Is HIPEC an option in the treatment of Ovarian Cancer

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Department of Obstetrics and Gynecology
Disclosures

• I have no financial relationships to disclose
What is HIPEC?

• Cytoreductive Surgery
• Hypertermic Intraperitoneal Chemotherapy
What is Cytoreductive Surgery

- The surgeon must remove all visible tumor in the abdomen.
  - Hysterectomy + oophorectomy
  - Pelvic peritonectomy
  - Bowel resections,
  - Splenectomy,
  - Liver resection,
  - Diafragma stripping and resection
  - Pericard resection,
  - Total peritonectomy,
  - Distal Pancreatectomy
  - Cholecystectomy
  - Portal Dissection
No visible Tumor
HIPEC? When?

- HIPEC should only be used in patients with peritoneal carcinomatosis and
- These patients should not have tumors outside of the abdomen
Indications

• Cancers Making Carcinomatosis in Peritoneum
• Peritoneal Tumors
  • Primer peritoneal cancer
  • Peritoneal mesothelioma
  – Metastatic Cancers
  • Gastro Intestinal Cancers
    – Gastric
    – Colorectal
    – Appendix/Pseudomyxoma Peritonei

• Ovarian cancers
Patient Selection

- Appropriate patient selection provides good survival
- The purpose of cytoreduction should be to remove all visible tumor
- Complete cytoreduction should be performed in these patients.
  - Patients' general conditions should be appropriate
Patient Selection

- Functional status of the patient
- Primer tumor
- Systemic chemotherapy response
- Assessment of disease spread
  - Symptoms
  - These patients should not have tumors outside of the abdomen
  - CT, PET, MRI
  - Diagnostic Laparoscopy

- If you make a good preoperative evaluation;
  - Can Increase the chance of optimal surgery,
  - Can Reduce complication rate.
Where should be perform?

• The physician in HIPEC centers must have been trained in cancer surgery.
• Must be experienced in patient selection.
• Multidisciplinary centers should be applied.
  – Gynecologic Oncologist
  – Medical Oncologist
  – Radiation Oncologist
  – Radiologist
  – Experienced pathologist
# Chemotherapeutic Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular weight (Daltons)</th>
<th>Intraperitoneal dose (mg/m²)</th>
<th>Area under concentration-time curve ratio*</th>
<th>Drug penetration distance</th>
<th>Thermal enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alkylating agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitomycin C⁸³</td>
<td>334.3</td>
<td>35</td>
<td>10–23.5</td>
<td>2 mm</td>
<td>+</td>
</tr>
<tr>
<td><strong>Platinum compounds</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cisplatin⁸⁴</td>
<td>300.1</td>
<td>90–250</td>
<td>13–21</td>
<td>1–3 mm</td>
<td>+</td>
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<tr>
<td>Carboplatin⁸⁵</td>
<td>371.3</td>
<td>350–800</td>
<td>1.9–5.3</td>
<td>0.5 mm</td>
<td>+</td>
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<tr>
<td>Oxaliplatin⁸⁶</td>
<td>397.3</td>
<td>460</td>
<td>3.5</td>
<td>1–2 mm</td>
<td>+</td>
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<tr>
<td><strong>Antimicrotubule agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Paclitaxel⁸⁷</td>
<td>853.9</td>
<td>20–175</td>
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<td>More than 80 cell layers</td>
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<tr>
<td>Docetaxel⁸⁸</td>
<td>861.9</td>
<td>40–156</td>
<td>207</td>
<td>NA</td>
<td>+</td>
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<tr>
<td><strong>Topoisomerase interactive agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mitoxantrone⁸⁹</td>
<td>517.4</td>
<td>28</td>
<td>15.2</td>
<td>5–6 cell layers</td>
<td>±</td>
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<tr>
<td>Doxorubicin⁹⁰</td>
<td>543.5</td>
<td>60–75</td>
<td>162</td>
<td>4–6 cell layers</td>
<td>+</td>
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<tr>
<td><strong>Antimetabolites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Fluorouracil⁸⁴</td>
<td>130.1</td>
<td>650</td>
<td>NA</td>
<td>0.2 mm</td>
<td>-</td>
</tr>
</tbody>
</table>

*Assuming a concentration-time curve ratio of 1, the drug penetration distance is 1 mm.**
When To Use HIPEC in Ovarian Cancer?

