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

	Lung cancer patients	Death
Europe	410,220	353,848
USA	214,226	167,545
Asia	1,045,695	936,051
Japan	94,855	75,119

(GLOBOCAN 2012)

Approval of PDT for Lung Cancer

1977	Dougherty	PDT of skin cancer by HpD+Argon dye laser (ADL)
1978	Kato, Konaka, Aizawa	In vitro and experimental study of PDT by canine lung cancer model.
1980	Kato & Hayata	Clinical application of endoscopic PDT of early lung cancer, HpD+ADL
1984	Hayata Research Group	Fundermental, investigation and clinical reaserch PDT supported by the government.
1986	Kato Research Group	Multi-institutional clinical researches on early stage of lung, esophagus, stomach and cervix supported by the government.
1989	***Kato et al***	***Multicentric phase II clinical Trial of early stage cancers of lung, esophagus, stomach and cervix. Phtofrin+ADL or Eximer dye laser (EDL)***
1993	***Jap Government approved PDT of early ca of lung, esophagus, stomach, cervix. Photofrin+ADL, EDL***	
1998	***Kato & Furukawa***	***Multicentric phase II clinical trial for early lung cancer Lasephyrin+Diode Laser (DL)***
2002	***Jap Government approved PDT of early lung cancer. Laserphyrin+DL***	
2009	***Jap Governmental approval for PDT of advanced lung cancer. Laserphyrin+DL***	

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%
Furuse,K.,Kato,H., et al. J Clin Oncol 11:1852-1857, 1993

Governmental approval: 1993

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: Reponse rate: 94.9%, Complete remission rate: 84.6%
Toxicity: No serious adverse drug reactions were observed.
Skin photosensitivity: Skin irritation disappeared with 2 weeks.
Kato H, Lung Cancer 42: 103-111, 2003

Governmental approval: 2002

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***

Current Status in Clinical Practice

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

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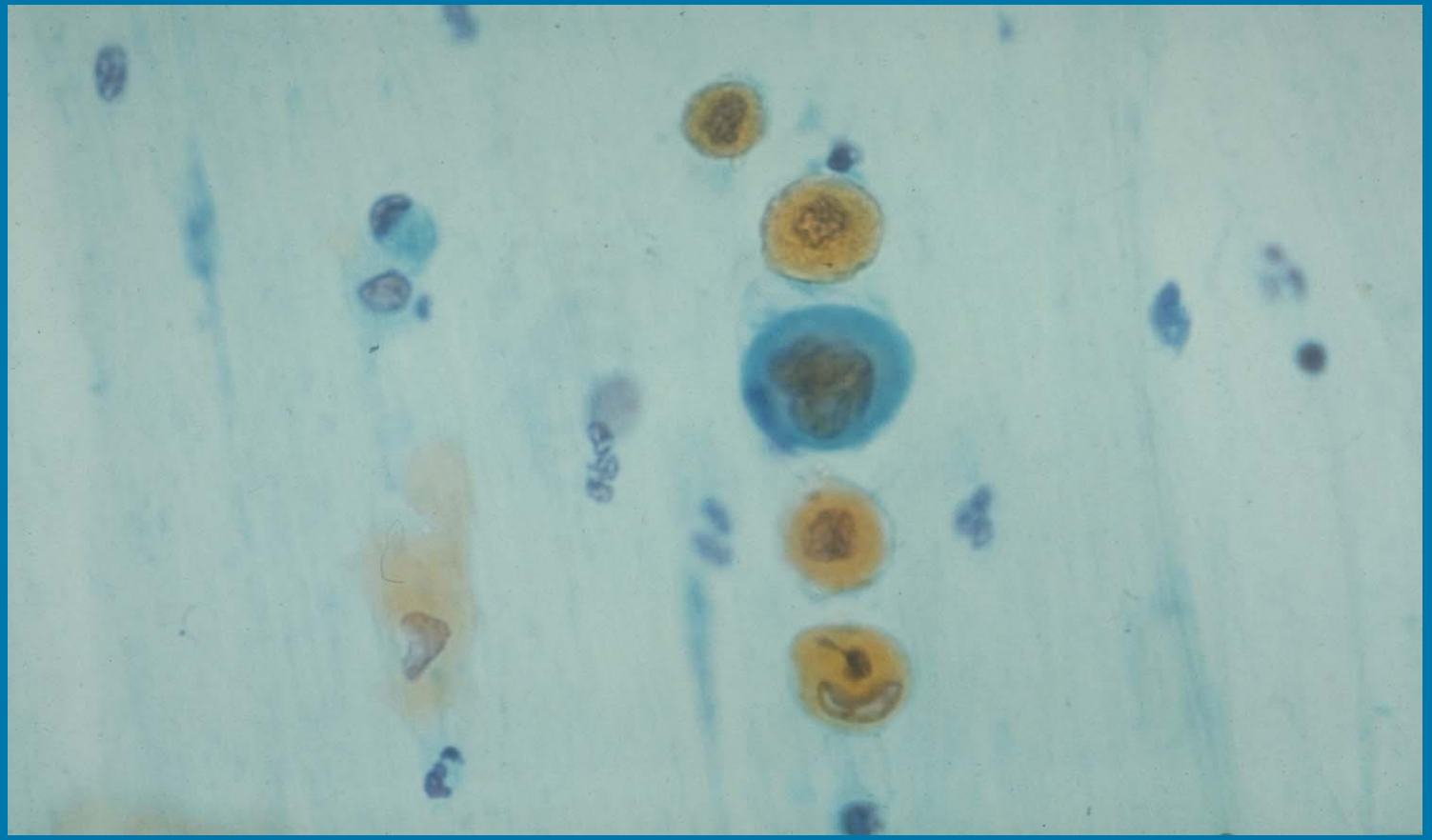
Squamous Cell Carcinoma in Situ, Sputum



