

Incomplete surgical management of epithelial ovarian cancer.

Can it be improved?

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Epithelial Ovarian Cancer

- Fourth most frequent cause of “cancer-related” death
- 65% diagnosed with stage III-IV disease
- Initial response: 80% platinum sensitive
- 5 year survival rate: 15-20%
- Second look laparotomy
 - Historically: no effect on survival
 - 1/3 macroscopic
 - 1/3 microscopic
 - 1/3 negative
 - 50% of patients with a negative second look laparotomy will recur

Ovarian cancer survival by stage of diagnosis

Stage	5-year survival rate (%)
I	85–90
II	80
III	15–20
IV	5

Ovarian cancer staging system by FIGO

Stage		Description	5-year survival Rate (%)
1. I		Growth limited to the ovaries	90 (30%)
	Ia	One ovary involved	92
	Ib	Both ovaries involved	85
	Ic	Ascites present, or positive peritoneal washing, tumor on the surface of the ovary	82
		} no ascitis capsule intact	
2. II		Growth limited to pelvis	57 (10%)
	IIa	Extension to the uterus and the tubes	69
	IIb	Extension to other pelvic tissues	56
	IIc	Like Ic	51
3. III		Growth extending to abdominal cavity, including peritoneal surface and omentum	24 (32%)
	IIIa	Microscopic abdominal implants, negative nodes	39
	IIIb	Macroscopic abdominal implants, < 2 cm, negative nodes	25
	IIIc	Abdominal implants > 2 cm and/or positive nodes	17
4. IV		Metastases to distant sites (positive pleural cytology, parenchymal liver metastasis)	12 (28%)

Recommended surgical staging procedures

- Peritoneal washings
- Total abdominal hysterectomy and bilateral salpingo-oophorectomy
(Unilateral salpingo-oophorectomy may be appropriate for selected patients with Stage IA disease who desire to defer definitive surgery until completion of childbearing.)
- Infracolic omentectomy
- Pelvic and para-aortic lymph-node sampling
- Peritoneal biopsies from:
 - cul-de-sac
 - rectal and bladder serosa
 - right and left pelvic sidewalls
 - right and left paracolic gutters
 - right and left diaphragms
 - any adhesions

Surgical staging practice in patients with early ovarian carcinoma

Authors (year)	Period under study	Country	# patients	FIGO Stage	% receiving complete staging
Trimbos 1990	1981- 1988	Netherlands	43	IA-IIA	5%
Högber 1993	1984- 1987	Sweden	148	I-II*	20%
Junor 1994	1987	UK	123	I-II#	0% for GS 76% for OBG
Munoz 1997	1991	USA	785	I-II	10%
Zanetta 1998	1981- 1991	Italy	351	I	28%
Petignat 2000	1989- 1995	Switzerland	37	I-II	3%

OBG : Obstetrician-gynecologist GS : General surgeon

*Adequate staging did not include lymph node sampling

#Adequate staging included TAH-BSO with or without omentectomy

Results of restaging laparotomies in women with apparent early stage ovarian carcinoma

Authors (year)	Number of patients	FIGO stage at initial surgery	% upstaged
Bagley 1973	5	I-II	60%
Young 1983	100	IA-IIB	31%
Helewa 1986	25	I	20-25%
Buchsbaum 1989	140	I-II	22,4%
Archer 1991	24	I-II	20,8%
Soper 1992	30	I-II	30%
Stier 1998	45	IA-IIB	16%
Leblanc 2000	28	I	21%

Influence of operating physician's specialty on patient survival

Authors (years)	# patients	Study period	Surgeons	Survival by managing surgeon	<i>P</i> values
Mayer 1992	47	1981- 1987	GYO vs OBG vs GS	GYO > OBG and GS	<i>P</i> <0.005
Nguyen 1993	1,377	1983- 1988	GYO vs OBG vs GS	GYO and OBG > GS	<i>P</i> <0.004
Kehoe 1994	1,184	1985- 1987	OBG vs GS	OBG >GS	<i>P</i> <0.00001
Puls 1997	54	unknown	GYO vs OBG	GYO > OBG	<i>P</i> <0.05
Woodman 1997	691	1991- 1992	OBG vs GS	OBG > GS	<i>P</i> <0.01

GYO: Gynecologic oncologist
 OBG: Obstetrician-gynecologist
 GS: General surgeon

Intra and postoperative complications after surgical staging of early epithelial ovarian cancer

Authors	# patients	# complications (%)	Visceral	Vascular	Infection
Buchsbaum 1989	154	74 (29%)	23	1	30
Trimbos 1990	46	14 (30%)	3	3	5

Clinical Studies in Gynecology

- Endometrial Destruction (PF, ALA, BPD)
- Condyloma
- Cutaneous metastasis of breast cancer
- Cervical and vulvar dysplasia
- Peritoneal cavity (ovarian cancer, endometriosis)

Second look surgery: Why perform it?