• Primary Cytoreduction
• Interval Cytoreduction
• Secondary Cytoreduction

• Recurrent platinum-sensitive patients are the most studied and seem to be the most appropriate group.
The Impact of HIPEC in Ovarian Cancer-1

- Retrospective non-randomized study
- 5 years overall survival significantly higher in the group receiving HIPEC
  - (63.4% vs. 52.8%, p = 0.0078)

Ryu KS, Gynecol Oncol. 2004
The Impact of HIPEC in Ovarian Cancer-2

- In Stage III patients
- 5-year overall survival
- In patients with residual tumor less than 1 cm in secondary surgery and patients undergoing HIPEC was 65.6%
- in the control group was 40.7%
- (p=0.0046)

Ryu KS, Gynecol Oncol. 2004
HIPEC in Persistant and Recurrent Ovarian Cancer

• There was no significant difference in overall survival after optimal cytoreduction in platinum-sensitive and platinum-resistant relapses

HIPEC in Primary Advanced Ovarian Cancer
The first phase-2 clinical trial

- 47 patients
- Prospektive non-randomize
- 22 patient primary,
- 25 hasta secondary Cytoreduction
- HIPEC (Cisplatin 75 mg/m2)

- Overall survival: 30.4 months
- DFS: 27.4 months

Di Giorgio A, Cancer. 2008
4 centers, Phase-II Trial

26 patients;
- Cytoreductive surgery
- HIPEC(Cisplatin+Doxorubicin)
- After HIPEC, Paclitaxel+Carboplatin, 6 cycles

Median Follow-up: 26 months

5 years overall survival: 60.7%

5 years DFS: 15.2% (median 30 months)
A critical appraisal of hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of advanced and recurrent ovarian cancer

Luise M. Chiva *, Antonio Gonzalez-Martin

MD Anderson Cancer Center Madrid, Spain

• Retrospektif review
• 22 paper
• N=1450 patients
• Different Protocols

493 Primer
957 Rekürurrent

Luise M. Chiva, Gynecologic Oncology 136 (2015) 130–135
## Adjuvan HIPEC-OS/DFS

<table>
<thead>
<tr>
<th>Year</th>
<th>First author</th>
<th>Ref.</th>
<th>N</th>
<th>OS (m)</th>
<th>DFS (m)</th>
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</thead>
<tbody>
<tr>
<td>2010</td>
<td>Helm</td>
<td>[8]</td>
<td>26</td>
<td>41</td>
<td>16</td>
<td>33%</td>
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<tr>
<td>2011</td>
<td>Deraco</td>
<td>[10]</td>
<td>26</td>
<td>nr</td>
<td>30</td>
<td>60%</td>
</tr>
<tr>
<td>2013</td>
<td>Gonzalez-Bayon</td>
<td>[12]</td>
<td>15</td>
<td>78</td>
<td>21</td>
<td>72%</td>
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<tr>
<td>2013</td>
<td>Bakrin</td>
<td>[13]</td>
<td>12</td>
<td>52</td>
<td>12</td>
<td>33%</td>
</tr>
<tr>
<td>2014</td>
<td>Cascales</td>
<td>[14]</td>
<td>23</td>
<td>–</td>
<td>nr at 3 y</td>
<td>–</td>
</tr>
<tr>
<td>2014</td>
<td>Massari</td>
<td>[15]</td>
<td>2</td>
<td>36</td>
<td>12</td>
<td>–</td>
</tr>
</tbody>
</table>

|      |                  |      |    |        |         | 40% |

Total: 248 patients

Survival results from the front-line therapy series.

