City of Hope

THIRD ANNUAL

ISSPP Congress 2022

International Society for the Study of Pleura and Peritoneum

THE NEXT GREAT DEBATE

Is There a Role of HIPEC in Ovarian Cancer? (CON)

Christina Fotopoulou, MD, PhD
Chair in Gynaecological Cancer Surgery
Department of Surgery and Cancer
Faculty of Medicine
Imperial College London, UK

Or else: "HIPEC: HOPE or HYPE in the fight against advanced ovarian cancer

Fotopoulou, Sehouli, Mahner, Harter, van Nieuwenhuysen, Gonzalez-Martin, Vergote, Chiva, du Bois. Annals of Oncology 2018, 2018 Aug 1;29(8):1610-1613.

Disclosures

- Consultant for AstraZeneca, Ethicon, GlaxoSmithKline, MSD, Roche, and Tesaro.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their products and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

HIPEC not recognized –yet- as standard of care

Gynaecological Cancers 1 www.thelancet.com/oncology Vol 23 August 2022

Clinical research in ovarian cancer: consensus recommendations from the Gynecologic Cancer InterGroup

*Ignace Vergote, Antonio Gonzalez-Martin, Domenica Lorusso, Charlie Gourley, Mansoor Raza Mirza, Jean-Emmanuel Kurtz, Aikou Okamoto, Kathleen Moore, Frédéric Kridelka, Iain McNeish, Alexander Reuss, Bénédicte Votan, Andreas du Bois, Sven Mahner, Isabelle Ray-Coquard, Elise C Kohn, Jonathan S Berek, David S P Tan, Nicoletta Colombo, Rongyu Zang, Nicole Concin, Dearbhaile O'Donnell, Alejandro Rauh-Hain, C Simon Herrington, Christian Marth, Andres Poveda, Keiichi Fujiwara, Gavin C E Stuart, Amit M Oza, Michael A Bookman, on behalf of the participants of the 6th Gynecologic Cancer InterGroup (GCIG) Ovarian Cancer Consensus Conference on Clinical Research**

Statement 5

Intraperitoneal chemotherapy and HIPEC (30 of 33 groups approved, two opposed‡, one abstained)

1 Any form of intraperitoneal therapy or HIPEC cannot be regarded as a reference treatment within clinical trials

- ✓ Statement 5 on intraperitoneal therapy and hyperthermic intraperitoneal chemotherapy (HIPEC) was much debated with an approval rate of only 30 out of 33 GCIG groups (two groups opposing and one abstaining).
- ✓ It should be highlighted that this statement is not about standard of care, but about accepting intraperitoneal therapy and HIPEC as reference treatment groups within clinical trials.

2022

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Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1		Recruiting	**HIPEC** for Platinum-Resistant Recurrent **Ovarian Cancer**	• Epithelial **Ovarian Cancer**	• Procedure: **HIPEC**	• Myong Cheol Lim Goyang-si, Gyeonggi-do, Korea, Republic of
2		Completed	Short-course **HIPEC** in Advanced Epithelial **Ovarian Cancer**	• **Ovarian Cancer**	• Procedure: Cytoreductive Surgery (CRS) • Procedure: **Hyperthermic Intraperitoneal Chemotherapy**	

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Status

Recruitment :

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- Active, not recruiting
- Suspended

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1		Completed	**HIPEC** in **Ovarian Cancer**, Case-Controls Study With 10-years Follow up	• **Ovarian Cancer** • **HIPEC**	• Procedure: cytoreduction and HIPEC	
2		Recruiting	Comparative Effectiveness of **HIPEC** Following Interval Debulking Surgery in Patients With Advanced-stage **Ovarian Cancer**	• **Ovarian Cancer**	• Procedure: HIPEC	• Ajou University Hospital Suwon, Gyeonggi, Korea, Republic of
3		Active, not recruiting	Short-course **HIPEC** in Advanced Epithelial **Ovarian Cancer**	• **Ovarian Cancer**	• Procedure: Cytoreductive Surgery (CRS) • Procedure:	

Ann Surg Oncol (2015) 22:1570–1575
DOI 10.1245/s10434-014-4157-9

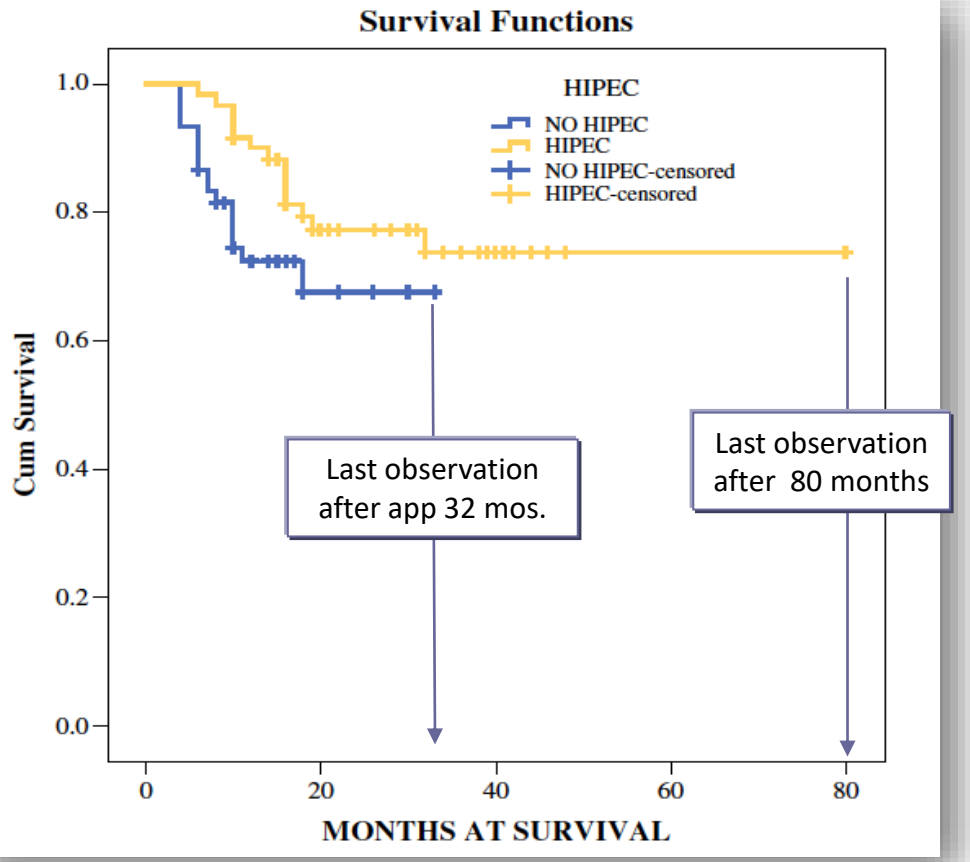
Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOL

ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

(2015)

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. Efsta
MD[1], and S. Giassas, MD[2]



BRIEF REPORT

Brief Report About the Role of Hyperthermic Intraperitoneal Chemotherapy in a Prospective Randomized Phase 3 Study in Recurrent Ovarian Cancer From Spiliotis et al

Philipp Harter, MD, PhD, Alexander Reuss, MSc,† Jalid Sehouli, MD, PhD,‡ Luis Chiva, MD, PhD,§ and Andreas du Bois, MD, PhD**

Ann Surg Oncol (2017) 24:S631
https://doi.org/10.1245/s10434-017-6129-3

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SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

LETTER – GYNECOLOGIC ONCOLOGY

Survival Analysis in a Randomized Trial of HIPEC in Ovarian Cancer

Álvaro Sanz Rubiales, MD, PhD[1] and María Luisa del Valle, MD, PhD[2]

Ann Surg Oncol (2017) 24:S630
https://doi.org/10.1245/s10434-017-6151-5

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LETTER – GYNECOLOGIC ONCOLOGY

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

Thales Paulo Batista, MD, MS[1,2]

The NEW ENGLAND JOURNAL of MEDICINE

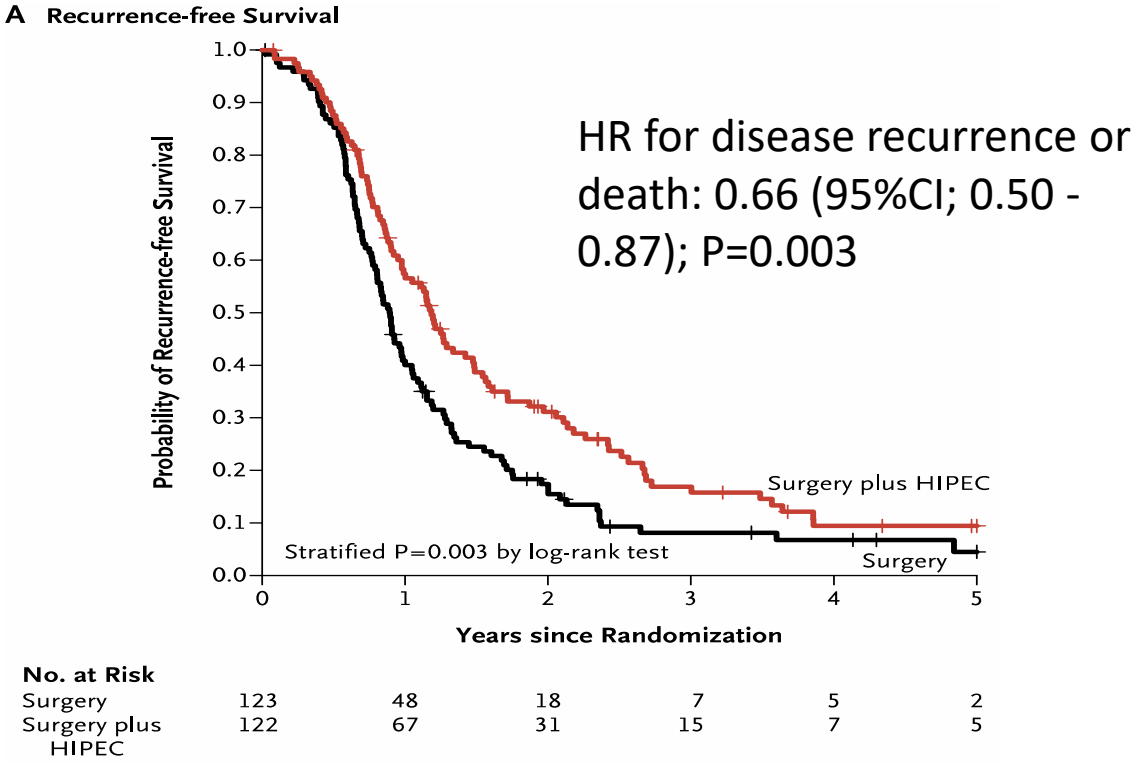
The first valid RCT for HIPEC in ov ca

ORIGINAL ARTICLE

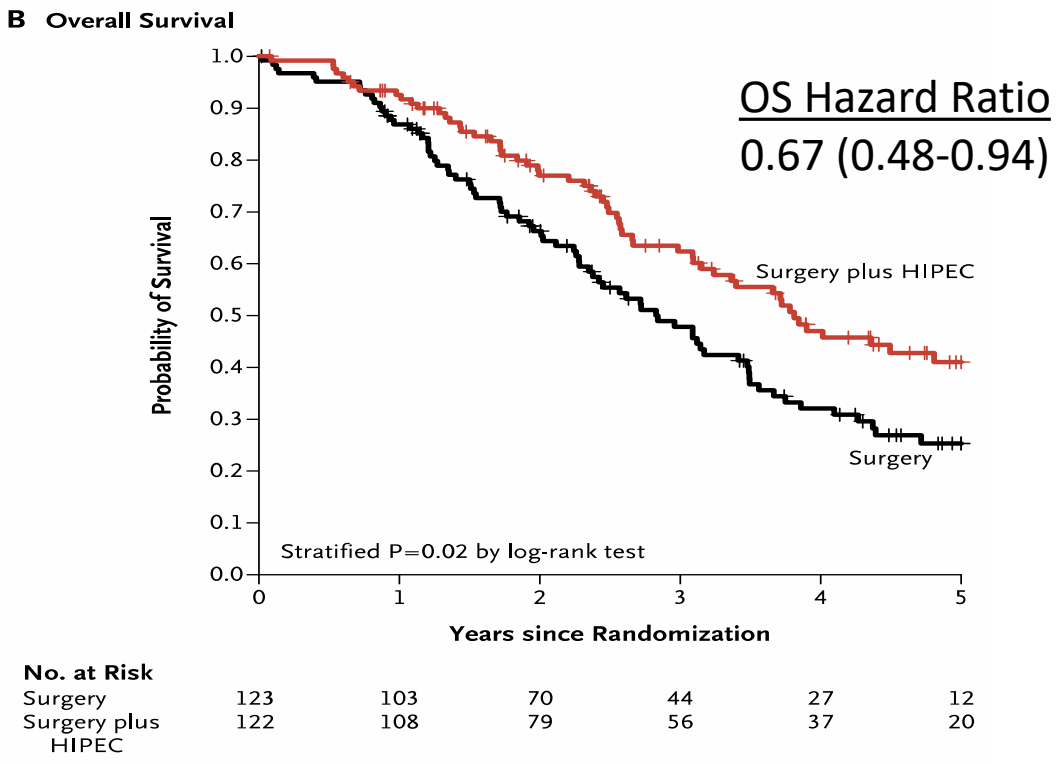
Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

W.J. van Driel, S.N. Koole, K. Sikorska, J.H. Schagen van Leeuwen, H.W.R. Schreuder, R.H.M. Hermans, I.H.J.T. de Hingh, J. van der Velden, H.J. Arts, L.F.A.G. Massuger, A.G.J. Aalbers, V.J. Verwaal, J.M. Kieffer, K.K. Van de Vijver, H. van Tinteren, N.K. Aaronson, and G.S. Sonke

2018, 276 patients

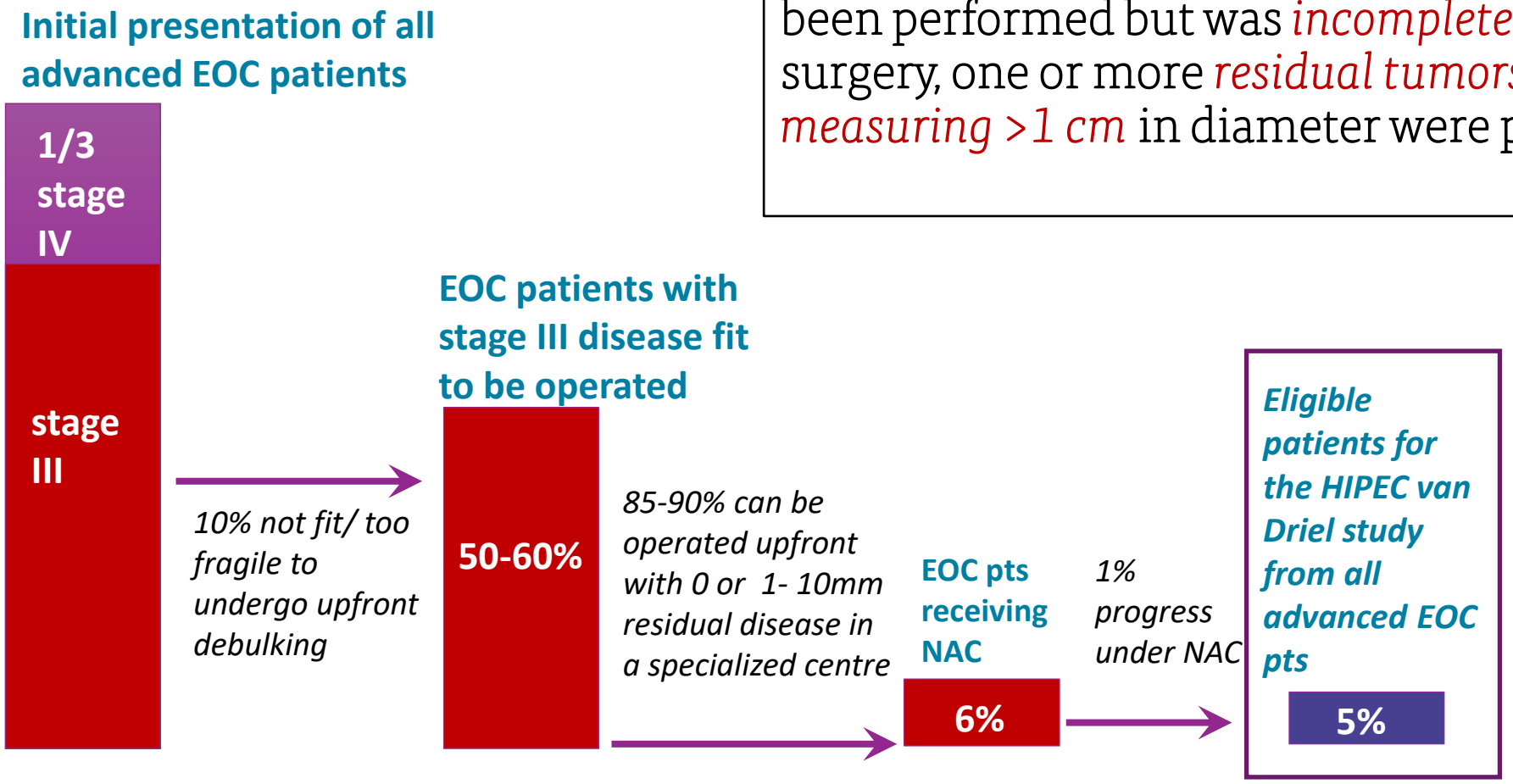


HR for disease recurrence or death: 0.66 (95%CI; 0.50 - 0.87); P=0.003



OS Hazard Ratio
0.67 (0.48-0.94)

