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Cytoreductive Surgery and HIPEC In Epithelial Ovarian Carcinoma (EOC)

Almog Ben-Yaacov, MD
Department of General and Oncological Surgery (Surgery C)
Surgical Oncology Group led by Prof Aviram Nissan
The Chaim Sheba Medical Center
Tel Hashomer, Israel

No disclosures

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- Background/History
- Indications
- Epithelial Ovarian Cancer
- IP chemotherapy
- Role of cytoreduction
- The role of CRS+HIPEC in EOC

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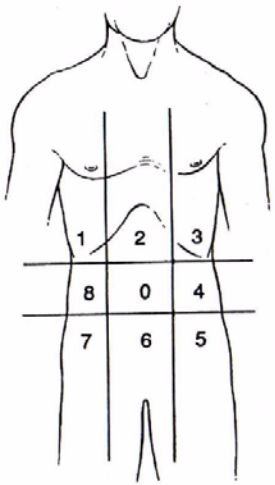
Peritoneal Surface Malignancies

- **Primary peritoneal surface malignancies**
  - Mesothelioma
  - Primary peritoneal carcinoma
- **Secondary peritoneal surface malignancies**
  - Adenocarcinoma of the appendix
  - Colorectal cancer
  - Gastric cancer
  - **Ovarian cancer**
  - Rare tumors

Staging

Peritoneal Cancer Index

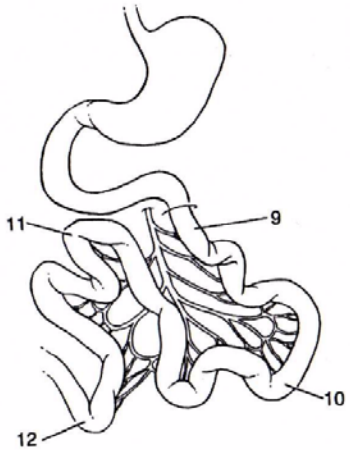


Regions	Lesion Size
0 Central	____
1 Right Upper	____
2 Epigastrium	____
3 Left Upper	____
4 Left Flank	____
5 Left Lower	____
6 Pelvis	____
7 Right Lower	____
8 Right Flank	____
9 Upper Jejunum	____
10 Lower Jejunum	____
11 Upper Ileum	____
12 Lower Ileum	____

PCI ☐

Lesion Size Score

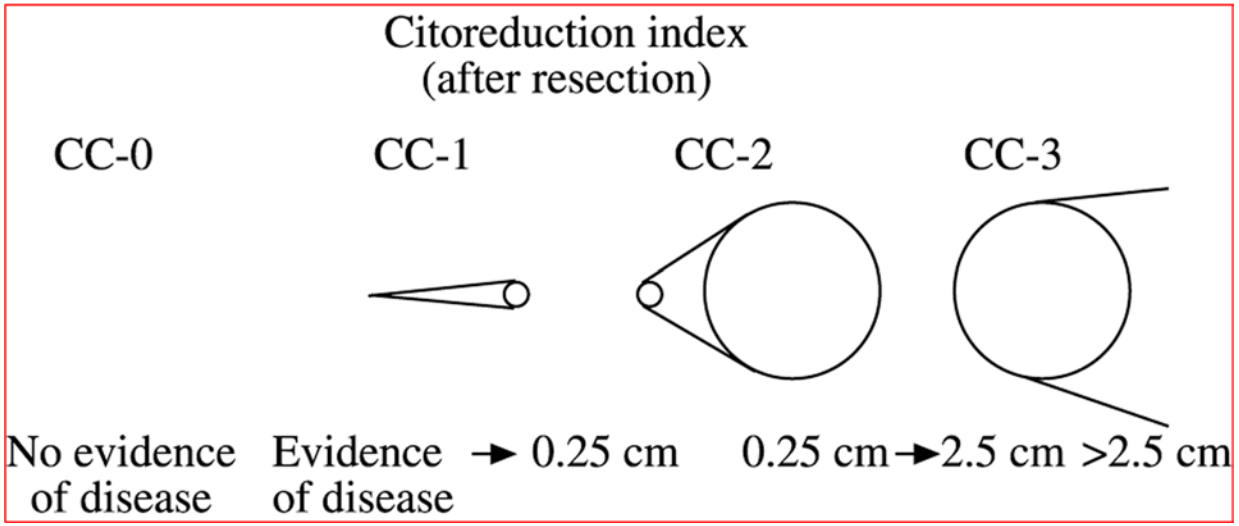
LS 0 No tumor seen
LS 1 Tumor up to 0.5 cm
LS 2 Tumor up to 5.0 cm
LS 3 Tumor > 5.0 cm or confluence



CC scroe – **Complete** Cytoreduction

- Remove **all macroscopic** tumors

- CC score (Vs optimal debulking)



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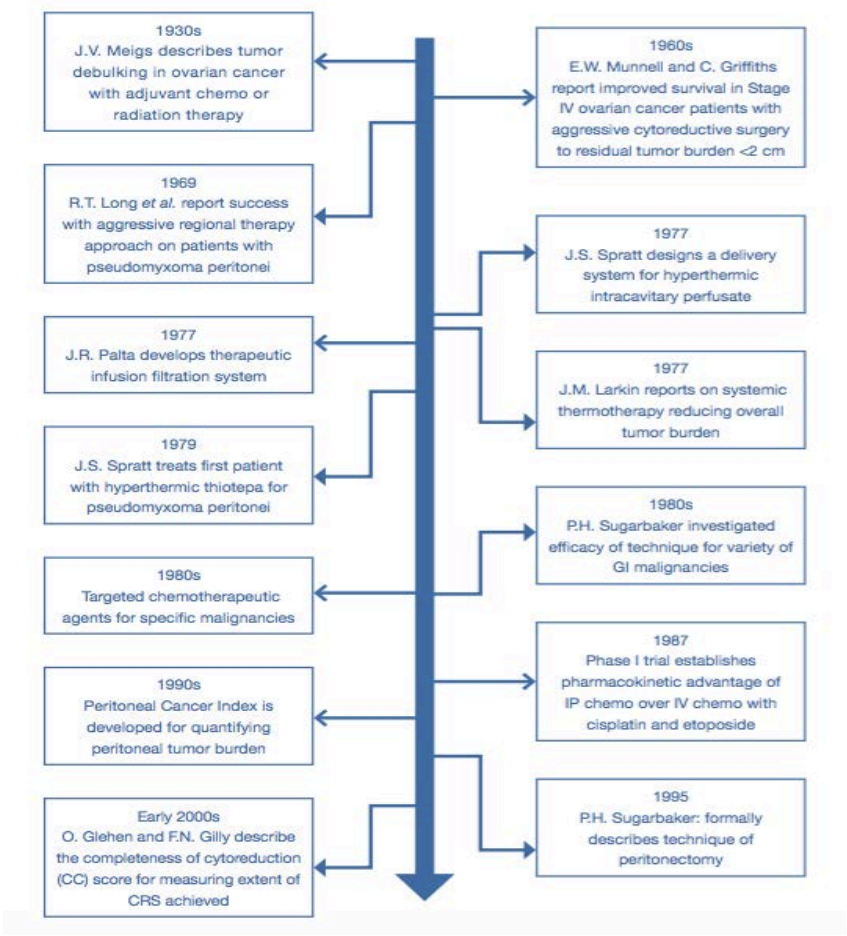
Global Perspective

