Recent Progress of Diagnostic and Therapeutic Bronchoscopies

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Tokyo Medical University
Eradication of lung cancer

What should we do?
- Prevention
- Early detection
- Early localization
- Therapeutic modality
Present methodologies for early detection

Central type
Sputum cytology

Peripheral type
X-ray screening
CT screening
Importance of sputum cytology in 1970’s

Lung cancer detection rate and it’s histology

Detection rate:  
- man 60/100,000
- woman 15

Histologic type:  
- Squamous cell carcinoma 45%
- Adenocarcinoma 35%
- Large cell carcinoma 10%
- Small cell carcinoma 9%
Sputum-pooling box for mail (TMU Box, 1974)
Screening by Cytotechnologists

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Early squamous carcinoma cells
First experience of patient with carcinoma in situ

_Cis_ was detected by sputum cytology (1978)

Spur of r-mid. & lower lobe br.
Occult Lung Cancers detected by Sputum Cytology

No. of Cases

<table>
<thead>
<tr>
<th>Year</th>
<th>1960</th>
<th>65</th>
<th>70</th>
<th>75</th>
<th>80</th>
<th>85</th>
<th>90</th>
<th>95</th>
<th>2000</th>
<th>05</th>
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<tr>
<td>Cases</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>29</td>
<td>31</td>
<td>50</td>
<td>70</td>
<td>96</td>
</tr>
</tbody>
</table>
Problems in sputum cytology

1. 40% of patients with central type lung cancer do not complain of sputum.
2. Detection rate in sputum-producing patients with central type lung cancer is 84%.
3. Even in sputum-positive patients localization is difficult:
   Outside the bronchial tree – nasal cavity, nasal sinus, larynx, pharynx, oral cavity
   Inside the bronchial tree - certain cis in large bronchi or peripheral bronchi
Future technologies for early detection

Central type
Malignancy Associated Changes
+ Bio-Molecular Informations

Peripheral type
CT screening
+ Bio-Molecular Informations
Methodologies for early localization

- Fiberoptic bronchoscopy (FB)(1965)
- Fluorescence bronchoscopy (PDD)(1978)
- Video bronchoscopy (VB)(1988)
- Auto fluorescence bronchoscopy (AFB)(1991)
FiberopticBronchoscope
# Fiberoptic Bronchoscope

<table>
<thead>
<tr>
<th>MAKER</th>
<th>MODEL</th>
<th>TYPE</th>
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<td>OES BRONCHO FIBERSCOPE</td>
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<td>BRO-Y3S</td>
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<td>FTS</td>
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<td>MACHIDA</td>
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<tr>
<td>KARL STORZ</td>
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### Fiberoptic Bronchoscope

<table>
<thead>
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<tbody>
<tr>
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</tr>
<tr>
<td>PENTAX</td>
<td>FB-10V</td>
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<tr>
<td>PENTAX</td>
<td>FB-18V</td>
<td>BRONCHO FIBERSCOPE</td>
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<tr>
<td>PENTAX</td>
<td>FB-19TV</td>
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<tr>
<td>PENTAX</td>
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<td>PORTABLE BRONCHO SCOPE</td>
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<tr>
<td>PENTAX</td>
<td>FB-18RBS</td>
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# Ultra thin Fiberoptic Bronchoscope

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<td>BF type XP40</td>
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<td>KARL STORZ</td>
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<td>MANIATURE FIBERSCOPE</td>
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## Video Bronchoscope

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<td>VIDEO BRONCHOSCOPE</td>
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<td>PENTAX</td>
<td>EB-1830T3</td>
<td>VIDEO BRONCHOSCOPE</td>
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<td>PENTAX</td>
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<td>PENTAX</td>
<td>EB-1970K</td>
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# Ultrasound Bronchoscope

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<tr>
<td>PENTAX</td>
<td>FB-19UV</td>
<td>ULTRASOUND BRONCHO FIBERSCOPE</td>
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</table>

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*Tokyo Medical University*
Endoscopic Criteria
Central Type Early Stage Lung Cancer

Japan Society of Lung Cancer 1995

1. Endoscopically invisible type
2. Thickened type
   Bronchial mucosa swells
3. Nodular type
   Broad based lesion with height : width ratio of $< 1$
4. Polypoid type
   Narrow based lesion with height : width ratio of $\geq 1$
5. Mixed type
Bronchoscopic criteria of early stage lung cancer
- Invisible type -

Orifice of left B3 bronchus

Invisible
July, 1982

Nodular
August, 1983
Bronchoscopic criteria of early stage lung cancer
- Thickened type -

Right middle and lower lobe bronchi

1978
Bronchoscopic criteria of early stage lung cancer
- Nodular type -

Bifurcation between left B3 and B1+2 bronchi
Bronchoscopic criteria of early stage lung cancer
- Polypoid type -

