Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion in the treatment of Taxan- and Platin refractory, recurrent ovarian cancer

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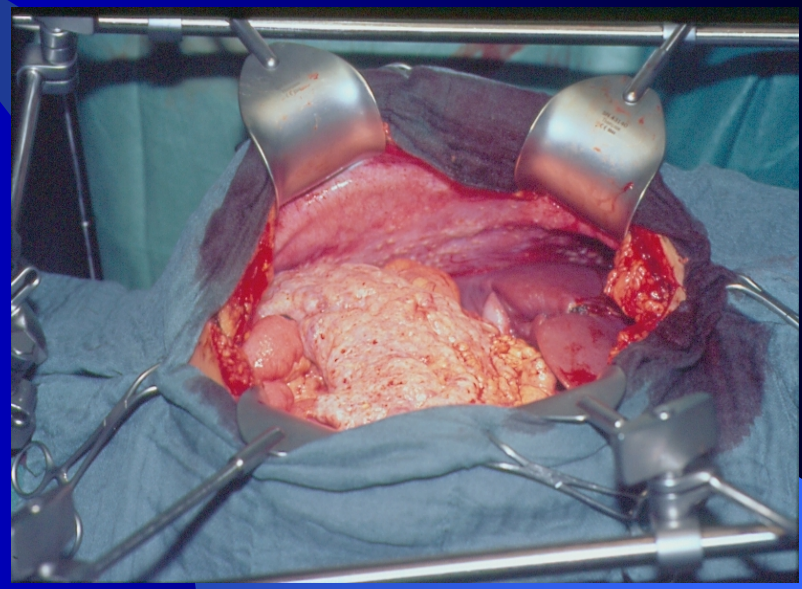


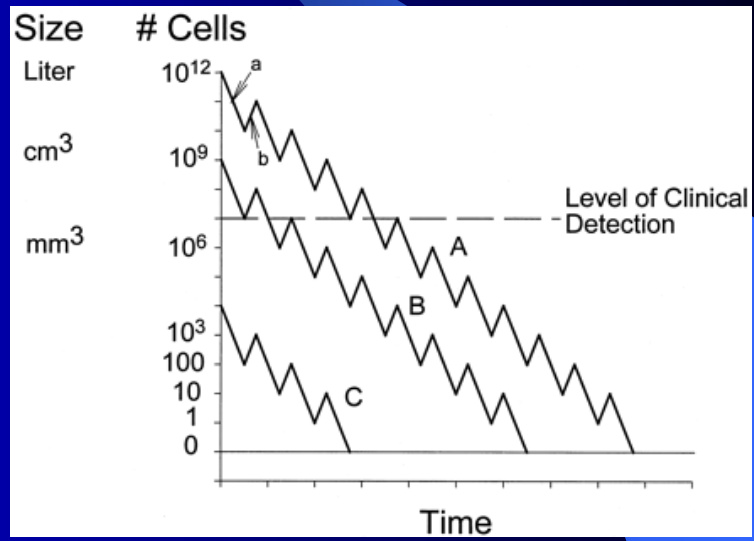
ovarian cancer

- Ovarian carcinoma often presents at an advanced stage and the outlook for patients is poor with an overall 5-year survival rate of 23 %.
- The optimal salvage therapy for recurrent ovarian carcinoma has not been clearly established.
- Response rates to different chemotherapeutic agents are in the range of 19 – 27 % leading to a 8 – 12 months survival time°.
- Role of second debulking has not been clearly definded in recurrent ovarian carcinoma.

° Markman M, Bookman MA; Second-line treatment of ovarian cancer, The Oncologist 2001;5:26-35

Concept of cytoreduction
- theoretic basis -

- According to the log – kill hypothesis, chemotherapeutic agents kill a constant fraction of cells, rather than a specific number of cells after each dose.



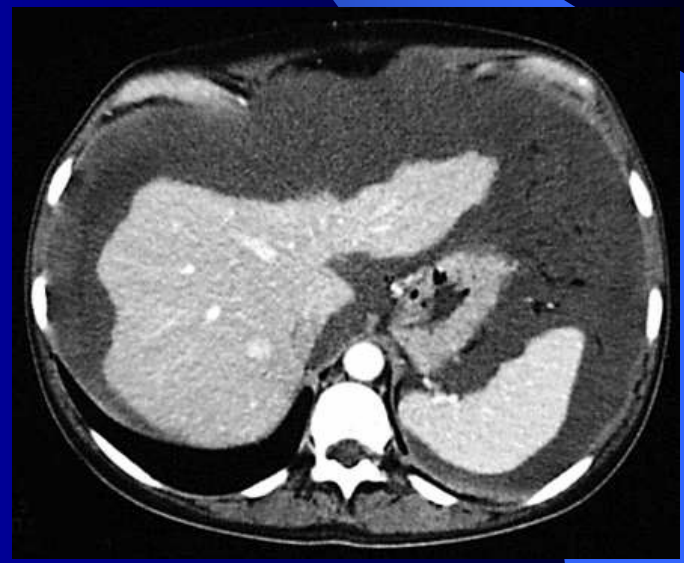
- Therefore, reducing the initial tumor volume increases the likelihood that repeated cycles of chemotherapy will reduce the number of viable tumor cells.

- Reducing the total tumor volume to be treated also substantially diminishes the chances of cancer cells developing drug resistance

aim of study

We investigated the effect of an aggressive approach consisting of second cytoreductive surgery plus hyperthermic intraperitoneal perfusion followed by adjuvant systemic chemotherapy.

