HIPEC Does Not Play A Role in the Treatment of Advanced Ovarian Cancer

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Definition of (Becoming) a New Standard Of Care

- **Showing superiority regarding OS/PFS within a prospective randomized trial**
- **Less toxicity…**
- **Better quality of life…**
- **Cost reduction…**

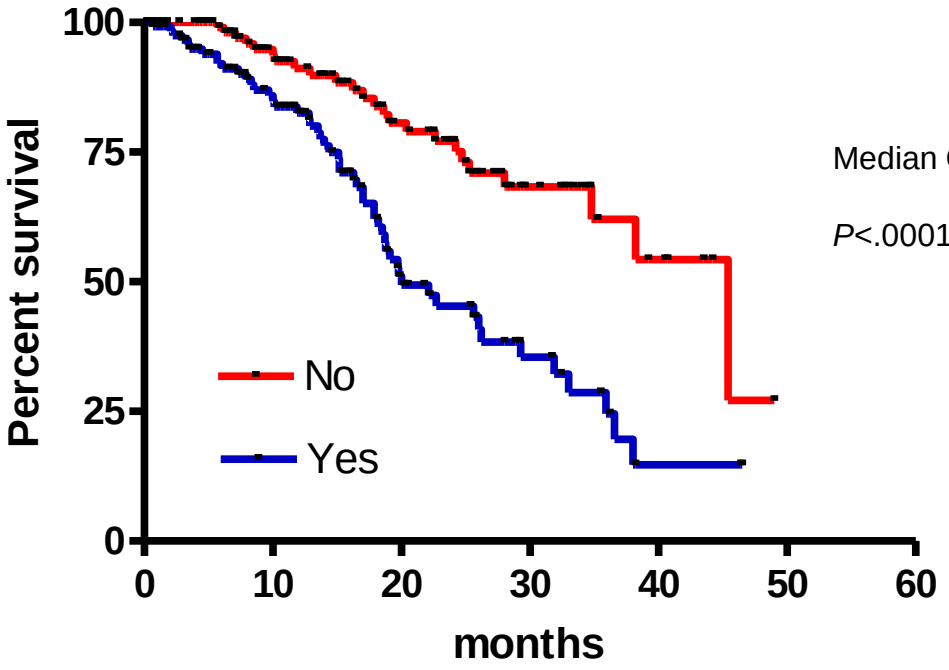
Cost Reduction

- **Cost reduction itself unlikely**
- **Additional rate of HIPEC ~4500€**
- **Higher rate of complications**
- **…no cost reduction in the first weeks**
- **But maybe cost effective in case of prolonging survival?**

HIPEC, hyperthermic intraperitoneal chemotherapy

Does Peritoneal Carcinomatosis Need A Special Treatment?

Is peritoneal carcinomatosis a prognostic factor ?



Median OS: PC No: 45.4 months
Yes: 20.0 months
P<.0001; HR: 0.37 (95% CI: 0.24 – 0.59)

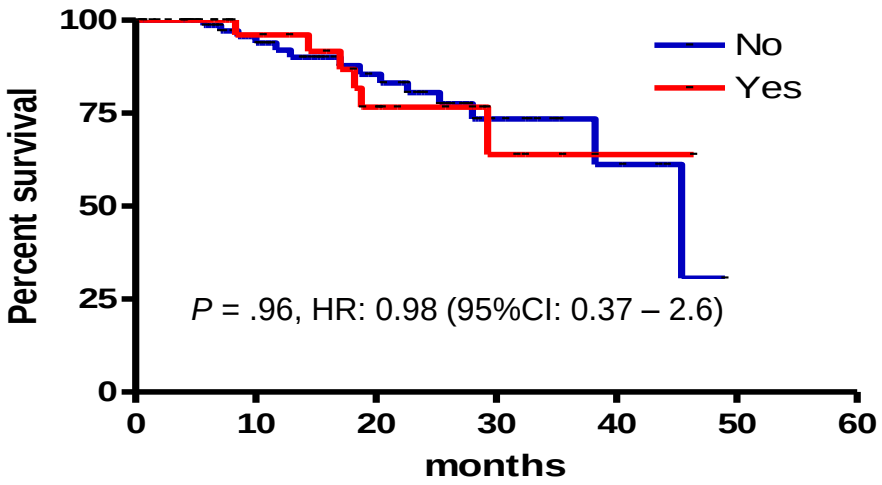
Or “only” a negative predictor for complete resection?