History



J. V. Meigs

OB/GYN

Dr John Spratt

Professor of Surgery

University of Louisville

Paul H. Sugerbaker

Washington DC, USA

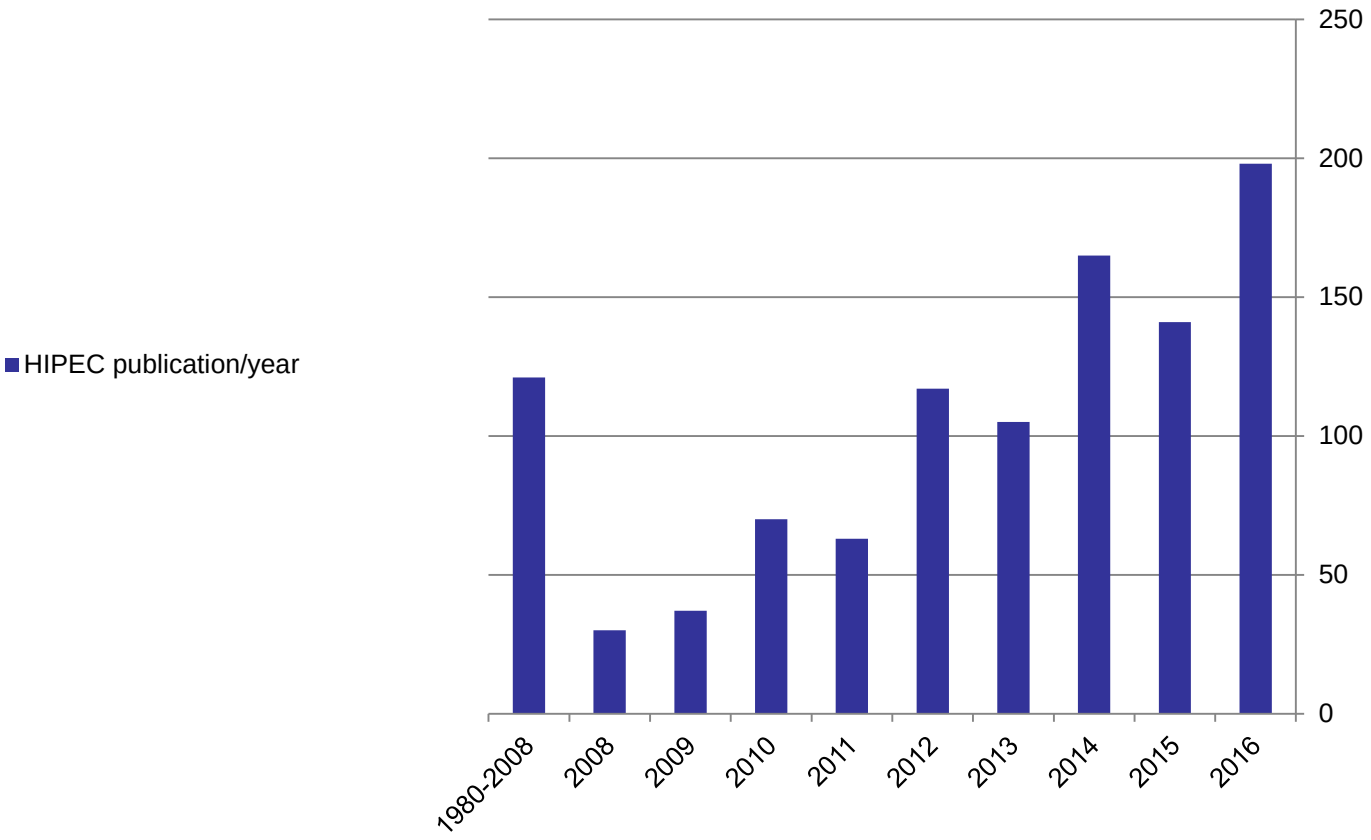
- 1998 – The first **PSOGI**-meeting in Basingstoke England with Bill Heald and Paul H. Sugarbaker as Conference Directors <20 surgeons

- (**PSOGI** – Peritoneal Surface Oncology Group International)

Since than…

- Getting acceptance
- More than 400 centers
- 10th PSOGI washington – 700 surgeons worldwide

HIPEC publication/year



In recent years, following the commercial development of safe and efficacious perfusion systems, more and more medical centers are performing cytoreduction and HIPEC.

Epithelial Ovarian (Carcinoma (EOC

.No need for Introduction…

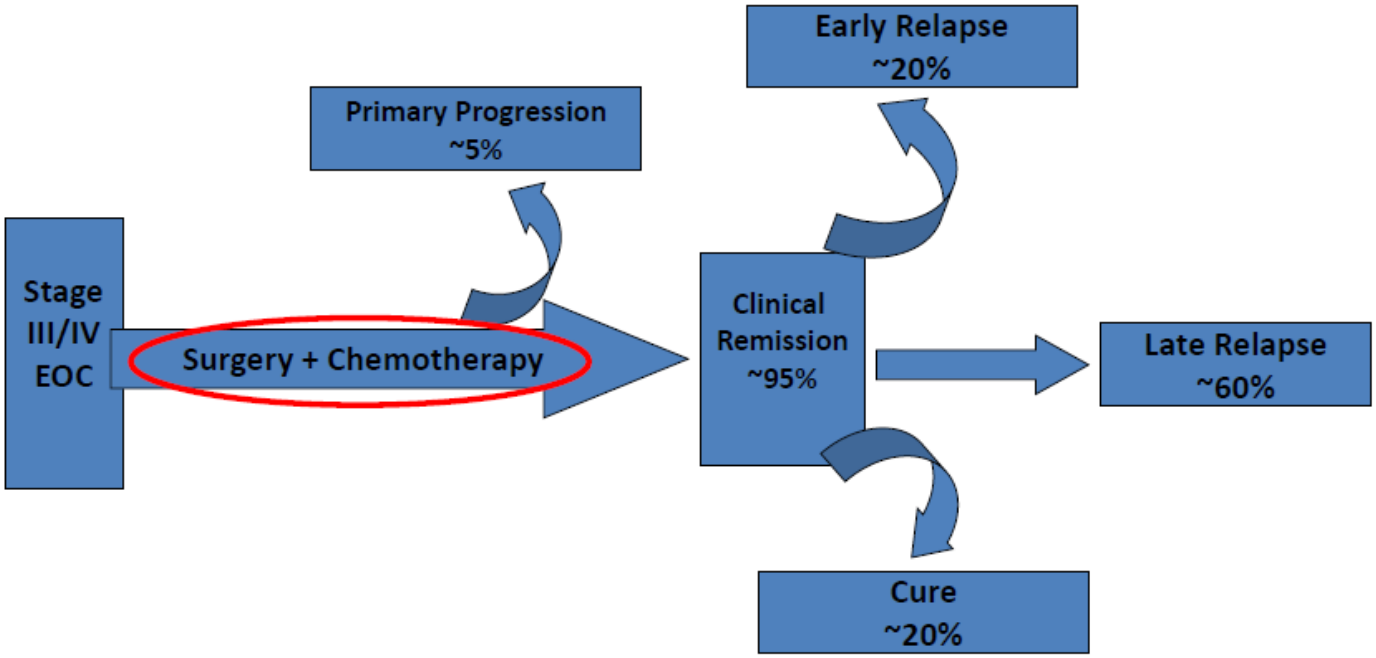
•Bad prognosis

- With current therapy 5-year survival rates are:
  - FIGO IIIB 41.5%
  - FIGO IIIC 32.5%
  - FIGO IV 18.6%

