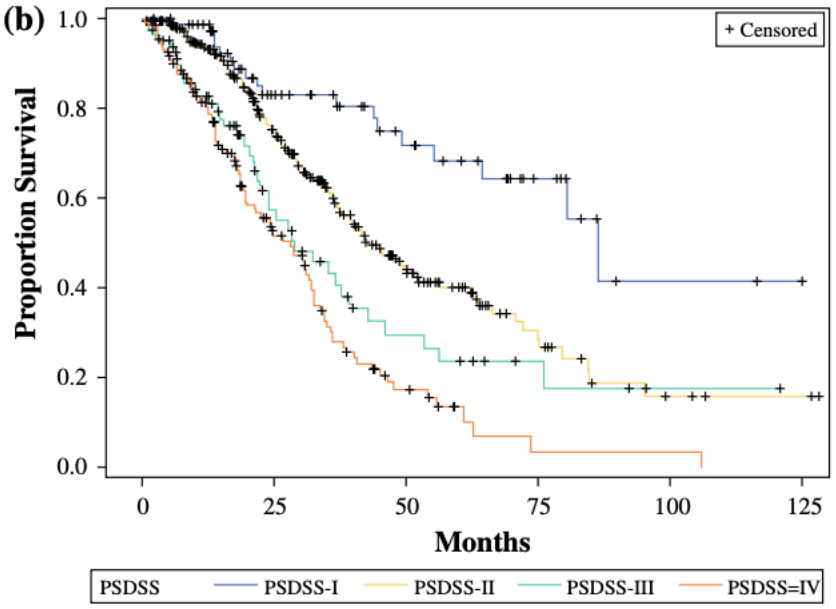
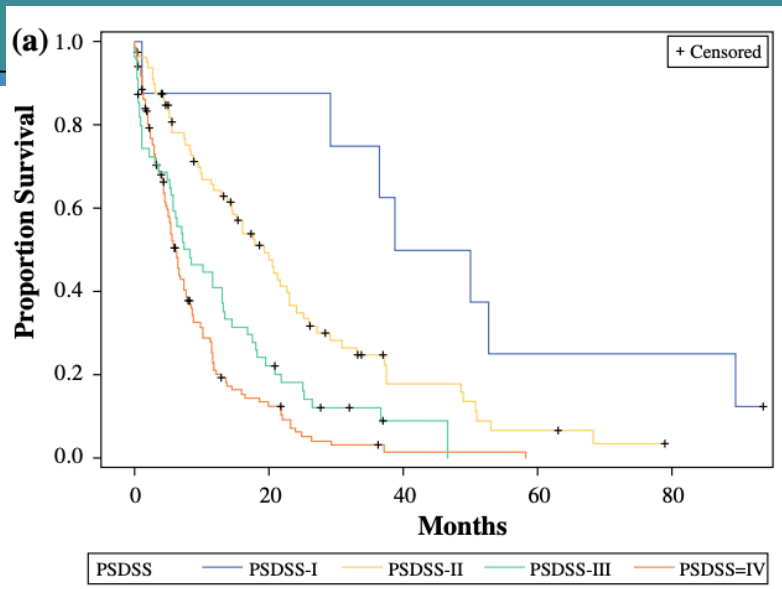
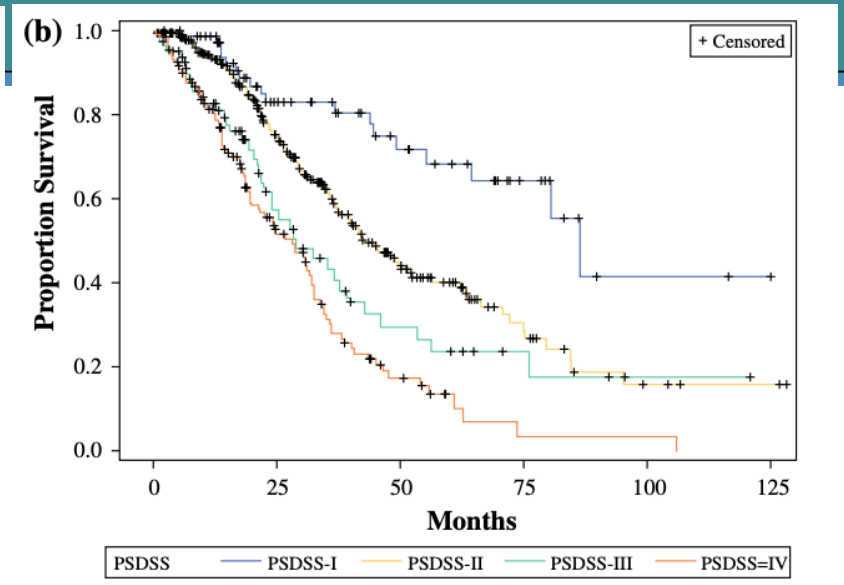