Bronchoscopy

Fiberoptic bronchoscopy

Digital bronchoscopy

Fluorescence bronchoscopy

Digital Bronchoscopy with AFD/PDD System

AFD: Autoflurescence 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

Photodynamic Therapy

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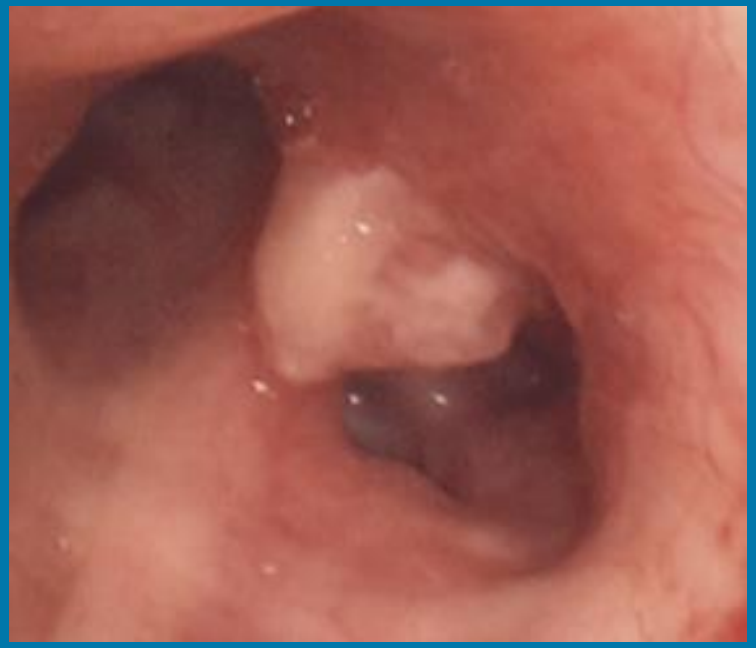
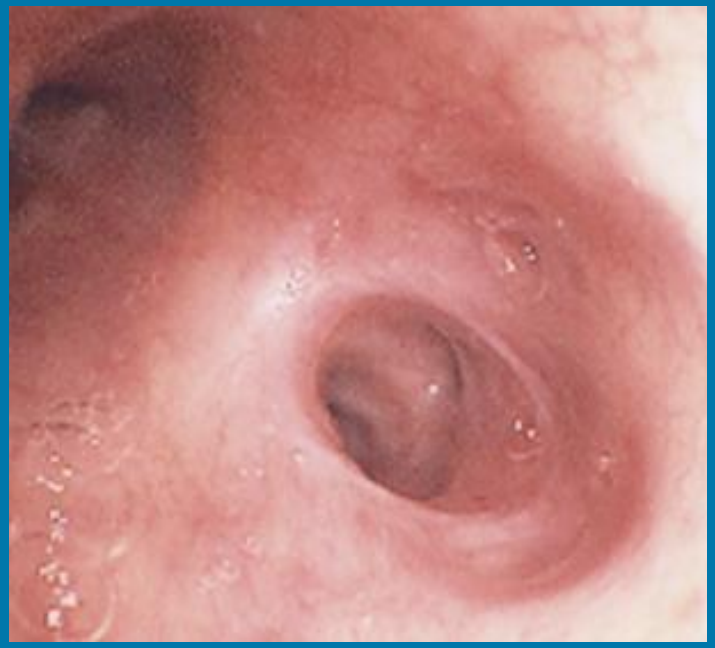
PDT for Early Stage Central Type Lung Cancer