(Heintz AP. *Int J Gynecol Obstet.* 2006:95 Suppl 1)

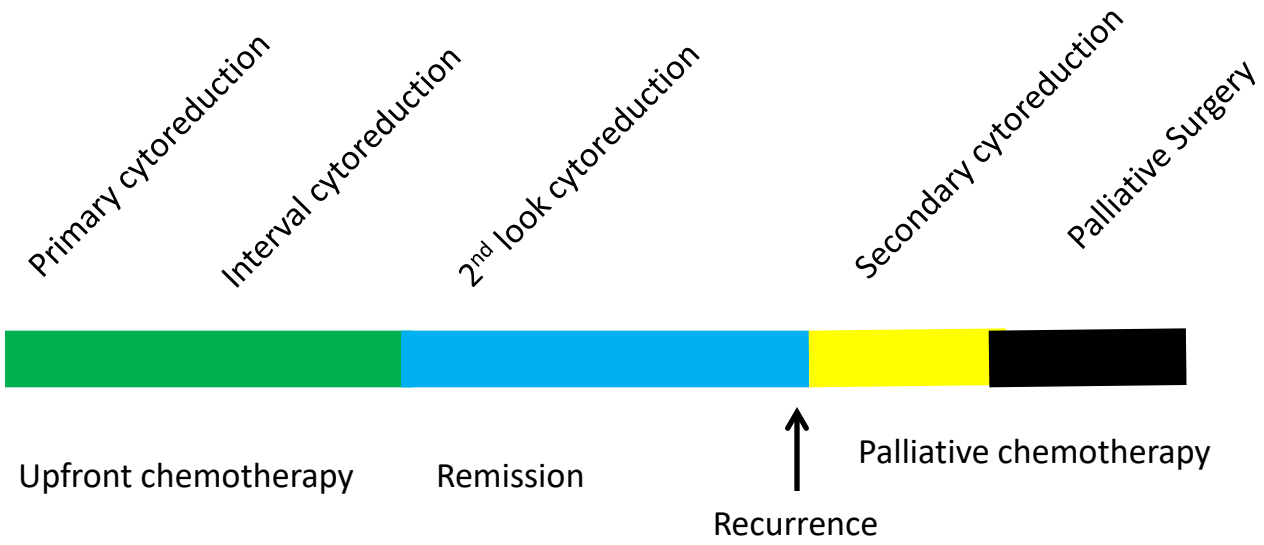
•But…

Advanced Ovarian Cancer- Natural History



With permission: Chi D and Ivanovitch O. MSKCC

The role of Cytoreductive Surgery in Stage III-IV EOC



Modified from: Chi D and Ivanovitch O. MSKCC

Current Frontline Therapy

- Standard front-line treatment of EOC involves the combination of surgery and chemotherapy. (Platinum compound + Taxene)

- The prognosis of patients with EOC was reported to be related to the amount of residual disease at the end of surgery and to their response to platinum compounds

Frontline Therapy

Major current debate centers on:

- Extent of surgery
- Whether neoadjuvant chemotherapy is of benefit

Why IP chemotherapy?

- **Visceral metastasis**
  - Rich blood supply D/T angiognensis

- **Peritoneal metastasis**
  - Tumor layers
  - Ascitis
  - Limited blood supply

Why Hyperthermia?

- To improve drug penetration into the tissues
- Improve cytotoxicity
- Direct killing effect of heat

Frontline IP Therapy

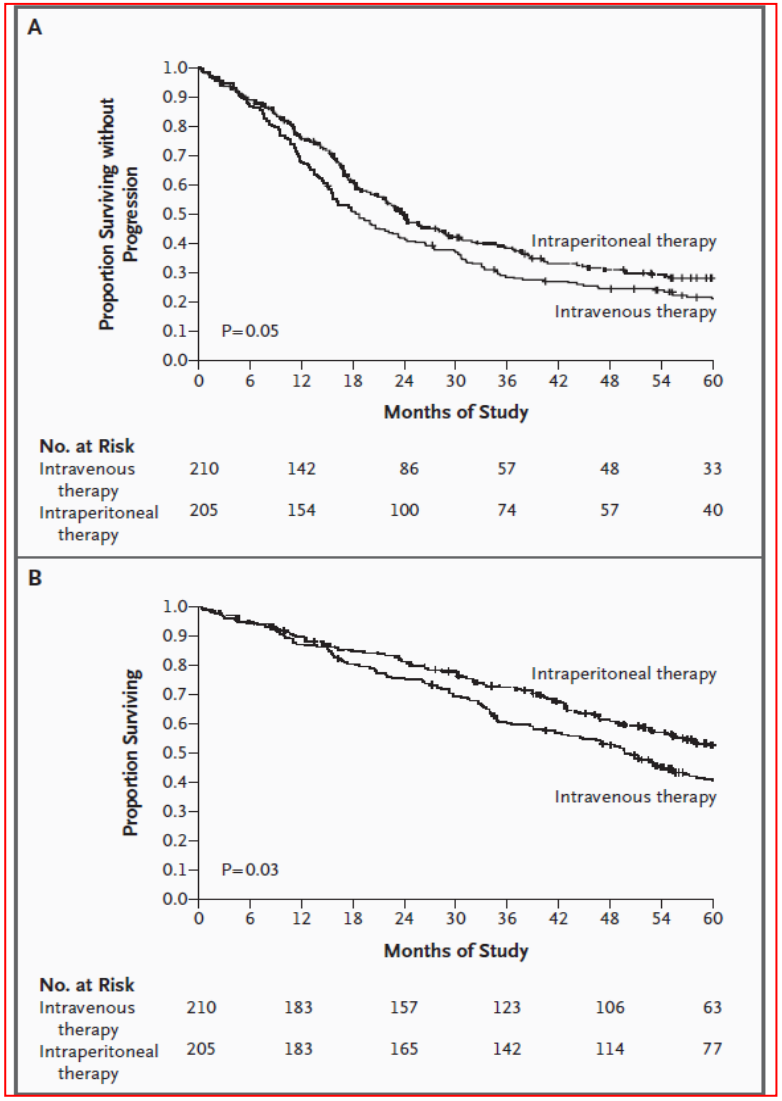
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer

Deborah K. Armstrong, M.D., Brian Bundy, Ph.D., Lari Wenzel, Ph.D., Helen Q. Huang, M.S., Rebecca Baergen, M.D., Shashikant Lele, M.D., Larry J. Copeland, M.D., Joan L. Walker, M.D., and Robert A. Burger, M.D., for the Gynecologic Oncology Group*

