Review of PDT for Lung Cancer and Future

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**Lung Cancer, Present Status**

Worldwide increase of cancer patients
No improvement of death rate of cancer patients

<table>
<thead>
<tr>
<th>Region</th>
<th>Lung cancer patients</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>410,220</td>
<td>353,848</td>
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<tr>
<td>USA</td>
<td>214,226</td>
<td>167,545</td>
</tr>
<tr>
<td>Asia</td>
<td>1,045,695</td>
<td>936,051</td>
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<tr>
<td>Japan</td>
<td>94,855</td>
<td>75,119</td>
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</tbody>
</table>

(GLOBOCAN 2012)
# Approval of PDT for Lung Cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors/Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977</td>
<td>Dougherty</td>
<td>PDT of skin cancer by HpD+Argon dye laser (ADL)</td>
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<tr>
<td>1984</td>
<td>Hayata Research Group</td>
<td>Fundamental investigation and clinical research PDT supported by the government.</td>
</tr>
<tr>
<td>1986</td>
<td>Kato Research Group</td>
<td>Multi-institutional clinical researches on early stage of lung, esophagus, stomach and cervix supported by the government.</td>
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<tr>
<td>1989</td>
<td>Kato et al</td>
<td>Multicentric phase II clinical Trial of early stage cancers of lung, esophagus, stomach and cervix. Photofrin+ADL or Eximer dye laser (EDL)</td>
</tr>
<tr>
<td>1993</td>
<td>Jap Government approved</td>
<td>PDT of early ca of lung, esophagus, stomach, cervix. Photofrin+ADL, EDL</td>
</tr>
<tr>
<td>2009</td>
<td>Jap Governmental approval</td>
<td>for PDT of advanced lung cancer. Laserphyrin+DL</td>
</tr>
</tbody>
</table>

NSCGH, TMU & IUHW
Multicentric Phase II Trial for Lung Cancer

Photofrin + Argon dye laser or Excimer dye laser PDT

June 1989~February 1992
5 institutions
54 patients with 64 stage 0/I central type lung squamous cell carcinoma
Photofrin: 2mg/kg, iv 48 hours prior to laser photoradiation
Lights: ADL (Cooper, Spectra Physics), EDL(Hamamatsu); 150J/cm²
Efficacy: Complete remission 84.5%
Toxicity: No serious adverse reactions were observed.
Skin photosensitivity: 1.9%

Governmental approval: 1993

NSCGH, TMU & IUHW
Multicentric Phase II Trial for Lung Cancer

Laserphyrin + Diode Laser PDT

October 1997~March 2000
10 institutions
42 patients with 46 stage 0/I central type lung squamous cell carcinoma
Laserphyrin: 40mg/m2, 4 hours prior to laser, Light dosage: 100J/cm2
Efficacy: Response rate: 94.9%, Complete remission rate: 84.6%
Toxicity: No serious adverse drug reactions were observed.
Skin photosensitivity: Skin irritation disappeared with 2 weeks.

Governmental approval: 2002

NSCGH, TMU & IUHW
Extending Approvals of Laserphyrin

1. Malignant Brain Tumor (Grade 3&4) Multicentric Phase II Clinical Trial
   (Prof. Iseki, TWMC and TMU)  Approved 2013.9

2. Recurrent esophageal cancer after chemo-radiotherapy
   Multicentric Phase II Clinical Trial
   (Prof. Muto, Kyoto Univ.)  Approved 2015.5
Central type lung cancer

1. Curative treatment
   Early stage (stage 0 & Cis) primary squamous cell ca.
   Single, Multiple

2. Palliative treatment
   Advanced central type squamous cell carcinoma
   Neo-adjuvant treatment for surgery
   Combination with chemotheray and/or radiotherapy
   QOL
What is Early Stage Lung Cancer?

Our Japanese criteria since 1975
Clinically curative lung cancer
Pathologically no invasion to vessels, lymph ducts and no metastasis

Location
1. Central bronchus (ESCLC)
   Trachea – segmental bronchi
   Endoscopically early stage squamous carcinoma
   (1995, Japan Lung Cancer Society set a standard criteria)
   WHO, UICC & IASLC Staging: Stage 0, Tis
2. Peripheral lung (ESPLC)
   Subsegmental-Terminal alveolar bronchi, less than 2cm
   WHO, UICC & IASLC Staging: AIS, MIA, alveolar wall, Adenocarcinoma
What is ESCLC treated curatively by PDT?

