Surgical management of Peritoneal Carcinomatosis from colorectal cancers

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Declaration of interest

<table>
<thead>
<tr>
<th>BOARDS</th>
<th>Congress and teaching</th>
<th>Trials</th>
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<tbody>
<tr>
<td>0</td>
<td><strong>Merck</strong></td>
<td><strong>Fresenius</strong></td>
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<tr>
<td></td>
<td><strong>Ipsen</strong></td>
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<td></td>
<td><strong>Gamida</strong></td>
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<td><strong>Novartis</strong></td>
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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.
PM have a poorer prognosis than the other metastases

Data of 2 prospective randomized trials about chemo (oxali and Irinotecan)
2095 patients

Median survival:

Without PC: 17.6 m
With PC: 12.7 m

P<0.01

PM have a poorer prognosis than the other metastases

Dutch Eindhoven Cancer Registry: 1074 metastatic patients (200 with PC)
Pathologic response under chemo: comparison between LM and PC

<table>
<thead>
<tr>
<th></th>
<th>LM</th>
<th>PC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete responses</td>
<td>10%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Major responses</td>
<td>36%</td>
<td>20%</td>
</tr>
<tr>
<td>&gt;50% of died cell</td>
<td></td>
<td></td>
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Kohne CH. Et al. **3825 pts** Ann Oncol 202; 13: 308-17
PM have a poorer prognosis than the other metastases

Randomized Deutch trials **Cairo1 and Cairo 2** based on Xelox

<table>
<thead>
<tr>
<th></th>
<th>Without PM</th>
<th>With PM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nb Median S.</td>
<td>Nb Median S.</td>
<td></td>
</tr>
<tr>
<td><strong>Cairo 1</strong> (no targeted therapy)</td>
<td>739 17</td>
<td>34 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cairo 2</strong> (with targeted therapy)</td>
<td>689 21</td>
<td>47 15</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*(Klaver Y. et al. EJSO 2012; 38: 617-623)*
At last, appearance of PM is frequently considered as a funest event and only palliative treatments are proposed

- Is it justified?
- Is it possible to cure PM?
In fact, the prognosis of optimally treated LM and PM are the same!

1993-2009

287 hepatectomy: 38.5%

119 CCRS+HIPEC: 36.5%

How to treat PC with a curative intent?

- By using **complete** cytoreductive surgery (CCRS)
- Plus or minus Hyperthermic intraperitoneal chemotherapy (HIPEC)
- With the assistance of the systemic chemotherapy
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.
If R2: HIPEC is contraindicated

French Registry:
- 523 PC treated
- 1990 - 2007
- in 23 centres

Astonishing (and illogical)!

- Levine et al. Experience of 1000 patients treated with HIPEC. (J Am Coll Surg 2014; 218: 573-87)

- 1000 pts treated between 1991 and 2013

- Division in 5 time periods (quintiles)
  - First quintile: 65% of R2
  - Last quartile: 47% of R2

In our personnel practice: 0% of R2
Current results of systemic chemotherapy

Randomized Deutch trials **Cairo1 and Cairo 2** based on Xelox: median survivals

<table>
<thead>
<tr>
<th></th>
<th>Without PM</th>
<th>With PM</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cairo 1 (no targeted therapy)</td>
<td>17 months</td>
<td>10 months</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cairo 2 (with targeted therapy)</td>
<td>21 months</td>
<td>15 months</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*(Klaver Y. et al. EJSO 2012; 38: 617-623)*
Comparison of therapeutic results for colorectal PM: Review

- 2492 patients from 19 selected studies

<table>
<thead>
<tr>
<th></th>
<th>Nb</th>
<th>Median S.</th>
<th>5-year S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete CS + chemo.</td>
<td>1408</td>
<td>12 months</td>
<td>13%</td>
</tr>
<tr>
<td>CCS + HIPEC</td>
<td>1084</td>
<td>33 months</td>
<td>40%</td>
</tr>
</tbody>
</table>

Current evidence have demonstrated the efficiency of CCS+ HIPEC for which should now embraced as the standard of cure.

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

Is it possible to obtain definitive cure with CCRS + HIPEC?

Prospective study of our patients treated between January 1995 and December 2005 (n=93).
Learning curve = worst results.

