Traitement curatif des Carcinoses Péritonéales d’origine Colorectale

Pour quels patients ?

F. Quénet
ICM Val d’Aurelle
Montpellier

SFCO Lyon 2013
Treatment of Colorectal Peritoneal Carcinomatosis With Systemic Chemotherapy: A Pooled Analysis of North Central Cancer Treatment Group Phase III Trials N9741 and N9841


- 2101 patients
- 17.4% patients presented PC as the sole presentation of mCRC (n = 44, 2.1%)
- **Median OS PC was 12.7**
  HR = 1.32, 95% CI, 1.15 to 1.50; \( P < .001 \)
- After 7 years median follow-up
  2,009 (98.5%) of 2,095 patients with known PC status have died.
Population-based survival of patients with peritoneal carcinomatosis from colorectal origin in the era of increasing use of palliative chemotherapy

Y. L. B. Klaver\(^1\), V. E. P. P. Lemmens\(^2\), G. J. Creemers\(^3\), H. J. T. Rutten\(^1\), S. W. Nienhuijs\(^1\) & I. H. J. T. de Hingh\(^1\)

\(^1\)Department of Surgery, Catharina Hospital, Eindhoven; \(^2\)Department of Research, Eindhoven Cancer Registry, Comprehensive Cancer Centre South (IKZ), Eindhoven; \(^3\)Department of Internal Medicine, Catharina Hospital, Eindhoven, The Netherlands

- 395 solely PC (44%)
- 3 Periods of time:
  - 1995-1999
  - 2000-2005
  - 2005-2008

Median OS
Patients without distant metastasis

<table>
<thead>
<tr>
<th>Period</th>
<th>5FU/AF</th>
<th>Median OS</th>
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<tbody>
<tr>
<td>1995-1999</td>
<td>12 Months</td>
<td></td>
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<tr>
<td>2000-2005</td>
<td>oxaliplatin &amp; CPT11</td>
<td>14 Months</td>
</tr>
<tr>
<td>2005-2008</td>
<td>Beva / cetux</td>
<td>19 Months</td>
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</table>
Survival Results
CRS & HIPEC is no Longer an Experimental Treatment

- Dutch Trial: 105 patients
  - Complete cytoreduction: median OS 42.9 months
  - After a 8-year follow up: 5-year survival rate 45% for R1

- French multicentric study: 523 patients
  - Median OS 33 months
  - 5-year OS 41%
    (D.Elias & al JCO 2010)
Survival Results
CRS & HIPEC is no Longer an Experimental Treatment

Results obtained prospectively by 2 experienced centers between 1998 and 2007 using oxaliplatin

- 5-year OS of the 146 patients: 42%
- Median overall survival: 41 months
Is There a Possibility of a Cure in Patients With Colorectal Peritoneal Carcinomatosis Amenable to Complete Cytoreductive Surgery and Intraperitoneal Chemotherapy?

Diane Goëry, MD,∗ David Malka, MD, PhD† Dimitri Tzanis, MD,∗ Vinicius Gava, MD,∗ Valérie Boige, MD, PhD,† Clarisse Eveno, MD,∗ Léon Maggiori, MD,∗ Frédéric Dumont, MD,∗ Michel Dureux, MD, PhD,† and Dominique Elias, MD, PhD†

After a median follow-up of 77 months (range, 60–144 months), 5-year and 10-year disease-free survival rates were 16% at 5 years and 13% at 10 years (Fig. 1), and overall survival rates were 35% at 5 years and 15% at 10 years (Fig. 1), and overall survival rates were 35% at 5 years and 15% at 10 years (Fig. 1). In contrast, liver resection is widely accepted as a standard of care for patients with resectable colorectal liver metastases, although more cures are uncommon after systemic chemotherapy alone in the metastatic setting. Nevertheless, long-term survival and even cure have been reported in a minority of patients with colorectal peritoneal carcinomatosis, especially after complete cytoreduction and intraperitoneal chemotherapy (CRPC).

Conclusions:

Among all the patients treated with CRPC (n = 471), 232 patients (49.4%) had peritoneal disease combined with extraperitoneal disease, 23 patients (4.9%) had recurrence. In the remaining 88 patients, recurrent disease was confined to the peritoneal cavity in 23 patients (21%), 23 patients (21%) had peritoneal disease combined with extraperitoneal disease, and 4 patients (3.7%) died postoperatively (days 7–38).

**Patients Cured of Colorectal Peritoneal Carcinomatosis**

**Methods:** From 1995 to 2006, 107 patients (median age, 48 years; range, 19–67 years) underwent complete CRS, followed by IPC. Postoperative complications were to evaluate long-term outcome after CRS and IPC and to identify the prognostic factors associated with a cure.

**Results:** Of those 107 patients, 146 underwent complete CRS with IPC. Postoperative complications were to evaluate long-term outcome after CRS and IPC and to identify the prognostic factors associated with a cure.