X-ray negative
CT negative

Central type squamous cell carcinoma!

WHO, UICC & IASLC Staging: Stage 0, Tis

Endoscopic criteria (Japan Lung Cancer Society, 1995)
1 Bronchoscopically invisible type
2 Thickening type
3 Nodular type
4 Polypoid type
5 Mixed type
Importance of Early Detection

- 1988 Lung cancer screening program
- Health check examination

For Central type
- Sputum cytology (smokers)
  - Symptoms: sputum, bloody sputum
- Bronchoscopy
  - Symptoms: cough, bloody sputum

For Peripheral type
- CT
Sputum Pooling Box for Sputum Cytology

Since 1974

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Squamous Cell Carcinoma in Situ,  Sputum
Bronchoscopy

- Fiberoptic bronchoscopy
- Digital bronchoscopy
- Fluorescence bronchoscopy
Digital Bronchoscopy with AFD/PDD System

AFD: Autofluorescence Diagnosis,  PDD: Photodynamic Diagnosis

Laserphyrin

Light source: 408nm diode laser
Record AF by ultra-small CCD

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Who are indicated for Early Detection?

High risk people to lung cancer
- Positive sputum cytology
- Heavy smoker
- High risk occupations
- COPD
- Emphysema
Symptoms
- Bloody sputum
- Sputum or Cough
Multiple lung cancer patient
Post operative patients

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Photodynamic Therapy
PDT for Early Stage Central Type Lung Cancer

Lt B1+2, 3 (Sq.ca.) 79-year old man

Before PDT

3M after PDT
PDT for Early Stage Central Type Lung Cancer

Lt. u. br. (Sq.ca.) 68-year old man

Before PDT

3M after PDT
PDT for Early Stage Central Type Lung Cancer

Lt. u. br. (Sq.ca.)  68-year old man

Before PDT  

3M after PDT
PDT for Early Stage Central Type Lung Cancer

Carina (Sq. cell carcinoma) 63-year-old man

Laserphyrin + SAFE 3000

Before PDT  PDD  3 M after PDT

NSCGH, TMU & IUHW
PDT for Early Stage Central Type Lung Cancer

Carina (Sq.ca.) 79-year old man

Before PDT

3M after PDT

NSCGH, TMU & IUHW
### Results of PDT for ESCLC

**1980-2010**

#### Photofrin® vs Laserphyrin®

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>No.</td>
<td>59</td>
<td>264</td>
<td>91</td>
</tr>
<tr>
<td>Photosensitizer</td>
<td>Photofrin</td>
<td>Photofrin (Laserphyrin in 16)</td>
<td>Laserphyrin</td>
</tr>
<tr>
<td>Size (cm) &amp; CR (rate,%)</td>
<td>≤ 1.0</td>
<td>97.8%</td>
<td>93.9%</td>
</tr>
<tr>
<td></td>
<td>1.0-2.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


NSCGH, TMU & IUHW
5-Year Survival Rate, PDT in ESCLC

- Cancer specific survival: 92.5%
- Overall survival: 57.6%
ESCLC treated with PDT

   CR: 85% (59 lesions)  
   CR: 70% (23 lesions)  
   CR: 83% (39 lesions)  
   Phase II clinical study of PDT using mono-L-aspartyl chlorin e6 (NPe6, Laserphyrin) and diode laser  
   Before PDT, the depth of tumor invasion was estimated by EBUS (endobronchial ultrasonography)
Guidelines of PDT for ESCLC

PDT with quality and safety for the patients with lung cancer

1. Doctor should be member of JPA, JSLSM.
2. Doctor should master about photosensitizer and laser equipment.
3. Doctor should have ability to diagnose early stage lung cancer.
   - Endoscopical early-stage lung cancer
   - Normal chest X-ray and CT imaging
   - No evidence of metastasis to lymph nodes
   - Peripheral margin of the tumor
   - Superficial tumor not more than 2.0 cm in diameter
4. Doctor should check the output of laser equipment.
5. Informed consent of PDT to patient.
6. Patient should put sunglasses avoiding direct sunlight.
7. Doctor should frequently perform bronchoscopies to remove necrosis after PDT.