Eligibility criteria of the van Driel study: "Newly diagnosed stage III OvCa that were referred for NAC because their abdominal disease was *too extensive for primary cytoreductive surgery* or because surgery had been performed but was *incomplete* (i.e., after surgery, one or more *residual tumors measuring >1 cm* in diameter were present)".



Heitz et.al. Gynecol Oncol 2016; Kehoe et.al. Lancet 2015

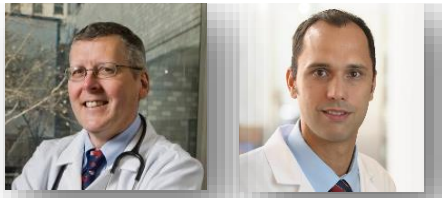
How do the HIPEC trial patients compare to other upfront trials or NACT trials?

Studies: AGO – NACT – HIPEC	PFS median mos	OS median mos
AGO-OVAR 3	17.2	42.3
AGO-OVAR 5	17.9	41.1
AGO-OVAR 7	18.8	49.1
AGO-OVAR 9	20.5	53.2
AGO-LION	25.5	69.2
EORTC NACT	12	30
CHORUS NACT	12	24
NACT- control arm- non-HIPEC*	11 worst ever	34
Dutch NACT HIPEC*	14	45

* only stage FIGO III (no FIGO IV) !!!

by du Bois, A, Harter P.

The NEW ENGLAND JOURNAL of MEDICINE



From Memorial Sloan Kettering Cancer Center, New York.

EDITORIAL

Ovarian Cancer Treatment — Are We Getting Warmer?

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

N Engl J Med 2018; 378:293-294 | January 18, 2018 | DOI: 10.1056/NEJMe1714556

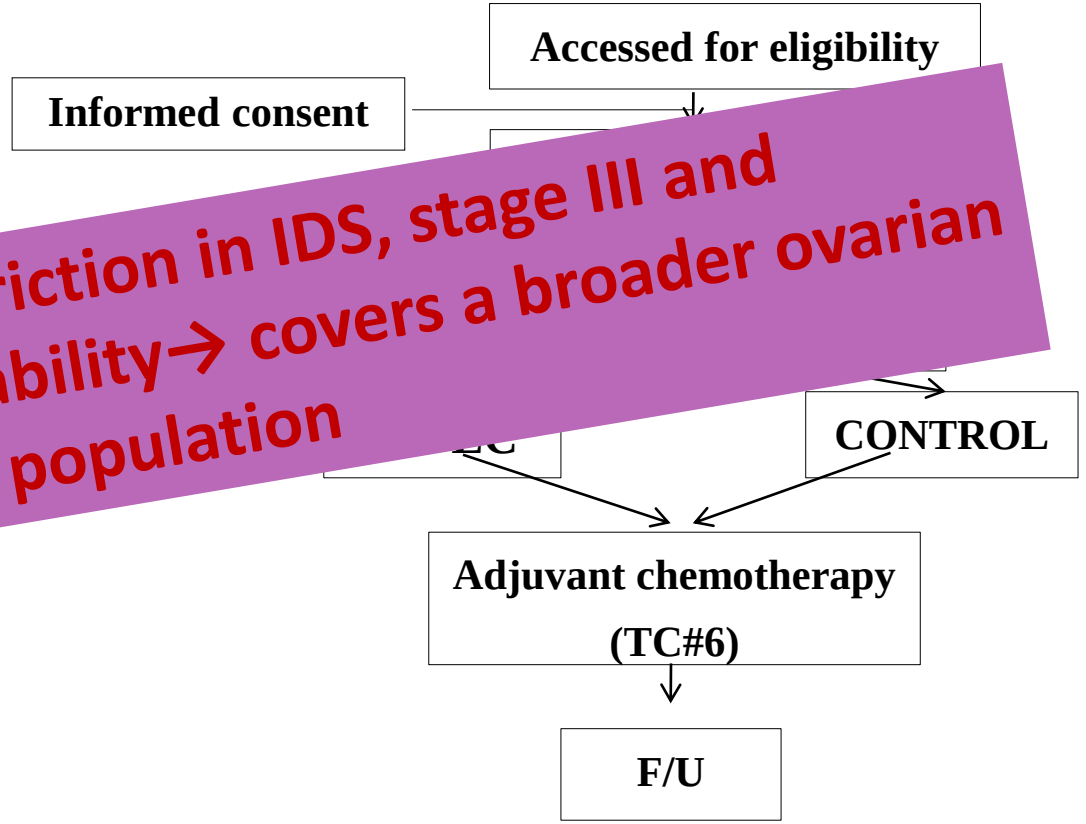
"This res *on to date* *that*
a single a *ion of ovarian*
cancer m *ents with*
cancer"

…but: "we need to exercise a high degree of caution not to extrapolate to all EOC-patients positive data from a study that applies to only a rather small sub-cohort of EOC-patients that has significant pitfalls"

… so is it perhaps about asking the right question?

