MANAGEMENT OF RECURRENT OVARIAN CANCER WITH CRS & HIPEC

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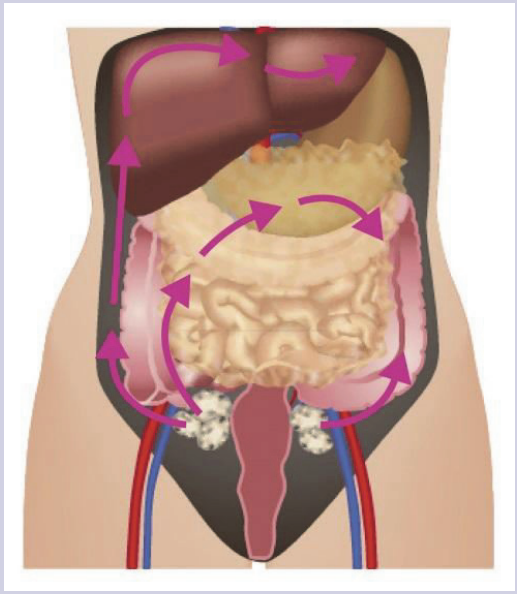
CAUSES OF RECURRENCE

- Tumor biologic behaviour
- Chemoresistance
- Incomplete cytoreduction



Halkia E, Spiliotis J, Sugarbaker P. Diagnosis and management of peritoneal metastases from ovarian cancer. Gastroenterology Research and Practice, 2012/

APPROACH TO RECURRENCE

- While there is not much one can do about the biologic profile of the tumor or its chemoresistance, the factor of cytoreduction can be improved.

INCOMPLETE CYTOREDUCTION

Table 4 Success Rates of Primary Cytoreductive Surgery in Stage III and IV Ovarian Cancer

Residual Disease	Stage IIB-IV[a]	Stage III[b]	Stage III[c]	Stage IIIC-IV[d]	Stage IV[e]	Stage IV[f]
Microscopic	30%	23%	15%	19%	8%	8%
0.1-1.0 cm	32%	42%	36%	22%	22%	50%
> 1 cm	38%	35%	50%	53%	31%	42%

[a]Wimberger et al. 2007.[24]
[b]Winter et al. 2007.[26]
[c]Chi et al. 2006.[28]
[d]Vergote et al. 2010.[30]
[e]Winter et al. 2008.[27]
[f]Rauh-Hain et al. 2011.[29]

due to upper abdomen disease??

Schorge JO et al. Cytoreductive surgery for advanced ovarian cancer: quo vadis?. Oncology (Williston Park) 2011.

PRIMARY CYTOREDUCTION

CYTOREDUCTIVE SURGERY

- **debulking surgery:** surgery aimed to reduce disease burden
- **cytoreductive surgery:** a series of peritonectomy procedures and visceral resections aimed at the complete removal of tumor from the abdominal cavity

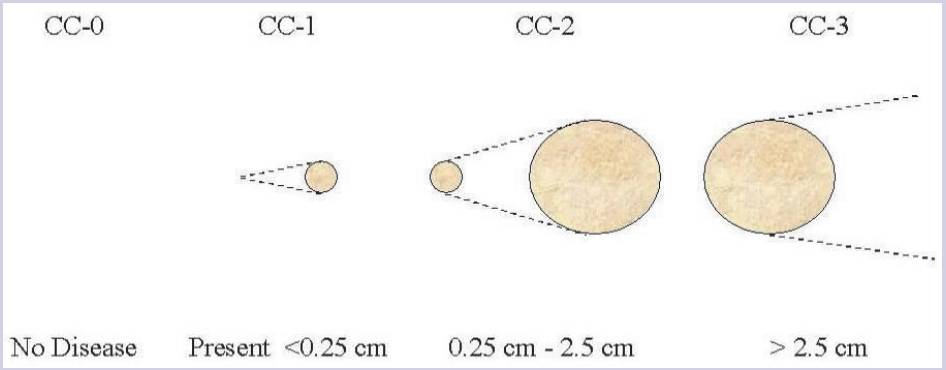
Table 1 Peritonectomy procedures and resections that are combined to complete a cytoreduction procedure

PERITONECTOMY	RESECTIONS
Anterior parietal peritonectomy	Old abdominal incisions, umbilicus, and epigastric fat pad
Left upper quadrant peritonectomy	Greater omentectomy and spleen
Right upper quadrant peritonectomy	Tumor on Glisson's capsule of the liver
Pelvic peritonectomy	Uterus, ovaries, and rectosigmoid colon
Omental bursectomy	Gallbladder and lesser omentum

Sugarbaker PH. Peritonectomy procedures. Ann Surg. 1995.

CYTOREDUCTIVE SURGERY

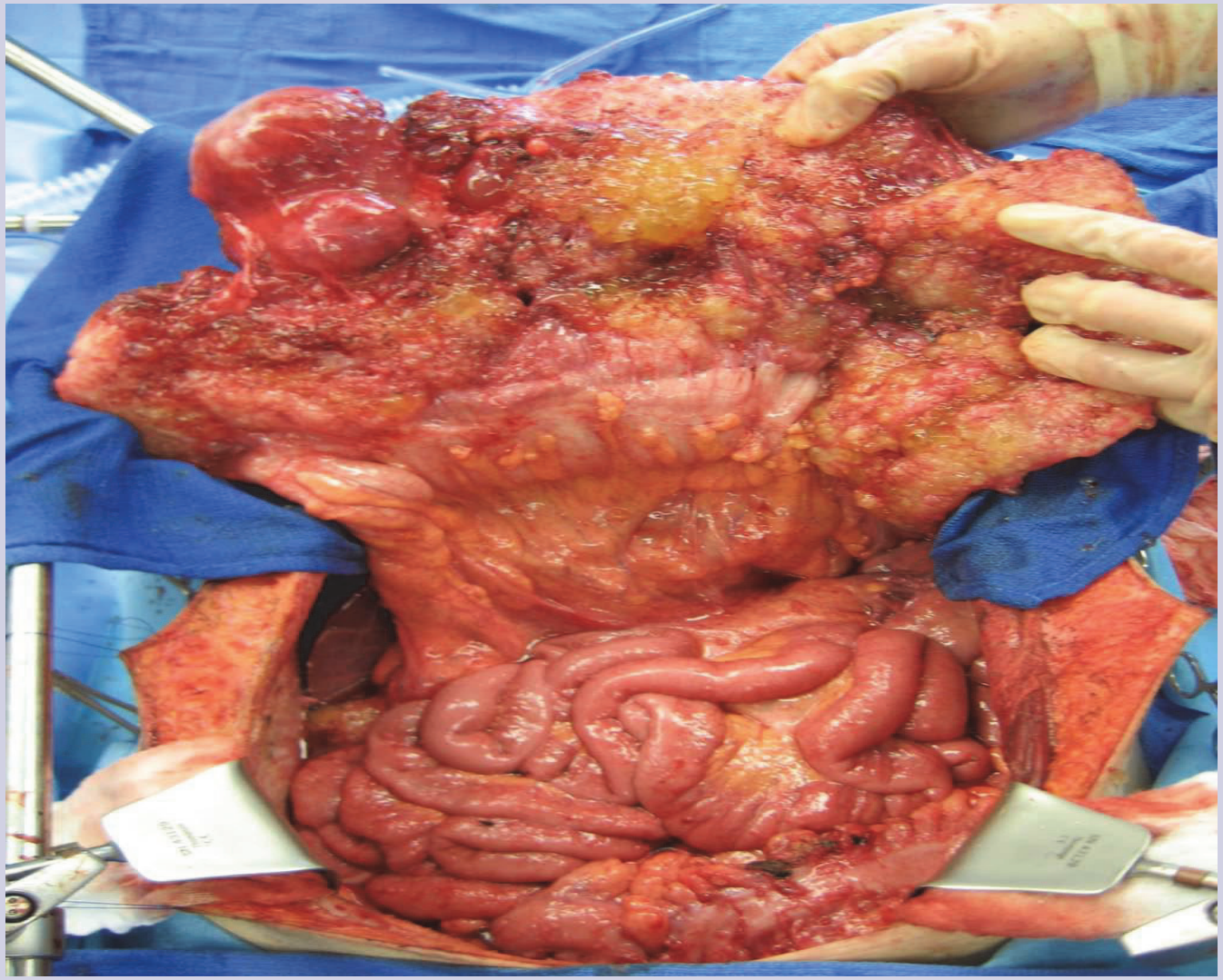
- Gynecologic Oncology Group (GOG):
  - optimal cytoreduction = the largest residual tumor nodule ≥ 1 cm
- for peritoneal surface malignancy surgeons:
  - optimal cytoreduction = residual tumor ≈ 0



