Management of Peritoneal Metastases (PM) from colorectal cancers: New Perspectives

Dominique ELIAS
# Declaration of interest

<table>
<thead>
<tr>
<th>BOARDS</th>
<th>Congress and teaching</th>
<th>Trials</th>
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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

Survival after metastasis diagnosis among colorectal cancer patients diagnosed between 2003-2008

Dutch Eindhoven Cancer Registry: 1074 metastatic patients (200 with PC)
PM have a poorer prognosis than the other metastases

Randomized Deutch trials Cairo 1 and Cairo 2 based on Xelox

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<th>Without PM</th>
<th>With PM</th>
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<tr>
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<td>Nb Median S.</td>
<td>Nb Median S.</td>
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<td>Cairo 1 (no</td>
<td>739 17</td>
<td>34 10</td>
<td>&lt;0.001</td>
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<td>targeted therapy)</td>
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<td>Cairo 2 (with</td>
<td>689 21</td>
<td>47 15</td>
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(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: 35% of R0/R1
- Last quartile: 53% of R0/R1

In our personal practice: 100 % of R0/R1!
Current results of systemic chemotherapy

Randomized Deutch trials **Cairo 1 and Cairo 2** based on Xelox: median survivals

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<th>With PM</th>
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<tr>
<td>Cairo 1 (no targeted therapy)</td>
<td>17 months</td>
<td>10 months</td>
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<tr>
<td>Cairo 2 (with targeted therapy)</td>
<td>21 months</td>
<td><strong>15 months</strong></td>
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(Klaver Y. et al. EJSO 2012; 38: 617-623)
Comparison of therapeutic results for colorectal PM: Review

- 2492 patients from 19 selected studies

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<tr>
<td>Incomplete CS + chemo.</td>
<td>1408</td>
<td>12 months</td>
<td>13%</td>
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<tr>
<td>CCS + HIPEC</td>
<td>1084</td>
<td>33 months</td>
<td>40%</td>
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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%

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)
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
- No HIPEC
- Systemic Chemo

6 months
- Before
- Interval
- After

- Systemic Chemo

Before HIPEC Systemic Chemo

After 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.)
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
Equivalences and difference between LM and PM

![Graph showing survival probability over time with different categories and p-value]
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

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<th>High-risk: $\geq 40%$</th>
<th>No High-risk: $\leq 20%$</th>
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<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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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%

Patients at risk

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ProphyloCHIP Trial

« high risk » patients

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

Randomization

Standard arm
Surveillance

Experimental arm
Systematic 2\textsuperscript{nd} look plus HIPEC

n = 130 patients
1\textsuperscript{st} 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.