Hyperthermic intraperitoneal chemotherapy (HIPEC) in women with primary advanced peritoneal, ovarian, and tubal cancer: a multicenter randomized controlled trial *(NCT01091636)*

- 5L N/S + cisplatin 75 mg/m^2
- 42-43^{o}C
- 90 min
- Closed method



No restriction in IDS, stage III and inoperability→ covers a broader ovarian cancer population

Lim and Bristow, ASCO 2017

JAMA Surgery | Original Investigation

Survival After Hyperthermic Intraperitoneal Chemotherapy and Primary or Interval Cytoreductive Surgery in Ovarian Cancer
A Randomized Clinical Trial

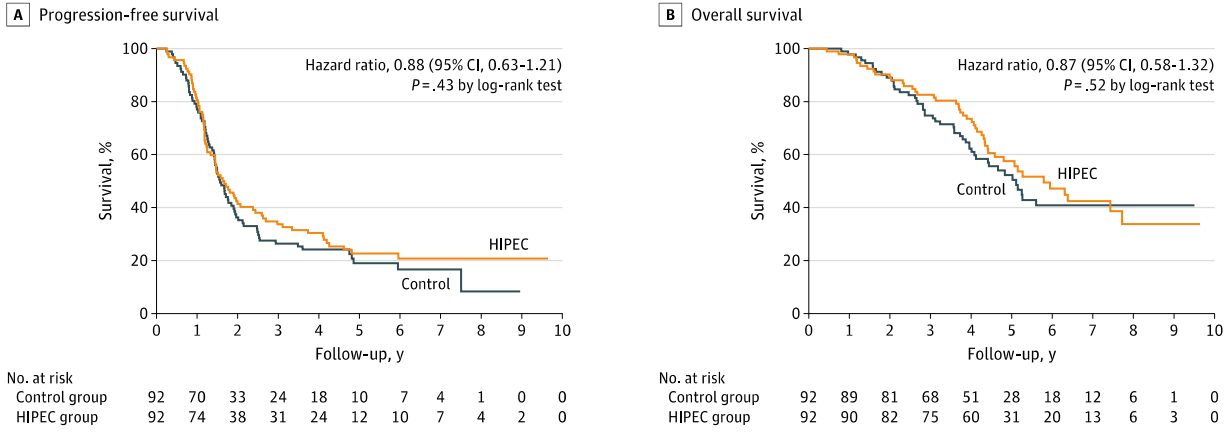
Myong Cheol Lim, MD, PhD; Suk-Joon Chang, MD, PhD; Boram Park, PhD; Heon Jong Yoo, MD, PhD; Chong Woo Yoo, MD, PhD; Byung Ho Nam, PhD; Sang-Yoon Park, MD, PhD; for the HIPEC for Ovarian Cancer Collaborators

2022

CONCLUSIONS AND RELEVANCE The addition of HIPEC to cytoreductive surgery did not improve progression-free and overall survival in patients with advanced epithelial ovarian cancer. Although the results are from a subgroup analysis, the addition of HIPEC to interval cytoreductive surgery provided an improvement of progression-free and overall survival.

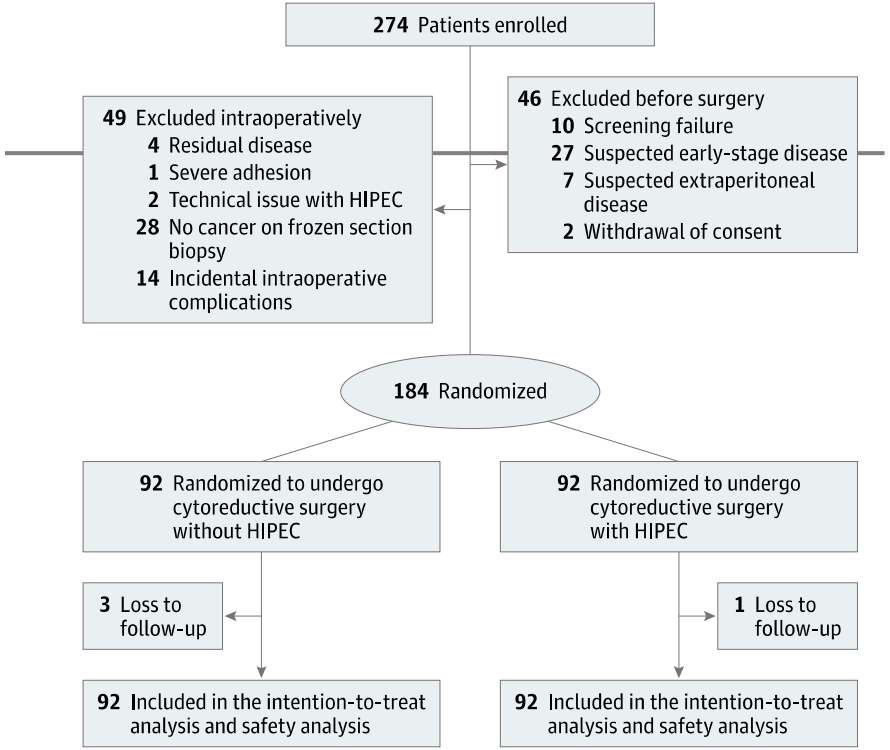
TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01091636

Figure 2. Kaplan-Meier Estimates of Progression-Free Survival and Overall Survival as Preplanned Intention to Treat



