PHOTODYNAMIC DIAGNOSIS & THERAPY

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Presentation Plan

• Introduction photomedicine
• Photodetection (PDD)
• Photodynamic Therapy (PDT)
• Conclusion / Perspective
Photodynamic Principle

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


! LASERS + OPTICAL FIBERS !

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

Fluorescence detection

Photodynamic Therapy

S\_0

S\_1

S\_2

Energy

Absorption

Fluorescence

Phosphorescence

Spectroscopy

Photodynamic Energy Transfer

collision energy transfer

\( \tau = 1 \text{ ns} \)

\( \tau = 10 \mu\text{s} \)

\( t = 250 \text{ ns} \)

\( \Delta d = 45 \text{ nm} \)

Singlet Oxygen production

**O\_2**

**O\_2**

**O\_2**

400 nm

630 nm

630 nm

700 nm

 ISC

IC

ISC
PHOTORADIATION THERAPY OF CANCER
(Laser-Hematoporphyrin Derivative)

Cancer

Inject HPD (drug) in vein

48-72 hours

Drug selectively retained by cancer cells

Fiber optic bundle

Argon Laser

Dye Laser

514 nm
488 nm
(Blue-Green Light)

625-635 nm
(Red Light)

\[
\begin{align*}
sens + hv & \rightarrow \overset{1}{sens}^* \\
\overset{1}{sens}^* & \rightarrow \overset{3}{sens}^* \\
\overset{3}{sens}^* + O_2 & \rightarrow O_2 + sens \\
O_2 + substrate & \rightarrow \text{oxidation} \\
sens = \text{HPD}
\end{align*}
\]

\(^1O_2\) Kills Cells
Photosensitizers

- **Porphyrians**
  - Photofrin (PF)
  - "Aminolevulinic acid (ALA)", Protoporphyrin IX (PpIX)
- **Chlorins**
  - m-Tetrahydroxyphenyl chlorin (mTHPC): Temoporfin (Foscan, Foslip)
  - Benzoporphyrin derivative mono-acid (BPD): Verteporfin (Visudyne)
  - Tin ethyl etiopurpurin (SnET2)
- **Phtalocyaninines**
Photofrin Approval

- Superficial bladder cancer (Canada 1993)
- Early and late oesophageal and lung ca (Netherlands 1994)
- Advanced oesophageal ca (USA 1995)
- Early ca of stomach, oesophagus, lung, cervix and cervical dysplasia (Japan 1994)
Approvals of second generation photosensitizers

- Temoporfin (Foscan, Biolitec): PDT head and neck cancer (USA 2001)
- Meth-aminolaevulinate (Metvix, Galderma): PDT actinic keratosis, basal cell carcinoma (EU and Australia 2003)
- Verteporfin (Visudyne, QLT, Novartis): macular degeneration of the retina (USA and EU 2002)
PHOTODETECTION
Problematic

Early cancers are easier to treat

Advanced cancer Difficult to treat

Localized

Radiography, endoscopy, MRI

Early cancer are difficult to detect

Metastases

Contrast
Early lesion / normal surrounding

Early cancers are easier to treat

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Early cancer are difficult to detect

Metastases

Contrast
Early lesion / normal surrounding

Matthieu Zellweger, Février 2000
Fluorescence Spectroscopy of Exogenous, Exogenously-Induced and Endogenous Fluorophores for the Photodetection and Photodynamic Therapy of Cancer.
Haem Biosynthesis

5-ALA synthase

Uptake of exogenous 5-ALA

Coproporphyrinogen III

Uroporphyrinogen III

Protoporphyrinogen IX

Protoporphyrin IX

Fe^{2+}

Haem

Feedback control

Mitochondria

Cytoplasm

Lower rate in tumour cells

Higher rate in tumour cells

Ferrochelatase

PBG Deaminase

Glycine + succinyl CoA

5-ALA

5-ALA
Haem Biosynthesis

5-ALA synthase

Uptake of exogenous 5-ALA

Cycline + succinyl CoA

5-ALA

Feedback control

5-ALA

Ferrochelatase

haem

Fe^{2+}

Protoporphyrin IX

Protoporphyrinogen IX

Mitochondria

Lower rate in tumour cells

Higher rate in tumour cells

PBG Deaminase

Uroporphyrinogen III

Coproporphyrinogen III

Cytoplasm

Lower rate in tumour cells

Higher rate in tumour cells
Combined Diagnosis System

- Rigid Telescopes
- Fiberscopes
- OP - Microscopes

- White Light
- ALA-Mode
- Autofluorescence-Mode
PHOTODETECTION
Clinical Data

M. Kriegmair,
Ludwig Maximillians-University Munich
Neurosurgery

Special Fluorescence Microscope
Cooperation w/ Carl Zeiss

Early Tumor Detection with Marker Substance

High grade Glioma

Stummer, Reulen
Munich-Großhadern
Detection of Early Stage Bronchial Carcinomas (AF)

