遊離癌細胞と末梢血循環癌細胞：肺癌外科医の立場から

奈良県立医科大学附属病院　呼吸器外科

澤端　章好

目次

- □肺癌手術の実際
- □肺癌手術症例における遊離腫瘍細胞(ITC)の含意
- □肺癌手術症例における末梢血循環腫瘍細胞(CTC)の含意
  - CTCとは?
  - CTCの肺癌手術症例における特徴
  - CTC抽出法
  - CTCをターゲットとしたLiquid biopsy

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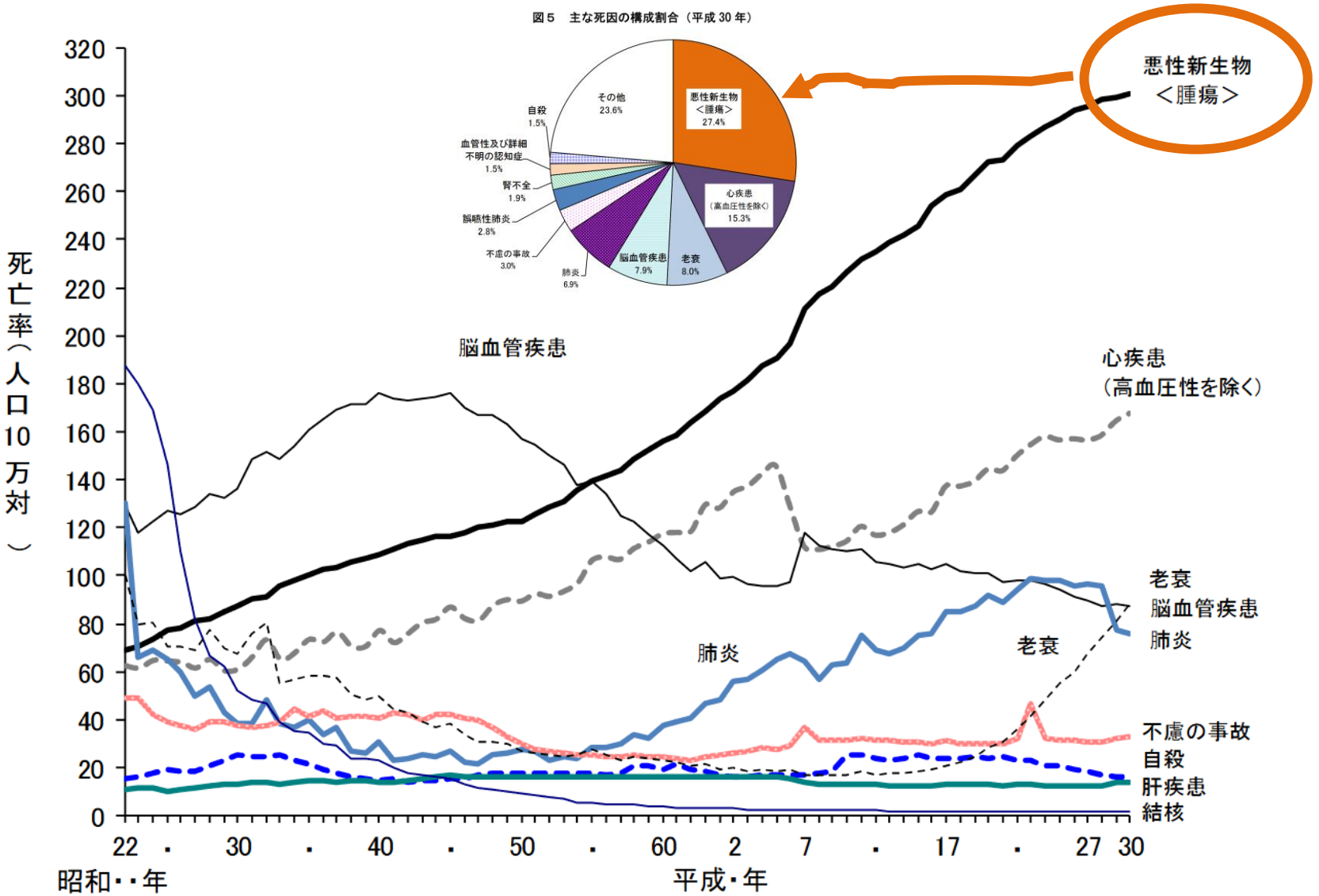
主な死因別にみた死亡率（人口10 万対）の年次推移

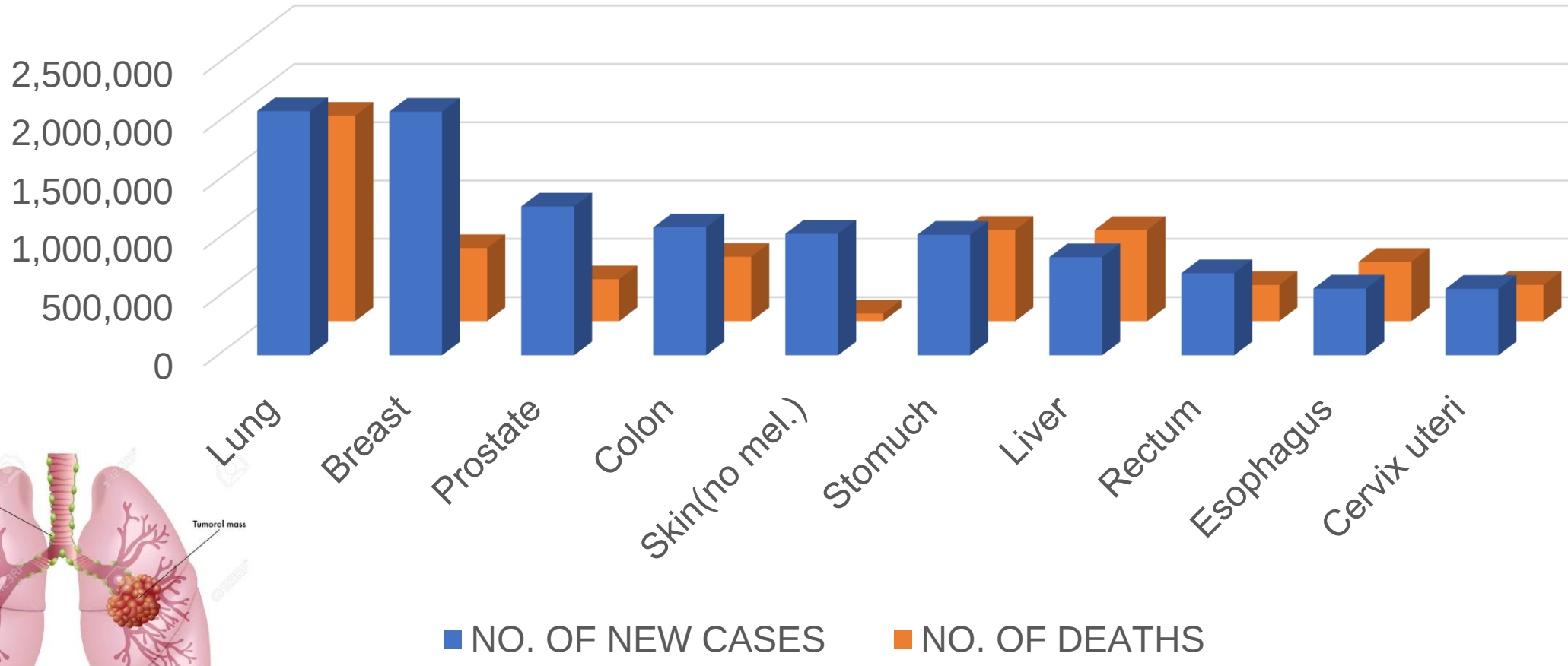


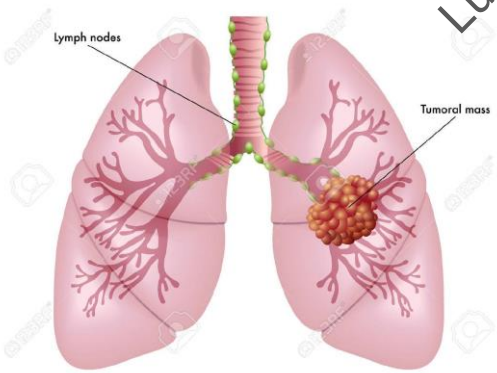
2019年の死亡数

	1位	2位
男性	肺	胃
女性	大腸	肺
男女計	肺	大腸

https://womanslabo.com/wp-content/uploads/2019/12/0919be5f4b98b3af154dccf5bc3621a3.png
https://womanslabo.com/wp-content/uploads/2019/12/e54aaf1a67ed3e19ea9a63f78211cdf8.png

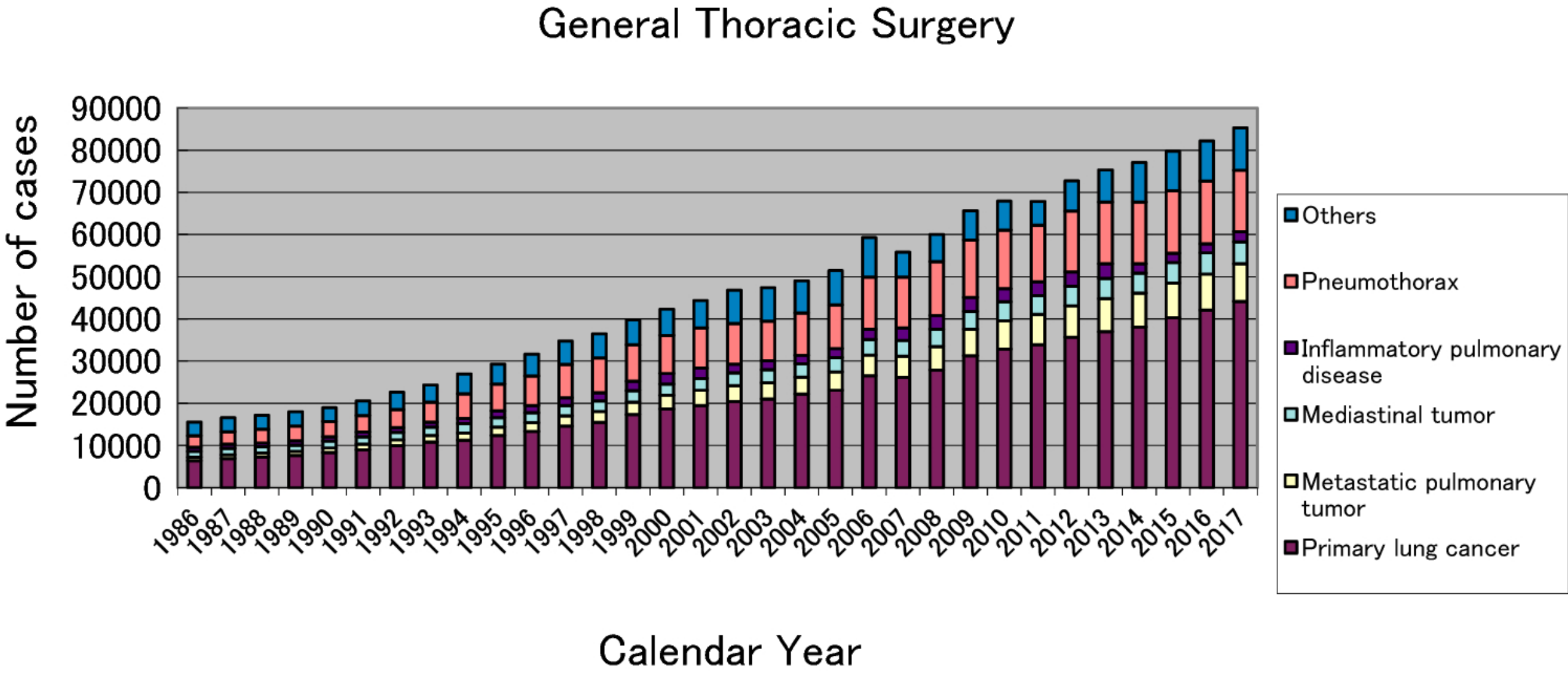
肺癌：2018年のがんの新しい症例と死亡の主な原因





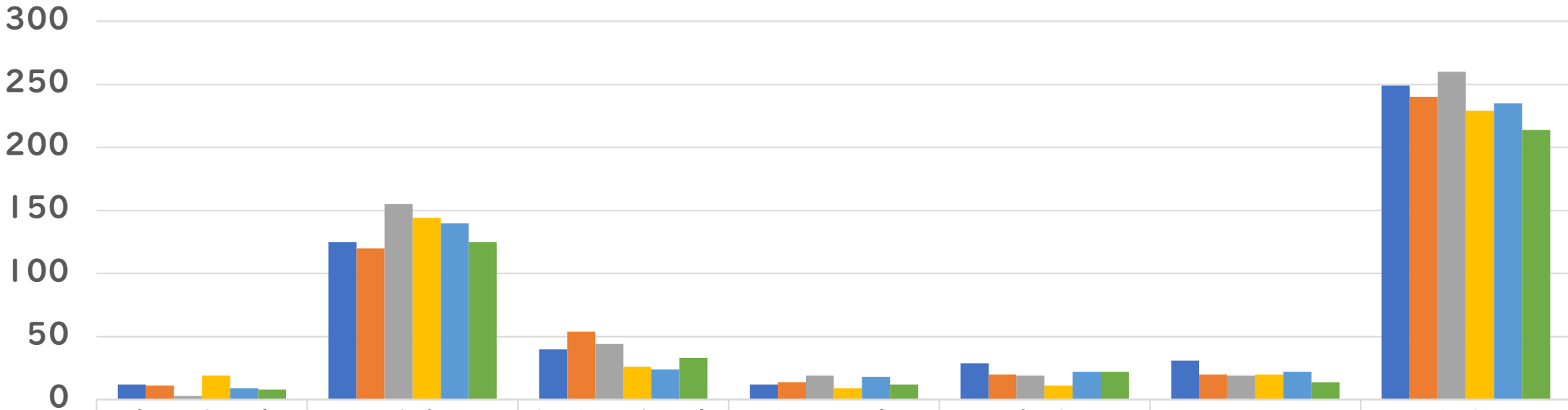
Bray F, et al. CA Cancer J Clin. 2018;68:394-424.

本邦の呼吸器外科手術; 2017 肺癌、45,000件 -



Thoracic and cardiovascular surgeries in Japan during 2017

奈良県立医科大学　呼吸医外科　手術件数



	良性肺腫瘍	肺癌	転移性肺腫瘍	縦隔腫瘍	気胸	その他	総数
2015	12	125	40	12	29	31	249
2016	11	120	54	14	20	20	240
2017	3	155	44	19	19	19	260
2018	19	144	26	9	11	20	229
2019	9	140	24	18	22	22	235
2020	8	125	33	12	22	14	214

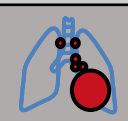
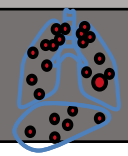
肺癌の治療戦略

- 積極的: 時には集学的
  - ✓全身
    - ✓殺細胞性薬剤, 分子標的薬,免疫チェックポイント阻害剤, 他
  - ✓局所
    - ✓手術, 放射線, その他

- 緩和的

https://d1f5hsy4d47upe.cloudfront.net/4f/4f390c78dfe07c31a636dd95fc85cc8a_t.jpeg

手術:完全切除の可能性に基づいて行われる

Stage IA	T1	N0	M0	
Stage IB	T2	N0	M0	
Stage IIA	T1	N1	M0	
Stage IIB	T2, T3	N1, N0	M0	
Stage IIIA	T1–3, T3	N2, N1	M0	
Stage IIIB	T4, any T	Any N, N3	M0	
Stage IV	Any T	Any N	M1	

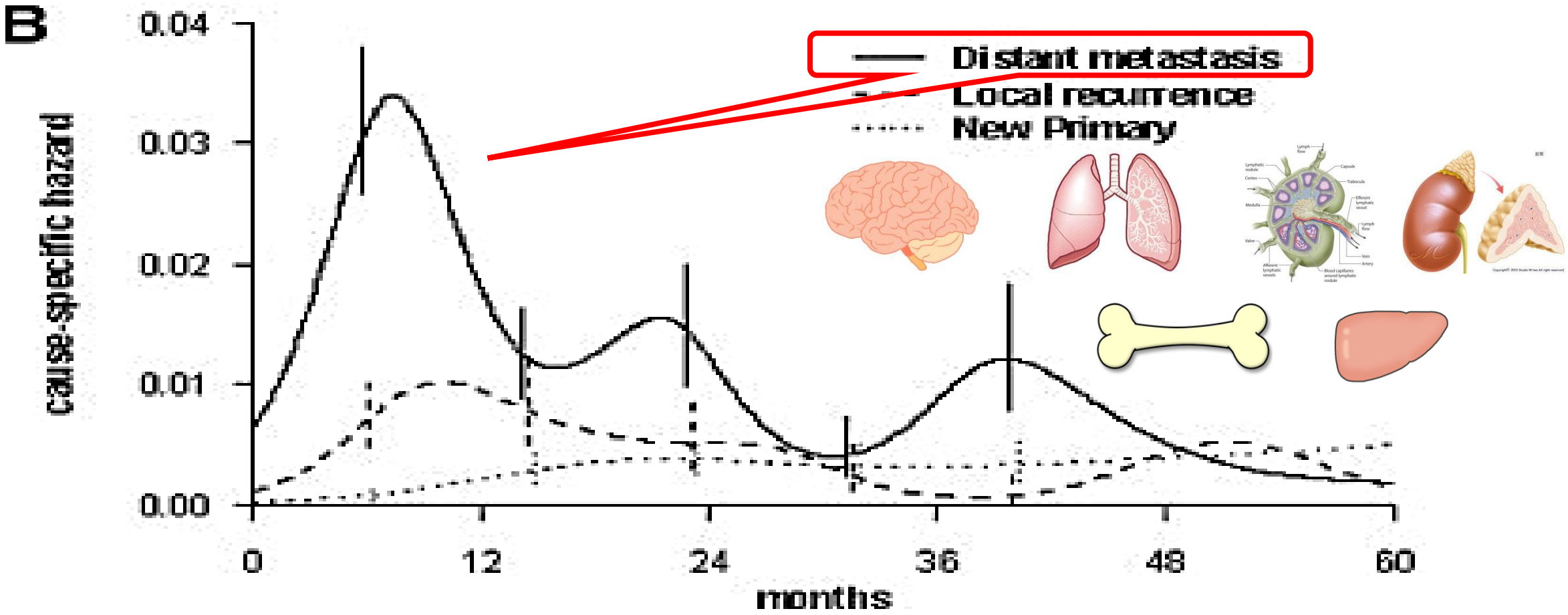
積極的適応
(完全切除の可能性あり)

切除可能

症例に応じて

T = primary tumor; N = nodal involvement; M = distant metastasis.

肺癌術後の死亡原因：
転移が一番多くピーク時がある



Demichel et al. J Thorac Oncol. 2012;7: 723–730

なぜ手術後に再発が起こるのですか?

∴遺残腫瘍細胞

- 微小転移：Micro-metastasis (<2mm)
- 遊離癌細胞：Isolated tumor cell (< 200μm)
- 末梢血循環癌細胞：Circulating tumor cell (CTC)
  - ●：静止
  - ●：移動/静止

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https://jp.freepik.com/premium-vector/samurai-sword_6696687.htm#page=1&query=samurai&position=35

骨髄およびリンパ節のIHCによるITC

p-NOMO

Organ	BM	Regional LN
Renal	～20%	
Brest	～30%	～15%
Gastric	～30%	～90%
Colorectal	～30%	～50%
Prostate	～35%	～45%
NSCLC	～50%	～15%
Pancreatic	～50%	～75%
Esophareal	～40%	～50％、～25%

Hermanek et al. Classification of isolated tumor cells and micrometastasis. Cancer 1999

骨髄

肺癌手術症例における骨髄ITC陽性率と予後

最新の前向き観察研究では　無再発生存期間、全生存期間で有意差なし

Author（yr）	n		陽性率(%)	3-YSR(%)		p-value
				P	N	
Pantel(’96)1)	66		18	25	70	<0.01
Ohgami(’97)2)	39		9	45	78	<0.01
Passilic(‘99)3)	150		12	36	77	<0.01
Poncelet(’01)4)	99		22	70	55	N.S.
Osaki(’02)5)	115		28	69	85	N.S
Yasumoto(’03)6)	351		32	72	88	N.S
Rufutto('09)7)	57	FCM Aneu.	11	27	56	<0.01
Ruche('11)8) $	821	cluster = P	8	64	65	N.S.

