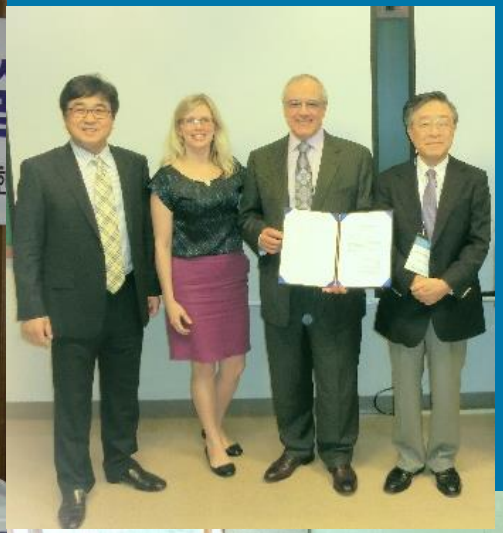
안녕하세요

안녕하세요



History of PDT and Future

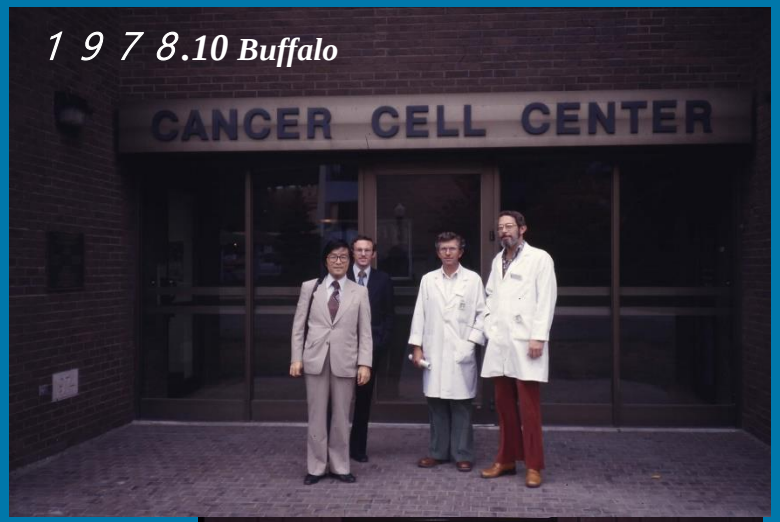
Harubumi Kato, MD, PhD

Niizashiki Central General Hospital

Tokyo Medical University

International University of Heaoth and Welfare

PDT people, first generation 1978



International PRT Meeting 1977-1985

PRT: Photoradiation Therapy

Thomas J Dougherty
Gerald Huth
Edward Profio
Don Doiron
Edgar King
Charles Gomer
David Sanderson
Denis Cortese
Pierr Band
Vincent
Svaazand
Andreoni
Keneth Weishaupt
Kennedy
David Kessel
Yoshihiro Hayata
Harubumi Kato
Katsuo Aizawa

Barbara Henderson
Eric Edel
G. Jori
Berns
Johan Moan
Willhelm Star
Dieter Jochum
Hubert van den Berg
McCaughan
Balchum
Pasquela Spinelli
F.Calzavara
Luigi Corti
Fernando Toniollo
Massimo Torre
Philip Monnier
Susumu Nakajima
Haruo Hisazumi
Hirohito Kuroda
Carruth

PDT People

1977-1996

NSCGH, TMU & IUHW

Photosensitizers

Past practice: Hematoporphyrin derivative (HpD)(1978)

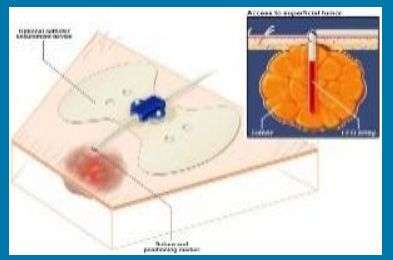
Present status: Photofin (1994)
Laserphyrin (NPe6) (2003)
Visudyne (BPD-MA), Puriyn (tin ethyl etiopurpurin)
Foscan (m-THPC), Lutex (lutetium texaphyrin)
5-aminolaevulinic acid (ALA), ATX-S10
Zinc(II)-naphthalocyanine

Future: ***Benzoporphyrin derivatives***
DDS: Phthalocyanine-nanoparticle
Infrared range: Texaphyrin
X-ray excitation: Photosensitizer+Au, Tangsten
Immuno-PDT: Antibody+Photosensitizer