Right B9 bronchus
Problems on Early Localization
Central Type Lung Cancer

Endoscopically **INVISIBLE** lesion
Fluorescence bronchoscopy

*Photodynamic diagnosis*

Auto-fluorescence

Optical coherence tomography (OCT)
PDD by krypton ion laser and image intensifier

1979
PDD of experiment canine lung cancer

1979

Tokyo Medical University
Prof. Profio and Doiron’s PDD machine

1980

Tokyo Medical University
Clinical Trial of Photodynamic Diagnosis

1980

Prof. Profio & Doiron’s technology
Clinical experience of PDD with carcinoma in situ
## Photodynamic Diagnosis

<table>
<thead>
<tr>
<th>Name</th>
<th>(year)</th>
<th>System</th>
<th>Sensitivity</th>
<th>False positive</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Balchum O.J.</td>
<td>(1982)</td>
<td>Krypton ion laser with HpD</td>
<td>22/22</td>
<td>9/16</td>
<td>Recent Results Cancer Res 82:97-120</td>
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<td>Lam S.</td>
<td>(1990)</td>
<td>Krypton ion laser with Photofrin</td>
<td>10/10</td>
<td>not mentioned</td>
<td>Chest 97:333-337</td>
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Autoﬂuorescence Video Bronchoscope

PENTAX   SAFE 3000

Light source: 408nm diode laser

Record AF by ultra-small CCD
Photodynamic Diagnosis for Early Stage Lung Cancer

68-year-old man, Squamous cell carcinoma, Lt. Upper lobe br.

Photosensitizer: Laserphyrin + Pentax SAFE 3000 PDD

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63y, man Carina (Sq. cell carcinoma)

Photosensitizer: Laserphyrin + SAFE 3000

White light Pentax SAFE 3000 PDD
83y, man  
Lt. B3 (Sq. cell carcinoma)

Photosensitizer: Laserphyrin + SAFE 3000

Before PDT  
PDD
65y, man  
Rt. Upper bronchus (Sq. cell ca.)

Photosensitizer: Laserphyrin + SAFE 3000
Fluorescence bronchoscopy

Photodynamic diagnosis (1979~)

**Auto-fluorescence diagnosis (1991~)**
- LIFE system (Xillix) (1991)
- SAFE-1000 (Pentax) (1992)
- D-light system (Storz) (2001)
  (Video endoscope)
LIFE system (Xillix) (1991)
Disadvantages of AF Fiberoptic Bronchoscopy

1. Poor resolution by fiberoptic bronchoscope

2. False positive caused by inflammation, bleeding and shadow due to the bronchial cartilage ring and folds
Autoﬂuorescence Video Bronchoscope

PENTAX SAFE 3000

Light source: 408nm diode laser
Record AF by ultra-small CCD
68y man
Rt. B¹a-b
Squamous cell carcinoma (CIS)
AF Video Bronchoscope
PENTAX SAFE-3000

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AF Video Bronchoscope

72y man  Bloody sputum  PENTAX SAFE-3000

Nodular squamous cell ca. at the left upper lobe bronchus
## Autofluorescence Bronchoscopy

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Institution</th>
<th>Sensitivity (BF/AF, %)</th>
<th>Specificity (BF/AF, %)</th>
<th>P.P.V. (BF/AF, %)</th>
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<tr>
<td>Lam</td>
<td>1993</td>
<td>LIFE</td>
<td>48 / 73</td>
<td>94 / 99</td>
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<td>Kato</td>
<td>1995</td>
<td>SAFE</td>
<td>76 / 91</td>
<td>53 / 62</td>
<td>63 / 71</td>
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<td>Tril in U.S.</td>
<td>1998</td>
<td>LIFE</td>
<td>25 / 67</td>
<td>90 / 66</td>
<td>39 / 33</td>
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<td>Kurie</td>
<td>1998</td>
<td>LIFE</td>
<td>43 / 38</td>
<td>57 / 56</td>
<td>25 / 16</td>
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<td>Vemans</td>
<td>1999</td>
<td>LIFE</td>
<td>78 / 89</td>
<td>88 / 61</td>
<td>32 / 14</td>
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<tr>
<td>Kato</td>
<td>1999</td>
<td>SAFE</td>
<td>66 / 92</td>
<td>54 / 56</td>
<td>62 / 71</td>
</tr>
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</table>

*(Abnormal lesion: dysplasia and cancer)*
Auto-fluorescence diagnosis of dysplasia

- W(+), AF(+): 42%
- W(+), AF(-): 15%
- W(-), AF(+): 41%
- W(-), AF(-): 2%
Evaluation of the PDT efficacy by PDD
Evaluation of the PDT Response

63y, man Carina (Sq. cell carcinoma)
Photosensitizer: Laserphyrin + SAFE 3000

Before PDT  Pentax SAFE 3000 PDD  Immediately after PDT

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Evaluation of the PDT Response

83y, man  Lt. B3 (Sq. cell carcinoma)

Photosensitizer: Laserphyrin + SAFE 3000

Before PDT  PDD  Immediately after PDT

Tokyo Medical University
Evaluation of the PDT Response

65y, man

Rt. Upper bronchus (Sq. cell ca.)