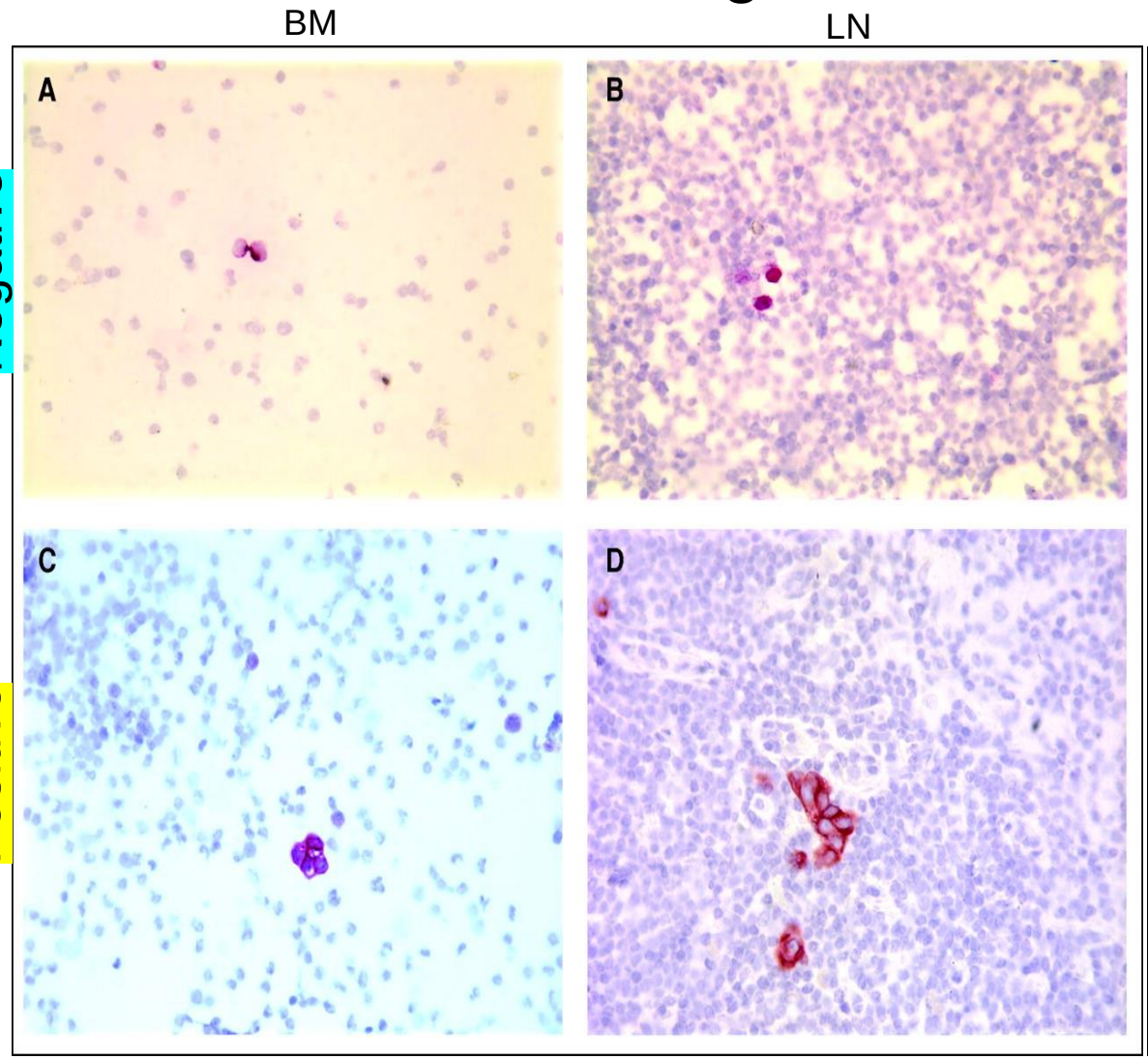
IHC (cytokeratin)　FACS

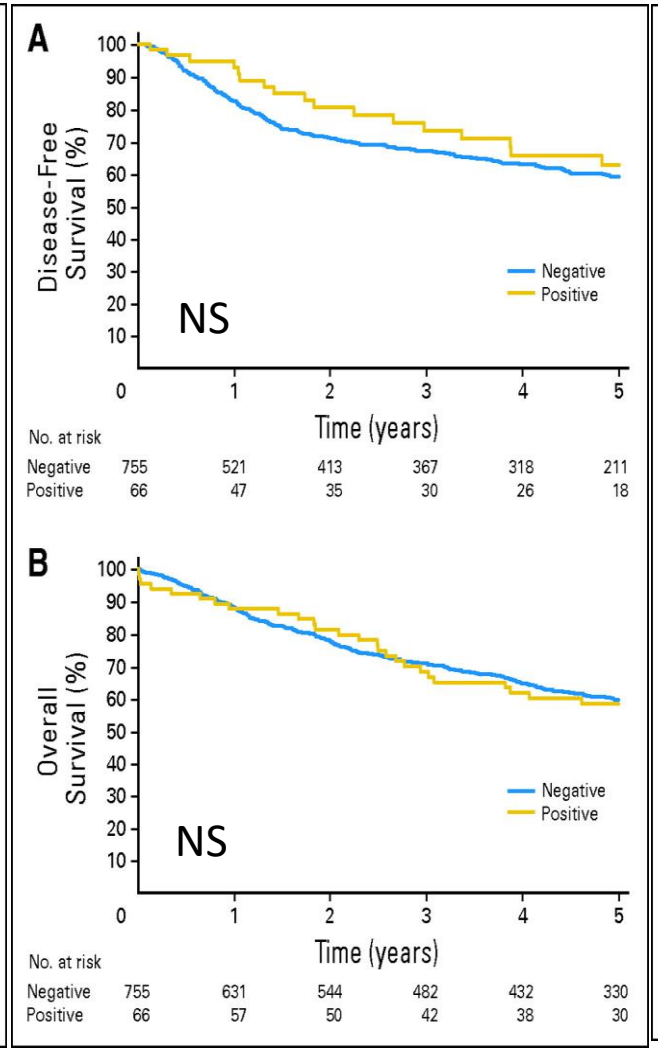
$, 前向き観察研究　ACOSOG Z0040 Trial

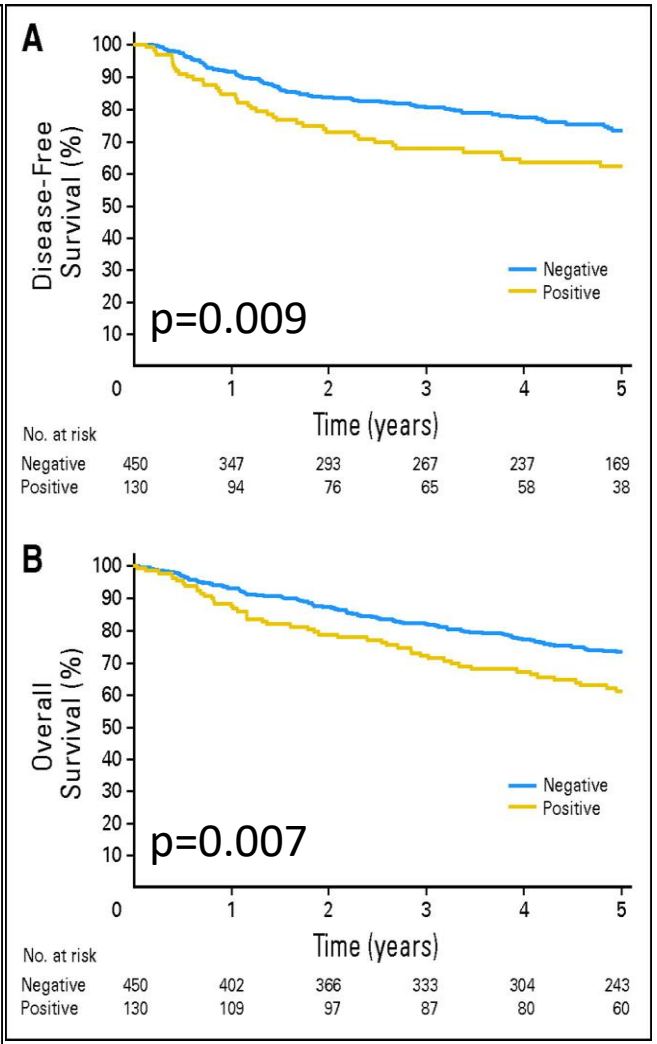
1) Lancet 1996, 2) ATS 1997, 3) ATS 1999, 4) EJCTS 2001 5) JCO 2002,6) ATS 2003 7)EJCTS 2009 8) JCO 2011

リンパ節

Occult Metastases in Lymph Nodes Predict Survival in Resectable Non–Small-Cell Lung Cancer: Report of the ACOSOG Z0040 Trial

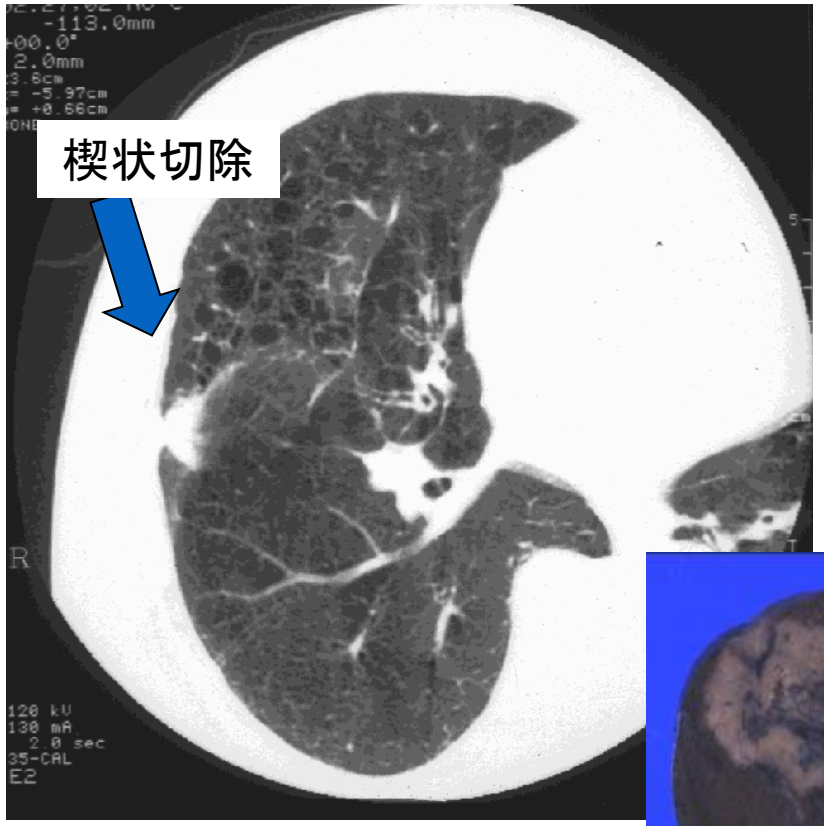




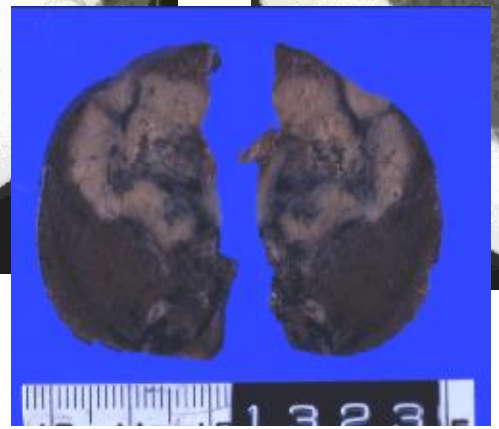


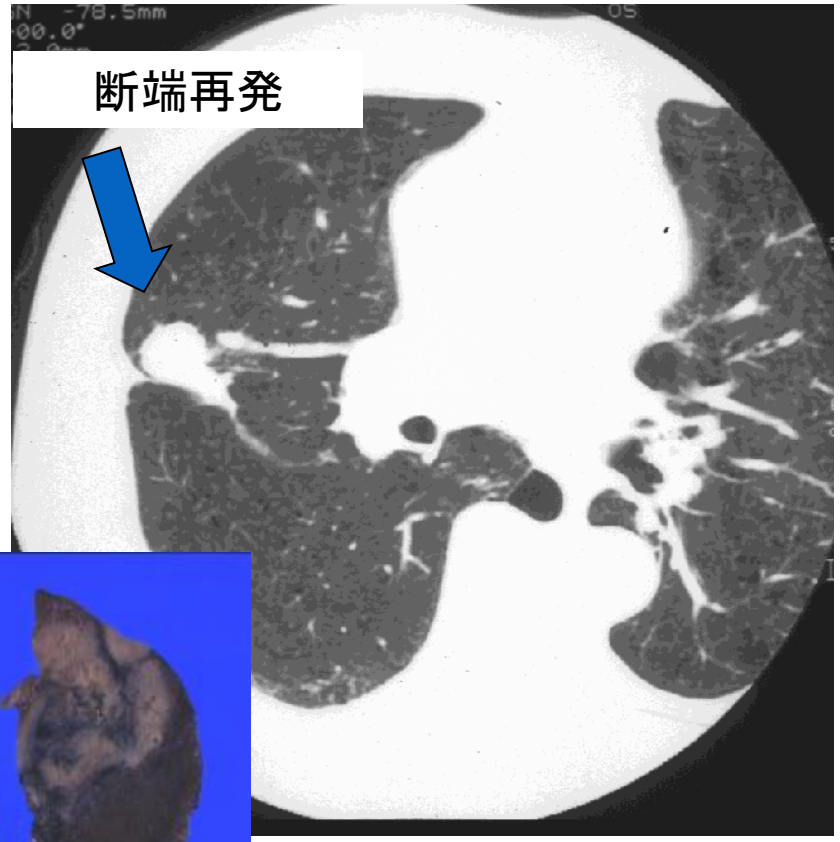
Rusch V W et al. JCO 2011;29:4313-4319

楔状切除後の断端再発　遺残遊離癌細胞！



Dec, 1996





Aug, 1997

断端：組織診（－）、細胞診（＋）

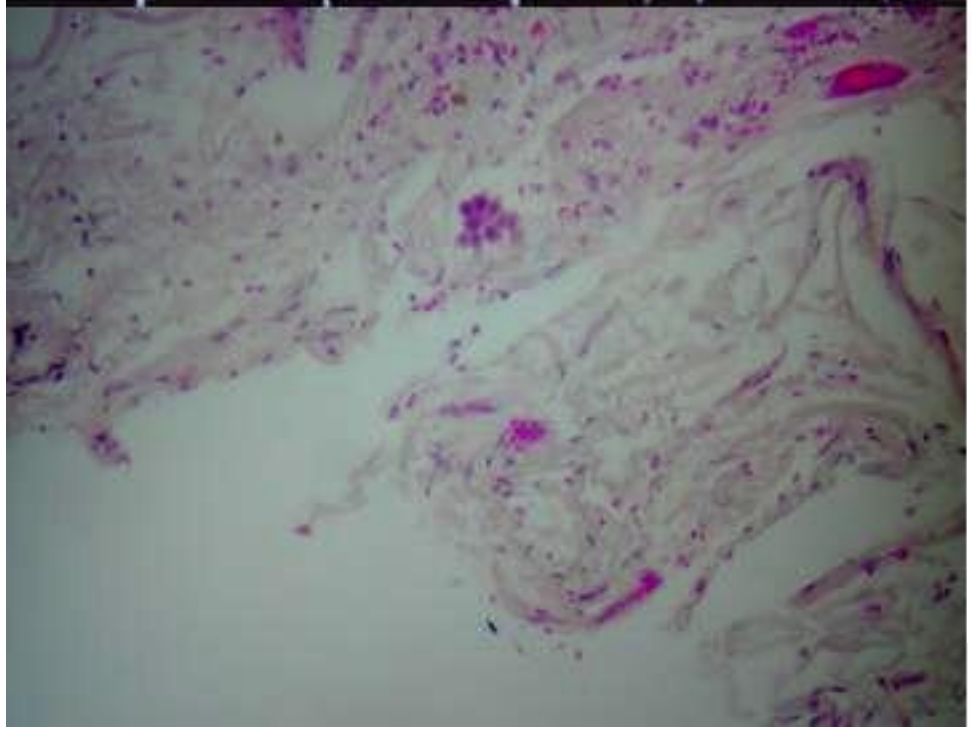
断端細胞診：再発の予測因子
組織学的陰性でも陽性のことがある

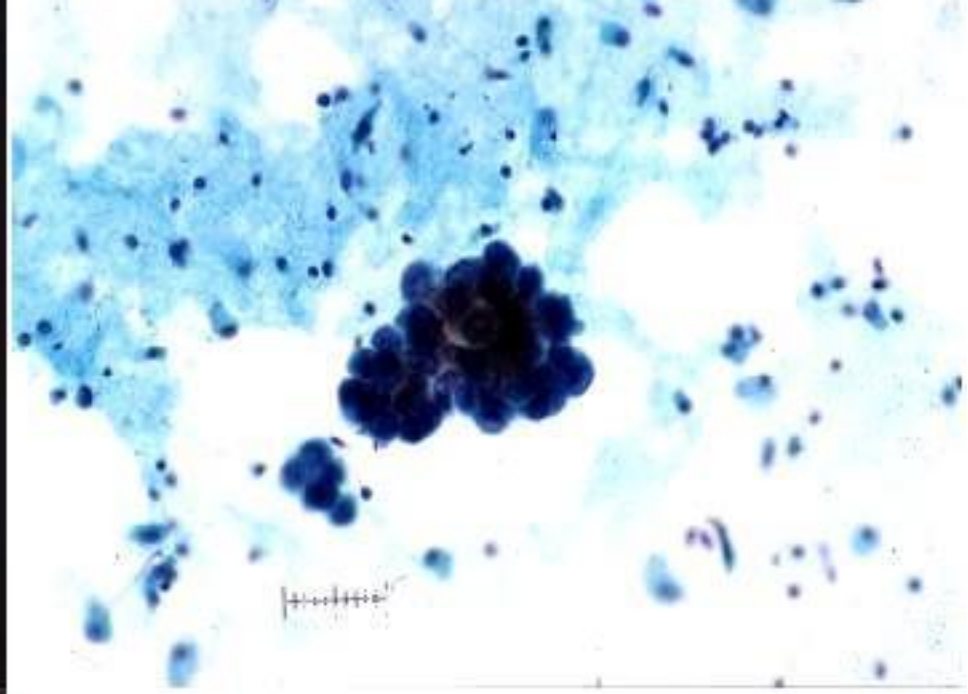
Table 2. Cases of Margin Relapse

No.	Age (yr)	Sex	Lobe	Tumor Histology	Margin[a]	Diameter (mm)	Distance[b] (mm)	Duration[c] (mos)	Treatment for Relapse	Survival (mos)	Other Lesions at Death
1	76	M	RU	SQ	N/P	25	15	8	Reop	D 26	Bilateral lung
2	76	F	RU	AD	N/P	20	10	11	No[d]	D 24	Bilateral lung Pleura
3	70	M	RL	AD	P/P	20	1	4	Rtx	D 11	Brain
4	70	M	RL	AD	N/P	20	10	12	Pleurodesis[e]	D 15	Pleura

Sawabata N Ann Thorac Surg 2002;74:1953–1957

Case 2





断端細胞診悪性陽性の１例

- 肉眼的には腫瘍の連続はなく断端陰性であるが、細胞診では悪性陽性であった
- 腫瘍の連続性はないが、肺実質に腫瘍細胞を認める

Sawabata N ATS 2002;74:1953–1957

Surgical margin cytology

Run-across method

Adapted from Sawabata N et al J Thorac Cardiovasc Surg. 1999;117:618-9.