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



Before PDT



3M after PDT

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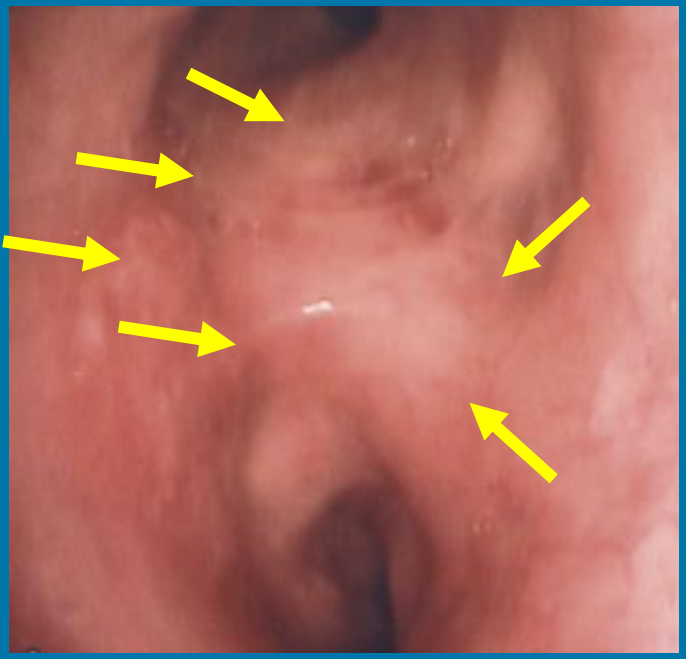
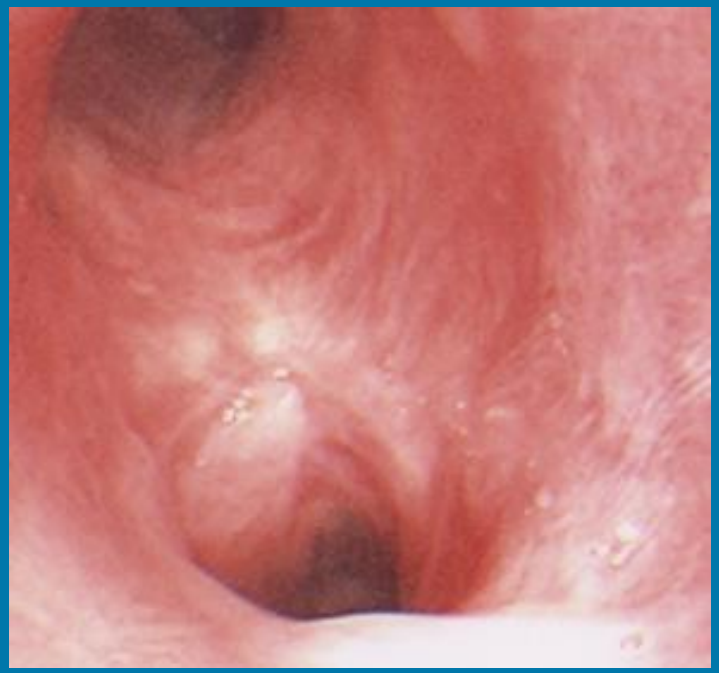
PDT for Early Stage Central Type Lung Cancer

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



Before PDT



3M after PDT

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PDT for Early Stage Central Type Lung Cancer

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

Before PDT

3M after PDT

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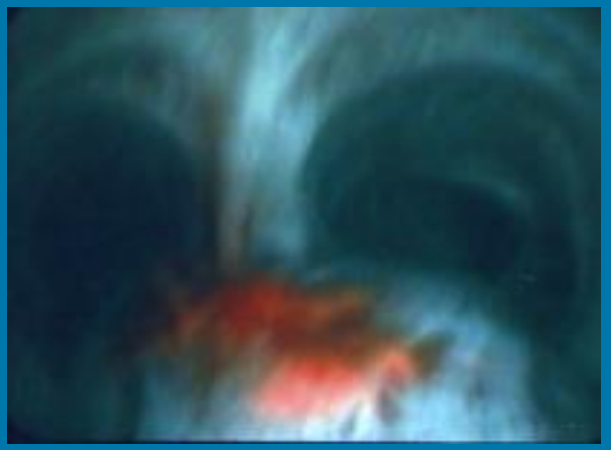
PDT for Early Stage Central Type Lung Cancer

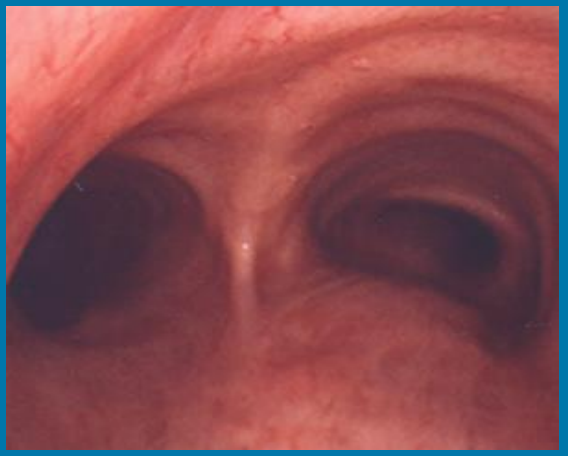
Carina (Sq. cell carcinoma) 63-year-old man