Photosensitizer: Laserphyrin + SAFE 3000

Before PDT

PDD

Immediately after PDT

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Fluorescence Diagnosis

1. Detection of “invisible” lesions
2. Improvement of localization
3. Judgement of resection line
4. Accurate laser Tx (PDT etc)
(5. Depth Dx: EBUS, OCT)
**New Technologies**

*Early localization*

- Ultra-thin scanning fiber bronchoscope (SFB)
- Fluorescence bronchoscopy
  - Photodynamic diagnosis
  - Auto-fluorescence diagnosis
- Endo-cytoscope
- Optical coherence tomography (OCT)
- Confocal bronchoscopy
- Navigated bronchoscopy
Recent Advanced Optical Technologies

Optical Coherence Tomography
Endoscopy System (Pentax SOCT-1000)
Depth of Invasion

1. Endobronchial Ultrasonography (EBUS)

2. Optical Coherence Tomography (OCT)
Resolution and penetration of diagnostic tools

**OCT**
- Resolution: 13μm (3μm)
- Penetration: 3mm

**ULTRASOUND**
- Resolution: 100 μm
- Penetration: 10cm

**AF**
- Resolution: 1 μm
- Penetration: 1mm
Pentax SOCT-1000

PIU Unit
(Micro-optic Lens assembly)

OCT Probe

Light guide

OCT Imaging Platform
Clinical findings of OCT in Bronchoscopy

Normal

(Pentax SOCT-1000)

Trachea

Segmental bronchi
Clinical Findings of OCT in Bronchoscopy

80 y, man
Squamous cell ca.
Lt. B1+2

(Pentax SOCT-1000)
Clinical findings of OCT in Bronchoscopy

Sialadenoma papilliferum
Rt. B3bii
52y, woman

(Pentax SOCT-1000)
OCT Findings of Cis of Bronchus

Squamous cell carcinoma  Rt. B1a-B1b spur  68y, Man

SAFE 3000 AF  Pentax SOCT-2000

Abnormal mucosa
OCT Findings of Cancer and Dysplasia

Normal epithelium

dysplasia

Tumor

cartilage

dysplasia

Tumor

normal
OCT Findings of Cancer and Dysplasia

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Squamous cell ca. with submucosal invasion

Pentax SOCT-2000

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OCT Findings of Cis and Invasive Ca

Invasive cancer (Destruction of basement membrane)
VTR
Bronchial OCT Image  (Pentax SOCT-2000)

Normal alveoli
Bronchial OCT Image (Pentax SOCT-2000)

VTR

Normal alveoli
Alveoli

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Bronchial OCT Image  (Pentax SOCT-2000)

BAC

BAC, mucinous type
Thickening of alveolar wall
Dilatation of alveoli
Increase of interstitial tissue
Bronchial OCT Image  (Pentax SOCT-2000)

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Bronchial OCT Image  (Pentax SOCT-2000)

normal

BAC (mucinous)
Optical Coherence Tomography

Analysis of tissue structure by light interference

Clear image can be obtained
Possibility of optical biopsy
# OCT of Central Type Lung Cancer

(Permex SOCT-1000)

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Location</th>
<th>Pathology</th>
<th>Normal Br.</th>
<th>Tumor</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Layer Structure</td>
<td>Alveoli</td>
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<tr>
<td>1</td>
<td>60</td>
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<td>Rt. B4+5</td>
<td>Sq. ca.</td>
<td>+</td>
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<td>2</td>
<td>56</td>
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<td>Lt. B6a</td>
<td>Sq. ca.</td>
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<td>+</td>
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<td>3</td>
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<td>Trachea</td>
<td>Sq. ca.</td>
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<td>N</td>
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<tr>
<td>4</td>
<td>68</td>
<td>Man</td>
<td>Rt. B1a</td>
<td>Sq. ca.</td>
<td>+</td>
<td>N</td>
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<td>5</td>
<td>77</td>
<td>Man</td>
<td>Lt. upper br.</td>
<td>Small</td>
<td>+</td>
<td>+</td>
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+ : Detected,  - : Not Detected,  N : Not performed
**OCT findings of resected lung (Pentax SOCT-1000)**

<table>
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<tr>
<th>Findings</th>
<th>Seen in</th>
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<td><strong>Normal Bronchus</strong></td>
<td>layered structure</td>
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<tr>
<td><strong>Alveoli</strong></td>
<td>honeycomb structure</td>
</tr>
<tr>
<td><strong>Tumor</strong></td>
<td>loss of layered structure</td>
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</table>
Optical Coherence Tomography