- to define the role of second cytoreductive surgery in recurrent ovarian carcinoma
- to define prognostic parameters

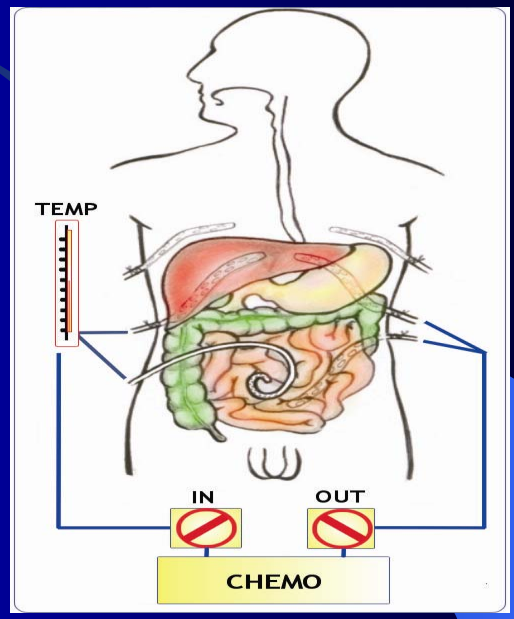


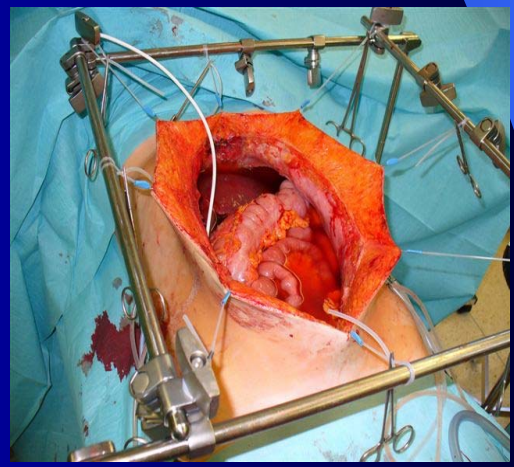
surgical technique

- electrosurgical resection of larger tumor formations
  - Including resection of small and large bowel, splen, stomach etc.
- peritonectomy
- hyperthermic peritoneal perfusion
- reconstruction by bowel anastomosis

hyperthermic peritoneal perfusion (HIPEC)

Technique	Open Coliceum technique
Temperature	41.5 – 42.0 C°
Perfusion time	60 min.
Perfusion volumen	4000 ml
Flow	1500 ml / min.



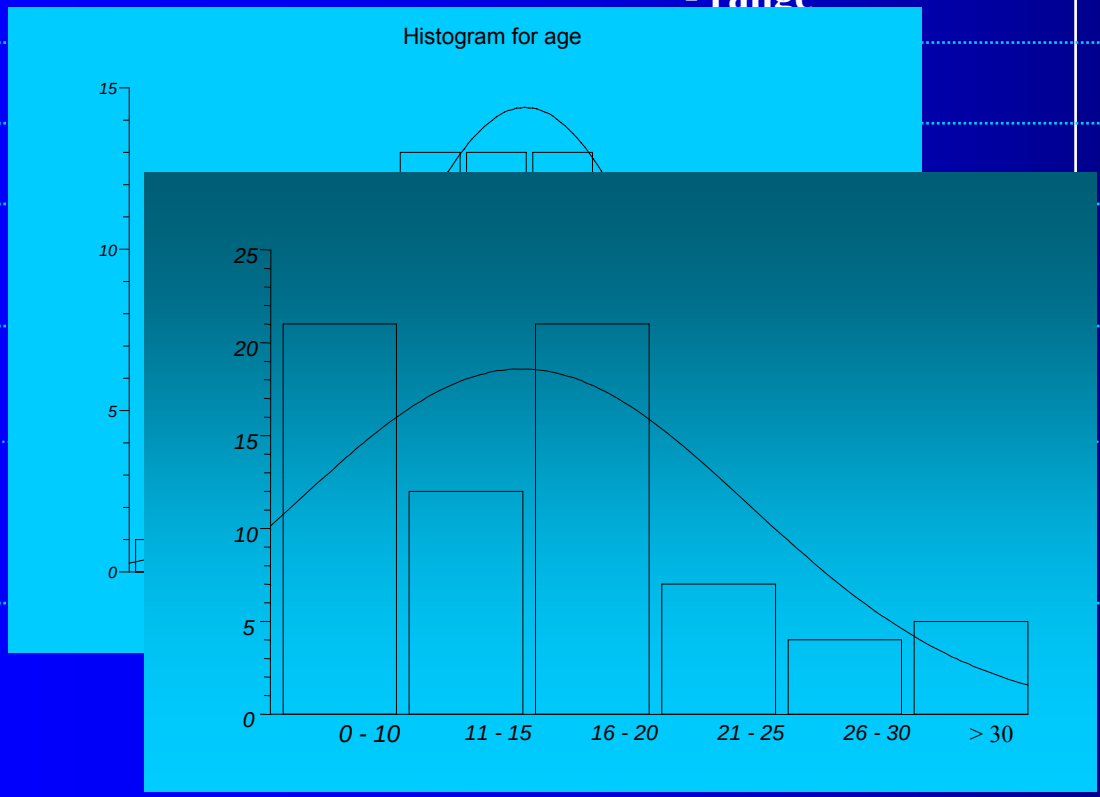


chemotherapy

	Protocol 1 **4 / 02 - 12 / 05**	**Protocol 2** **1 / 06 – 5 / 06**
HIPEC	Mitomycin 20 mg/m² Mitoxantron 20 mg/m²	Adriamycin 25 mg/m² Mitoxantron 15 mg/m²
postoperativ intraperitoneal chemotherapy	5-Fluorouracil 500 mg / m² d1 – d3	Paclitaxel 20 mg/m² d1 – d2
adjuvant chemotherapy	Topotecan 0.5 mg / m² d1 -d 5 Gemcitabine 800 mg / m² d 1, 600 mg / m² d 8 for 3 cycles	Adriamycin 40 mg/m² Mitoxantron 15 mg/m² f for 3 cycles