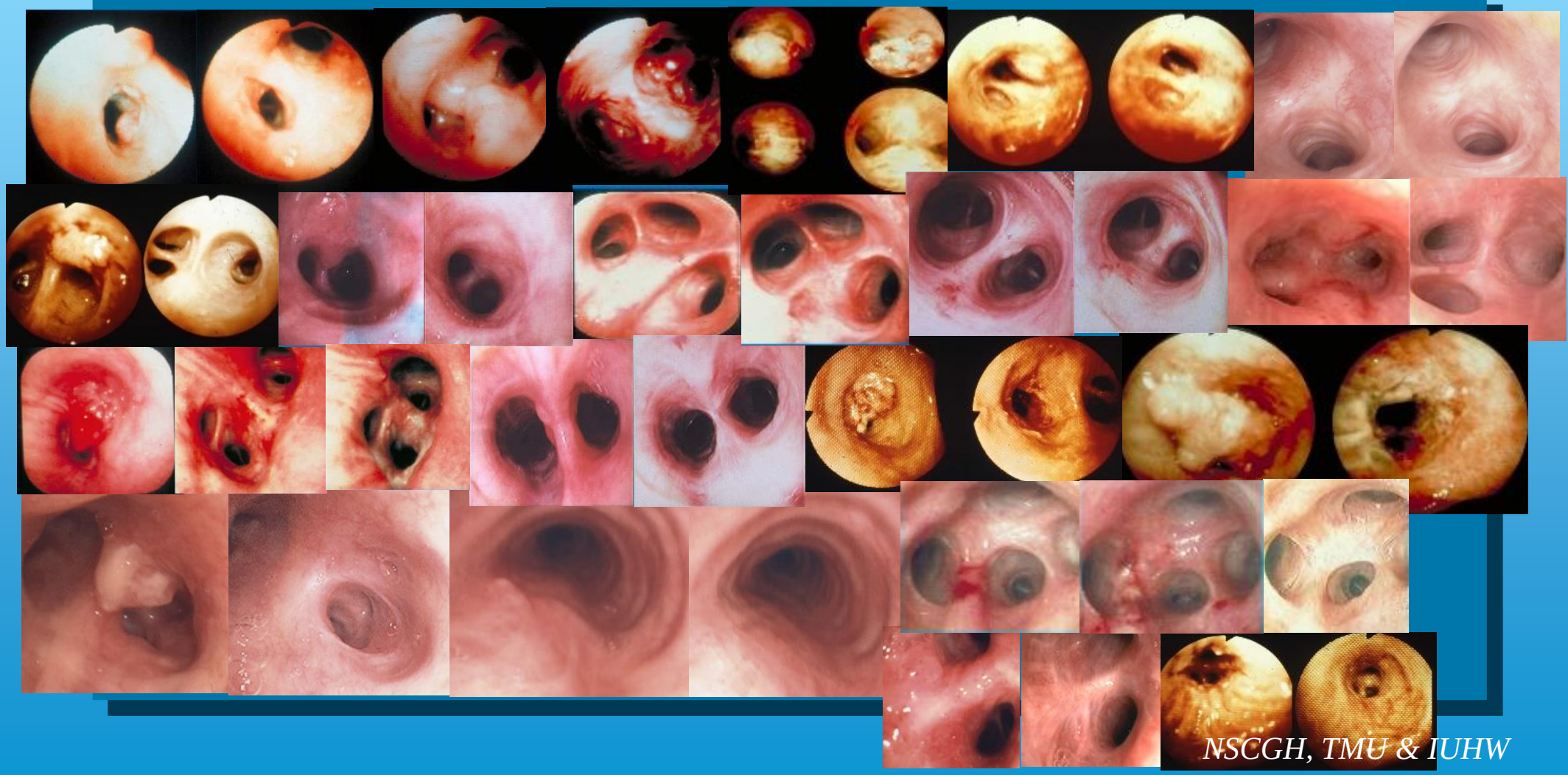
Light Sources

Past: Argon dye laser (1978~):
Spectra Physics, Cooper LaserSonics, Fuji Shashin
Gold vapor laser (1983~): Quentron
Cooper vapor laser (1984~)
Excimer dye laser (1985~): Hamamatsu Photonics
YAG-OPO laser (1995~):
Ishikawajima Harima heavy Industry
Present: Diode laser (1995~):
Panasonics, Diomed, DUSA
Future: X-ray, Synchrotron Radiation

PDT Lasers, First and Second Generation

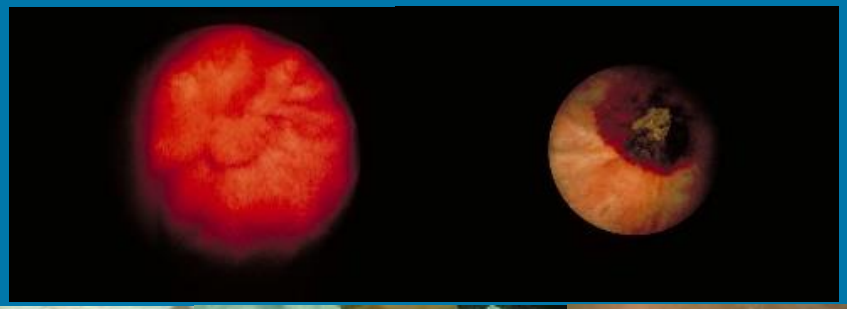


PDT Results of Lung Cancer



NSCGH, TMU & IUHW

Other Cancer Cases by PDT



Foundation of International Photodynamic Association (IPA) April 1986

The 1st Conference Tokyo

International Photodynamic Association (IPA)