Laserphyrin + SAFE 3000

Before PDT



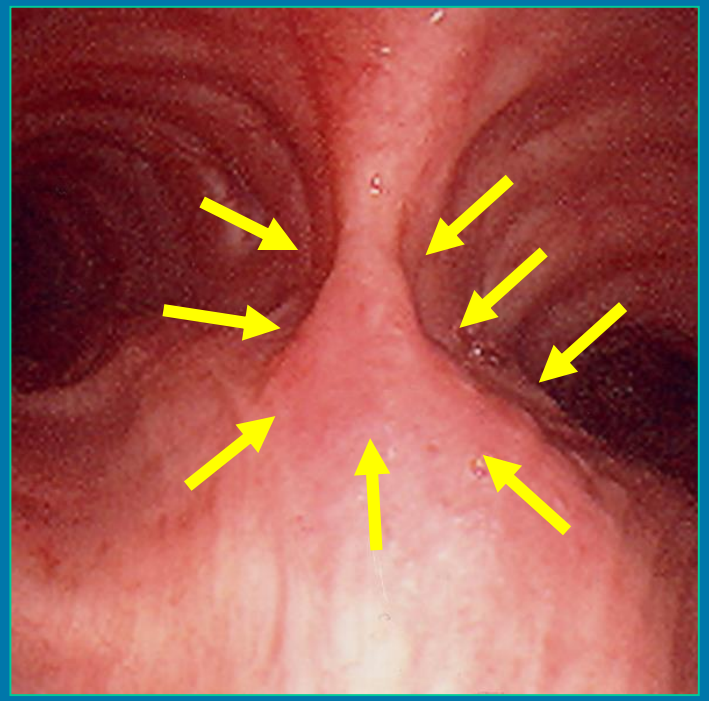
PDD



3 M after PDT

PDT for Early Stage Central Type Lung Cancer

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



Before PDT

3M after PDT

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Results of PDT for ESCLC

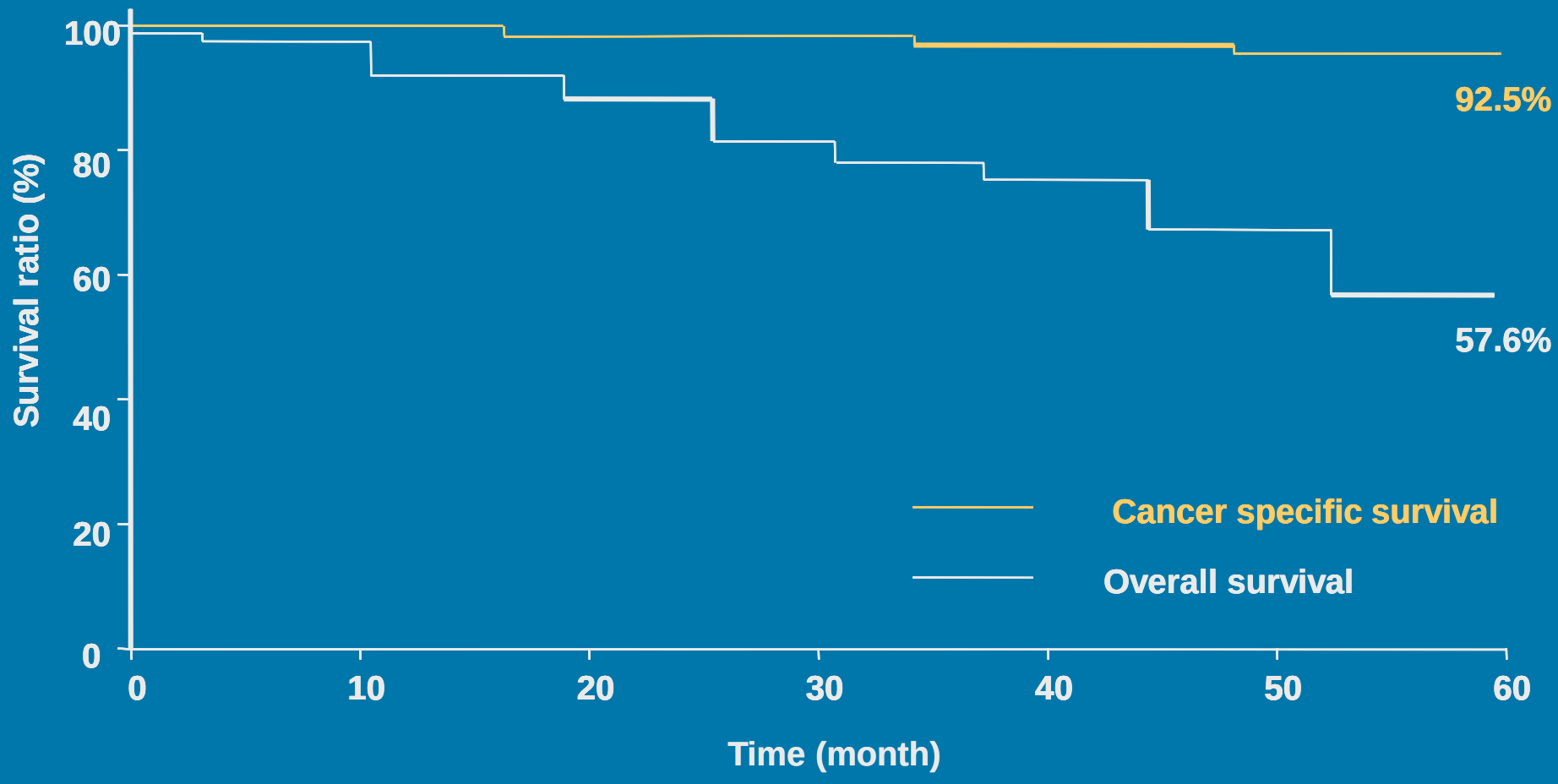
1980-2010

Photofrin® vs Laserphyrin®

	Furuse et al (1989-1992)	Kato et al (1980-2004)	Usuda et al (2002-2010)
No.	59	264	91
Photosensitizer	Photofrin	Photofrin(Laserphyin in 16)	Laserphyrin
Size (cm) & CR (rate,%)			
≦ 1.0	97.8%	93.9%	94.0%
1.0-2.0	50.0%	80.0%	***90.4%***
2.0<	37.5%	44.1%	---