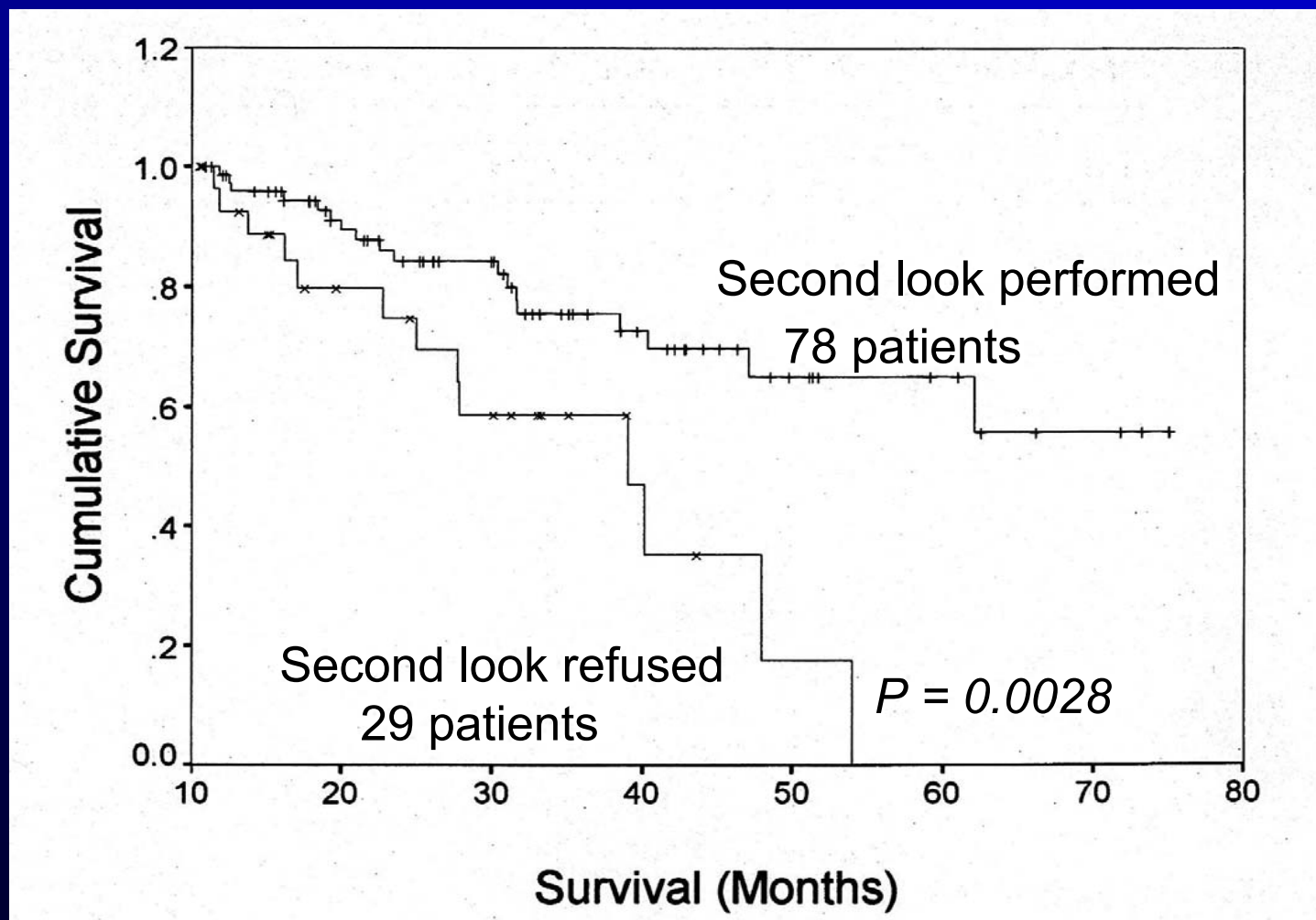
- **Contra**

- Recurrence rates of 50 % after negative second look surgery
- Absence of proven salvage therapy
- Lack of demonstrable survival benefit

