

Multi-disciplinary Approach to Complex Surgical Patients and HIPEC

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- There is no financial conflict of interest to disclose

- Overview of surgical management of ovarian cancer
- IP chemotherapy
- HIPEC
- Beaumont experience

Epithelial Ovarian Cancer

US (2022):

- New cases: 22,440
- Deaths: 14,080
- Most cases are diagnosed in advanced stages
- 75% stage III-IV
- 5 year survival decreases as stage of disease increases (29% vs. 92%)

Clinical presentation

The majority of ovarian cancers are diagnosed at an advanced stage

- Confined to primary site (15 %)
- Spread to regional lymph nodes (17 %)
- Distant metastases (61%)
- Unstaged (7%)

Initial Therapy of Advanced Stage Ovarian Cancer

- Cytoreductive Surgery (CRS)
(Tumor Debulking)

+

- Combination of chemotherapy

- Cisplatin + Paclitaxel +/- Bevacizumab

or

- Carboplatin + Paclitaxel +/- Bevacizumab

Rationale for primary debulking

- Rapid symptom relief (ascites, omental cake, bowel obstruction)
- Improved tumor perfusion
- Increased tumor growth fraction

Rationale for neoadjuvant chemo (NAC)

Shrinking tumor mass preoperatively

- Improve resectability
- Increase chance of optimal debulking
- Shorten operative time and decrease risks
- May decrease the radicality of surgery in some cases



Cytoreductive Surgery (CRS)

Give Me 5 Hours, I'll Give You 2 Years!!

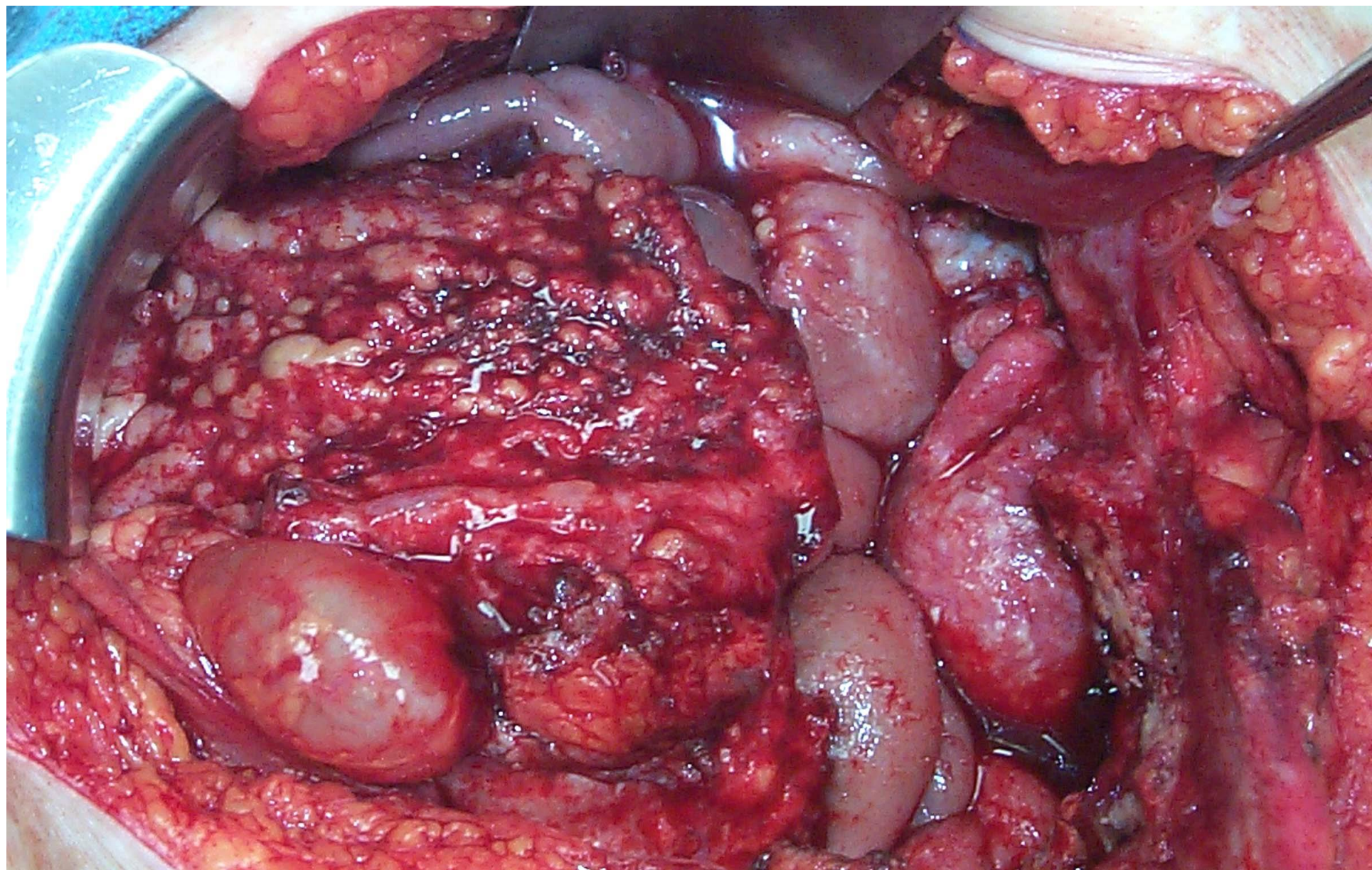
Surgery

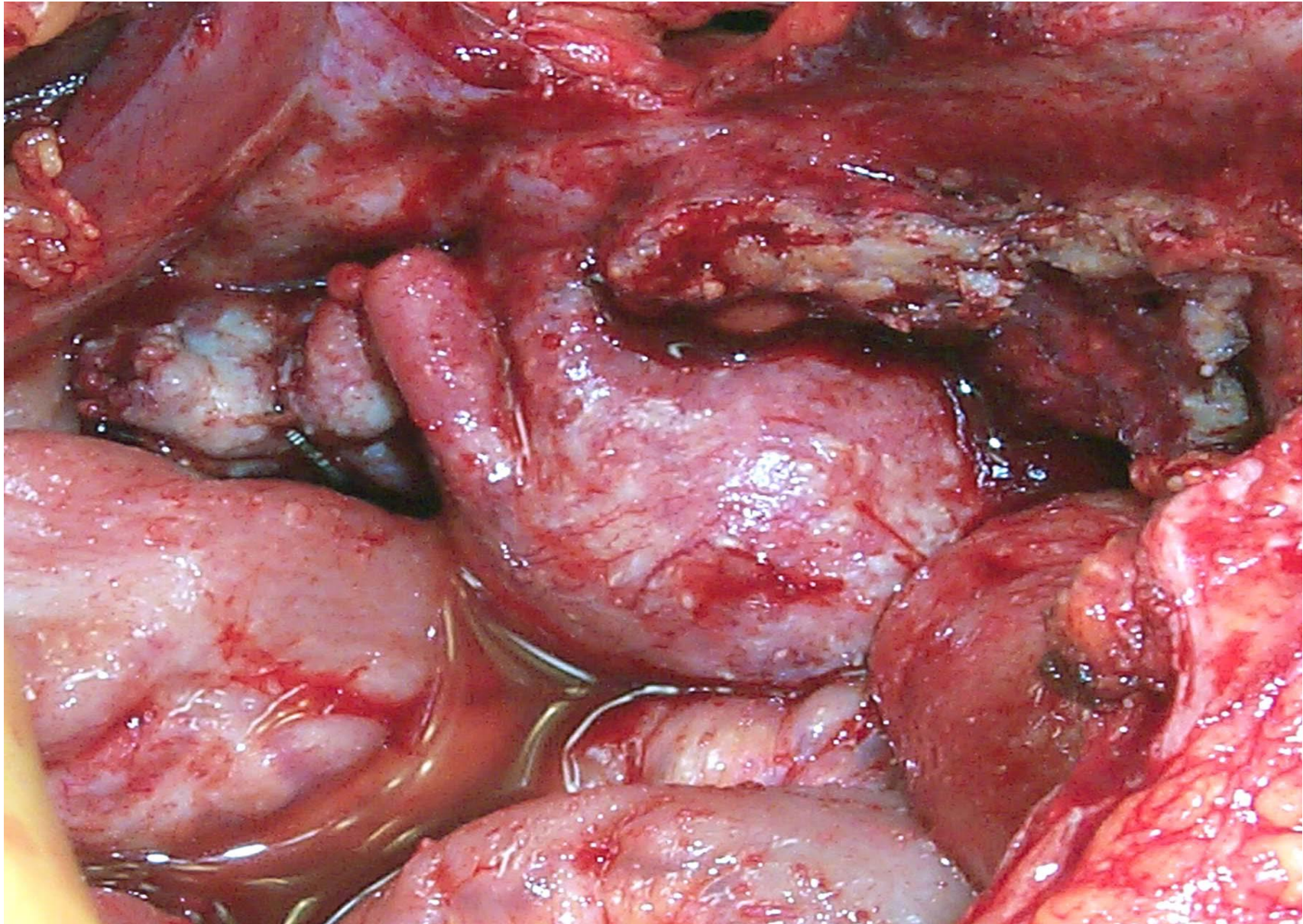
- Radical Surgical debulking
- Cytoreductive surgery for ovarian cancer appears to improve survival *only* when no or very small volume residual tumor is left behind

Standard cytoreductive surgery

Removal of

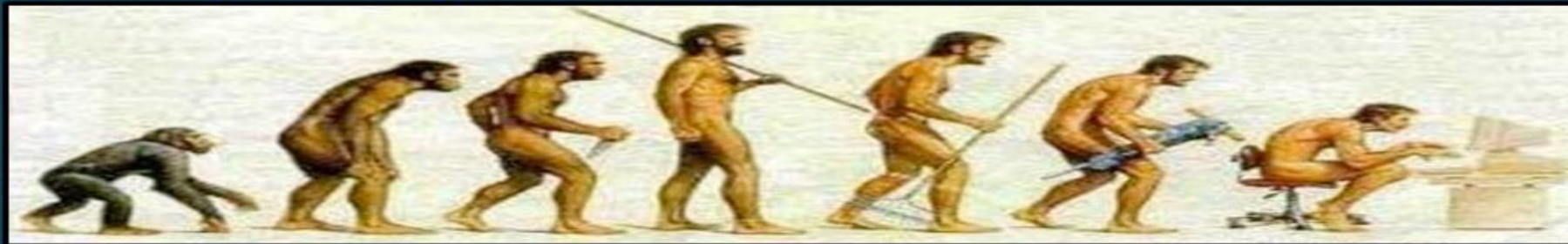
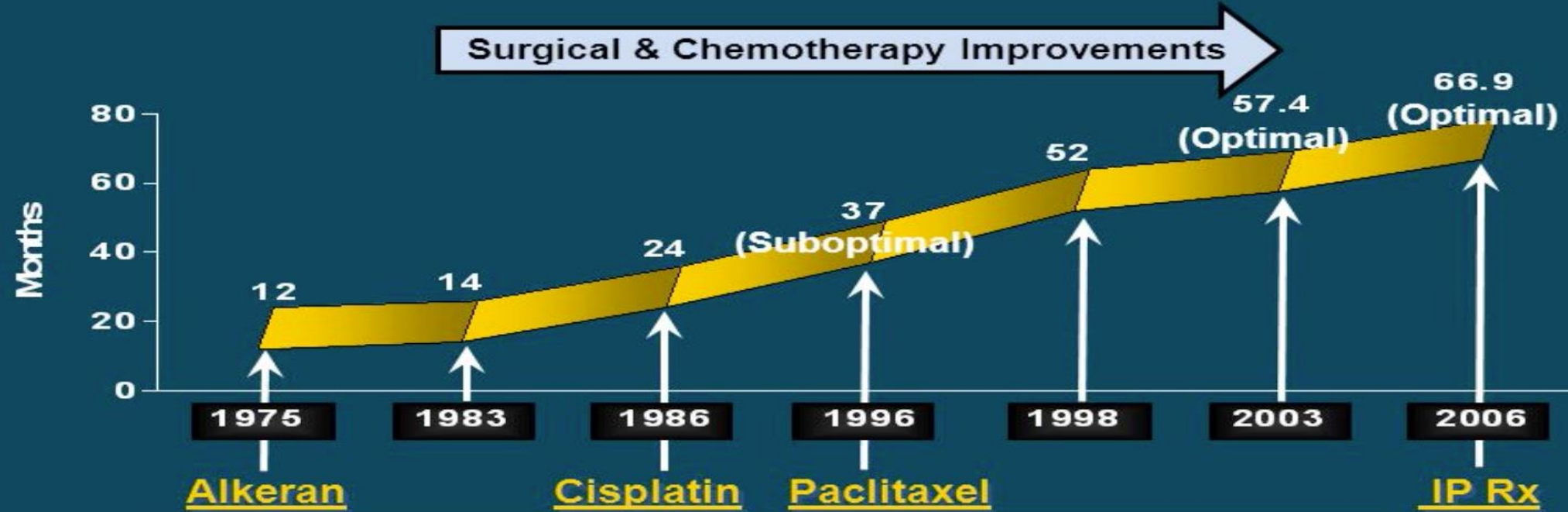
- The internal genitalia (TAH BSO)
- Omentum
- Peritoneal tumor implants