Ikeda,N,etal Laser in Surg and Med 43:749-754, 2011

5-Year Survival Rate, PDT in ESCLC



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ESCLC treated with PDT

1. Hayata Y, Kato H (Chest, 82:10-14, 1982)
2. Kato H, Cortese DA (Clin Chest Med, 6:237-253, 1985)
3. Furuse K. (J Clin Oncol., 11:1852-1857, 1993)
   CR: 85% (59 lesions)
4. Cortese D. (Mayo Clin Proc., 72:595-602, 1997)
   CR: 70% (23 lesions)
5. Kato H. (Lung Cancer, 42: 103-111, 2003)
   CR: 83% (39 lesions)
   Phase II clinical study of PDT using mono-L-aspartyl chlorin e6 (NPe6, Laserphyrin) and diode laser
6. Miyazu Y. (Am J Respir Crit Care Med., 165:832-837, 2002)
   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. Docotor 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

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Current Status of PDT for Advanced Lung Cancer

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)

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New Strategy for ESPLC

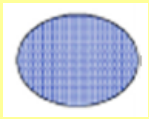
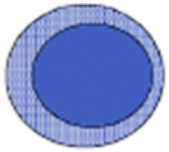
Increase of adenocarcinoma
Increase of multiple primary lung cancers

Carcinogenetic process of adenocarcinoma
Definitive diagnosis of GGO shadows

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

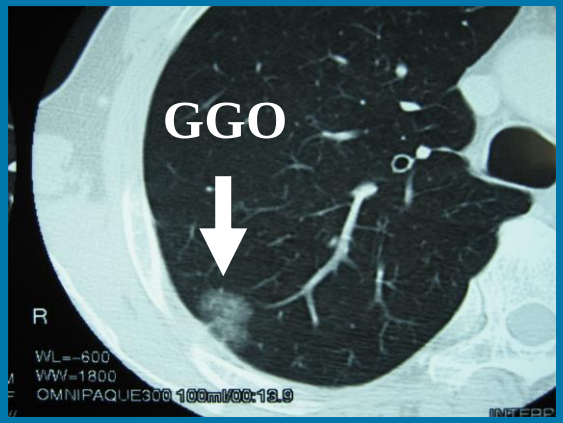
GGO: ground glass opacity, AIS: Adenocarcinoma in situ
MIA: Minimal invasive adenocarcinoma
LPA: Lepidic predominant adenocarcinoma

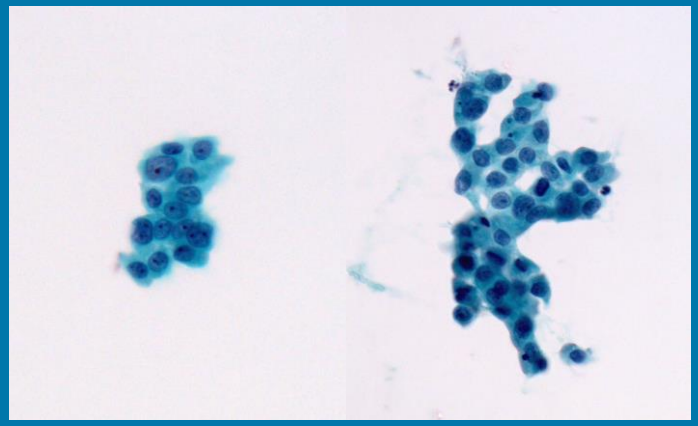
Early Stage Peripheral Type Lung Cancer (ESPLC)