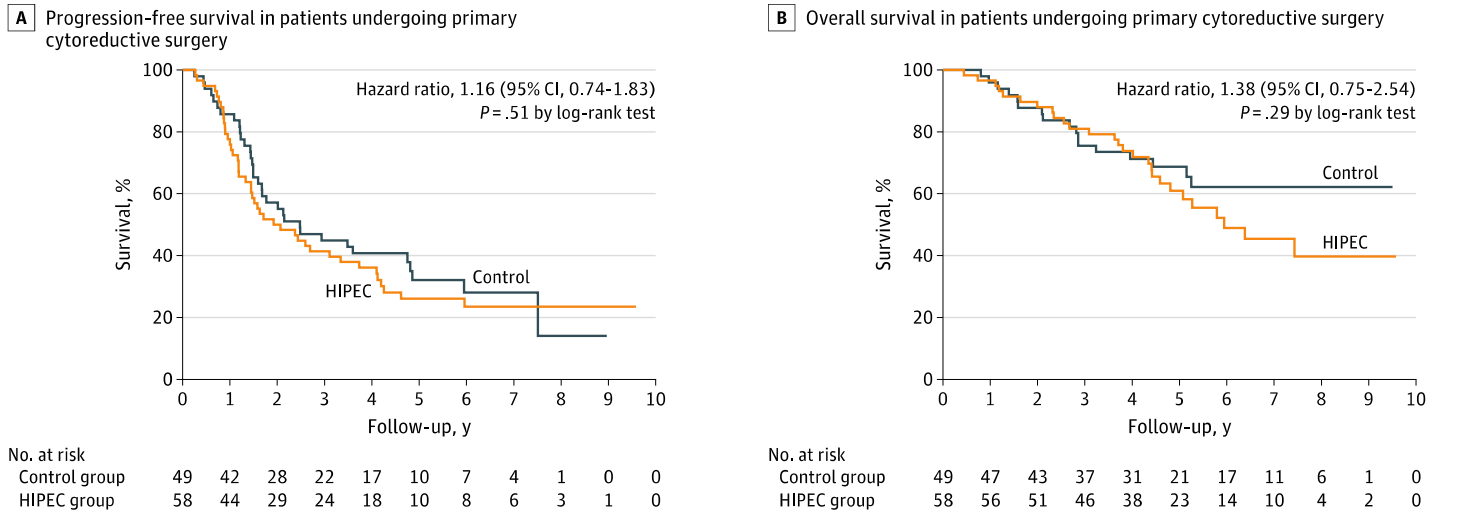
A, Events of progression or death were observed in 74 patients (80.4%) in the control group and in 71 patients (77.2%) in the hyperthermic intraperitoneal chemotherapy (HIPEC) group. The Kaplan-Meier estimate of patients who were without progression and alive at 24 months was 36.3% in the control group and 41.3% in the HIPEC group. B, A total of 47 patients (51.1%) in the surgery group and 45 (48.9%) patients in the HIPEC group died. The Kaplan-Meier estimate of patients who were alive at 60 months was 52.3% in the control group and 57.5% in the HIPEC group.

Figure 1. Flowchart of Enrollment and Randomization



HIPEC indicates hyperthermic intraperitoneal chemotherapy.

Figure 3. Kaplan-Meier Estimates of Progression-Free Survival and Overall Survival According to the Primary Treatment as Preplanned Intention to Treat



Among the patients undergoing primary cytoreductive surgery prespecified subgroup analysis, the Kaplan-Meier estimate of patients who were free of progression and death at 24 months was 57.1% in the control group and 50% in the hyperthermic intraperitoneal chemotherapy (HIPEC) group (A), and the Kaplan-Meier estimate of patients who were alive at 60 months was 68.7% in the control group and 61% in the HIPEC group (B). Among the patients undergoing interval cytoreductive surgery after neoadjuvant chemotherapy prespecified subgroup analysis, the Kaplan-Meier estimate of patients who were free of progression and death at 24 months was 11.9% in the control group and 26.5% in the HIPEC group (C), and the Kaplan-Meier estimate of patients who were alive at 60 months was 32.2% in the control group and 52% in the HIPEC group (D).

CONCLUSIONS AND RELEVANCE

The addition of HIPEC to cytoreductive surgery did not improve progression-free and overall survival in patients with advanced epithelial ovarian cancer.

Although the results are from a subgroup analysis, the addition of HIPEC to interval cytoreductive surgery provided an improvement of progression-free and overall survival.

Lim et.al. JAMA Surg 2022

Is perhaps HIPEC used as a tool to compensate for insufficient cytoreduction - again-?

Secondary Cytoreduction and Carboplatin Hyperthermic Intraperitoneal Chemotherapy for Platinum-Sensitive Recurrent Ovarian Cancer: An MSK Team Ovary Phase II Study

Oliver Zivanovic, MD[1]; Dennis S. Chi, MD[1]; Qin Zhou, MS[1]; Alexia Iasonos, PhD[1]; Jason A. Konner, MD[1]; Vicky Makker, MD[1]; Rachel N. Grisham, MD[1]; Amy K. Brown, MD[2]; Stacy Nerenstone, MD[2]; John P. Diaz, MD[3]; Eric D. Schroeder, MD[3]; Carrie L. Langstraat, MD[4]; Viktoriya Paroder, MD[1]; Yulia Lakhman, MD[1]; Krysten Soldan, RN[1]; Katy Su, MS[1]; Ginger J. Gardner, MD[1]; Vaagn Andikyan, MD[1]; Jianxia Guo, MD[5]; Elizabeth L. Jewell, MD[1]; Kara Long Roche, MD[1]; Tiffany Troso-Sandoval, MD[1]; Stuart M. Lichtman, MD[1]; Lea A. Moukarzel, MD[1]; Kimberly Dessources, MD[1]; Nadeem R. Abu-Rustum, MD[1]; Carol Aghajanian, MD[1]; William P. Tew, MD[1]; Jan Beumer, MD[5]; Yukio Sonoda, MD[1]; and Roisin E. O'Cearbhaill, MD[1]

SCS ***without*** neoadjuvant chemotherapy

CONCLUSION

HIPEC with carboplatin was well tolerated but did not result in superior clinical outcomes. This study does not support the use of HIPEC with carboplatin during secondary cytoreductive surgery for platinum- sensitive recurrent ovarian cancer.

