Complete CytoReductive Surgery and HIPEC

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1. The peritoneum as an organ
2. Technique of HIPEC
3. HIPEC for pseudomyxoma and mesothelioma
4. HIPEC for PC from colorectal origin
5. High risk colon cancer: novel approaches
The peritoneum is an organ

- Own histologic structure
- Own circulations and drainages
- Its surface = the body square surface
- But, 1 tumor seeding progressive diffusion in all the abdominal cavity

Like other organs, it needs an own and particular treatment.
Principles of CCRS + HIPEC

• Surgery must resect all the visible (macroscopic) disease (> 1 mm of Ø).

• HIPEC has the ambition to treat the remaining non visible (microscopic) disease.

*Recall: with HIPEC, the penetration of drugs is limited to 1 mm in depth.*
Aggressive surgery (CCRS+HIPEC) as a Standard

1. Peritoneal Pseudomyxoma

2. Peritoneal Mesothelioma
Pseudomyxomas

- Definition: > 90% of mucinous compounds (+++)

- Origin: appendix (> 90%)

- From **benign** to **malign** forms (Ronnett):
  - Low grade = Diffuse peritoneal adenomucinosis
  - Intermediate grade
  - High grade = Mucinous peritoneal carcinomatosis
Scalloping
Grade 0  ???
Grade 1: Unicellular border
Grade 1: unicellular border, without atypia nor mitosis
Grade 3: + présence of tumor blocs with atypia and mitosis
2298 pts treated with CRS + HIPEC


- 16 specialized centres (1993 to 2011)
- Mortality: 2%, major morbidity: 24%

- Median survival: 196 months (16 years)
- 10-year overall survival: 63%

- Prognostic factors (multivariate):
  - Histologic subtype (+++)
  - Completeness of cytoreductive surgery (+++)
  - High peritoneal index
  - Older age (> 53y)
Versus the classical attitude: « maximal » cytoreductive surgery

97 patients treated in the MSK

- 53% of CCRS
- 31% had also received IP chemotherapy
- Mean nb of cytoreductive surgery: 2.2
- Mean delay for recurrence: 2 years
- At 5-years, 88% presented recurrence
- 10-year overall survival: 21%

Malignant Peritoneal Mesotheliomas

- **Low grades:**
  1. Papillary
  2. Adenoid
  3. Cystic

- **High grades:**
  1. Epithelioid
  2. Sarcomatoid
  3. Biphasic
Papillary Type
Epithelioid Type
Epithelioid Type
Epithelioid Type
Sarcomatoid
Cystic Type
405 pts treated with CRS + HIPEC

(Multi-institutional registry, Yan T et al. J Clin Oncol 2009)

- 8 specialized centres, 1989-2009
- 80% of epithelial tumors
- 46% of complete cytoreductive surgery, HIPEC=92%
- Postop mortality: 2%

- Median survival: 53 months
- 5-year survival : 47%

- Prognostic factors (multivariate):
  - Epithelial subtype, and absence of lymph node metastasis
  - Completeness of cytoreduction
  - HIPEC
Versus the classical treatment

- Systemic chemo:
  - Premetexed + Platine
  - Gem-oxali
  - Tom-oxali
  - Vinorelbine + Platine

- Median survival: 12-15 months
- 5-years survival: 15-25%
Survival with classical treatment

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Nb Pts</th>
<th>Median/months</th>
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<tbody>
<tr>
<td>Markman</td>
<td>1992</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Neumann</td>
<td>1999</td>
<td>74</td>
<td>12</td>
</tr>
<tr>
<td>Eltabbali</td>
<td>1999</td>
<td>15</td>
<td>12.5</td>
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Aggressive surgery as a very promising therapeutic approach

- Colorectal carcinomas
Peritoneal Carcinomatosis (PC) of CRC

- 7%-10% at primary diagnosis
- 25% at recurrent disease

Verwaal VJ; Ann Surg Oncol 2005
Bleichrodt RP; Ann Surg 2006

- modern chemo $\rightarrow$ 23.9 months median OS

Elias D., J Clin Oncol 2009

25-35% peritoneal disease (only site) but limited in only 3%

Concept of CCRS + HIPEC for locoregional disease control
strategies in metastatic CRC

Palliative therapy

- Palliative resection + Systemic chemotherapy + biologicals

Curative therapy

- Cytoreductive surgery + HIPEC + syst CHT

Survival vs. Time

- Median survival:
  - Palliative: 6.3 mo → 23.9 mo
PM have a poorer prognosis than the other metastases

Data of 2 prospective randomized trials about chemo (oxali and Irinotecan) 2095 patients with colorectal metastases.

