HIPEC for ovarian cancer: HYPE or HOPE?

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Imperial College London
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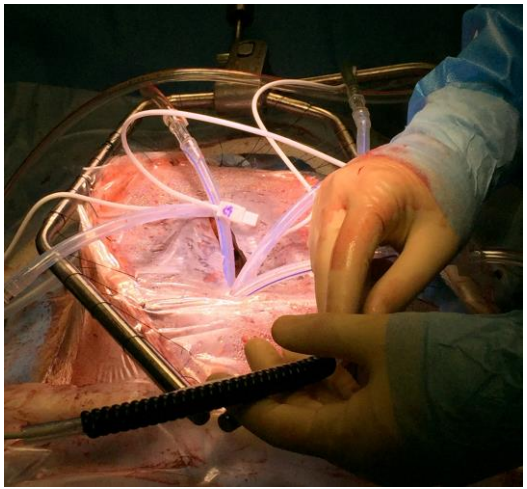

Faculty Disclosure

	No, nothing to disclose
x	Yes, please specify:

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Radical treatments for gynaecological cancers: HOPE or HYPE?

Editorial

Annals of Oncology

C. Fotopoulou[1,2,3,4*], J. Sehouli[2,3,4], S. Mahner[4,5], P. Harter[4,6], E. Van Nieuwenhuysen[7,8], A. Gonzalez-Martin[9,10], I. Vergote[7,8], L. Chiva[10,11] & A. Du Bois[4,6]

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

patients to strive a combined maximal surgical effort with HIPEC in all settings of the disease, we agree with the authors of the editorial accompanying the original article [14], that we need to ex-

doi:10.1093/annonc/mdy198
Published online 4 June 2018

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

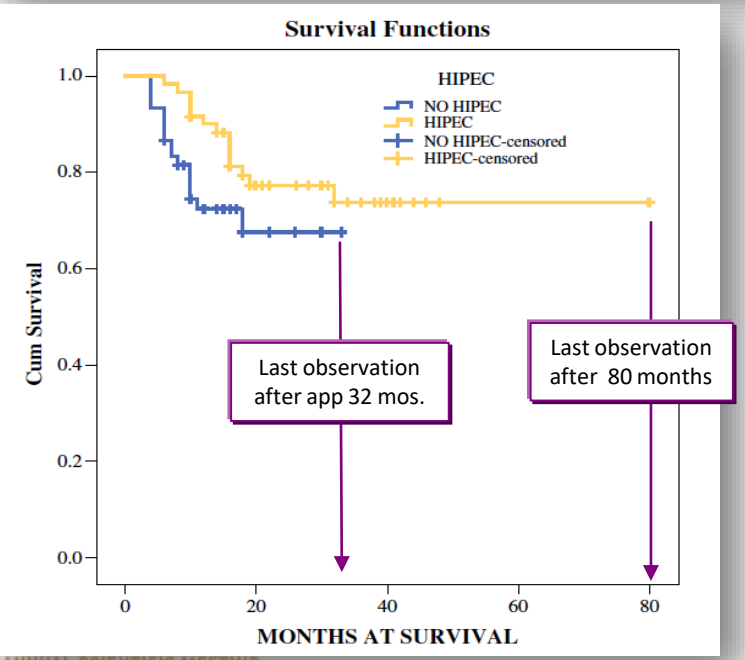
Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOL

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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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]

A valid study?

1. Inhomogenous patients cohort with impalanced characteristics: platinum resistant/ sensitive
2. No definition of statistical endpoints
3. Different length of observation periods in arms and parallel non-randomized trial in same centre?
4. Two external reviewers have shown no differences after extracting HRs by two different methods.
5. "No info at all on PFI.
6. No info on complications, on chemo etc.
7. No CONSORT, no registration of trial (EudraCT or NCT trials.gov.com o.a.)
8. No reply of the authors to numerous objections

By Harter P.