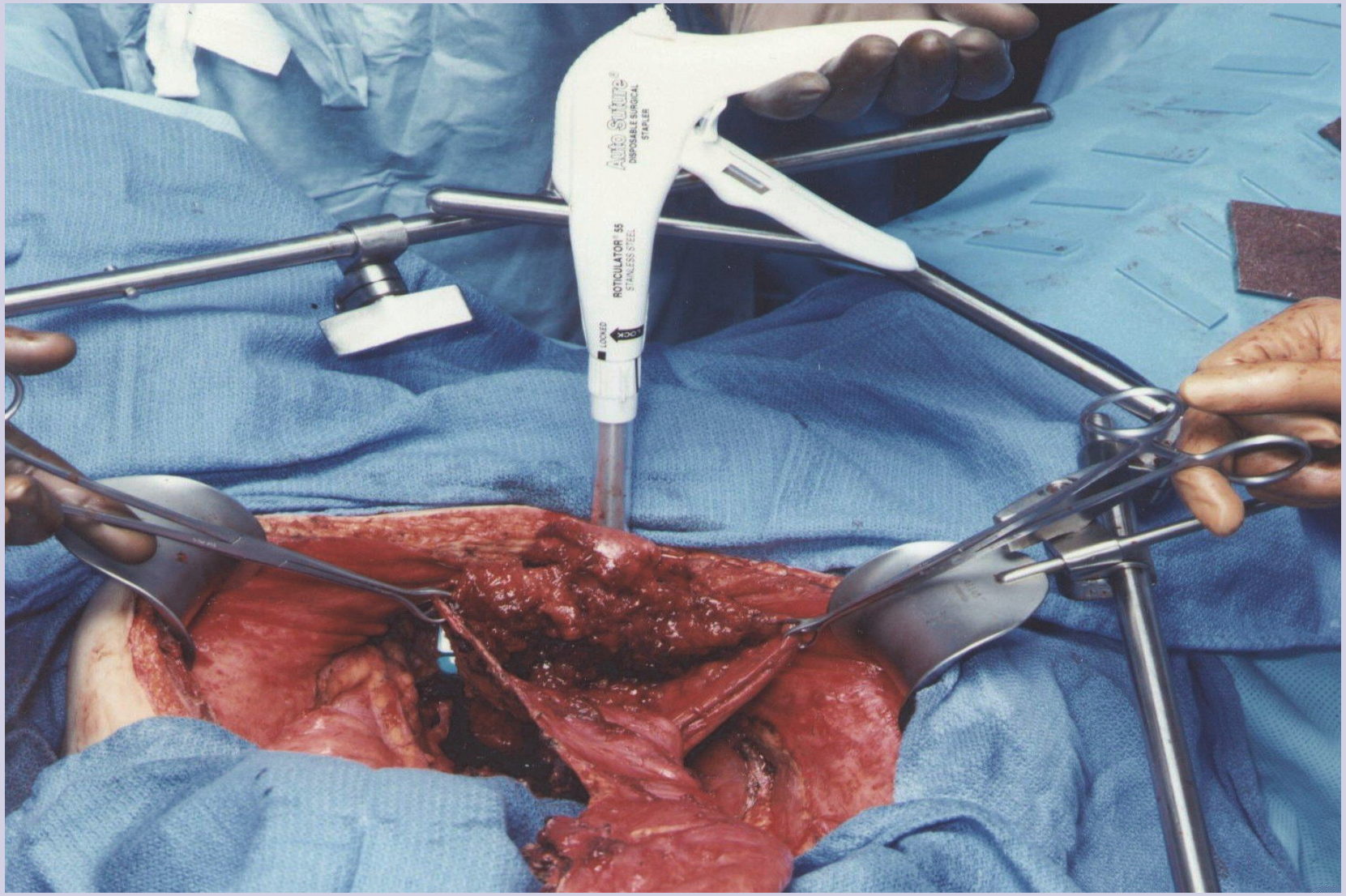
Ozols RF et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2003.

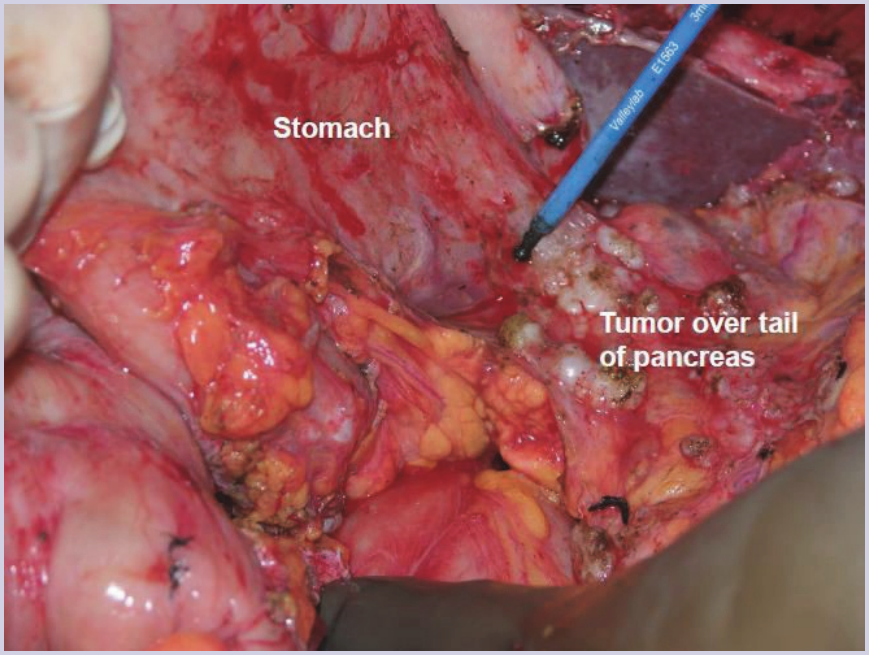
Sugarbaker PH. Managing the peritoneal surface component of gastrointestinal cancer. Oncology (Williston Park) 2004.