patient data I

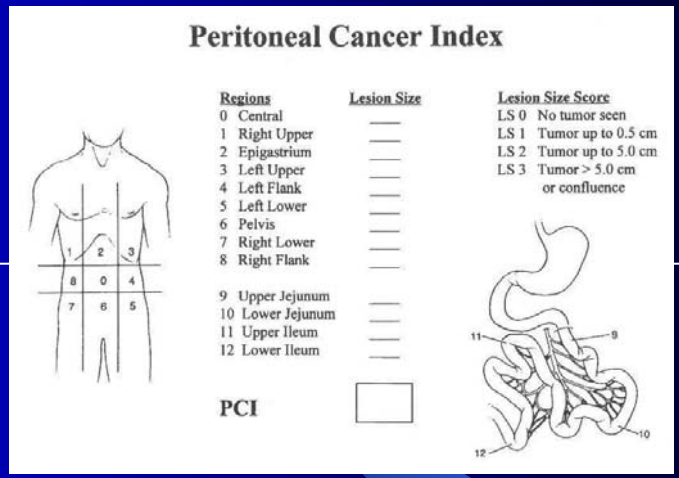
number		**70**
time		**4 / 02 – 5/06**
age	**- mean**	**56,7 years**
	- range	**25 - 81**
		83
		60 - 100
		15.9
		4 - 39
		33 months
		2 – 110
		15.8 months
		1 - 49



patient data II

number of previous chemotherapies - mean	2.5
- range	1 - 8
Platin resistance	51 /70 72.8 %
- progressive within 6 months	22
- progressive within 12 months	29
Taxol resistance	42 / 70 60.0 %
- progressive within 6 months	18
- progressive within 12 months	22

operations



- resections — n = 78
  - two step strategy — n = 2
  - re-resecetion — n = 6
- completeness of resection — 57 / 70 — 81.4 %
- peritonectomy procedures — per operation — 2.98
  range — 0 – 5
- resection of diaphragm — n = 24 — 34.2 %

results II

number of peritonectomy procedures		
total		209
mean		2.98
number of bowel anastomoses		
total		180
mean		2,3
completeness of cytoreduction		
CC 0	(no rest)	38
CC 1	(< 2.5 mm)	17
CC 2	(< 2.5 cm)	7
CC 3	(> 2.5 cm)	8

(2 two-step procedure)

complications (grade III / IV)

surgical failure

• dehiscence of laparotomy	2
• bowel perforation	2
• bleeding	1
• paralysis	1

chemotherapy dependent side-effects

• anemia	1
• thrombocytopenia	2
• leucocytopenia	2

procedure dependent

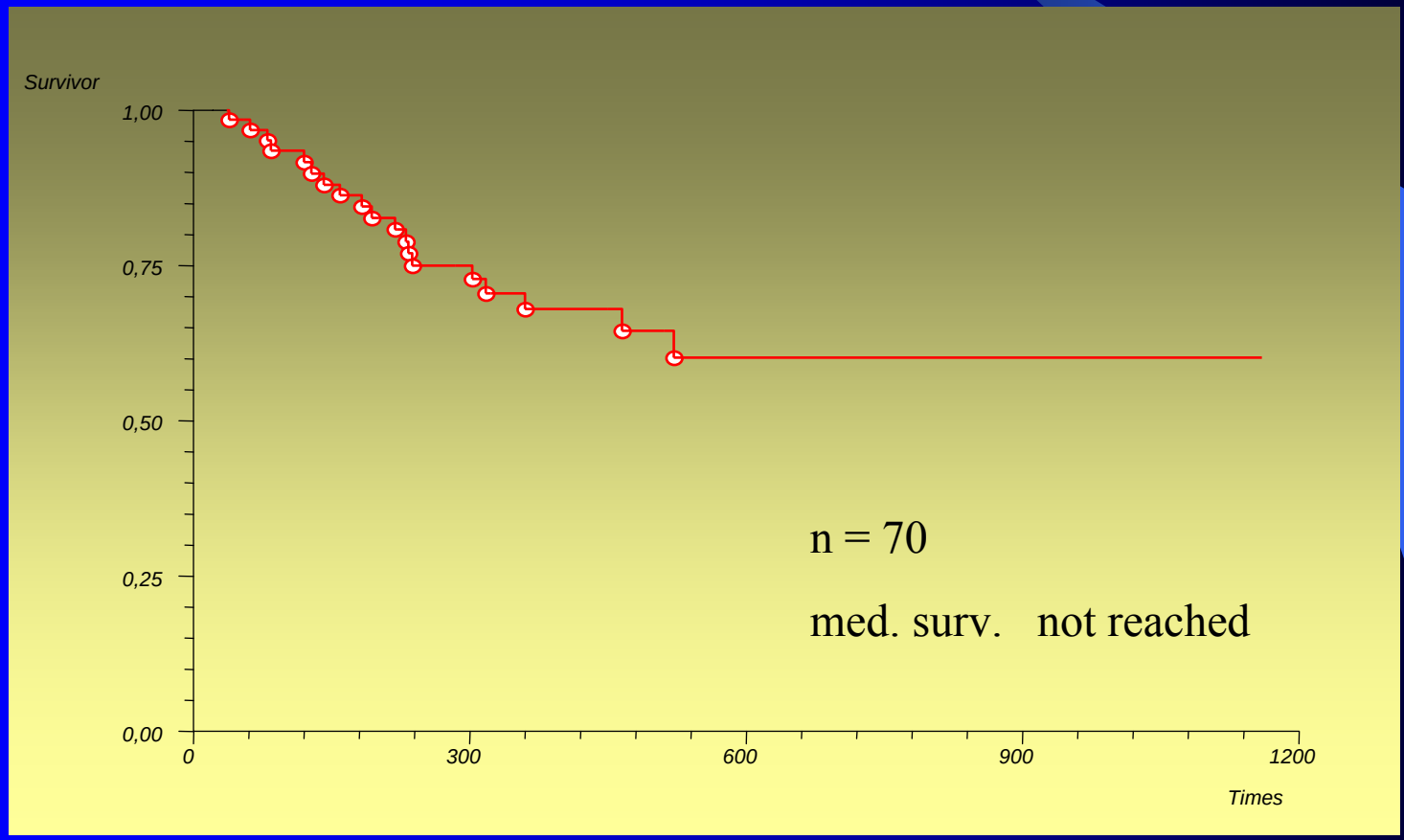
• convulsive attack	1
• stroke	1
• lung embolism	2
• thrombosis	1