Median Survival using PSDSS

- I : 86 months
- II : 42 months
- III: 29 months
- IV: 28 months

Colorectal Cancer

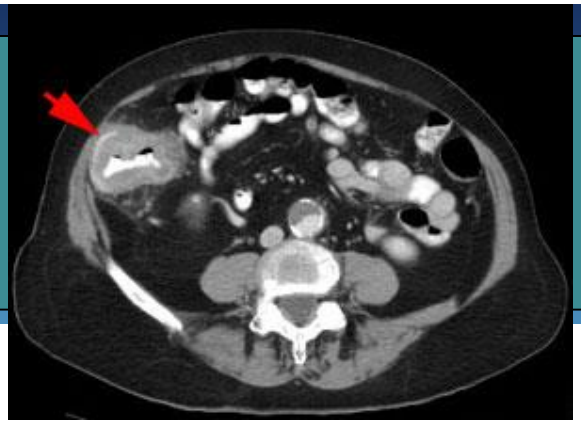




	Systemic Chemo	CRS/HIPEC
PSDSS I	45m	86m
PSDSS II	19m	42m
PSDSS III	8m	29m
PSDSS IV	6m	28m

Eequivel J et al. Peritoneal Disease Severity Scoring System. Ann Surg Onc 2014

Colorectal Cancer



PRODIGE 7

- RCT, phase III, Multicenter
- CRS vs CRS/HIPEC with oxaliplatin (132 pt and 133 pts)
- Median OS: 41.7m vs 41.2 m

- Inclusion of HIPEC using Oxaliplatin resulted in more complications
- 60d grade 3-5 morbidity: 24.1% vs 13.6%

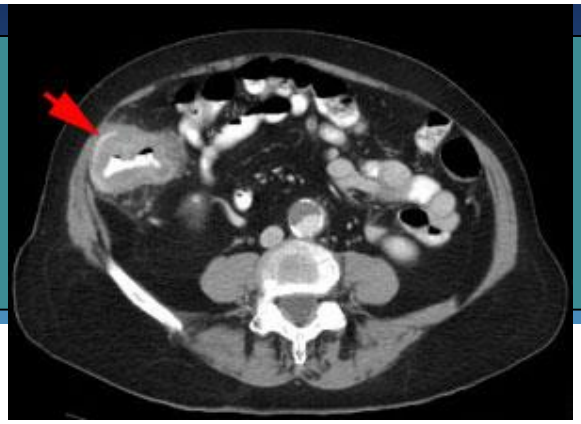
** marked improvement compared to systemic chemo alone (OS: 14m)

** CRS is beneficial

** Unclear if HIPEC or the use of Oxaliplatin is of no benefit

PRODIGE 7. Abstract. JCO 36. No. 18_suppl

Colorectal Cancer



Considerations

>Tumor burden − PCI score: Cutoff 20, ?17

>Ability to achieve complete cytoreduction: necessary

>Tumor histology/type: (poor outcome) G3, signet ring cell, LVI, LN positive

>Response to systemic therapy: no progression

>Disease free interval

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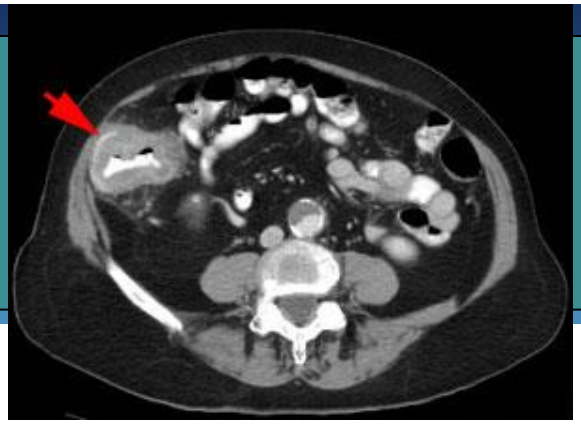
Colorectal Cancer



- **Treatment**
- Synchronous & Metachronous Metastatic disease
  - Peritoneal disease: Chemotherapy (3-6m) followed by CRS/HIPEC if no progression
  - Unsuspected peritoneal disease: Colectomy if symptomatic. If asymptomatic, chemo first followed by CRS/HIPEC

Extra-peritoneal metastatic disease is **NOT a contraindication for surgical resection of metastatic disease. Liver mets and lung mets that are resectable can be treated at same time as peritoneal disease.