**Conclusions:** Only 1 patient, included in the noncured group, developed recurrent disease after complete CRS and IPC. In the remaining 88 patients, recurrent disease was confined to the peritoneal cavity in 23 patients (21%), 23 patients (21%) had peritoneal disease combined with extraperitoneal disease, and 4 patients (3.7%) died postoperatively (days 7–38).

**FIGURE 1.** Overall survival and disease-free survival in 107 patients who underwent complete CRS with IPC.

16% were considered cured...
PRODIGE7 TRIAL

PC Resectable

Complete Cytoreduction R1 / R2<1mm

Stratif. R1/R2

HIPEC Oxaliplatin • Systemic Chemo

6 months
• Before
• Interval
• After

No HIPEC • Systemic Chemo

Stratif. Prior Systemic chemo
La CCR + CHIP, pour quels patients?

Contre indications générales:

- **Absolues**
  - Age > 75 ans
  - Mauvais état général

- **Relatives**
  - Occlusion intestinale par plus d’une sténose
Mortalité globale 4.1%,
Parmis les 6 patients décédés, 4 patients avaient un PCI of >20

Morbidité globale 47.2%.
OX: 34.9% OXIRI: 52.4%, (p=0.05)

En analyse multivariée
- Anastomose colorectale (OR=3.67, 95%CI 1.68-7.98, p=0.001)
- Anastomose ureterale (OR=4.39, 95%CI 1.07-17.85, p=0.039)
- Sexe féminin (OR=2.43, 95%CI 1.14-5.18, p=0.021)

Le taux de complications intra-abdominales pas significativement différent
(18.6% in ox-alone vs. 19.4% in ox-irino, p=0.67)
La CCR + CHIP, pour quels patients?

Contre indications carcinologiques

- Atteinte rétropéritonéale étendue
  - La sténose urétérale n’est pas une CI

- Métastases extra-abdominales
  - TEP
  - Discussion métastase pulmonaire
  - Problème des métastases ganglionnaires rétropéritonéales
Problèmatique spécifique des métastases ovariennes

- Fréquentes
- « Equivalent » de carcinose
- Problème de la fertilité chez la femme jeune
- Souvent résistantes à la chimio systémique
- Source de dissémination ganglionnaire rétropéritonéale

Ne sont jamais une contre indication

Nécessitent parfois une exérèse préalable à la chimiothérapie systémique
In HIPEC Procedures, Which are the determining factors in improving survival?

Complete CRS is probably the most important factor

Completeness of cytoreduction

French Multicentric Study 523 patients

(D.Elias & al JCO 2010)
Preoperative assessment

CT scan: Sensitivity: 60-79%

Pet-Scan: Se 57%

Under-estimation of the extent of disease
Sensitivity < 30% if < 0.5mm

PC diagnosed preoperatively in 55% of cases

Jacquet et al. Cancer 1993
De Bree et al. J Surg Oncol 2004
Dromain et al. Abdom Imaging 2008
In our opinion, although such a per-protocol analysis was performed on 120 cases, as shown in Table 2, the diagnostic accuracy of laparoscopy in advanced ovarian cancer was evaluated in 31 of 120 cases (25.8%). The table provides the accuracy of laparoscopic assessment for each parameter (per-protocol analysis).

### TABLE 2

**Accuracy of laparoscopic assessment for each parameter (per-protocol analysis)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Not evaluable, n (%)</th>
<th>False positive, n (%)</th>
<th>False negative, n (%)</th>
<th>NPV, %</th>
<th>PPV, %</th>
<th>Specificity, %</th>
<th>Accuracy, n (%)</th>
<th>Cohen’s kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omental cake</td>
<td>3 (2.5)</td>
<td>5 (4.2)</td>
<td>2 (1.7)</td>
<td>95.8</td>
<td>92.8</td>
<td>90.2</td>
<td>110 (94.0)</td>
<td>0.878</td>
</tr>
<tr>
<td>Peritoneal carcinomatosis</td>
<td>1 (0.8)</td>
<td>15 (12.6)</td>
<td>1 (0.8)</td>
<td>97.9</td>
<td>78.9</td>
<td>75.8</td>
<td>103 (86.5)</td>
<td>0.733</td>
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<tr>
<td>Diaphragmatic carcinomatosis</td>
<td>2 (1.6)</td>
<td>8 (6.7)</td>
<td>3 (2.5)</td>
<td>92.9</td>
<td>89.6</td>
<td>83.0</td>
<td>107 (90.7)</td>
<td>0.802</td>
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<tr>
<td>Mesenteral retraction</td>
<td>31 (25.8)</td>
<td>4 (4.4)</td>
<td>4 (4.4)</td>
<td>94.0</td>
<td>82.6</td>
<td>94.0</td>
<td>81 (91.0)</td>
<td>0.766</td>
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<tr>
<td>Bowel infiltration</td>
<td>12 (10.0)</td>
<td>8 (7.4)</td>
<td>11 (10.1)</td>
<td>81.7</td>
<td>83.3</td>
<td>86.0</td>
<td>89 (82.4)</td>
<td>0.646</td>
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<tr>
<td>Stomach infiltration</td>
<td>8 (6.6)</td>
<td>4 (3.5)</td>
<td>3 (2.6)</td>
<td>97.0</td>
<td>63.6</td>
<td>96.1</td>
<td>105 (93.7)</td>
<td>0.632</td>
</tr>
<tr>
<td>Superficial liver metastasis</td>
<td>4 (3.3)</td>
<td>5 (4.3)</td>
<td>4 (3.4)</td>
<td>95.7</td>
<td>78.3</td>
<td>94.7</td>
<td>107 (92.2)</td>
<td>0.752</td>
</tr>
</tbody>
</table>

NPV, negative predictive value; PPV, positive predictive value.