Cytoreductive surgery is a series of peritonectomies and visceral resections

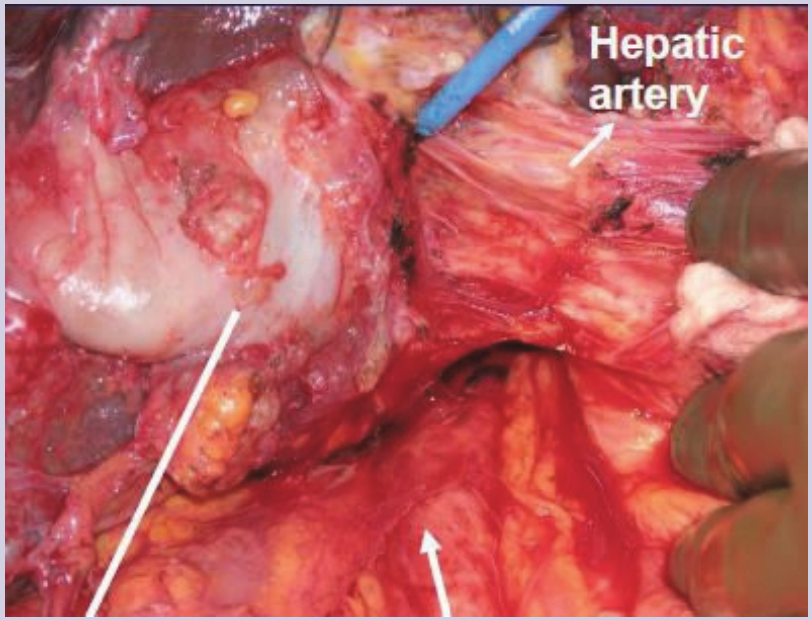


PELVIC PERITONECTOMY

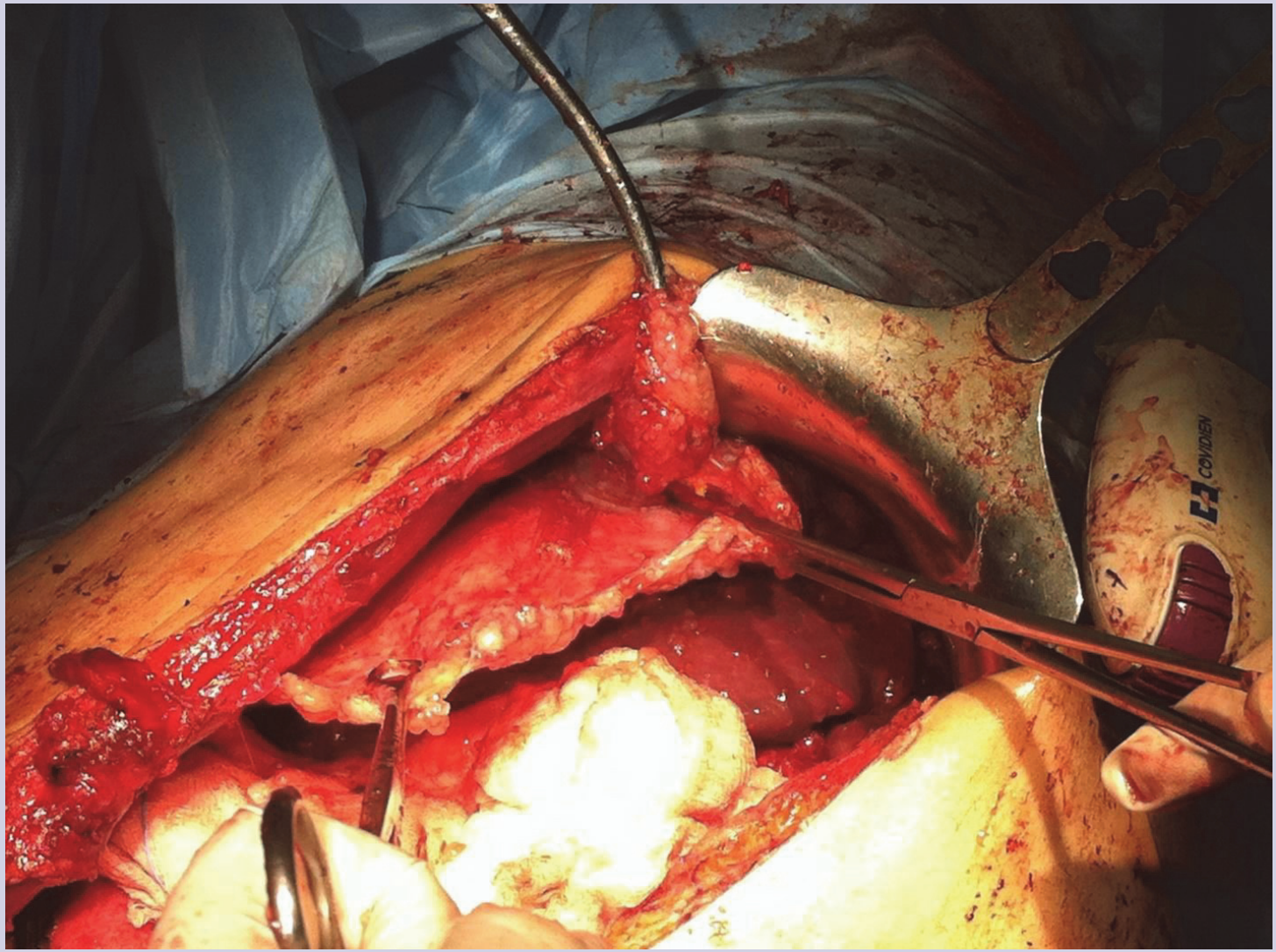




Which surgeon is most suitable to perform these procedures?

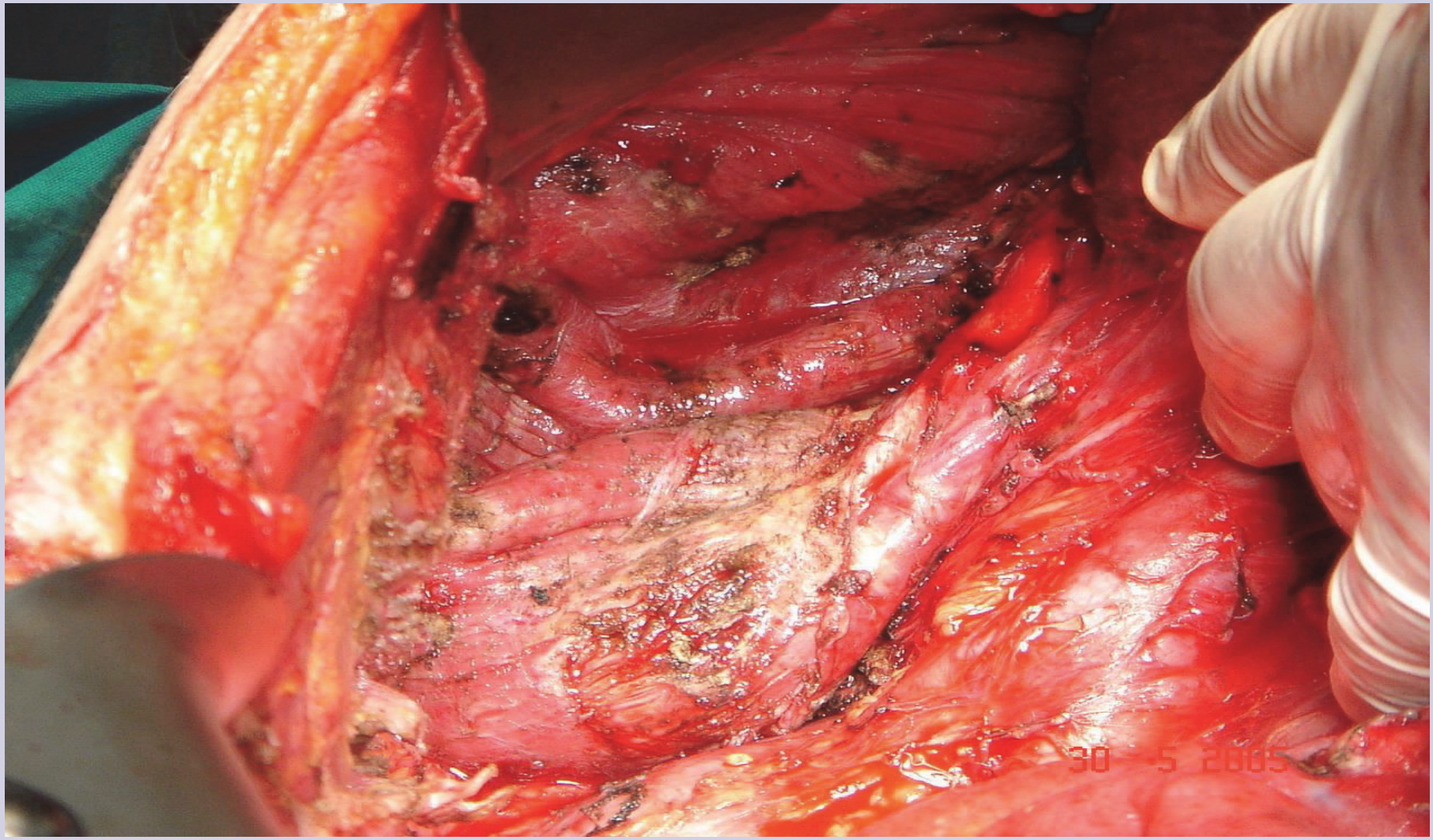


(R) SUBDIAPHRAGMATIC PERITONECTOMY



Halkia E, Efstathiou E et al. Management of diaphragmatic peritoneal carcinomatosis. JBUON 2014