Analysis of tissue structure by light interference

Clear image can be obtained
Possibility of optical biopsy
Future of OCT for Lung Cancer

1. Early detection of lung cancer by sputum cytology and CT screening.
2. Early localization of lung cancer by bronchoscope (BS), fluorescence BS and CT.
3. Optical biopsy by OCT for definitive diagnosis of early stage lung cancer.
Future Strategy for the Therapy of Early Lung Cancer

Laserphyrin
Pentax SAFE 3000

BS
AF
Image Processing
OCT
US-Echo
PDD
PDT
Recent Advanced Optical Technology for Definitive Diagnosis

OCT (Investigational)

Confocal Endomicroscope (Investigational)

Ultra-Thin Scanning Fiber Bronchoscope
Confocal Endomicroscope

Images courtesy of Dr Ralf Kiesslich, Mainz University Hospital, Germany
Confocal Endomicroscope

Images courtesy of Dr Ralf Kiesslich, Mainz University Hospital, Germany
Confocal Endomicroscope

Images courtesy of Dr Ralf Kiesslich, Mainz University Hospital, Germany
Confocal Endomicroscope

Images courtesy of Dr Ralf Kiesslich, Mainz University Hospital, Germany

Tokyo Medical University
Recent Advanced Optical Technology for Definitive Diagnosis

OCT (Investigational)

Confocal Endomicroscope (Investigational)

*Ultra-Thin Scanning Fiber Bronchoscope*
Advanced Optical Technology
Ultra thin Scanning Fiber Bronchoscope

Features
• Ultrathin (1.6 mm O.D.)
• Full color (RGB) images
• 15 Hz frame rate
• 500 lines resolution
• 80 degrees FOV

Components
• Scanning single-mode (illumination fiber)
• Piezo tube actuator
• Three RGB laser sources
• Twelve collection fibers

Ultra-Thin Scanning Fiber Bronchoscope

Future optical technologies

Ultra-thin Scanning fiberbronchoscope

- Auto-fluorescence
- Photodynamic diagnosis
- OCT
- Raman Spectroscopy-Proteomics
- Photodynamic therapy
Future optical technologies

Percutaneous Needle Procedures

- OCT
- Raman spectroscopy-Proteomics
- Photodynamic therapy
- Local thermotherapy
Future optical technologies

Definitive diagnosis

- OCT
- Confocal endomicroscope
- Raman spectroscopy-Proteomics
Present status of PDT for lung cancer
History of PDT for lung cancer
**History of Clinical PDT**

1903  Josionek & Tappeiner  Skin cancer, eosin + white light
1960  Lipson               Development of hematoporphyrin derivative (HpD)
1979  Dougherty            Skin cancer, HpD+argon dye laser (ADL)
1979  Laws                 Brain tumor, HpD+ADL
1980  Hayata & Kato        Endoscopic PDT,
                                 Early stage lung cancer, HpD+ADL
1981  Kato & Ono           Endoscopic PDT,
                                 Esophageal ca., Gastric ca. HpD+ADL
1982  Soma & Kato          Cervical ca., HpD+ADL
1983  Tsuchiya, Kato & Ono Bladder ca., HpD+ADL
1985  Kato, Konaka & Aizawa Vocal cord ca., HpD+ADL
History of PDT in TMU, 1980
Indications of PDT for Lung Cancer

Curative intent
   Early lung ca.*, central type, squamous ca.
   Curative rate: 84%
   (*cis, submucosal invasion to cartilage, area within 1cm)

Palliative for QOL
   Advanced lung cancer, central type, NSCLC
   High effective rate

Neo-adjuvant PDT
   Preoperative PDT for the reduction of resection volume

Investigational trial of curative treatment of peripheral ca.
   BAC detected by CT screening
1. Photofrin-PDT altered expression of IL-6 and IL-10 in vivo. 
   (Gollnick, S., et al., Cancer Res., 1997)
2. NPe6-PDT increased the expression of mRNA of IL-2, IL-6 and TNF-α. 
   Especially, IL-6 expression modulates cellular sensitivity to PDT. 
   (Usuda, J. and Kato, H., et al., Int. J. of Cancer, 2001)
3. PDT-generated tumor cell lysates were potent vaccines and PDT-generated vaccines were tumor specific. 
   (Gollnick, S., et al., Cancer Res., 2002)
4. Tumor oxygenation, extent of tumor damage, vascular damage were 
   correlated with induction of inflammation as measured by IL-6, macrophage inflammatory protein 1, 2. 
   (Henderson, B.W., et al., Cancer Res., 2004)
Photosensitizer

Cancer treatment

Photofin (1994)
Laserphyrin (NPe6) (2003)
Visudyne (BPD-MA)
Puriyn (tin ethyl etiopurin)
Foscan (m-THPC)
Lutex (lutetium texaphyrin)
ATX-S10
Absorption Spectrum and Structure of Laserphyrin