The rate of complete resection was 74% in pts without peritoneal carcinomatosis and 26% in pts with carcinomatosis in DESKTOP I

Harter P, et al. *Ann Surg Oncol.* 2009;16(5):1324-1330.

Does Peritoneal Carcinomatosis Need A Special Treatment?

TuR=0 with PC and non-PC



No difference in survival if complete resection was achieved, irrespective of intraoperative findings regarding peritoneal carcinomatosis

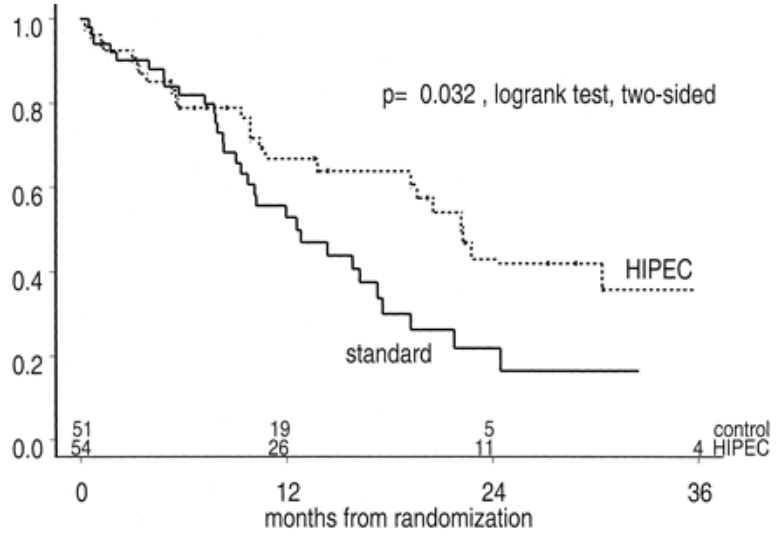
Peritoneal carcinomatosis is not a prognostic factor, “only” a negative predictor for a successful surgery

PC, peritoneal carcinomatosis

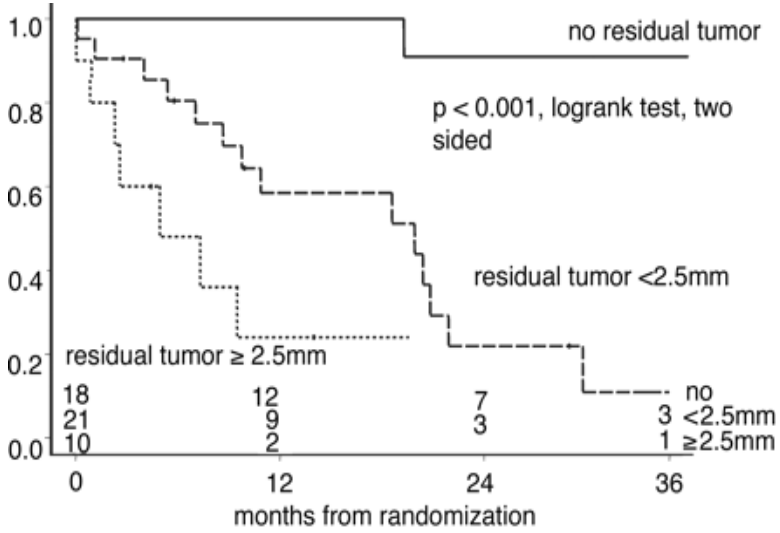
Harter P, et al. *Ann Surg Oncol.* 2009;16(5):1324-1330.

Randomized Study Surgery + HIPEC -> IV Versus IV-Therapy in Recurrent Colorectal Cancer (n = 105)