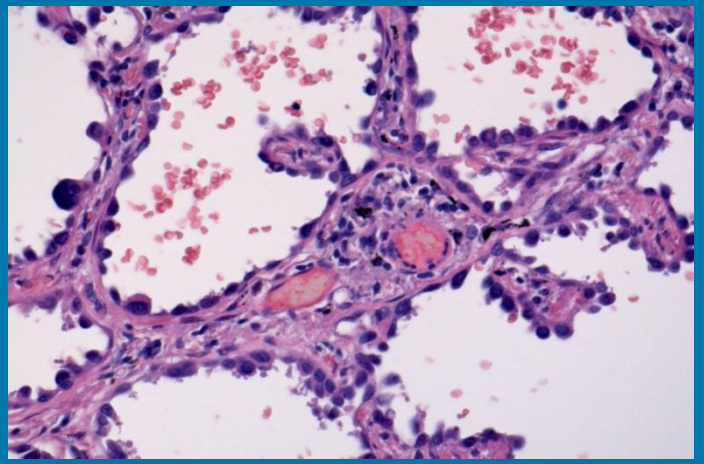
cT	CT image on HRCT							IASLC
	Solid part	0cm	0cm	≤0.5cm†	0.6–1.0cm†	1.1–2.0cm†	2.1–3.0cm†	
	Total tumor size including GG	≤0.5cm	0.6–3.0cm‡‡	≤3.0cm‡‡	0.6–3.0cm‖	1.1–3.0cm‖	2.1–3.0cm‖	
	Pathologic Differential Diagnosis	AAH‡ , AIS , MIA	AIS , MIA , LPA	MIA , LPA , AIS	LPA , Invasive AD , MIA	LPA , Invasive , AD	Invasive , AD	
	Clinical stage		cTis‡‡	cT1mi‡‡	cT1a	cT1b	cT1c	
pT	Invasive part	0cm	0cm	≤0.5cm‡‡	0.6–1.0cm†	1.1–2.0cm†	2.1–3.0cm†	
	Total tumor size including lepidic growth part	Usually ≤0.5cm‡	≤3.0cm‡‡	≤3.0cm‡‡	0.6–3.0cm‖	1.1–3.0cm‖	2.1–3.0cm‖	
	Pathology	AAH	AIS	MIA	Lepidic predominant AD or Inasive AD with lepidic component	Invasive AD with a lepidic componemt or lepidic predominant AD	Invasive AD with lepidic component	
	Pathologic stage		pTis‡‡	pT1mi‡‡	pT1a	pT1b	pT1c	

Adenocarcinoma in situ (AIS)

pT1N0M0
StageIA







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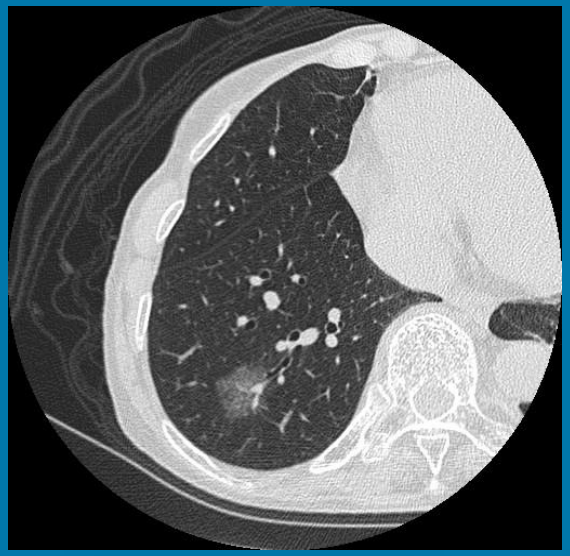
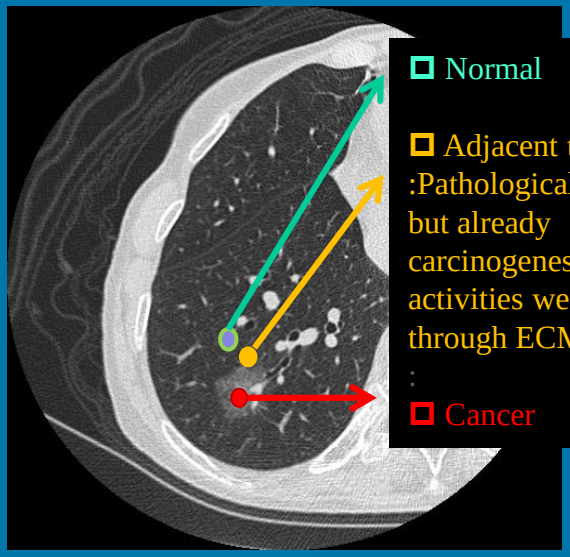
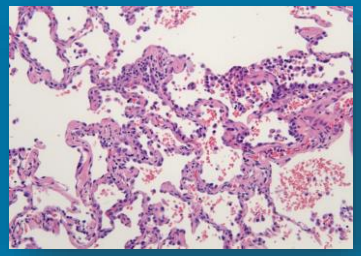
MS-based Proteomics on ESPLC

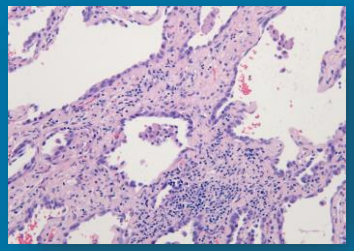




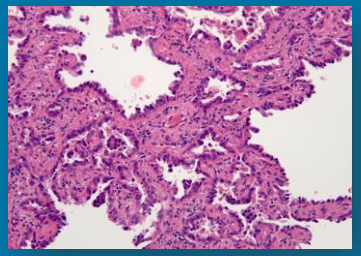
- Normal
- Adjacent to tumor :Pathologically normal but already carcinogenesis-related activities were initiated through ECM receptors.
- Cancer



Adenocarcinoma in situ (AIS)



Minimally invasive adenocarcinoma (MIA)



Lepidic predominant adenocarcinoma (LPA)

Kato Y, et al: A proteomic profiling of laser-microdissected lung adenocarcinoma cells of early lepidic-type. Clinical and Translational Medicine 4:24:1-13,2015