Luise M. Chiva, Gynecologic Oncology 136 (2015) 130–135
HiPEC-Rekürren
(Platinum sensitive first relaps)

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>N</th>
<th>Homog</th>
<th>Os</th>
<th>Dfs</th>
</tr>
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<tbody>
<tr>
<td>2011</td>
<td>Fagotti</td>
<td>42</td>
<td>Yes</td>
<td>38</td>
<td>24</td>
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<tr>
<td>2013</td>
<td>Gonzalez Bayon</td>
<td>19</td>
<td>Yes</td>
<td>62</td>
<td>18</td>
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<tr>
<td>2013</td>
<td>Bakrin</td>
<td>247</td>
<td>Yes</td>
<td>42</td>
<td></td>
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<tr>
<td>2013</td>
<td>Furet</td>
<td>17</td>
<td>Yes</td>
<td>30</td>
<td>11</td>
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<tr>
<td>2014</td>
<td>Robella</td>
<td>70</td>
<td>Yes</td>
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<tr>
<td>2014</td>
<td>Massari</td>
<td>11</td>
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<td>12</td>
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<tr>
<td>2010</td>
<td>Helm</td>
<td>83</td>
<td>Most Sensitive</td>
<td>23</td>
<td>29</td>
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<tr>
<td>2009</td>
<td>Carrabin</td>
<td>10</td>
<td>9/10 Sensitive</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Luise M. Chiva, Gynecologic Oncology 136 (2015) 130–135

Nejat Özgül
nozgul@gmail.com
Conclusions

• In primary and recurrent cases, HIPEC has no benefit in survival.
• It should not be recommended as a routine treatment.
• It can only be applied as part of clinical trials.
HIPEC-Reküren Over Kanseri (Review)

- 16 study,
- 1168 patients
- HIPEC : 953 patients (%81.6)
- OS: 26.7-35 months
- DFS: 8.5-48 months

HIPEC offers hope in the treatment of recurrent ovarian cancer. Randomized controlled trials are needed.
Cytoreductive Surgery and HIPEC in Recurrent Epithelial Ovarian Cancer: A Prospective Randomized Phase III Study

<table>
<thead>
<tr>
<th>Survival by disease stage</th>
<th>Mean survival</th>
<th>Stage IIIc survival (months)</th>
<th>Stage IV survival (months)</th>
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</thead>
<tbody>
<tr>
<td>HIPEC</td>
<td>26.9</td>
<td>26.4</td>
<td></td>
</tr>
<tr>
<td>Non-HIPEC</td>
<td>14.2</td>
<td>11.9</td>
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</table>

Cytoreductive Surgery and HIPEC in Recurrent Epithelial Ovarian Cancer: A Prospective Randomized Phase III Study

<table>
<thead>
<tr>
<th>Survival by stage and platinum responsiveness</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean survival</td>
<td>Stage IIIc survival (months)</td>
<td>Stage IV survival (months)</td>
</tr>
<tr>
<td>HIPEC</td>
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<tr>
<td>Platin Sensitive</td>
<td>27.28</td>
<td>25.4</td>
</tr>
<tr>
<td>Platin Resistant</td>
<td>26.08</td>
<td>27</td>
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<tr>
<td>Non-HIPEC</td>
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<tr>
<td>Platin Sensitive</td>
<td>15.7</td>
<td>13.5</td>
</tr>
<tr>
<td>Platin Resistant</td>
<td>10.7</td>
<td>9.37</td>
</tr>
</tbody>
</table>

• There is no entry to register clinical trials in database
• There is much more questions raised by the article regarding methods and statistical analysis
• There is no information about how the end point was measured: from randomization, from surgery, or from diagnosis?
• There is any information of which statistical test was used to compare the primary end point between the treatment group
• No data on progression-free survival (PFS) or time to recurrence were presented.
• Randomization procedures remain vague and not transparent.

• Unpublished data
• A cohort of 200 patients with relapsed or residual ovarian cancer including the years 2005–2017.

• Median survival rates
  – CRS+ HIPEC + systematic CT Grub
    • 38 months in the 80 patients
  – CRS+ Non-HIPEC + systematic CT Grub
    • 23.8 months in the 60 patients
Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer


N ENGL J MED 378;3  NEJM.ORG  JANUARY 18, 2018

The New England Journal of Medicine
Primary End Point: DFS
Secondary End Point: OS and Side Effect Profile
DFS

- HİPEC Grub:
  - DFS: +3.5 months

Overall Survival

- HİPEC Grub:
  - Median OS: +11 months

Van Driel Study

- Interval Debulking Surgery in patients with stage 3 epithelial ovarian cancer;

+HIPEC:

Longer DFS and OS were achieved without increasing side effects.