Lavage & Current method

Adapted from Sawabata N. Gen Thorac Cardiovasc Surg. 2013;61:9-16

断端細胞診陽性の予測因子：多施設前向き研究

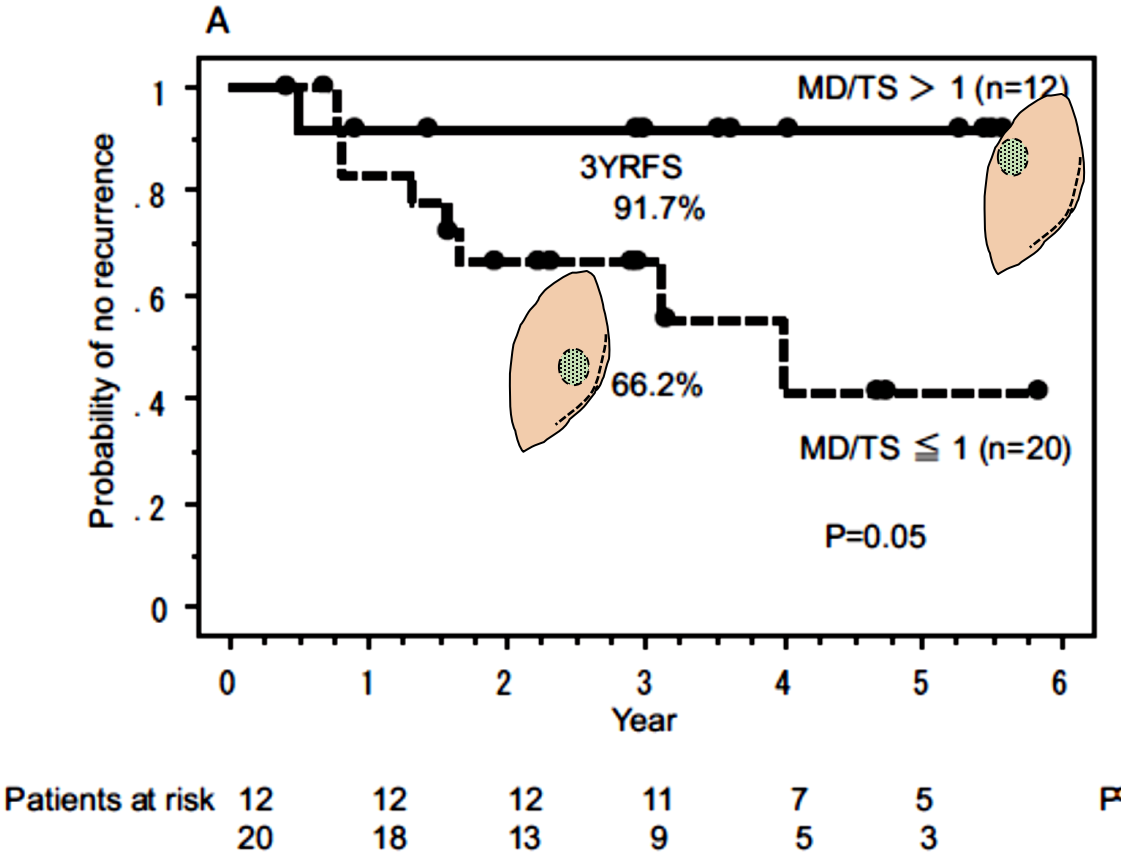
		Univariable			Multivariable		
Variable	n	RR	95%CI	*p*-value	RR	95%CI	*p*-value
腫瘍サイズ	118	1.063	1.005-1.124	0.03	1.096	1.002-1.130	0.006
腫瘍断端距離	118	0.840	0.772-0.915	<0.0001	0.853	0.798-0.908	0.003
Location							
Easy	29	1.000			1.000		
Difficult	89	0.149	0.058-0.380	<0.001	0.802	0.187–1.320	0.754
Stapler							
Type A	85	1.000			1.000		
Type B	18	2.542	0.900-7.175	0.078	2.153	0.601–7.717	0.239
Type C	15	16.520	3.465-78.77	0.0004	7.972	1.257–50.54	0.027
Thoracotomy							
Open	72	1.000					
VATS	46	0.466	0.211-1.028	0.058			

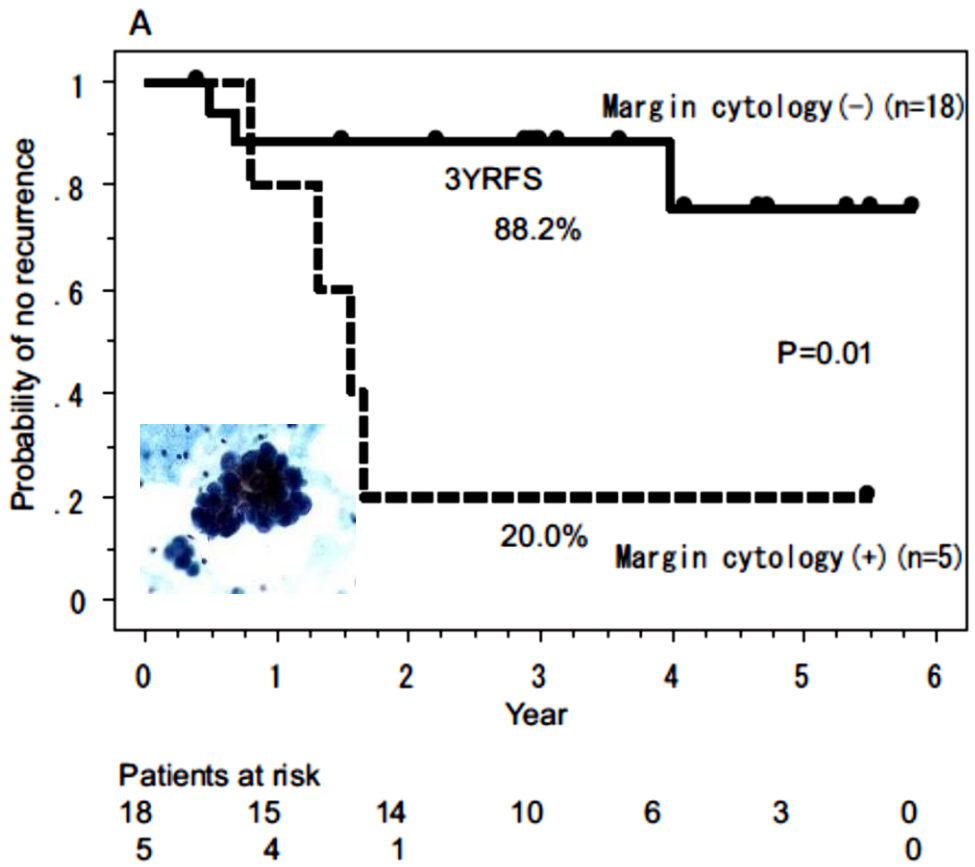
再発予測因子

Sawabata N et al Thoracic Surgery Study Group of Osaka University Ann Thorac Surg 2004;77:415-20

c-Stage I非小細胞肺癌に対する最適な縮小肺切除術 ―高リスク症例に対する断端距離/腫瘍サイズおよび断端細胞診の意義

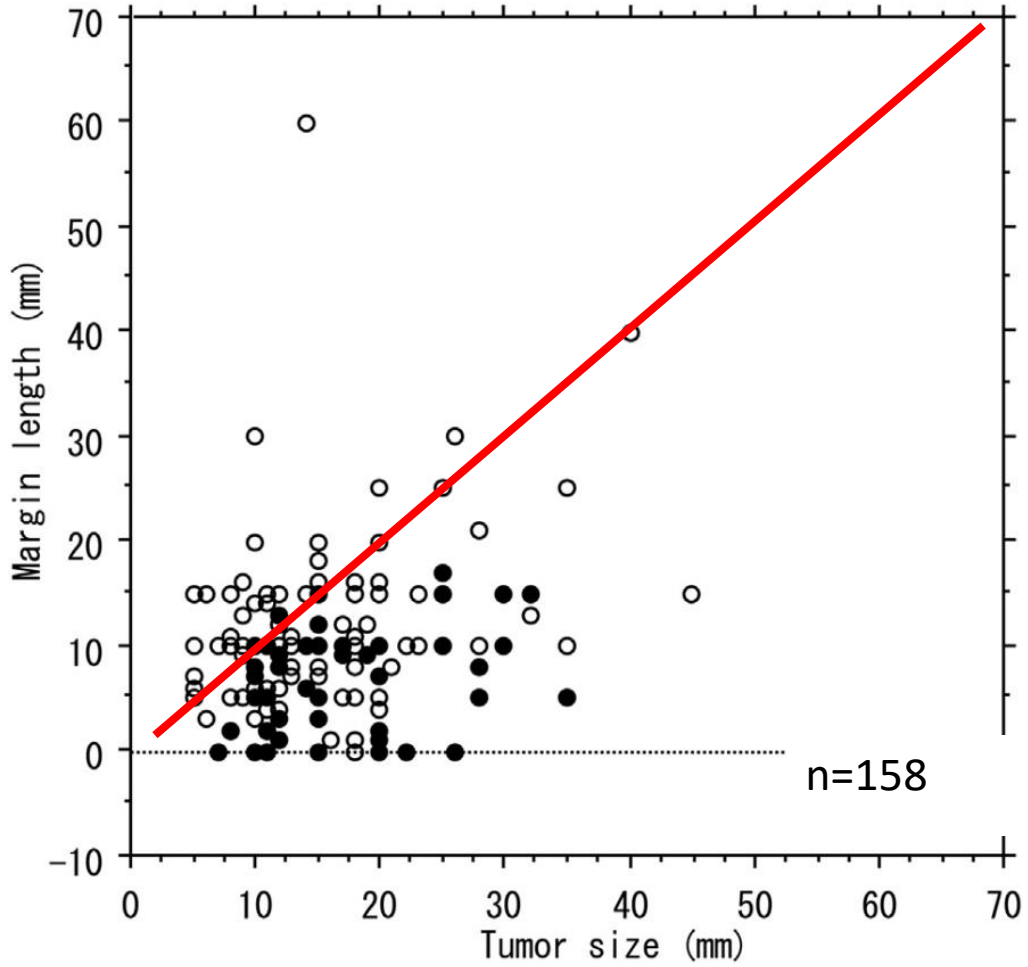
(Supplementary analysis of KLSG0801; multicenter prospective study)



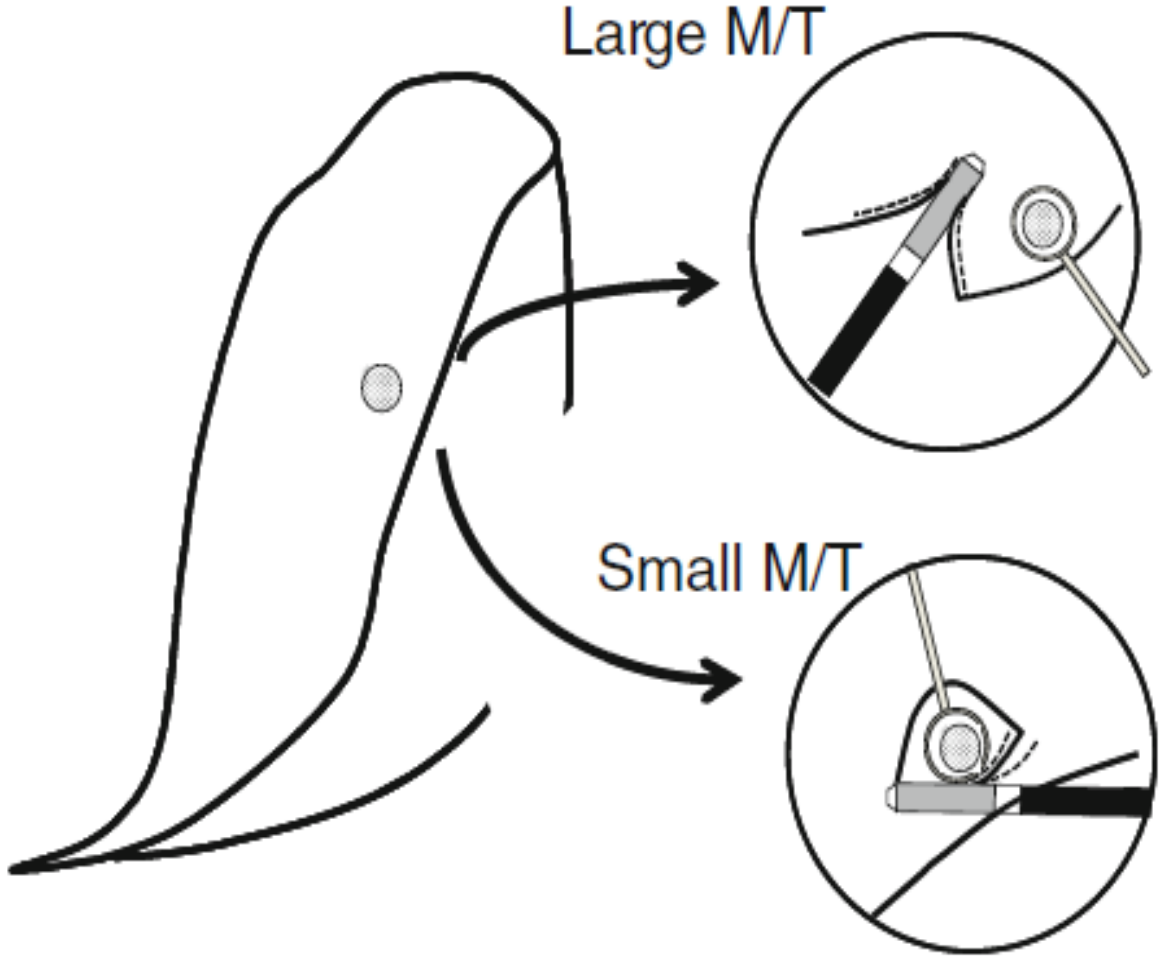


Takahashi N et al. General Thoracic and Cardiovascular Surgery (2019) 67:690

縮小肺切除断端悪性細胞：切除方法を工夫することで回避可能？



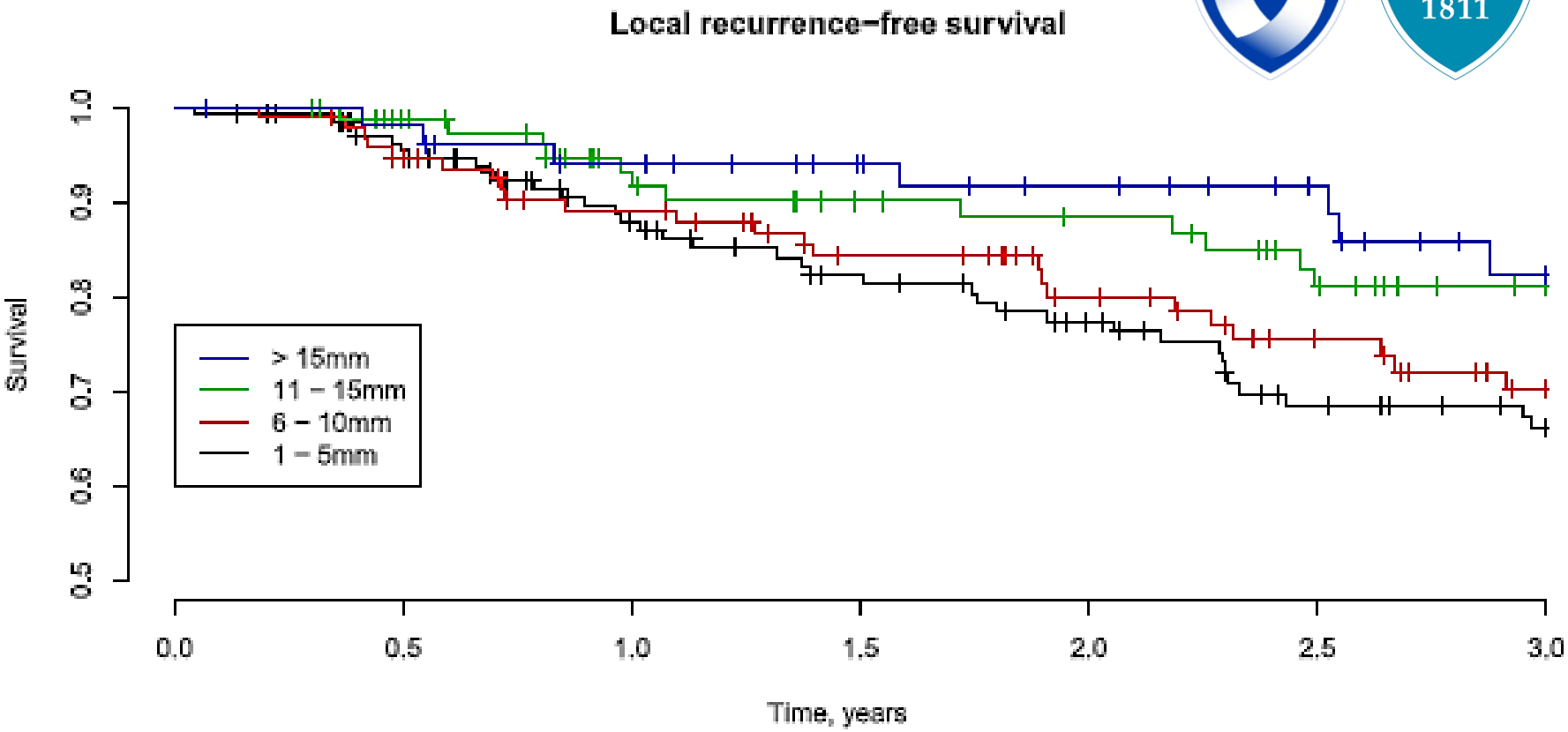
Sawabata N J Thorac Cardiovasc Surg. 2014



Sawabata N et al GTCS 2013 61; 9-16

Relationship between margin distance and local recurrence among patients undergoing wedge resection for small (≤2 cm) non–small cell lung cancer