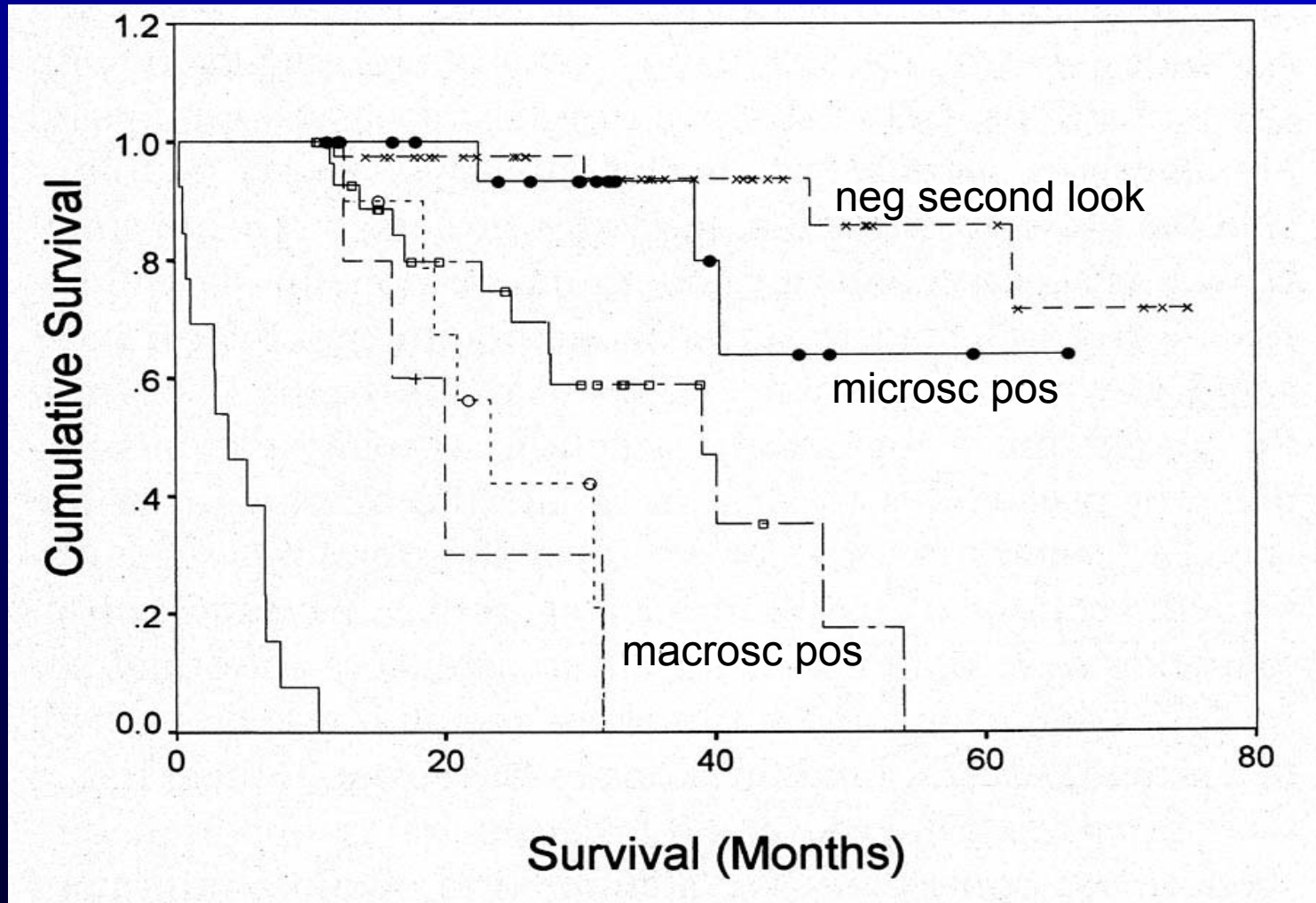
- **Pro**

- No proven alternative surveillance techniques (CT, Ca125, etc.)
- Possible survival benefit of secondary cytoreduction
- Possible long term survival benefit for patients undergoing second line chemotherapy with minimal residual disease.

Survival by performance of second look



Survival by outcome of second look



Enhanced diagnosis through photodetection

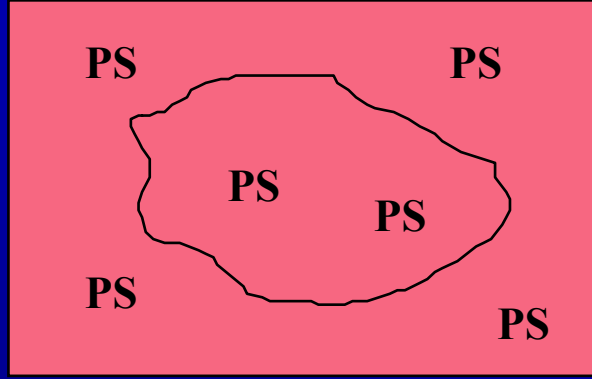
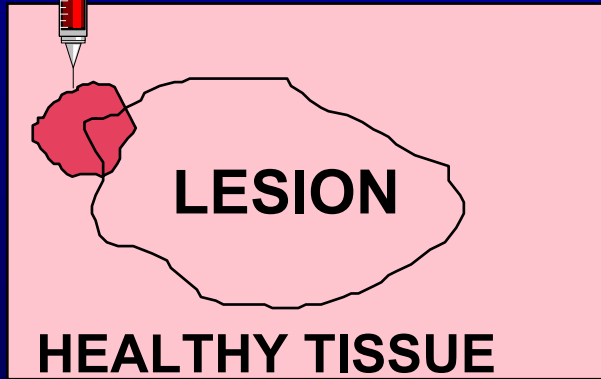
- *Photodetection* of ovarian cancer peritoneal implants in the animal model
- Determination of the best Photosensitizer
- *Photodetection* of ovarian cancer peritoneal implants in ovarian cancer patients

Photodynamic Principle

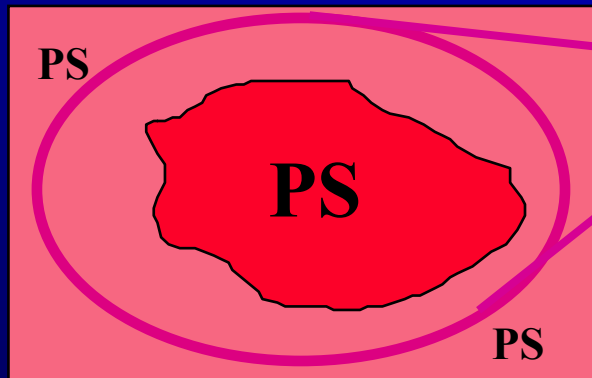
- Use of a photo-enhancing or photo-sensitizing chemical to aid in the diagnosis or treatment of a target cell

Principle of PDT

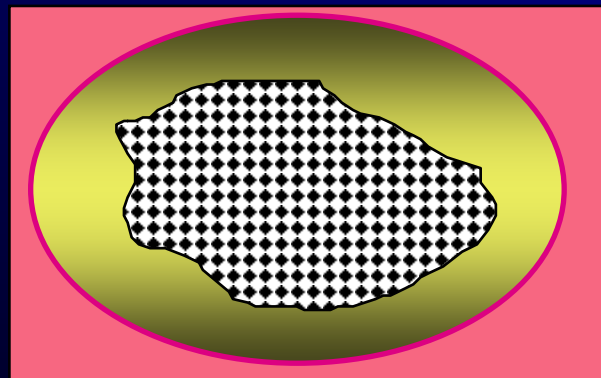
PHOTOSENSITIZER ADMINISTRATION
(systemic or topical)