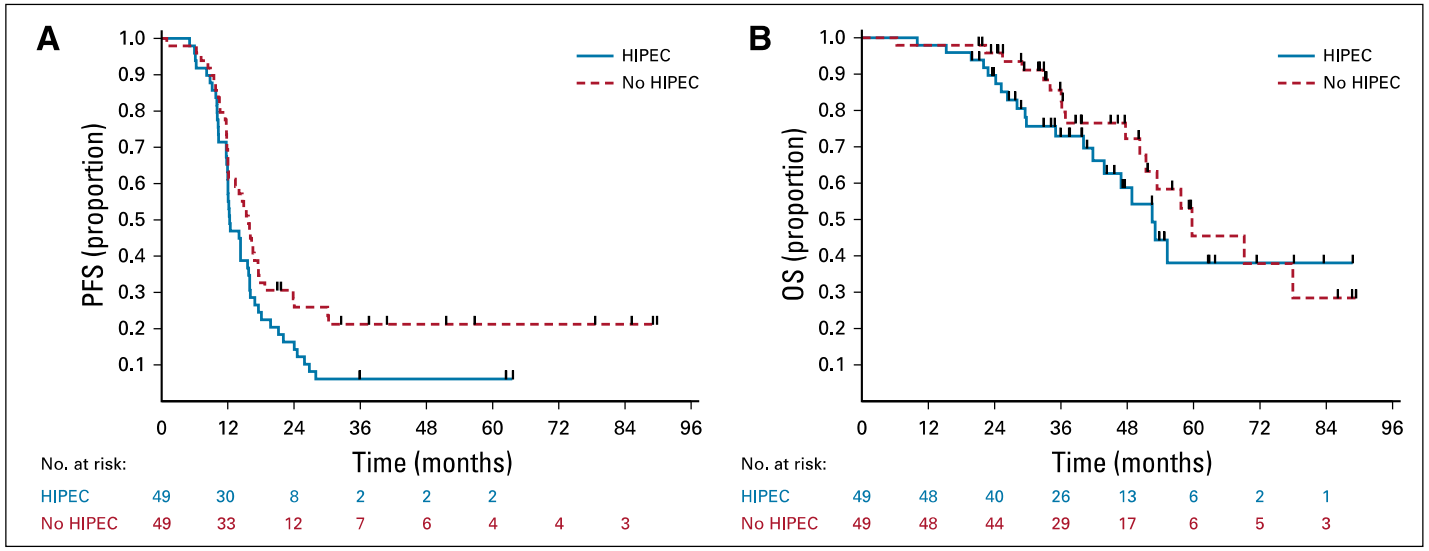


FIG 3. (A) PFS by treatment arm. Kaplan-Meier survival plots of PFS. (B) OS by treatment arm. Kaplan-Meier survival plots of OS. HIPEC, hyperthermic intraperitoneal chemotherapy; OS, overall survival; PFS, progression-free survival.

Variable	HIPEC Arm (n = 49)	Standard Arm (n = 49)	*P*
Operative time, minutes, (range)	475 (235-813)	296 (83-678)	< .001
Estimated blood loss, mL, (range)	402 (30-1,550)	340 (50-1,550)	.2
Bowel resection, No. (%)	18 (37)	32 (65)	.008
Complete gross resection, No. (%)	40 (82)	46 (94)	.12
≥ Grade 3 complications, No. (%)	12 (24)	10 (20)	.81
Length of inpatient stay, days, (range)	6 (1-26)	5 (2-22)	.05

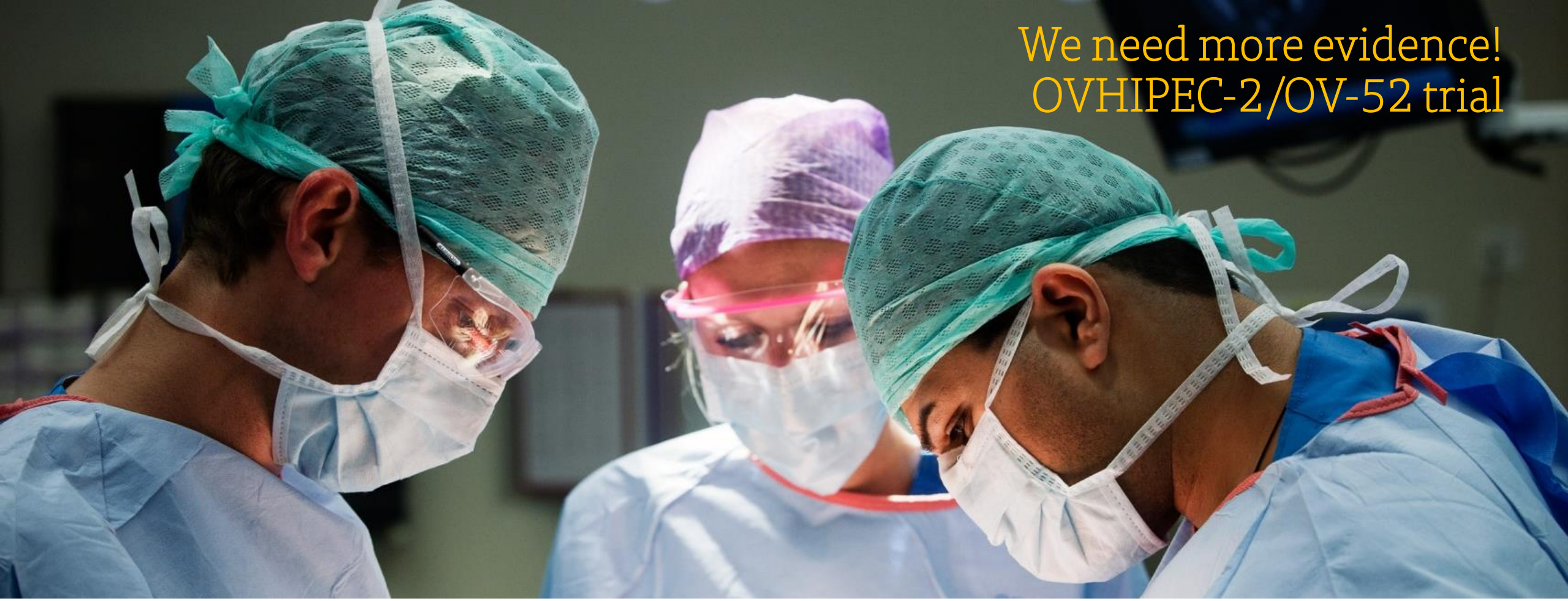
So: HYPE or HOPE?