Chemotherapy

The 'Evolution' of Treatment for Advanced Ovarian Cancer and Effect on Survival

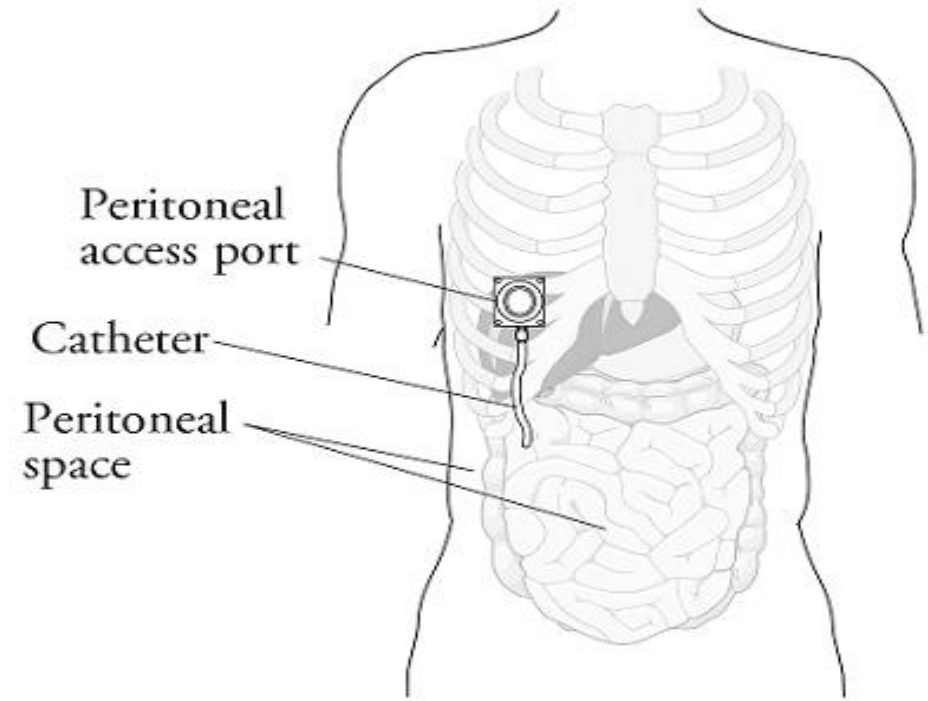


Background for Ovarian Cancer Therapy

- **1965**- Cisplatin noted to inhibit bacterial cell division at MSU by Barnett Rosenthal
- **1967**- Paclitaxel is isolated from the Pacific yew by researchers at the NCI during plant derivatives research initiative
- **1978**- Cisplatin is FDA approved for use in ovarian and testicular cancer
- **1983**- Cyclophosphamide and doxorubicin established as SOC treatment for ovarian cancer Omura. GOG22. *Cancer* 1983
- **1989**- Cisplatin therapy established as SOC treatment for ovarian cancer AND the benefits/definition of optimal cytoreduction are adopted Omura. GOG52. *J Clin Onc.*1989
- **1992**- Paclitaxel is FDA approved for use in ovarian cancer
- **1996**- Combination of IV cisplatin and paclitaxel established as SOC treatment in optimally debulked ovarian cancer. McGuire. GOG111.*NEJM*.1996
- **2003**- Combination of IV carboplatin and paclitaxel established as SOC treatment in optimally debulked ovarian cancer. Ozols. GOG158. *J Clin Onc.* 2003

- The initial response rate is high
- however, approximately 20 % of EOC are naturally resistant to platinum
- Of those with platinum-sensitive disease (80%) that achieve a frontline complete pathologic response confirmed at a second surgery, 60 % will recur within 5 years.

Intra Peritoneal Chemotherapy (IP)



Rationale for Intra Peritoneal chemotherapy in Ovarian Cancer

- The peritoneal cavity is the principal site of disease in ovarian cancer
- Debulking to minimal residual disease improves outcomes and leaves minimal residual tumor
- Intensity of intravenous therapy is limited by systemic toxicity

Rationale for Intra Peritoneal chemotherapy in Ovarian Cancer

- Intraperitoneal delivery of chemotherapy enhances drug delivery at the peritoneal surface and may improve outcomes by eliminating residual microscopic peritoneal disease more efficiently than intravenous administration of chemotherapy.
- If residual peritoneal tumor is exposed to increased concentration of drug for prolonged period of time, it may increase local response and decrease systemic side effects

Development of Intraperitoneal Chemotherapy in Ovarian Cancer

- 1978: Dedrick presents theoretical model for IP therapy in ovarian cancer
- 1982-1992: multiple pharmacokinetic and phase I studies show
 - *10-20 fold increase* in cisplatin and carboplatin and 1,000 fold increase in paclitaxel peritoneal concentrations achieved and maintained longer with IP infusion compared to IV
 - Successful intraperitoneal infusion with indwelling catheters
- 1987-1998: multiple Phase II studies show survival benefit with IP cisplatin

Randomized Phase III trials of intravenous vs intraperitoneal chemotherapy in optimally cytoreduced ovarian cancer

- 1996: GOG #104/SWOG#8501
- 2004: GOG #114
- 2006: GOG #172

GOG 172

Reasons for discontinued IP

- **58% (119/205) of the pts did not complete 6 cycles of IP**
- 34% due to catheter complication
 - Infection, blocked, leakage, access problems
- 29% not IP catheter related
 - N/V/dehydration, renal/metabolic, disease progression
- 37% possibly IP infusion or catheter related
 - Other infection, abdominal pain, refusal, bowel complication, other

GOG #172: Quality of Life

Assessment Point	Intravenous Mean score	Intrapertioneal Mean score	Mean Difference (95% CI)	P value
Before randomization	112	106	5.0 (1.2-8.8)	0.03
before fourth cycle	115	103	8.9 (5.3-12.5)	<0.001
3-6 wks after sixth cycle	118	111	5.2 (1.3-9.1)	0.009
12 mos after sixth cycle	127	126	1.2 (-5.1-2.8)	0.56

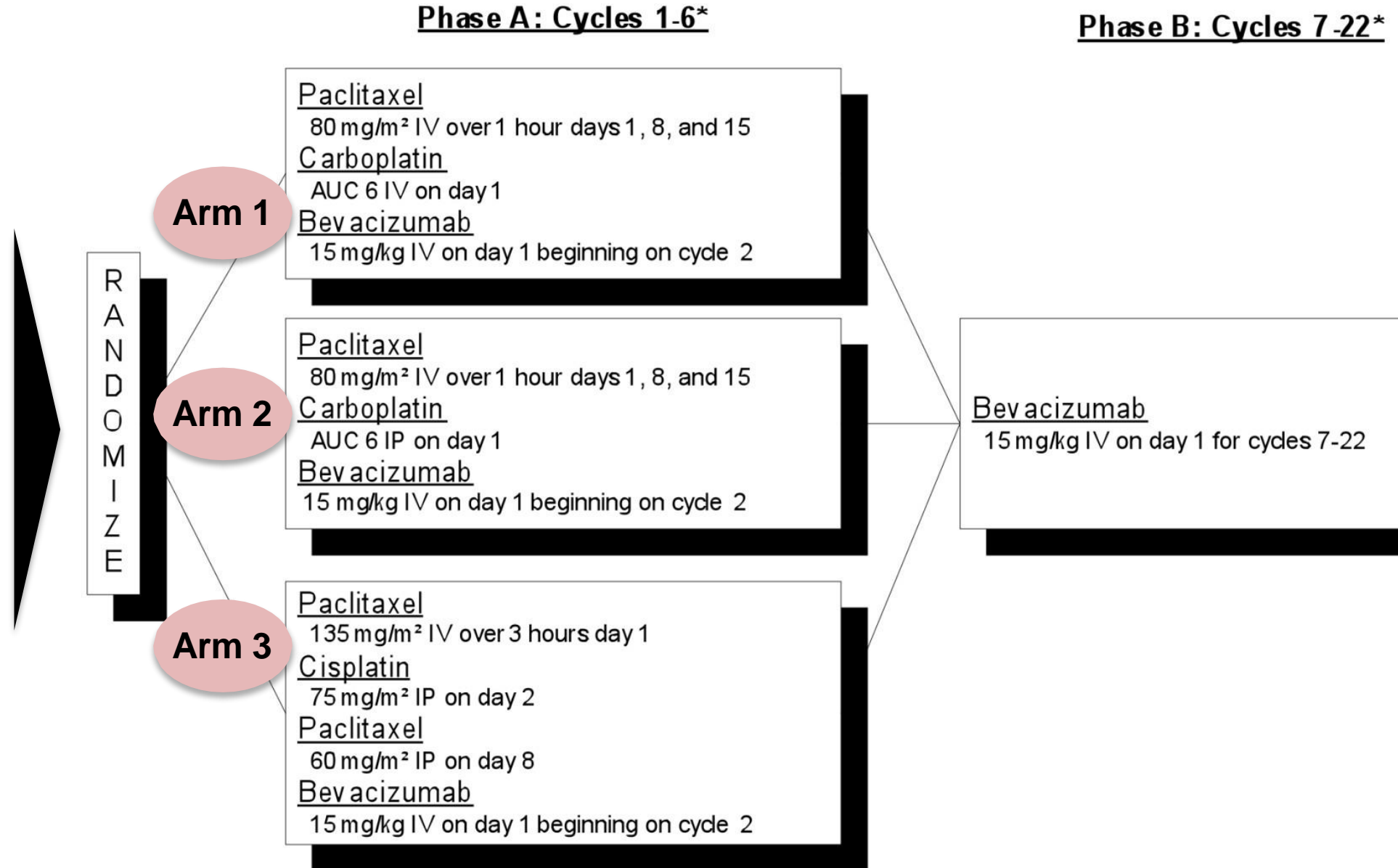
Limited clinical adoption of IP chemotherapy

- Pt selection
 - Limited to stage III, what about II or IV?
 - Increased toxicity lead to selection bias against patients who are older, malnourished, had post op complications, or poor support system
 - Great for peritoneal disease, but what about retroperitoneal lymphadenopathy
- Facility limitations
 - Need beds (not recliners), nurses skilled at IP port access
- IP port
 - Physicians uncomfortable with placement, obesity limiting access

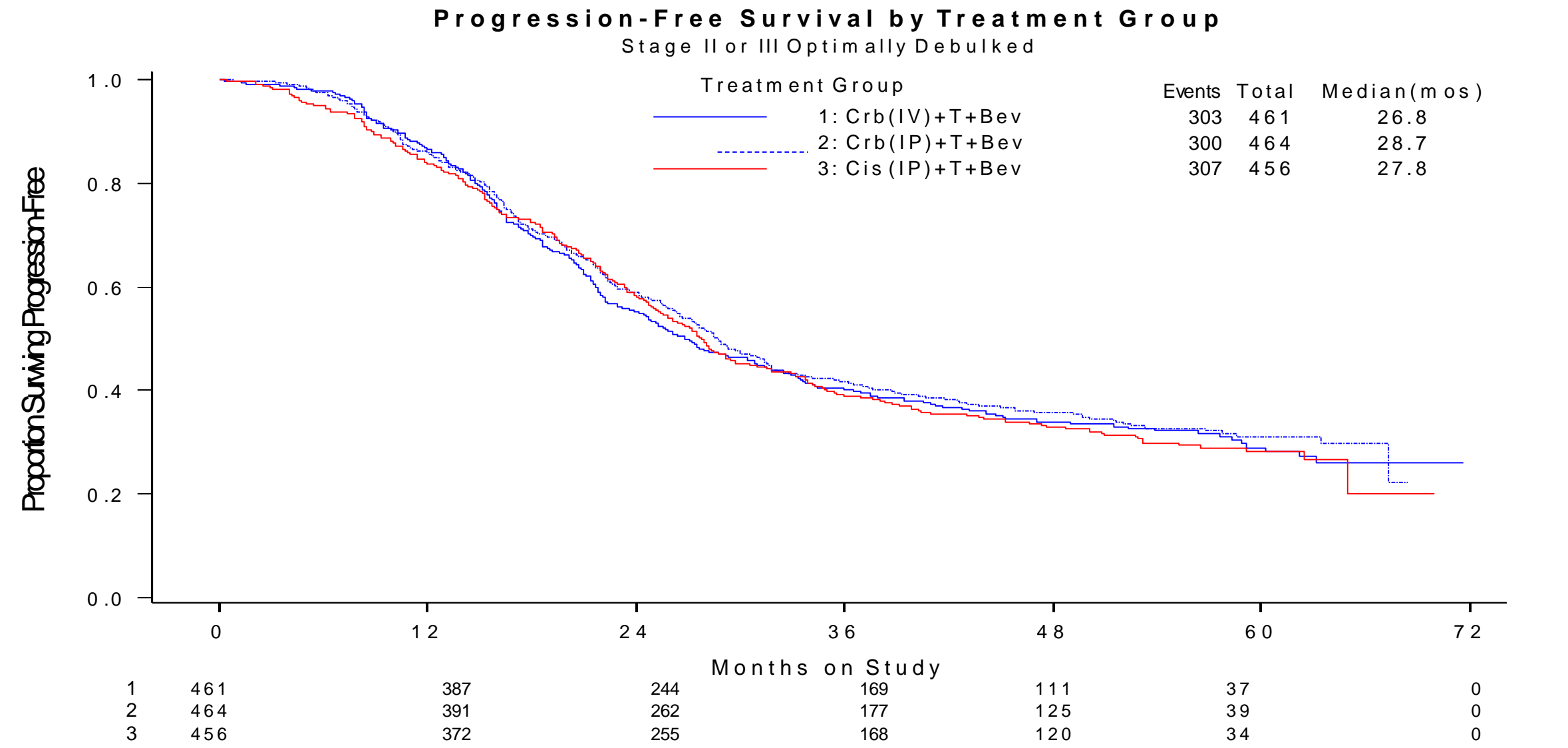
GOG 252: Schema

Eligibility

- Stage II-III Epithelial Carcinoma: Ovary, Fallopian Tube, Peritoneal
- Resected to optimal: less than or equal to 1 cm visible tumor by surgeon report
- Exploratory: suboptimal (7%) and Stage IV (5%)