BASE OF (R) SUBDIAPHRAGMATIC PERITONECTOMY



Halkia E, Efstathiou E et al. Management of diaphragmatic peritoneal carcinomatosis. JBUON 2014

CANCER CELL ENTRAPMENT IN THE ROUND LIGAMENT OF LIVER & GALLBLADDER

Halkia E et al. Ann Ital Surg 2015 (in press)

TUMOR LOCATION	ROUND LIGAMENT				GALLBLADDER			
	RESECTIONS, n	MACRO POS(+), n	HISTOL POS(+), n	HISTOL POS(+), %	RESECTIONS, n	MACRO POS(+), n	HISTOL POS(+), n	HISTOL POS(+), %
PSEUDOMYXOMA	20	16	14	70	20	5	7	35
OVARIAN	66	21	32	48.4	66	7	10	15.1
COLON	42	16	21	50	42	14	16	38
MESOTHELIOMA	7	3	3	42.8	7	1	1	14.2
GASTRIC	10	2	2	20	10	5	6	60
APPENDICEAL	28	24	18	64.2	28	19	12	42.8
VARIOUS	7	1	2	28.5	7	1	1	14.2
TOTAL	**180**	**83**	**94**	**52.2**	**180**	**52**	**53**	**29.4**

SECONDARY CYTOREDUCTION

Gynecol Oncol. 2015 Jan;136(1):25-9. doi: 10.1016/j.ygyno.2014.11.005. Epub 2014 Nov 8.

The role of secondary cytoreduction in low-grade serous ovarian cancer or peritoneal cancer.

Crane EK[1], Sun CC[1], Ramirez PT[1], Schmeler KM[1], Malpica A[2], Gershenson DM[3].

- Retrospective analysis, 1995 – 2012
- N = 41 pts
- Mean time from primary to secondary cytoreduction = 33.2m
- Complete cytoreduction at the second operation was feasible in 35% and median survival in those patients was **60.3 months VS 10.7 months** in patients with incomplete cytoreduction

- **Secondary cytoreduction was beneficial to 35% of patients with recurrent disease**

J Exp Clin Cancer Res. 2013 Sep 2;32:61. doi: 10.1186/1756-9966-32-61.

Secondary cytoreduction surgery improves prognosis in platinum-sensitive recurrent ovarian cancer.

Xu X[1], Chen X, Dai Z, Deng F, Qu J, Ni J.

- **Important point:**
  - Optimal **secondary cytoreduction in ASYMPTOMATIC recurrence** offers an OS of 79 months VS 53.9 months in SYMPTOMATIC recurrence

- **Factors affecting OS:**
  - Complete primary cytoreduction
  - *Asymptomatic recurrence* = ↑ tumor markers, suspicious diagnostic studies
  - Long time from primary cytoreduction to diagnosis of recurrence

Gynecol Oncol. 2015 Jan;136(1):18-24. doi: 10.1016/j.ygyno.2014.09.017. Epub 2014 Oct 2.

Impact of secondary cytoreductive surgery on survival in patients with platinum sensitive recurrent ovarian cancer: Analysis of the CALYPSO trial.

Lee CK[1], Lord S[2], Grunewald T[3], Gebski V[2], Hardy-Bessard AC[4], Sehouli J[5], Woie K[6], Heywood M[7], Schauer C[8], Vergote I[9], Scambia G[10], Ferrero A[11], Harter P[12], Pujade-Lauraine E[13], Friedlander M[14].

- 975 patients were randomized
- 20% secondary cytoreduction & systemic chemotherapy
- 80% only systemic chemotherapy
- prolonged OS in the secondary cytoreduction group
- Median OS 49.9 months vs. 29.7 months
- 3-yr survival in the secondary cytoreduction group:
  - residual tumor < 5cm: 72%
  - residual tumor > 5cm: 28%

- **Benefit from secondary cytoreduction in well selected patients**

Eur J Surg Oncol. 2013 Jul;39(7):786-91. doi: 10.1016/j.ejso.2013.02.006. Epub 2013 Mar 13.

Outcomes and patterns of secondary relapse in platinum-sensitive ovarian cancer: implications for tertiary cytoreductive surgery.

Tang J[1], Liu DL, Shu S, Tian WJ, Liu Y, Zang RY.

- Retrospective study: 159 patients with second recurrence
- 83 patients underwent tertiary cytoreduction & systemic chemotherapy
- 76 patients received only systemic chemotherapy
- Median Survival
  - tertiary cytoreduction & MICROSCOPIC residual disease: 32.9m
  - tertiary cytoreduction & MACROSCOPIC residual disease: 14.6m
  - systemic chemotherapy only: 15m

- **Even tertiary cytoreduction outbalances treatment with systemic chemotherapy only**

Ann Surg Oncol. 2014 Sep 12. [Epub ahead of print]

The Role of Hyperthermic Intraperitoneal Chemotherapy Using Paclitaxel in Platinum-Sensitive Recurrent Epithelial Ovarian Cancer Patients with Microscopic Residual Disease after Cytoreduction.

Cascales-Campos PA[1], Gil J, Feliciangeli E, Gil E, González-Gil A, López V, Ruiz-Pardo J, Nieto A, Parrilla JJ, Parrilla P.

- In a recent patient series of patients with platinum sensitive recurrence treated with CRS & HIPEC (with paclitaxel), it was reported that the presence of tumors with undifferentiated histology was the only independent factor associated with a reduced disease free survival (DFS), with a 1-year DFS of 77% and a 3-year DFS of 45%, denoting a tendency versus patients who did not undergo HIPEC.

J Surg Oncol. 2014 Nov;110(6):661-5. doi: 10.1002/jso.23688. Epub 2014 Jun 24.

Cytoreduction surgery with hyperthermic intraperitoneal chemotherapy in recurrent ovarian cancer improves progression-free survival, especially in BRCA-positive patients- a case-control study.

Safra T[1], Grisaru D, Inbar M, Abu-Abeid S, Dayan D, Matcevevsky D, Weizman A, Klausner JM.

- Another recent study correlated response to HIPEC in the treatment of recurrent ovarian cancer to their BRCA status, demonstrating that the benefit from HIPEC is greater in BRCA mutation carriers.

Minerva Chir. 2014 Feb;69(1):27-35.

Treatment of peritoneal carcinomatosis from ovarian cancer by surgical cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC).

Robella M[1], Vaira M, Marsanic P, Mellano A, Borsano A, Cinquegrana A, Sottile A, De Simone M.

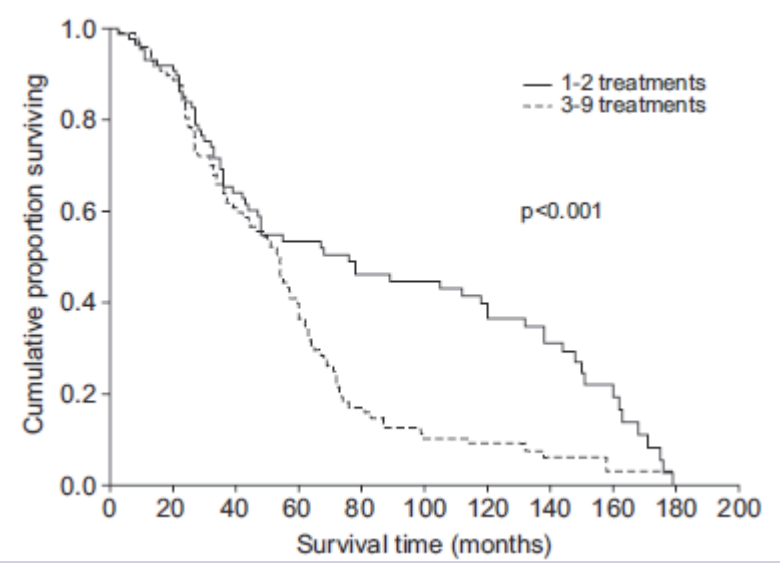
- In a recent series of 70 EOC patients, divided in two groups (first recurrence after surgery and adjuvant chemotherapy, six months after chemotherapy versus multiple relapses), survival was similar in the two groups after CRS & HIPEC.