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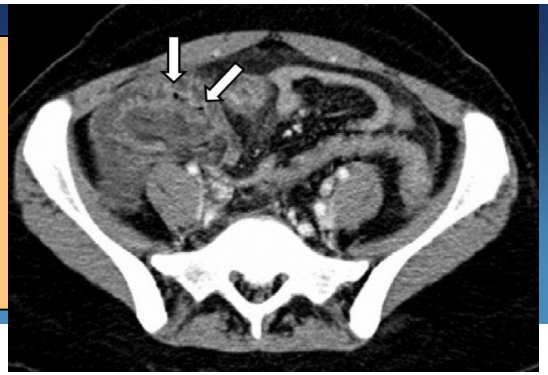
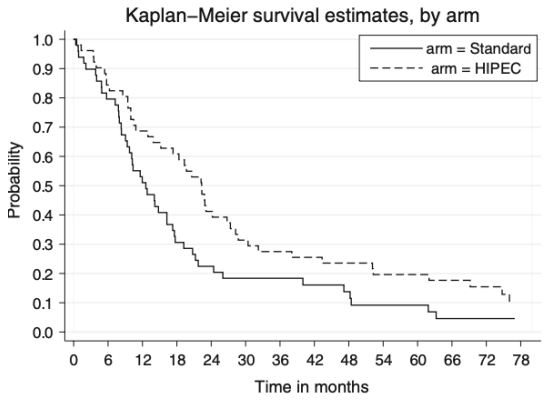
Moderately, Poorly Differentiated Appendiceal Adenocarcinoma



- 25-40% chance of lymph node metastasis
- Somewhat responsive to chemotherapy

- Systemic tx alone:12.6m
- CRS/HIPEC + chemo: 22.4m



- CRS/HIPEC outcomes based on response to chemotherapy
  - > Stable or responsive disease (44%): 44 months
  - > Progressive disease (14%): 21 months

Verwaal VJ, et al. RTC of CRC/HIPEC vs Systemic Chemo. JCO 2003

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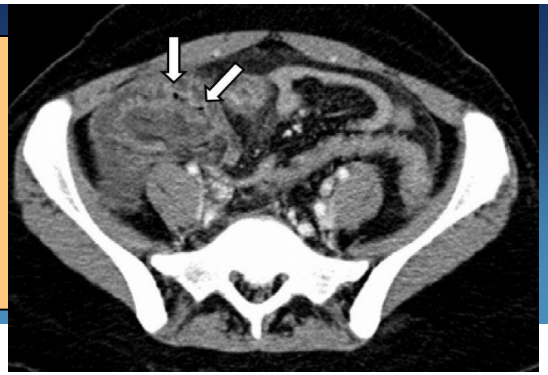
Moderately, Poorly Differentiated Appendiceal Adenocarcinoma



Considerations

- Tumor burden − PCI score: ?17,?20
- Ability to achieve complete cytoreduction: necessary
- Tumor histology/type: Mucinous (good), signet ring cell (bad)
- Response to systemic therapy: no progression
- Disease free interval

Grotz TE et al. Patient Selection for CRS?HIPEC in Moderate and Poorly Differentiated Appendiceal adenocarcinoma. Ann Surg Onc 2017

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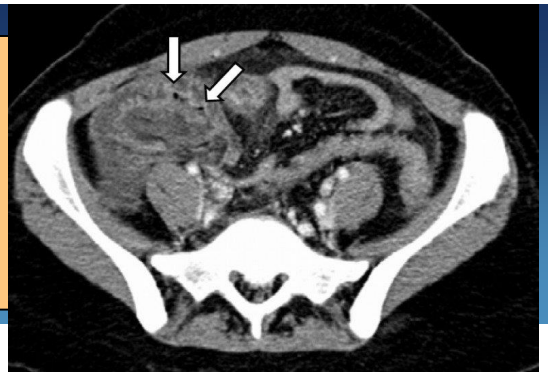
Moderately, Poorly Differentiated Appendiceal Adenocarcinoma



Treatment

- No peritoneal disease, appendix cancer
  - → R colectomy, followed by adj tx (treat like colon cancer)

- Peritoneal disease prior to or during appendectomy, suspect appendiceal cancer
  - → diagnostic laparoscopy for biopsy (of peritoneal met)
  - → chemotherapy is mainstay of treatment
  - → CRS/HIPEC can be considered for good responders

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Gastric Cancer

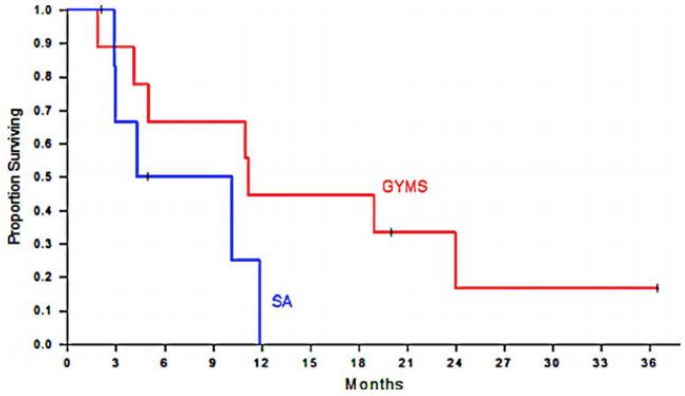
Gastric Cancer

- 30-40% of Stage II-III cancer will have peritoneal disease
- Metachronous, 50% is limited to peritoneal cavity