The 1st	World Conference of IPA	1986	Hayata	Tokyo
2nd		1988	Carruth	London
3rd		1990	Dougherty	Buffalo
4th		1992	Spinelli	Milan
5th		1994	Cortese	Florida
6th		1996	Kaye	Melbourne
7th		1998	Patrice	Nantes
8th		2001	Lam	Vancouver
9th		2003	Kato	Miyazaki
10th		2005	Jocham	Munich
11th		2007	Zhu	Shanghai
12th		2009	Kessel	Seattle
13th		2011	Kostron	Innsbruck
14th		2013	Ahn	Seoul
15th		2015	Bagnato	Rio de Janeiro
16th		2017	Arnaut	Portugal
17th		2019	Hasan	Boston

Photodynamic Diagnosis (PDD)

Pentax SAFE 3000

PDT effectiveness 1

Lung ca
- Early CR 93.8-78% (1982-2004, Kato, Cortese, Monnier , Furuse)
- Advanced PR 100-55% (1982-1999, Kato, Vincent, Balchum, McCaughan, LoCicero, Sutedja, Wieman, Moghissi)

Esophageal ca
- Early CR 83-84% (1996-1998, Savary, Grosjean, Okushima, Nakamura)
- Advanced PR 100-32% (1995-2000, Lightdale, Moghissi)

Gastric ca
- Early CR 100 -80% (1987-1998, Tajiri, Mimura, McCaughan, Ell)
- Advanced PR 70.5-50% (2000, Patrice, Jim)

Colorectal ca
- Advanced CR 20-14.2% (1986-1990, Herrera-Omelas, Barr)

Cervical ca
- Early CR 96.4- 42.8% (1996-1999, Muroya, Monk, Hillemanns)

PDT effectiveness 2

Bladder ca CR 78.2- 30.4% (1983-1998, Hisazumi, Tsuchiya, Benson, Prout, Nseyo, Kriegmair, Uchibayashi)
Prostata ca CR 100% (1990, Windal)
Skin ca (BCC) CR 90.9%-88% (1978-1999, Dougherty, Kennedy, Wilson, Fijan, Kubler)
Skin meta of breast ca CR+ PR 98.2-7.1% (1987-1998, Dougherty, Shuh, Sperduto, Khan)
Brain tumor CR 26.7% (1990- , Muller, Kostron, Kaneko)
Oral cavity sq ca CR 91-87% (1996-2000, Fan, Hopper)

Pre-malignant diseases
Barrett's esophagus CR 80% (1999, Overholt)
Bowen's disease CR 100% (1992-1996, Jone, Caimduff, Morton)
Cervical dysplasia CR 100% (1996, Muroya)