Japanese Photodynamic Association, Japan Society of Laser Surgery and Medicine
NSCGH, TMU & IUHW
1. Palliative treatment for the improvement of QOL
   Obstructive pneumonia or atelectasis

2. Chemo/radiotherapy + PDT
   + Immunological response

3. Neoadjuvant PDT for surgery
   Possibility of extended surgery after PDT
   Possibility of reduction surgery after PDT
**Indication Criteria for Advanced Lung Cancer**

**Inclusion**

1. Dyspnea due to stenosis or obstruction of central bronchus
2. Obstructive pneumonia or atelectasis
3. Possibility of extended surgery after PDT
4. Possibility of reduction of resection volume after PDT
5. Recurrence after radio/chemotherapy
6. Maintenance of QOL in combination with radio/chemotherapy
7. ECOG Performance Status 0-II
8. Adequate organ function
9. Life expectancy at least 12 weeks
10. Written informed consent

**Exclusion**

1. Serious complications
New Strategy for Early Stage Peripheral Lung Cancer (ESPLC)
New Strategy for ESPLC

Increase of adenocarcinoma
Increase of multiple primary lung cancers

Carcinogenetic process of adenocarcinoma
Definitive diagnosis of GGO shadows

Non-invasive treatment of AIS and MIA lesions?
Invasive treatment of LPA?

GGO: ground glass opacity, AIS: Adenocarcinoma in situ
MIA: Minimal invasive adenocarcinoma
LPA: Lepidic predominant adenocarcinoma

NSCGH, TMU & IUHW
### Early Stage Peripheral Type Lung Cancer (ESPLC)

<table>
<thead>
<tr>
<th>cT</th>
<th>Pathologic Differential Diagnosis</th>
<th>Clinical stage</th>
<th>Invasive part</th>
<th>Pathology</th>
<th>Pathologic stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid part</td>
<td></td>
<td></td>
<td></td>
<td>AAH, AIS, MIA</td>
<td>pTis‡‡</td>
</tr>
<tr>
<td>Total tumor size including GG</td>
<td>≤0.5cm</td>
<td>cTis‡‡</td>
<td></td>
<td>AIS, MIA, LPA</td>
<td>pT1i§§</td>
</tr>
<tr>
<td></td>
<td>0.6-3.0cm‡‡</td>
<td>cT1mi‡‡</td>
<td></td>
<td>MIA, LPA, AIS</td>
<td>pT1a</td>
</tr>
<tr>
<td></td>
<td>≤3.0cm‡</td>
<td></td>
<td></td>
<td>LPA, Invasive AD, MIA</td>
<td>pT1b</td>
</tr>
<tr>
<td></td>
<td>0.6-3.0cm‡‡</td>
<td></td>
<td></td>
<td>LPA, Invasive AD</td>
<td>pT1c</td>
</tr>
<tr>
<td></td>
<td>1.1-3.0cm‡‡</td>
<td></td>
<td></td>
<td>Invasive, AD</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>pT</th>
<th>Pathology</th>
<th>Pathologic stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive part</td>
<td>AAH</td>
<td>pTis‡‡</td>
</tr>
<tr>
<td></td>
<td>AIS</td>
<td>pT1i§§</td>
</tr>
<tr>
<td></td>
<td>MIA</td>
<td>pT1a</td>
</tr>
<tr>
<td></td>
<td>Lepidic predominant AD or Invasive AD with lepidic component</td>
<td>pT1b</td>
</tr>
<tr>
<td></td>
<td>Lepidic predominant AD or Invasive AD with lepidic component</td>
<td>pT1c</td>
</tr>
</tbody>
</table>

CT image on HRCT:
- 0cm
- 0cm
- ≤0.5cm†
- 0.6-1.0cm†
- 1.1-2.0cm†
- 2.1-3.0cm†

Total tumor size:
- ≤0.5cm
- 0.6-3.0cm‡‡
- ≤3.0cm‡
- 0.6-3.0cm‡‡
- 1.1-3.0cm‡‡
- 2.1-3.0cm‡‡

