HIPEC as standard or optional in first line treatment for ovarian carcinoma?

Willemien van Driel
NKI-AVL Amsterdam

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- No disclosures

Hipec – still controversial?

How a Recent Study Heats up the Debate Over Intraperitoneal Chemotherapy in Newly Diagnosed Advanced Ovarian Cancer

By Bradley J. Monk, MD, FACS, FACOG
May 25,

HIPEC: HOPE or HYPE in the fight against advanced ovarian cancer?

Ovarian Cancer Treatment — Are We Getting Warmer?

David R. Spriggs, M.D., and Oliver Zivanovic, M.D.

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Survival Ovarian carcinoma

- Global survival trends remains stable over the last 30 years
- Age adjusted 5 year survival: 30-50%

- Survey of the Dutch cancer registry over 30 years
  - More patients received adequate staging procedures
  - More patients treated with optimal surgery and chemotherapy (55% → 67%)
  - 5-year survival increased
  - 10 year survival remained stable

Allemani et al, lancet, 2018
Timmermans et al, Gyn Oncol 2017

What evidence do we have?

- Retrospective studies
- Prospective cohort studies
- Randomised control trial

Overview of non-randomised studies

- Heterogenous group of patients
- Various treatment regimens
- Morbidity:11-78%
- Improved survival is described

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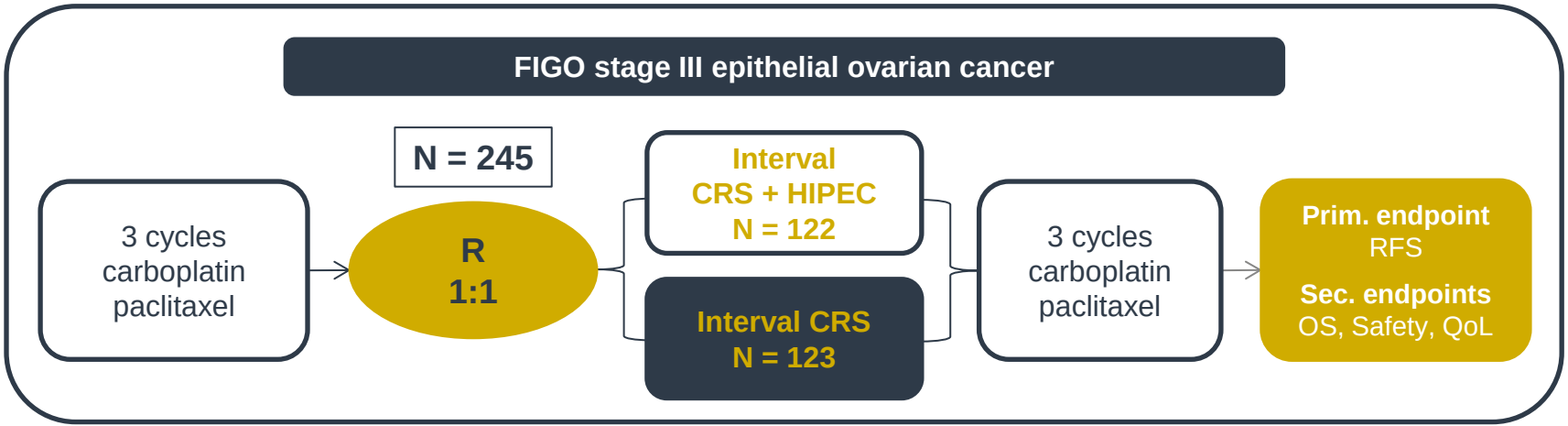
Study design



- Patients were ineligible for primary cytoreductive surgery (CRS) because of extent of disease
- Follow-up visits were performed every 3 months for the first 2 years, then every 6 months thereafter
- Tumor assessments with CT scans were performed 6, 12, and 24 months after the last chemotherapy
- The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 were used for grading toxicity