Median survival:
Without PC: **17.6 m**
With PC: **12.7 m**
P<0.01

Retrospective comparative study
In the control group: 3.4 lines of chemo
Median survivals: **25 months vs 60 months**

How to select patients

1. Patient characteristics (comorbidity, general condition...)

2. Excluded generalised metastatic disease
   - CT/MR abdomen – thorax
   - FDG-PET, PET-CT

3. Extent of peritoneal disease
   - MRI the new standard?
     - laparoscopy: **understaging**
       (to avoid unnecessary laparotomy)
   - explorative laparotomy
Female patient 54 yrs

2006 left hemicolecotomy (pT3N2), adjuvant chemotherapy

2008 peritoneal metastases: PCI 8, CCR-O + HIPEC (oxali)

adjuvant FOLFOX

2010 intraperitoneal recurrences: FOLFIRI- Bevacizumab

2011 bone metastases

June 2013 temporary break chemotherapy, stable disease
Explorative laparotomy

Non-resectable disease entire SB (mesenteric site)

Diffuse diafragmatic involvement

No palliative resection, stoma or bypass
The Peritoneal carcinomatosis Index (PCI) (Ranging from 1 to 39)
extent of disease relates to chance of obtaining complete cytoreduction
Survival according to the **Radicality** of the Surgery (p< 0.0001)
Dichotomization: PCI 12

Survival Functions

Cum Survival vs Survival (mth)

p = 0.013

PCI < 12

PCI > 12
discussion

What is a reasonable PCI?

Does ‘neoadjuvant’ systemic chemo ever work?

Is limited liver disease a contra-indication?
French multicentric randomized trial « Prodige 7 »

PC Resectable → Complete Cytoreduction R1 / R2<1mm

HIPEC Oxaliplatin → 6 months
- Before
- Interval
- After

No HIPEC → Systemic Chemo

Systemic Chemo
Current status of Prodige 7 trial

- End-point: To improve OS from 30 months to 48 months

- The 270 patients have already been randomized.
A future for this combined approach to treat early colorectal PM?

- Survival results are very high when the PCI is low (72% when PCI from 1 to 5).

- Surgery is easier and morbidity is lower when the PCI is low

PM must be detected and treated at a very early stage!
High risk for peritoneal disease

- tumor perforation

- pT4a tumor

  LPI = Local Peritoneal Involvement
  - grade 3 = through serosal surface
  - grade 4 = free tumor cells

- ovarian metastasis

Shepherd et al  *Gastroenterology 1997, Histopathology 2005*
Who are High-risk patients?

Systematic review of the literature published from 1941-2011

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<tr>
<th>High-risk: ≥ 40%</th>
<th>No High-risk: ≤ 20%</th>
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<tbody>
<tr>
<td>- Synchronous PM (resected): 54-75%</td>
<td>- T4 tumor: 8-17%</td>
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<td>- Ovarian metastases: 56-62%</td>
<td>- Positive cytology: 9-36%</td>
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<td>- Perforated primary tumor: 24-54%</td>
<td>- Histologic subtype: 11-36%</td>
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<td>- Occlusion / Bleeding: &lt; 15%</td>
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How to detect PM at an early stage?

- No symptom, no imaging, no biological markers
- The only way: to propose a second-look
- But, it is not possible to propose it to all patients
- We must select a population of high-risk patients
- Then to prove that effectively they present early PC, that CCRS+HIPEC is feasible and not too morbid, and at last, that this new approach improves overall survival.
Second-look trial: Phase 1-2

- 41 patients included between 1999 and 2009
- They received 6 months of chemo., then
- Second-look at 1 year

- Macroscopic PM was present in 56%
- It was early cases (mean PCI = 8)

- 100% undewent HIPEC
- Mortality: 2%, morbidity: 10%

- Minimal synchronous PC resected with the primary tumour: PM in 60%
- Ovarian metastases resected: PM in 62%
- Perforated primary tumour: PM in 37%
Survival rates

Peritoneal recurrence: 17%

5-y overall survival 90%

5-y disease free survival 44%
ProphyloCHIP Trial

« high risk » patients

6 months IV Folfox IV then:
Work-up that must be negative

Randomization

Standard arm

Surveillance

Experimental arm

Systematic 2nd look plus HIPEC

n = 130 patients
1st endpoint: 3-y Disease-free survival; to improve DFS from 40% to 65%
To conclude: Current indications of aggressive cytoreductive surgery + HIPEC

Clearly recommended for:
- Pseudomyxomas
- Mesotheliomas

In pass to be recommended:
- Colon-rectum
- Second-look for high-risk patients

Not recommended for:
- Stomach
- Sarcomas

Investigation must go on for:
- Ovary
- NET