Maintenance chemotherapy or not in ovarian cancer stages IIIA, B, C, and IV after disease recurrence

Journal of BUON **17:** 735-739, 2012

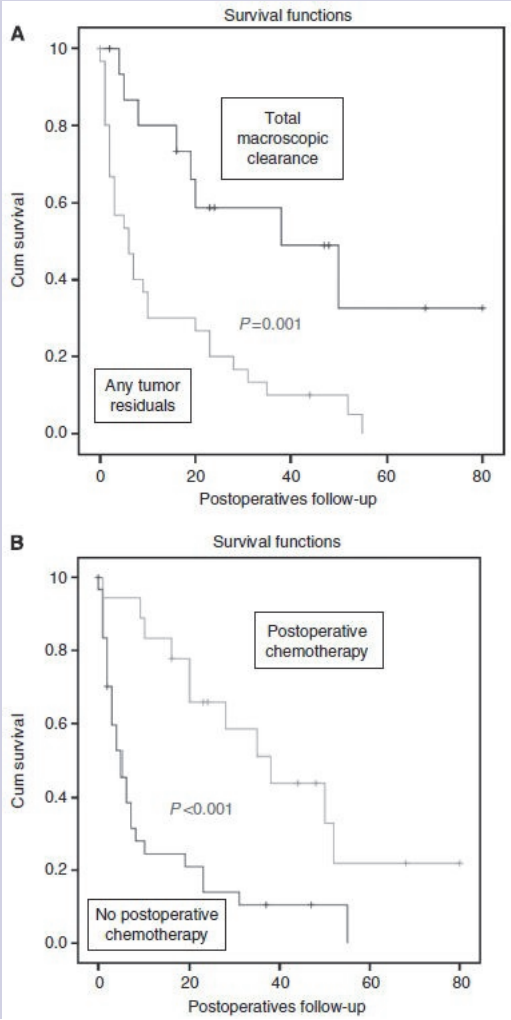
G.P. Stathopoulos[1], Ch. Papadimitriou[2], G. Aravantinos[3], S.K. Rigatos[4], N. Malamos[4], J.G. Stathopoulos[1], M. Kaparelou[1], J. Koutantos[1], Ch. Andreadis[5]

[1]First Oncology Clinic, "Errikos Dunant" Hospital; [2]Oncology Department, "Alexandra" Hospital; [3]Oncology Department, "Ag. Anargyri" Cancer Hospital; [4]Oncology Department, "Marika Iliadi" Hospital, Athens; [5]Oncology Department, "Theagenio" Cancer Hospital, Thessaloniki, Greece



In ovarian cancer patients with advanced disease, multiple chemotherapy lines (3-9) offer no advantage over 1 or 2 lines, with respect to OS.

PRIMARY, SECONDARY,TERTIARY, QUATERNARY CYTOREDUCTION!!



BJC

British Journal of Cancer (2013) 108, 32–38 | doi: 10.1038/bjc.2012.544

Keywords: ovarian cancer relapse; quaternary cytoreduction; overall survival; morbidity; tumour dissemination

Quaternary cytoreductive surgery in ovarian cancer: does surgical effort still matter?

C Fotopoulou*[,1,4], K Savvatis[2,4], P Kosian[1], I E Braicu[1], G Papanikolaou[1], K Pietzner[1], S-C Schmidt[3] and J Sehouli[1]

- n = 49 patients who underwent quarternary cytoreduction
- mean OS = 23.05m
- mean OS in CC-0 = 43m VS13.4m in incomplete cytoreduction (**p = 0.001**)
- mean OS of patients who received adjuvant chemotherapy = 40.5m VS12.3 m in patients who did not (**p< 0.001**)

Even quarternary cytoreduction may offer

WHEN TO ADMINISTRATE HIPEC?

PATIENT SELECTION

Table 4: Prognostic-predictive factor for "optimal" HIPEC in recurrent EOC.

(i) Age < 65
(ii) Performance status >80
(iii) Interval from initial diagnosis >12 months
(iv) Peritoneal Cancer Index <20
(v) Completeness of Cytoreduction CC-0 or CC-1
(vi) Absence of retroperitoneal lymph nodes
(vii) Platinum-sensitive

Halkia E, Spiliotis J, Sugarbaker P. Diagnosis and Management of Peritoneal Metastases from Ovarian Cancer. Gastroenterology Research and Practice 2012.

Table 1. Timing of HIPEC in the Course of Ovarian Cancer Treatment

in combination with cytoreductive surgery (CRS):
1. upfront CRS and HIPEC: as first treatment for newly diagnosed ovarian cancer
2. interval CRS and HIPEC: after neo-adjuvant chemotherapy without previous resection except for biopsies
3a. consolidation CRS and HIPEC: after upfront (near) complete CRS and a full course of chemotherapy in patients with a clinically complete response
3b. secondary CRS and HIPEC: after upfront incomplete CRS followed by chemotherapy in patients with a partial response or stable disease
4. salvage CRS and HIPEC: for recurrent ovarian cancer after initial complete response to CRS and chemotherapy
without cytoreductive surgery (CRS):
5. palliative HIPEC without CRS for unresectable ovarian cancer with refractory ascites

Mulier S et al. Survival benefit of adding Hyperthermic IntraPEritoneal Chemotherapy (HIPEC) at the different time-points of treatment of ovarian cancer: review of evidence. Curr Pharm Des 2012.

CONSOLIDATION CRS & HIPEC

- after CRS and adjuvant chemotherapy and complete response (CR)

	stage	median OS	5-yr OS	median DFS	5-yr DFS
CRS & HIPEC & ACT	III/IV	53.7-130m	42.4%	29.6-82.8m	24.2%
CRS & ACT					
3Cy		48m		14m	
12Cy		53m		22m	

STATISTICALLY SIGNIFICANT

Mulier S et al. Survival benefit of adding Hyperthermic IntraPEritoneal Chemotherapy (HIPEC) at the different time-points of treatment of ovarian cancer: review of evidence. Curr Pharm Des 2012.

SECONDARY CRS & HIPEC

- after CRS and adjuvant chemotherapy and partial response (PR) or stable disease (SD)

	stage	median OS	5-yr OS	median DFS	5-yr DFS
CRS & HIPEC & ACT	III	60m	53.8-66,1%	26.4-56m	26.9%
CRS & ACT		33.7m		10.7m	

$p < 0.002$

Mulier S et al. Survival benefit of adding Hyperthermic IntraPEritoneal Chemotherapy (HIPEC) at the different time-points of treatment of ovarian cancer: review of evidence. Curr Pharm Des 2012.

THE FIRST RANDOMIZED STUDY ABOUTTHE ROLE OF HIPEC IN RECURRENCE

Ann Surg Oncol
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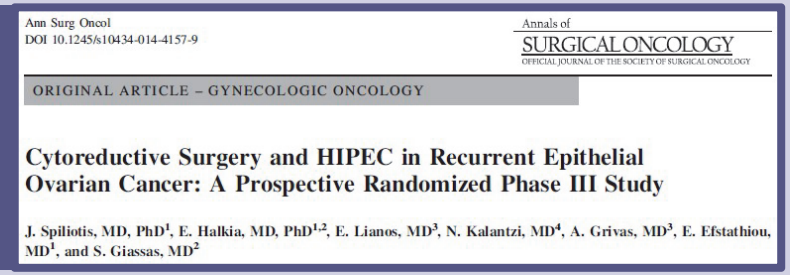
- In an 8-year period (2006-2013), our team has treated 120 women suffering from advanced EOC (IIIc and IV), who recurred after initial treatment with cytoreductive or debulking surgery.
- The patients were randomized into two groups, with similar demographic, clinical and therapeutic features.
- On the first group of patients (group A, n = 60), cytoreductive surgery was followed by the administration of HIPEC and subsequent systemic chemotherapy.
- The second group of patients (group B, n = 60) underwent cytoreductive surgery followed by systemic chemotherapy.