The Cure = no recurrence during a minimal delay of 5 years

- Median follow-up: 99 months
- Median Survival: 34 months (currently: 60 months)
- Overall 5-year survival: 32% (currently: 48%)

Absolute cure at 5 years: 17/107 pts = 16%
At 10 years:
102/612 pts = 16.7%

At 5 years without rec.
24/148 pts = 16%

Table 1. Characteristics of 102 Actual 10-Year Survivors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
</tr>
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<tbody>
<tr>
<td>Disease status</td>
<td></td>
</tr>
<tr>
<td>NED</td>
<td>99*</td>
</tr>
<tr>
<td>AWD</td>
<td>2</td>
</tr>
<tr>
<td>DOD</td>
<td>1</td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>146</td>
</tr>
<tr>
<td>Disease recurrence</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>16</td>
</tr>
<tr>
<td>Lung</td>
<td>7</td>
</tr>
<tr>
<td>Liver/lung</td>
<td>6</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
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</table>
Our results (comparison of LM and PM)

Prognostic factors (CRS+HIPEC)

- French registry (1990 – 2007)
- 523 patients treated in 23 centres
- Mortality: 3%, grade 3-4 morbidity: 30%

- Two major prognostic factors (+++):
  1. The completeness of the cytoreductive surgery
  2. The extent of the peritoneal disease (PCI)

Survival according to the **Radicality** of the Surgery (p< 0.0001)
The Peritoneal carcinomatosis Index (PCI) (Ranging from 1 to 39)
Survival according to the Extent of the Péritoneal Carcinomatosis (p< 0.0001)
Prognostic impact of the efficiency of the systemic chemo.

- Morphological (radiologic) response: no strong impact on survival rate.

- Pathologic response: strong impact on survival

<table>
<thead>
<tr>
<th>Pathologic response</th>
<th>5-year survival</th>
</tr>
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<tbody>
<tr>
<td>Complete (10%)</td>
<td>75%</td>
</tr>
<tr>
<td>Major (20%)</td>
<td>57%</td>
</tr>
<tr>
<td>Minor / none</td>
<td>15%</td>
</tr>
<tr>
<td>(&gt; 50% residual cancer cells)</td>
<td></td>
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What is the exact gain due to HIPEC alone?

- We do not know in human
- There is many proofs in animal models
- Only a randomized trial will give the answer
French multicentric randomized trial « Prodige 7 »

- PC Resectable
- Complete Cytoreduction R1 / R2<1mm
- HIPEC Oxaliplatin
- Systemic Chemo
- 6 months
  - Before
  - Interval
  - After
- No HIPEC
- Systemic Chemo
Current status of Prodigie 7 trial

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

- The 270 patients have already been randomized.
Current proposed guidelines for colorectal PM

- CCRS + HIPEC is the gold standard treatment for patients:
  - With a good general status
  - With a PCI index lower than 16
  - Who are chemosensitive
  - With no other metastases (excepted ovarian metastases or 1-5 LM easily resectable or ablatable.)
A case control of similar pts (61 with PC alone and 37 with PC+LM)

- Median PCI of each group: 11 (range: 2-26)
- Median nb of LM: 2 (range: 1-16)

Median survivals:
- PC alone: 49 months
- PC + LM: 32 months

P=0.042

Equivalence between LM and PM

- 287 hepatectomy
- 119 CCRS+HIPEC
- Exclusion of [Hepatec + CCRS-HIPEC] (n=37)
- Follow-up > 5 years

- Subgroups according to the global tumor load:
  - LM in 2 groups: ≤ 10 LM, and > 10 LM
  - PM in 3 groups: PCI 1-5, 6-15, > 15

Same overall global survival
Overall survival for the 2 gps of LM
Overall Survival for the 3 gps of PM

![Graph showing survival probability over months for different PCI categories.](image)
Equivalences and difference between LM and PM
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!
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.
Who are High-risk patients?