Progression Free Survival Optimal Stage II-III

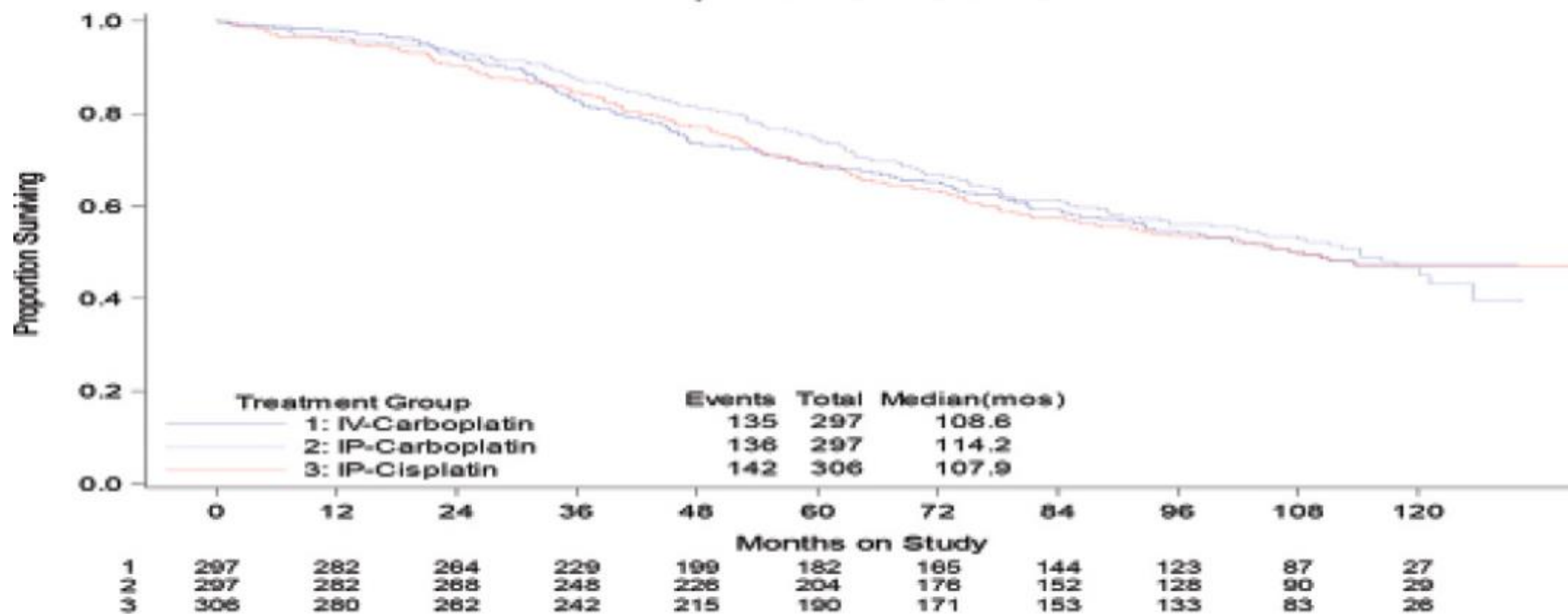


GOG 252

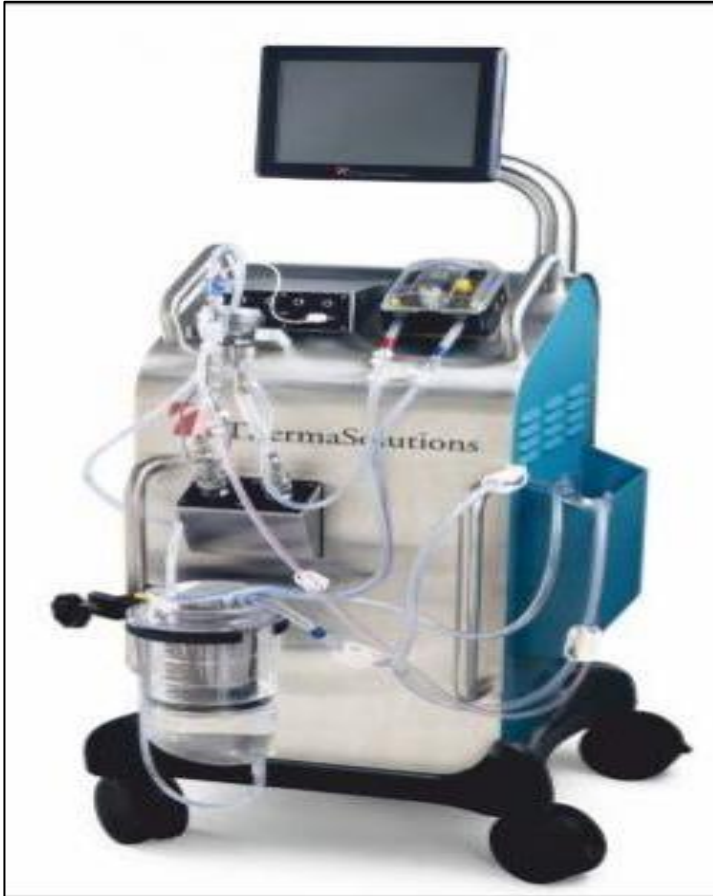
- The overall survival of these patients was 108.6, 114.2, and 107.9 months, respectively.
- The proportional hazard model stratified by stage indicates the hazard of death is 38.5% higher among those with nadir values of CA-125 > 10.
- The quality of life was best in the intravenous arm.

Microscopic Disease only 10-year F/u

Overall Survival
by Randomized Treatment



Hyperthermic Intra Peritoneal Chemotherapy (HIPEC)



HIPEC

**Give me Two Hours
and**

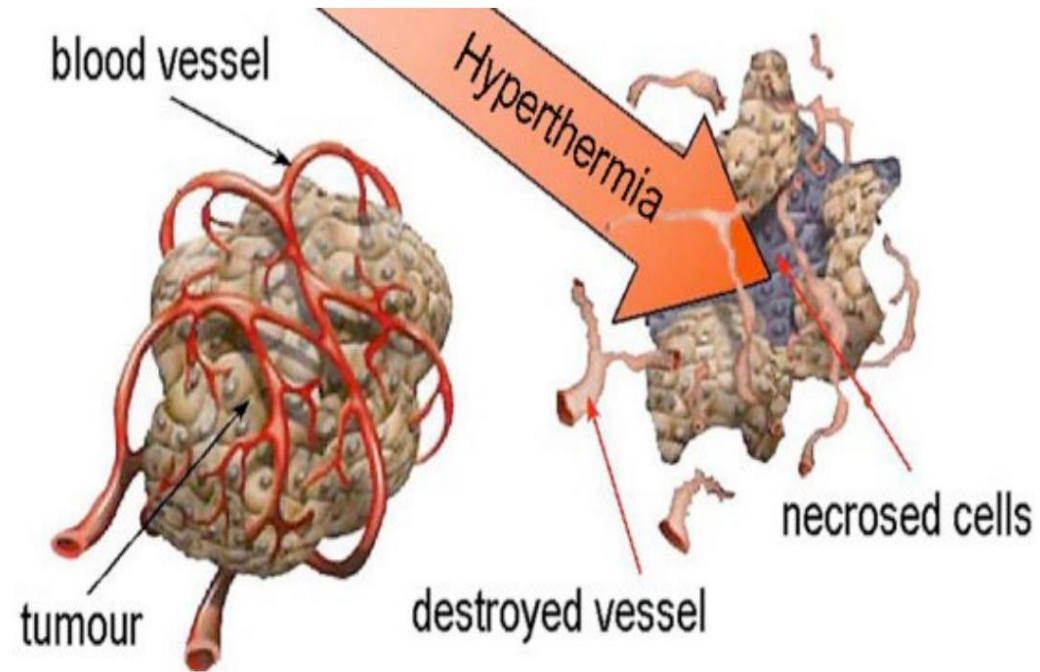
I will give you one more Year!!

HIPEC

- Intraperitoneal chemotherapy during surgery that can be delivered under hyperthermic conditions.

Why hyperthermia?

- Robust experimental and clinical evidence that malignant cells are selectively destroyed by hyperthermia between 41°C and 43°C
- Microcirculation in most malignant tumors exhibits a decrease in blood flow or even complete vascular stasis in response to hyperthermia.
- Accumulation of lactic acid and acidic microenvironment of malignant cell causes accelerated cell death of the more fragile malignant cells subjected to hyperthermia, as compared to normal cell



Rationale

- Opportunity to further improve survival in patients newly diagnosed with advanced ovarian cancer
- Intraperitoneal chemotherapy is associated with improved survival (particularly in patients in whom bevacizumab is not planned)
- HIPEC is potentially more feasible
 - Issues with IP chemotherapy: Toxicity, catheter complications, inconvenience
 - HIPEC only requires a single administration when all peritoneal surfaces are exposed

Rationale

- Because it is delivered immediately following CRS, this avoids the problem of “**cancer cell entrapment**” by postoperative adhesions, which limits distribution of chemotherapy agents to all sites.
- It represents a single-shot treatment and cannot easily be repeated every month.

Rationale (cont).

Theoretical advantages of hyperthermia

- Heat increases tumor cell membrane permeability → improved chemotherapy drug uptake
- Potentiates cytotoxicity of platinum compounds by increasing formation of DNA adducts
- Activates heat shock proteins, inhibits angiogenesis, promotes protein denaturation

Rationale (cont).

Potential concerns regarding HIPEC

- Inherent potential morbidity
- Longer postoperative recovery → delay or withdrawal from subsequent IV chemotherapy → worse prognosis

What do we know?

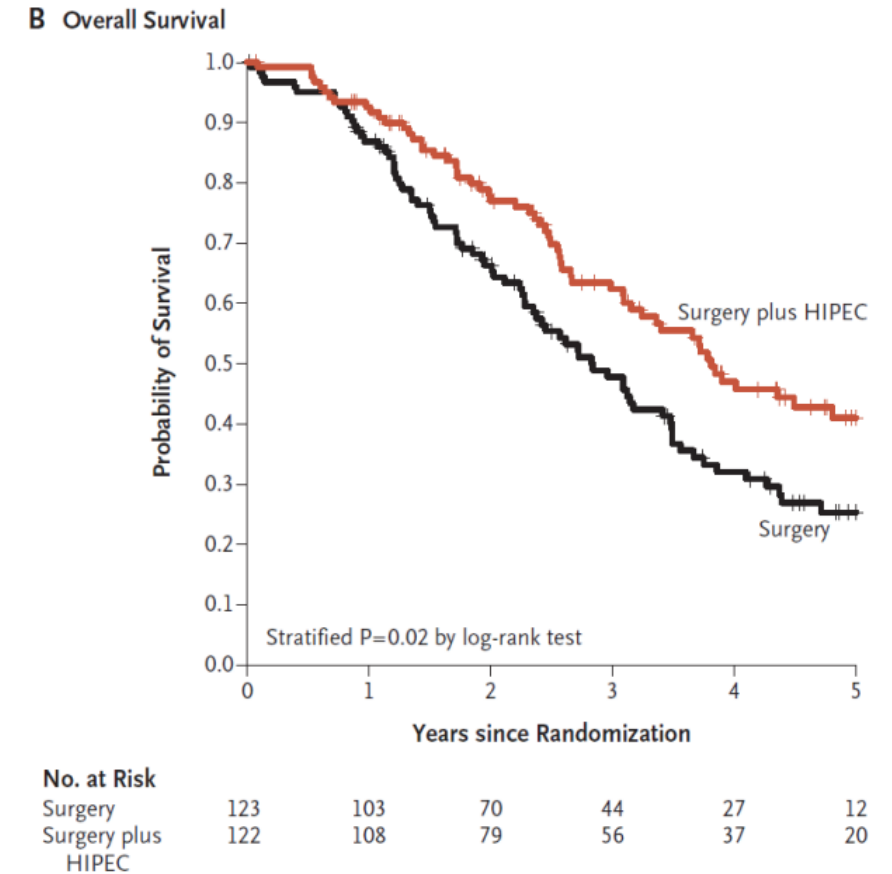
- Addition of HIPEC to CRS results in survival benefit in patients who receive NAC in the front line setting (OVHIPEC Trial and pooled meta-analysis data)
- Uncertain whether this survival benefit applies to patients who are eligible for primary CRS (OVHIPEC 2 Trial)
- There may not be a survival benefit of secondary CRS with HIPEC (carboplatin)

What do we know (cont.)?