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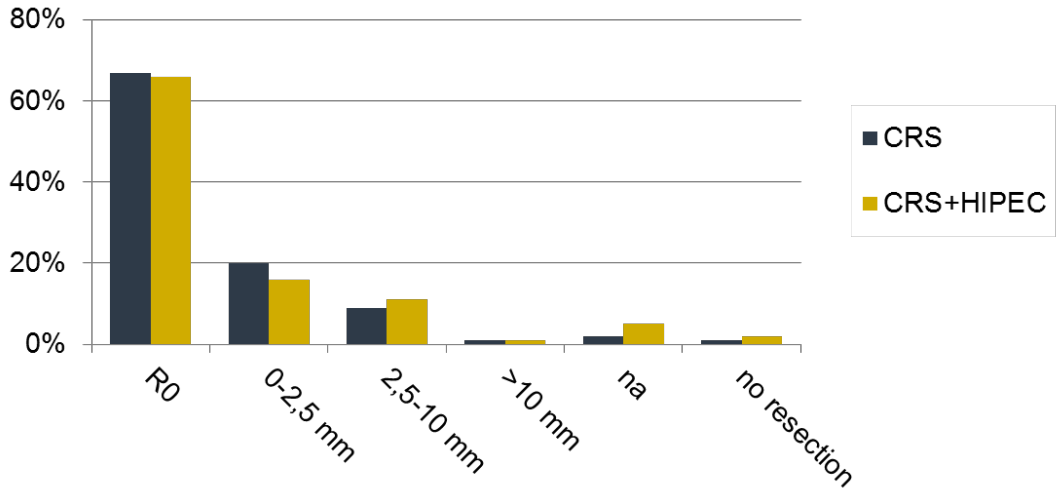
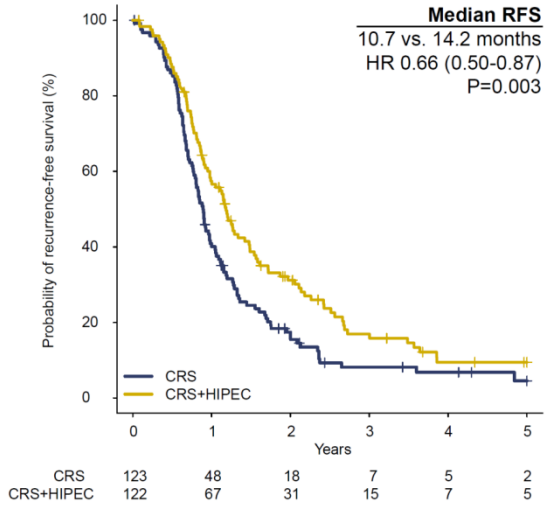
OVHIPEC study