$\downarrow \Delta t$



$\leftarrow \Delta t$



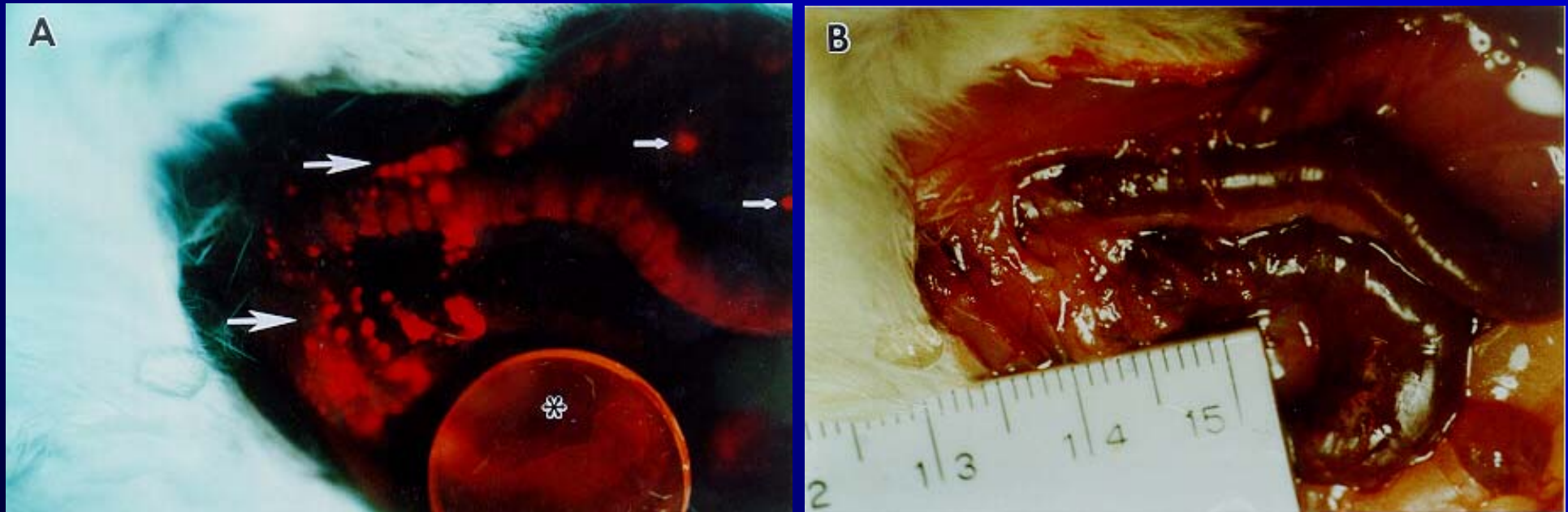
"SELECTIVE" DESTRUCTION

"SELECTIVE" ILLUMINATION

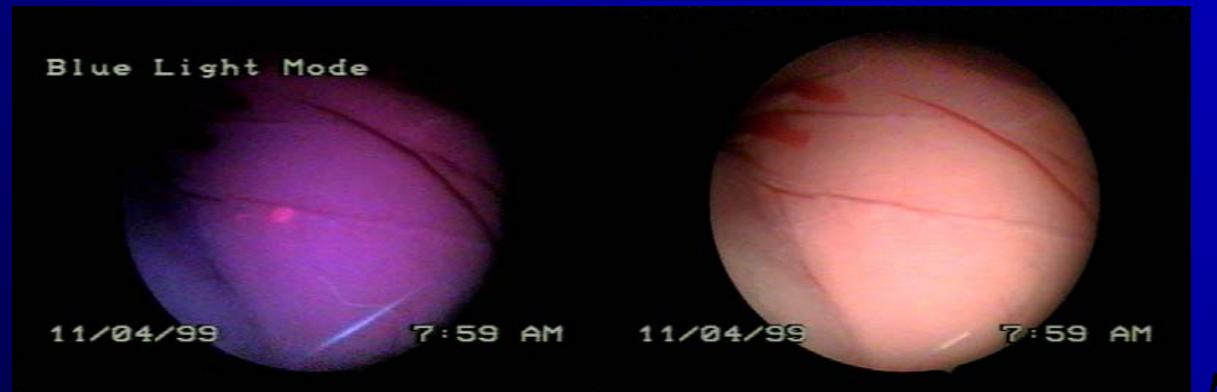
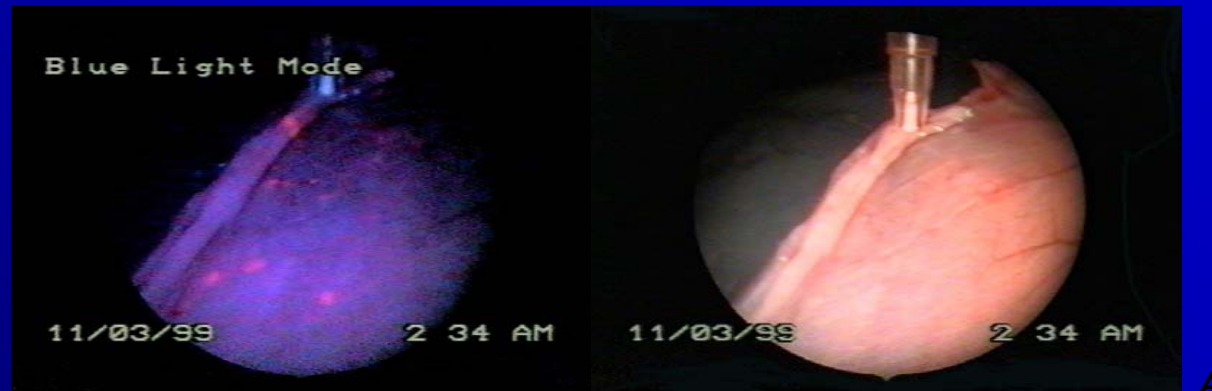
NuTu-19 Ovarian Cancer Animal Model

- **Completely analogous to human epithelial ovarian cancer**
- **Cell line - NuTu-19 - Spontaneous mutation**
- **Histology - Poorly differentiated ovarian adenocarcinoma with papillary features**
- **Growth pattern - I.P. serosal nodules with local tissue invasion (omentum, diaphragm, liver, peritoneum)**
- **Malignant ascites - average vol. 50-70ml in 6 weeks**
- **Survival - 10^6 cells I.P are 100% fatal, mean survival of 50 days**
- **Non-immunogenic tumor developed in an immunocompetent host**