complication rate grad III / IV	**16 / 78**	**20.5 %**
mortality	**0 / 78**	**0 %**

comparison
complications
- International Survey 2004 / 35 centers -

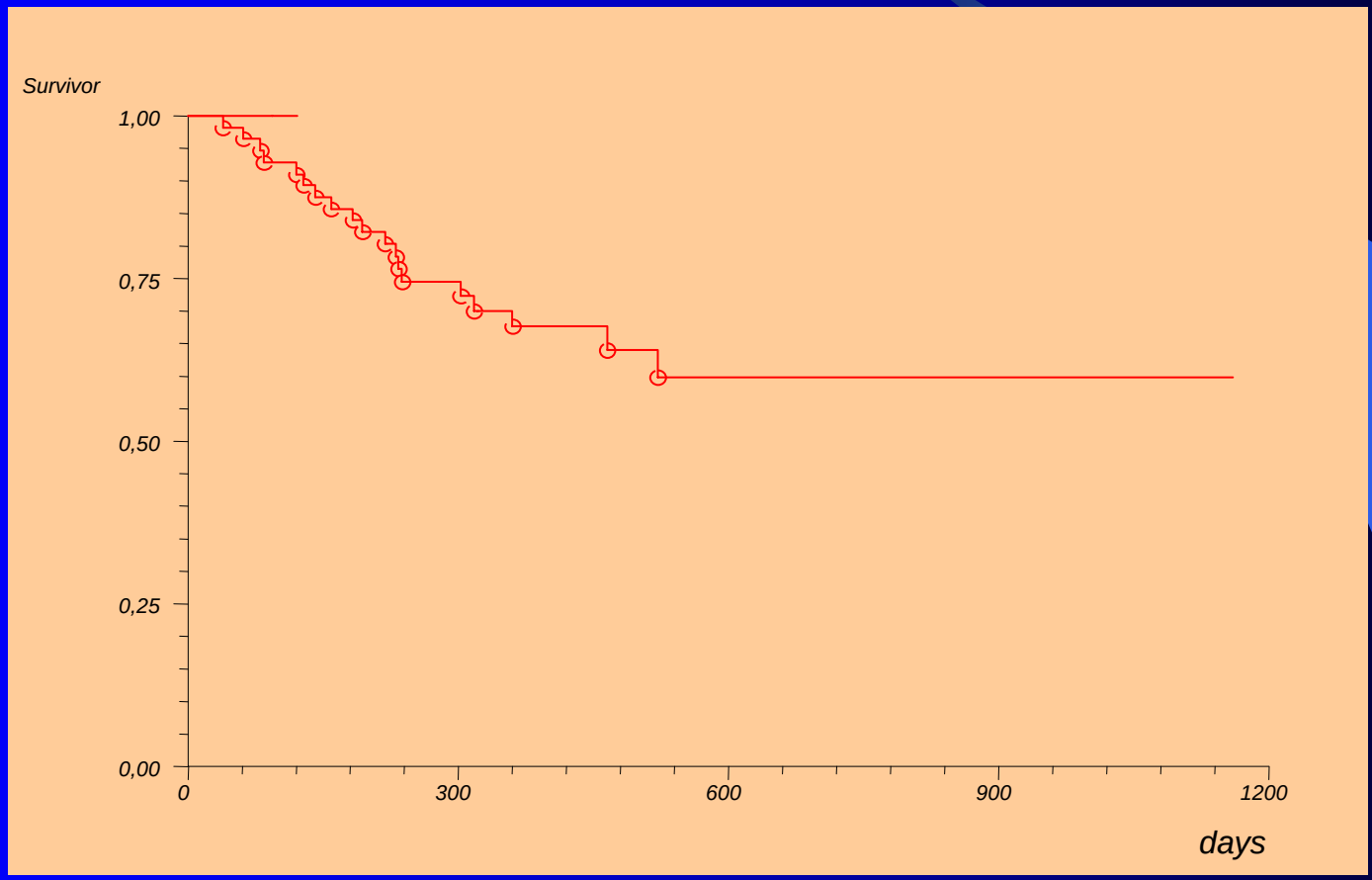
	survey	Hammelburg
thrombembolic events	min = 0 % max = 12 % mean = **2.83 %**	3 / 78 **3.8 %**
anastomotic leckeage	min = 0 % max = 20 % mean = **3,77 %**	0 / 78 **0 %**
morbidity	min = 0 % max = 60 % mean = **24.5 %**	16 / 78 **20.5 %**
mortality	min = 0 % max = 10.0 % mean = **1,76 %**	0 / 78 **0 %**