Clinical stage:
- cTis‡‡
- cT1mi‡‡
- cT1a
- cT1b
- cT1c
Adenocarcinoma in situ (AIS)

pT1N0M0
Stage IA

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MS-based Proteomics on ESPLC

- Normal
- Adjacent to tumor: Pathologically normal but already carcinogenesis-related activities were initiated through ECM receptors.
- Cancer

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Semi-Quantitative Pair-wise Comparison of Proteins Expressed between Sub-Groups

**LPA vs MIA**

LPA: Lepidic predominant adenocarcinoma
MIA: Minimally invasive adenocarcinoma

Protein ratio in log2, \( R_{SC} \); Normalized Spectral Abundance Factor, NSAF

- Statistical significance was evaluated by \( \chi^2 \) or G-test.


NSCGH, TMU & IUHW
GGO Lung Cancer: Expression variations of 840 proteins identified

- AIS: \( n=3 \)
- MIA: \( n=3 \)
- LPA: \( n=3 \)
- Pseudo-Normal: \( n=3 \)

AIS: Adenocarcinoma in situ
MIA: Minimally invasive adenocarcinoma (MIA)
LPA: Lepidic predominant adenocarcinoma

1. Therein, there seems to be a similarity between AIS and MIA but
2. LPA demonstrated a quite different protein expression pattern.

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STRING PPI Networks extracted using significant 70 node proteins in LPA.
Numerous advanced cancer related pathways were already activated, which include ErBb (Yellow circles) and HIF-1 (Red circles) Cancer Pathways.
Summary of PPI Enrichment Analysis for Proteome DataSets of GGO-lung Adenocarcinomas

- AIS was rather associated with pathways of focal adhesion, adherence junction, tight junction and leukocyte transendothelial migration.

- MIA had a strong association predominantly with pathways of proteoglycans in cancer and with PI3K-Akt.

- LPA was associated broadly with numerous tumor-progression pathways including ErbB, Ras, Rap1 and HIF-1 signalings.

- Surprisingly, it was indicated that Pseudo-normal cells near tumors seem to have already communication through ECM-receptor interaction resulting in activation of pathways in cancer.

Early Detection for ESPLC

Lung cancer screening
Health check examination

*Early stage peripheral lung cancer (ESPLC)*

CT Findings:

- GGO
- GGO+solid

NSCGH, TMU & IUHW
Therapeutic Strategy for ESPLC

Previously demonstrated highly effectiveness for ESCLC

References
CR 93.8-78%

New multi centric trial for ESPLC by PDT
suppoted by Japanese Government

Prof. Jitsuo Usuda, Department of Surgery, Nihon Medical University
Adequate Therapy for Lung Cancer

Early detection of lung cancer by sputum cytology and CT screening.

Early localization of lung cancer by bronchoscope (BS), fluorescence BS and CT.

Possible molecular diagnosis and/or optical biopsy by OCT for definitive diagnosis of early stage lung cancer.

Non-invasive treatments, **PDT** for early stage lung cancer.
## Medical Expenses of PDT vs Surgery

<table>
<thead>
<tr>
<th>Description</th>
<th>Cost</th>
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<tbody>
<tr>
<td><strong>PDT</strong></td>
<td></td>
</tr>
<tr>
<td>DPC</td>
<td>249,430yen ($2,772)</td>
</tr>
<tr>
<td>PDT procedure</td>
<td>87,100 ($ 967)</td>
</tr>
<tr>
<td>Laserphyrin</td>
<td>387,200 ($ 4,302)</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>25,000 ($ 277)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>760,000yen ($ 8,444)</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
</tr>
<tr>
<td>DPC</td>
<td>274,200yen ($ 3,046)</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td>1,050,000 ($ 11,666)</td>
</tr>
<tr>
<td>Anesthesia, drugs</td>
<td>300,000 ($ 3,333)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1,700,000yen ($18,888)</td>
</tr>
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</table>


NSCGH, TMU & IUHW
Effort Toward Lung Cancer Eradication

- Smoking cessation
  - Early detection
    - Early localization
      - Selection of therapy
        - Early treatment
Thank you for your attention