Depth of invasion

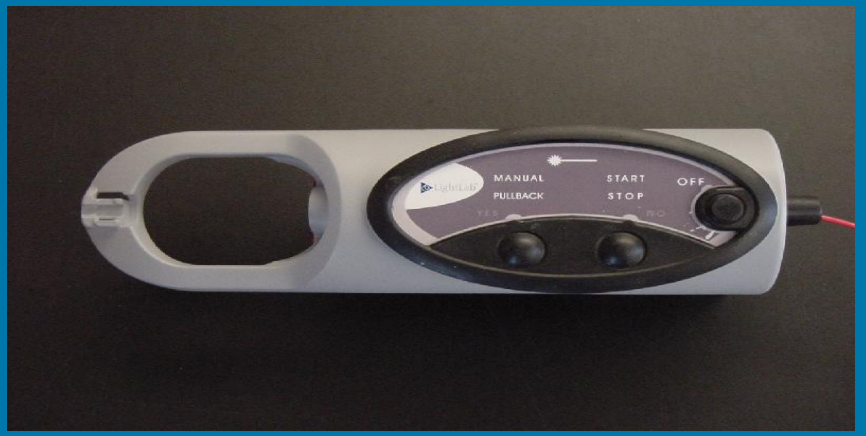
Optical Coherent Tomography (OCT) 1998

Optical Coherent Tomograohy

2002

Pentax SOCT-1000

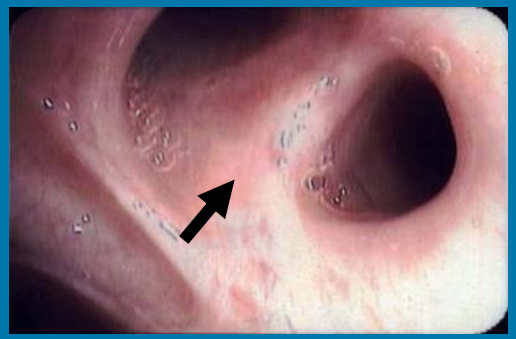
OCT Imaging Platform



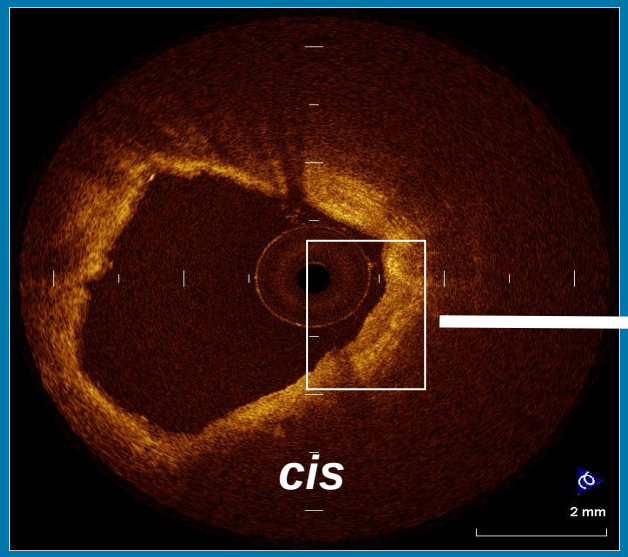
OCT Probe

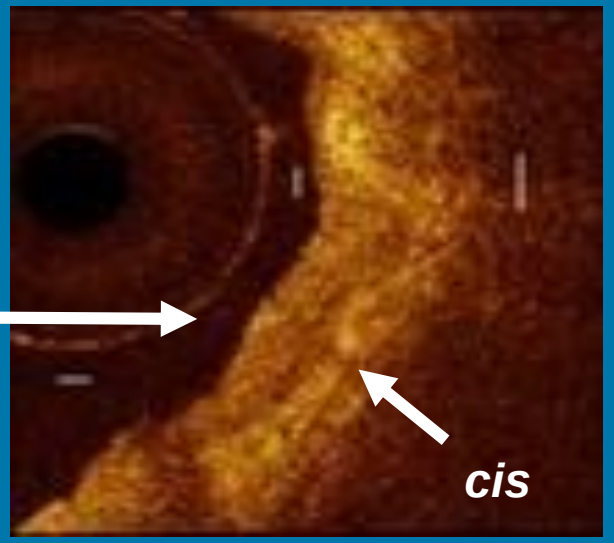
OCT Findings of Cis of Bronchus

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



SAFE 3000 AF

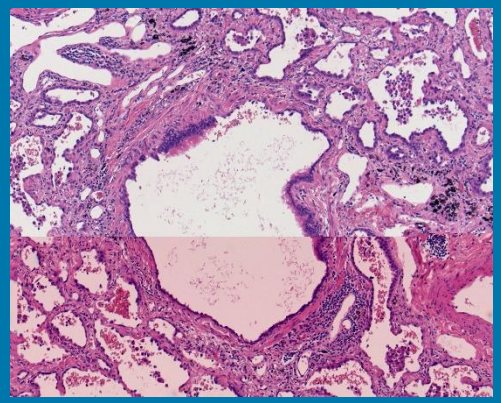


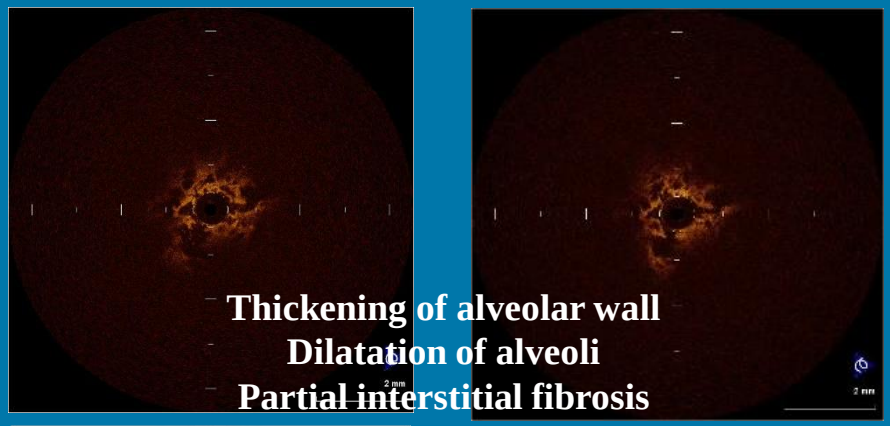


Pentax SOCT-2000

Optical Coherent Tomography (OCT)