In vivo fluorescence (A) and light images (B) of omental tumor nodules and small bowel mesentery tumor nodules. Transparent omentum is overlying the small bowel. . Fluorescence was excited using a uv lamp 3 hr after ip administration of 200 mg/kg ALA. Control fluorescence disk is indicated by an asterisk



Epithelial ovarian cancer PDD in NuTu-19 rat model

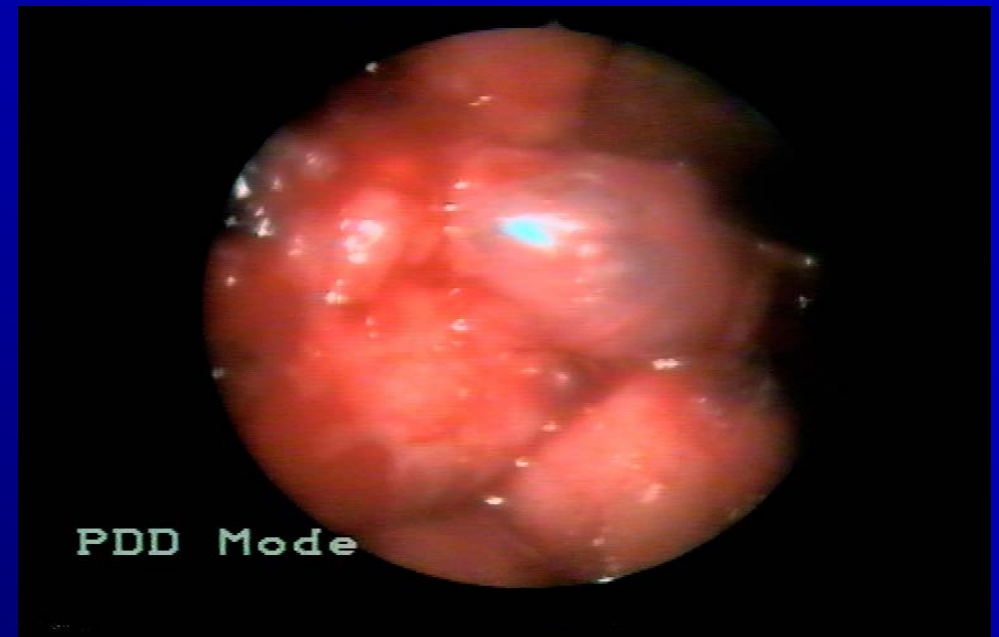


8mM h-ALA IV prior to photodetection 2 hours later

Numbers of metastases detected with white and blue light detection for different concentrations of h-ALA and ALA

Concentration [mM]	Time after inst.	White light	Bluelight	Ratio
4	2.5	9	19	2.1
4	2.5	0	4	8
8	2.0	21	37	1.8
8	2.0	36	57	1.6
8	2.0	13	29	2.2
8	2.0	4	24	6
12	2.0	3	8	2.7
20	2.0	9	25	2.8
8 (ALA)	2.0	10	16	1.6

Human Epithelial Ovarian cancer PDD



10mg/ml ALA applied topically prior to photodetection

Ovarian cancer PDD second-look feasibility Study

Stage III-IV ovarian + 6-8 cycles taxoid platinum chemotherapy

Clinical complete response

Second-look operation with white light and PDD.

Retrospective Data
No second-look

Neg. second-look operation
with white and PDD.

Pos. second-look operation
with white light or PDD

Lesions < 1/2 cm via
white or PDD or
microscopic disease

Macroscopic lesions
> 1/2cm via
white or PDD

Second-line
chemotherapy

Second line
chemotherapy.

Survival data.

Survival data.

Survival data

Retrospective
survival data.

CONCLUSIONS

- Photodetection has been shown to be efficient in the animal model and feasible in patients
- Photodetection of ovarian cancer peritoneal implants, not visible by other methods, is a conceivable goal for the future
- The impact on survival has to be demonstrated in further studies