Frontline IP Therapy



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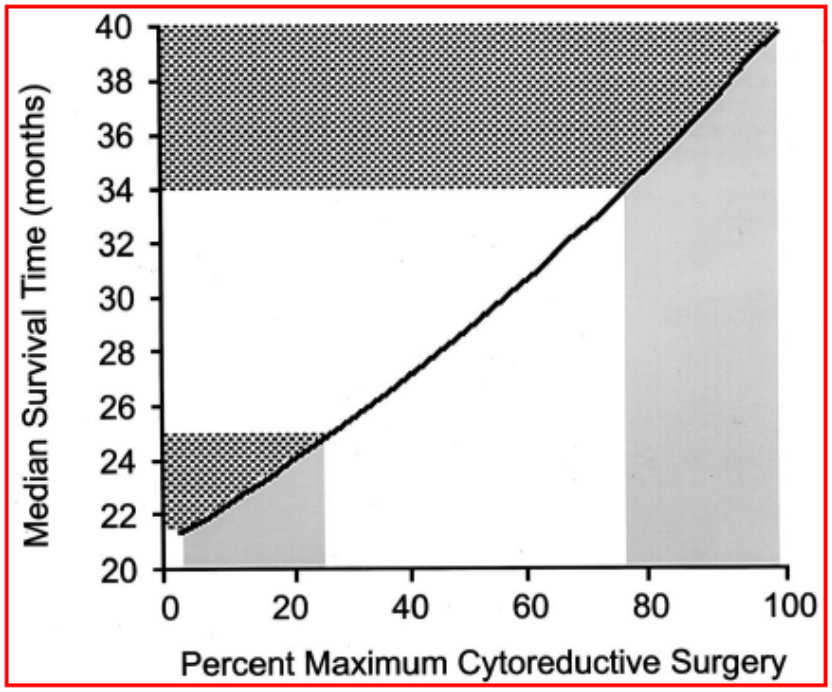
Completnece of cytoreduction

Extent of Cytoreductive Surgery

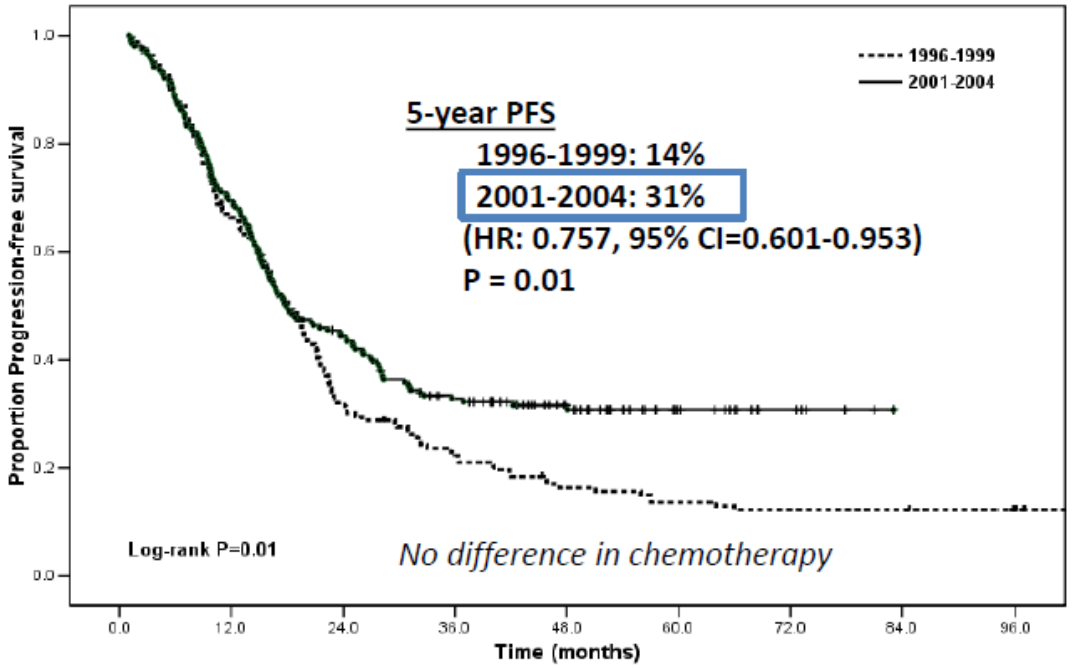


Each 10% increase in maximal cytoreduction associated with a 5.5% increase in median survival time.

Bristow RE et al. J Clin Oncol 2002;20:1248-59.

The value of efficient control of upper abdominal disease

Progression-Free Survival (PFS)



Chi DS et al. Gynecol Oncol 2009

Eisenhauer EL, Chi D. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer.
Gynecol Oncol 2006;.90–103:1083

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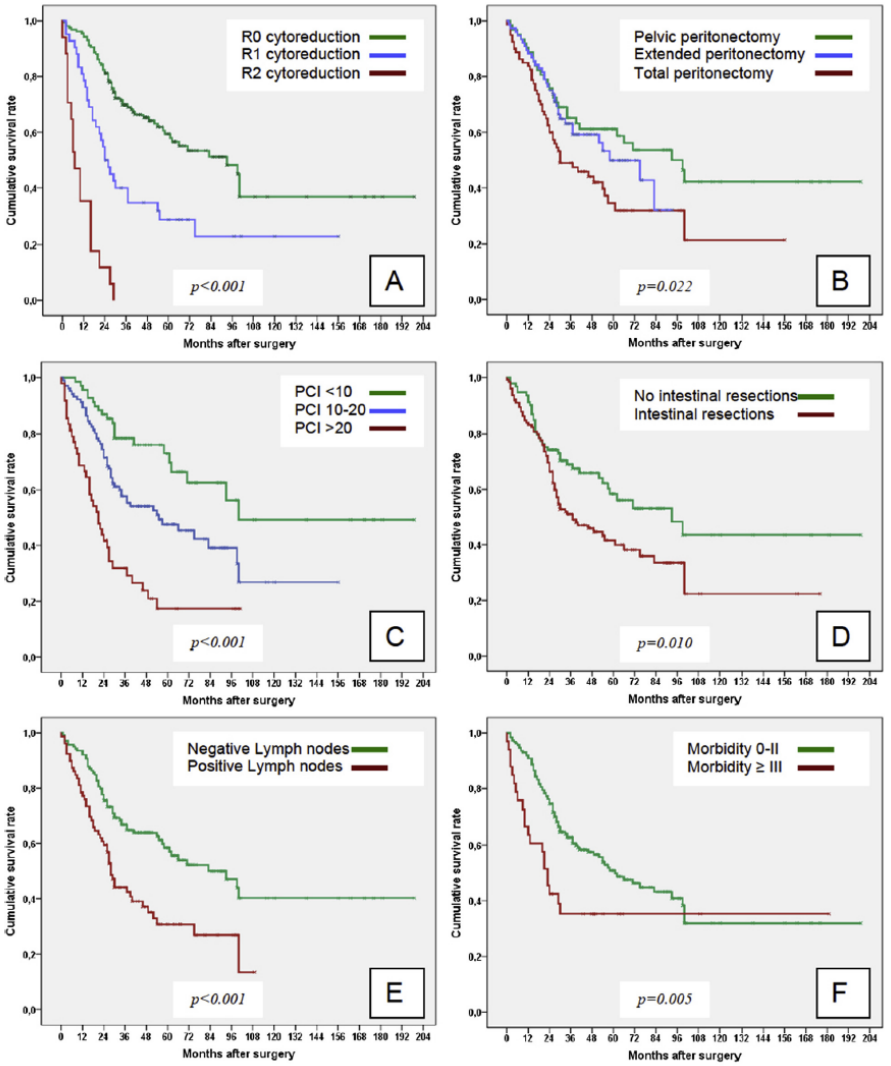
Available online at www.sciencedirect.com
ScienceDirect
EJSO
the Journal of Cancer Surgery
EJSO 42 (2016) 224–233
www.ejso.com