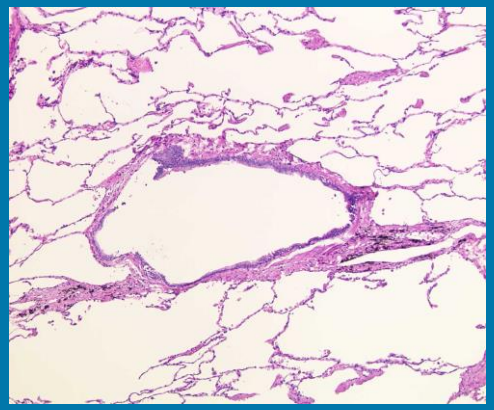
BAC

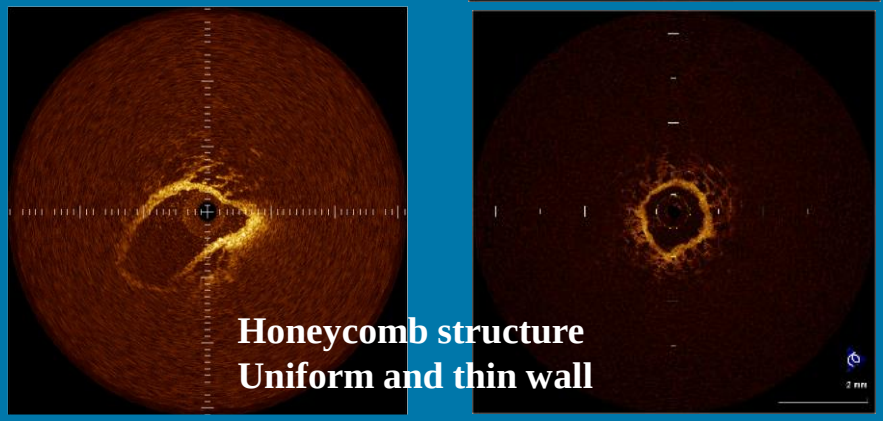




Thickening of alveolar wall
Dilatation of alveoli
Partial interstitial fibrosis

Normal Bronchiolus, alveoli





Honeycomb structure
Uniform and thin wall

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	

ESCLC treated with PDT

(ESCLC: Early Stage Central Type Lung Cancer)

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)

New Strategy for ESPLC

(ESPLC: Early Stage Peripheral Type Lung Cancer)

Increase of adenocarcinoma
Increase of multiple primary lung cancers

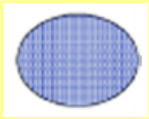
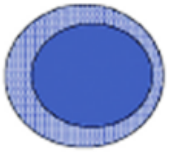
Carcinogenetic process of adenocarcinoma
Definitive diagnosis of GGO shadows

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

GGO: ground glass opacity,
AAH: Atypical alveolar cell hyperplasia, AIS: Adenocarcinoma in situ
MIA: Minimal invasive adenocarcinoma, LPA: Lepidic predominant adenocarcinoma