Talaporfin (Laserphyrin)

Hemoglobin

Photofrin

Absorbance

Wavelength

300 400 500 600 700

630nm 664nm

Tokyo Medical University

(NPe6)
## Light Source

<table>
<thead>
<tr>
<th></th>
<th>Hamamatsu Photonics Inc</th>
<th>IHL</th>
<th>Coherent Inc</th>
<th>Panasonic</th>
<th>Diomed Ltd</th>
<th>DUSA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wavelength (nm)</strong></td>
<td>630</td>
<td>630</td>
<td>630</td>
<td>664</td>
<td>630 / 652 / 730</td>
<td>633</td>
</tr>
<tr>
<td><strong>Photosensitizer</strong></td>
<td>Photofrin</td>
<td>Photofrin</td>
<td>Photofrin</td>
<td>NP-6</td>
<td>Photofrin mTHPC/Lutex</td>
<td>ALA</td>
</tr>
<tr>
<td><strong>Power (mW)</strong></td>
<td>160</td>
<td>300</td>
<td>200</td>
<td>200</td>
<td>2000</td>
<td>100</td>
</tr>
<tr>
<td><strong>Type of laser</strong></td>
<td>Excimer dye</td>
<td>YAG-CPO</td>
<td>Argon dye</td>
<td>Diode</td>
<td>Diode</td>
<td>Diode</td>
</tr>
<tr>
<td><strong>Character</strong></td>
<td>Pulse laser, low maintence</td>
<td>tunable</td>
<td>firstly applied</td>
<td>small maintence free</td>
<td>small maintence free</td>
<td>small maintence free</td>
</tr>
<tr>
<td><strong>Price (US$)</strong></td>
<td>450,000</td>
<td>380,000</td>
<td>280,000</td>
<td>not fixed</td>
<td>60,000</td>
<td>not fixed</td>
</tr>
</tbody>
</table>

*Tokyo Medical University*
PDT EDL-2
Hamamatsu Photonics Co. 1998

Tokyo Medical University
Panasonics Diode laser, PD Laser

Tokyo Medical University
Photodynamic therapy
First PDT for Early Stage Lung Cancer
- 1980 -

74y man, Right B2b bronchus

before

after
PDT for Early Stage Lung Cancer

59y woman, Right upper bronchus 1981

before

after
PDT for Early Stage Lung Cancer

Carina (Sq. cell carcinoma)  63-year old man
Photosensitizer: Laserphyrin + SAFE 3000

Before PDT  PDD  Immediately after PDT  3 M after PDT
### PDT for Early Stage Lung Cancer

<table>
<thead>
<tr>
<th>Lt. B3 (Sq. cell carcinoma)</th>
<th>83-year old man</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photosensitizer: Laserphyrin + SAFE 3000</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Before PDT</th>
<th>PDD</th>
<th>Immediately after PDT</th>
<th>4 M after PDT</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Before PDT" /></td>
<td><img src="image2.png" alt="PDD" /></td>
<td><img src="image3.png" alt="Immediately after PDT" /></td>
<td><img src="image4.png" alt="4 M after PDT" /></td>
</tr>
</tbody>
</table>
PDT for Early Stage Lung Cancer

Rt. Upper bronchus (Sq. cell carcinoma)  65-year old man
Photosensitizer: Laserphyrin + SAFE 3000
PDT for early stage lung cancer

- 68-year-old man, Squamous cell carcinoma, Lt. Upper lobe br.
- Laserphyrin 40 mg/m², diode laser, 100 J/cm², 150 mW (11 min)

Before PDT
- Cancer

Pentax SAFE 3000 PDD
- Fluorescence

2 months after PDT
- Complete response (CR)
PDT for Early Stage Lung Cancer

Lt B1+2, 3  79-year old man

Before PDT  3M after PDT
PDT for Early Stage Lung Cancer

Rt B1-2

75-year old man

Before PDT

3M after PDT

Tokyo Medical University
PDT for Early Stage Lung Cancer

Lt. upper bronchus
Before PDT

68-year old man
2M after PDT
PDT for Early Stage Lung Cancer

Lt. main bronchus 63-year old man

Before PDT 3M after PDT
PDT for Early Stage Lung Cancer

Before PDT

3 days after PDT

3 months after PDT
Photodynamic therapy of early lung ca.