Overall survival

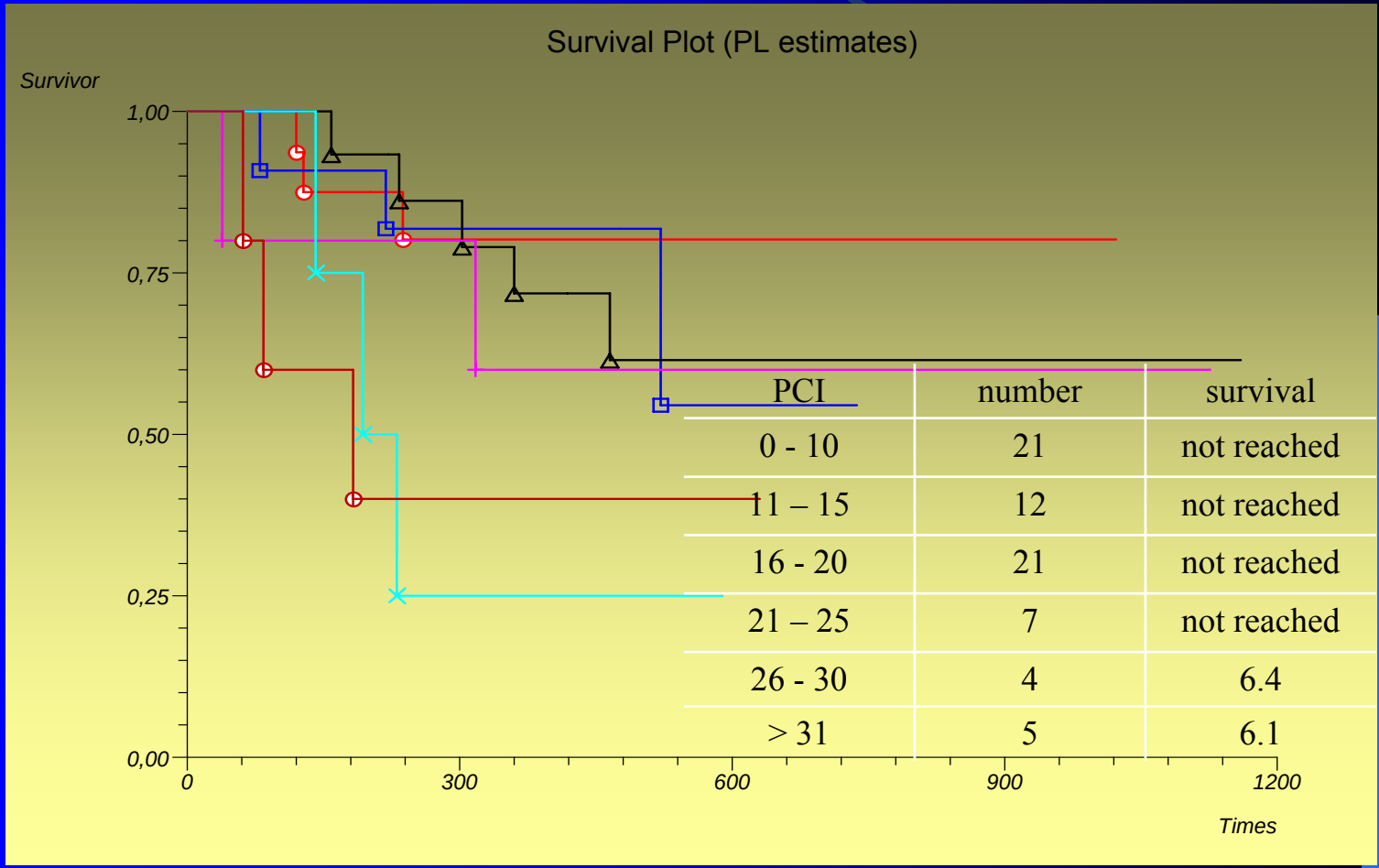


Survival dependent to chemotherapeutic protocol

protocol I : 4/02-12/05, protocol 2 : 1/06 – 5/06



Survival dependent to extent of peritoneal carcinosis (PCI – Index)