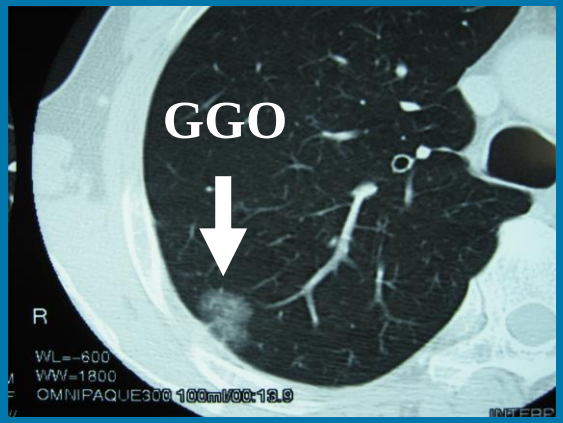
ESPLC

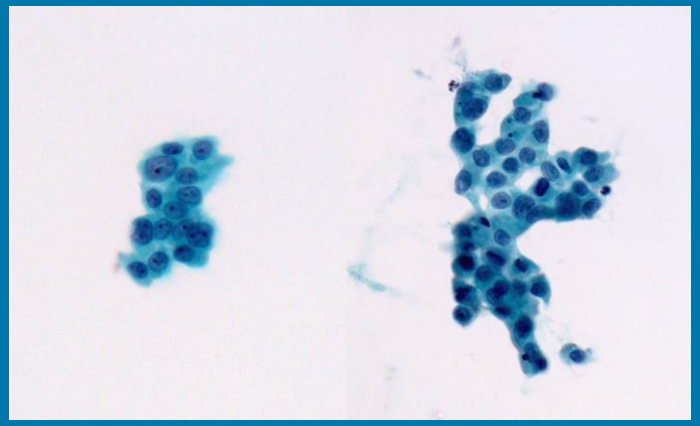
Early Stage Peripheral Type Lung Cancer

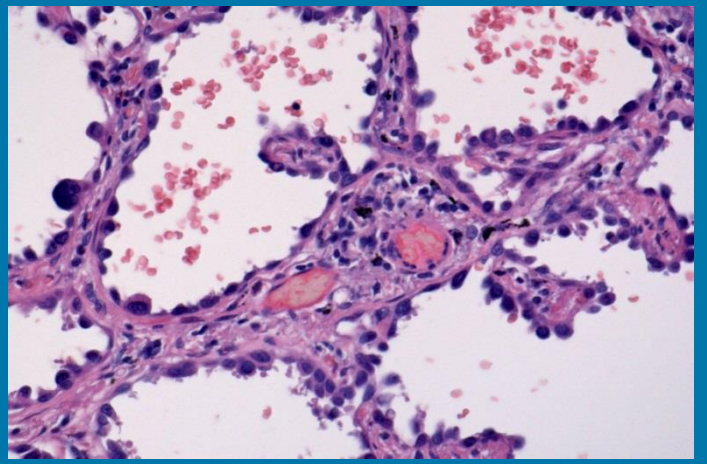
cT	CT image on HRCT						
	Solid part	0cm	0cm	≤0.5cm†	0.6–1.0cm†	1.1–2.0cm†	2.1–3.0cm†
	Total tumor size including GG	≤0.5cm	0.6–3.0cm‡‡	≤3.0cm‡‡	0.6–3.0cm‖	1.1–3.0cm‖	2.1–3.0cm‖
	Pathologic Differential Diagnosis	AAH‡ , AIS , MIA	AIS , MIA , LPA	MIA , LPA , AIS	LPA , Invasive AD , MIA	LPA , Invasive , 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)

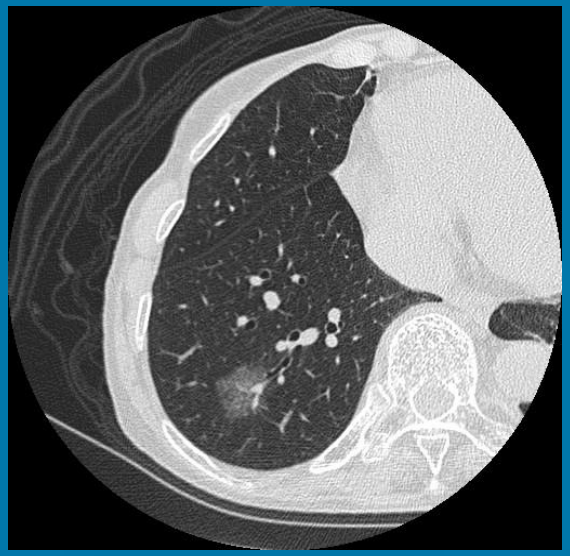
pT1N0M0
StageIA

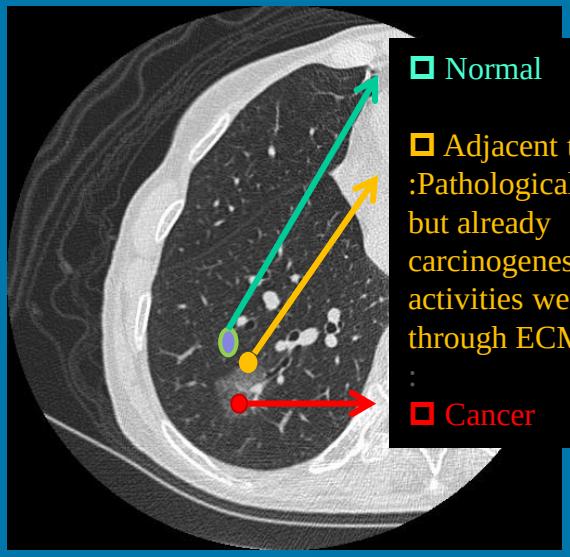




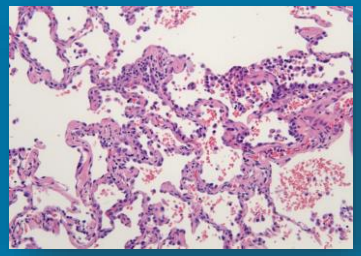


MS-based Proteomics of ESPLC

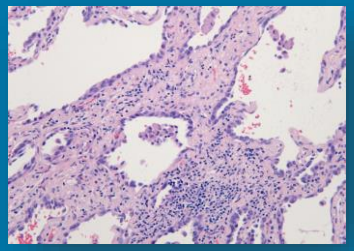




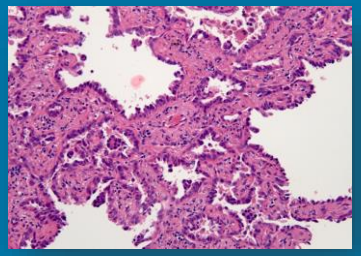
- Normal
- Adjacent to tumor :Pathologically normal but already carcinogenesis-related activities were initiated through ECM receptors.
- Cancer