RCT 34 patients

- Chemo (8pts) vs CRS/HIPEC (9pts)

  4.3m vs 11.3m



**All in chemo arm died <12m

**CRS/HIPEC: 3 pts lived 2 year, 1 pt alive at end of study

Rudloff U et al. CRS HIPEC for Gastric Ca. GYMSSA trial. J Surg Onc 2014

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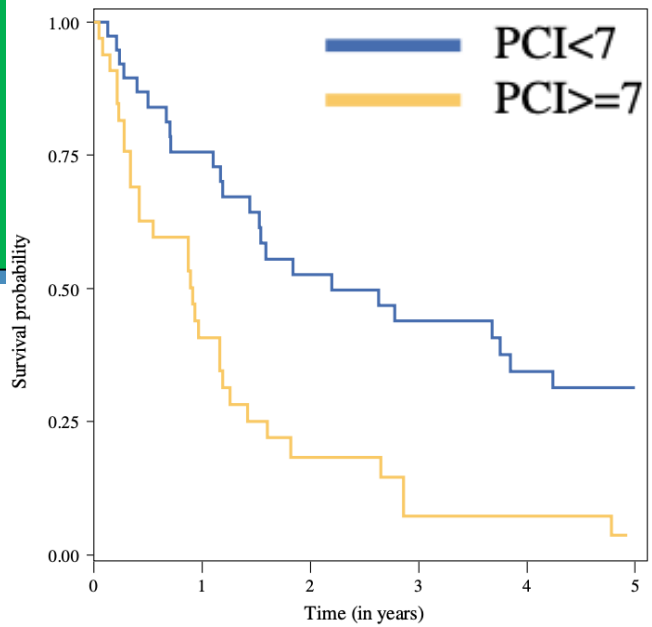
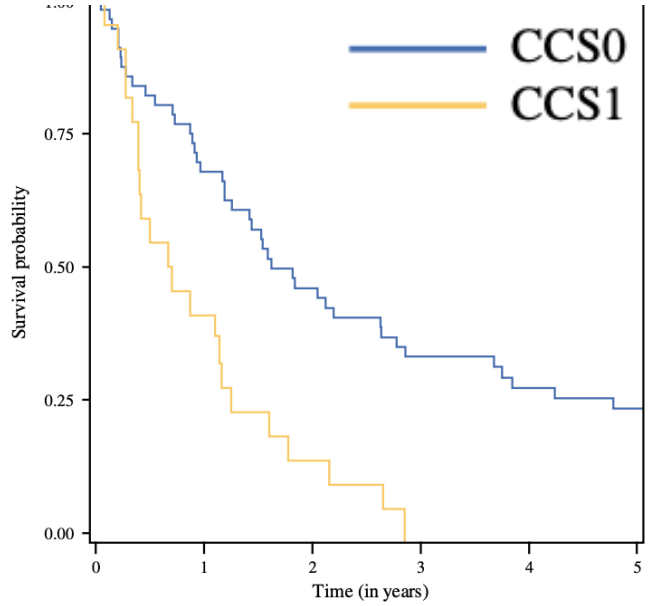
Gastric Cancer

- Retrospective review 81 pts from 5 institutions
  - > Median OS: 17.3m
  - > 5 year OS: 18%
  - > Cured: 11%