Systematic review of the literature published from 1941-2011

- **High-risk**: ≥ 40%
  - Synchronous PM (resected): 54-75%
  - Ovarian metastases: 56-62%
  - Perforated primary tumor: 24-54%

- **No High-risk**: ≤ 20%
  - T4 tumor: 8-17%
  - Positive cytology: 9-36%
  - Histologic subtype: 11-36%
  - Occlusion / Bleeding: < 15%

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%

Overall survival
Disease free survival

Patients at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
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<tbody>
<tr>
<td></td>
<td>41</td>
<td>31</td>
<td>24</td>
<td>19</td>
<td>18</td>
<td>12</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>34</td>
<td>15</td>
<td>11</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
ProphyloCHIP Trial

« high risk » patients

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

Randomization

Standard arm

Experimental arm

Surveillance

Systematic 2nd look plus HIPEC

n = 130 patients
1st endpoint: 3-y Disease-free survival; to improve DFS from 40% to 65%
Conclusions

- For eligible patients, CCRS+HIPEC is currently the gold standard treatment.

- CCRS + HIPEC is able to definitively cure many patients.

- Its results are similar to those obtained with hepatectomy for LM.

- It gives very high results when the PCI is low.

- The second-look approach for high-risk patients could be the main future of CCRS+HIPEC.
Thank-you
Case #1

Female, age 60 years, WHO PS 0
January 2012: Sigmoidectomy for pT3N2M0 adenocarcinoma, followed by 6 months of adjuvant chemotherapy (FOLFOX) until August 2011
CT-scan: no suspicious lesions; FDG-PET scan: several hot-spots in peritoneum.

Treatment options
1) Exploratory laparotomy, and, if possible, resection of metastases
2) Cytoreductive surgery + HIPEC
3) Systemic treatment with palliative intent
4) Systemic treatment, and if decrease in CEA then laparoscopy to assess the extent of the disease.
Case #1

**Treatment options**
1) Exploratory laparotomy, and, if possible, resection of metastases
2) Cytoreductive surgery + HIPEC
3) Systemic treatment with palliative intent
4) **Systemic treatment, and if decrease in CEA then laparoscopy to assess the extent of the disease.**

Low PCI (peritoneal cancer index) (< 15) : cytoreductive surgery + HIPEC
High PCI: continue systemic treatment
Case #2

Male, age 66 years, WHO PS 0
January 2014: During laparoscopic sigmoidectomy, accidental discovery of peritoneal deposits, which showed adenocarcinoma. No other distant metastases. pT3N1M1 PCI = 5

Treatment options
1) Systemic treatment with palliative intent
2) Cytoreductive surgery during same surgical procedure
3) Cytoreductive surgery + HIPEC after 1-2 months
4) Systemic treatment during 3 months, if no disease progression: followed by cytoreductive surgery + HIPEC
Case #2

Treatment options

1) Systemic treatment with palliative intent
2) Cytoreductive surgery during same surgical procedure
3) Cytoreductive surgery + HIPEC after 1-2 months
4) Systemic treatment during 3 months, if no disease progression: followed by cytoreductive surgery + HIPEC
Case #3

Male, age 66 years, WHO PS 0
January 2014: During laparoscopic sigmoidectomy, accidental discovery of many peritoneal deposits, which show adenocarcinoma. No other distant metastases. pT3N1M1
PCI = 22

Treatment options
1) Systemic treatment with palliative intent
2) Cytoreductive surgery during same surgical procedure
3) Cytoreductive surgery + HIPEC after 1-2 months
4) Systemic treatment (3 months), if no disease progression followed by cytoreductive surgery + HIPEC
5) Systemic treatment (3 months), then reassessment by laparoscopy
Case #3

Treatment options

1) **Systemic treatment with palliative intent**
2) Cytoreductive surgery during same surgical procedure
3) Cytoreductive surgery + HIPEC after 1-2 months
4) Systemic treatment (3 months), if no disease progression followed by cytoreductive surgery + HIPEC
5) **Systemic treatment (3 months), then reassessment by laparoscopy**
Case #4

Female, age 56 years, WHO PS 0
June 2014: During laparoscopic sigmoidectomy, accidental discovery of metastasis in left ovary, which was removed. No other distant metastases, no peritoneal disease. pT3N0M1

Treatment options
1) Expectancy
2) Adjuvant systemic treatment (6 months)
3) Cytoreductive surgery + HIPEC after 1-2 months
4) Adjuvant systemic treatment (6 months), and if the following work-up is negative: surgery + HIPEC
Case #4

Treatment options

1) Expectancy
2) Adjuvant systemic treatment (6 months)
3) Cytoreductive surgery + HIPEC after 1-2 months
4) Adjuvant systemic treatment (6 months), and if the following work-up is negative: surgery + HIPEC