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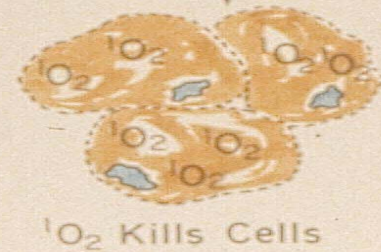
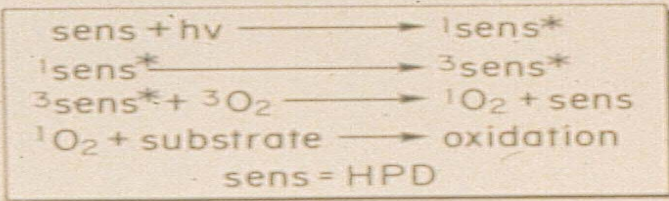
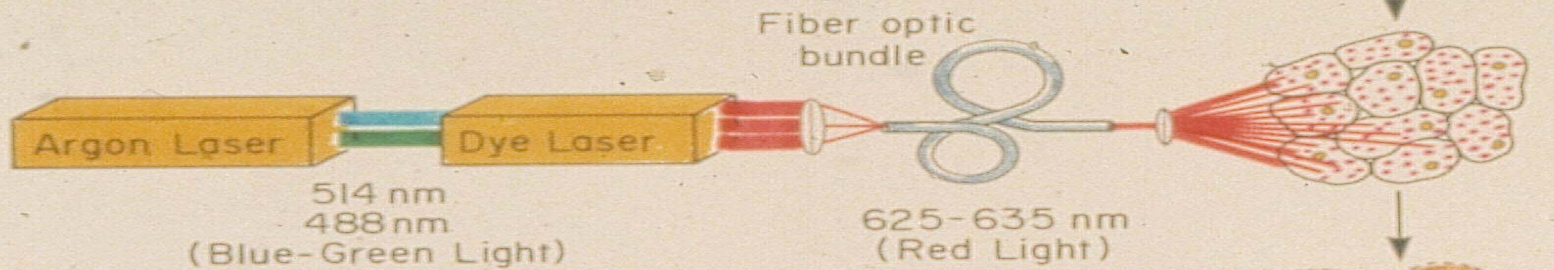
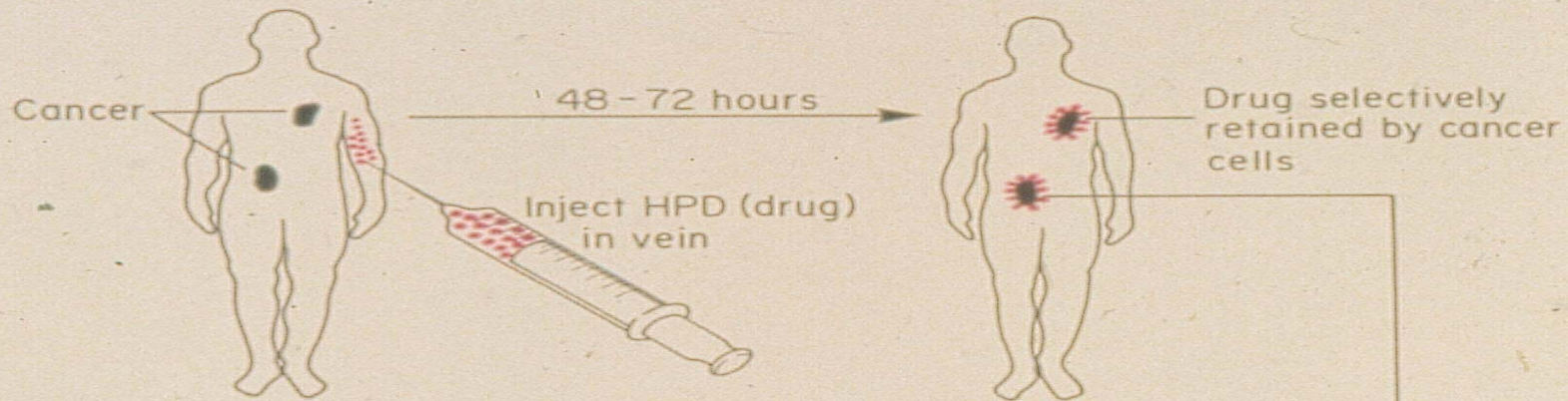
The nurse team

Frederic Bylebyle

Werner Marie-Lore

Patrick Ubaud

PHOTORADIATION THERAPY OF CANCER (Laser-Hematoporphyrin Derivative)



“The facts remains that a large number of patients are being treated almost to the point of “cure” and an additional stroke of some sort is needed.”

(DiSaia, Clinical Gynecological Oncology, Mosby-Year Book, 1997)

Photosensitizers

- Porphyrins
 - Photofrin (PF)
 - "Aminolevulinic acid (ALA)",
Protoporphyrin IX (PpIX)
- Chlorins
 - m-Tetrahydroxyphenyl chlorin (mTHPC)
 - Benzoporphyrin derivative mono-acid (BPD)
 - Tin ethyl etiopurpurin (SnET2)
- Phtalocyanines

generation PS

PS	Dose (mg/kg)	D / L (hours)	WL (nm)	Light dose (J/cm²)
mTHPC	0.075 - 0.15	96	652 (red) 514 (green)	5 - 20 75 - 120
ALA-PpIX	60 Topical 20%	4 - 6	635 and 405 (red and blue)	10 - 200
BPD-MA	0.3	1 - 2	690 (red)	50 - 150
NPe6	0.5 - 1	4 - 8	664 (red)	50 - 100
Lu-Tex	0.6 - 7	3	732 (red)	150
SnET2	1.2	24	660 (red)	200