- HIPEC is safe (Level 1 evidence)
- NCCN → Consider HIPEC with cisplatin in patients with stage III ovarian cancer at the time of interval CRS if complete or near complete cytoreduction is achieved

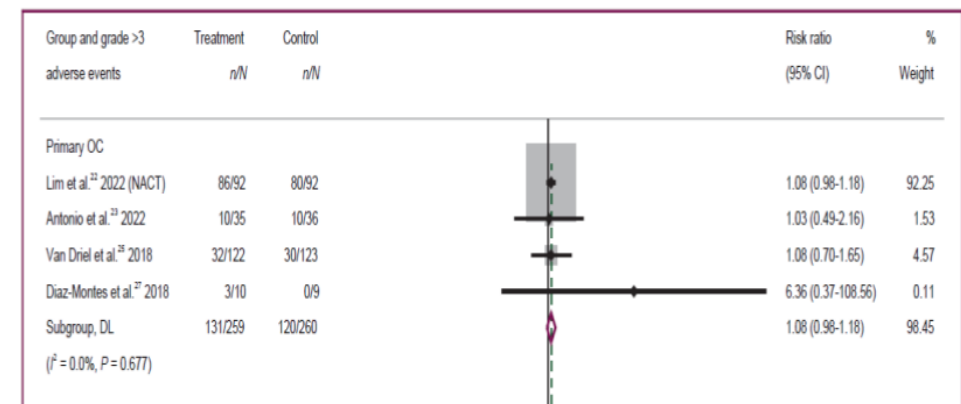
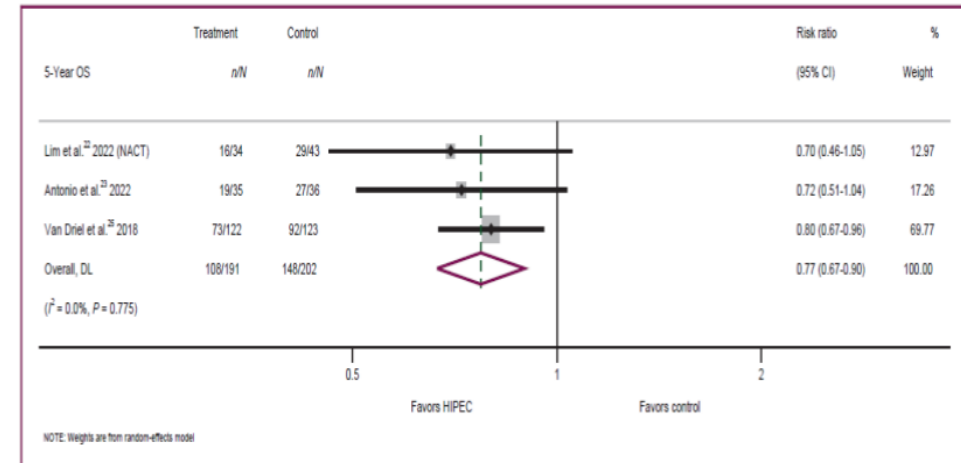
OVHIPEC Trial

- 245 patients with initially unresectable stage III ovarian cancer who underwent optimal ICS randomized to +/- HIPEC after 3 cycles NAC (=> SD)
- **HIPEC improved PFS by 4 months and OS by 12 months**
- Similar toxicities, QoL and time to re-initiate IV chemotherapy



Pooled (meta-analysis) Data

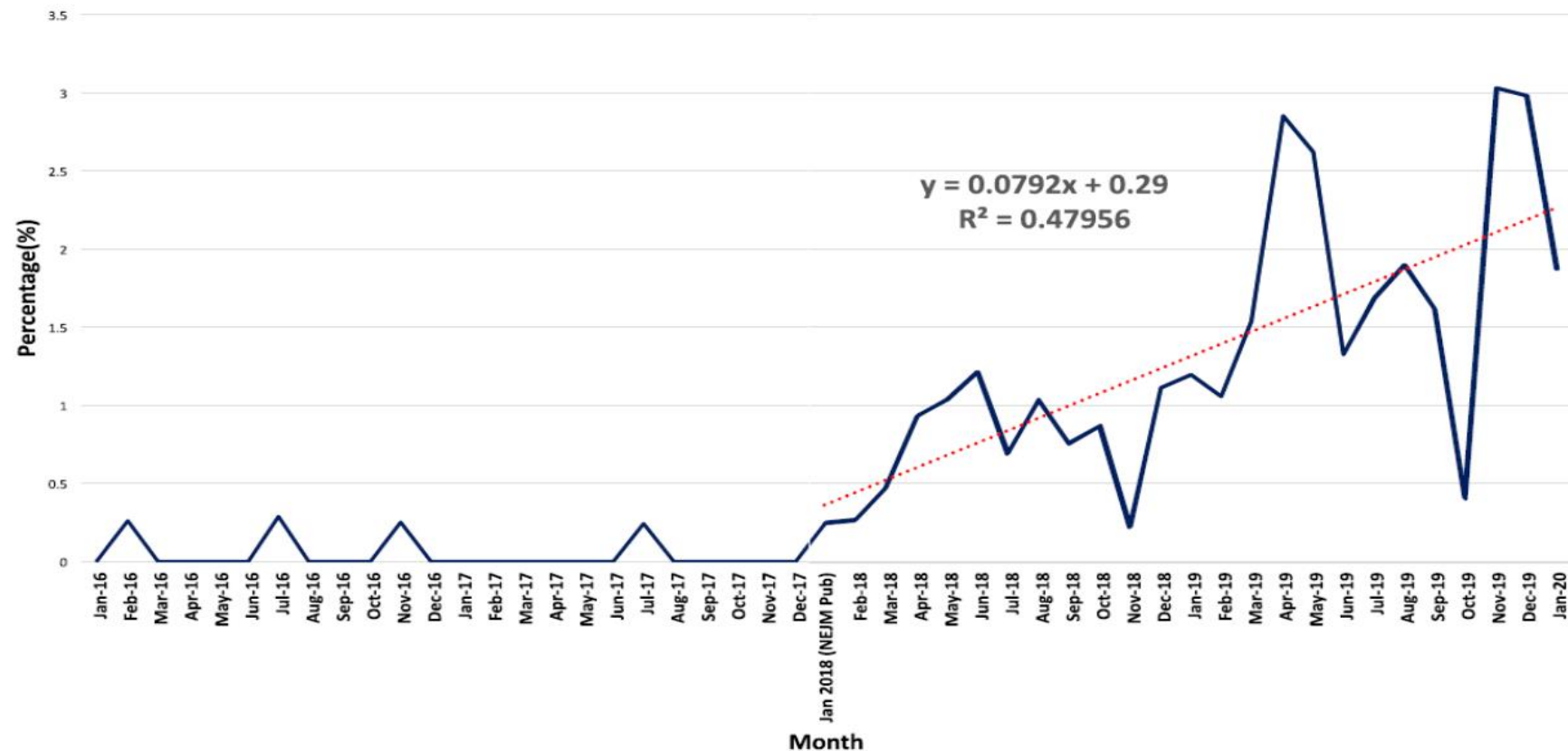
- 519 patients randomized across four trials (**two** with HIPEC after NAC and **two** with primary CRS+HIPEC)
- HIPEC significantly improved OS (RR=0.77) in NAC → HIPEC cohort only
- Patient/drug selection in NAC group may be a confounder



HIPEC utilization has increased since January, 2018

L.M. Charo, J. Jou, P. Binder et al

Gynecologic Oncology 159 (2020) 681–686



Monthly percentage of ovarian surgeries performed with HIPEC from Jan 2016 – Jan 2020

Beaumont (Corewell East) HIPEC Experience

Beaumont

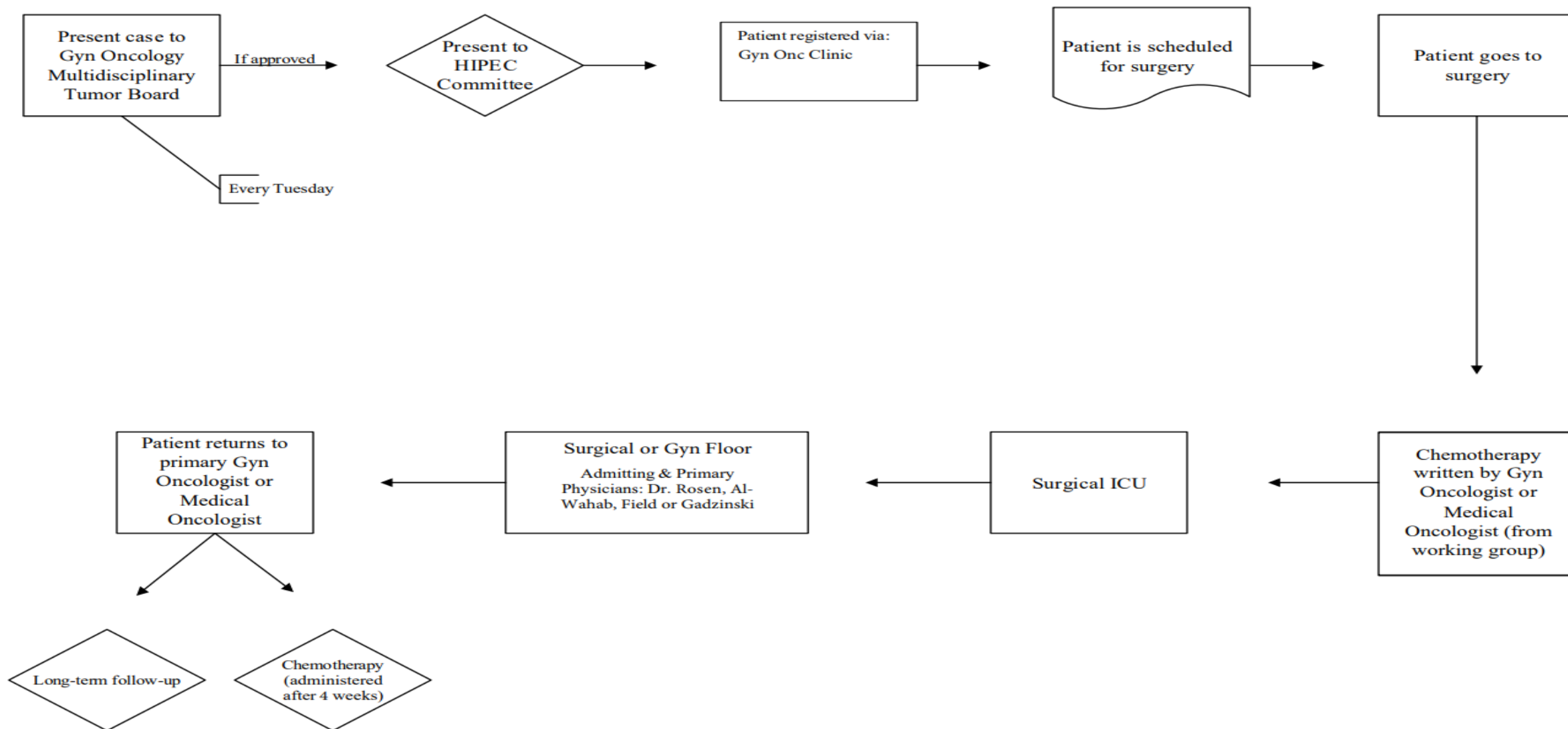


Our HIPEC Experience



Beaumont Health, Royal Oak
Hyperthermic IntraPeritoneal Chemotherapy Patient Process

Target Start Date: March 1, 2018



Legend:

Process Step

Decision

Scheduling

Patient selection

- Medically fit (ECOG PS ≤ 1)
- Absence of extra-abdominal disease (positive pleural cytology is a potential exception)
- Chemo-sensitive disease s/p NAC (initially)
- R0/R1 (optimal) cytoreduction

Personnel: Multidisciplinary team

- Gynecologic oncologist, Surgical oncologists, Anesthesia, OR Nursing, Chemopharmacist
- Perfusionist → Should manage the HIPEC pump intraoperatively
- De novo program → Consider having team attend a HIPEC course, visit a high volume center or invite visiting GO with HIPEC expertise to your facility