** Only PCI <7 had long term survival

** Only CCS0 had long term survival

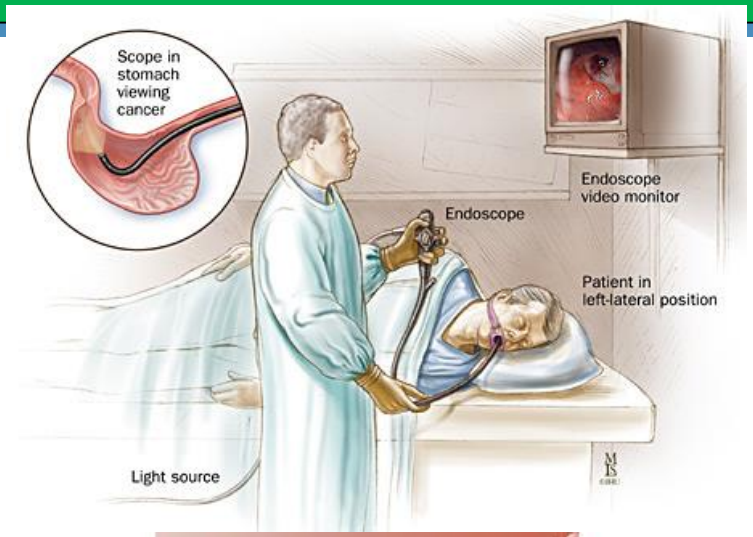


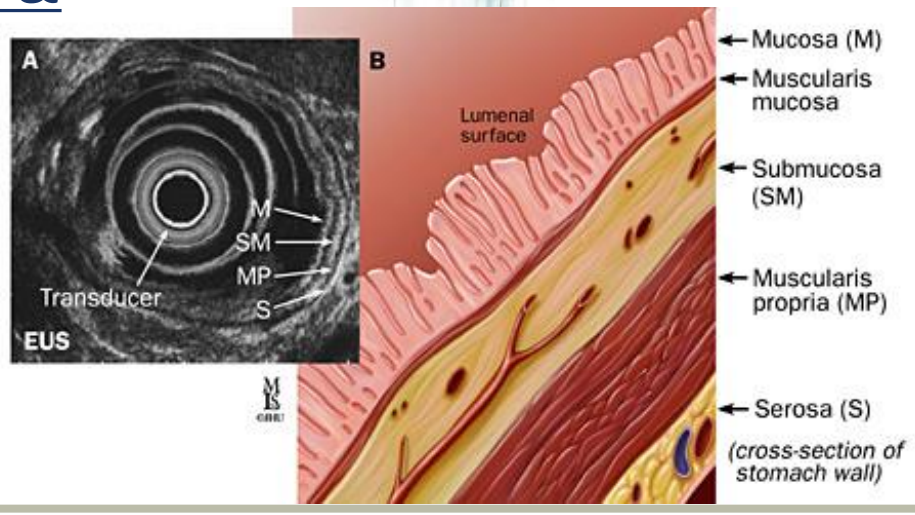


Chia CS et al. CRS HIPEC for Gastric Ca. Ann Surg Onc 2016

Gastric Cancer – Diagnosis and Staging

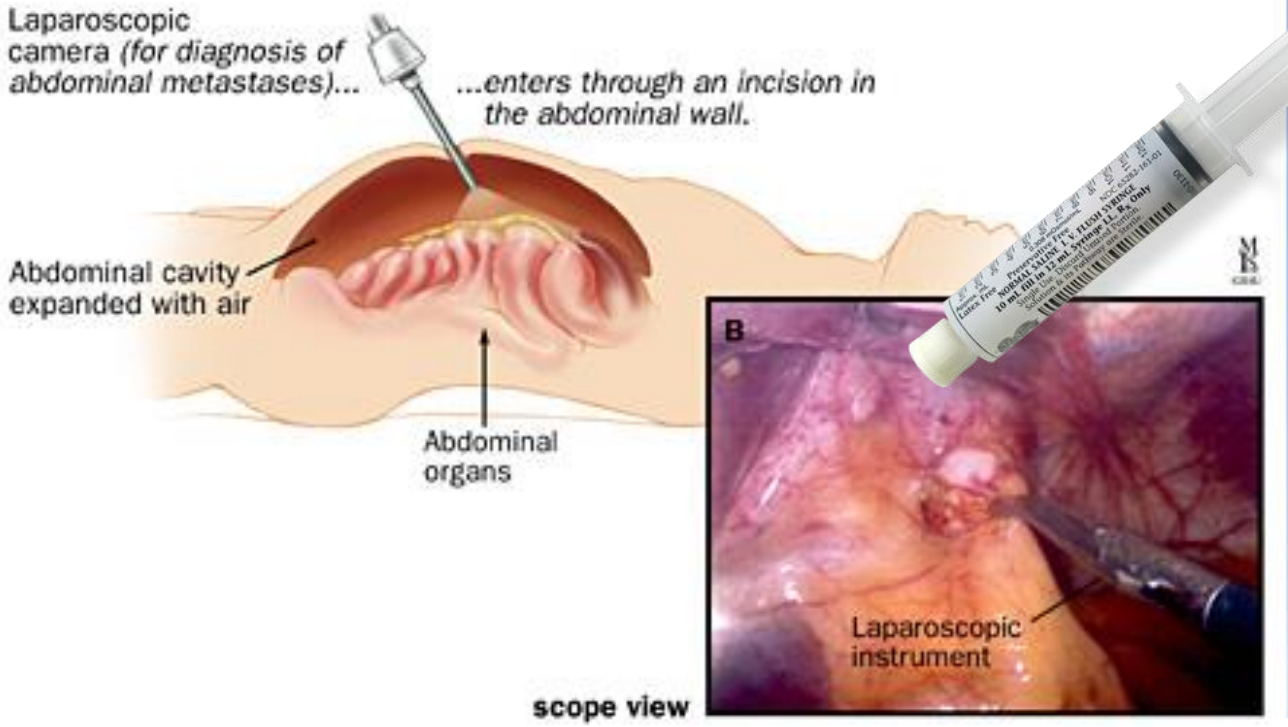
- H&P
- Upper GI endoscopy and biopsy
- ***EUS***
- Chest/Abdomen/Pelvis CT
- PET CT
- ***Diagnostic Laparoscopy & Peritoneal washings***