Peritonectomy procedures and HIPEC in the treatment of peritoneal carcinomatosis from ovarian cancer: Long-term outcomes and perspectives from a high-volume center

F.C. Muñoz-Casares [a,*], F.J. Medina-Fernández [a], Á. Arjona-Sánchez [a], Á. Casado-Adam [a], J.M. Sánchez-Hidalgo [a], M.J. Rubio [b], R. Ortega-Salas [c], M.C. Muñoz-Villanueva [d], S. Rufián-Peña [a], F.J. Briceño [a]

[a] Surgical Oncology Unit, Department of General and Digestive Surgery, University Hospital Reina Sofía, Córdoba, Spain
[b] Department of Oncology, University Hospital Reina Sofía, Córdoba, Spain
[c] Department of Pathology, University Hospital Reina Sofía, Córdoba, Spain
[d] Unit of Research, Maimonides Institute for Research in Biomedicine (IMIBIC), Córdoba, Spain



Appendix- absolut benefit

2298 patients from 16 specialized units underwent CRS for PMP.

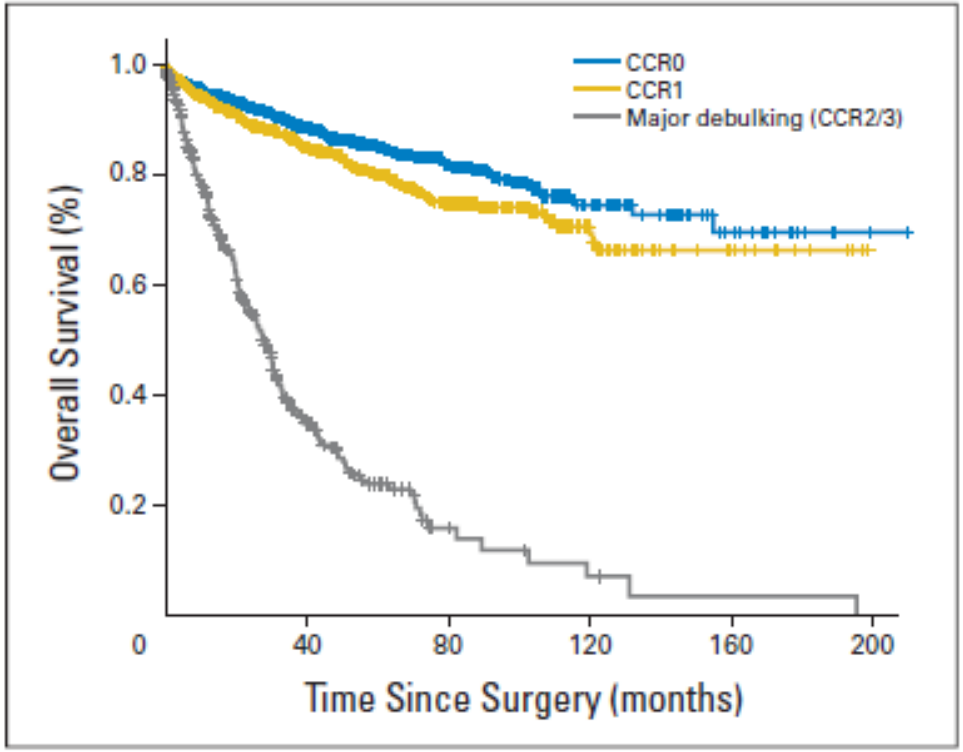


Fig 2. Prognostic impact of completeness of cytoreduction (CCR) in surgery on overall survival ($P < .001$).

J Clin Oncol. 2012 Jul 10;30(20):2449-56. doi: 10.1200/JCO.2011.39.7166. Epub 2012 May 21.

Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

Chua TC, Moran BJ, Sugarbaker PH, Levine EA, Glehen O, Gilly FN, Baratti D, Deraco M, Elias D, Sardi A, Liauw W, Yan TD, Barrios P, Gómez Portilla A, de Hingh IH, Ceelen WP, Pelz JO, Piso P, González-Moreno S, Van Der Speeten K, Morris DL.

Complete cytoreduction CC0-1 translates into survival benefit

+

IP therapy is better than IV therapy

=

Upfront CRS+HIPEC

Why CRS+HIPEC?

Colon level one evidence – in the NCCN guidelines and Wetern Europen guidlines

Randomized Trial of Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy and Palliative Surgery in Patients With Peritoneal Carcinomatosis of Colorectal Cancer

By Vic J. Verwaal, Serge van Ruth, Eelco de Bree, Gooike W. van Slooten, Harm van Tinteren, Henk Boot, and Frans A.N. Zoetmulder

Purpose: To confirm the findings from uncontrolled studies that aggressive cytoreduction in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) is superior to standard treatment in patients with peritoneal carcinomatosis of colorectal cancer origin.

Patients and Methods: Between February 1998 and August 2001, 105 patients were randomly assigned to receive either standard treatment consisting of systemic chemotherapy (fluorouracil-leucovorin) with or without palliative surgery, or experimental therapy consisting of aggressive cytoreduction with HIPEC, followed by the same systemic chemotherapy regime. The primary end point was survival.

Results: After a median follow-up period of 21.6 months, the median survival was 12.6 months in the standard therapy arm and 22.3 months in the experimental therapy arm (log-rank test, $P = .032$). The treatment-related mortality in the aggressive therapy group was 8%. Most complications from HIPEC were related to bowel leakage. Subgroup analysis of the HIPEC group showed that patients with 0 to 5 of the 7 regions of the abdominal cavity involved by tumor at the time of the cytoreduction had a significantly better survival than patients with 6 or 7 affected regions (log-rank test, $P < .0001$). If the cytoreduction was macroscopically complete (R-1), the median survival was also significantly better than in patients with limited (R-2a), or extensive residual disease (R-2b; log-rank test, $P < .0001$).

Conclusion: Cytoreduction followed by HIPEC improves survival in patients with peritoneal carcinomatosis of colorectal origin. However, patients with involvement of six or more regions of the abdominal cavity, or grossly incomplete cytoreduction, had still a grave prognosis.