Beaumont HIPEC Experience During Primary ICS

- Operative time (median, range) = 7.2 hours (5.1-14.1 hours)
- Additional procedures = 70% (rectosigmoid resection > small bowel resection > diaphragm stripping > splenectomy > liver resection > pericardial and mediastinal resection)
- Resection status (R) ➤ R0 = 25% ➤ R1 = 65% ➤ R2a = 10%
- Thirty-day mortality = 0
- Acceptable and expected toxicities with minimal impact on QoL indices

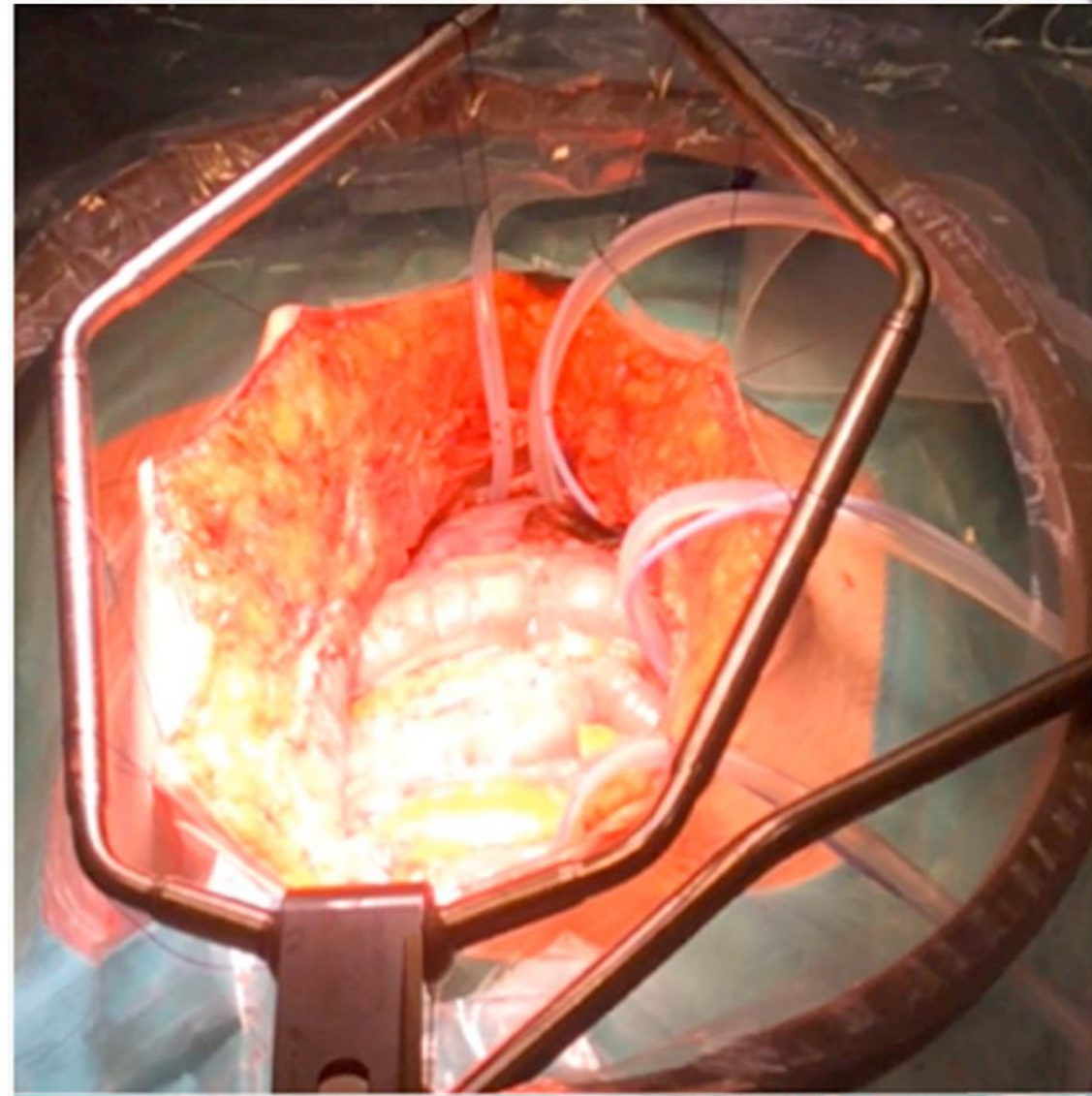
HIPEC techniques

- Open abdomen technique
- Closed abdomen technique

HIPEC: Open technique

“Coliseum technique”, as described by Sugarbaker

- Once the cytoreductive phase has been finalized, a catheter and four closed suction drains are placed through the abdominal wall and made watertight with a purse string suture at the skin.
- A different number of temperature probes secured to the skin edge may be used for intraperitoneal temperature monitoring

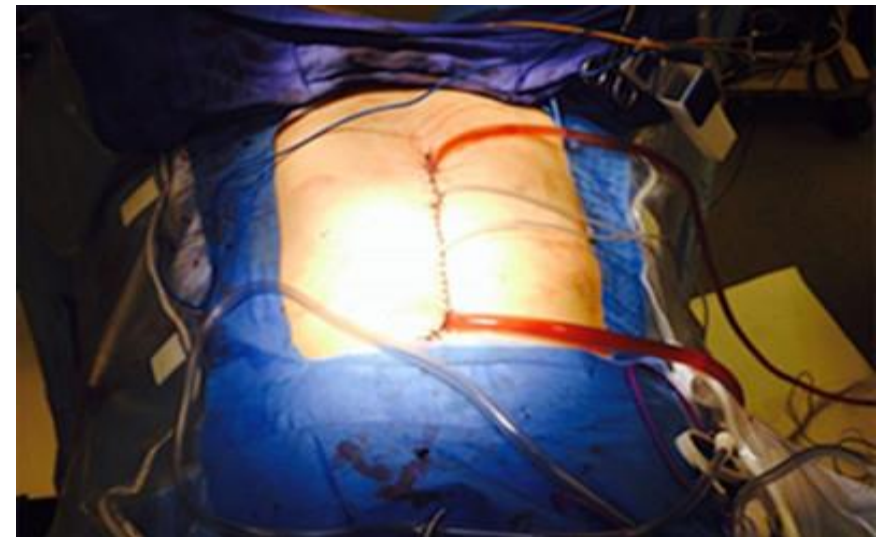
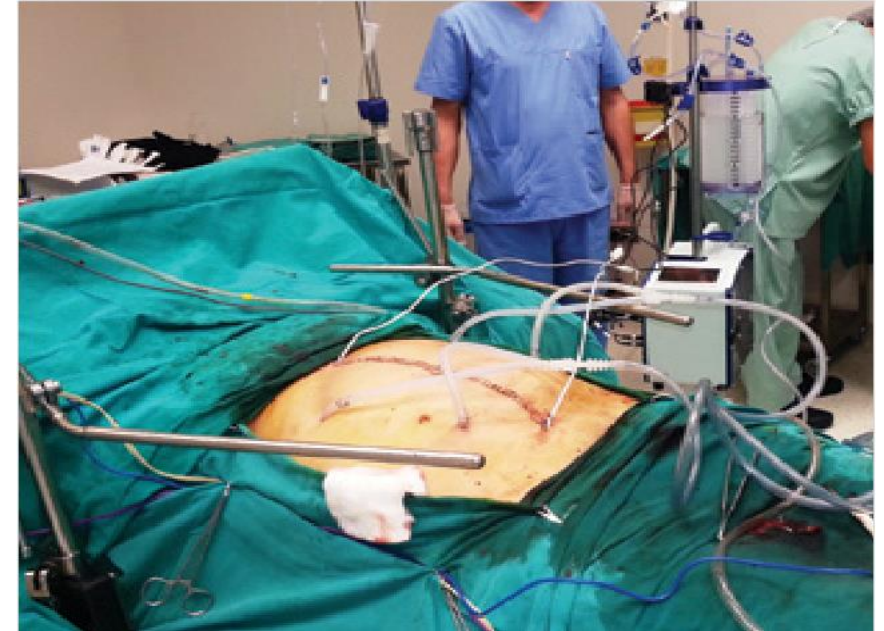


HIPEC: Open technique

- Advantage: heated chemotherapy is adequately distributed throughout the abdominal cavity
- Disadvantage:
- Heat dissipation that makes it more difficult to initially achieve a hyperthermic state.
- The increased exposure of operating room personnel to chemotherapy.
- Because the abdomen is open during the perfusion, heated chemotherapy could give way to aerosol formation, creating a risk of inhalation exposure.

HIPEC: Closed technique

- Catheters and temperature probes are placed in the same fashion but the laparotomy skin edges are sutured watertight so that perfusion is done in a closed circuit.
- The abdominal wall is manually agitated during the perfusion period in an attempt to promote uniform heat distribution.
- A larger volume of perfusate is generally needed



HIPEC: Closed technique

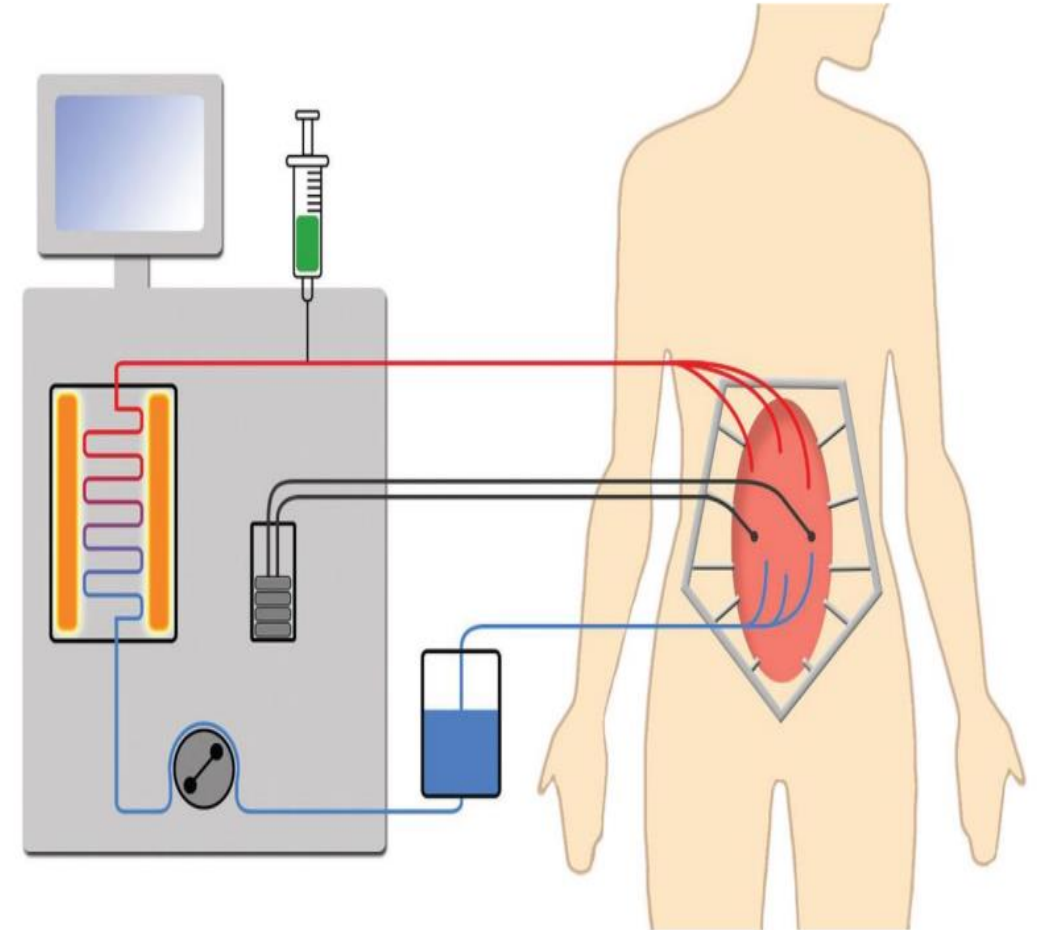
Advantages:

- The ability to rapidly achieve and maintain hyperthermia as there is minimal heat loss.
- There is minimal contact or aerosolized exposure of the operating room staff to the chemotherapy.
- The only way for exposure is leakage through the surgical wound or catheter wounds.

Disadvantage: is the lack of uniform distribution of the chemotherapy.