1. There is a serious difference between DFS and OS. Patients received additional treatment?
2. Stage 3 subtypes are not specified.
3. How were Stage IV patients ruled out?
4. What is the ratio of patients with complete response in both groups?
5. Korean Study?
Randomized trial of hyperthermic intraperitoneal chemotherapy (HIPEC) in women with primary advanced peritoneal, ovarian, and tubal cancer. (Korean Study)

<table>
<thead>
<tr>
<th></th>
<th>HİPEC</th>
<th>Non-HiPEC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grubs</td>
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<td></td>
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</tr>
<tr>
<td>2-yııl PFS</td>
<td>43.2%</td>
<td>43.5%</td>
<td>p=0.569</td>
</tr>
<tr>
<td>5-yııl PFS</td>
<td>20.9%</td>
<td>16.0%</td>
<td>p=0.569</td>
</tr>
<tr>
<td>5-yııl OS</td>
<td>51.0%</td>
<td>49.4%</td>
<td>p=0.574</td>
</tr>
<tr>
<td>NEOADJUVAN Grub</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PFS ay</td>
<td>20</td>
<td>19</td>
<td>p = 0.137</td>
</tr>
<tr>
<td>OS ay</td>
<td>54</td>
<td>51</td>
<td>p = 0.407</td>
</tr>
</tbody>
</table>

HIPEC has no superiority in primary disease

Lim MC, 2017. Journal of Clinical Oncology
Critis of Van Driel Study

• The main criticism was focused on the biases introduced by the design and the selection of the endpoints of the trial: included participants not completely representative of OC patients,

• The primary outcome of PFS instead of OS, a curiously slow recruitment (only 245 patients in 9 years)

• Surprisingly, there was not an increased toxicity in HIPEC arm

• HIPEC may be considered as a therapeutic option to complement complete IDS in patients with advanced ovarian cancer stage IIIC.
Hyperthermic Intraperitoneal Chemotherapy Does Not Add Benefit in Patients With Advanced Colorectal Cancer

(Abstract LBA3503)

• At a median follow-up of 64 months, the median OS was 41.2 months in the non-HIPEC group vs 41.7 months in the HIPEC group.
• PFS was also similar between the two groups: median of 11.1 months in the non-HIPEC group vs 13.1 months in the HIPEC group.
• The overall mortality rate at 30 days after surgery was 1.5% in both groups, and there was no difference in the rate of side effects during the first 30 days.
• At 60 days the rate of complications in the HIPEC group was almost double that in the non-HIPEC group.

Francois Q et al. ASCO 2018
HIPEC: HOPE or HYPE in the fight against advanced ovarian cancer?

• No evidence for the broad implementation of HIPEC in the entire stage III and IV population with epithelial ovarian cancer

• Potential role in initially inoperable patients but one needs to ask the reasons of inoperability (insufficient effort or true adverse tumorbiology?)

• If patients inoperable due to extensive disease and poor Performance Status, how can they tolerate extra exposure to HIPEC?

• TRUST study and further studies

Annals of Oncology 2018
Is there a role for HIPEC in ovarian cancer?

- Hyperthermic intraperitoneal chemotherapy (HIPEC) is promoted by some as a standard treatment for peritoneal carcinomatosis of epithelial ovarian cancer (EOC) and other tumor entities, despite lack of robust data supporting this.

- Publicly available evidence addressing the value of HIPEC in EOC is rather inconclusive, revealing contradictory and inconsistent results while some studies even report harm to the patients from a higher morbidity.

- On this ground, we cannot recommend the implementation and use of HIPEC outside of a randomized clinical trial setting.

Philipp Harter, Andreas du Bois, Jalid Sehouli, Sven Mahner, Ignace Vergote, Luis Chiva Antonio Gonzalez-Martin, Christina Fotopoulou

Limitations of HIPEC

Different drugs/doses/application durations

No Homogeneous Series

Small single Center series

Limited Randomize Phase- III studies
Peritoneal Carcinomatosis

- Major problem in cancer treatment;
- Difficult to identify with imaging
- Strength of management
- QOL
Operative Risks

• Fistula
• Anastomotic leakage
• Pulmonary embolism
• Deep vein thrombosis
• Re-Operation
• Hematological Problems
• Mortality
Morbidity and Mortality

• Major morbidity is seen in 27% of cases.
  – Overall morbidity rate: 49%

• The most common major complication is leakage of anastomosis and reoperation in the first 30 days

• Mortality rate in first 30 days: %1.6

• The most common cause of death after HIPEC is SEPSIS due to abscess and anastomosis leakage.