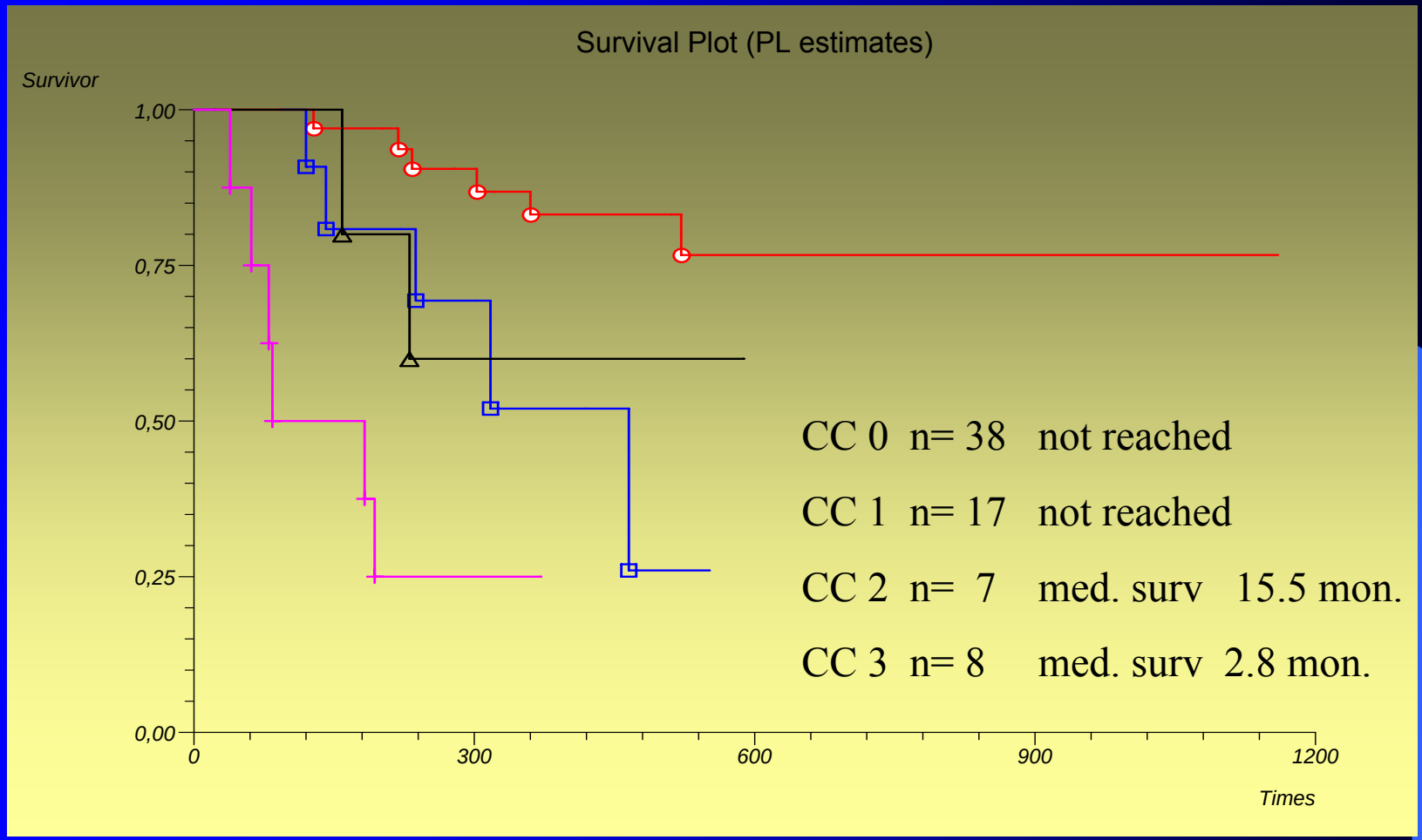


PCI	number	survival
0 - 10	21	not reached
11 – 15	12	not reached
16 - 20	21	not reached
21 – 25	7	not reached
26 - 30	4	6.4
> 31	5	6.1

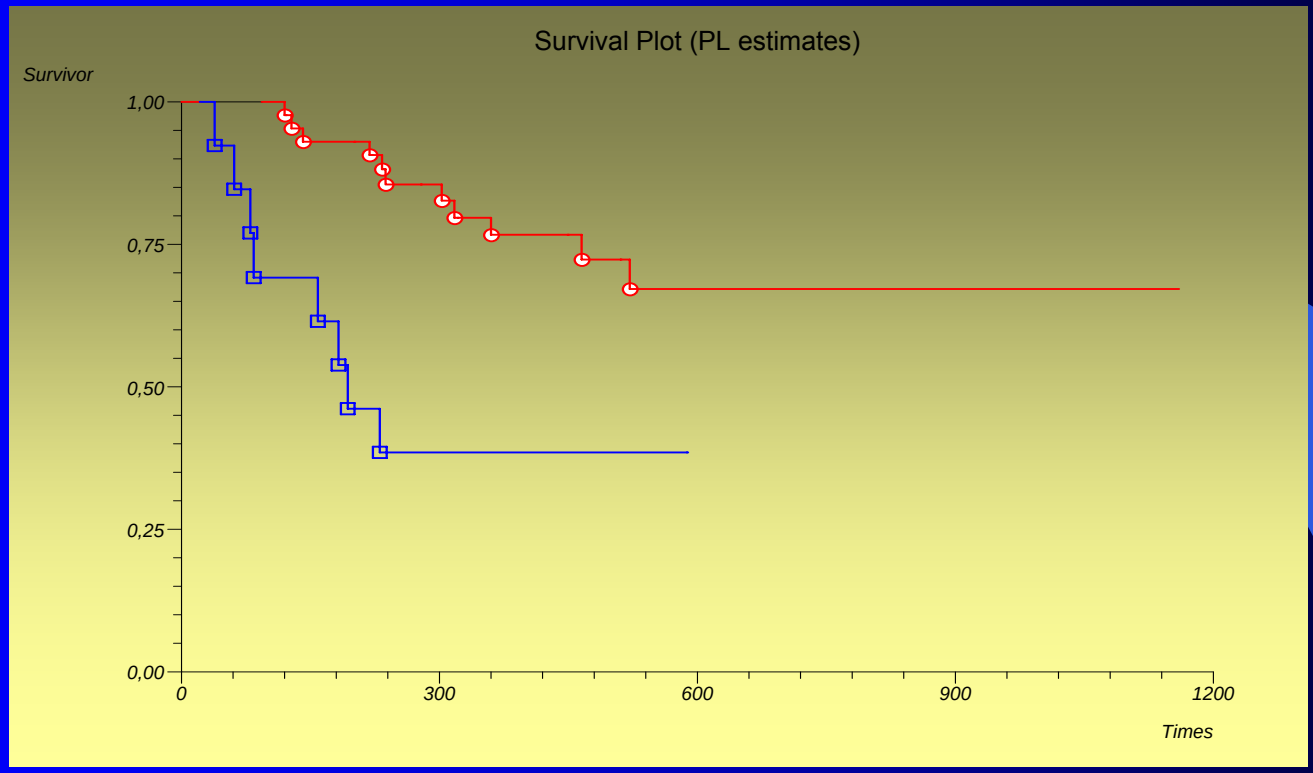
probability for complete resection

PCI Index	number	completeness of resection %
1 -10	21	100
11 - 15	12	91.7
15 - 20	21	85.7
21 - 25	7	42.9
26 - 30	4	25.0
> 31	5	20.0

Survival dependent to completeness of resection



Survival dependent to completeness of resection



CC 0/1	n = 55	med. surv	not reached
CC 2/3	n = 15	med. surv	6.4 months
Log rank test		p = 0,0007	HR .237

Second Cytoreduction with HIPEC for recurrent ovarian cancer

author	pts.	morbidity	mortality	median survival
Sebbag 2000	33	33 %	3 %	31.0 months
Deraco 2001	27	11 %	4 %	55 % at 2 years
Kecmanovic 2003	11	---	0 %	22.0 months.
Look 2003	28	---	0 %	45.8 months
Chatzigeorgiou 2003	20	---	0 %	29.0 months
Piso 2004	19	36.8 %	5.3 %	33.0 months
Plaisant 2004	13	---	7,7 %	25.5 months
Reichman 2005	13	---	---	55.0 % at 3 years