KT 79y, man

Before

Before

1M after

4M after

7M after

11M after
PDT of early lung ca.  66y man

Before

5M after
Characteristics of patients who underwent PDT
(Feb. 1980-Dec. 2006)

<table>
<thead>
<tr>
<th>Description</th>
<th>Number/Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>235 patients (310 lesions)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Man</td>
<td>229 patients (304 lesions)</td>
</tr>
<tr>
<td>Woman</td>
<td>6 patients (6 lesions)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>37-84</td>
</tr>
<tr>
<td>Average</td>
<td>72.2</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>304 lesions</td>
</tr>
<tr>
<td>Severe dysplasia</td>
<td>2 lesions</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>1 lesions</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>3 lesions</td>
</tr>
</tbody>
</table>
# Bronchoscopical features (Feb. 1980-Mar. 2006)

## Bronchoscopical findings

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickened type</td>
<td>253 lesions</td>
</tr>
<tr>
<td>Nodular type</td>
<td>44</td>
</tr>
<tr>
<td>Polypoid type</td>
<td>13</td>
</tr>
</tbody>
</table>

## C-stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>228</td>
</tr>
<tr>
<td>IA</td>
<td>82</td>
</tr>
</tbody>
</table>

## Distant margin of the tumor

<table>
<thead>
<tr>
<th>Margin</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visible</td>
<td>248</td>
</tr>
<tr>
<td>Invisible</td>
<td>62</td>
</tr>
</tbody>
</table>

## Total

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>310 lesions</td>
</tr>
</tbody>
</table>
Results of PDT for early stage lung cancer

<table>
<thead>
<tr>
<th>Tumor size(cm)</th>
<th>No. of lesions</th>
<th>CR (rate,% )</th>
<th>PR (rate,% )</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>66</td>
<td>63 (95.4%)</td>
<td>3</td>
</tr>
<tr>
<td>0.5 ≤ &lt;1.0</td>
<td>155</td>
<td>147 (94.8%)</td>
<td>9</td>
</tr>
<tr>
<td>1.0 ≤ &lt;2.0</td>
<td>53</td>
<td>43 (87.7%)</td>
<td>10</td>
</tr>
<tr>
<td>2.0 ≤</td>
<td>36</td>
<td>15 (41.7%)</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>310</td>
<td>268 (86.4%)</td>
<td>42</td>
</tr>
</tbody>
</table>

Tokyo Medical University
5-year survival rate after PDT

- Cancer specific survival: 57.6%
- Overall survival: 92.5%
Early stage lung cancers treated with PDT

   CR: 85% (95 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)
The indication criteria of PDT for lung cancer

1. Patients with the endoscopically evaluated early stage lung cancer.
2. Patients with normal chest X-ray and CT images.
3. No metastasis to lymph nodes and no distant metastasis revealed by routine clinical diagnostic methods (N0M0).
4. Tumors located from the bifurcation of the trachea to subsegmental bronchi, with the peripheral margin of the lesions endoscopically visible.
5. Tumor size not more than 2 cm in diameter.
PDT for advanced lung cancer

1. Palliative treatment for the improvement of QOL
2. Neoadjuvant PDT for surgery
PDT for QOL, Advanced Lung Cancer
PDT for QOL, Advanced Lung Cancer
PDT for QOL, Advanced Lung Cancer
## Improvement of Patients Condition

<table>
<thead>
<tr>
<th></th>
<th>Before PDT</th>
<th>After PDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂ (AV+SD)mmHg</td>
<td>66 ± 21</td>
<td>82 ± 14</td>
</tr>
<tr>
<td>PS (AV+SD)mmHg</td>
<td>1.8 ± 0.5</td>
<td>0.8 ± 0.4</td>
</tr>
</tbody>
</table>
# PDT in Advanced Lung Cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of cases</th>
<th>Response (significant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayata, Kato 1982</td>
<td>15</td>
<td>100% (53%)</td>
</tr>
<tr>
<td>Vincent 1984</td>
<td>17</td>
<td>76.5 (41)</td>
</tr>
<tr>
<td>Balchum 1984</td>
<td>22</td>
<td>95 (95)</td>
</tr>
<tr>
<td>McCaughan 1986</td>
<td>18</td>
<td>100 (97)</td>
</tr>
<tr>
<td>LoCicero 1990</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>Sutedja 1992</td>
<td>15</td>
<td>73.3</td>
</tr>
<tr>
<td>Wiman 1998</td>
<td>211</td>
<td>55</td>
</tr>
</tbody>
</table>
Bronchoplasty after preoperative PDT

78y man, Sq.Ca., Stage IIA (T1 N1 M0)
Bronchoplasty by Preoperative PDT

Resection of bifurcation between the left upper and lower bronchi

Before PDT

After PDT

After resection
### PDT plus Bronchoplasty for early stage lung cancer

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Journal</th>
<th>Patients</th>
<th>Preoperative PDT Purpose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kato H. et al.</td>
<td>1985</td>
<td>J Thorac Cardiovasc Surg</td>
<td>15</td>
<td>For the purpose of either reducing the extent of resection or increasing operability.</td>
<td>5 of 15 patients of stage I, originally candidates for pneumonectomy or bilobectomy, became possible to sleevelobectomy</td>
</tr>
<tr>
<td>Okunaka T, Kato H</td>
<td>1999</td>
<td>Dig Thera End</td>
<td>26</td>
<td>Initial purpose of PDT to reduce extent of resection was achieved 22 out of 26.</td>
<td>7 patients, stage I, tumor invasion to the main bronchus or trunks intermedius became possible to sleevelobectomy</td>
</tr>
</tbody>
</table>
**Present status of PDT for Lung Cancer**

