Photodétection et traitement photodynamique en gynécologie

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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

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)

Number (percentage) of animals per group that died after PDT (3 hours time interval)

Drug and light dose	Died / Number of animals (time)
200 mg/kg (1.6 J/cm^2, 25min)	4/4 (1 at 5.5h, 2 at 1D, 1 at 3D)
100 mg/kg (1.6 J/cm^2)	2/4 (1 at 2D, 1 at 18D)
50 mg/kg (1.6 J/cm^2)	0/4
50 mg/kg (3.2 J/cm^2)	2/4 (1 at 3D, 1 at 13D)

Major A et al, Am J Obst Gynecol 2000

Site of Metastases in Patientes with Apparent Stage I and II Ovarian Cancer

Ref.	Diaphragm	Aortic Lymph Nodes	Pelvic Nodes	Omentum	Positive cytology
18		4/21 (19.0 %)	2 /21 (9.5 %)		
21	2/58 (3.4 %)	6 /52 (11.5 %)	1/11 (9.1 %)	6/57 (10.5 %)	
22	3/72 (4.2 %)			7/79 (8.9 %)	
23					7/36 (19.4 %)
24	1/31 (3.2 %)	0/5 (0 %)		0/5 (0 %)	8/31 (25.8 %)
25		2/10 (20.0 %)	0/10 (0 %)		
26	7/16 (43.8 %)				
27		5/26 (19.2 %)	0/9 (0 %)	1/21 (4.8 %)	
28					16/44 (36.4 %)
29					1/10 (10.0 %)
Total	**13/177 (7.3 %)**	**17/114 (14.9%)**	**3/51 (5.9 %)**	**14/162 (8.6 %)**	**32/121 (26.4 %)**

Modified from Berek JS, Hacker NF, Staging and second-look operations in ovarian cancer. In : Piver MS, ed. Ovarian malignancies. Edinburgh : Churchill Livingstone, 1987 : 112, with permission

Clinical Studies in Gynecology

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

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; no ascitis capsule intact	92
	Ib	Both ovaries involved; no ascitis capsule intact	85
	Ic	Ascites present, or positive peritoneal washing, tumor on the surface of the ovary	82
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 node	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%)**

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“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)

Potential of Photodynamic Therapy

Preferential Localization of Photosensitizers

- Cell metabolism
  - Activated cell uptake
  - Proliferative rate (mitochondrial potential)
  - Specific marker
- Neovasculature
- pH

Good Photosensitizer

- Low cutaneous phototoxicity
- Non-toxic in dark
- Target localizer
- High absorption in wavelength regions of 600-900 nm
- Low cost light sources
- High singlet oxygen quantum yield

CONCLUSIONS

- ALA-PDT did not succeed in our animal model
- 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