…. and finally

N Engl J Med 2018;378:230-40.
DOI: 10.1056/NEJMoa1708618

The NEW ENGLAND JOURNAL of MEDICINE

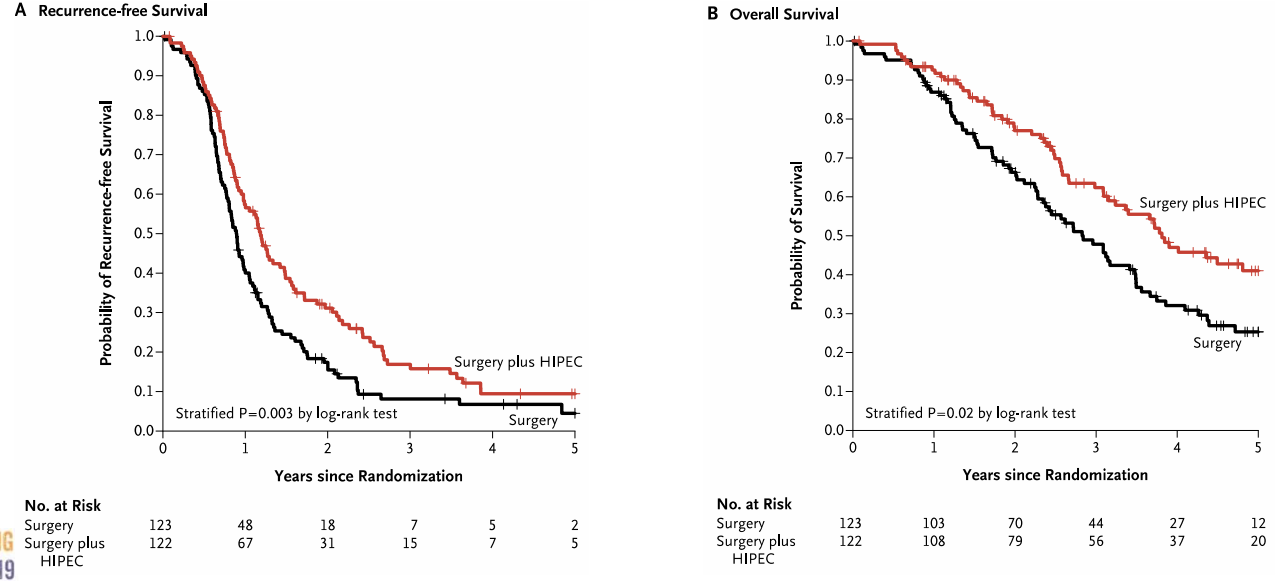
ORIGINAL ARTICLE

Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

276 patients

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

HR ratio for disease recurrence or death= **0.66;** 95% CI, 0.50 - 0.87; P=0.003

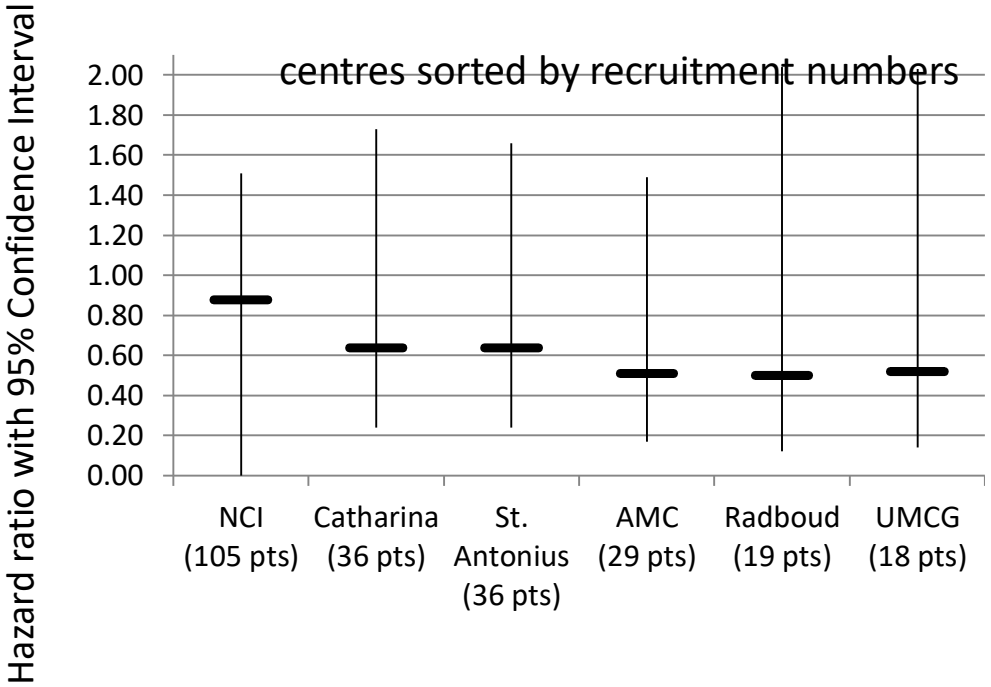


Limitations of the study

- The authors did not stratify for important prognosticators such as:
- ✓ BRCA-status
- ✓ histologic subtype
- Failure to report on other significant outcome measures such as rates of complete and partial response and details of surgical procedures
- No definition of the criteria of inoperability and how patients were allocated to NAC
- Imbalanced recrtuitment

Recruitment numbers per center; two further centers recruiting only one patient each (Antwerp and CMSE) not included.