J Clin Oncol 21:3737-3743. © *2003 by American Society of Clinical Oncology.*

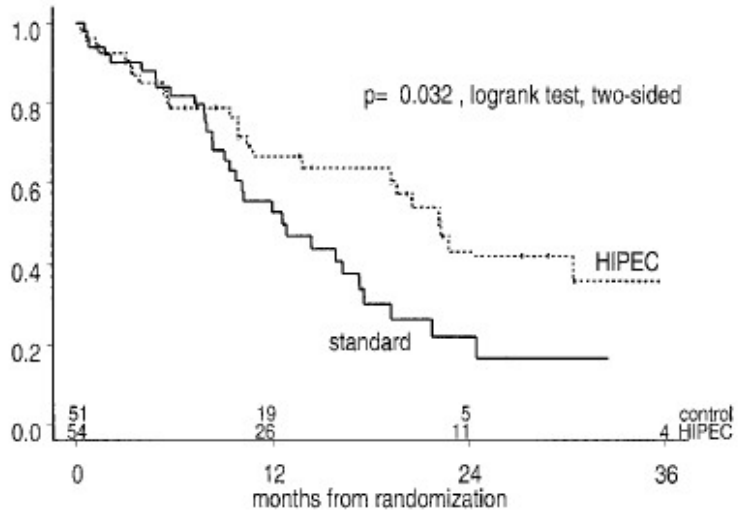


Fig 2. Kaplan-Meier survival curve, comparing standard treatment to hyperthermic intraperitoneal chemotherapy (HIPEC).

VOLUME 27 · NUMBER 6 · FEBRUARY 10 2009
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Complete Cytoreductive Surgery Plus Intraperitoneal Chemohyperthermia With Oxaliplatin for Peritoneal Carcinomatosis of Colorectal Origin

Dominique Elias, Jérémie H. Lefevre, Julie Chevalier, Antoine Brouquet, Frédéric Marchal, Jean-Marc Classe, Gwenaël Ferron, Jean-Marc Guilloit, Pierre Meeus, Diane Goéré, and Julia Bonastre

Two-year and 5-year overall survival rates were 81% and 51% for the HIPEC group, respectively, and 65% and 13% for the standard group, respectively.

Median survival was 23.9 months in the standard group versus 62.7 months in the HIPEC group (*P* .05, log-rank test).

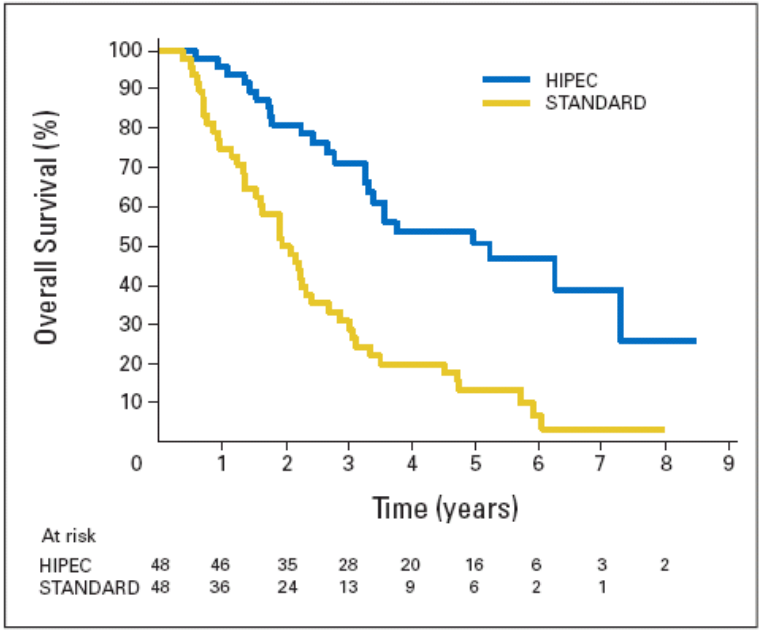


Fig 1. Overall survival of group receiving cytoreductive surgery, hyperthermic intraperitoneal chemotherapy (HIPEC), and systemic treatment versus those receiving standard treatment.

Mesothelioma

Ann Surg Oncol (2012) 19:1416–1424
DOI 10.1245/s10434-012-2237-2

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

ORIGINAL ARTICLE – REGIONAL CANCER THERAPIES

Cytoreductive Surgery with Selective Versus Complete Parietal Peritonectomy Followed by Hyperthermic Intraperitoneal Chemotherapy in Patients with Diffuse Malignant Peritoneal Mesothelioma: A Controlled Study

Dario Baratti, MD[1], Shigeki Kusamura, PhD[1], Antonello Domenico Cabras, MD[2], and Marcello Deraco, MD[1]

[1]Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [2]Department of Pathology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

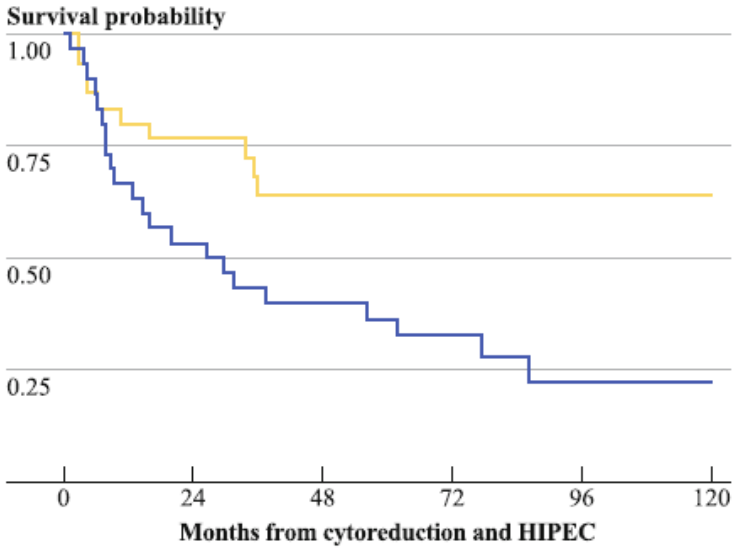


FIG. 1 Overall survival in patients undergoing surgical cytoreduction with selective (*blue line*) or complete (*yellow line*) parietal peritonectomy, combined with hyperthermic intraperitoneal chemotherapy (HIPEC). The difference was statistically significant ($P = 0.027$, log rank test)

HIPEC in Frontline Therapy for EOC

- The use of HIPEC as frontline therapy in EOC makes theoretic sense in view of the high rates of recurrence following standard treatment

- Experience reported in the literature is increasing

HIPEC for Consolidation of Frontline therapy

- The recurrence rate following front-line treatment of EOC is high
- There is no proven method of reducing this rate
- IP consolidation makes sense because recurrence is often in the peritoneal cavity
- HIPEC may have a role to play
  (EORTC, Chorus trials)

CRS-HIPEC for Recurrent Disease

Available online at www.sciencedirect.com

ScienceDirect

EJSO 39 (2013) 1435–1443

EJSO the Journal of Cancer Surgery

www.ejso.com

Peritoneal carcinomatosis treated with cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for advanced ovarian carcinoma: A French multicentre retrospective cohort study of 566 patients☆

N. Bakrin [a,b], J.M. Bereder [c], E. Decullier [a,d], J.M. Classe [e], S. Msika [f], G. Lorimier [g], K. Abboud [h], P. Meeus [i], G. Ferron [j], F. Quenet [k], F. Marchal [l], S. Gouy [m], P. Morice [m], C. Pomel [n], M. Pocard [o], F. Guyon [p], J. Porcheron [i], O. Glehen [b,q,*], from the FROGHI (FRench Oncologic and Gynecologic HIPEC) Group[n]

CRS-HIPEC for Recurrent Disease

- 13 medical centers over long period of time
- 474 patients with recurrent disease
- Complete cytoreduction in 74.9%
- Grade 3-4 morbidity 31% mortality 0.8%