Balanced study for:
Age
Histology
Pre-treatment
Extend of disease at surgery

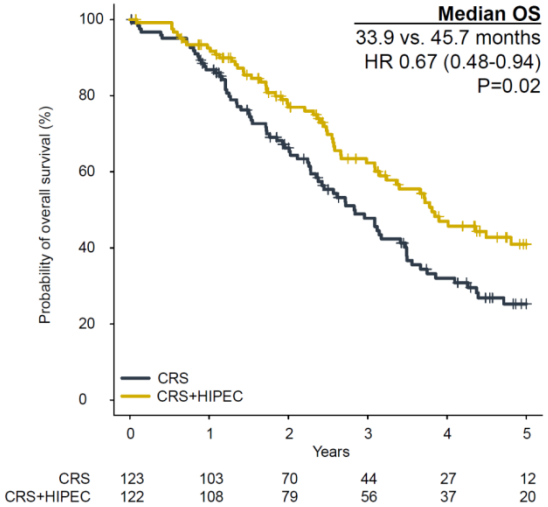
Surgical details



Recurrence-free survival



Overall survival



Increase of 10% in overall survival after 5 years in favor of HIPEC group

van Driel et al. NEJM 2018

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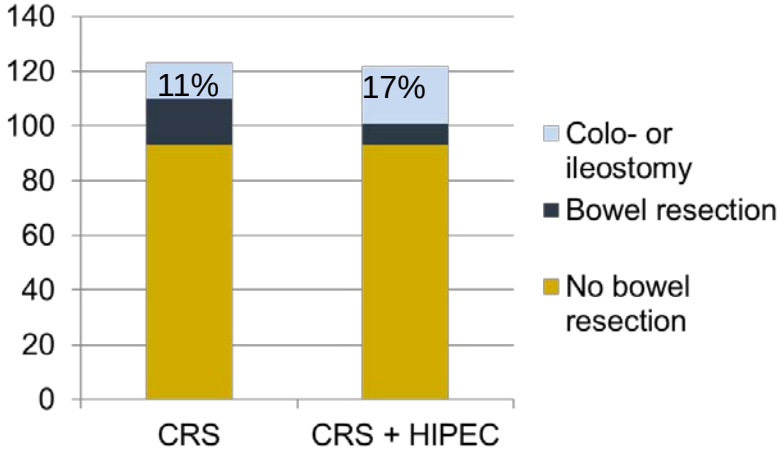
Surgical details



Postoperative findings

No difference in:
- Days in hospital
- Reinitiation of routine chemotherapy
- Nr of patients receiving 6 cycles of chemotherapy
- Adverse Events
- Quality of life

Difference:
- 1 day ITU admission for HIPEC
- Longer surgery (146 min) due to HIPEC procedure

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Critical points raised

- Groups supposedly not balanced for
  - BRCA
  - S
  - response
  - histological type
  - Difference per institute

Randomisation

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Histology

	CRS	CRS+HIPEC
HGSC	107 (87%)	112 (92%)
Non HGSC	15	9

Non HGSC includes:

- Clear cell carcinoma
- Carcinosarcoma
- Endometrioid
- Low grade serous carcinoma

RFS

Subgroup	Surgery	Surgery plus HIPEC	Hazard Ratio (99% CI)
	no. of events/total no.		
Age			
≥65 yr	43/45	34/43	0.63 (0.35–1.15)
<65 yr	67/78	65/79	0.72 (0.46–1.12)
Histologic type			
High-grade serous	96/107	91/112	0.69 (0.48–1.02)
Other	14/15	7/9	0.56 (0.17–1.86)
Previous surgery			
No	100/111	90/110	0.71 (0.49–1.03)
Yes	10/12	9/12	0.47 (0.14–1.61)
No. of involved regions			
0–5	73/83	62/83	0.64 (0.41–1.01)
6–8	37/40	37/39	0.66 (0.35–1.23)
Laparoscopy before surgery			
No	95/105	86/103	0.69 (0.47–1.02)
Yes	15/18	13/19	0.61 (0.23–1.63)

Figure S2. Forest plot for overall survival

OS

Subgroup	Surgery	Surgery-plus-HIPEC	Hazard Ratio (99% CI)
	no. of events/total no.		
Age			
≥65 yr	28/45	24/43	0.82 (0.40-1.68)
<65 yr	43/78	37/79	0.69 (0.34-1.35)
Histologic type†			
High-grade serous	62/107	57/112	0.76 (0.47-1.21)
Other	14/15	4/9	0.31 (0.07-1.37)
Previous surgery‡§			
No	71/111	56/110	0.66 (0.42-1.05)
Yes	5/12	5/12	0.77 (0.15-3.94)
No. of involved regions‡			
0 – 5	46/83	34/83	0.62 (0.35-1.12)
6 – 8	30/40	27/39	0.74 (0.38-1.48)
Laparoscopy before surgery			
No	63/105	51/103	0.67 (0.41-1.09)
Yes	13/18	10/19	0.62 (0.20-1.90)