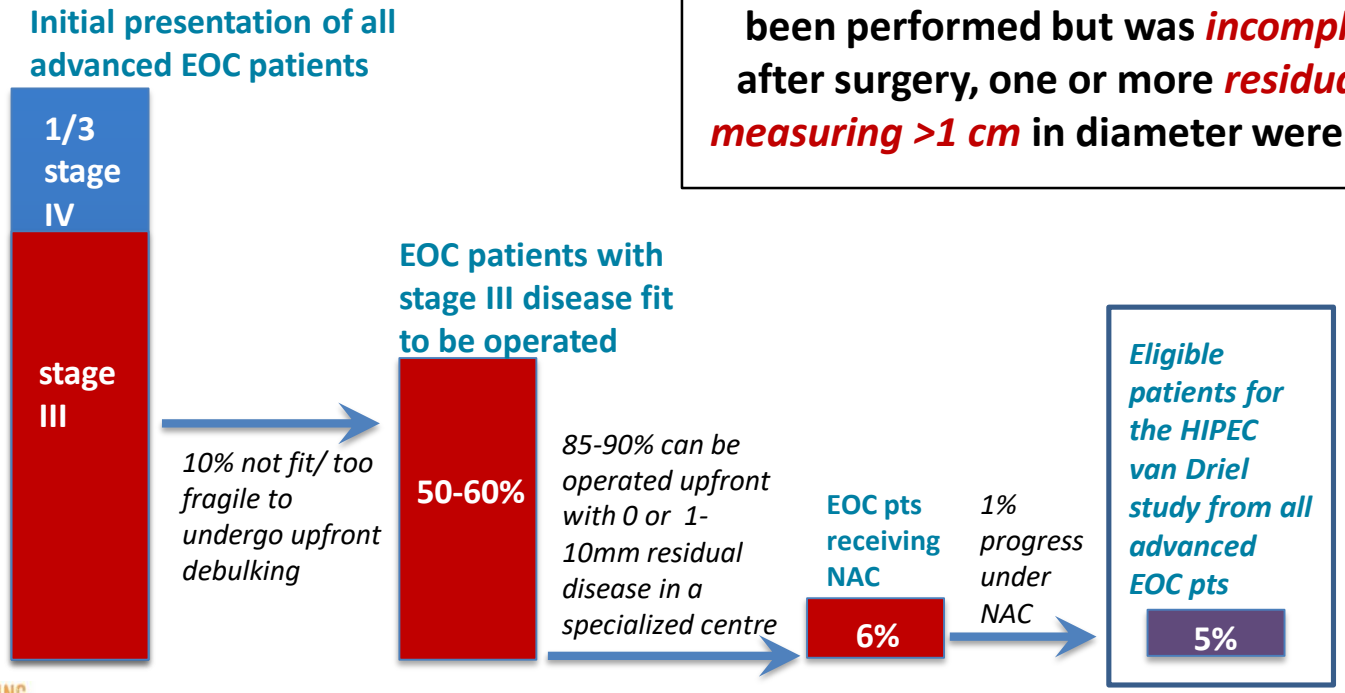
43% of the pts were recruited by one center alone (Netherlands Cancer Institute)



….the impact of HIPEC was *lowest in the most actively recruiting center*. In the small recruitment centers—where HR for survival seems more relevant, they did on average only 1-2 HIPEC cases/year. It is unknown whether the same team would operate in both arms or whether 'HIPEC surgeons' had to step in after randomization to HIPEC.