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

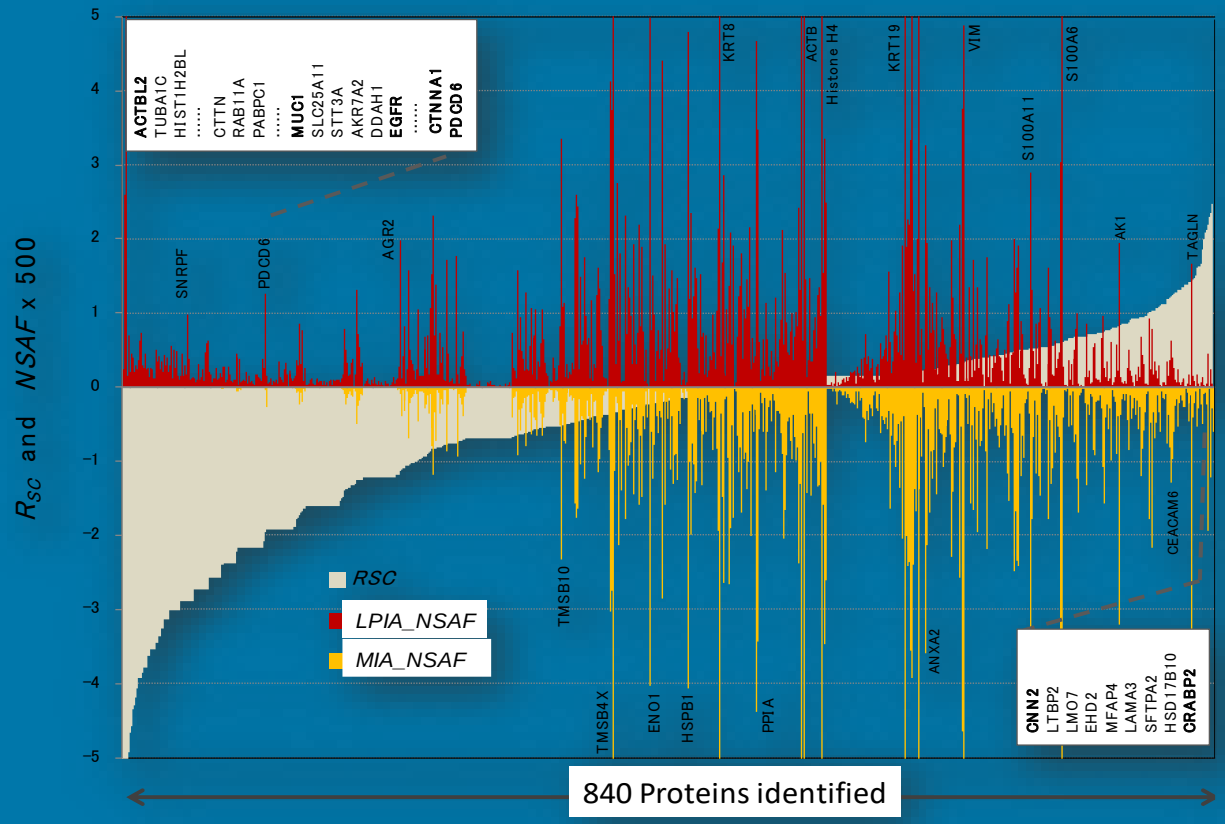
LPA vs MIA

LPA: Lepidic predominant adenocarcinoma

MIA: Minimally invasive adenocarcinoma

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

- **Statistical significance was evaluated by χ^2 or G- test.**



Kato Y, et al: A proteomic profiling of laser-microdissected lung adenocarcinoma cells of early lepidic-type. Clinical and Translational Medicine 4:24:1-13,2015

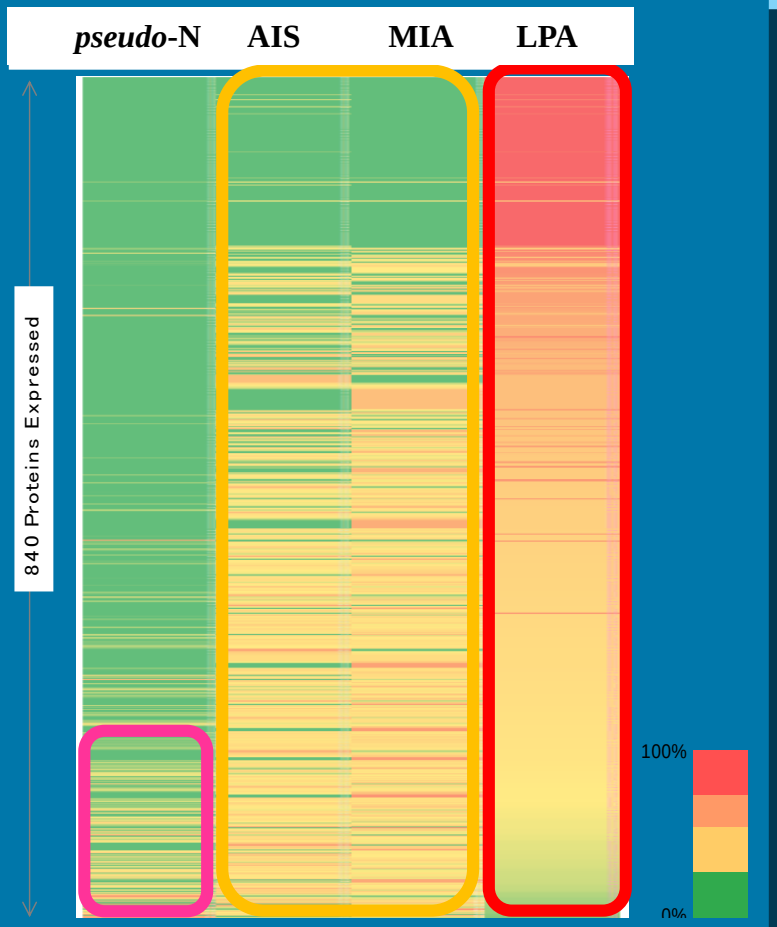
Protein Expression Patterns throughout Disease Stages