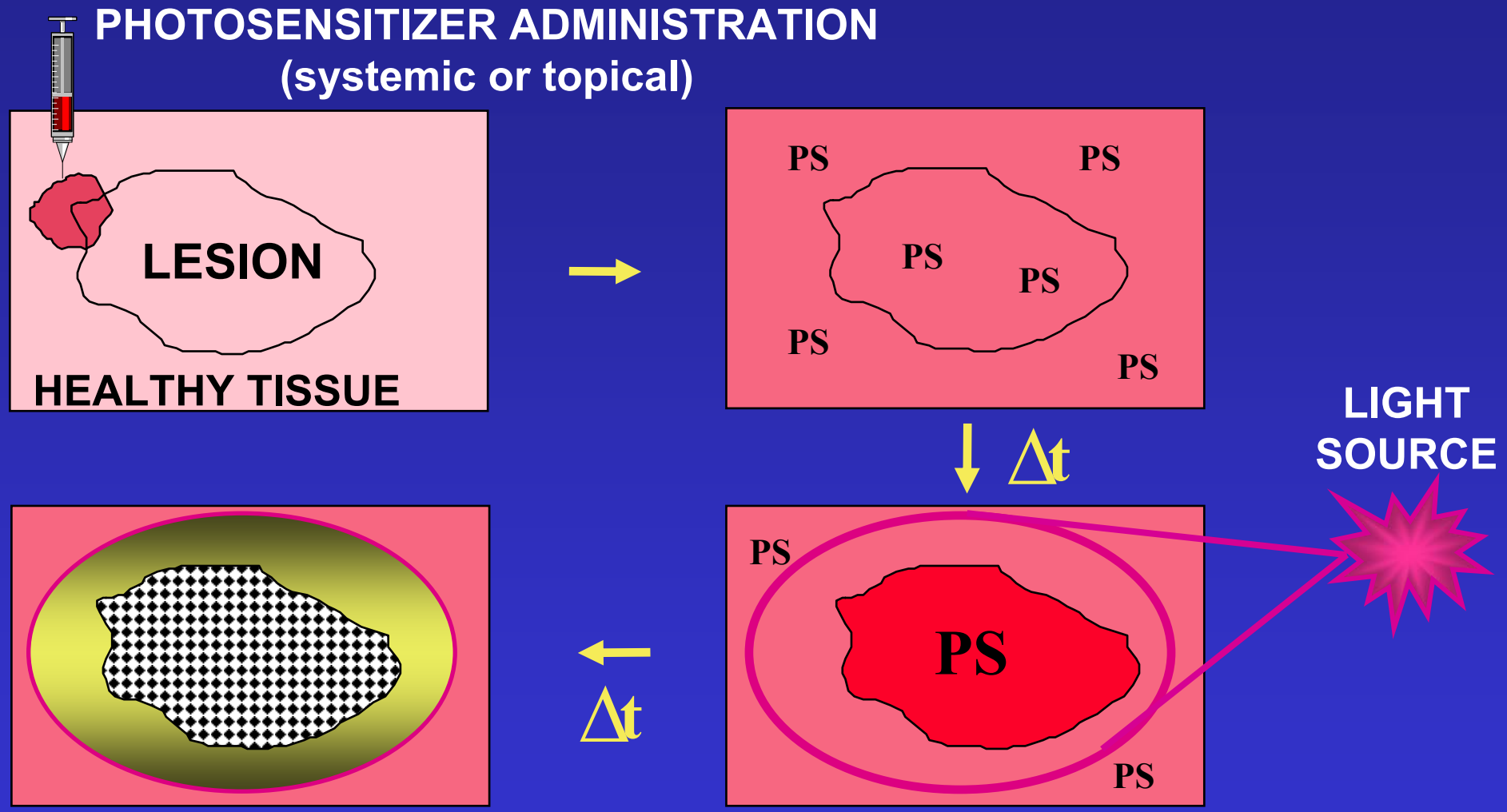
AIMS

- To evaluate *photodetection* of ovarian cancer peritoneal implants in the animal model
- To study phamcocinetics of the photosensitizer precursor aminolevulinic acid (ALA)
- To evaluate *photodetection* of ovarian cancer peritoneal implants in patients
- To analyse toxicity of ALA *photodynamique therapy* (PDT) in the animal model

generation PS

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

Principle of PDT



Historical

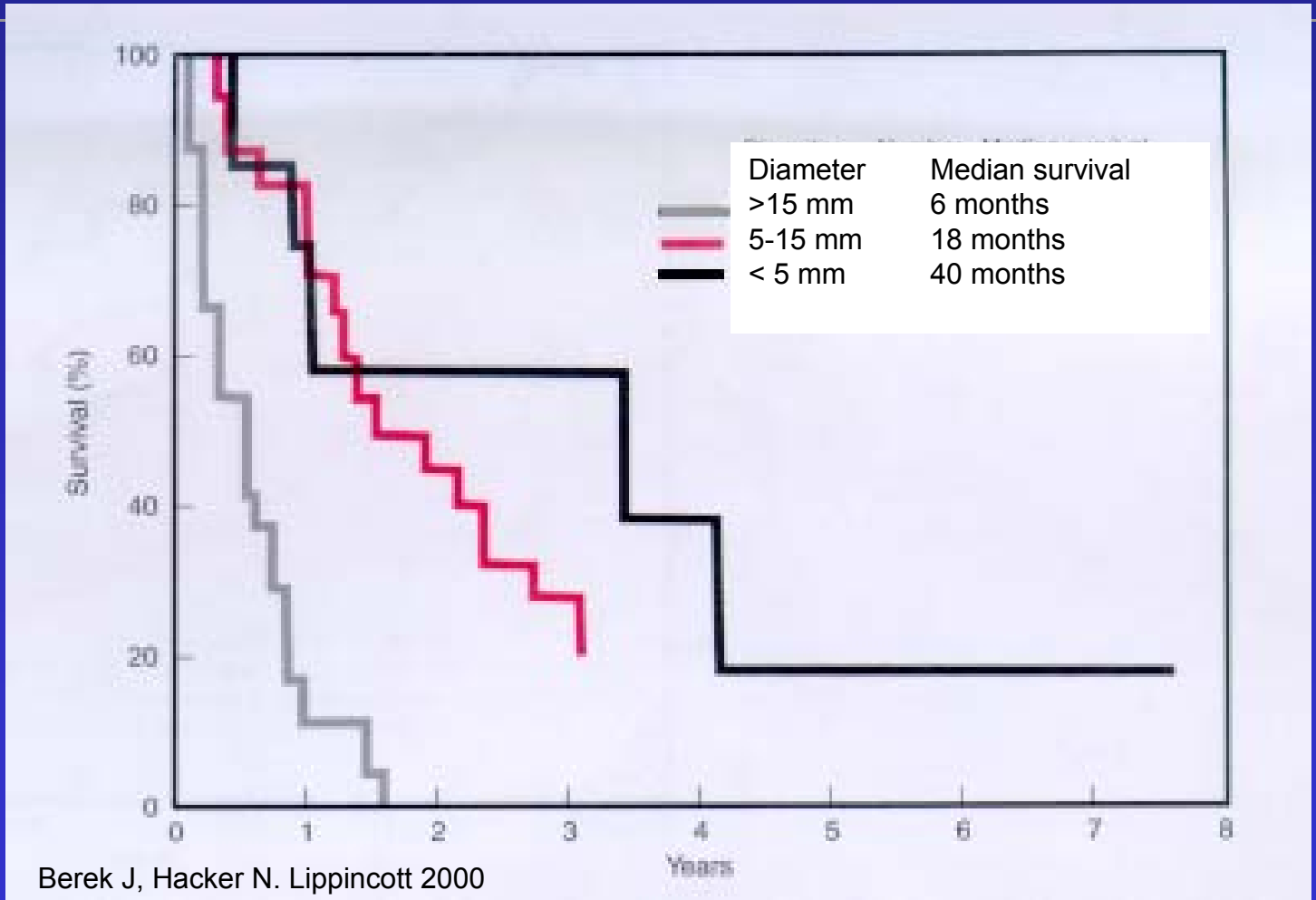
1976 J. F. KELLY + M. E. SNELL - First clinical PDT of a bladder carcinoma with HPD. (J. Urol., 115, 150, 1976).

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.

Survival versus diameter of largest residual disease



Berek J, Hacker N. Lippincott 2000