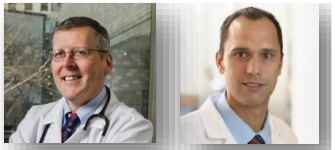
Fotopoulou et.al. Annals of Oncology 2018

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

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

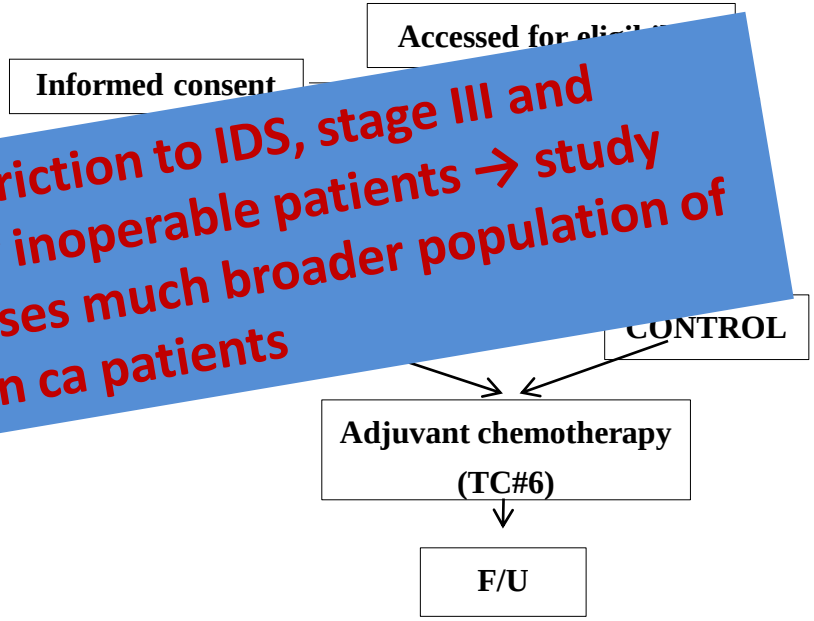
"This res *on to date* *that a single a* *ion of ovarian cancer m* *nts with cancer"*

…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

(study identifier: NCT01091636)



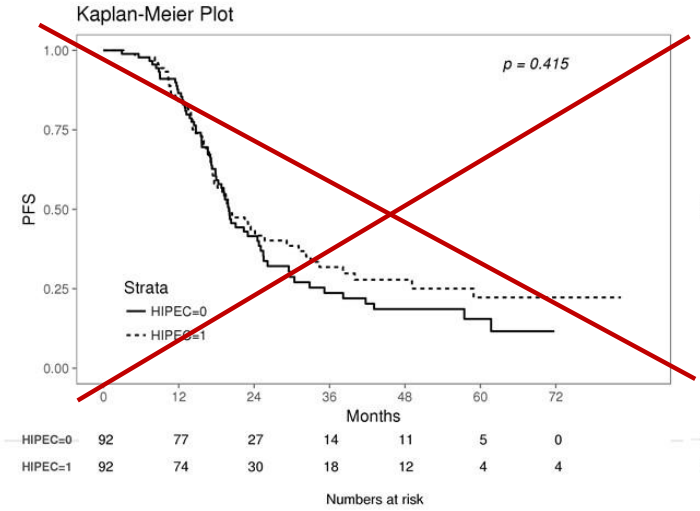
NO restriction to IDS, stage III and initially inoperable patients → study addresses much broader population of ovarian ca patients

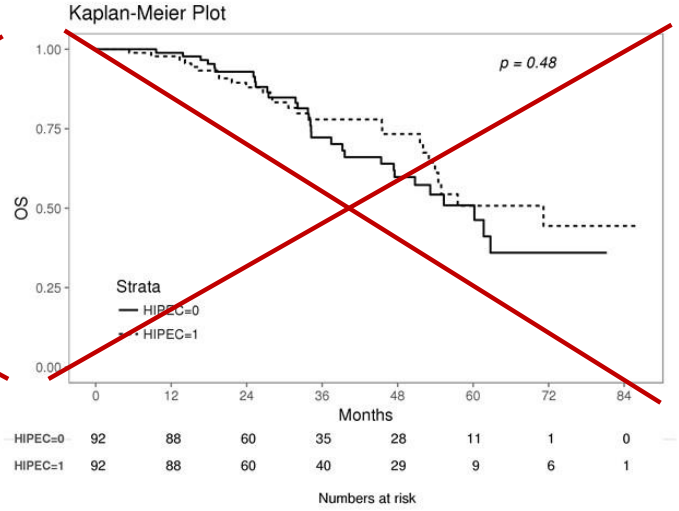
- 5L N/S + cisplatin 75 mg/m^2
- 42-43^{o}C
- 90 min
- Closed method