HIPEC TECHNIQUE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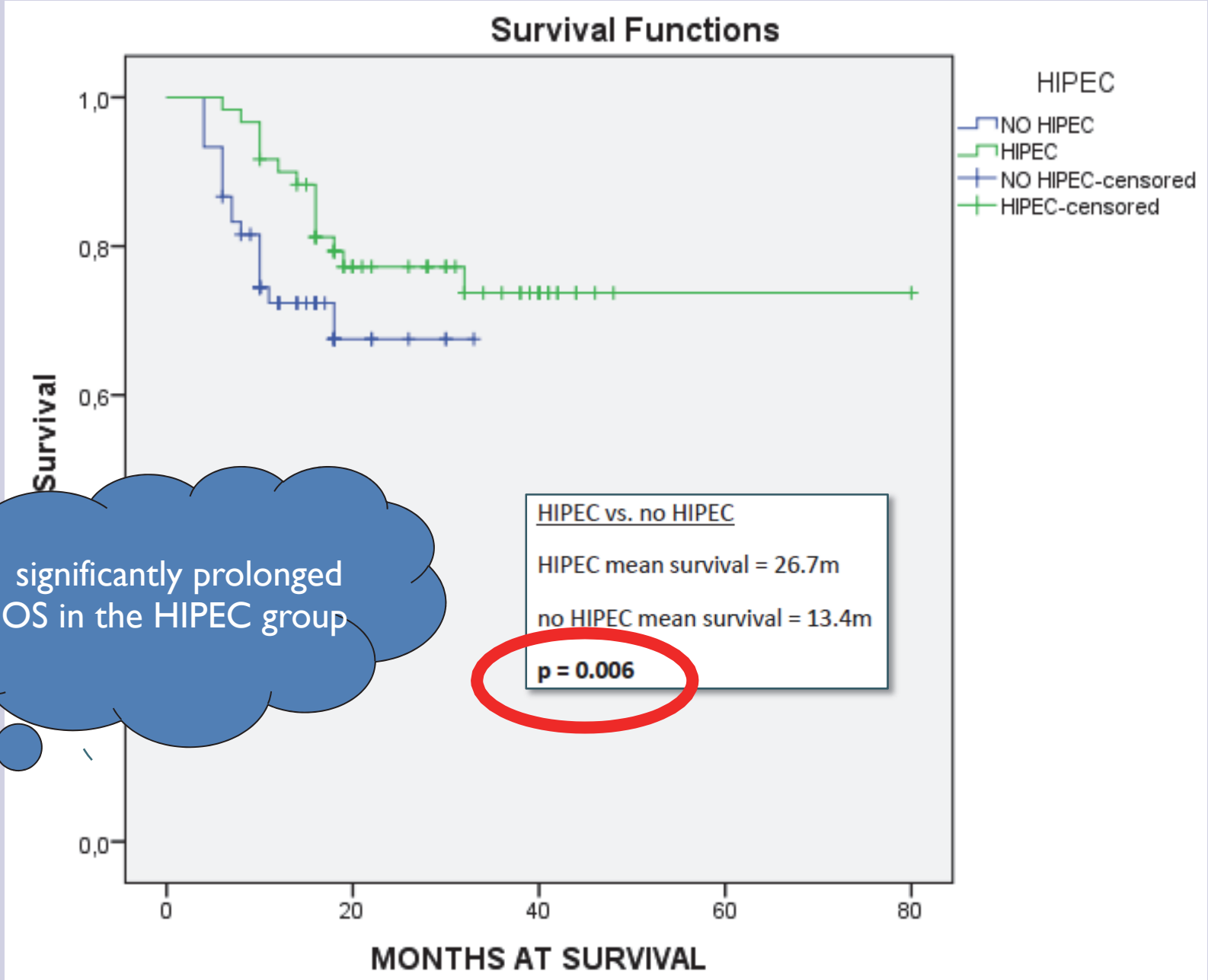
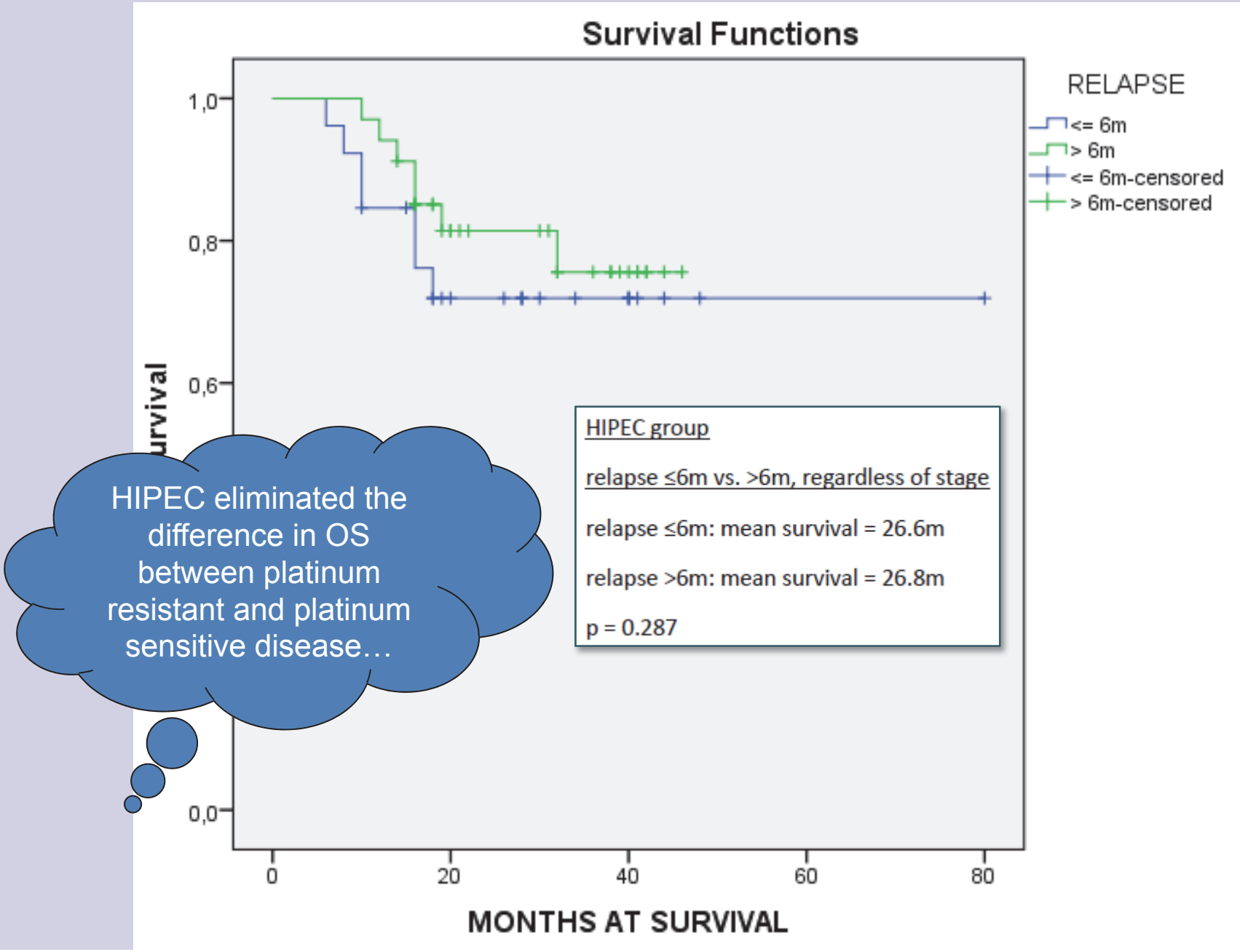
- The HIPEC protocols used were:
  - **for platinum sensitive disease (n = 34)**
    - cisplatin 100 mg/m^2 AND
    - paclitaxel 175 mg/m^2