## Importance de la carcinose

<table>
<thead>
<tr>
<th>PCI</th>
<th>Survie à 5 ans (%)</th>
</tr>
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<tbody>
<tr>
<td>1-6</td>
<td>44</td>
</tr>
<tr>
<td>7-12</td>
<td>22</td>
</tr>
<tr>
<td>13-19</td>
<td>29</td>
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<tr>
<td>&gt;19</td>
<td>7</td>
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Prognostic impact of the extent of carcinomatosis (ie, peritoneal cancer index; P < .001) on overall survival.

Elias D et al. JCO 2010;28:63-68
The use of neoadjuvant systemic chemotherapy was found to be a positive prognostic indicator (p=0.040).

Kaplan Meier survival distribution based on the use of neoadjuvant systemic chemotherapy

Impact on a microscopic metastatic dissemination?
La CCR+CHIP est théoriquement réservée aux patients répondeurs

120 patients

- Median OS : 36.2 mois
- 5-year survival rates 33%

Patients non répondeurs
- Median OS 31.4 mois
- 5-year survival rates 26%

### Carcinose et métastases hépatiques

<table>
<thead>
<tr>
<th>Groupes</th>
<th>Survie médiane (mois)</th>
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<tbody>
<tr>
<td>PCI&lt;12 pas de MH</td>
<td>76</td>
</tr>
<tr>
<td>PCI&lt;12 1 à 2 MH</td>
<td>40</td>
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<tr>
<td>PCI&lt;12 3 MH et plus</td>
<td>27</td>
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</tbody>
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**FIGURE 1.** Overall survival of PC and LM group versus PC alone group after curatively intended surgery.

**FIGURE 2.** Disease-free survival of PC and LM group versus PC alone group after curatively intended surgery.

**FIGURE 3.** Overall survival according to the number of LM and PCI after curatively intended surgery.
## Conclusion

- Age < 75 ans
- Bon état général
- Objectif de résection complète
- PCI < 20
- RCP centre expert CHIP
- Chimio néoadjuvante
- Moins de trois métastases hépatiques

### Dans PRODIGE 7 : 68% des patients effectivement réséqués

<table>
<thead>
<tr>
<th>VILLE</th>
<th>CENTRE</th>
<th>I. PRINCIPAL</th>
<th>PATIENTS ENREGISTRES</th>
<th>PATIENTS RANDOMISÉS</th>
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<tr>
<td>PIERRE BENITE</td>
<td>Hôpital Lyon Sud</td>
<td>Pr Olivier GLEHEN</td>
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<td>Centre Val d’Aurelie</td>
<td>Dr François QUENET</td>
<td>88</td>
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<td>VILLEJUIF</td>
<td>Institut Gustave Roussy</td>
<td>Dr Dominique ELIAS</td>
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<td>Centre René Gauducheau</td>
<td>Pr Jacques PAINEAU</td>
<td>34</td>
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<td>Dr Guillaume PORTIER</td>
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<td>Pr Patrick RAT</td>
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<td>CHU de Grenoble</td>
<td>Dr Catherine ARVIEUX</td>
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<td>ANGERS</td>
<td>Centre Paul Papin</td>
<td>Dr Gérard LORIMER</td>
<td>10</td>
<td>5</td>
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<td>CLERMONT-FERRAND</td>
<td>Hôtel Dieu</td>
<td>Pr. Denis PEZET</td>
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<tr>
<td>NANCY</td>
<td>Centre Alexis Vautrin</td>
<td>Dr Frédéric MARCHAL</td>
<td>4</td>
<td>4</td>
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<tr>
<td>PARIS (Tenon)</td>
<td>Hôpital Tenon</td>
<td>Dr Valérie LOI</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>LYON</td>
<td>Centre Léon Bérard</td>
<td>Dr Pierre MEEUS</td>
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<td>2</td>
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<td>STRASBOURG</td>
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<td>Dr Cécile BRIGANT</td>
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<td>NICE</td>
<td>Hôpital de l’Archet 2</td>
<td>Dr Jean-Marc BEREDER</td>
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<td>PARIS</td>
<td>Institut Curie</td>
<td>Dr Bernard BARANGER</td>
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<tr>
<td>COLOMBES</td>
<td>Hôpital Louis Mourier</td>
<td>Pr Simon MSIKA</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td><strong>380</strong></td>
<td><strong>257</strong></td>
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