Cytoreduktive OP + HIPEC vs IV



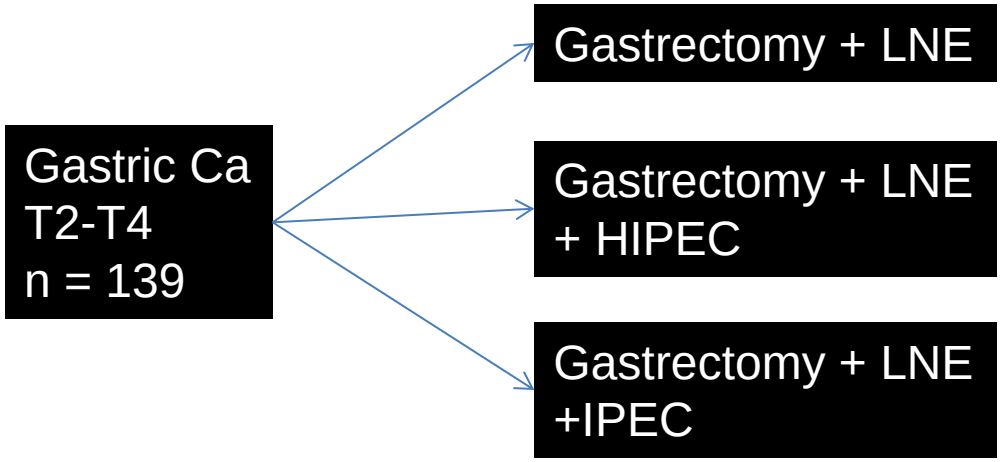
Prognostic Factor Residual Disease



- **Cytoreductive surgery + HIPEC -> IV better than IV/palliative management only**
- **Residual disease strongest prognostic factor (results caused by surgery, HIPEC, or both?)**
- **Morbidity: 54 % G3/4 toxicity (15% fistula); mortality: 8%**
- **1-year survival by IV only: 48%; 1-year survival HIPEC with residual tumor: 35% (if >2.5 mm only 20%)**
- **If complete resection is not possible, definitely no benefit from surgery + HIPEC**
- **Adverse effects from HIPEC?!**

Verwaal VJ, et al. *J Clin Oncol.* 2003;21(20): 3737-3743.

Primary Surgery Gastric Cancer



5-year survival: 42% (gastrectomy + LNE), 43% (+ IPEC), and 61% (+ HIPEC)

-> Only in an (unplanned?) subgroup analysis (Serosa+ and N+) was a statistically significant improvement found for HIPEC

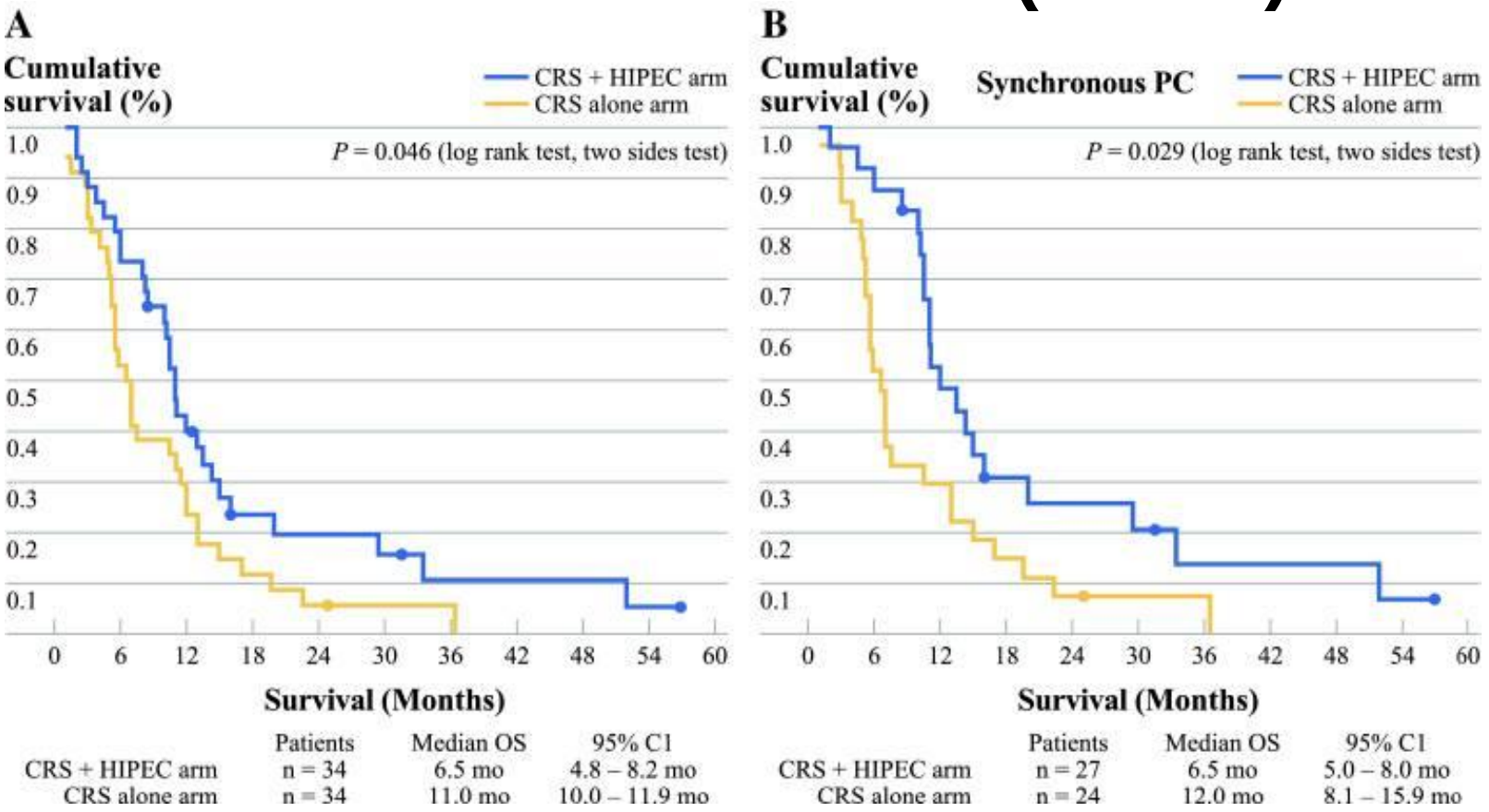
Yonemura Y, et al. *Hepatogastroenterology.* 2001;48(42):1776-1782.