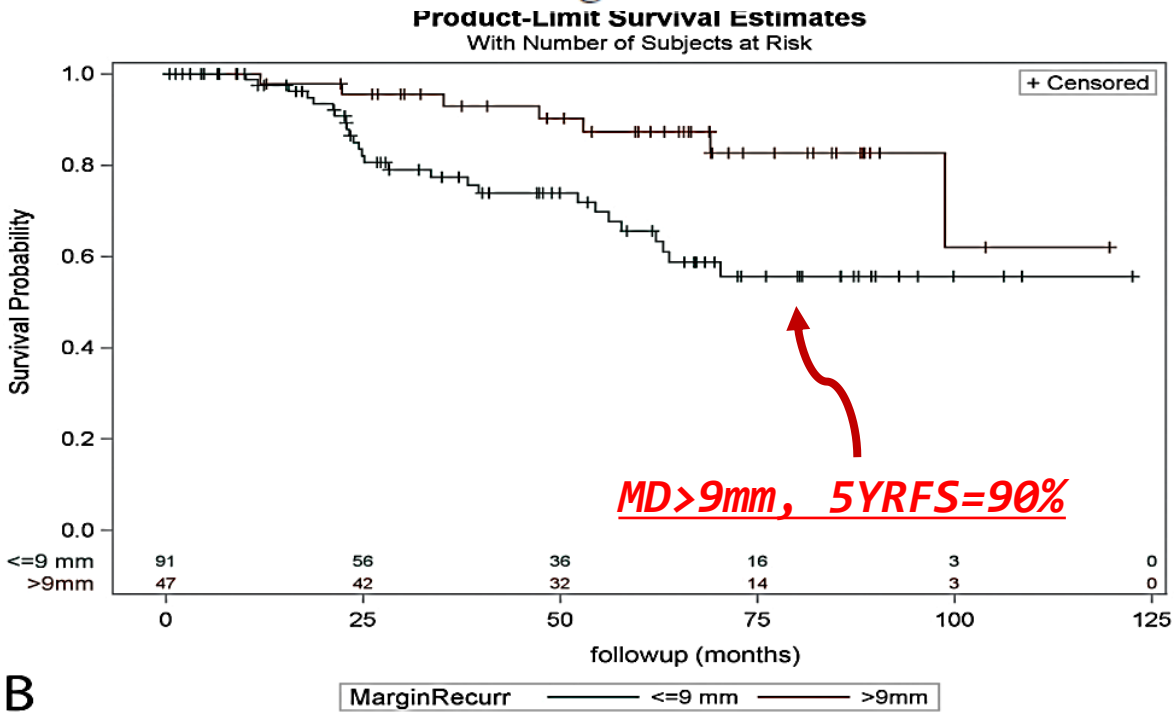
Kamran Mohiuddin, MD,[a] Sebastien Haneuse, PhD,[b] Tamar Sofer, PhD,[b] Ritu Gill, MD, MPH,[c] Michael T. Jaklitsch, MD,[a] Yolonda L. Colson, MD, PhD,[a] Jon Wee, MD,[a] Raphael Bueno, MD,[a] Steven J. Mentzer, MD,[a] David J. Sugarbaker, MD,[a] and Scott J. Swanson, MD[a]



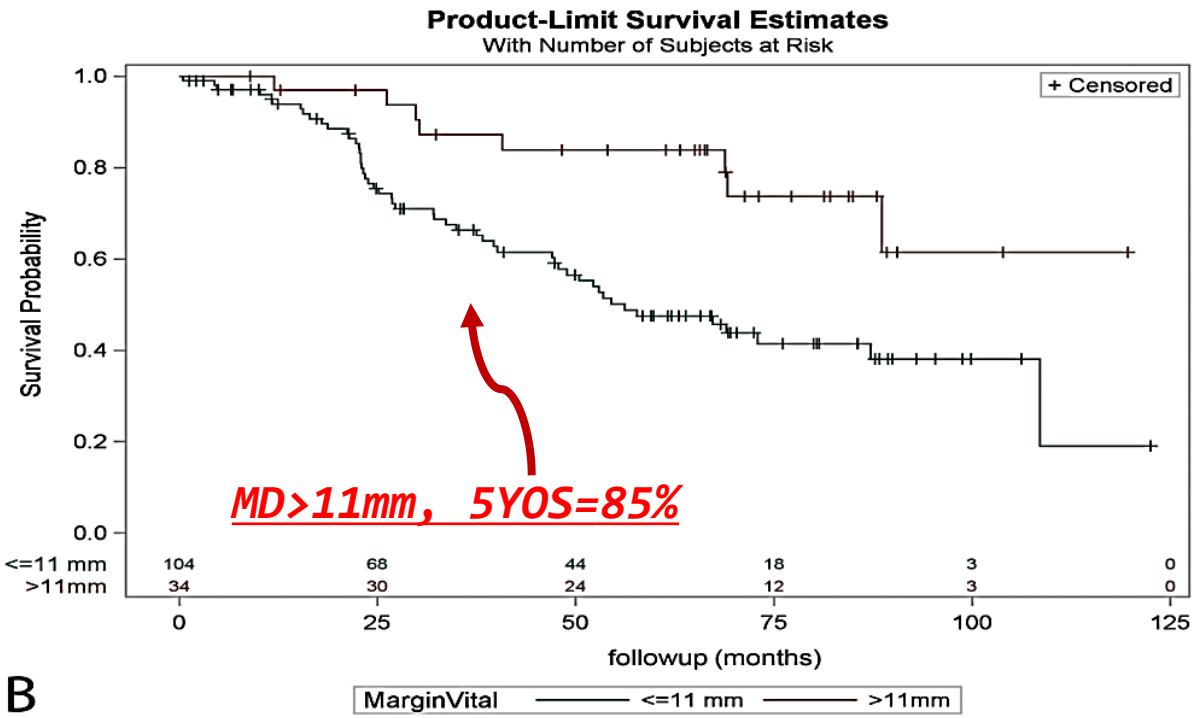
Mohiuddin k et al. J Thorac Cardiovasc Surg 2014;147:1169-77

The Impact of Margins on Outcomes After Wedge Resection for Stage I Non-Small Cell Lung Cancer

Andrea S. Wolf, MD, MPH, Scott J. Swanson, MD, Rowena Yip, MPH, Bian Liu, PhD, Elizabeth S. Tarras, MST, David F. Yankelevitz, MD, Claudia I. Henschke, PhD, MD, Emanuela Taioli, MD, PhD, and Raja M. Flores, MD, for the I-ELCAP Investigators