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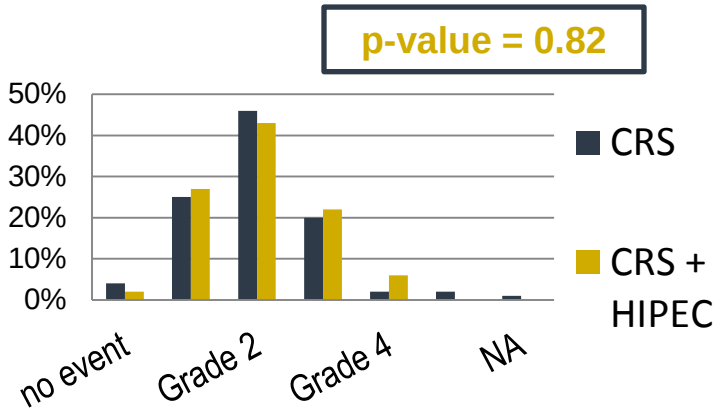
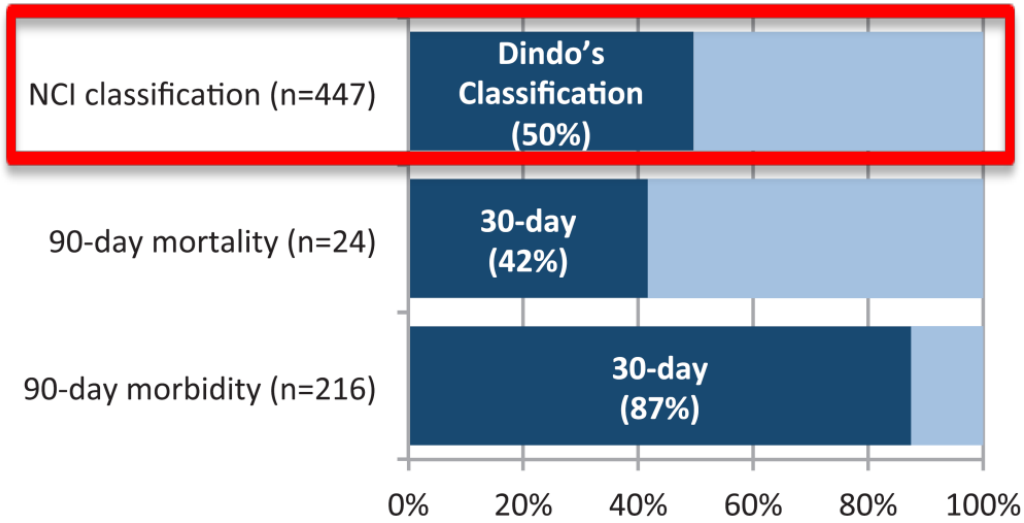
Adverse Events – NCI CTCAE vs Clavien Dindo





Alyami et al, Int J Hyperth 2017

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Study design and endpoints

- PFS as primary endpoint
- Standardization of the follow-up schedule
- Sample size: protocol amendment in 2012, version 4
  - Due to a long accrual sample size was adjusted from 280 to 240
- prognostically unfavorable stage III ovarian cancer due to extensive disease for whom primary CRS was not feasible
- Decision on treatment plan was made during MDT and reflects daily routine

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Comparable trials

		PDS	**1**	**2**	**3**	**4**	**5**	**6**
Diagnosis	**R**							
		1	2	3	IDS	4	5	6

OVHIPEC

Diagnosis		1	2	3	**R** IDS +/- HIPEC	4	5	6

- Survival is calculated from time of randomisation
- OVHIPEC study: 11 weeks from first cycle of chemotherapy to randomisation

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Control arm		RFS (months)	OS (months)
Vergote 2010	PDS vs IDS	12	30
Kehoe 2015	PDS vs IDS	12	24.1
Burger 2011	PDS +/- bevacuzimab	10.3	14.1
Fagotti 2018	PDS vs IDS	14	nr
OVHIPEC	IDS +/- HIPEC	10.7 → 13.5	33.9 → 36.7

Large difference between RFS and OS between arms?