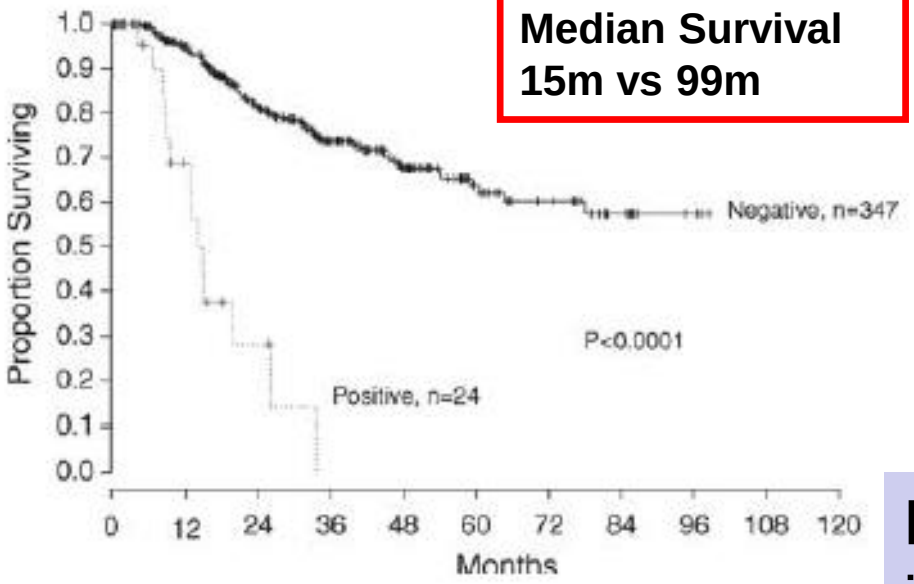
Gastric Cancer – Diagnosis and Staging

Macroscopic carcinomatosis – 20%
Positive cytology only – 10%

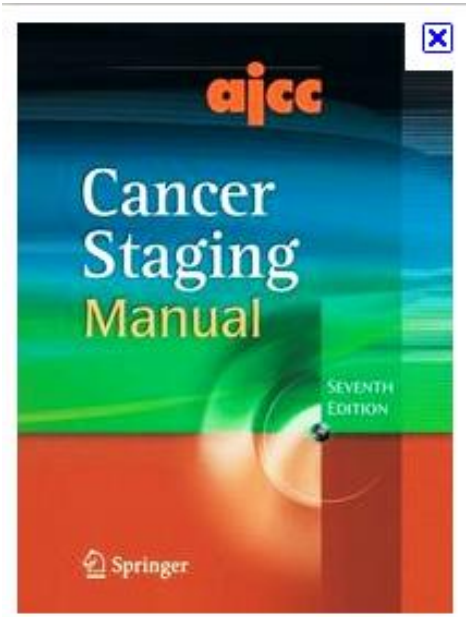


Gastric Cancer – Diagnosis and Staging

- **Positive Peritoneal Cytology (Cy+/P0)**



Median Survival
15m vs 99m



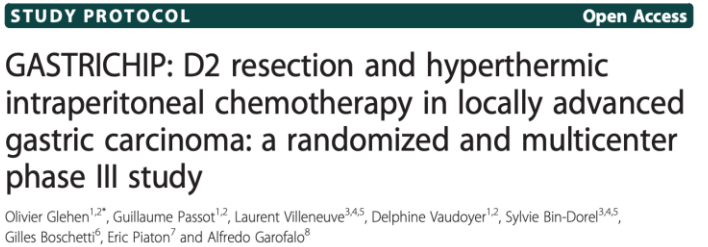
Positive Peritoneal cytology is classified as M1

Bentrem D. et al., Value of Peritoneal Cytology for Gastric Cancer. Ann Surg Onc 2005
American Joint Committee on Cancer 7th Ed