Lim and Bristow, ASCO 2017

Survival data: OS & PFS

In entire cohort,





	Non-HIPEC	HIPEC
Median PFS	20mo (95% CI, 18-25mo)	20mo (95% CI, 17.5-31.1mo)
2yr PFS	41.5% (95% CI, 32.2-53.6%)	43.1% (95% CI, 33.5-55.6%)
5yr PFS	15.5% (95% CI, 0.08-28.8%)	23.3% (95% CI, 13.5-36.6%)

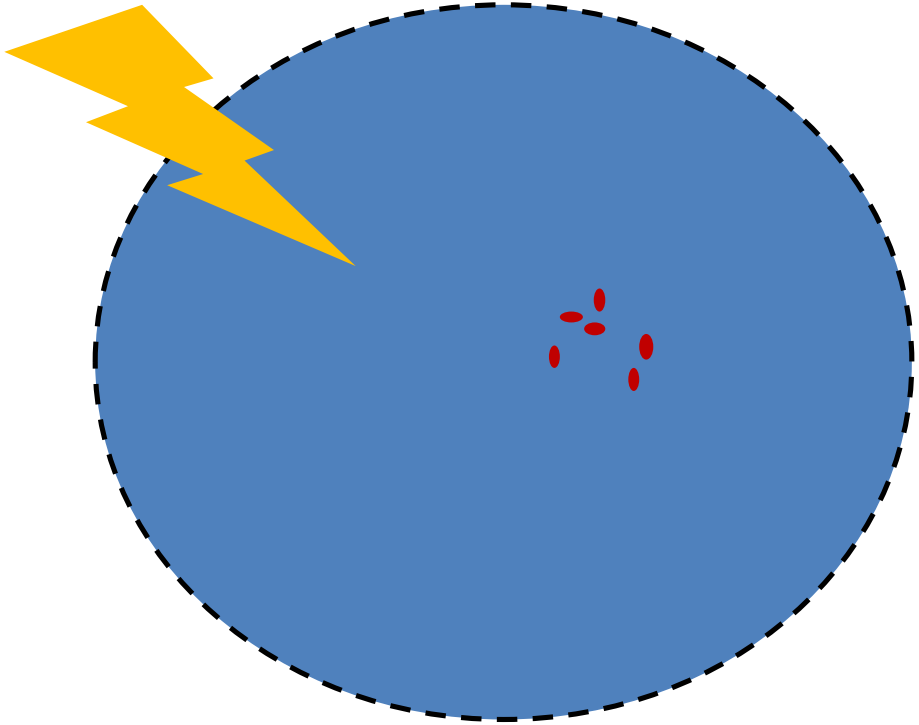
	Non-HIPEC	HIPEC
Median OS	60.2mo (95% CI, 47.5mo-NA)	71.2mo (95% CI, 53.9mo-NA)
2yr OS	92.9% (95% CI, 87.6-98.6%)	88.0% (95% CI, 81.3-95.3%)
5yr OS	46.3% (95% CI, 32.9-65.1%)	50.8% (95% CI, 37.0-69.6%)

Lim and Bristow, ASCO 2017

Avoid extrapolating results and conclusions from trials that affect only a small subgroup of patients to the entire patients population?

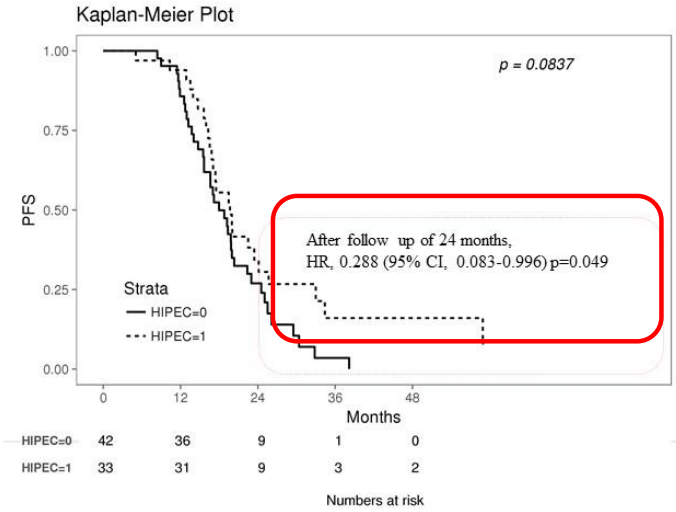
Is perhaps HIPEC used as a tool to compensate for insufficient cytoreduction - again-?