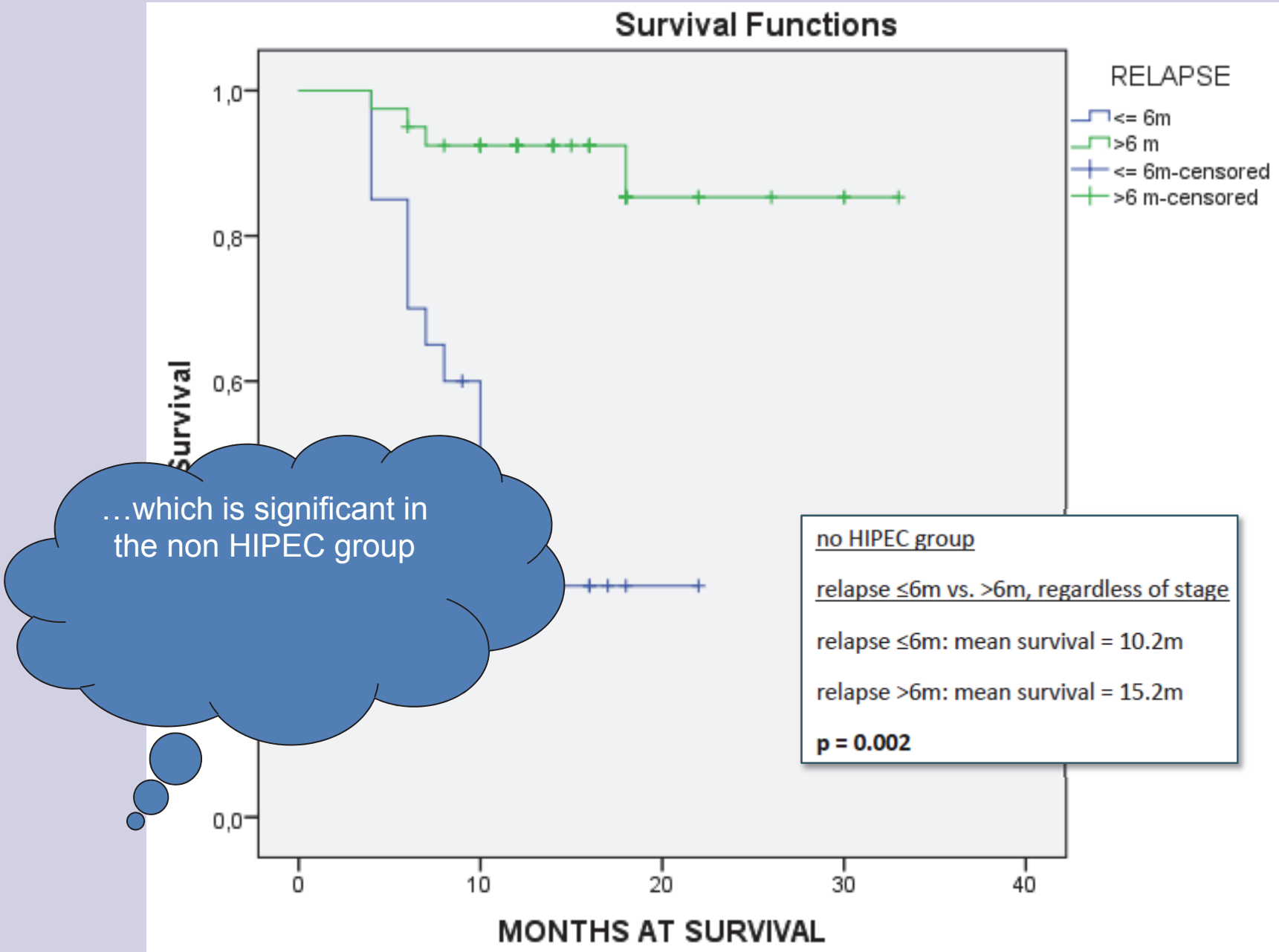
delivered for 60 minutes at 42.5°C

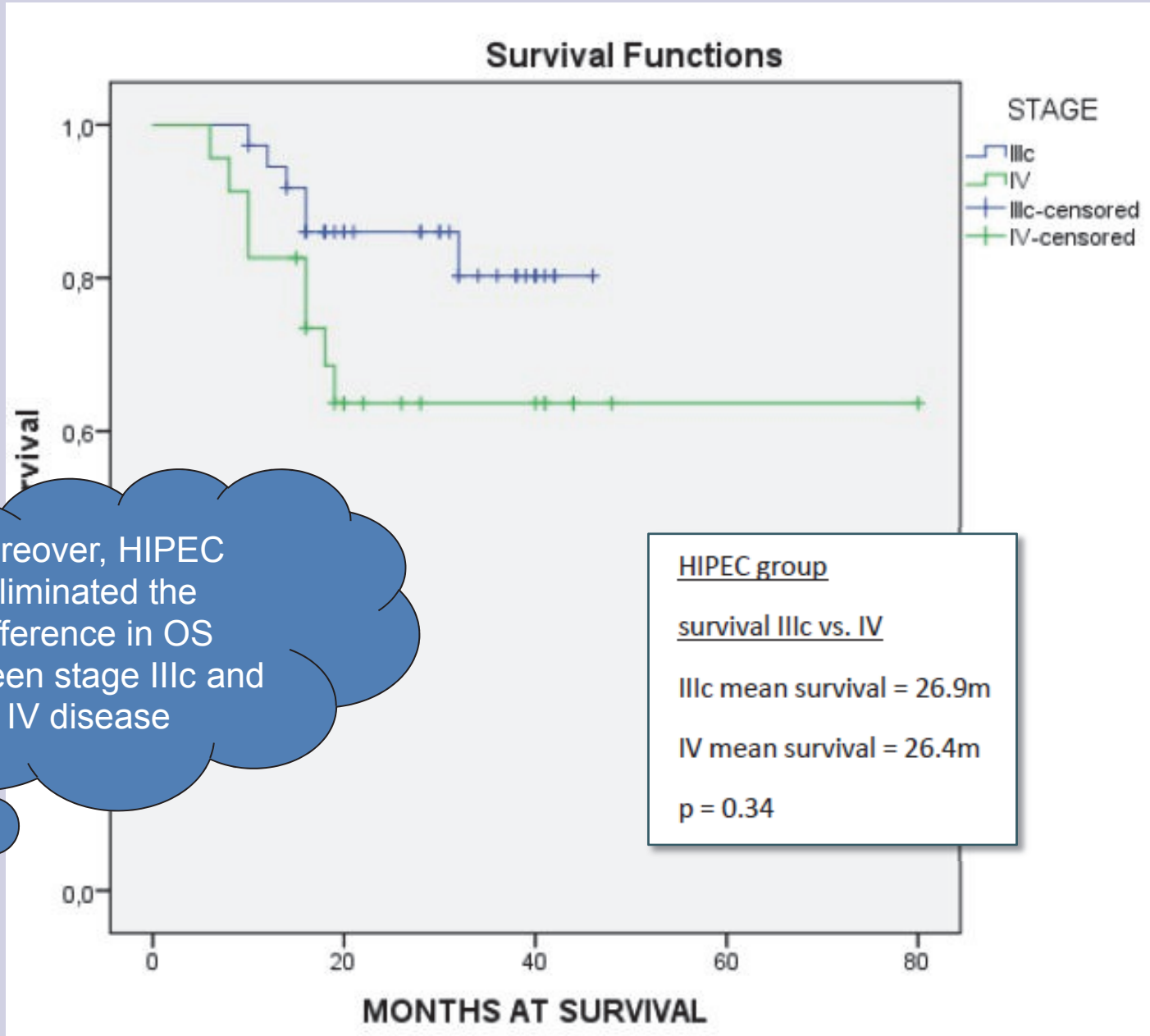
  - **for platinum resistant disease (n = 26)**
    - doxorubicin 35 mg/m^2 AND
    - paclitaxel 175 mg/m^2 OR mitomycin 15mg/m^2 delivered for 60 minutes at 42.5°C

- On 40 of the patients HIPEC was performed using the open (coliseum) technique, while on the remaining 20 the closed technique was performed.