Hyperthermia Delivery System

- Constant infusion of hyperthermic perfusate
- Continuous circuit generated by a pump, heat exchanger and temperature monitors (inflow and outflow)
- Custom made HIPEC machine (CMM), commercially available peritoneal perfusion device

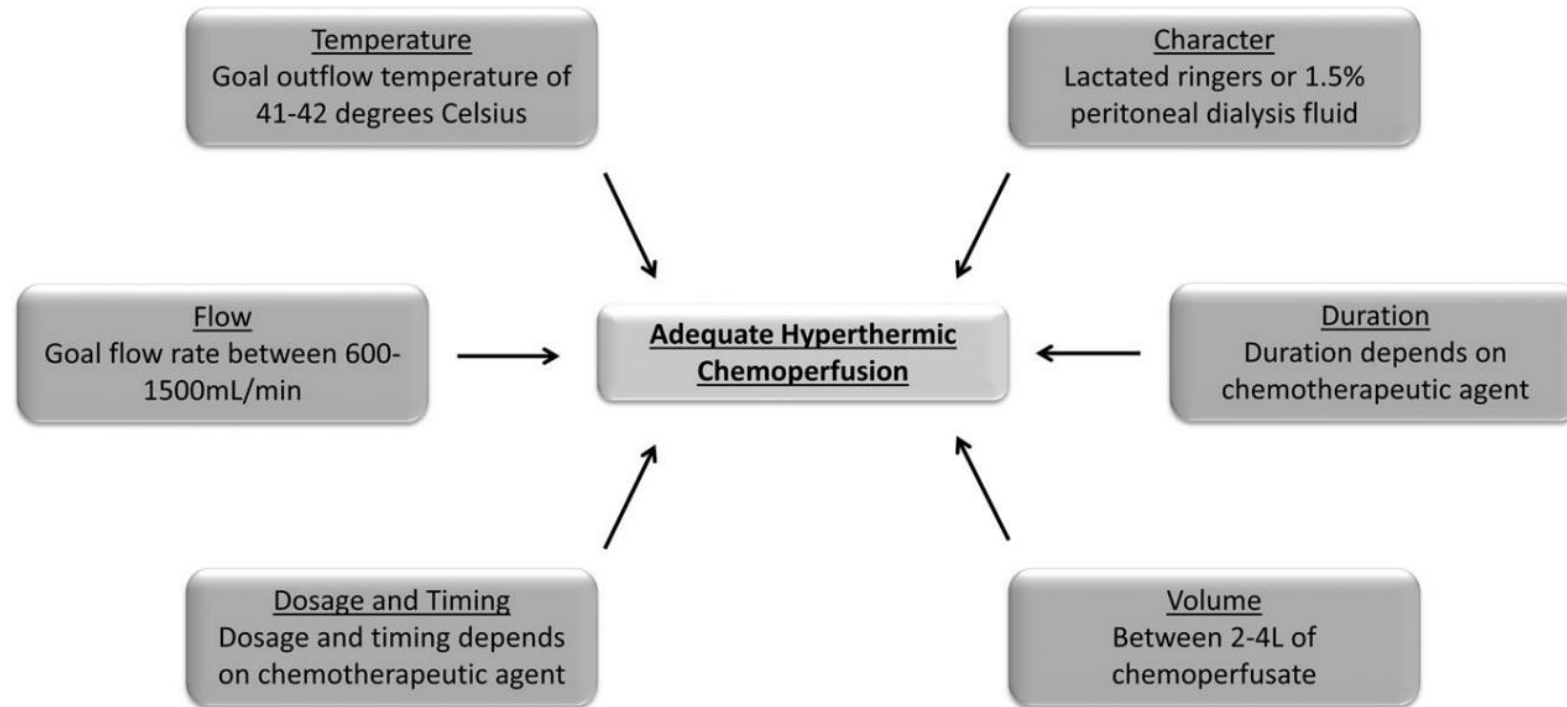


CMM: Cardiopulmonary bypass machine with heat exchanger



Several factors are adjusted to obtain optimal chemo-perfusion

Components of Chemoperfusion



Chemotherapy agents

- Premedication protocol → reduce hypersensitivity reactions, renal toxicity and PONV
- Carboplatin and paclitaxel have decreased penetration depth than cisplatin

Table 1

Premedication Protocol for Hyperthermic Intraperitoneal Chemotherapy.

Medication	Administration Instructions
Furosemide 40 mg IV	Given one hour prior to cisplatin with goal urine output of 100 cc/h.
Fosaprepitant 150 mg IV	Given 30 min prior to chemotherapy
Dexamethasone 10 mg IV	Given 30 min prior to chemotherapy
Diphenhydramine 50 mg IV	Given 30 min prior to chemotherapy
Famotidine 20 mg IV	Given 30 min prior to chemotherapy
Potassium chloride 20 mEq	To be given with Paclitaxel
Sodium Thiosulfate	9 g in 200 mL at the start of infusion, followed by a continuous infusion (12 g in 1000 mL) for 6 h

IV, intravenous.

Chemotherapy agents

- **Cisplatin 100 mg/m²**
 - ➤ Most studied/used in ovarian cancer
 - ➤ Significant toxicities seen in IP studies → carboplatin
- **Carboplatin 800 mg/m²**
 - ➤ Phase 1 and phase 2 (AHWFB)
 - ➤ MSK

Table. Cytotoxic Drugs Commonly Used for Intraperitoneal Administration

Drug	Heat synergy	Penetration depth, mm	Cell cycle-specific	Molecular weight	AUC IP:IV ratio
Carboplatin	Yes	0.5	No	371	2-10
Cisplatin	Yes	1.0-3.0	No	300	8-21
Mitomycin C	Yes	2.0	No	334	10-23.5
Oxaliplatin	Yes	1.0-2.0	No	397	3.5-16
Paclitaxel	Minimal	0.5	Yes	854	1000
Fluorouracil	Minimal	0.2	Yes	130	250

Safety precautions





- Additional PPE: chemotherapy safe gloves, eye protection, impermeable gowns
- Non-pregnant participants
- Use hazardous waste containers to dispose of material used to administer intraperitoneal chemotherapy
- Develop institutional policy for chemotherapy spillage and accidental exposure

Anesthesia considerations

- **Standard patient monitoring for cytoreductive surgery**
- **Core-temperature body probe** (esophageal > urinary catheter) to maintain normothermia
 - Hyperthermia → increased metabolic demand, increased HR and end tidal CO₂ → metabolic acidosis
 - Cooled IV fluids, cooling blankets, ice packs
- **Fluid management**
 - HIPEC increases capillary leakage and increases abdominal pressure → decreases venous return and decreases cardiac output
 - Recommend restrictive, goal directed (ERAS) fluid replacement
 - Renal perfusion targets to minimize AKI
 - ❖ CRS: 0.5 cc/kg/hr
 - ❖ HIPEC: 1-2 cc/kg/hr

HIPEC and Quality of Life

- CRS/HIPEC has NOT been shown to decrease long-term HRQL in other malignancies
- Data regarding HRQL after HIPEC in ovarian cancer is limited to interval CRS (EORTC QLQ-C30)

Current HIPEC Trials Evaluating HRQL	
	• OVHIPEC (phase III)
	• Short-course HIPEC (phase II)
	• CARCINOHIPEC (phase III)
	• KOV-HIPEC-01 (phase III)

**No difference in
HRQL outcomes**

Lustosa et al (2020) Revista do Colegio Brasileiro de Cirurgioes, 47;
Koole et al (2021) European Journal of Surgical Oncology, 47 (1), 101-7
Antonio et al (2022) Annals of surgical oncology, 29 (4), 2617-25; Kim et al (2022) Journal of Gynecologic Oncology, 33 (4)
Leimkühler, M et al. (2020) Annals of Surgical Oncology, 27, 3973-3983

Conclusion

- Primary surgery remains the standard of care if complete cytoreductive surgery is feasible.
- However, in patients with extensive disease in whom primary cytoreductive surgery is not feasible, HIPEC added to interval CRS improves outcomes without increasing toxic effects.
- CRS and HIPEC offer a significant survival benefit to pts with recurrent EOC.
- This observation applies to both platinum-sensitive and platinum-resistant disease.

Conclusion

- HIPEC may be associated with improved survival for newly diagnosed advanced ovarian cancer patients
- HIPEC is safe
- There is a compelling need to identify biomarkers to predict patient response to HIPEC
 - HR deficiency profiles
 - Immune cell gene signatures
- Combining HIPEC with other (targeted) IP therapies such as immunotherapies is promising

Acknowledgments

- Barry Rosen MD, Jill Gadzinski MD, Kevin McCool MD PhD, Stephany Acosta Torres MD – Gyn Oncologists
- Vandad Raofi, MD – Surgical Oncologist
- Allison Thomas MD – OBGYN resident

Beaumont

+



**Spectrum
Health**

Together, we are now



Corewell Health™

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Persistent and Recurrent Advanced Ovarian Carcinoma: A Multicenter, Prospective Study of 246 Patients

N. Bakrin, MD¹, E. Cotte, MD¹, F. Golfier, MD, PhD², F. N. Gilly, MD, PhD¹, G. Freyer, MD, PhD³, W. Helm, MD, PhD⁴, O. Glehen, MD, PhD¹, and J. M. Bereder, MD⁵

Barkin et al

- A prospective, multicentric study
- Recurrent or persistent EOC
- Treatment by cytoreductive surgery and HIPEC
- 1991 and 2008

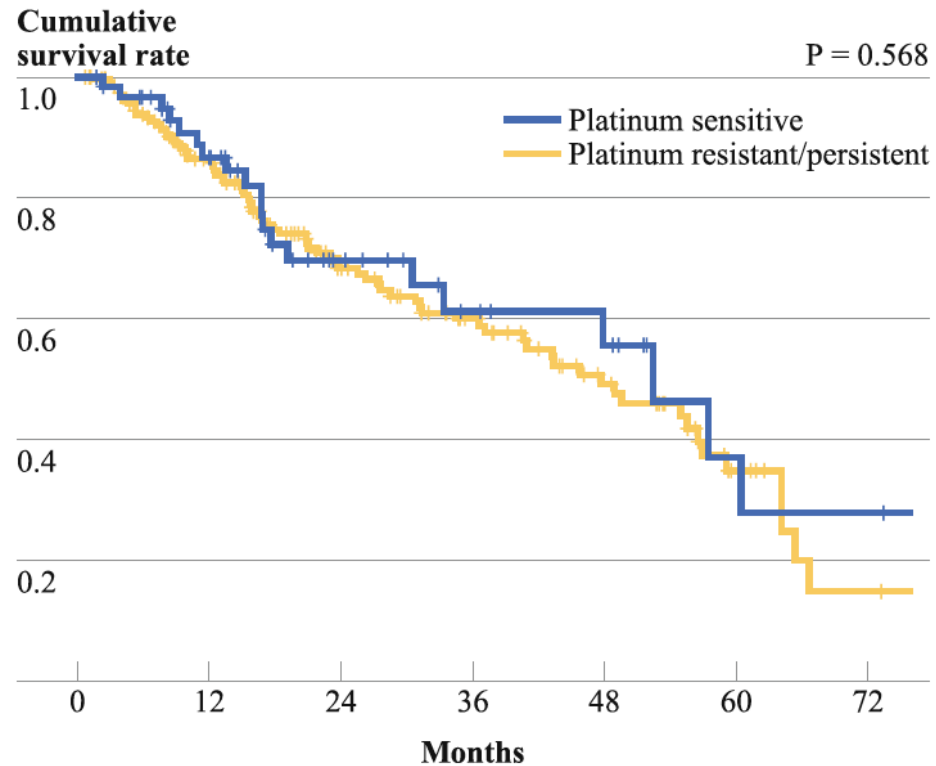
Barkin et al

- 246 patients underwent CRS and HIPEC
- 62 were platinum-resistant persistent or recurrent
- 184 were platinum-sensitive
- All patients received at least one regimen of platinum-based chemotherapy before CRS and HIPEC

Barkin et al

- An optimal surgery with no residual ≤ 2.5 mm residual tumor was achieved in 92.2 % of procedures.
- Cisplatin was used in 95.5 % of procedures, alone or in combination with doxorubicin or mitomycin C

Barkin et al: Survival analysis



Overall median survival was 48.9 months:
48 months for platinum-resistant
52 months for platinum-sensitive recurrent
disease.

The overall survival rates at 1, 3, and 5 years
were 86, 60, and 35 % respectively

There was no significant difference in survival
between platinum-resistant and platinum-sensitive
recurrence ($p = 0.568$)

Barkin et al: Complications

- 12 % incidence of serious (grade 3/4) complications
- Leukopenia (3 %)
- Intra-abdominal hemorrhage (2 %)
- Postoperative complications (5 %), including one postoperative death due to an anastomotic leak resulting in peritonitis and ARF

Barkin et al: Conclusion

- CRS and HIPEC is an aggressive combined therapy that achieved encouraging survival rates in patients with platinum- resistant persistent or recurrent and platinum-sensitive recurrent EOC.
- Morbidity and mortality rates are not negligible but stay within the range of acceptable risk.

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

J. Spiliotis, MD, PhD¹, E. Halkia, MD, PhD^{1,2}, E. Lianos, MD³, N. Kalantzi, MD⁴, A. Grivas, MD³, E. Efstathiou, MD¹, and S. Giassas, MD²

Spiliotis et al

**EOC stage 3C & 4
with recurrence after
initial treatment with
conservative or
debulking surgery and
systemic
chemotherapy**

R
A
N
D
O
M
I
Z
E

**Cytoreductive surgery with HIPEC
+ Systemic chemotherapy**

**Cytoreductive surgery without HIPEC
+ Systemic chemotherapy**

Spiliotis J, et al . Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol. 2015 May;22(5):1570-5. PubMed PMID: 25391263.