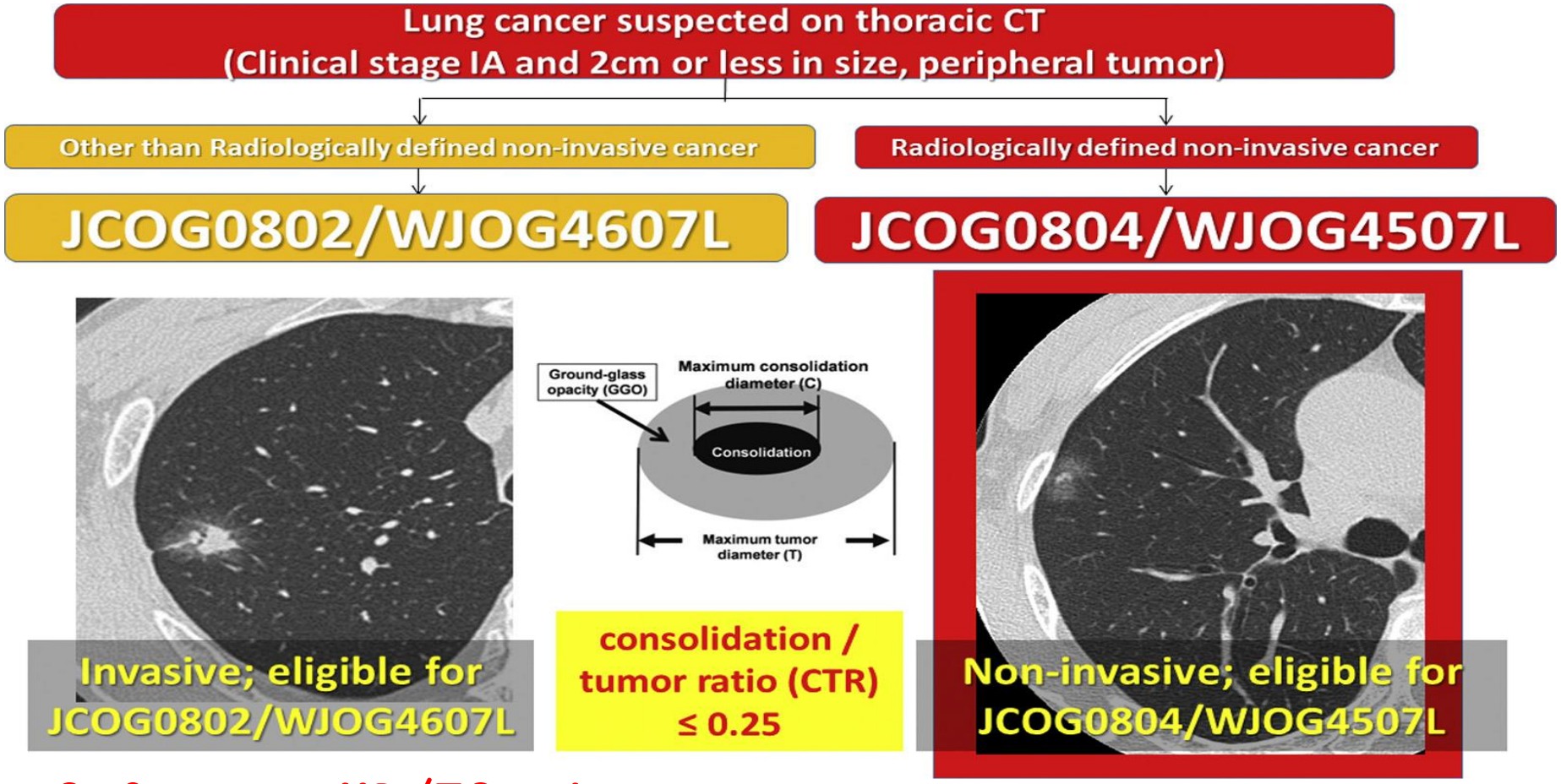
B



B

Walf AS et al Ann Thorac Surg 2017;104:1171

P-III 縮小肺切除における腫瘍断端距離

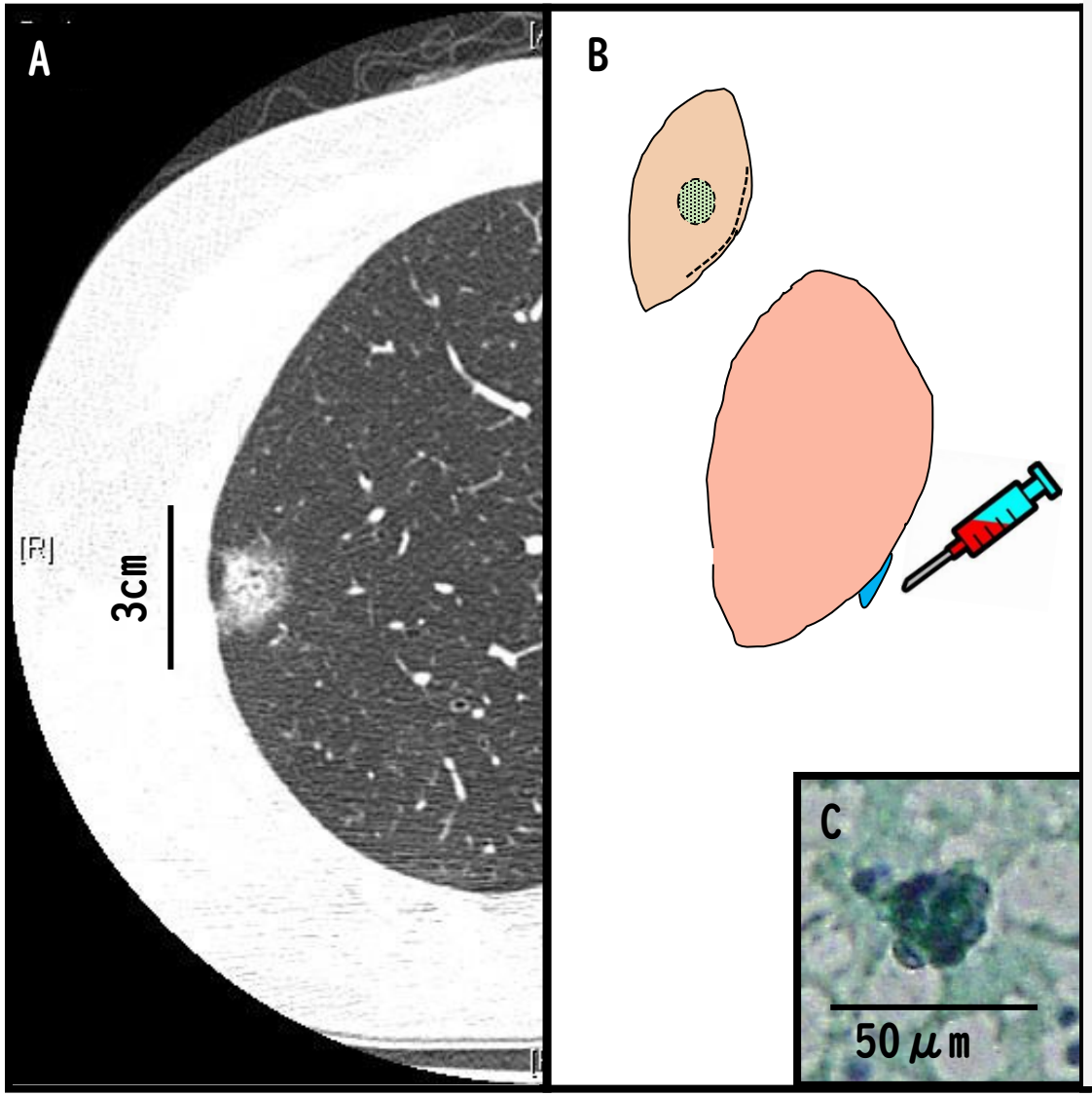


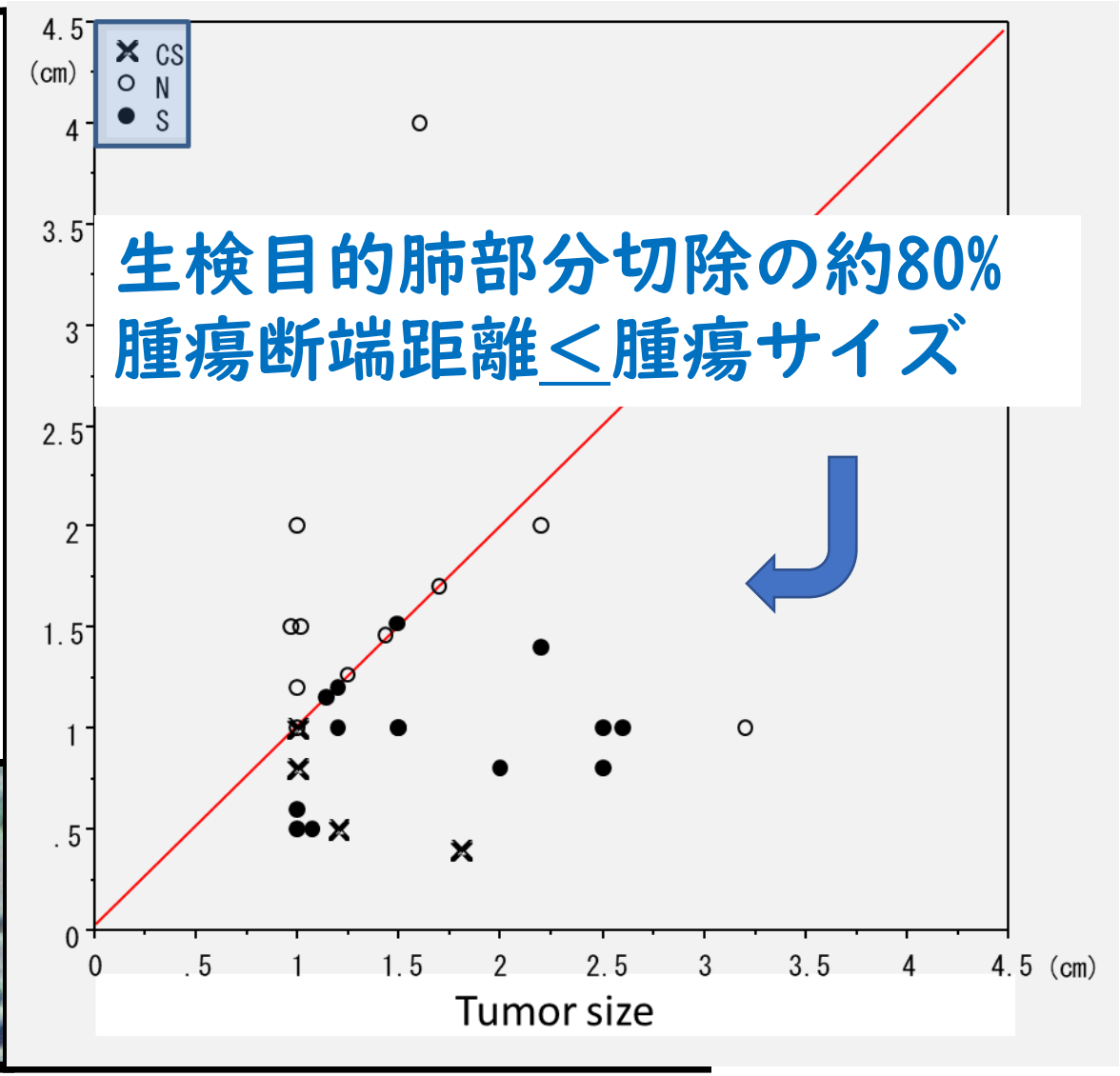
MD > 2.0cm or MD/TS> 1

MD > 0.5 cm

Adapted from Suzuki K et al. J Thorac Cardiovasc Surg 2019;158:895

肺部分切除後の残存肺葉にも癌細胞は存在

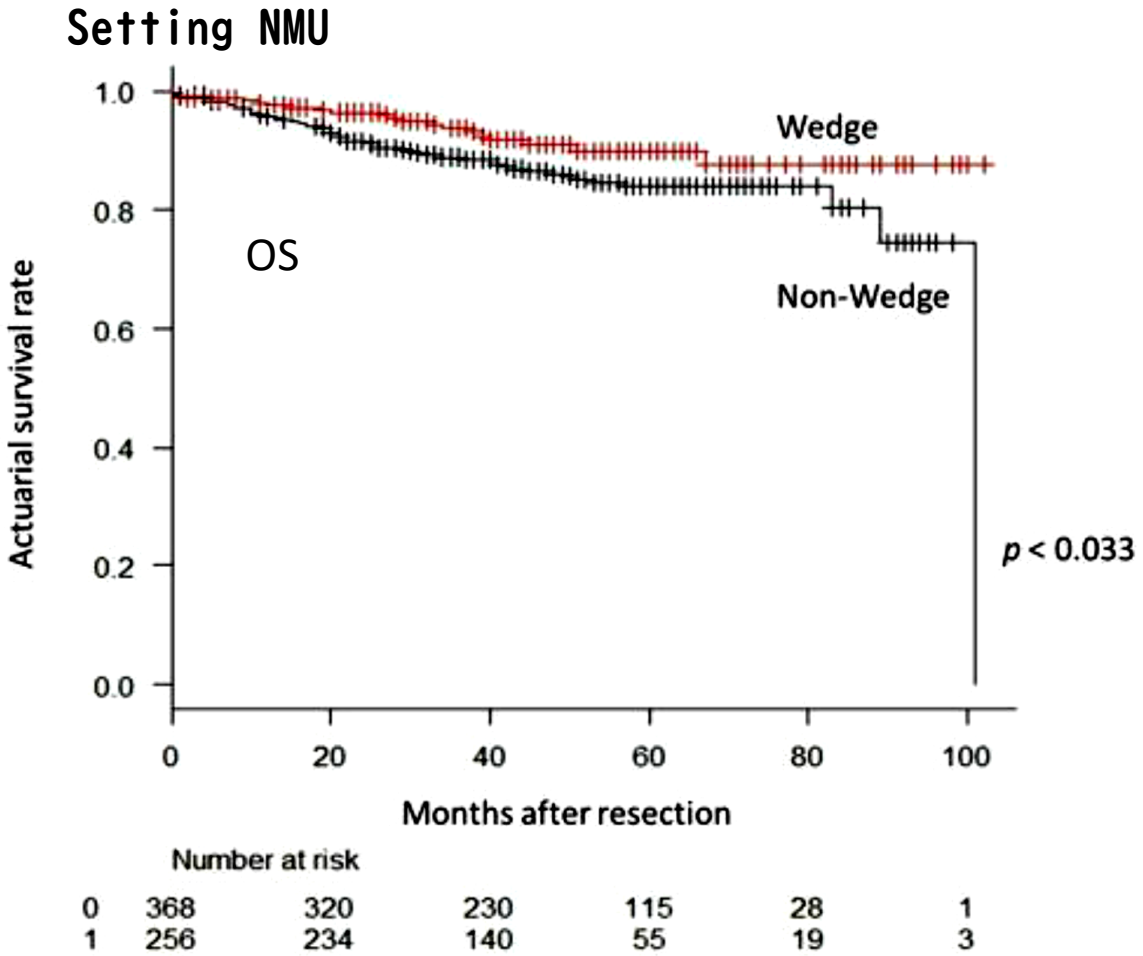


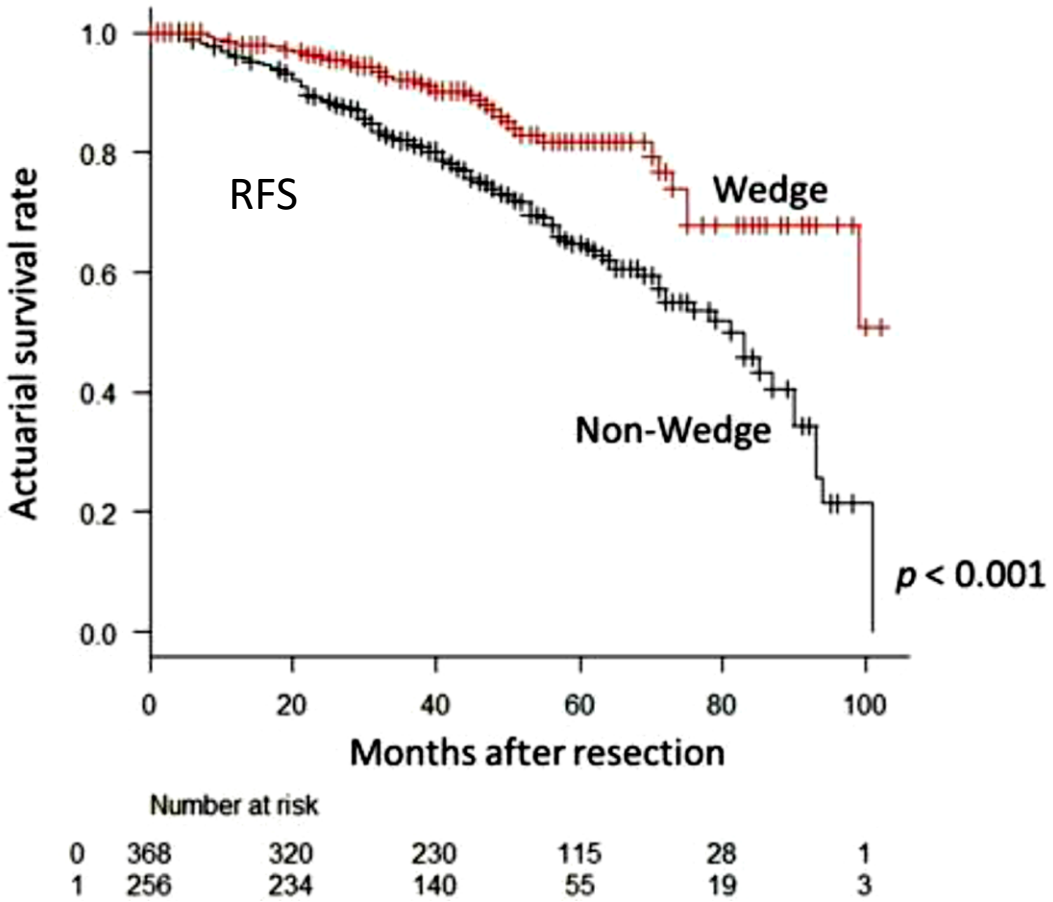


生検目的肺部分切除の約80%
腫瘍断端距離＜腫瘍サイズ

Sawabata, N, et al. Interactive cardiovascular and thoracic surgery (2016): 131-135.

術前の部切生検→肺葉切除：予後は悪くない

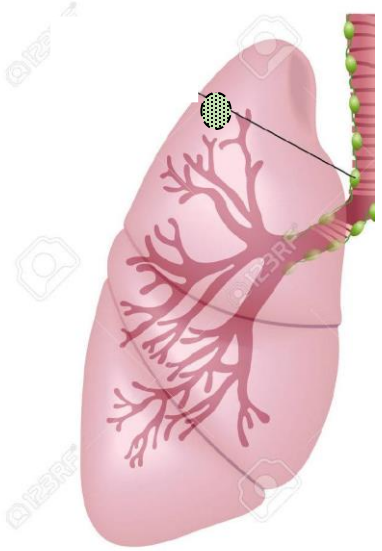




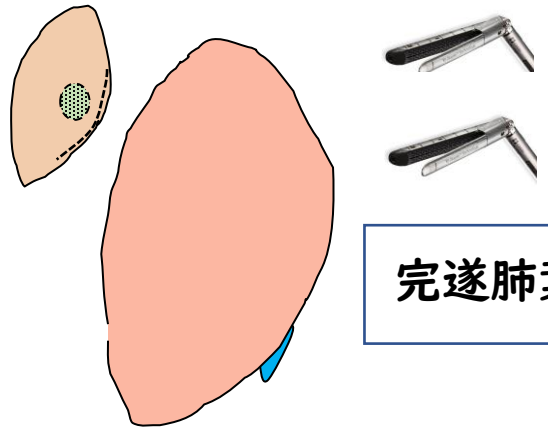
Yasukawa et al. in vivo 34: 779-785 (2020)

未診断末梢肺結節に対する治療方針

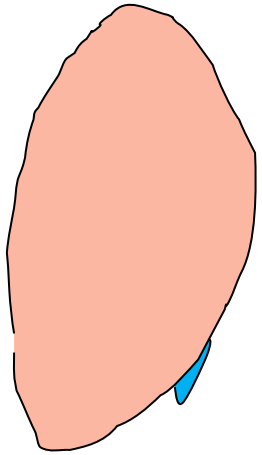
- Setting NMU



外科的生検



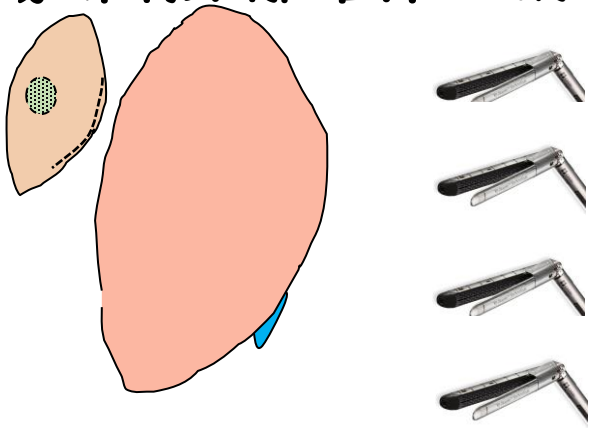
完遂肺葉切除



切除し易さ＞腫瘍断端距離確保

腫瘍断端距離確保＞切除し易さ

完遂楔状切除



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  - CTCの肺癌手術症例における特徴
  - CTC抽出法
  - CTCをターゲットとしたLiquid biopsy

https://jp.freepik.com/premium-vector/samurai-sword_6696687.htm#page=1&query=samurai&position=35

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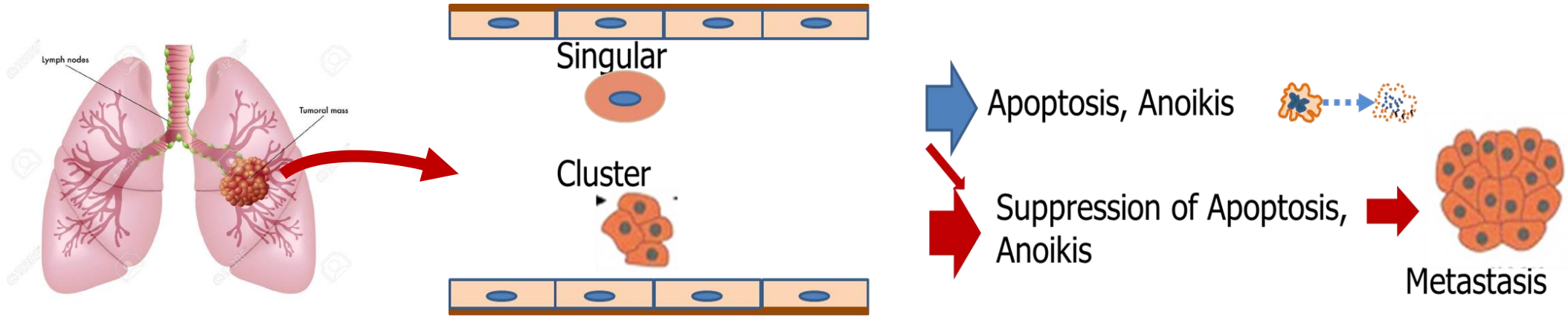
https://jp.freepik.com/premium-vector/samurai-sword_6696687.htm#page=1&query=samurai&position=35

CTC：癌病変から循環末梢血に出てきた腫瘍細胞

Circulating Tumor Cell (CTC)

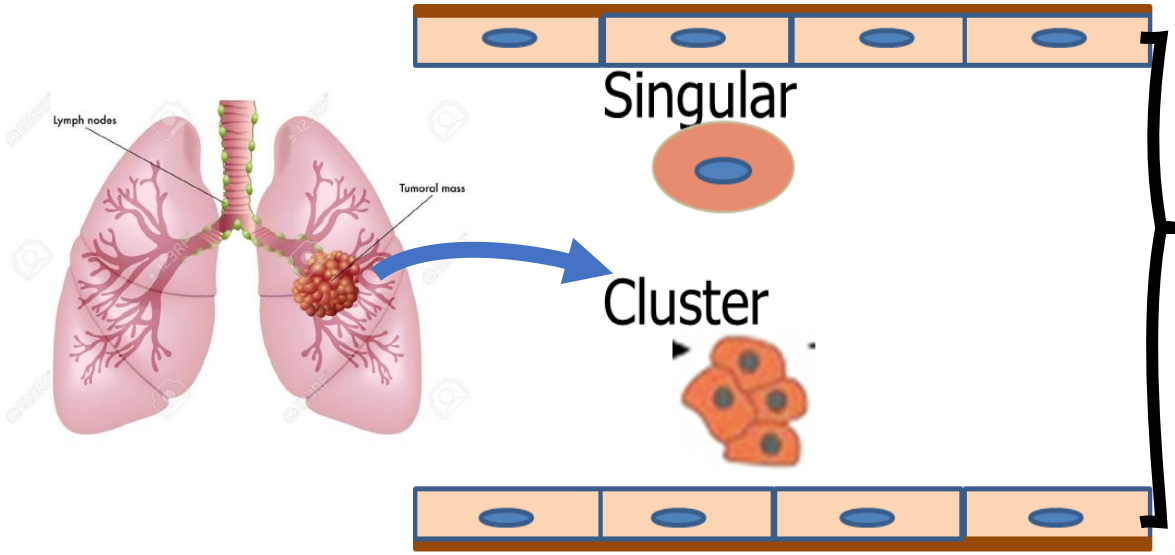
- Tumor Cells from Tumor to Circulation
  - ➢Singular ; 一過性> 持続性
  - ➢Clustered ; 持続性 > 一過性

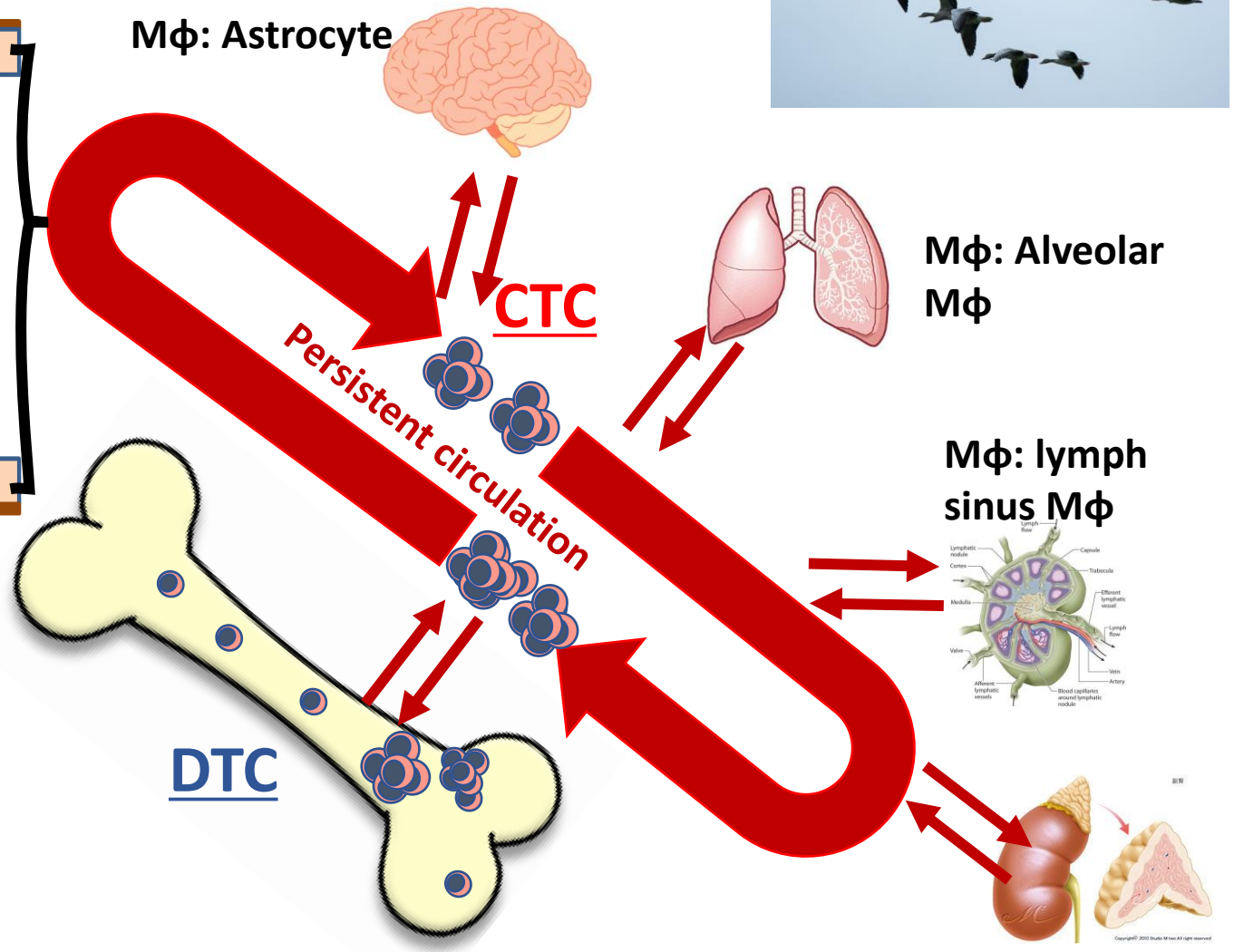
    Surrogate marker of Clustered CTC 1) CTC count, 2) apoptotic cells



Sawabata N. Cancers 2020, 12(10), 3065; https://doi.org/10.3390/cancers12103065

CTCは渡り鳥：move and stay

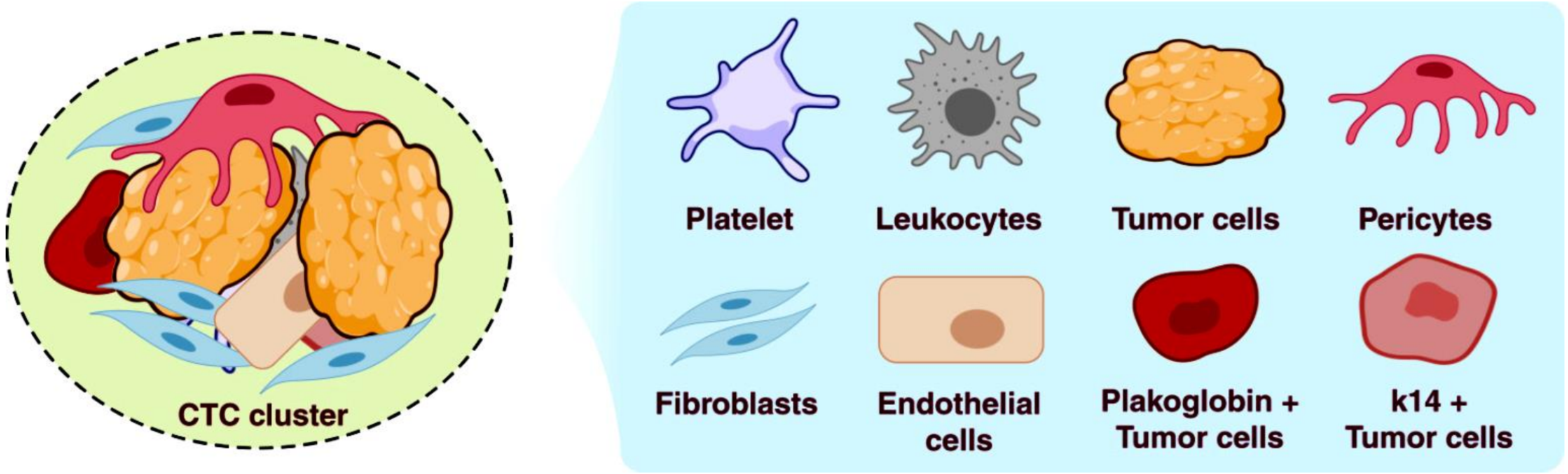




DTC: disseminated tumor cell
- ITC stays at some organ

1. 持続的な循環
2. 臓器に移動
3. 臓器から戻る
4. 持続的な循環

CTC clusters: 腫瘍細胞以外の細胞も存在することもある



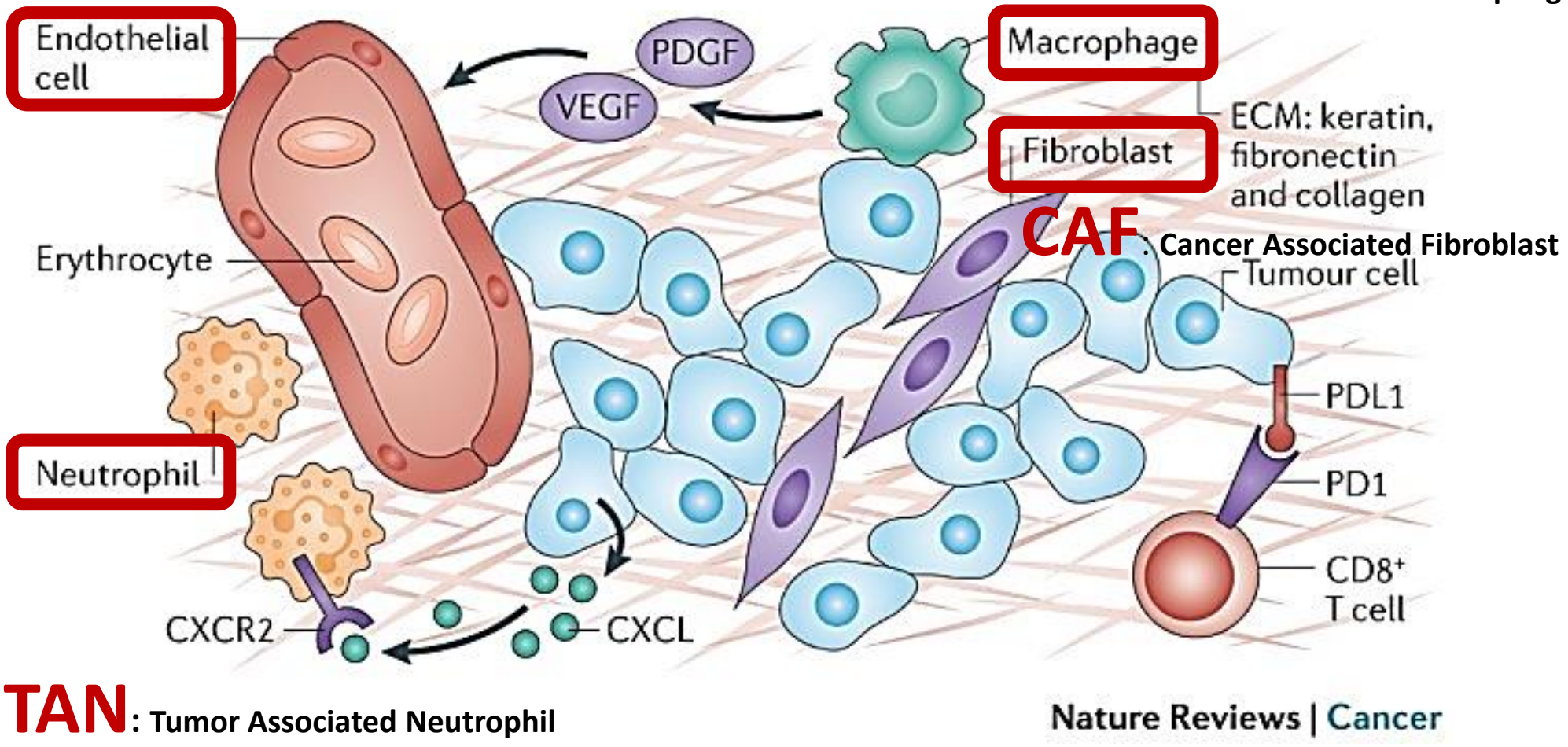
CTC clusters are made of cancer cells (homotypic) as well as non-cancerous stromal or immune cells bind through intracellular junctions (heterotypic). Non-cancerous cells include leucocytes, fibroblasts, endothelial cells and platelets. It is thought that heterotypic clusters have an increased survival advantage and immune evasion strategy by having immune cells integrated into the cluster.