Bakrin 2013, Deraco 2011
Factors Affecting Survival

• Clinical Factors
  – Age
  – Performans Status

• Surgical Factors
  – Degree of Carcinomatosis
  – Blood Loss
  – Operation Duration
  – Incomplete Resection
  – Liver Metastasis

• Pathological Factors
  – Poor Tumor Differentiation
  – Positive Lymph Nodes
Factors Affecting Complete Cytoreduction

- ECOG Performans ≤ 2
- The absence of a bilier obstruction
- Absence of ureteral obstruction
- Absence of intestinal obstruction at more than one site
- Clean Zone II
- Small bowel class 1 or class 2, but no class 3 and more
- PCI is under 20

Esquivel et al, Annals Surg Onc 2007
# Randomised HIPEC Trials in Ovarian Cancers

<table>
<thead>
<tr>
<th>NCT</th>
<th>Country</th>
<th>Setting</th>
<th>N</th>
<th>Primary Endpoint</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>02124421</td>
<td>USA</td>
<td>Upfront surgery +/- HIPEC</td>
<td>48</td>
<td>Safety</td>
<td>Open</td>
</tr>
<tr>
<td>01628380</td>
<td>Italy</td>
<td>IDS +/- HIPEC</td>
<td>94</td>
<td>PFS</td>
<td>Open</td>
</tr>
<tr>
<td>00426257</td>
<td>Netherlands</td>
<td>IDS +/- HIPEC</td>
<td>280</td>
<td>PFS</td>
<td>POSITIVE</td>
</tr>
<tr>
<td>02328716</td>
<td>Spain</td>
<td>Primary and recurrent OC Surgery +/- HIPEC</td>
<td>32</td>
<td>PFS</td>
<td>Closed; Results pending</td>
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<tr>
<td>01091636</td>
<td>Korea Lim</td>
<td>Primary and recurrent OC Surgery +/- HIPEC</td>
<td>170</td>
<td>PFS</td>
<td>NEGATIVE</td>
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<tr>
<td>01539785</td>
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<td>Recurrent sensitive. Surgery +/- HIPEC</td>
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<td>PFS</td>
<td>Open</td>
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<tr>
<td>01767675</td>
<td>USA Ch</td>
<td>Recurrent sensitive. Surgery +/- HIPEC</td>
<td>98</td>
<td>PFS</td>
<td>Open</td>
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<tr>
<td></td>
<td>Greece</td>
<td>Recurrent sensitive and resistant Surgery +/- HIPEC</td>
<td></td>
<td></td>
<td>POSITIVE?</td>
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<tr>
<td>01376752</td>
<td>France</td>
<td>Plt-sens relapse after 6 x chx: Surgery +/- HIPEC</td>
<td>444</td>
<td>OS</td>
<td>Open</td>
</tr>
</tbody>
</table>
Conclusions

• HIPEC can be considered as a treatment option only in patients who can perform maximal-optimal cytoreduction.
• Absence of phase III randomized trial data demonstrating of this strategy comparing alternative strategy
  – CRS+ non-HIPEC IP Chemotherapy
  – CRS+ Systemic Antineoplastic Therapy
  – CRS+ Both non-HIPEC IP Chemotherapy+ Systemic Antineoplastic Therapy
• Absence of phase III trial data demonstrating the optimal setting or most appropriate antineoplastic agents to be used
Conclusions

• HIPEC with cytoreduction is safe for well-selected cases and low mortality.

• Its impact is directly related to factors such as tumor biology and histology, patient selection (PCI), surgical technique and procedure (complete cytoreduction) and experienced centers.

• For Oncological Outcomes;
  – The results of ongoing randomized phase 3 clinical trials should be expected.
Future

• More clinical trials
• Procedure and standardization of drugs used
• Usability in other cancers
• Can be used in early stage tumors with fewer tumors
Thank you for your attention

Contact:
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nozgul@gmail.com