Spiliotis et al

- 2006–2013,
- 120 women with recurrent advanced EOC FIGO stage IIIC and IV
- Group A: 60 patients treated with CRS + HIPEC and then systemic chemotherapy.
- Group B: 60 patients treated with CRS only and systemic chemotherapy.

Spiliotis J, et al . Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol. 2015 May;22(5):1570-5. PubMed PMID: 25391263.

Spiliotis et al

Exclusion criteria:

- Gynecologic Oncology Group (GOG) performance status 3 or 4
- Evidence of pleural disease or lung metastasis
- More than three sites of bowel obstruction
- Evidence of bulking disease in retroperitoneal area or on the mesentery

Spiliotis J, et al . Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol. 2015 May;22(5):1570-5. PubMed PMID: 25391263.

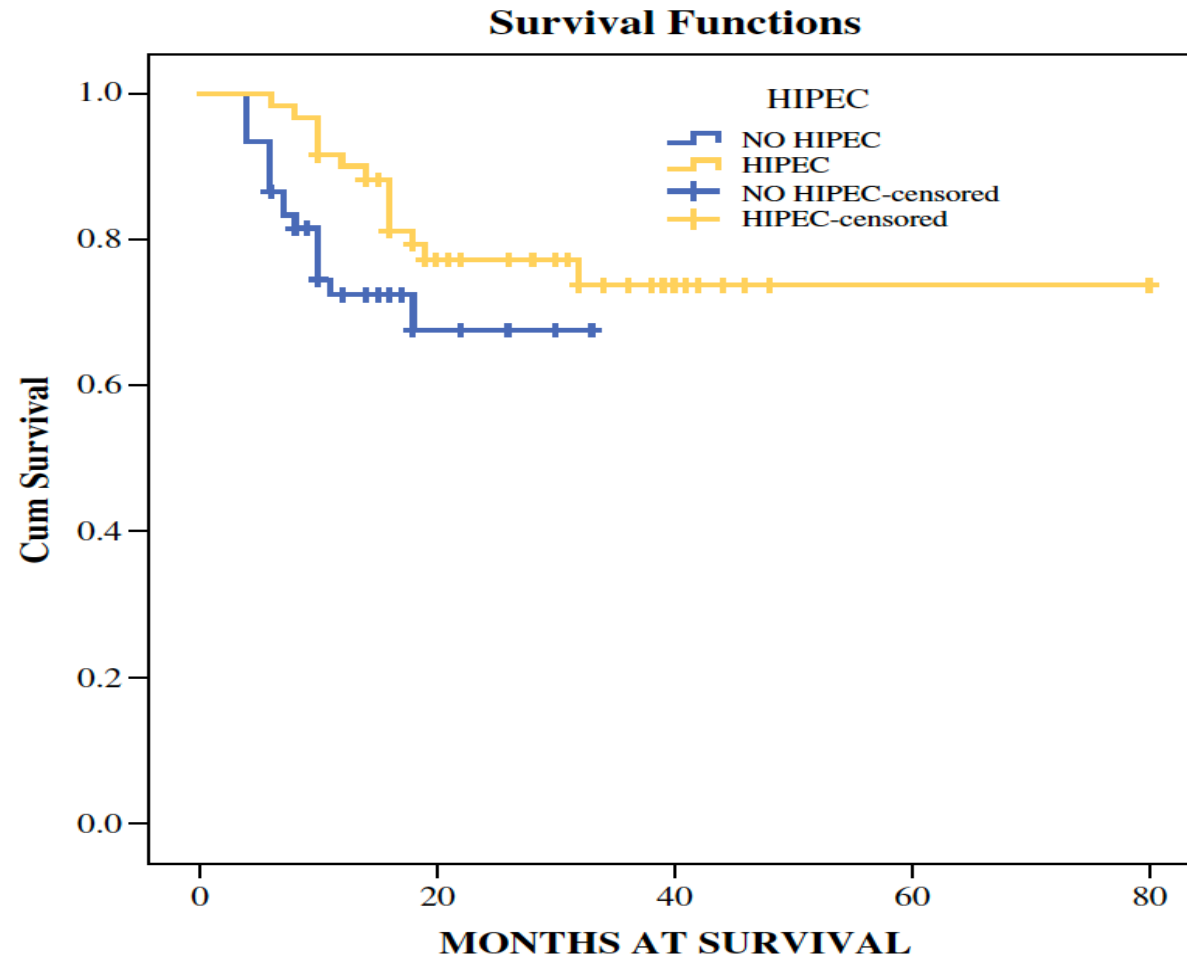
Spiliotis et al

HIPEC protocols

- Platinum-sensitive disease (n = 34): Cisplatin 100 mg/m² and Paclitaxel 175 mg/m² delivered for 60 min at 42.5 C.
- Platinum resistant disease (n = 26): Doxorubicin 35 mg/m² and (Paclitaxel 175 mg/m² or Mitomycin 15 mg/m²) delivered for 60 min at 42.5 C.

Spiliotis J, et al . Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol. 2015 May;22(5):1570-5. PubMed PMID: 25391263.

Spiliotis et al: Survival Analyses



Mean OS in the HIPEC group was 26.7 vs. 13.4 months in the non-HIPEC group

($p = 0.006$)

Spiliotis J, et al . Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol. 2015 May;22(5):1570-5. PubMed PMID: 25391263.

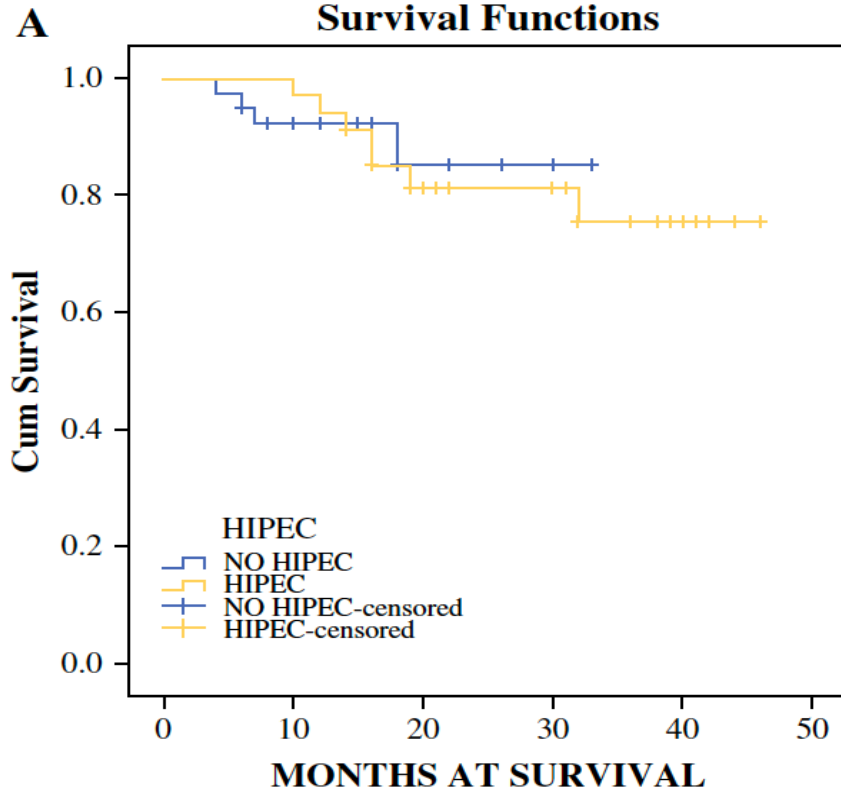
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Survival by stage

Mean survival	Stage III _c survival (months)	Stage IV survival (months)
HIPEC	26.9	26.4
Non-HIPEC	14.2	11.9

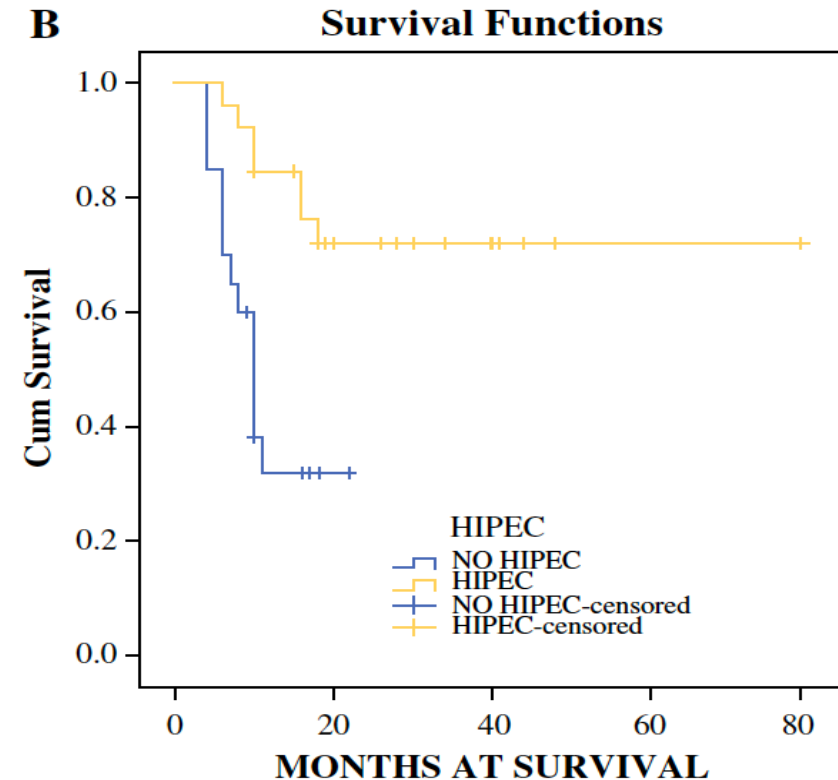
Spiliotis J, et al . Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol. 2015 May;22(5):1570-5. PubMed PMID: 25391263.

Platinum-sensitive disease



Survival was significantly higher in the HIPEC group (26.8 vs. 15.2 months in the non-HIPEC group, $p = 0.035$)

Platinum-resistant disease



No difference was observed (26.6 months in the HIPEC group vs. 10.2 months in the non-HIPEC group, NS)

Spiliotis et al

- Three-year survival was 75 % for HIPEC versus 18 % for Non-HIPEC .
- **HIPEC group:** the mean survival was not different between patients with platinum-resistant disease versus platinum-sensitive disease (26.6 vs. 26.8 months).
- **Non-HIPEC group:** there was a statistically significant difference between platinum-sensitive versus platinum-resistant disease (15.2 vs. 10.2 months, p 0.002).
- Complete cytoreduction was associated with longer survival.

Spiliotis et al : Conclusion

- CRS and HIPEC offer a significant survival benefit to pts with recurrent EOC.
- This observation applies to both platinum-sensitive and platinum-resistant disease.
- Maximum efficacy of HIPEC is noted when complete cytoreduction is achieved.

Spiliotis J, et al . Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol. 2015 May;22(5):1570-5. PubMed PMID: 25391263.