- Median survival for patients with recurrent disease was 35.4 months
- Median survival for patients with 1st look surgery was 52.7 months
- There was no survival difference between platinum- sensitive and –resistant patients
- PCI was the strongest predictor of survival

CRS-HIPEC for Recurrent Disease-Greece

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 ONCOLOGY

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]

TABLE 1 Characteristics of 120 patients

Characteristic	HIPEC	Non-HIPEC
n	60	60
Mean age, years	58.3	58.1
Mean no. of cycles of adjuvant chemotherapy	5	5
Mean preoperative CA-125 value (U/ml)	83.7	80.5

CRS-HIPEC for Recurrent Disease

Patients were randomized between:

Group A: (n=60) CRS+HIPEC –Cisplatinum+Paclitaxel

Group B: (n=60) CRS followed by systemic therapy

TABLE 3 Survival by stage and platinum responsiveness by HIPEC group

Mean survival	Stage III_c survival (months)	Stage IV survival (months)
HIPEC group		
Platinum sensitive	27.28	25.4
Platinum resistant	26.08	27
Non-HIPEC group		
Platinum sensitive	15.7	13.5
Platinum resistant	10.7	9.37

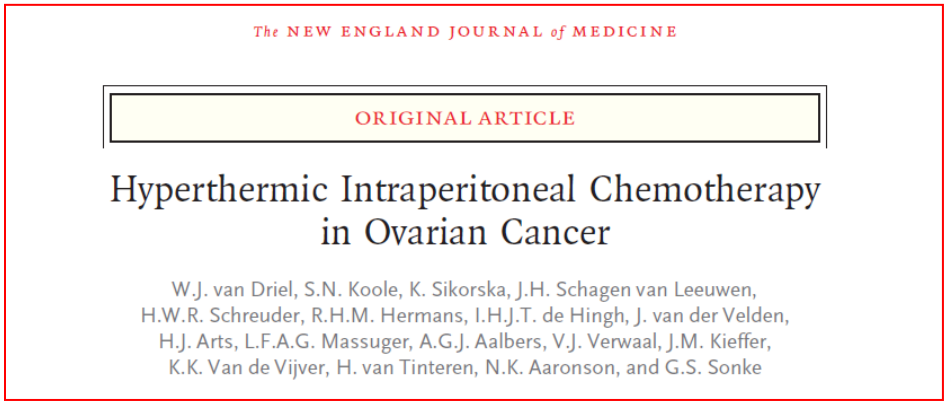
CRS-HIPEC for Recurrent Disease

TABLE 3 Series of HIPEC for the treatment of an ovarian cancer relapse

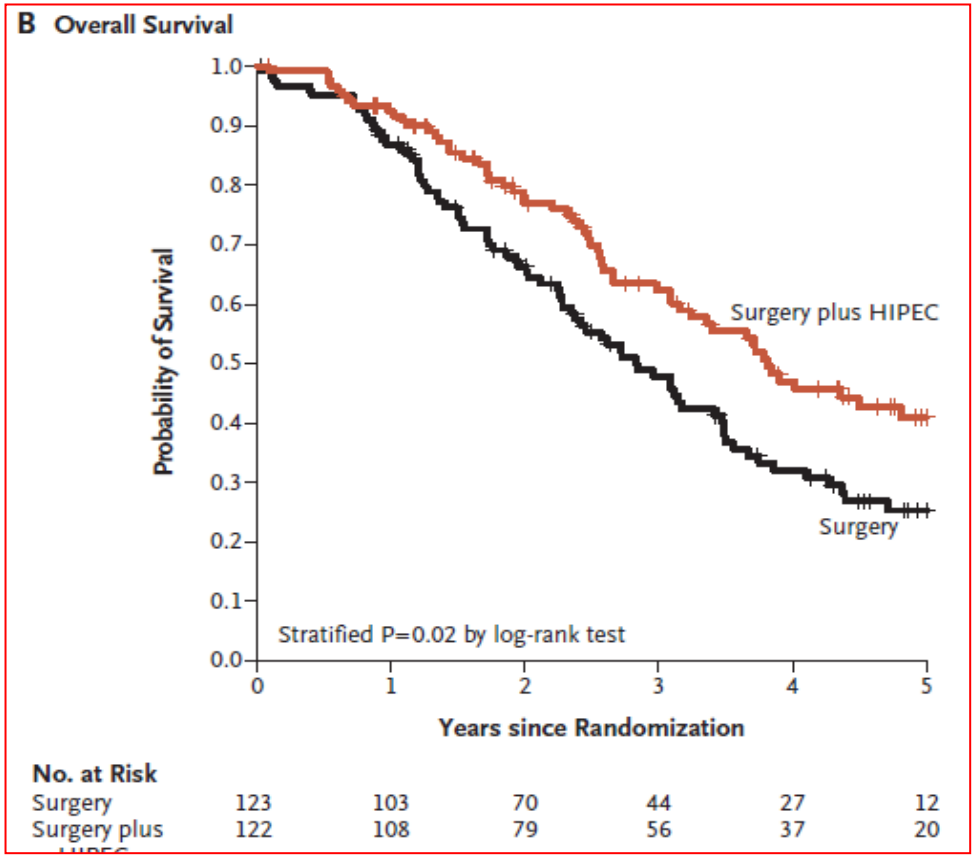
Author/(year of publication)	Number of patients	Drug	Duration (min)	cc0	OS	Dfs (ms)	Mortality	Morbidity	Control group
Chatzigeorgiou et al.[26]	20	Cicsplatin	120	–	29 ms	21	10 %	–	No
Zanon et al. [27]	30	Cisplatin	90	77 %	28 ms	17	3.3 %	16.7 %	No
Munoz-Casares et al.[17]	26	Paclitaxel	60	100 %	67 %[a]	48	0 %	29 %	Yes ($n = 12$)
Spiliotis et al.[19]	24	Cisplatin/Doxorubicin	90	83 %	–	–	–	40 %	Yes ($n = 24$)
Fagotti et al.[18]	30	Oxaliplatin	30	97 %	68.4 %[a]	–	0 %	35 %	Yes
Deraco et al.[28]	56	Cisplatin/Doxorubicin	90	84 %	25.7 ms	10,8	5.30 %	26.30 %	No
Ceelen et al.[29]	42	Cisplatin/Oxaliplatin	90	100 %	37 ms	13	0 %	21 %	No
Argenta et al.[30]	10	Carboplatin	–	–	NR	NR	0 %	20 %	No
Le Brun (2013)	49	Cisplatin/Eloxatin mitomycin	30–60	100 %	75.6 %[b]	23.9	NE	NE	Yes ($n = 26$)

Ovary – level I Evidence

- 3 cycles carbo+paclitaxel
- 122 pt CRS+HIPEC
- 123 interval CRS
- 3 cycles carbo+paclitaxel
- Primary end point – RFS
- Secondary end point - OS



Ovary – level I Evidence



Conclusions of Dutch trial

- For patients with FIGO stage III ovarian cancer treated with neo-adjuvant chemotherapy, adding HIPEC to interval cytoreductive surgery prolongs:

- Recurrence free survival – 3.5 months
- Overall survival – 12 months

- Without any difference in toxicity or quality of life

(With permission from Dr. Van Driel)

Our Experience

- 383 patients - total
- Ovary – 8%

- 59.9% female

- Mean age of 55 (8-84)

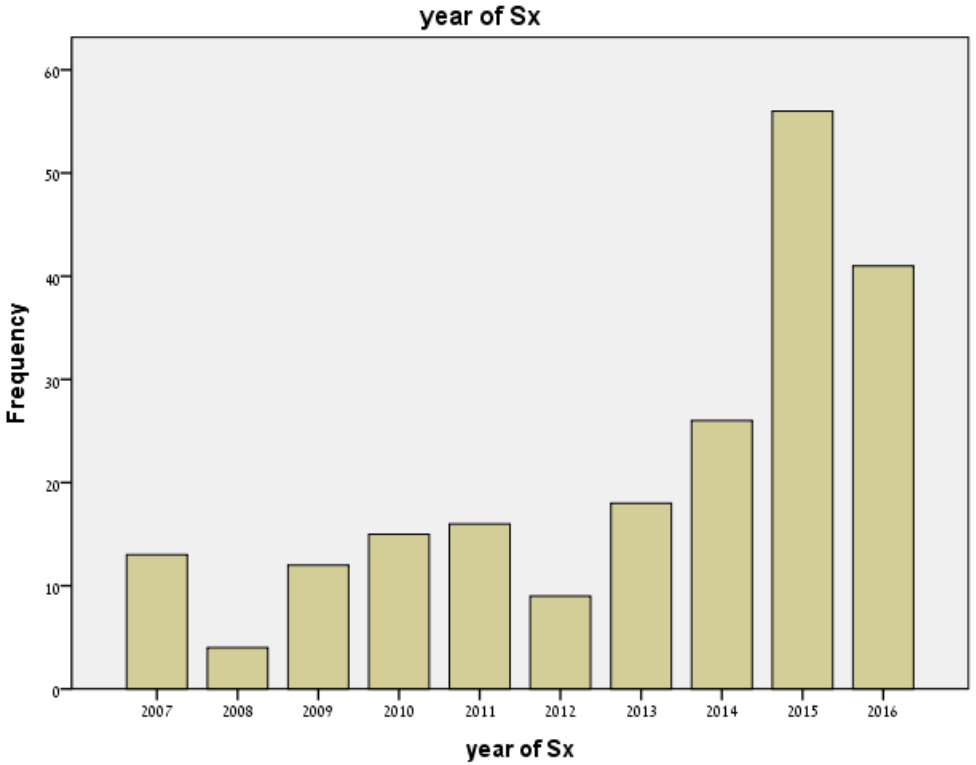
Cases per year

2015 – 76

2016 – 69

2017 – 70

2018 - 100

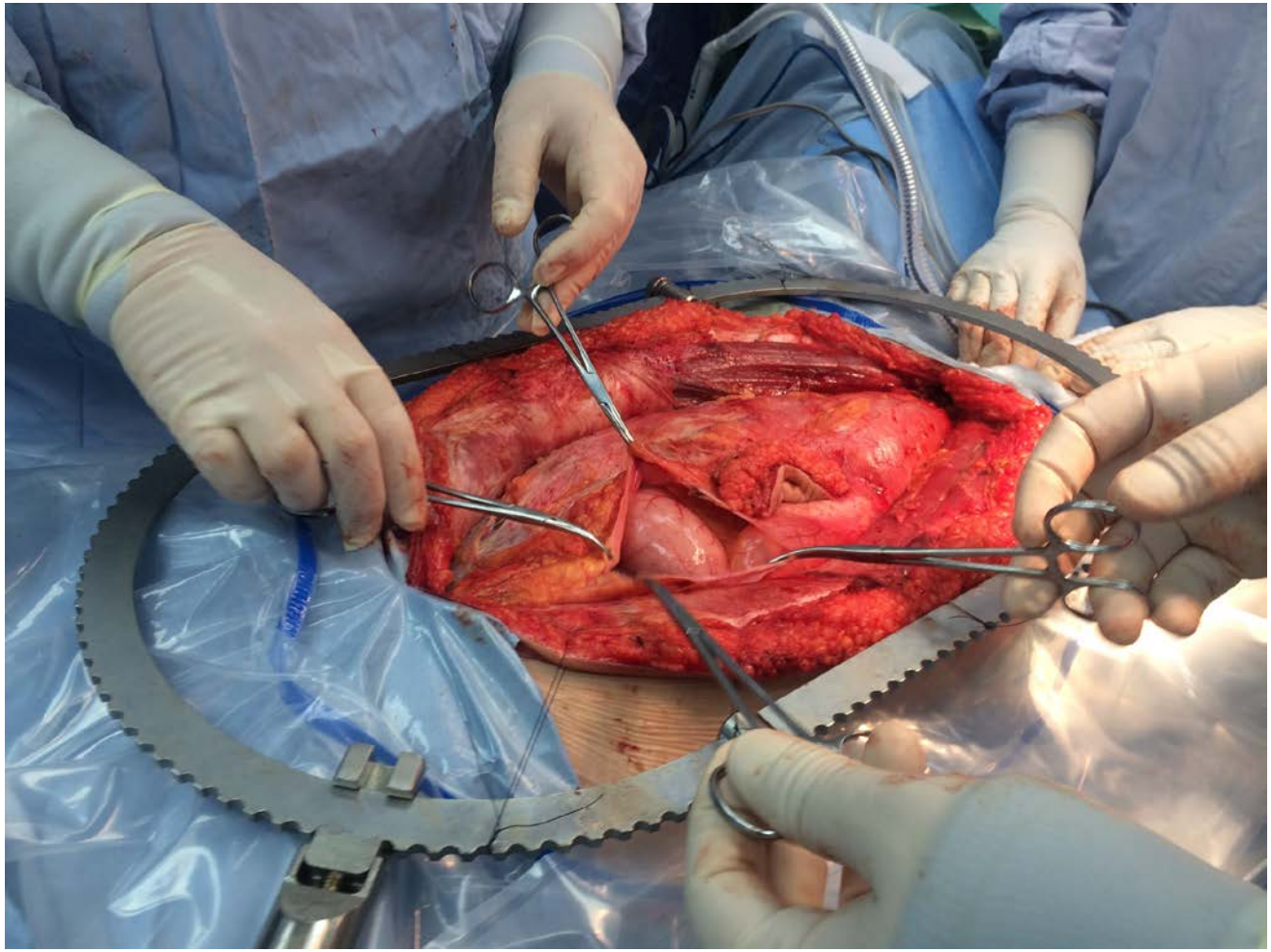


Overall survival:

	N (%)
NED (No evidence of disease)	145 (43%)
AWD (Alive with disease)	101 (30%)
DOD (Dead of disease)	62 (18.4%)

- Major complications 20 %
- Mortality – 2.1%

המרכז הרפואי ע"ש ח. שיבא תל-השומר



Summary

- The role of HIPEC in EOC is yet to be defined
- There is a growing body of evidence supporting the role of CRS+HIPEC in recurrent EOC
- There is scarce data regarding the addition of HIPEC to up-front or interval cytoreductive surgery however, the data is promising
- ***Collaboration is the key for success…***

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