: Sayuri Herath , et al (2020): Expert Review of Molecular Diagnostics, DOI: 10.1080/14737159.2020.1846523

肺癌微小環境：腫瘍関連細胞へのがん細胞のクロストーキング

TEC: Tumor-associated Endothelial Cell

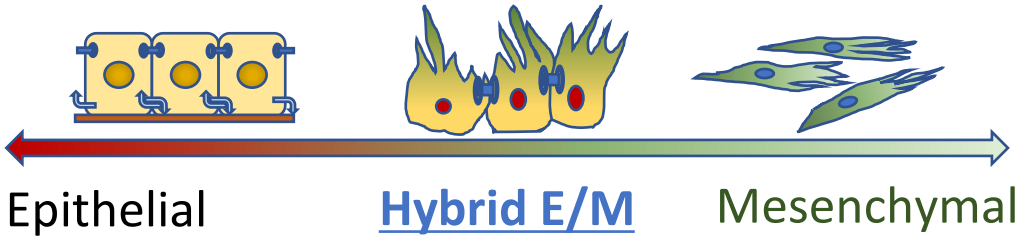
TAM: Tumor Associated Macrophage



TAN: Tumor Associated Neutrophil

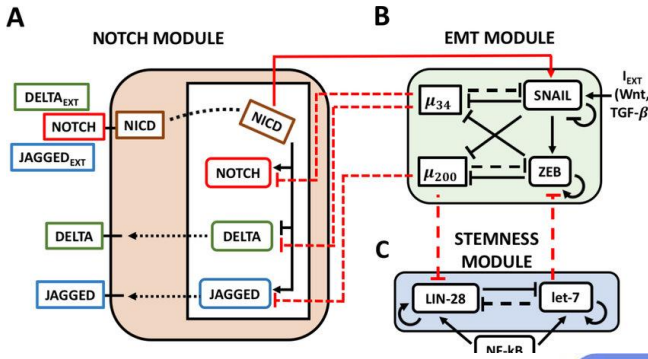
Chen, Z.et al. Nat Rev Cancer 14, 535–546 (2014).

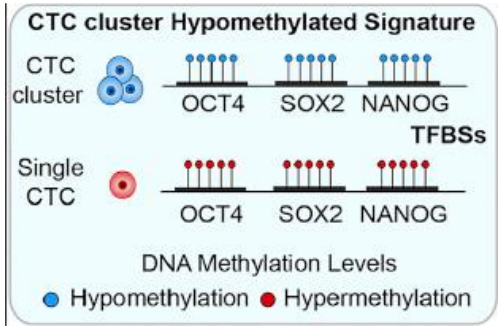
Clustered CTC

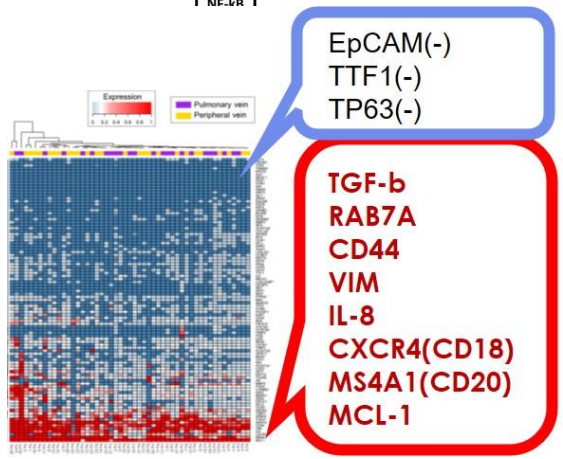


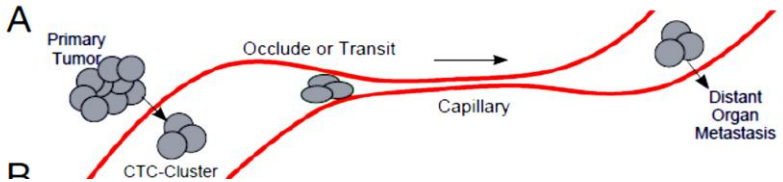
高悪性度/長期生存/回走性

- **Hybrid E/M (High potential of cluster formation)**
  - EMT circuit (TGF-β, wnt, NF-κβ, miR34, miR200)
    - Lu M et al PNAS 110:18144, 2013
  - Notch-Delta-Jagged signaling
    - Boareto M et al *Journal of The Royal Society Interface*, 2016;13:20151106
  - Hybrid cell lines: H1975 (Lung)
    - Jolly M et al. Oncotarget 17;27067, 2015
- **High rate of mesenchymal gene expression**
  - Murlidhar V, et al Cancer Res. 2017;77:5194
- **Stem cell like**
  - Hypomethylation of **OCT4, SOX2, NANOG**
    - Gkountela et al., 2019, Cell 176, 98–112
- **High mortility**
  - Clusters of circulating tumor cells traverse capillary-sized vessels
    - Au SM et al PNAS; 113: 4947 2016

