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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<tr>
<td>0</td>
<td>Merck</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)
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>
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<tbody>
<tr>
<td><strong>Nb</strong></td>
<td><strong>Median S.</strong></td>
<td><strong>Nb</strong></td>
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<tr>
<td><strong>Cairo 1 (no</strong></td>
<td>739</td>
<td>17</td>
</tr>
<tr>
<td><strong>targeted therapy)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cairo 2 (with</strong></td>
<td>689</td>
<td>21</td>
</tr>
<tr>
<td><strong>targeted therapy)</strong></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

<table>
<thead>
<tr>
<th></th>
<th>Without PM</th>
<th>With PM</th>
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</thead>
<tbody>
<tr>
<td>Cairo 1 (no targeted therapy)</td>
<td>17 months</td>
<td>10 months</td>
</tr>
<tr>
<td>Cairo 2 (with targeted therapy)</td>
<td>21 months</td>
<td>15 months</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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<th>Nb</th>
<th>Median S.</th>
<th>5-year S.</th>
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<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>
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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

Différence entre les moyennes de survie restreinte

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%
Actual 10-Year Survival After Resection of Colorectal Liver Metastases Defines Cure

At 10 years:
102/612 pts = 16.7%

Patients With Initially Unresectable Colorectal Liver Metastases: Is There a Possibility of Cure?

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>
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<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>
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</table>

Cured Patients (n = 24)

- Cured after resection of initial disease (n = 18)
  - After first hepatectomy (n = 16)
  - After second hepatectomy* (n = 1)
  - After secondary resection of concomitant EHD† (n = 1)

- Cured after resection of disease recurrence (n = 6)
  - After second hepatectomy (n = 3)
  - After fourth hepatectomy (n = 1)
  - After third hepatectomy and one EHD resection (n = 1)
  - After three EHD resections (n = 1)

IHDD recurrence only
IHDD and EHD recurrence
EHD recurrence only
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
- R
- HIPEC Oxaliplatin
- Systemic Chemo
- No HIPEC
- Systemic Chemo

6 months
- Before
- Interval
- After
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

![Graph showing overall survival probabilities with different PCI ranges from 1-5, 5-15, and 15-39, with corresponding survival probabilities at different months and at-risk counts.](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 symptoma, 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 proove 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%
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%
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
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 m
- PC + LM: 32 m

P=0.042