Historical

1976 J. F. KELLY + M. E. SNELL - First clinical PDT of a bladder carcinoma with HPD. (J. Urol., 115, 150, 1976).

1978 T. J. DOUGHERTY et al.- Clinical assessment of PDT (Cancer Res., 38, 2628, 1978).

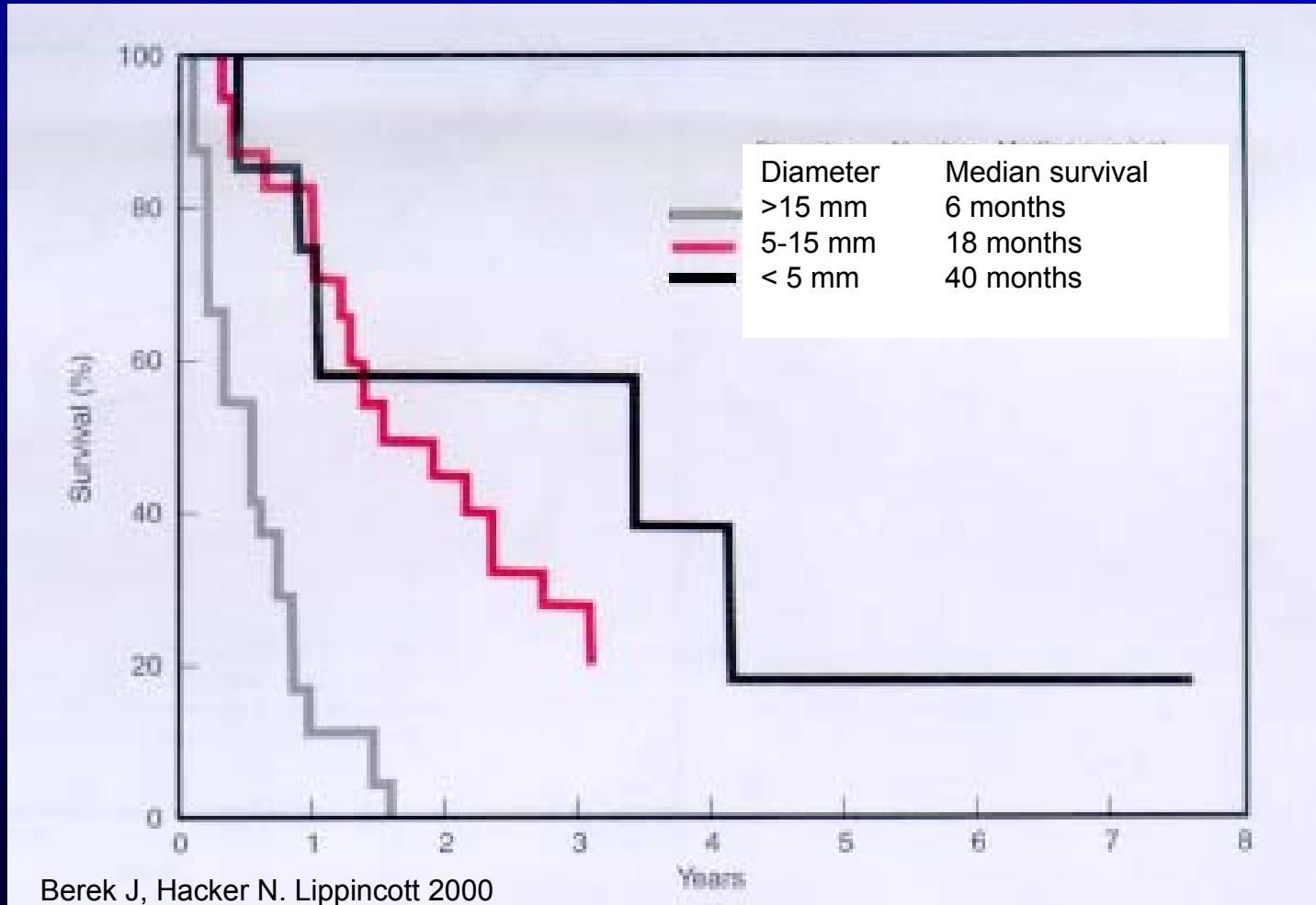
! LASERS + OPTICAL FIBERS !

1993 First approval (by the canadian health agency) of PDT with Photofrin® for the prophylactic treatment of bladder cancer.