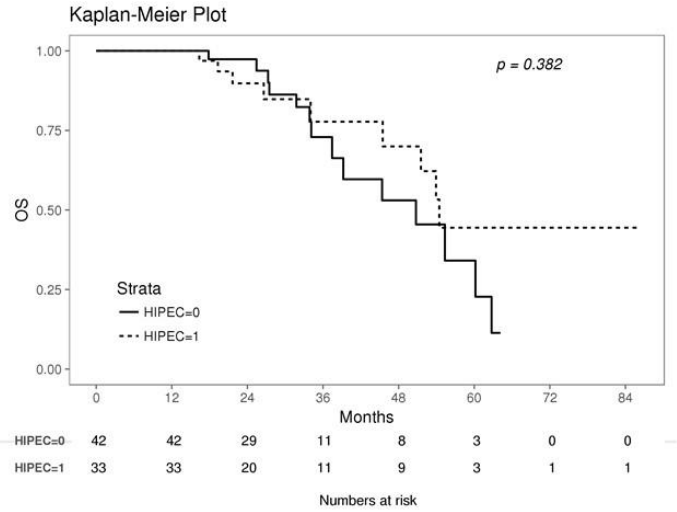
Surgery



Survival data: OS & PFS

In subgroup who received neoadjuvant chemotherapy,





	Non-HIPEC	HIPEC
Median PFS	18.0mo (95% CI, 15.6-22.4mo)	19.7mo (95% CI, 17.0-25.7mo)
2yr PFS	26.9% (95% CI, 16.1-45.0%)	34.3% (95% CI, 20.8-56.7%)
5yr PFS	3.5% (95% CI, 0.5-23.2%)	8.0% (95% CI, 1.5-42.8%)

	Non-HIPEC	HIPEC
Median OS	50.8mo (95% CI, 37.4mo-NA)	54.5mo (95% CI, 51.5mo-NA)
2yr OS	97.4% (95% CI, 92.4-100%)	89.8% (95% CI, 79.4-100%)
5yr OS	34.1% (95% CI, 15.7-74.0%)	44.4% (95% CI, 24.1-81.8%)

Lim and Bristow, ASCO 2017

…..a myth is down!

(…learning from the mistakes of others)

2018 ASCO: 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

So: HYPE or HOPE?

- 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

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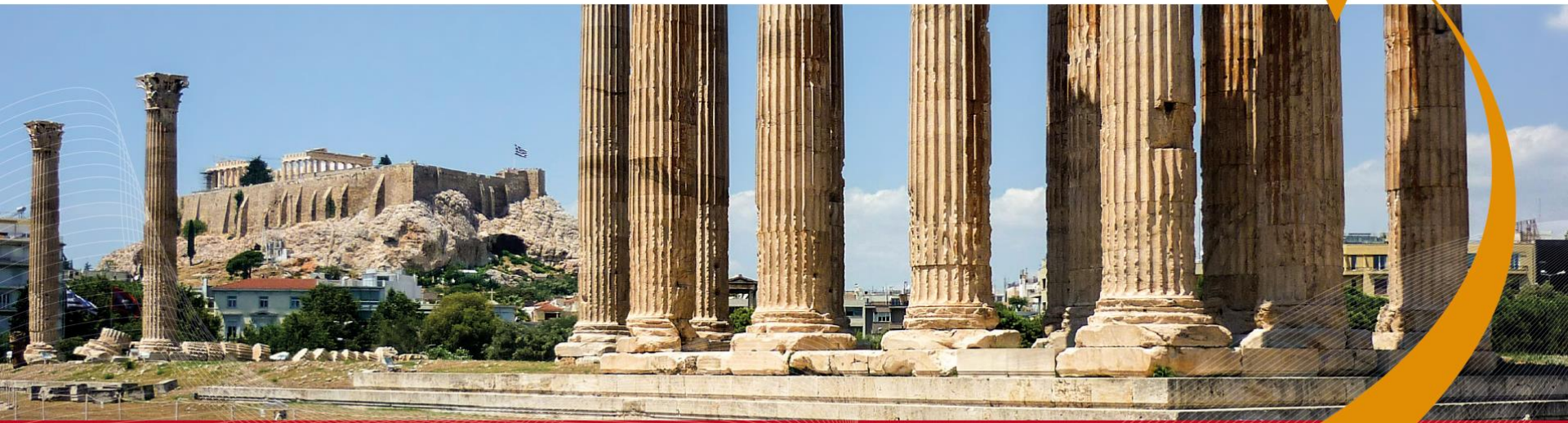

ATHENS, GREECE 2019

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