Gastric Cancer

HIPEC for Prophylaxis

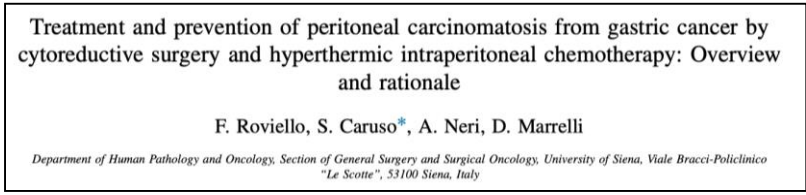
- Locally advanced gastric ca, **Adjuvant HIPEC**
- Multiples studies in Asia
  - > Improved 5 year survival
  - > Reduces peritoneal recurrence



STUDY PROTOCOL Open Access

GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: a randomized and multicenter phase III study

Olivier Glehen[1,2*], Guillaume Passot[1,2], Laurent Villeneuve[3,4,5], Delphine Vaudoyer[1,2], Sylvie Bin-Dorel[3,4,5], Gilles Boschetti[6], Eric Piaton[7] and Alfredo Garofalo[8]



Treatment and prevention of peritoneal carcinomatosis from gastric cancer by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: Overview and rationale

F. Roviello, S. Caruso*, A. Neri, D. Marrelli

Department of Human Pathology and Oncology, Section of General Surgery and Surgical Oncology, University of Siena, Viale Bracci-Policlinico "Le Scotte", 53100 Siena, Italy

- Currently Open Studies
  - > GASTRICHIP − Europe
  - > European Network on Excellence on GC

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Gastric Cancer

Laparoscopic Intraperitoneal Chemotherapy (LS-HIPEC)

- Repeated HIPEC (without CRS) with aim to resolve peritoneal cytology

- MD Anderson (B. Badgwell)
  - > Stage IV pts with peritoneum only low volume disease or cytology only
  - > After systemic chemo, HIPEC with Mitomycin C & Cisplatin
  - > 44 patients, 71 procedures
  - > 11 patients had resolution of peritoneal cytology and went on to gastrectomy.

Newhook et al. Ann Surg Onc 2019

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Gastic Cancer

Considerations

>Tumor burden − PCI score: Cutoff <7

>Ability to achieve complete cytoreduction: R0 is necessary

>Tumor histology/type: (poor outcome) signet ring cell

>Response to systemic therapy: no progression

>Disease free interval

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Mesothelioma

- Diffuse Malignant Peritoneal Mesothelioma − 10-30% of all mesothelioma
- Histologic Subtype is most important determinant
  - > Epithelioid
    - Most common − 75-90%
    - Least aggressive
  - > Sarcomatoid : Rapid progression and death
  - > Biphasic: Intermediate to epithelioid and sarcomatoid
- Other markers of aggressiveness
  - > Ki-67, mitotic rate, PET avidity

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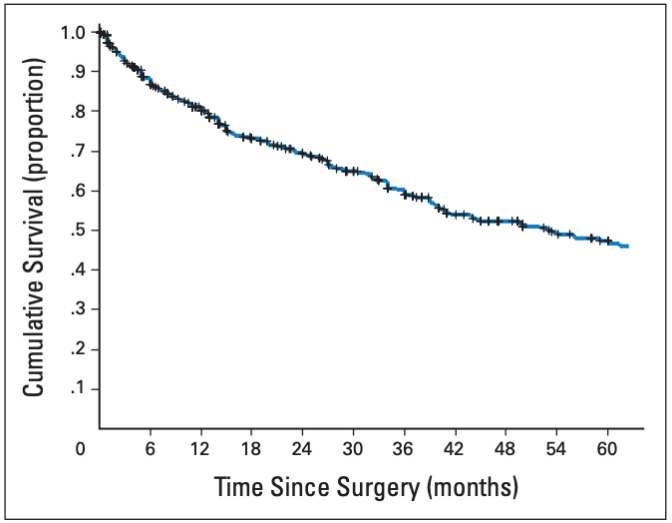
Mesothelioma

- Outcomes
  - > Historic (palliative surgery and systemic chemo) − 9-15 m
  - > With CRS/HIPEC − median survival: 53 months

- Improved survival
  - > Epithelial type (HR 27.5)
  - > Neg LN (HR 13.9)
  - > CC0/CC1 (HR 24.2)
  - > HIPEC (HR 9.5)



Yan TD et al. CRS HIPEC for Malignant Peritoneal Mesothelioma. JCO 2009

Mesothelioma

Treatment

- Epithelioid, Papillary, Benign Multicystic
  - → CRS/HIPEC
- Biphasic, Sarcomatoid
  - → Systemic chemo
  - → CRS/HIPEC if shows radiographic response

Yan TD et al. CRS HIPEC for Malignant Peritoneal Mesothelioma. JCO 2009

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Phase II Clinical Trial – CRS/HIPEC

NIH U.S. National Library of Medicine
ClinicalTrials.gov

CRS/HIPEC for Peritoneal Carcinomatosis of Peritoneal and Gastrointestinal Origin