Second Cytoreduction without HIPEC for recurrent ovarian cancer

Author	Follow up	stage	Mortality	Comments
Bristow et al. 1999	18 mo	IV	6 %	Med. survival with optimal vs. Supoptimal debulking 38 vs. 10 mo (*P* = .0004). Optimal debulking is an independent predictor of survival.
Eisenkop et al 1998	27 mo	IIIC/IV	2%	Med. survival with optimal vs. Suboptimal debulking 54 vs. 20 mo (*P* = .001). 5-year survival is 48% vs 29%. Optimal debulking is independent predictor of survival.
Curtin et al. 1997	1–78 mo	IV	-	Med. survival with optimal vs. Suboptimal debulking 40 vs. 18 mo (*P* = .01). Optimal debulking is independent predictor of survival by multivariate analysis.
Liu et al. 1997	—	IV	2%	Med. survival with optimal vs. Suboptimal debulking 37 vs 11 mo (*P* = .03).
Janicke et al. 1992	18 mo	IV	-	Survival 29 vs 9 mo for no residual vs < 2 cm residual disease (*P* = 0.004).
Bertelsen 1990	28–79 mo	III / IV	-	5-year survival with optimal vs. Suboptimal debulking 46% vs 14%. Survival correlates with degree of debulking (*P* < .01).

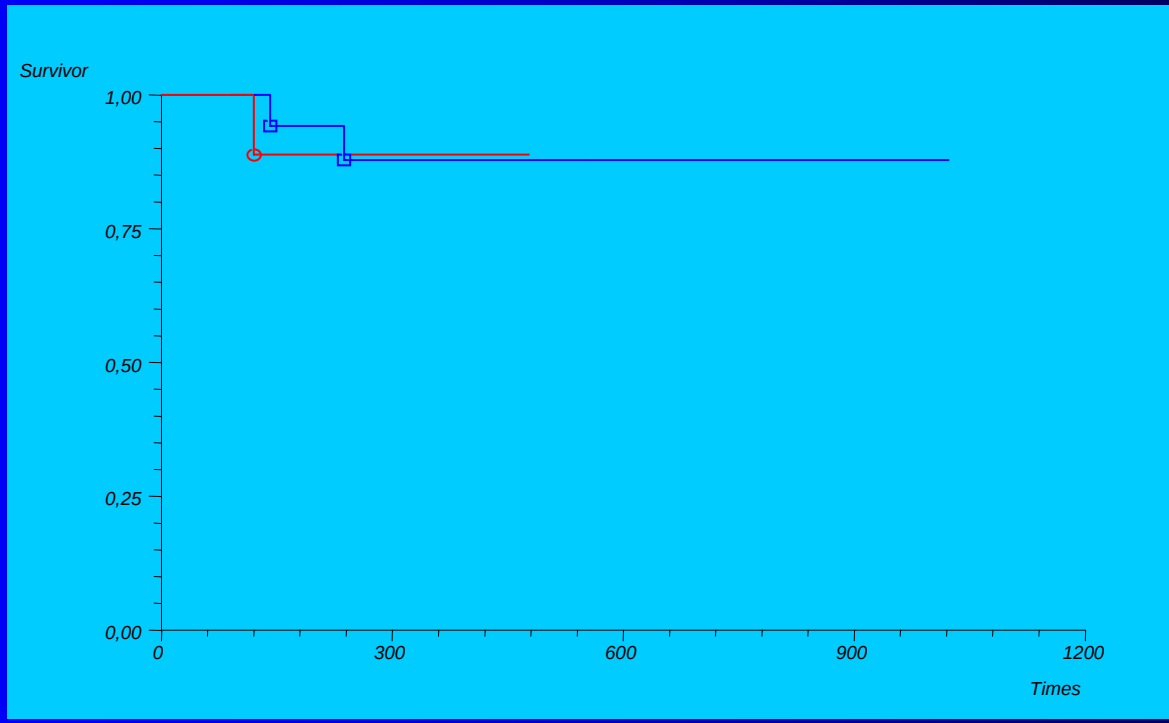
Second Cytoreduction for persistent ovarian cancer randomized studies

author	pts.	stage	med. survival	comments
Rose et al. 2004	424	III / IV	36.2 mon . Surgery 35.7 mon. Chemo alone	Second cytoreduction after insufficient primary surgery does not improve survival
Van Burg et al EORTC 1995	319	III / IV	26.0 mon. Surgery 20.0 mon. Chemo alone	Second cytoreduction after insufficient first attempt improve survival

predictive markers ?