K. Häußinger, F. Stanzel
Asklepios Munich- Gauting
PDD in Gynaecology

- Laparoscopic view of ovarian cancer after ip ALA-application
Light micrographs (A) and fluorescence (B) of a peritoneal nodule (size < 0.5 mm) 6 hr after ip ALA administration. Magnification (C) of the peritoneal serosa (boxed area in B) showing a thin layer of tumor matching with the fluorescence.

5-Year cumulative lethality of gynecologic malignancies in Geneva
Figure 1

Common sites of ovarian cancer metastases.

Ovarian cancer spreads fast to the whole abdominal cavity by exfoliation.
Epithelial Ovarian Cancer

- Fourth most frequent cause of “cancer-related” death
- 65% diagnosed with stage III-IV disease
- 80% chemo-sensitive (initial response)
- 5 year survival rate: 15-20%
- 50% of “cured” patients (negative second look laparotony) will recur
Potential of *In Vivo* Fluorescence

- **Staging laparotomy**

- **Second Look**
**Results of restaging laparotomies in women with apparent early stage ovarian carcinoma**

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Number of patients</th>
<th>FIGO stage at initial surgery</th>
<th>% upstaged</th>
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<tr>
<td>Bagley 1973</td>
<td>5</td>
<td>I-II</td>
<td>60%</td>
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<tr>
<td>Young 1983</td>
<td>100</td>
<td>IA-IIB</td>
<td>31%</td>
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<td>Helewa 1986</td>
<td>25</td>
<td>I</td>
<td>20-25%</td>
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<tr>
<td>Buchsbaum 1989</td>
<td>140</td>
<td>I-II</td>
<td>22.4%</td>
</tr>
<tr>
<td>Archer 1991</td>
<td>24</td>
<td>I-II</td>
<td>20.8%</td>
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<tr>
<td>Soper 1992</td>
<td>30</td>
<td>I-II</td>
<td>30%</td>
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<tr>
<td>Stier 1998</td>
<td>45</td>
<td>IA-IIB</td>
<td>16%</td>
</tr>
<tr>
<td>Leblanc 2000</td>
<td>28</td>
<td>I</td>
<td>21%</td>
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</table>
Survival by outcome of second look

- neg second look
- microsc pos
- macrosc pos

Cumulative Survival vs. Survival (Months)
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 > 1/2 cm via white or PDD

Second-line chemotherapy

Second line chemotherapy.

Survival data.

Survival data.

Survival data

Survival data

Retrospective survival data.
CONCLUSIONS

• Photodetection of ovarian cancer peritoneal implants, not visible by other methods, has been shown to be efficient and feasible in patients

• Survival advantage has to be demonstrated in clinical trials (second look and staging of first stage ovarian cancer)
PHOTODYNAMIC THERAPY
Photodynamic Therapy

Dye (PS) → Photons → \textit{ACTIVATED} → DYE → \(O_2\) → TOXICITY
Methaminolaevulinate (MAL) PDT in Aktinic Keratosis

Trond Warloe
Radium Hospital Oslo
MAL-PDT in Basal Cell Carcinoma

Trond Warloe
Radium Hospital Oslo
MAL-PDT in Basal Cell Carcinoma

Trond Warloe
Radium Hospital Oslo
CONCLUSIONS

• Photodynamic therapy (PDT) can be used efficiently in patients who were already treated with surgery, radiotherapy, and chemotherapy.

• PDT heals with better cosmetic results compared to other treatments (surgery, cryotherapy).

• PDT has no long-term side effects and has no limitations to repeat it.
Autofluorescence (ENT)

Early Tumor Detection without Marker Substance

Carcinoma of the left vocal cord, precancerous lesion right vocal cord (bacterial growth)

K. Malzahn, C. Arens, H. Glanz
Justus-Liebig-University Giessen