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

Protein Expression in LPA and MIA

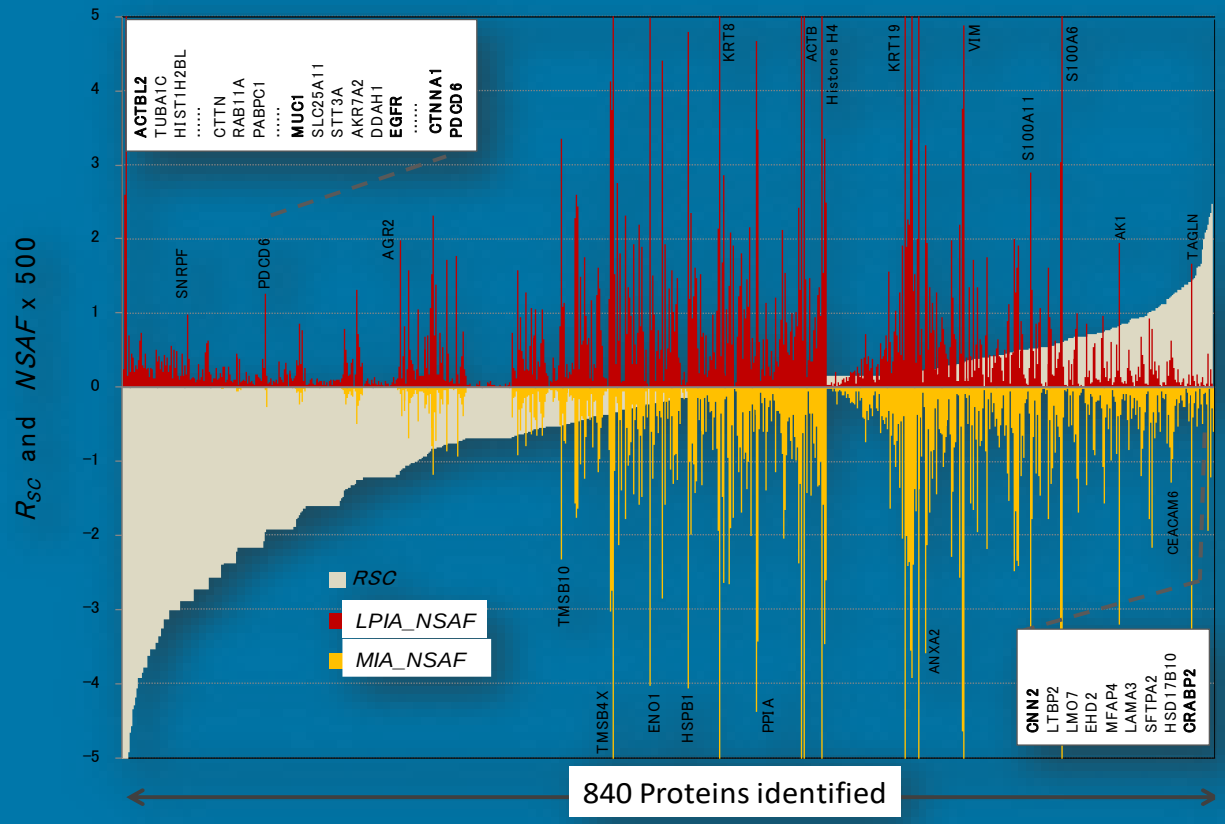
LPA vs MIA

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

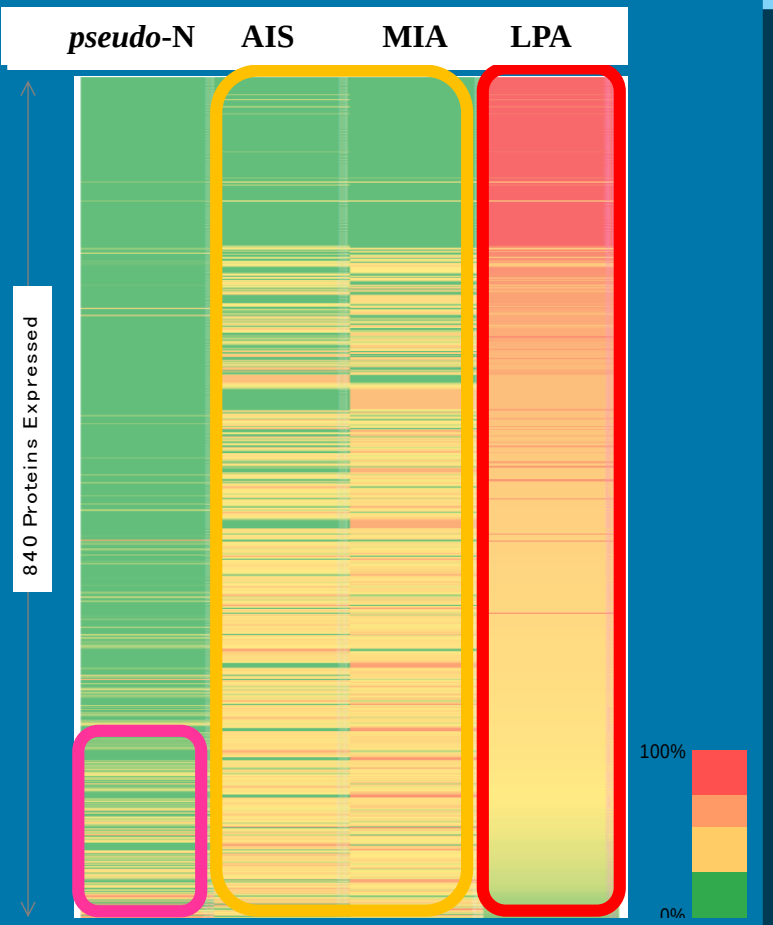
Protein Expression: Normal, AIS, MIA and LPA