hormon receptors

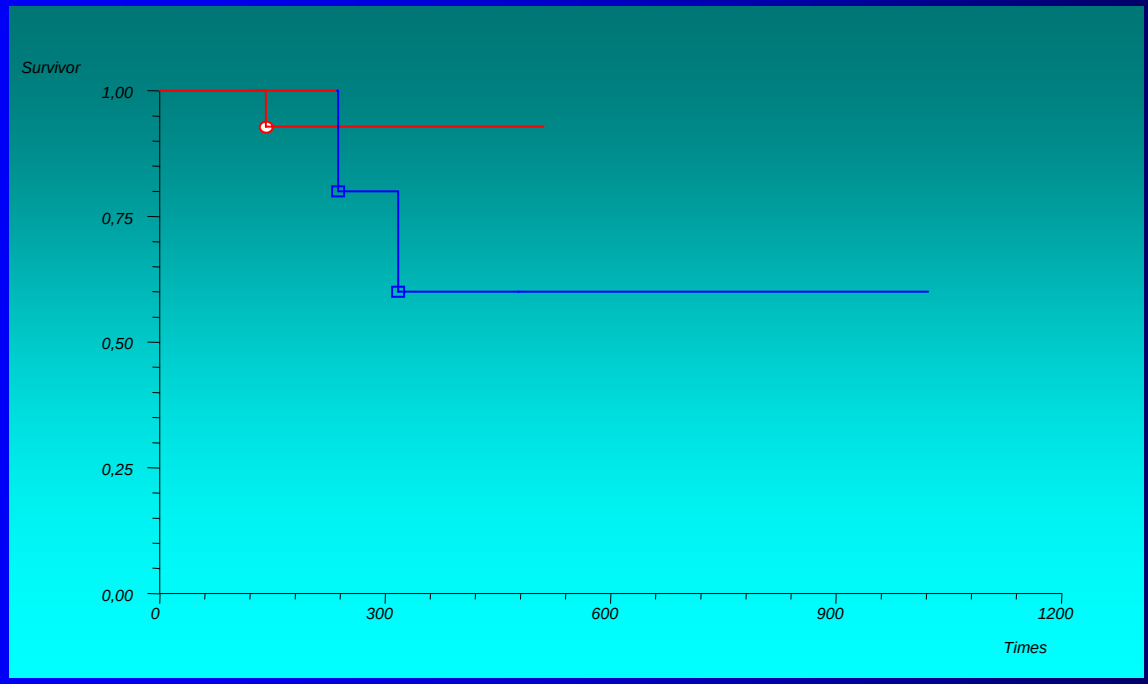
tested	n = 38
positive	n = 23
statistical significance	p = 0.972



predictive markers ?

Her-2/ neu

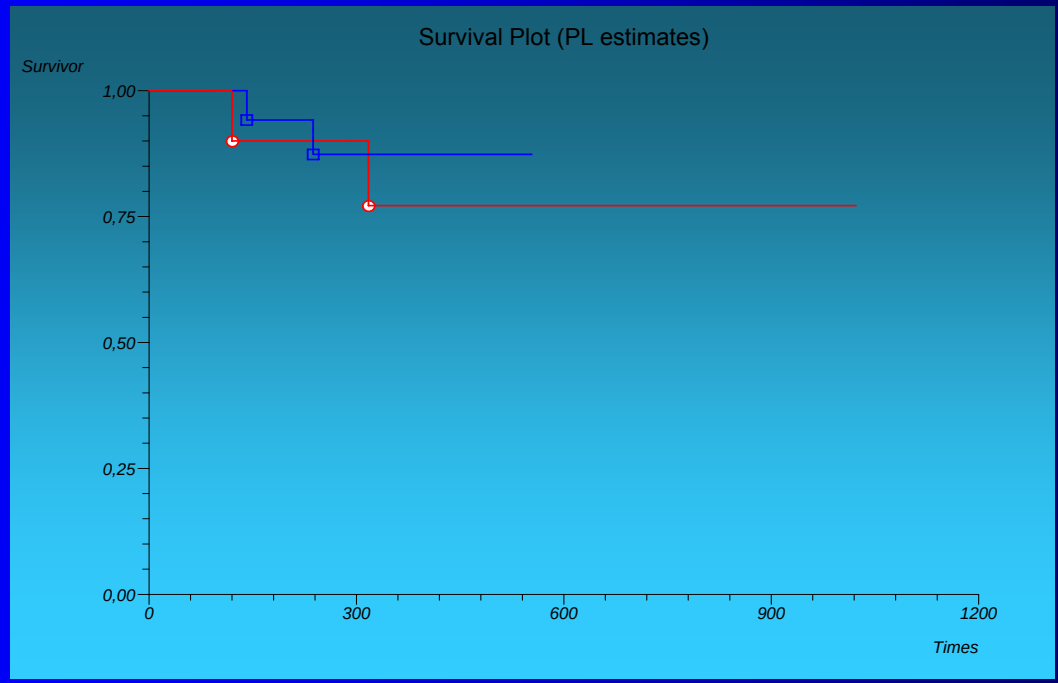
tested	n = 32
positive	n = 6
statistical significance	p = 0.18



predictive markers ?

C-KIT antigen

tested	n = 38
positive	n = 24
statistical significance	p = 0.61



prognostic factors I

factor	median survival	significance
general condition Karnofsky Index ≤ 70 vs. ≥ 80	6.4 vs. not reached	**p = 0,0001**
completeness of cytoreduction CC 0/1 vs. CC 2/3	5.3 vs. not reached	**p < 0,0001**
Peritoneal carcinosis Index < 22 vs. > 22	7.7 vs. not reached	**p = 0.0014**

prognostic factors II

factor	number	median survival	significance
age ≥ 70	n = 10	not reached	ns. p = 0.734
number or previous chemotherapies < 3 vs. ≥ 3		17.3 vs. not reached	ns. p = 0,257
Platin resistance	n = 52	not reached	ns. p = 0.61
Taxan resistance	n = 42	not reached	ns. p = 0.557
Infiltration of diaphragm	n = 24	not reached	ns. p = 0.187

Factors influencing survival

- optimal vs. suboptimal first cytoreduction
- symptomatic vs. asymptomatic disease
- small vs. bulky disease
- localized vs . extensive disease
- short vs. long disease free interval
- complete vs. incomplete second cytoreduction* (HR 2.86)
- presence vs. absence of ascites* (HR 2.41)
- good vs. reduced general condition* (HR 2.09)
- Platin containing chemo vs. non-Platin containing chemo* (HR 1.83)

* confirmed by AGO-OVAR – study

Pfisterer J et al. The role of surgery in recurrent ovarian cancer Int J Gyn Cancer 2005;15:195-198

conclusion

- Second debulking is an effective tool in the management of recurrent ovarian cancer.
- Postoperative morbidity and mortality is comparable to other major operations.
- Taxol- and/ or Platin- resistance seems not to be a contraindication for second debulking surgery.
- At this moment the value of perioperative, intraperitoneal chemotherapy is not clear.

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Thank you for your attention !