**Curative intent**
- Early lung ca.*, central type, squamous ca.
- Curative rate: 84%
  (*cis, submucosal invasion to cartilage, area within 1cm*)

**Palliative for QOL**
- Advanced lung cancer, central type, NSCLC
- High effective rate

**Neo-adjuvant PDT**
- Preoperative PDT for the reduction of resection volume

**Investigational trial of curative treatment of early peripheral lung cancer**
## Chest CT Screening

<table>
<thead>
<tr>
<th>Author</th>
<th>Detection rates of Early Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaneko M (Radiology 1996)</td>
<td>434 (/10⁵)</td>
</tr>
<tr>
<td>Sone S (Lancet 1998)</td>
<td>478</td>
</tr>
<tr>
<td>Noguchi M (TMU 1999)</td>
<td>2,931</td>
</tr>
<tr>
<td>Kusunoki Y (Chest CT screening 1999)</td>
<td>707</td>
</tr>
<tr>
<td>Henschke CI (Lancet 1999)</td>
<td>2,700</td>
</tr>
<tr>
<td>Sobue T (JCO 2002)</td>
<td>869</td>
</tr>
</tbody>
</table>

Detection rates by chest X-ray screening for residents of Tokyo (1994):
83.0 in men, 23.4 in women/100,000
Noguchi’s classification and lymph node meta.

<table>
<thead>
<tr>
<th>Nodal meta.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Localized BAC (LBAC)</td>
<td>0 %</td>
</tr>
<tr>
<td>B: LBAC with foci of collapse of alveolar structure</td>
<td>0</td>
</tr>
<tr>
<td>C: LBAC with foci of active fibroblast proliferation</td>
<td>28.4</td>
</tr>
<tr>
<td>D: Poorly differentiated adenoca.</td>
<td>47.7</td>
</tr>
<tr>
<td>E: Tubular adenoca.</td>
<td>55.6</td>
</tr>
<tr>
<td>F: Pappilary adenoca. with destructive growth</td>
<td>25</td>
</tr>
</tbody>
</table>

Cancer 1995

Tokyo Medical University
W/D adenocarcinoma
1.5cm Noguchi Type A pT1N0M0 IA

Tokyo Medical University
Noguchi Type B w/d adenoca. 1.3cm  pT1N0M0
Our Surgical Strategy

Solid lesion

Lobectomy is necessary.

Mixed lesion – GGO% evaluated

Lobectomy or limited op.
(Further investigation is required.)

Pure GGO

less than 1 cm – Follow up (op. if size increases)
1 cm or more – limited op. acceptable (!?)
Incidence of lymphatic invasion and nodal meta.

<table>
<thead>
<tr>
<th>Investigators</th>
<th>No. of Patients</th>
<th>&lt; 1cm</th>
<th>1 - 2 cm</th>
<th>2&lt; cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ishida et al, 1990</td>
<td>221</td>
<td>0</td>
<td>17</td>
<td>38</td>
</tr>
<tr>
<td>Asamura et al, 1996</td>
<td>337</td>
<td>NA</td>
<td>19.5</td>
<td>33.1</td>
</tr>
<tr>
<td>Nakamura et al, 1998</td>
<td>165</td>
<td>5.3</td>
<td>15.8</td>
<td>NA</td>
</tr>
<tr>
<td>Koike et al, 1998</td>
<td>496</td>
<td>6</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Yamanaka et al, 2000</td>
<td>67</td>
<td>0</td>
<td>9.4</td>
<td>14.3</td>
</tr>
<tr>
<td>Ohta et al, 2001</td>
<td>103</td>
<td>NA</td>
<td>20.4*</td>
<td>NA</td>
</tr>
</tbody>
</table>

*: adenocarcinoma
New Concept of Photodynamic Therapy

Personalized medicine

Selection of non-invasive lung cancer
Precise indication of PDT for lung cancer
Trans-Thoracic PDT for Peripheral Lung Cancer

Needle

Quartz fiber for laser

CT guided needle puncture

4 needles

Insertion of quartz fiber thru needle

Under PDT

Tokyo Medical University
PDT for Peripheral Lung Cancer
### PDT for Peripheral Lung Cancers