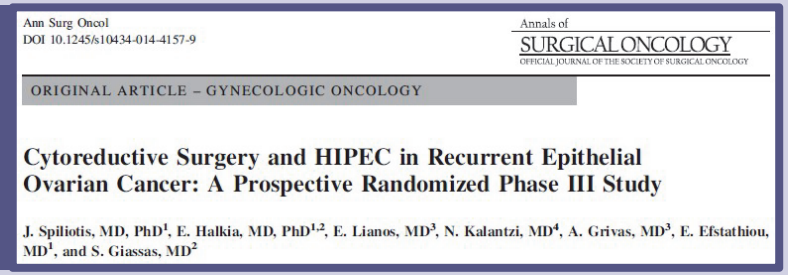

Survival Functions
HIPEC
NO HIPEC
HIPEC
NO HIPEC-censored
HIPEC-censored
Survival
1,0
0,8
0,6
0,0
0
20
40
60
80
MONTHS AT SURVIVAL
HIPEC vs. no HIPEC
HIPEC mean survival = 26.7m
no HIPEC mean survival = 13.4m
p = 0.006
significantly prolonged
OS in the HIPEC group


Survival Functions
RELAPSE
<= 6m
> 6m
<= 6m-censored
> 6m-censored
1,0
0,8
0,6
0,0
urvival
0
20
40
60
80
MONTHS AT SURVIVAL
HIPEC group
relapse ≤6m vs. >6m, regardless of stage
relapse ≤6m: mean survival = 26.6m
relapse >6m: mean survival = 26.8m
p = 0.287
HIPEC eliminated the difference in OS between platinum resistant and platinum sensitive disease…


Survival Functions
RELAPSE
<= 6m
>6 m
<= 6m-censored
>6 m-censored
1,0
0,8
0,6
0,0
Survival
0
10
20
30
40
MONTHS AT SURVIVAL
…which is significant in the non HIPEC group
no HIPEC group
relapse ≤6m vs. >6m, regardless of stage
relapse ≤6m: mean survival = 10.2m
relapse >6m: mean survival = 15.2m
p = 0.002


Survival Functions
STAGE
IIIc
IV
IIIc-censored
IV-censored
1,0
0,8
0,6
0,0
0
20
40
60
80
MONTHS AT SURVIVAL
HIPEC group
survival IIIc vs. IV
IIIc mean survival = 26.9m
IV mean survival = 26.4m
p = 0.34
Moreover, HIPEC eliminated the difference in OS between stage IIIc and IV disease

DISCUSSION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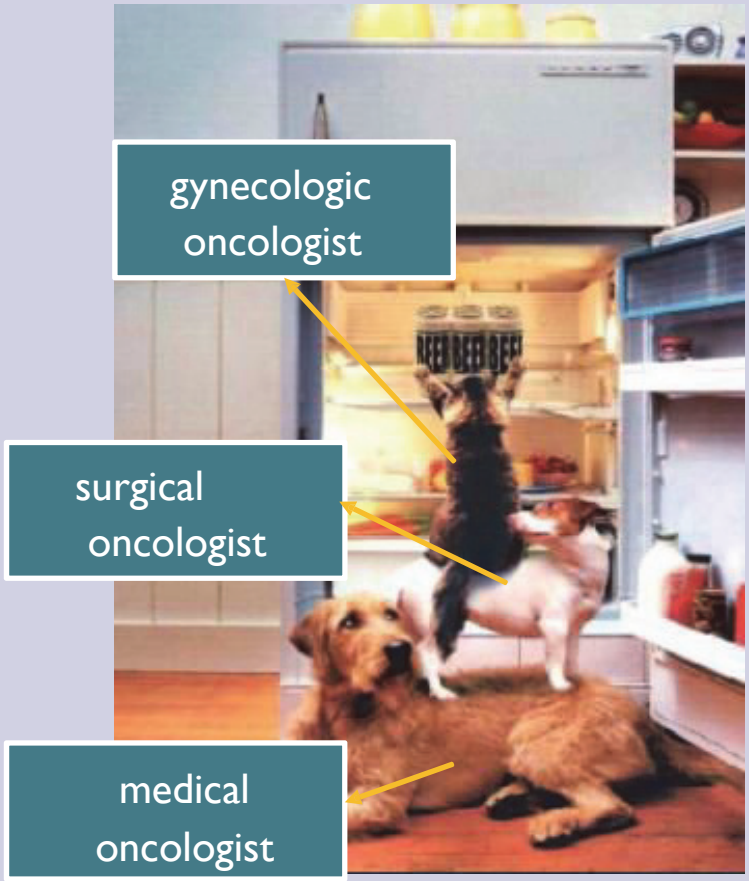
- This is the first randomized prospective study conducted over a long time period.

- More extensive research is required as to which factors modify platinum resistance in the HIPEC group.
  - doxorubicin?
  - hyperthermia?
  - epigenetics?

- It appears that the implementation of CRS & HIPEC at first recurrence is a possible option in the management of EOC.

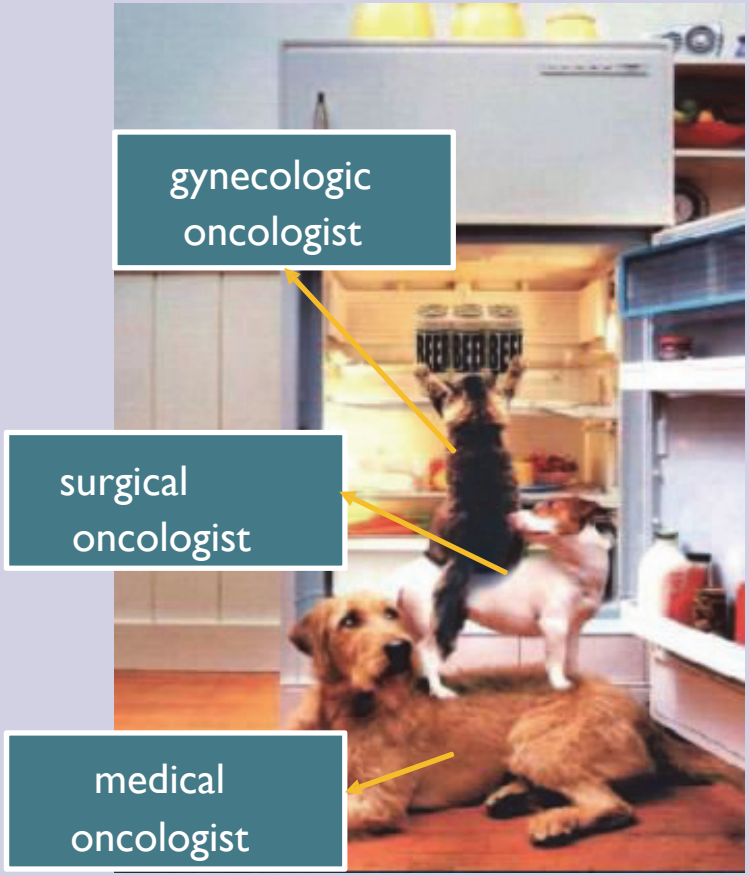
CONCLUSIONS

CONCLUSIONS



- Ovarian cancer management requires a multidisciplinary approach
- What should be taken into consideration in the formation of the management plan are:
  - disease stage
  - patient performance status
  - team experience with cytoreductive surgery

CONCLUSIONS



- The role of systemic chemotherapy is equally important with that of cytoreduction.
- HIPEC appears to prolong survival, but it can only be delivered in specific centres.
- Future directions:
  - new chemotherapeutic agents
  - target therapies
  - CRS education
  - HIPEC in selected cases, after the conduct of phase III RCTs

Invited Speakers

Aravantinos Gerasimos, Greece
Athanasiadis Ilias, Greece
De Bree Eelco, Greece
Deraco Marcello, Italy
Emmanouilides Chris, Greece
Esquivel Jesus, USA
Georgoulias Vasileios, Greece
Giassas Stylianos, Greece
Glehen Olivier, France
Halkia Evgenia, Greece
Hanna Nader, USA
Moran Brendan, England
Pelz Jörg, Germany
Rau Beate, Germany
Samandas Epaminondas, Greece
Selman Sokmen, Turkey
Sideris Lucas, Canada
Spiliotis John, Greece
Sugarbaker Paul, USA
Tentes Antonios-Apostolos, Greece
Youssef Haney, England

THANK YOU