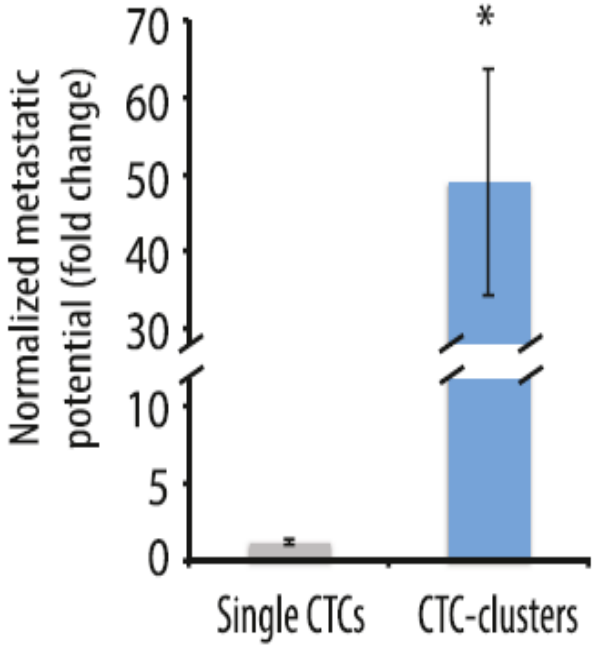


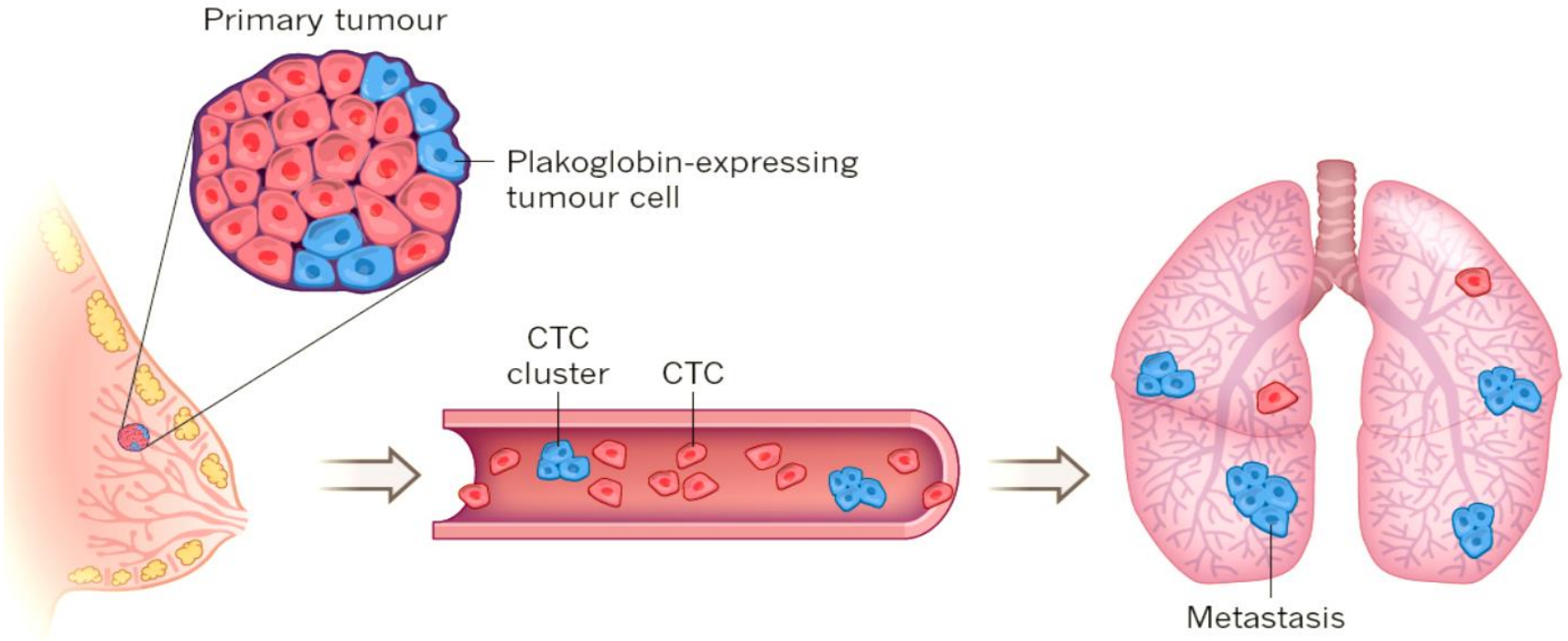






転移：主にclustered CTC経由





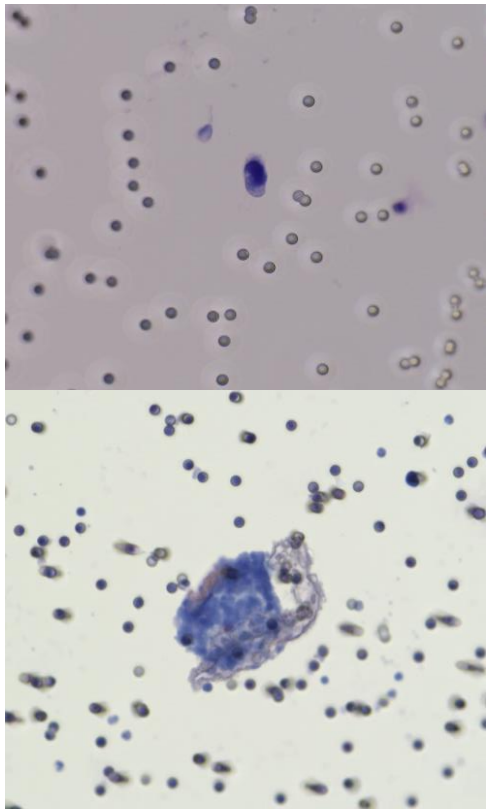
Aceto N et al. Cell 2014; 158;2011

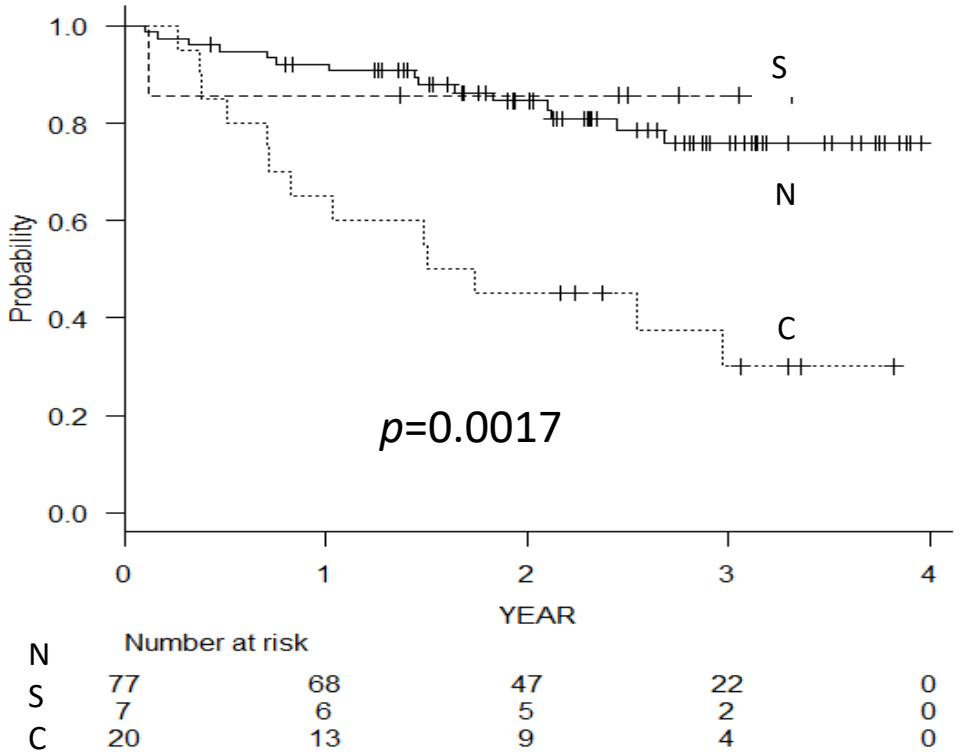
Bottos A et al. Nature 2014; 514: 309

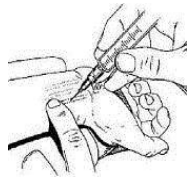
手術前にクラスター化CTCが同定された症例は再発する可能性が高い

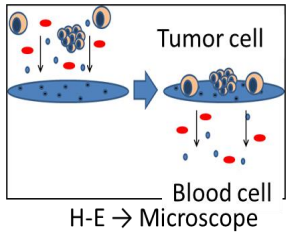
手術直前の末梢動脈血at OR c-stage I or II

ScreenCell®









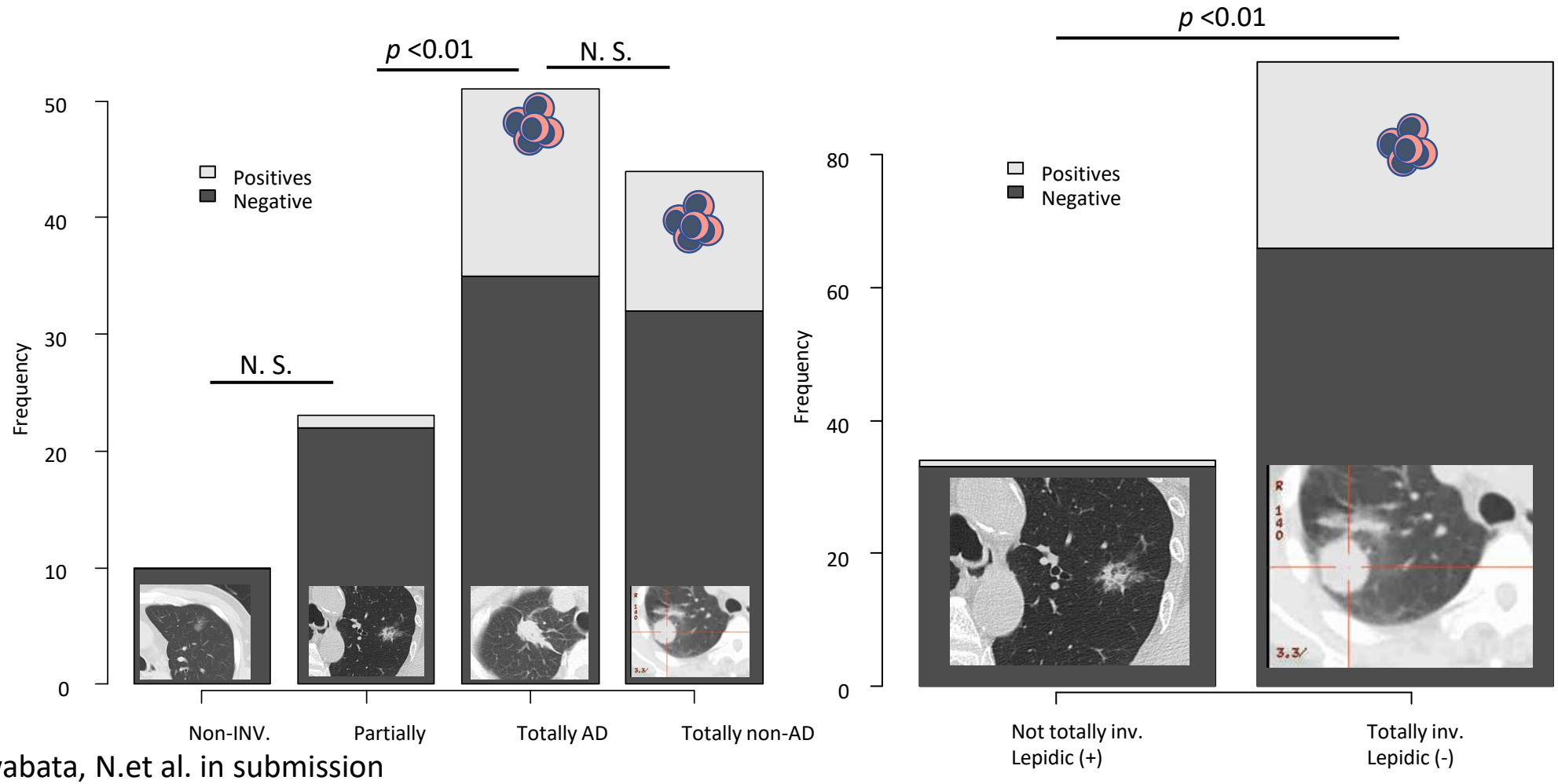
Clustered CTC 予測因子

- *p*-stage
- Tumor vessel invasion
- Tumor size
- CEA
- SUVmax

浸潤

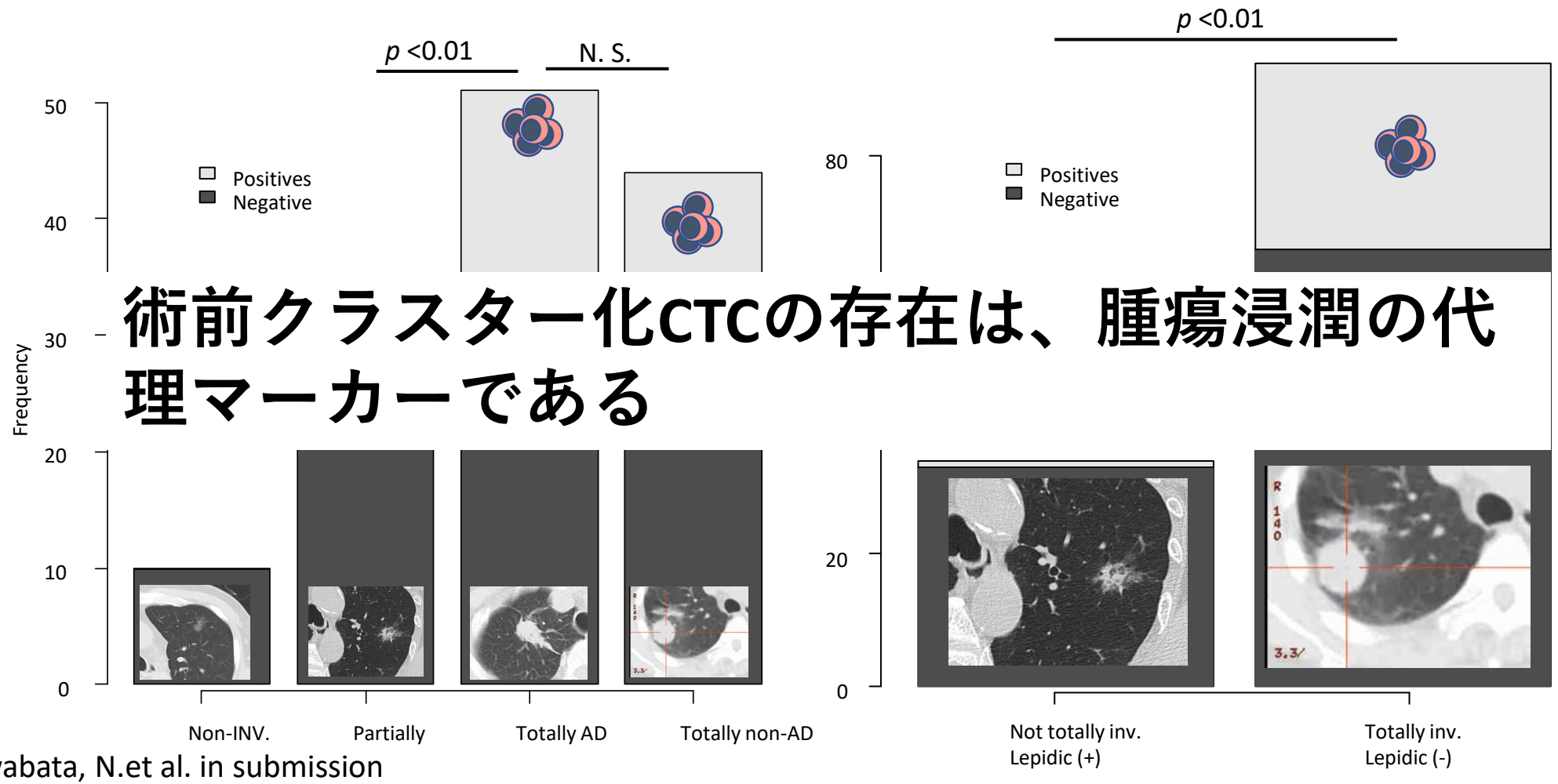
Sawabata, N. *et al.* Cluster circulating tumor cells in surgical cases of lung cancer. *Gen Thorac Cardiovasc Surg;*68:975-983 2020

腫瘍浸潤による術前クラスター化CTCの検出率は?



Sawabata, N.et al. in submission

腫瘍浸潤による術前クラスター化CTCの検出率は?



術前クラスター化CTCの存在は、腫瘍浸潤の代理マーカーである

Sawabata, N.et al. in submission

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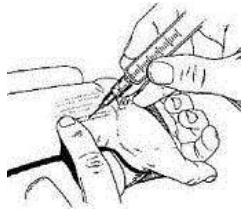
https://jp.freepik.com/premium-vector/samurai-sword_6696687.htm#page=1&query=samurai&position=35

手術はCTCsを誘発するか?



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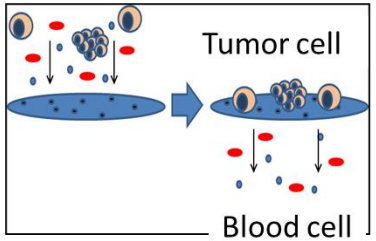
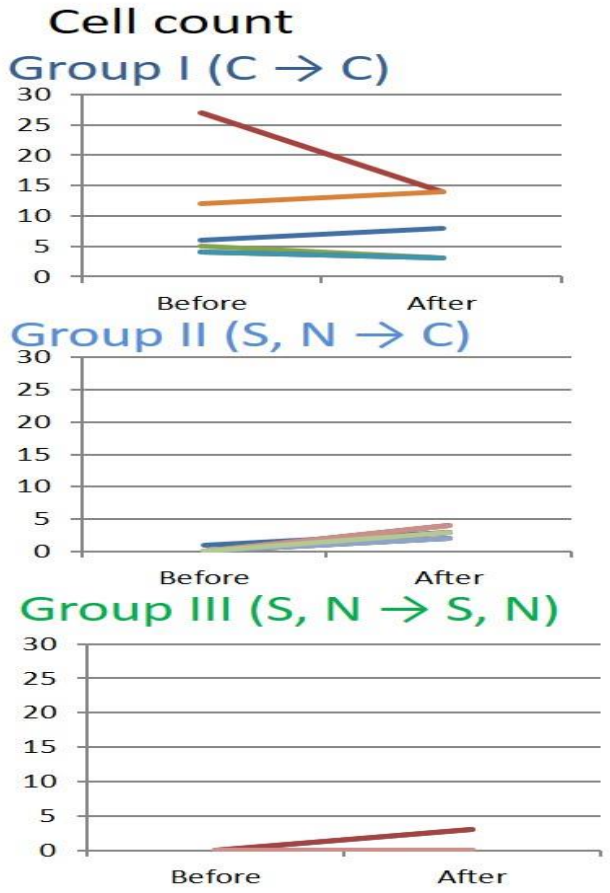
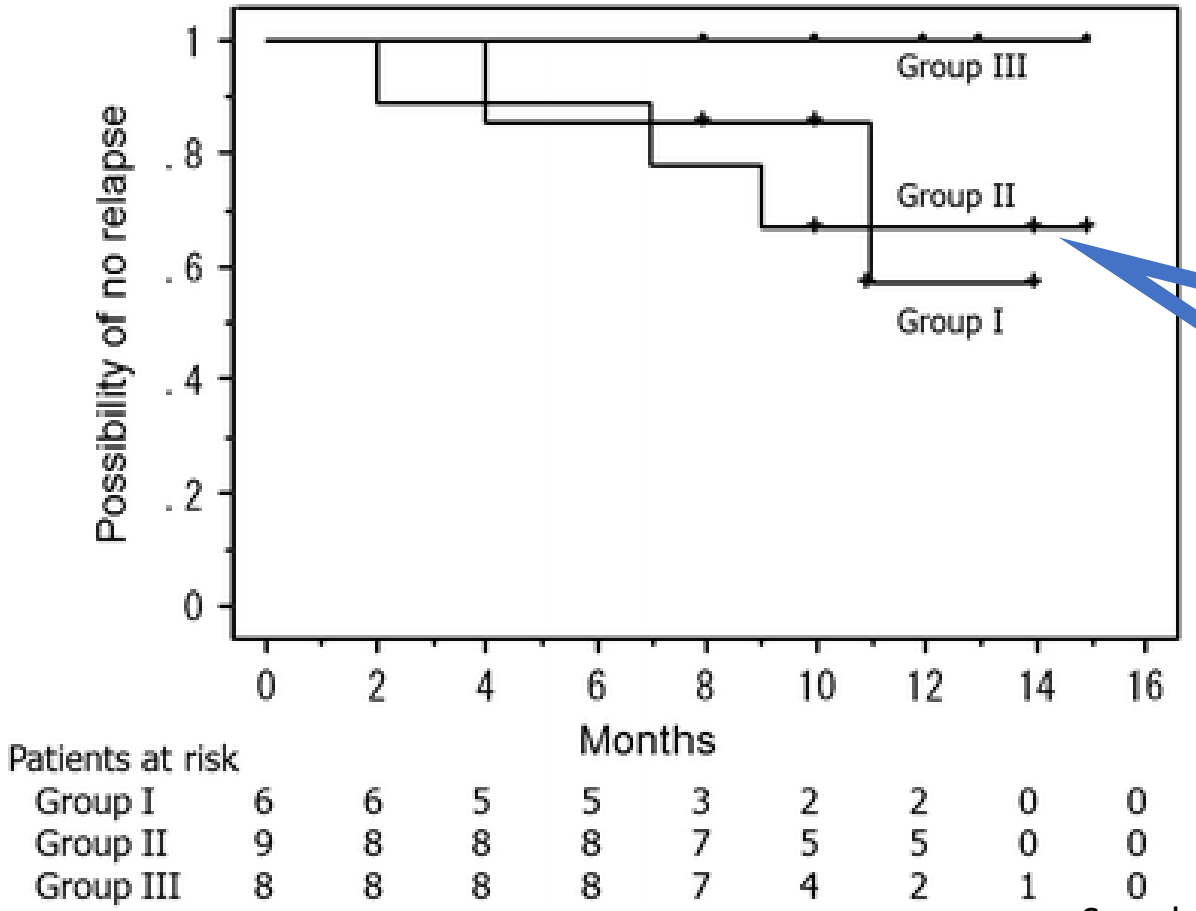


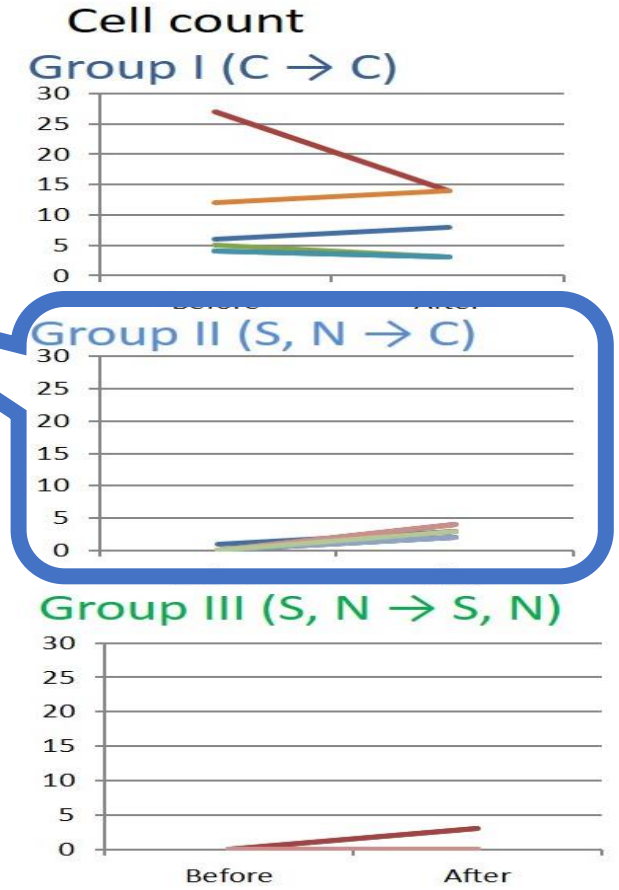
No.	Group	Before			After			6hr			PV		
		Morphology	Amount		Morphology	Amount		Morphology	Amount		Morphology	Amount	
			C	S		C	S		C	S		C	S
1	I	C	2	4	C	3	5	N	0	1	C	6	10
2	I	C	3	24	C	6	8	N	0	0	C	6	9
3	I	C	3	2	C	2	1	N	0	0	C	5	12
4	I	C	1	3	C	2	1	N	0	0	C	1	1
5	I	C	4	0	C	1	2	N	0	0	C	1	3
6	I	C	8	4	C	12	2	N	0	0	C	6	3
7	II	S	0	1	C	1	1	N	0	0	C	1	0
8	II	N	0	0	C	1	2	S	0	0	C	1	4
9	II	N	0	[illegible]	C	2	0	N	0	0	C	1	1
10	II	N	0	0	C	[illegible]	1	N	0	0	C	2	2
11	II	N	0	0	C	1	3	N	0	0	C	1	5
12	II	N	0	0	C	2	2	N	0	0	C	1	2
13	II	N	0	0	C	1	1	N	0	0	C	1	2
14	II	N	0	0	C	2	2	N	0	0	C	2	4
15	II	N	0	0	C	2	1	N	0	0	C	1	6
16	III	N	0	0	S	[illegible]	3	N	0	0	S	0	1
17	III	N	0	[illegible]	S	0	3	N	0	0	S	0	2
18	III	N	0	0	N	0	0	N	0	0	S	0	3
19	III	N	0	0	N	0	0	N	0	0	S	0	2
20	III	N	0	0	N	0	0	N	0	0	N	0	0
21	III	N	0	0	[illegible]	0	0	N	0	0	N	0	0
22	III	N	0	0	N	0	0	N	0	0	N	0	0
23	III	N	0	0	N	0	0	N	0	0	N	0	0
Total		C,6; S,1; N,16			C,15; S,2; N,6			C,0; S,1; N,22			C,16; S,3; N4		



Sawabata, N.et al. Surgery today 2016;46:1402-1409.

手術によって引き起こされるclustered CTCは予後因子である





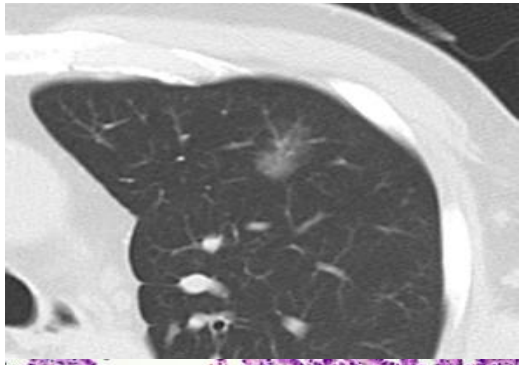
Sawabata, N.et al. Surgery today 2016;46:1402-1409.

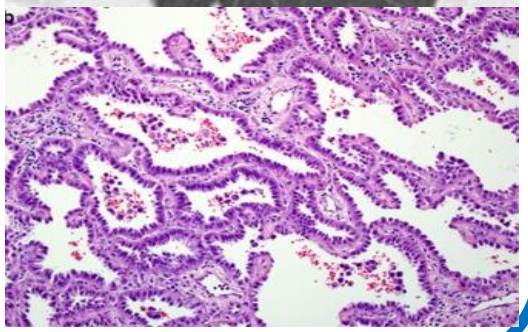
Dose surgery cause CTC in any degree of tumor invasiveness?

Non- invasive

Carcinoma in situ

Invasive size = 0

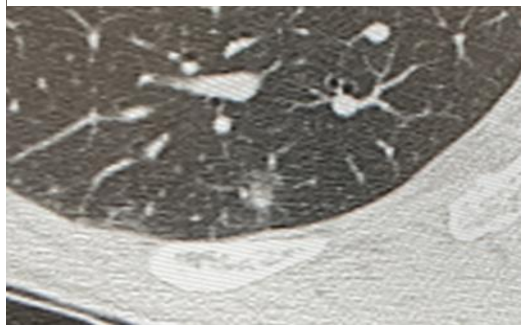


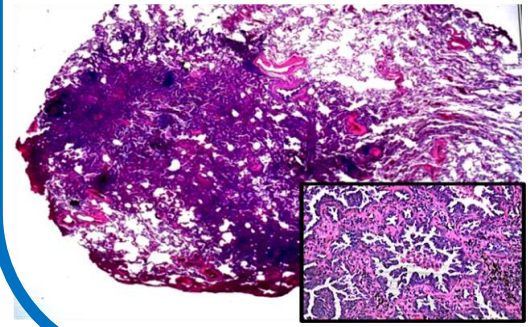


Partially invasive

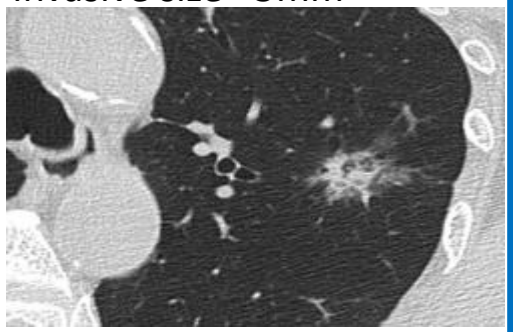
Min-inv Ca

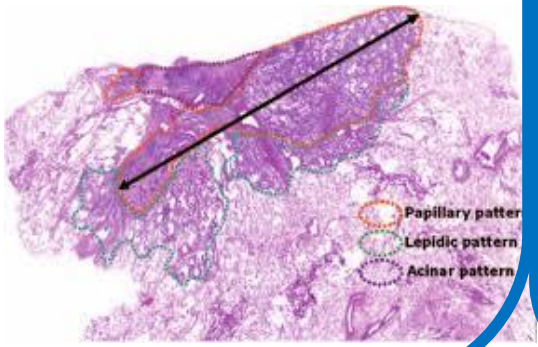
Invasive size < 5mm





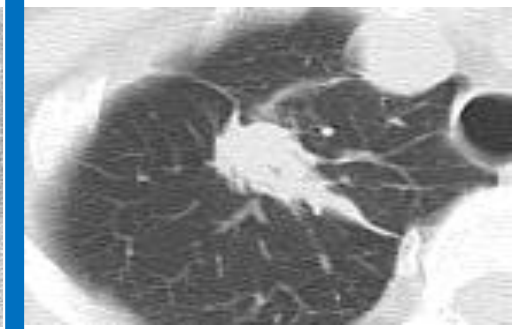
Invasive Ca
with lepidic lesion
Invasive size >5mm