Randomised Trial Surgery + HIPEC vs Surgery in Gastric Cancer With Peritoneal Metastases (n = 68)

- Single-center trial
- Includes primary and relapsed disesase
- Complete resection rate 58% in both arms
- Primary endpoint: Disease-specific survival

Yang XJ, et al. *Ann Surg Oncol.* 2011;18(6):1575-1581.

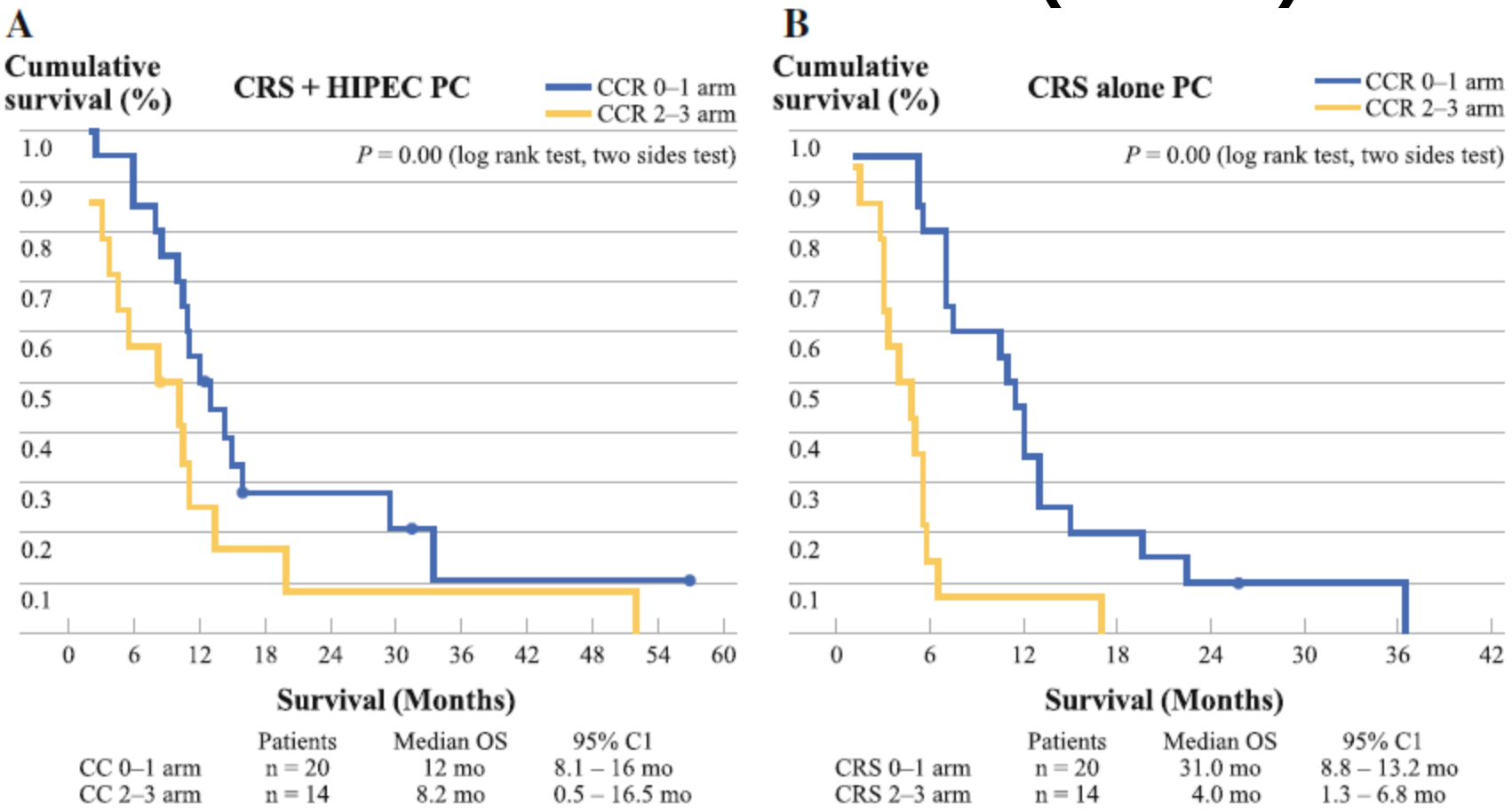
Randomised Trial Surgery + HIPEC vs Surgery in Gastric Cancer With Peritoneal Metastases (n = 68)