- It seems that HIPEC is not beneficial for patients without recent chemotherapy exposure
- 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 PS how can they tolerate extra exposure to HIPEC?
- TRUST study and further studies

2018 ASCO: Hyperthermic Intraperitoneal Chemotherapy Does Not Add Benefit in Patients With Advanced Colorectal Cancer

- ✓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.**

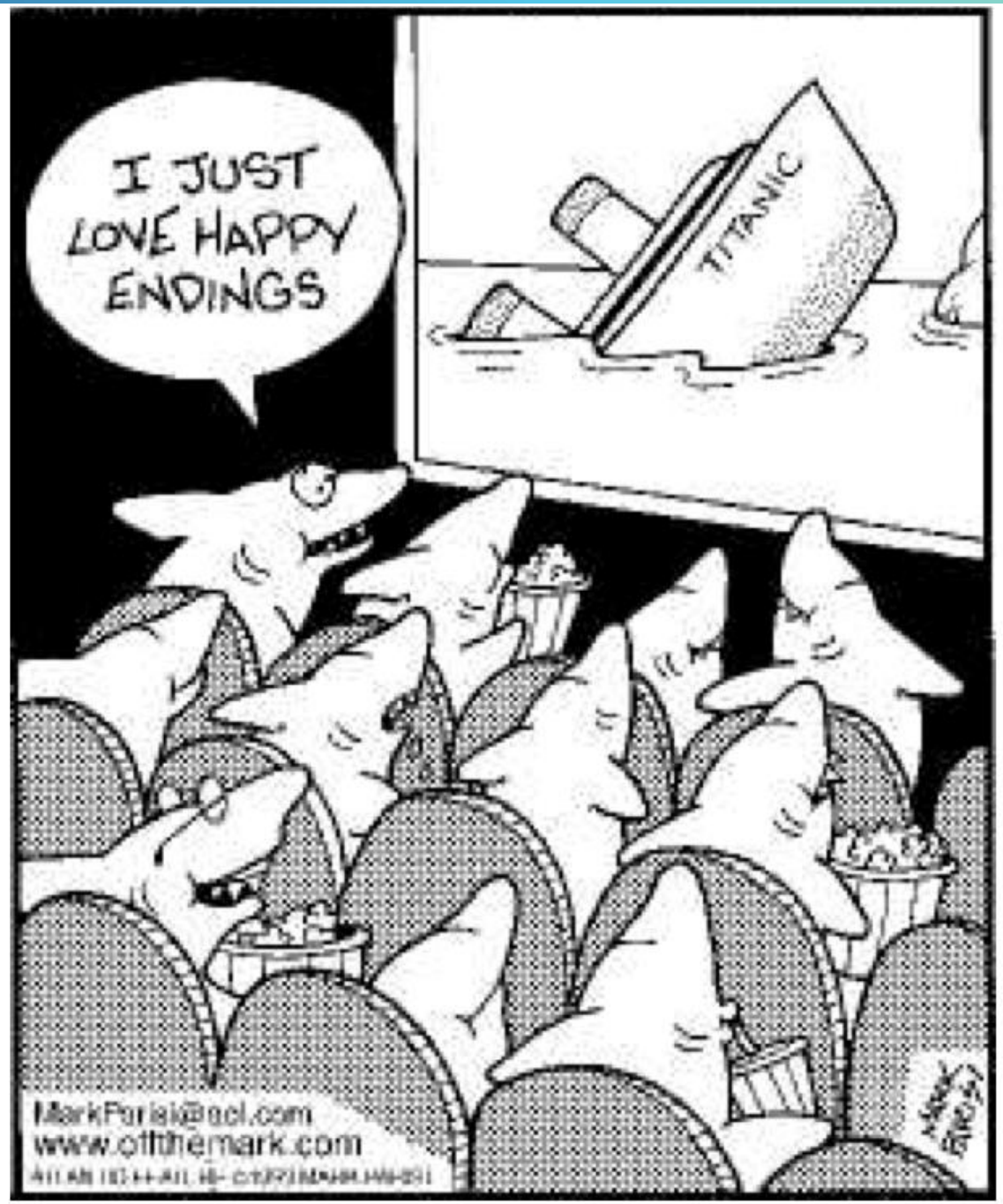
Quénet et al. Lancet Oncol 2021



We need more evidence!
OVHIPEC-2/OV-52 trial

Aim: To determine the beneficial effect of **primary cytoreductive surgery** in combination with HIPEC (treatment arm) compared to primary CRS without HIPEC (standard arm), in patients with FIGO stage III ovarian cancer, in whom **primary cytoreductive surgery resulting in no residual disease, or residual disease up to 2.5 mm, is reached**

ANTONI VAN LEEUWENHOEK
NEDERLANDS KANKER INSTITUUT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