	ΔRFS	ΔOS	
Armstrong, 2010 (iv vs iv/ip)	5.5	15.9	2,9 x higher
Perren, 2011 (+/- bevacizumab)	1.7	7.8	4,6 x higher
OVHIPEC	3.5	12	3,4 x higher

Comparison of 2 RCT on HIPEC and ovarian carcinoma

	Van Driel	Lim
Stage	III	III and IV
N	245	185
Surgery	IDS	PDS and IDS
Cisplatinum	100 mg/m2	75 mg/m2
Trial completed	Yes	no
Results published	Yes	Abstract only

Questions to be addressed

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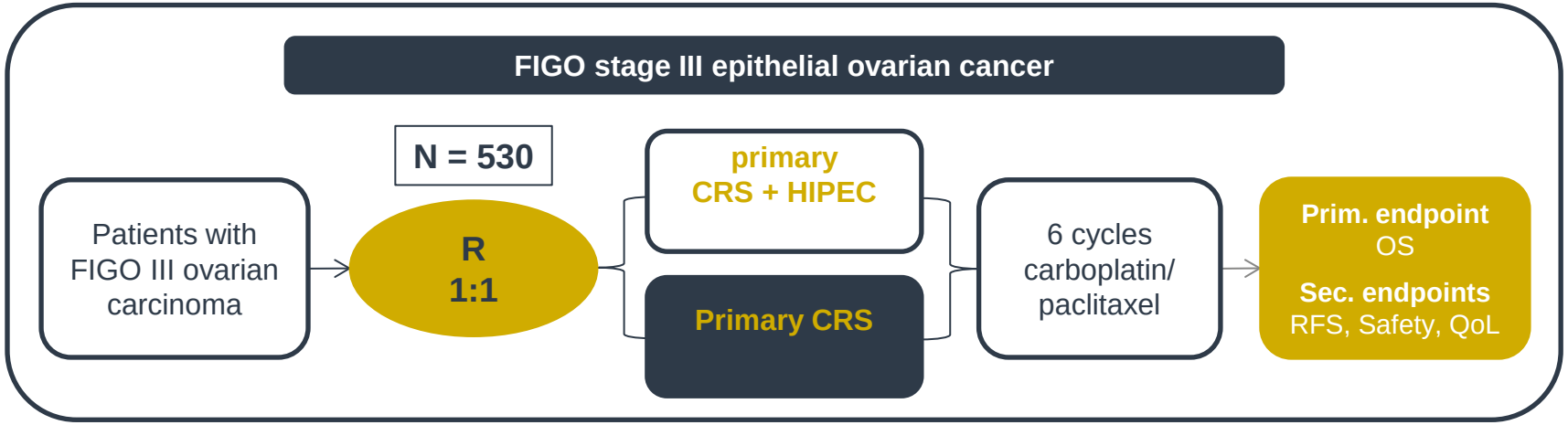
- Response rate and recurrence patterns
- HRD mutational analyses, somatic BRCA 1 and 2 analysis
- Can we identify subgroups who will benefit most of HIPEC
- Role of hyperthermia
- OVHIPEC-2 study:
  Primary cytoreductive surgery with or without HIPEC

OVHIPEC 2



Centers from Netherlands, UK, France, Denmark, Sweden, Ireland and Australia
International trialgroup
Funding of the Dutch cancer foundation
Waiting for funding by the governement

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Current status on HIPEC for ovarian carcinoma

- Adds to the treatment options currently available
- FIGO stage III, NACT and following interval CRS
- Primary CRS is not feasible due to extensive disease
- Cisplatinum 100 mg/m2 for 90 minutes
- Centralized care and monitoring treatment results

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