GGO Lung Cancer: Expression variations of 840 proteins identified

- AIS : *n*=3
- MIA: *n*=3
- LPA: *n*=3
- Pseudo-Normal: n=3

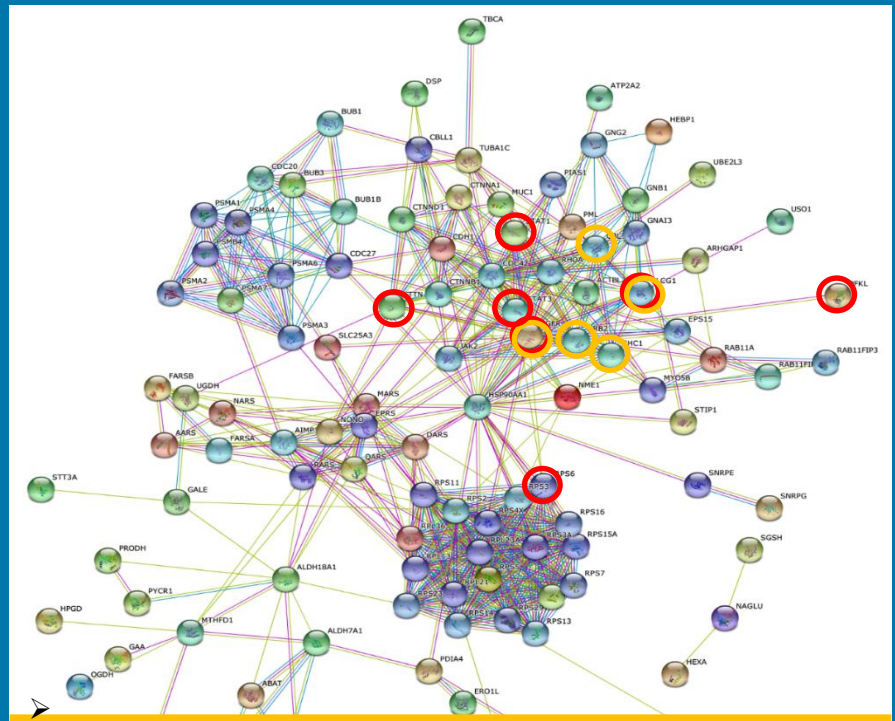
AIS: Adenocarcinoma in situ
MIA: Minimally invasive adenocarcinoma (MIA)
LPA: Lepidic predominant adenocarcinoma

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



Kato Y, et al: A proteomic profiling of laser-microdissected lung adenocarcinoma cells of early lepidic-type. Clinical and Translational Medicine 4:24:1-13,2015

STRING ver. 10 PPI Networks of LPA



- HIF－1
- ErBb

➢**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.**

Kato Y, et al: A proteomic profiling of laser-microdissected lung adenocarcinoma cells of early lepidic-type. Clinical and Translational Medicine 4:24:1-13,2015

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**.

Kato Y, et al: A proteomic profiling of laser-microdissected lung adenocarcinoma cells of early lepidic-type. Clinical and Translational Medicine 4:24:1-13,2015

Early Detection for ESPLC

Lung cancer screening
Health check examination

Early stage peripheral lung cancer (ESPLC)
CT Findings:
GGO
GGO+solid

Therapeutic Strategy for ESPLC

Previously demonstrated highly effectiveness for ***ESCLC***

Refferences

CR 93.8-78%

(1982-2004, Kato H, Cortese D, Monnier P , Furuse K)

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

PDT		760,000yen	($ 8,444)
	DPC	249, 430yen	($ 2,772)
	PDT procedure	87,100	(967)
	Laserphyrin	387,200	(4,302)
	Bronchoscopy	25,000	(277)
Surgery		1,700,000yen	($ 18,888)
	DPC	274,200yen	($ 3,046)
	Surgical procedure	1,050,000	(11,666)
	Anesthesia, drugs	300,000	(3,333)

H.Kato et al: Analysis of the Cost-effectiveness of PDT in Early Stage Lung Cancer. Diagnostic and Therapeutic Endoscopy; 6,9-16,1999

Effort Toward Lung Cancer Eradication

Smoking cessation

↓

Early detection

↓

Early localization

↓

Selection of therapy

↓

Early treatment

Thank you for your attention