#### Patients’ Backgrounds

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Location</th>
<th>Size</th>
<th>Histology</th>
<th>Reasons of PDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>M</td>
<td>Lt S(^{8-10})</td>
<td>80mm</td>
<td>Ad</td>
<td>low pulmonary function</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>M</td>
<td>Rt S(^{10})</td>
<td>40</td>
<td>Sq</td>
<td>low pulmonary function</td>
</tr>
<tr>
<td>3</td>
<td>74</td>
<td>M</td>
<td>Lt S(^{3})</td>
<td>35</td>
<td>Ad</td>
<td>low pulmonary function</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>M</td>
<td>Lt S(^{9})</td>
<td>52</td>
<td>Ad</td>
<td>low pulmonary function</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>F</td>
<td>Rt S(^{4})</td>
<td>25</td>
<td>Ad</td>
<td>low pulmonary function</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>M</td>
<td>Rt S(^{3})</td>
<td>12</td>
<td>Ad</td>
<td>low pulmonary function</td>
</tr>
<tr>
<td>7</td>
<td>75</td>
<td>M</td>
<td>Rt S(^{1})</td>
<td>50</td>
<td>Sq</td>
<td>low pulmonary function</td>
</tr>
<tr>
<td>8</td>
<td>73</td>
<td>M</td>
<td>Rt S(^{3})</td>
<td>15</td>
<td>Ad</td>
<td>low pulmonary function</td>
</tr>
<tr>
<td>9</td>
<td>58</td>
<td>M</td>
<td>Rt S(^{6})</td>
<td>13</td>
<td>Ad</td>
<td>congestive cardiomyopathy</td>
</tr>
</tbody>
</table>

*Tokyo Medical University*
## Results of PDT for Peripheral Lung Cancer

<table>
<thead>
<tr>
<th>Case</th>
<th>Power/fiber</th>
<th>Energy/fiber</th>
<th>Number of Insertion</th>
<th>Complications</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150 mW</td>
<td>200 J</td>
<td>4</td>
<td>None</td>
<td>PR</td>
</tr>
<tr>
<td>2</td>
<td>150 mW</td>
<td>200 J</td>
<td>5</td>
<td>None</td>
<td>PR</td>
</tr>
<tr>
<td>3</td>
<td>150 mW</td>
<td>400 J</td>
<td>3</td>
<td>None</td>
<td>NC</td>
</tr>
<tr>
<td>4</td>
<td>150 mW</td>
<td>400 J</td>
<td>4</td>
<td>Pneumothorax</td>
<td>NC</td>
</tr>
<tr>
<td>5</td>
<td>150 mW</td>
<td>800 J</td>
<td>1</td>
<td>None</td>
<td>PR</td>
</tr>
<tr>
<td>6</td>
<td>300 mW</td>
<td>800 J</td>
<td>4</td>
<td>None</td>
<td>PR</td>
</tr>
<tr>
<td>7</td>
<td>300 mW</td>
<td>800 J</td>
<td>6</td>
<td>None</td>
<td>PR</td>
</tr>
<tr>
<td>8</td>
<td>600 mW</td>
<td>800 J</td>
<td>4</td>
<td>Pneumothorax</td>
<td>PR</td>
</tr>
<tr>
<td>9</td>
<td>600 mW</td>
<td>800 J</td>
<td>5</td>
<td>None</td>
<td>PR</td>
</tr>
</tbody>
</table>
Light Emitted Diode, Light Sciences, USA

Intratumoral Photoactivation
Clinical application of LED

Intratumor PDT by LED under CT guidance

Before PDT

Tuomr necrosis (9.0x6.6cm)
42 days after PDT

Osteosarcoma of pelvis, PDT 1 hour after injection of 1.0mg/kg of Talaporfin (LS11) \(200\text{J/cm}^2\).
Study on metastasis related proteins by means of proteomic mass spectrometry

Possibility of Tailor-made PDT for Lung Cancer
A list of metastasis related proteins identified from the LC-MS signals

<table>
<thead>
<tr>
<th>Proteome pattern</th>
<th>意義</th>
<th>プロテオームパターン有意差</th>
<th>蛋白質名</th>
<th>SwissProt</th>
<th>N1特異的</th>
<th>あり</th>
<th>Metastasis associated protein</th>
<th>N1特異的</th>
<th>あり</th>
<th>Metastasis associated protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx specific</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>weakly lean to Nx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>almost equal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Significance |       |     |       |     |       |       |     |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |       |       |   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   |       |       |     |       |       |     |       |       |     |       |       |     |       |       |     |�
Future Endoscopic Lung Cancer Diagnosis

Confocal endomicroscope
OCT for staging
Proteomics analysis for staging
Ultra-thin fiberbronchial OCT
Future of Endoscopic Lung Cancer Therapies

PDT
Laser vaporization
Microwave coagulation

- Improvement of curative rate
- Low side effects
- Low cost treatment
- Personalized medicine
- Selection of non-invasive cancer
Effort Toward Lung Cancer Eradication

Smoking cessation

Early detection

Early localization

Selection of therapy

Early treatment