HIPEC improved DSS from 6.5 to 11 months in all pts and to 12 months in the subgroup of patients with synchronous peritoneal carcinomatosis

Yang XJ, et al. *Ann Surg Oncol.* 2011;18(6):1575-1581.

Randomised Trial Surgery + HIPEC vs Surgery in Gastric Cancer With Peritoneal Metastases (n = 68)



Patients with complete resection without HIPEC had best prognosis (Disesase-specific survival 31 months)

Yang XJ, et al. *Ann Surg Oncol.* 2011;18(6):1575-1581.

Randomised Trial Surgery + HIPEC vs Surgery in Gastric Cancer With Peritoneal Metastases (n = 68)

TABLE 2 Multivariate analysis on factors influencing survival

Covariate	χ^2	*P* value	Hazard ratio	95% CI
Sex (M vs. F)	0.099	0.753	1.101	0.605–2.002
Age (<60 years vs. ≥60 years)	0.638	0.425	1.275	0.702–2.317
PCI (low PCI vs. high PCI)	0.292	0.589	1.222	0.590–2.529
Treatment (CRS + HIPEC vs. CRS alone)	9.871	0.002	2.617	1.436–4.769
PC state (synchronous vs. metachronous)	5.438	0.02	2.228	1.136–4.367
CC (0–1 vs. 2–3)	8.585	0.003	2.794	1.405–5.556
Chemotherapy (≥6 vs. <6 cycles)	15.649	0	3.344	1.838–6.061
SAE (no vs. yes)	13.765	0	4.295	1.989–9.274

PCI Peritoneal carcinomatosis index, *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *PC* peritoneal carcinomatosis, *CC* completeness of cytoreduction, *SAE* serious adverse events

Most important prognostic factors:
Postoperative complications and systemic chemotherapy!

Yang XJ, et al. *Ann Surg Oncol.* 2011;18(6):1575-1581.

Randomised Trial Surgery + HIPEC vs Surgery in Gastric Cancer With Peritoneal Metastases (n = 68)

- Additional findings and remarks:
  - NCT00454519: this was another trial
  - Subgroup synchronous PC: *Ad hoc* analysis
    - Opposite result in metachronous subgroup
  - Why was the primary endpoint during (after?) the study changed to disease-specific survival?

    (= exclusion of postoperative fatal events!)
  - No data for OS
  - Systemic therapy after surgery not standardized