- Mitomycin C, 40mg, 42° C, 90min
- Pseudomyxoma Peritonei, Appendiceal, Colorectal, Gastric, Mesothelioma

- End Points: Completeness of cytoreduction, morbidity, mortality, PFS, OS, QOL

- Inclusion/Exclusion criteria
  - ECOG 0, 1
  - Normal renal, hepatic, and cardiac function

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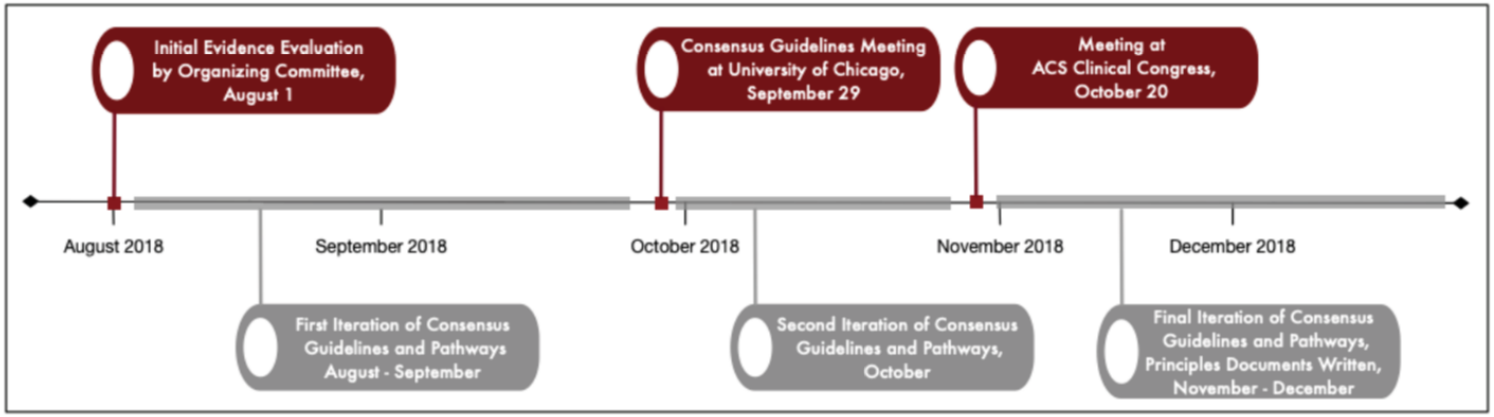
Management Guidelines for Peritoneal Surface Malignancies

2018
Chicago
Consensus
on Peritoneal Surface Malignancies

- Sept 2018
- Thought leaders
- Endorsement of Society of Surgical Oncology (SSO)
- 11 pathways developed
- Annals of Surgical Oncology in 2019

Figure 1: Timeline for the Development of the Chicago Consensus Guidelines for Peritoneal Surface Malignancies



What does NOT need to be considered when offering cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC)?

a) Original cancer type
b) History of systemic chemotherapy
c) Tumor burden (amount of tumor)
d) Ability to completely remove tumor
e) Functional status
f) None of the above

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e) Functional status
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Which is an appropriate indication for first-line therapy with CRS/HIPEC?

a) Massive abdominal distention with pseudomyxoma peritonei

b) Appendix cancer, high grade, with low volume peritoneal metastasis

c) Colorectal cancer, low grade, with metastasis to peritoneum and liver (resectable)

d) Gastric cancer, with cytology only peritoneal mets

e) All of the above

f) None of the above

Which is an appropriate indication for first-line therapy with CRS/HIPEC?

a) Massive abdominal distention with pseudomyxoma peritonei

b) Appendix cancer, high grade, with low volume peritoneal metastasis

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d) Gastric cancer, with cytology only peritoneal mets

e) All of the above

f) None of the above

Appendectomy is planned for appendiceal mass. During surgery some mucin pools are seen. Pathology from appendectomy shows low grade mucinous neoplasm (LAMN) without adenocarcinoma, negative margins, 1 negative lymph node.

What is next step?

a) No further treatment necessary.

b) Right colectomy

c) Right colectomy and referral for CRS/HIPEC

d) Referral for CRS/HIPEC

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c) Right colectomy and referral for CRS/HIPEC

d) Referral for CRS/HIPEC

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Summary of Recommendations

- CRS/HIPEC provides improved outcomes in select cases
- Only healthy patients are candidates for CRS/HIPEC
- Metastatic disease (synchronous and metachronous) **limited to the peritoneum** have likelihood of being candidates for CRS/HIPEC and should be considered
- In colorectal cancer, even pts with limited systemic disease (liver, lung) may be candidates for CRS/HIPEC
- **Mucinous spillage or tumors rupture**, in appendiceal and mucinous colorectal cancers should be evaluated for CRC/HIPEC

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