GGO Lung Cancer: Expression variations of 840 proteins identified

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

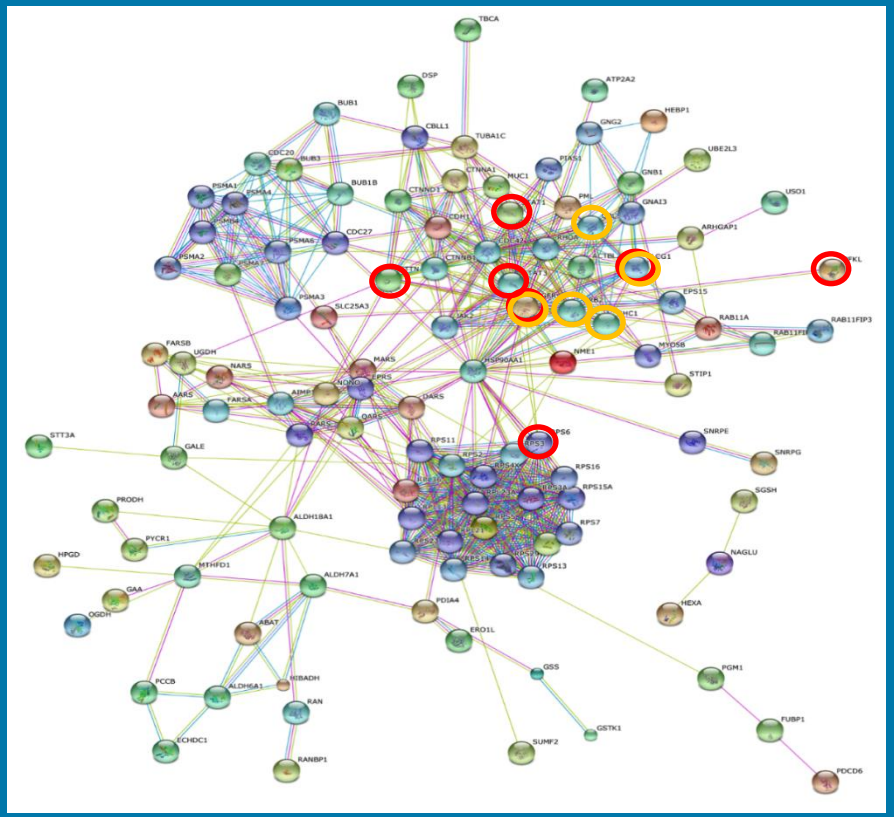
AIS: Adenocarcinoma in situ
MIA: Minimally invasive adenocarcinoma (MIA)
LPA: Lepidic predominant adenocarcinoma

➢ ***1. There seems to be a similarity between AIS and MIA but***
➢ ***2. LPA demonstrated a quite different protein expression pattern from AIS and MIA.***



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

PPI Analysis of LPA



STRING ver. 10 PPI Networks of LPA

PPI: protein and protein interaction

- ***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

Definitie diagnosis

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.

↓

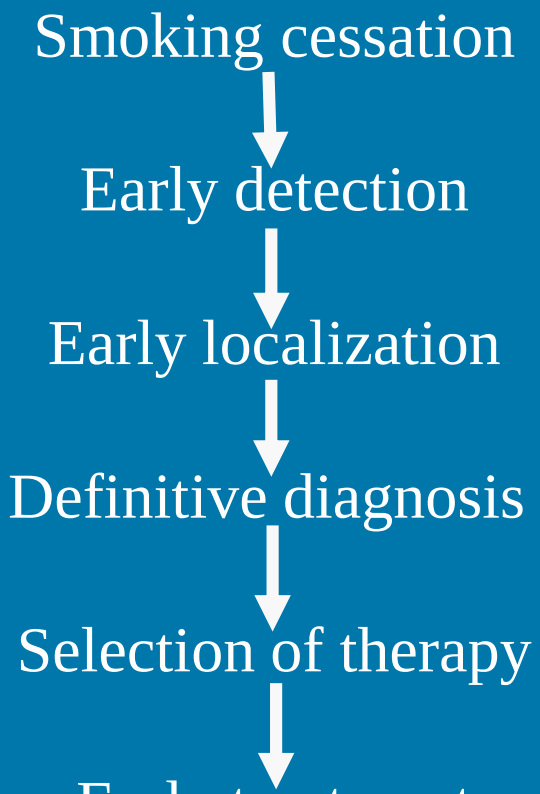
Non-invasive treatments, PDT for early stage lung cancer.

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



KPA Meeting 20170902

감사합니다

Oh! dangerous party

NSCGH, TMU & IUHW