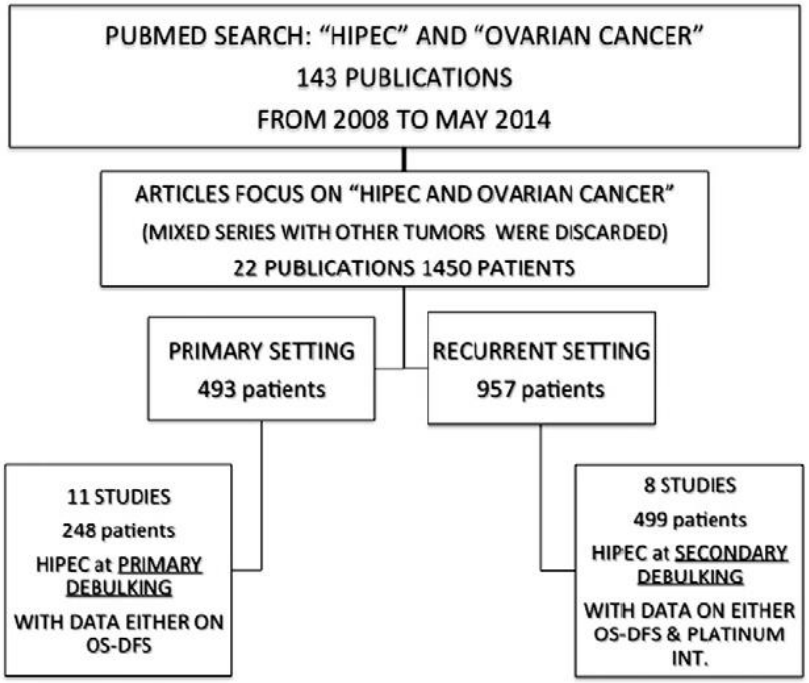
Is HIPEC a Promising New Treatment Option in Ovarian Cancer?

Limited evidence in colorectal and gastric cancer!

- except additional budget

Any evidence in ovarian cancer?

Systematic Review HIPEC in Ovarian Cancer



peutic regimens, time of administration, etc. This review has failed to show a clear survival benefit that justifies the use this technique as a standard daily practice. Therefore, it is our perspective that the currently available data regarding this approach is fractionated and very difficult to interpret. Thus, we believe that, based on the available information, neither gynecologic oncologists nor oncologic surgeons should offer this therapeutic approach to patients except in the context of a clinical

Chiva LM, et al. *Gynecol Oncol.* 2015;136(1):130-135.

Ann Surg Oncol (2012) 19:3998–4000
DOI 10.1245/s10434-012-2521-1

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SURGICAL ONCOLOGY
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EDITORIAL

The Role of Heated Intraperitoneal Chemotherapy (HIPEC) in Ovarian Cancer: Hope or Hoax?

Thomas J. Herzog, MD, FACS

been shown in myriad of phase I and phase II trials. It is time for randomized phase III trials with tightly defined populations to elucidate if there is added benefit and in which patients. Table 1 shows current trials that meet at least the criteria of randomization.[6] Our ovarian cancer patients deserve to know the relative benefits and risks of this interesting but unproven treatment modality.