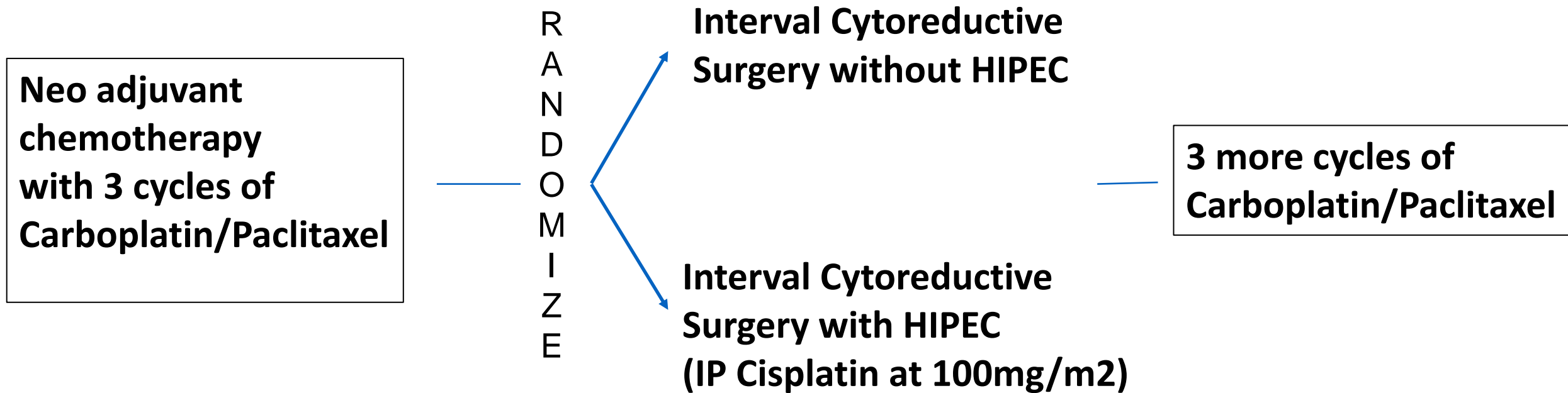
Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

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

Van Driel et al:

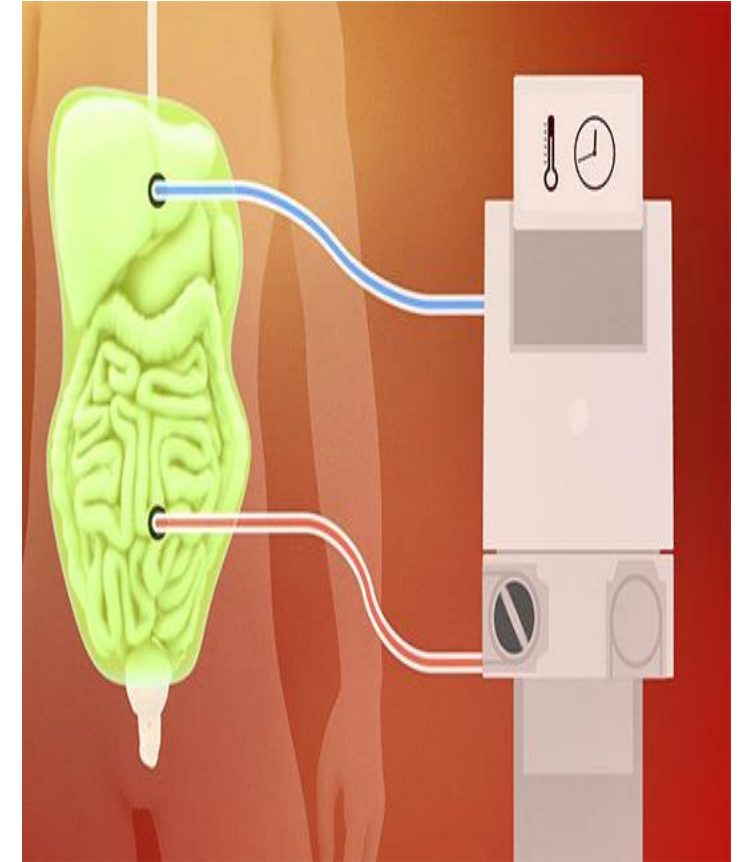
- Multicenter, randomized, phase 3 trial
- Pts who had received three cycles of neoadjuvant chemotherapy with Carboplatin(AUC 5-6 mg/ml/min) + Paclitaxel (175 mg/m²)
- Randomly assigned, in a 1:1 ratio, to undergo interval cytoreductive surgery either with HIPEC (surgery-plus- HIPEC group) or without HIPEC (surgery group).

van Driel et al



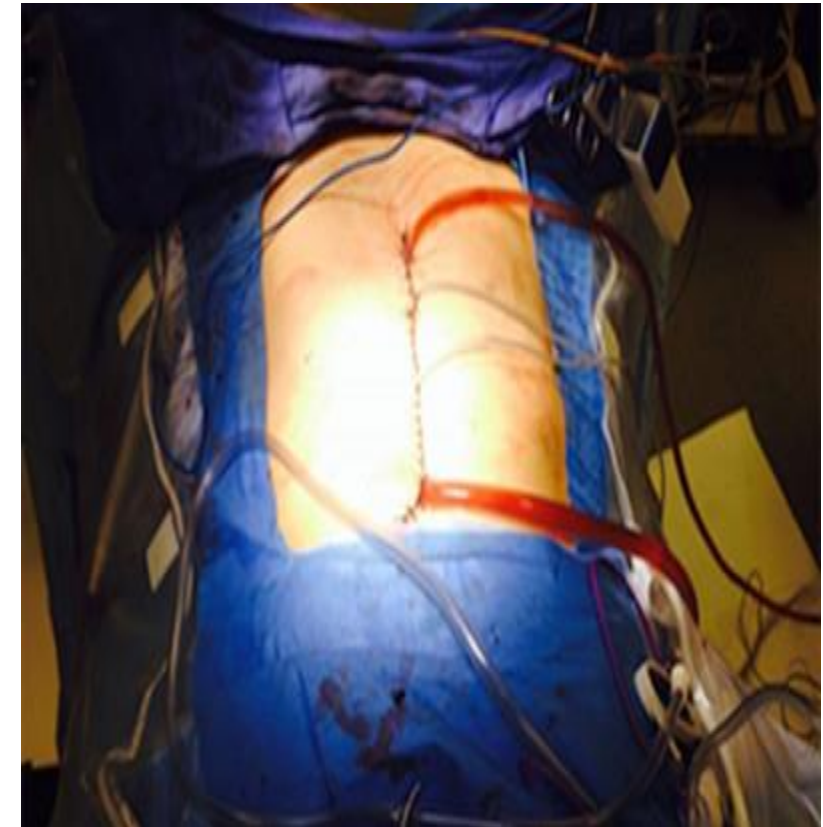
Van Driel et al: HIPEC Technique

- The abdomen is filled with saline that circulated continuously with the use of a roller pump through a heat exchanger.
- Intraabdominal temp of 40°C (104°F) is maintained.
- Perfusion with Cisplatin at a dose of 100 mg/m² and at a flow rate of 1 liter per minute is then initiated
- 50% of the dose perfused initially, 25% at 30 minutes, and 25% at 60 minutes.
- The perfusion volume is adjusted such that the entire abdomen was exposed to the perfusate.
- The HIPEC procedure takes 120 minutes in total, including the 90-minute perfusion period.



Van Driel et al: HIPEC Technique

- At the end of the perfusion, drains are used to empty the abdominal cavity as completely as possible.
- To prevent nephrotoxicity, *sodium thiosulphate* is administered at the start of perfusion as an IV bolus (9 g/m² in 200 ml), followed by a continuous infusion (12 g/m² in 1000 ml) over 6 hours.
- Urine production is maintained at a minimum of 1 ml/kg/hr during hyperthermic perfusion and for 3 hours after surgery.



Van Driel et al:

- Patients will receive an additional **three cycles** of Carboplatin and Paclitaxel after surgery.

van Driel et al: Results

- Median follow-up of **4.7 years**
- 62% of pts in the surgery group and 50% in the surgery-plus-HIPEC group had died (HR, 0.67; 95% CI, 0.48-0.94; P = 0.02).
- The **median overall survival** was **33.9 months** in the surgery group and **45.7 months** in the surgery-plus-HIPEC group.
- The percentage of patients who had **adverse events** of grade 3 or 4 **was similar** in the two groups (25% in the surgery group and 27% in the surgery-plus-HIPEC group, P = 0.76).

van Driel et al: Results

- **Recurrence or death** occurred in **89%** who underwent cytoreductive surgery without HIPEC (surgery group) and in **81%** who underwent cytoreductive surgery plus-HIPEC (surgery-plus-HIPEC group) (HR for disease recurrence or death, 0.66; 95% CI, (0.50-0.87); P = 0.003).
- The **median recurrence-free survival** was **10.7** months in the surgery group and **14.2** months in the surgery plus-HIPEC group.

CONCLUSIONS

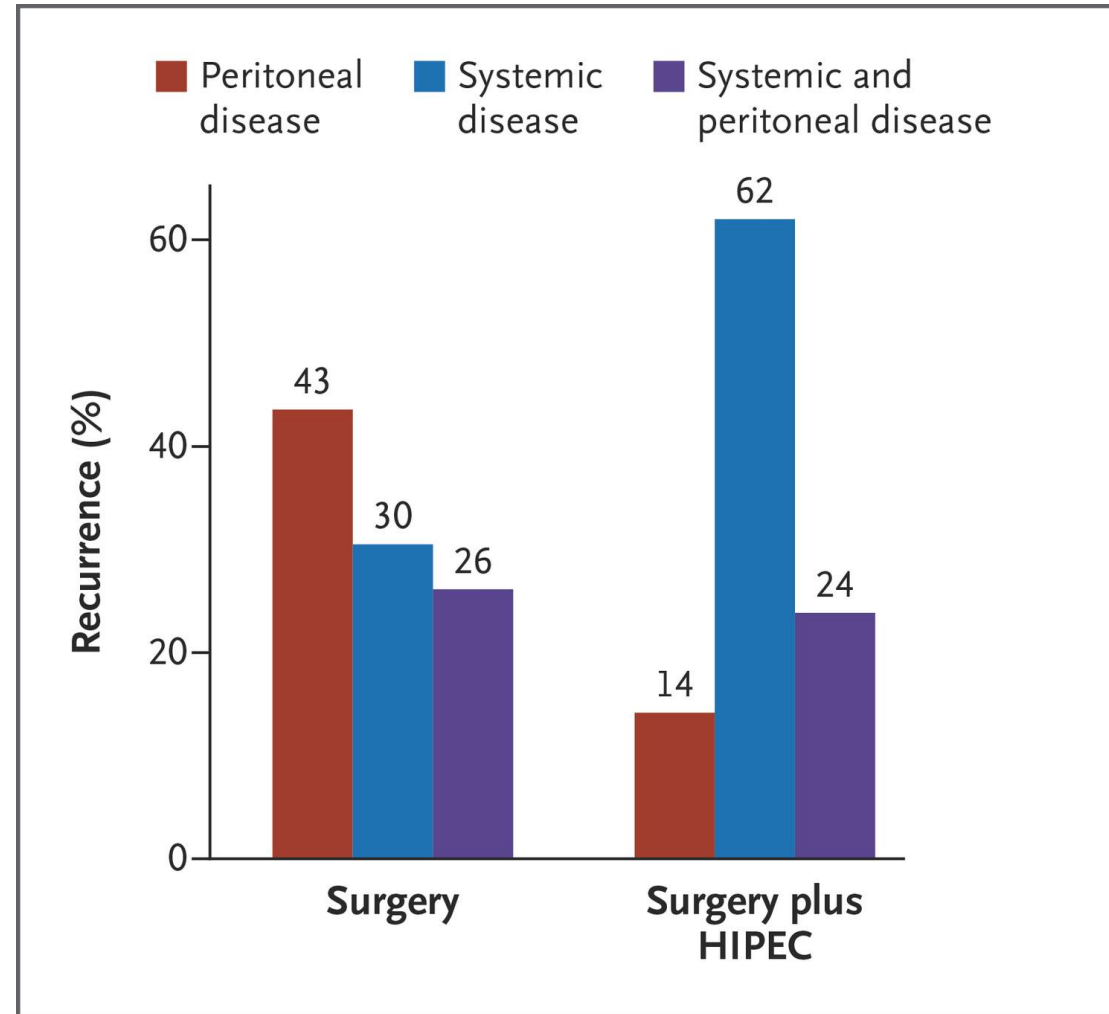
- Among patients with stage III epithelial ovarian cancer, the addition of HIPEC to interval cytoreductive surgery resulted in longer recurrence-free survival and overall survival than surgery alone and did not result in higher rates of side effects.

Future HIPEC Studies

CHORINE Cytoreduction and HIPEC in the Treatment of Ovarian Cancer) trial (ClinicalTrials.gov number, [NCT01628380](https://clinicaltrials.gov/ct2/show/study/NCT01628380))

- Retrospective case–control study
- Comparing surgery plus HIPEC with surgery alone in patients with ovarian cancer.
- Prelim data: longer survival among patients in the surgery-plus-HIPEC group than among those in the surgery group.
- but no significant difference in progression-free survival.
- Overall survival was significantly longer among patients treated with HIPEC.

CHORINE: Cytoreductive Surgery Alone or with Cytoreductive Surgery plus HIPEC.



Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in Relapse Ovarian Cancer Treatment (CHIPOR)

- Phase 3 Randomized clinical trial
- Recurrent ovarian cancer
- After carboplatin/Paclitaxel or Carboplatin/Doxil 6 cycles
- If complete response to chemotherapy —————> Surgery 5 to 8 weeks after the last second-line chemotherapy cycle.
- The HIPEC will be done at the end of the surgery. At the end of cytoreductive surgery, tumor residual disease must be null or very limited (residual < 0.25cm).

Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in Relapse Ovarian Cancer Treatment (CHIPOR)

- Recurrent Platinum sensitive ovarian cancer
- After 2nd chemotherapy with Carboplatin/Paclitaxel or Carboplatin/Doxil 6 cycles

5 to 8 wks

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**Cytoreductive surgery
without HIPEC**

**Cytoreductive surgery
with HIPEC
(IP Cisplatin at 75mg/m²)**

Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in Relapse Ovarian Cancer Treatment (CHIPOR)

Estimated Enrollment : 444 participants

Primary outcome: Overall survival (4 yr follow up)

Secondary outcome: Relapse free survival

Study Start Date :April 2011

Estimated Study Completion :December 2020

<https://clinicaltrials.gov/ct2/show/NCT01376752>