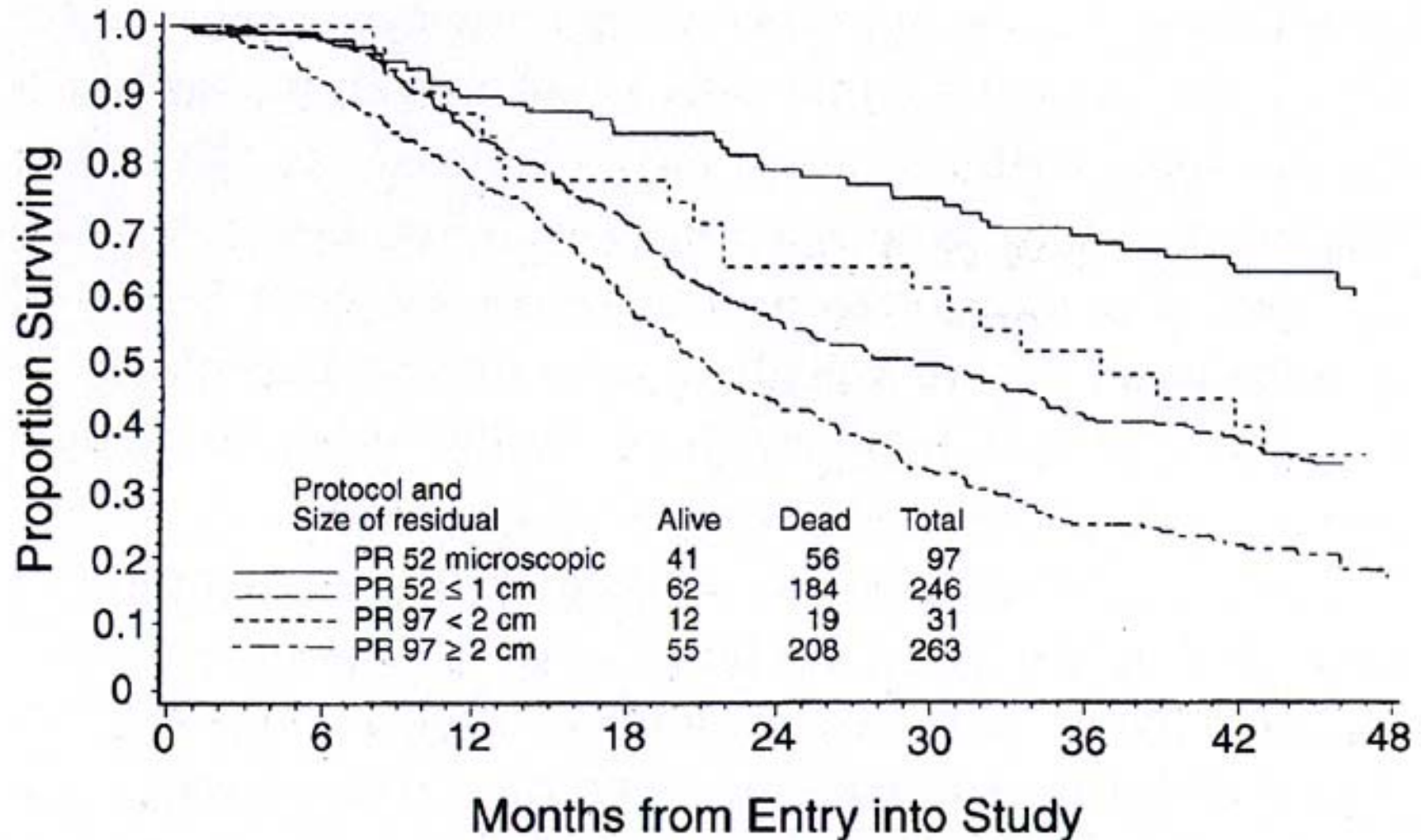
Potential of *In Vivo* Fluorescence

- Staging laparotomy
 - 30% upstaged (Young RC, JAMA, 1983; Zanetta G, Ann Oncol, 1998)
- Second Look
 - 50% recurrence of negative second-look after combination chemotherapy (DiSaia PJ, Mosby-Year Book, 1997)

Survival versus diameter of largest residual disease



Survival by initial tumor size



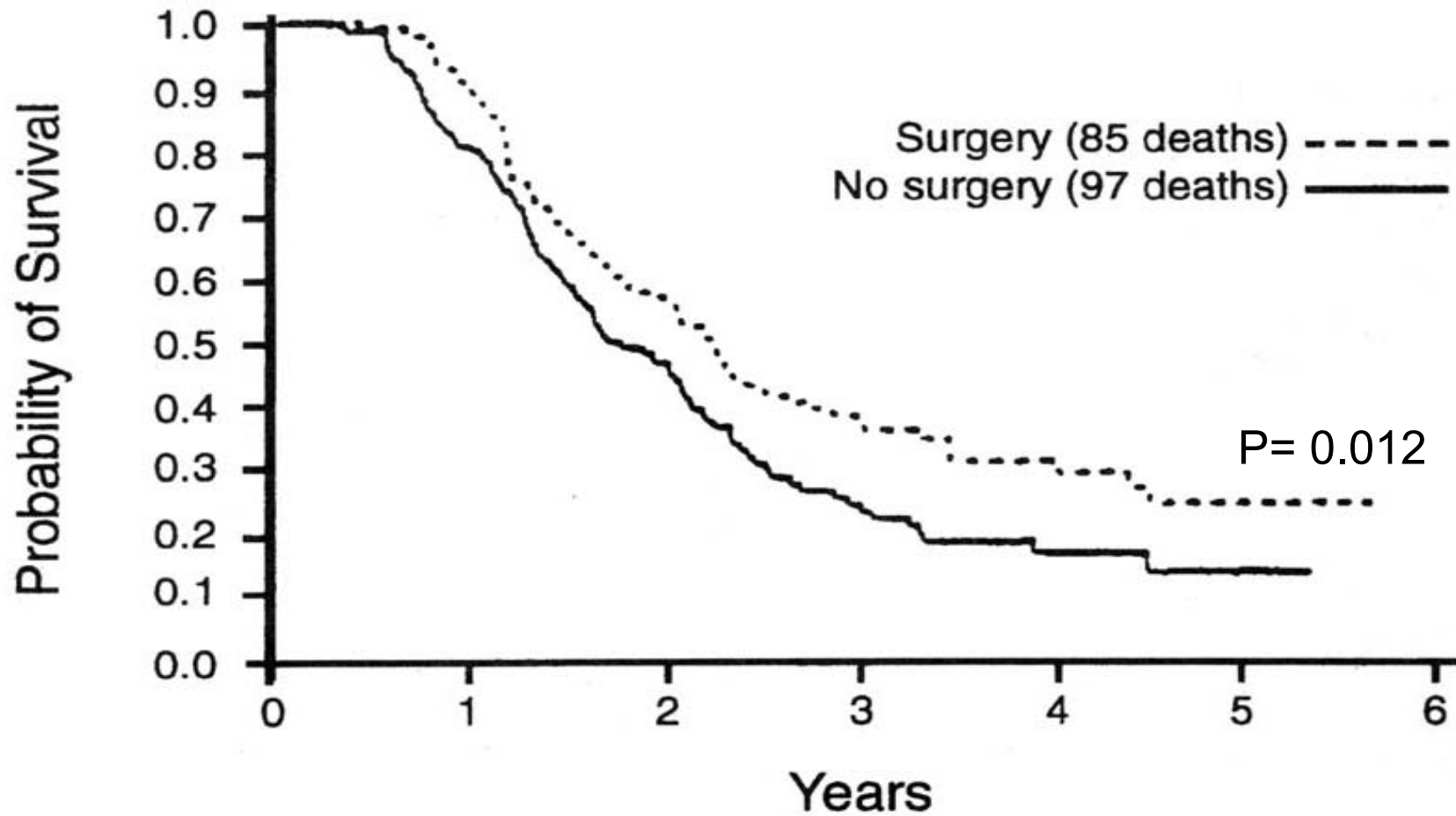


Table Summary of initial treatment recommendations for ovarian cancer by stage at presentation

After initial staging procedure/ cytoreductive surgery	Recommendation
Stage I A, grade 1 or 2	Observation
Stage I B, grade 1 or 2	Observation
Stage IA or IB, grade 3; Stage IC; Stage II	Paclitaxel + carboplatin, 3 cycles or participation in GOG 175
Stage III, optimally debulked	Paclitaxel + carboplatin, 6 cycles or participation in GOG 172
Stage III, suboptimally debulked; Stage IV	Paclitaxel + carboplatin, 6 cycles