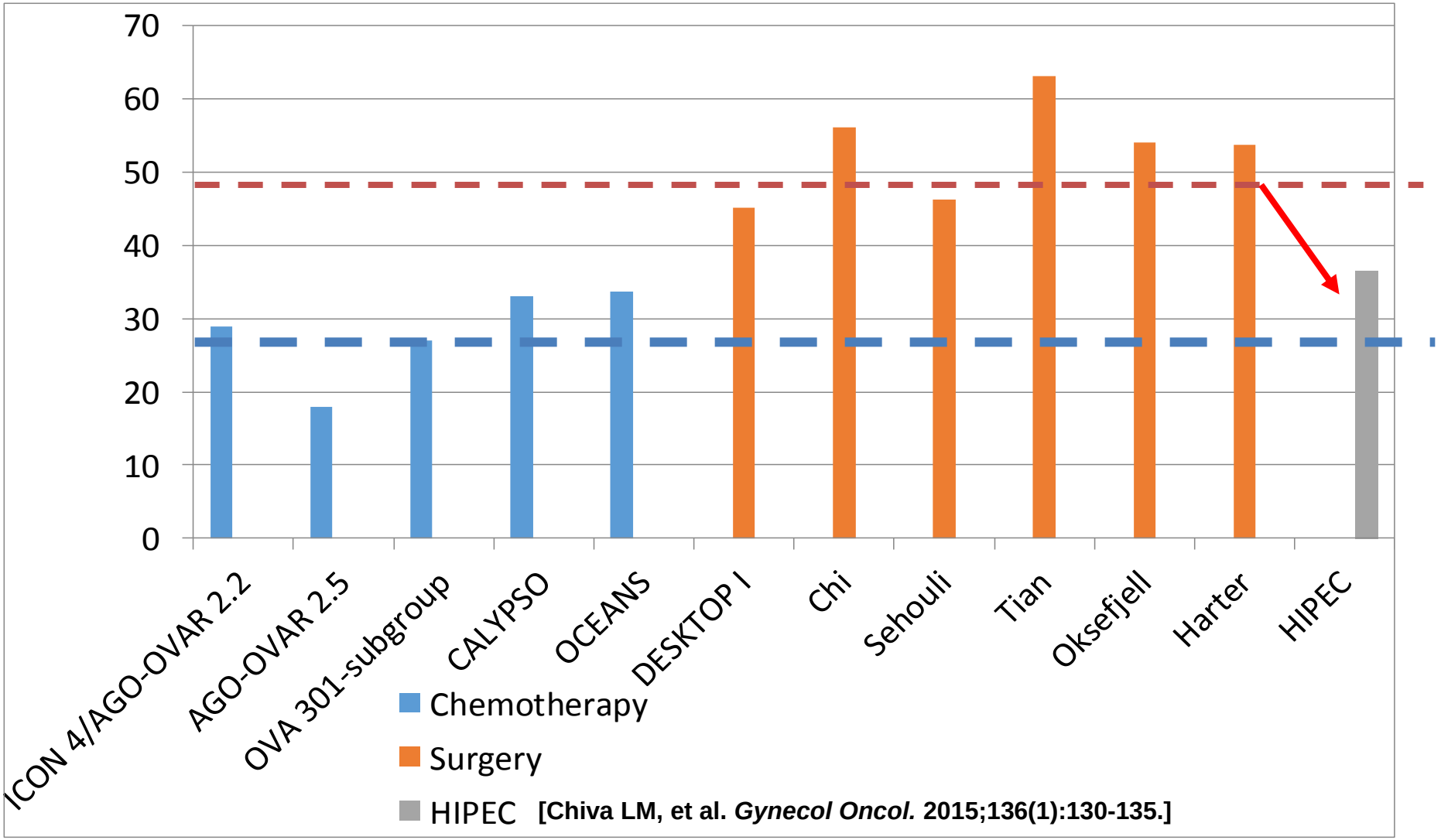
Herzog TJ. *Ann Surg Oncol.* 2012;19(1):3998-4000.

Statement by the Kommission OVAR on the Use of HIPEC to Treat Primary and Recurrent and Recurrent Ovarian Cancer

tals. Altogether, there is still no evidence that HIPEC leads to an improvement of prognosis in any gynecologic tumor, neither in primary therapy nor in treatment of relapse. The available data indicate an increased complication rate which might negatively impact the benefit-risk balance of this procedure. In addition, standard treatment with proven efficacy might be withheld due to application of unproven methods. The use of HIPEC outside of well designed, prospective and controlled clinical trials is therefore disregarded.

Harter P, et al. *Geburtshilfe Frauenheilkd.* 2013;73(3): 221-223.

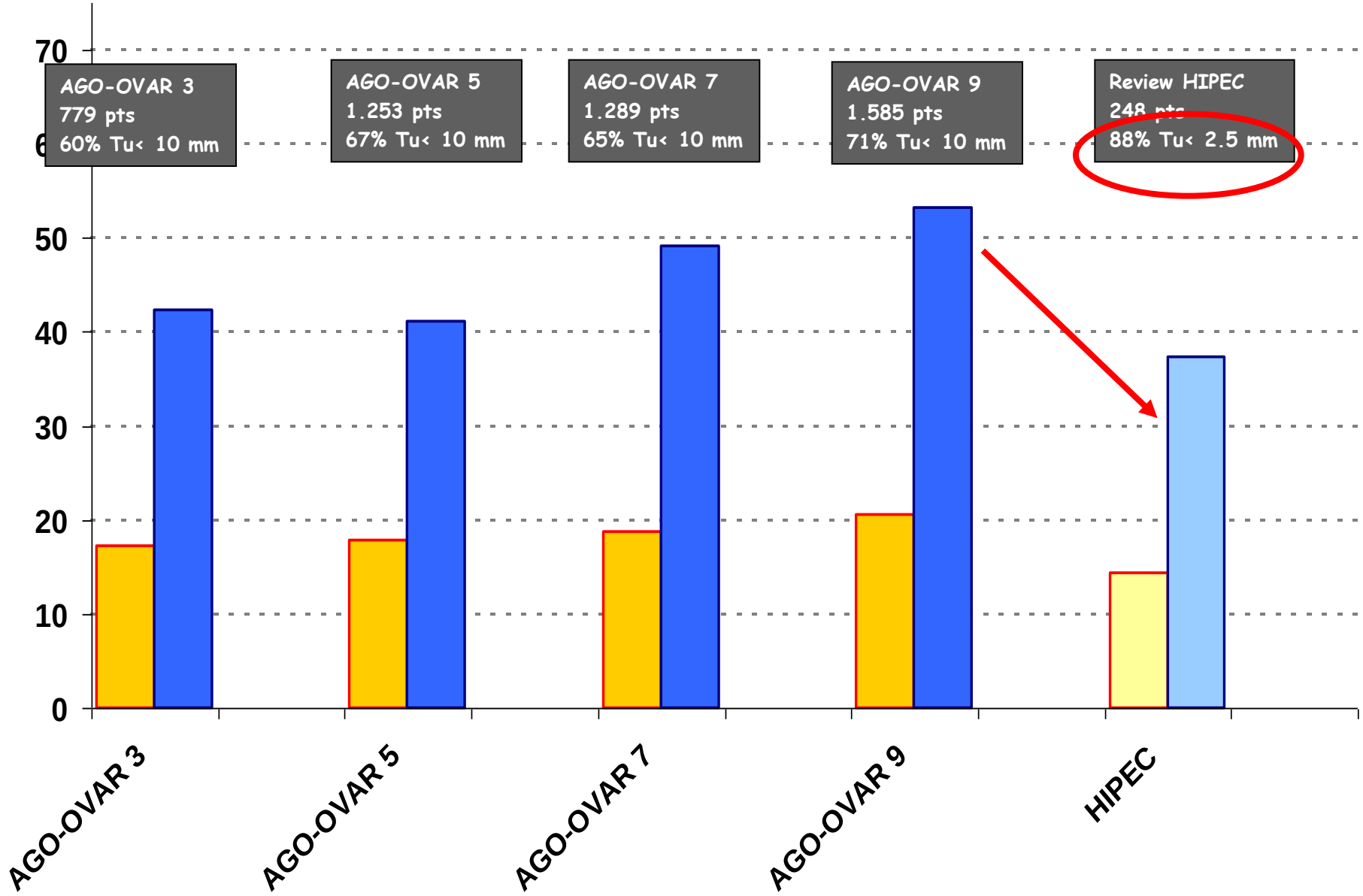
Randomized Chemotherapy Phase III Trials, Surgical Series (Platinum Sensitive) OS of Superior Arm/OS in Optimal Debulking



[Chiva LM, et al. *Gynecol Oncol.* 2015;136(1):130-135.]

PFS (median; months)
OS (median; months)

after primary debulking surgery compared to HIPEC series



Chiva LM, et al. *Gynecol Oncol.* 2015;136(1):130-135.

Ann Surg Oncol
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ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

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

J. Spiliotis, MD, PhD[1], E. Halkia, MD, PhD[1,2], E. Lianos, MD[3], N. Kalantzi, MD[4], A. Grivas, MD[3], E. Efstathiou, MD[1], and S. Giassas, MD[2]

- N = 120 patients with relapsed stage IIIC or IV disease
- Primary endpoint: Mean OS – at least unusual
- Inclusion criteria:
  - GOG performance status 0 or 1
  - not more than three sites of bowel obstruction
  - no evidence of disease beyond the abdomen
  - no splanchnic metastasis
  - no bulky disease in retroperitoneal area or on the mesentery

Spiliotis J, et al. *Ann Surg Oncol.* 2014 Nov 13 [Epub ahead of print].

Image not available

Randomized Trial Surgery + HIPEC vs Surgery in Ovarian Cancer (n = 120)

- Additional findings and remarks:
  - In manuscript not mentioned if this study was registered (and I could not find it in any database)
  - Report about statistics at a very low level
  - Who has reviewed this paper before publication?

This trial does not add any meaningful evidence for our daily work

Conclusions

-  **Standard of care in treatment of patients with recurrent ovarian cancer is systemic treatment**
-  **Additional cytoreductive surgery might be an option in selected patients (DESKTOP III, GOG 213)**
- 

immediately wasting resources with low quality trials
- 

performing HIPEC outside of randomized controlled trials!
- 

planning another HIPEC trial (> 6 are already ongoing)!
-  **consider interrupt ing your ongoing HIPEC trial for an interim analysis!**

2015

Progress and Controversies in Gynecologic Oncology Conference