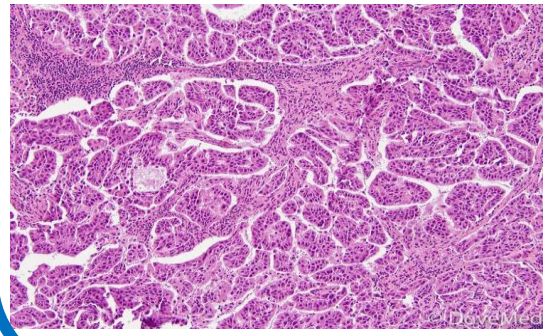




Totally invasive

Invasive carcinoma without
lepidic lesion

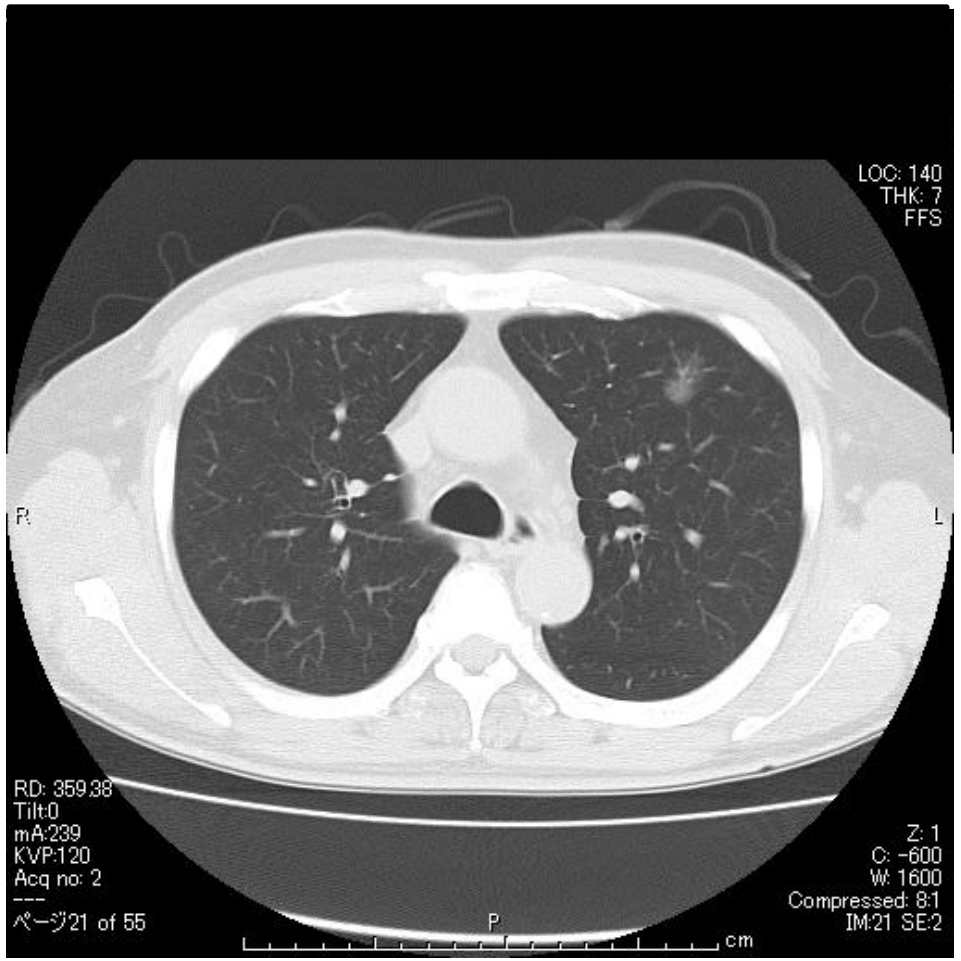


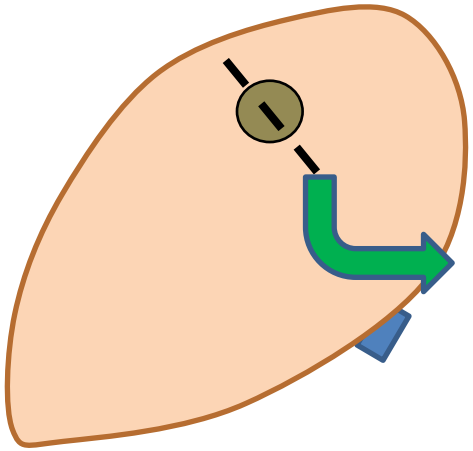


Metastasis

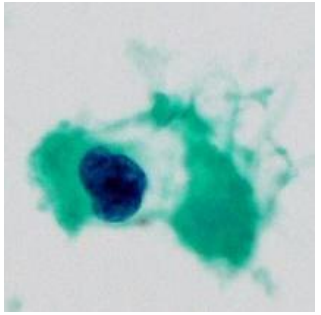
Never **Seldom** **Sometimes**

Non- invasive; Single CTC post surgery

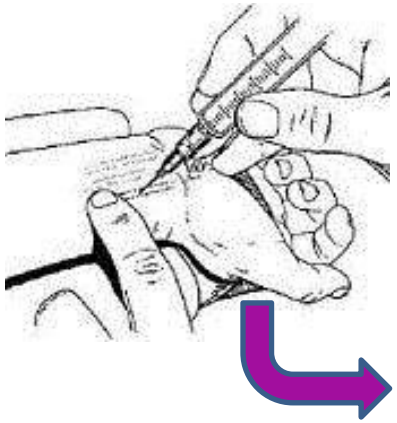




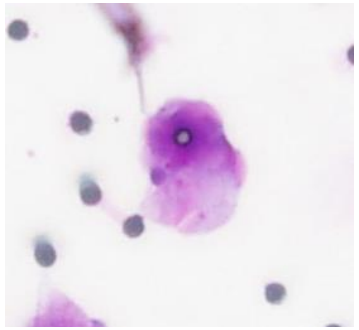
Stump smear

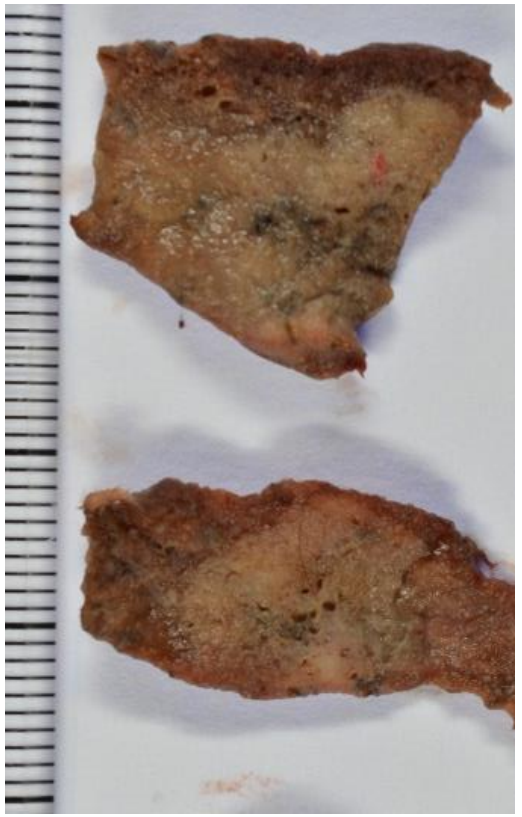


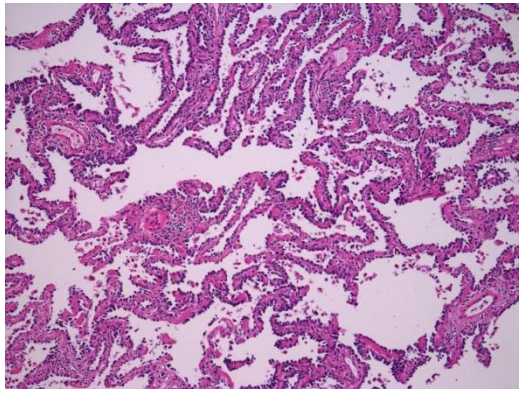
Just before Surg.
No CTC



At tumor resection
Single CTC

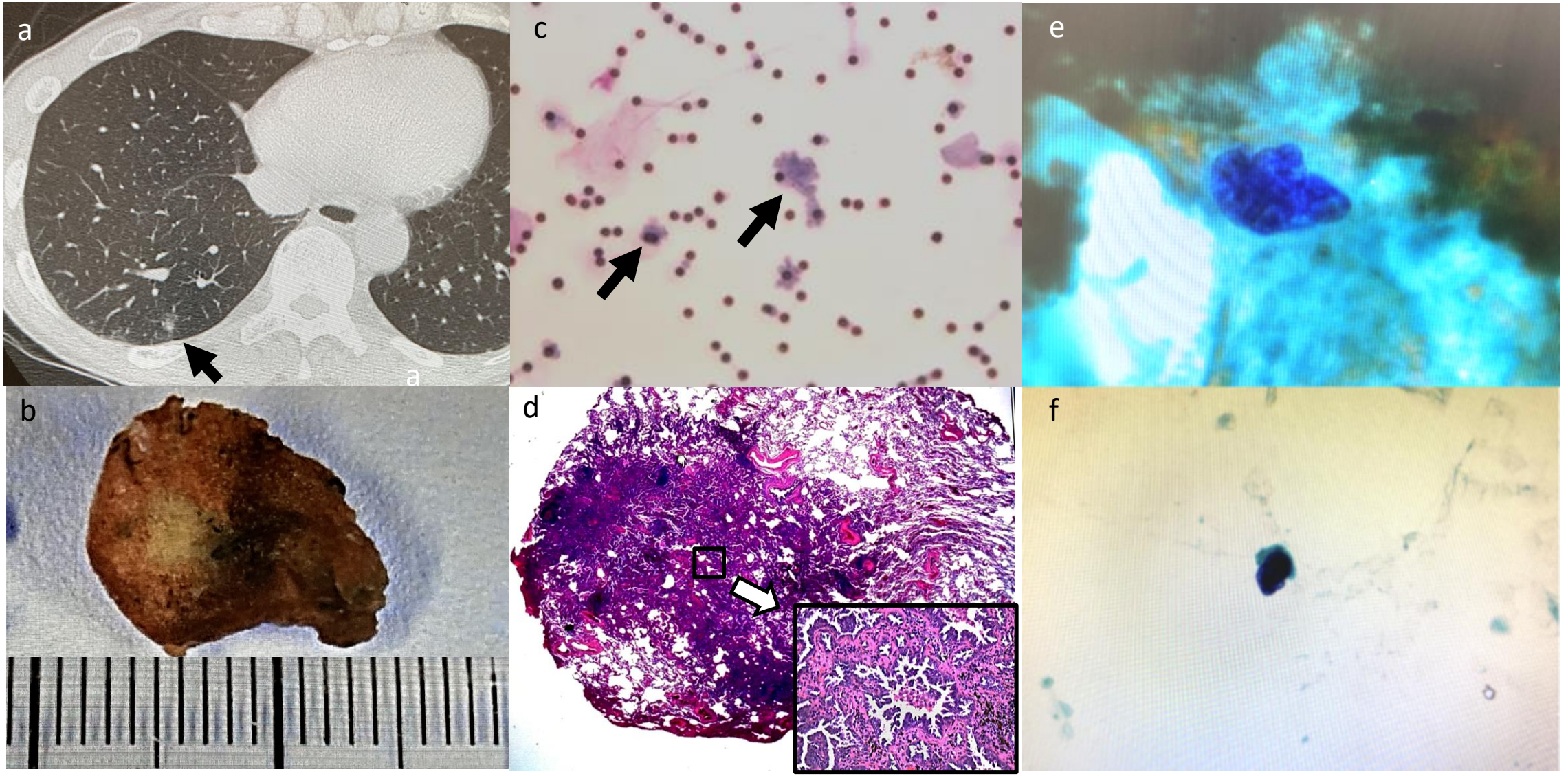




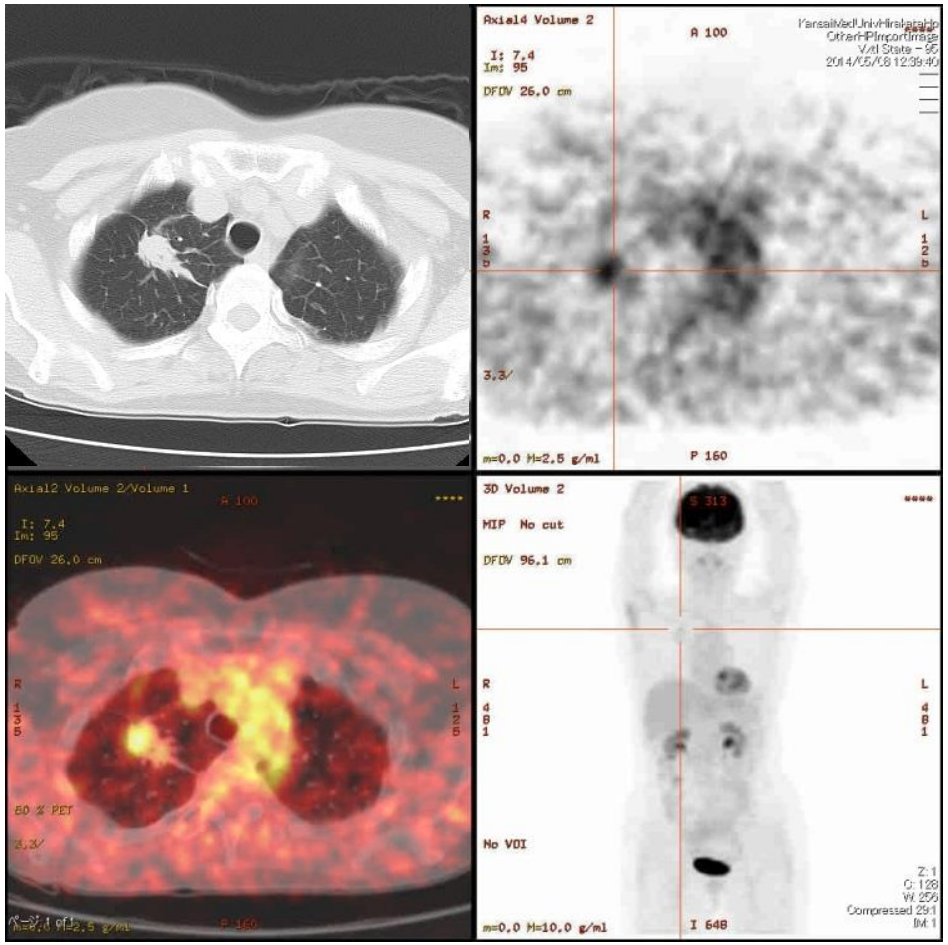


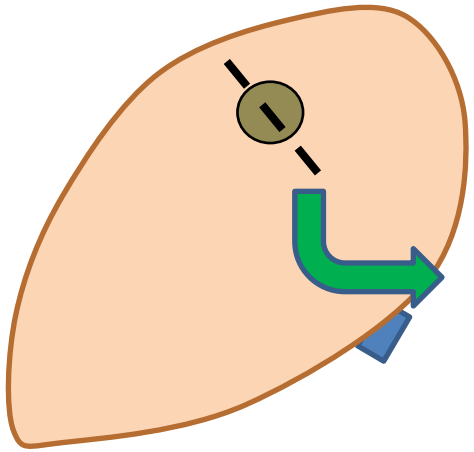
Sawabata, N.et al. (2016).Surgery today, 46(12), 1402-1409.

Partially invasive cancer; both single and clustered CTC post surgery：

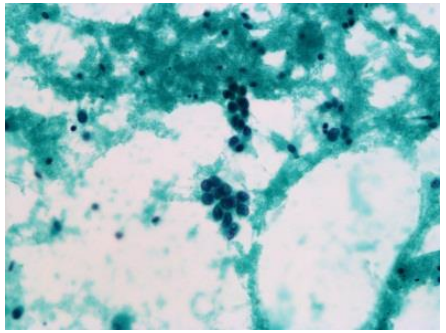


Totally invasive cancer (adenocarcinoma); Loosely clustering CTC post surgery

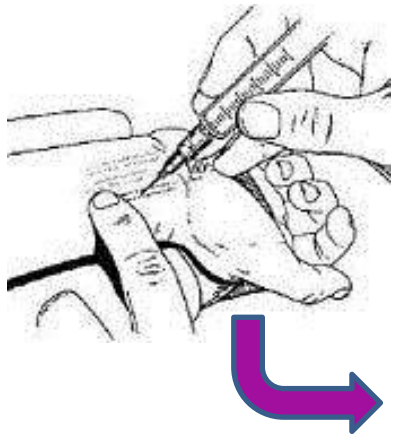




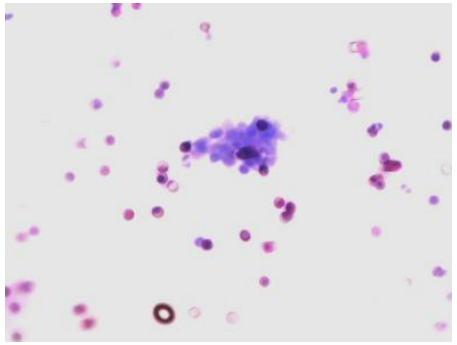
Stump smear



Just before Surg.
No CTC

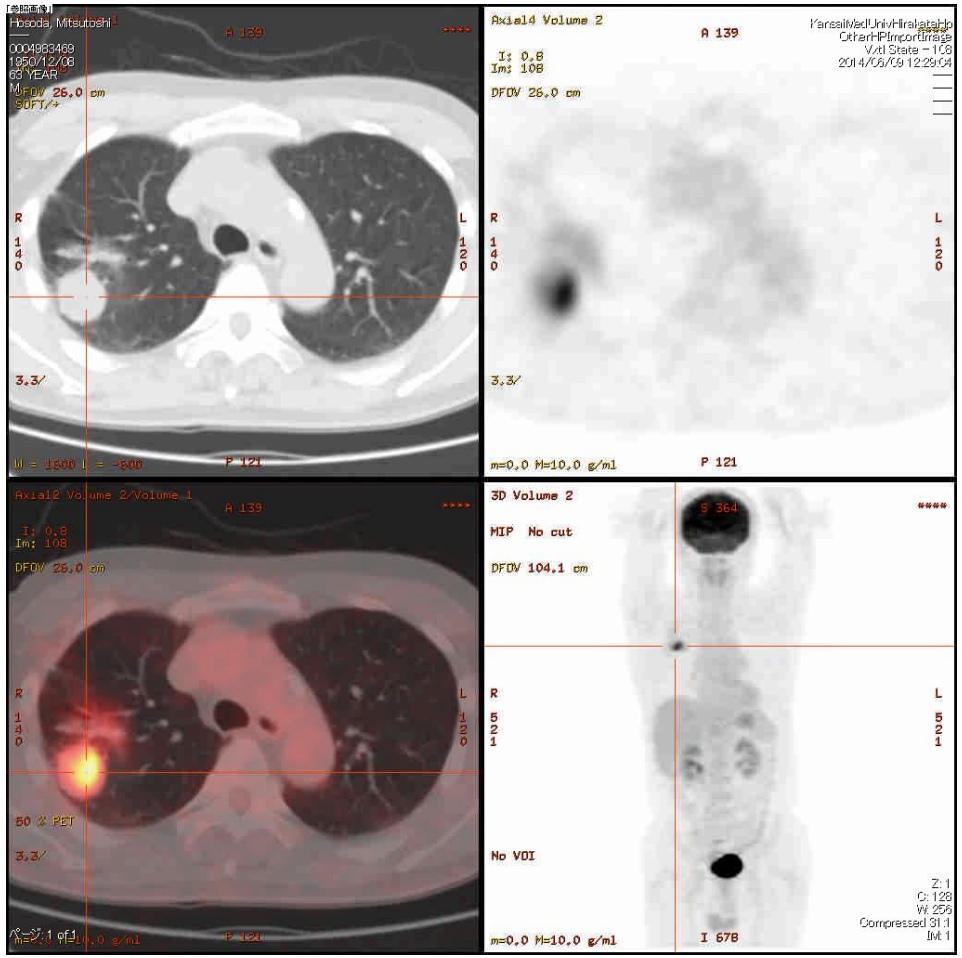


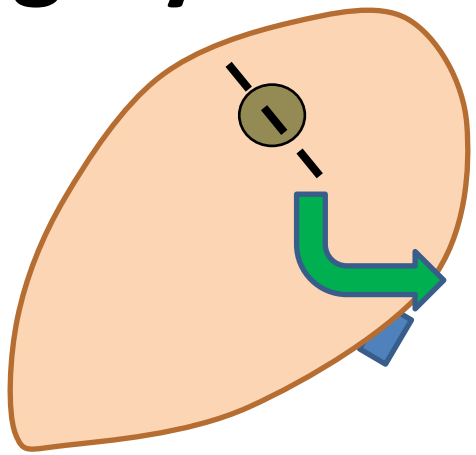
At tumor resection
Cluster CTC



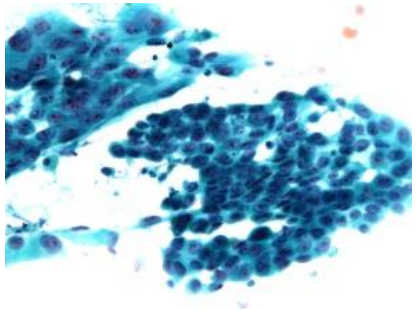
Sawabata, N.et al. (2016).Surgery today, 46(12), 1402-1409.

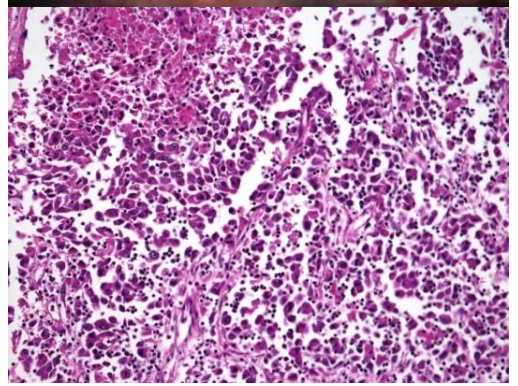
Totally invasive cancer; aggressive malignancy; tightly clustering CTC post surgery

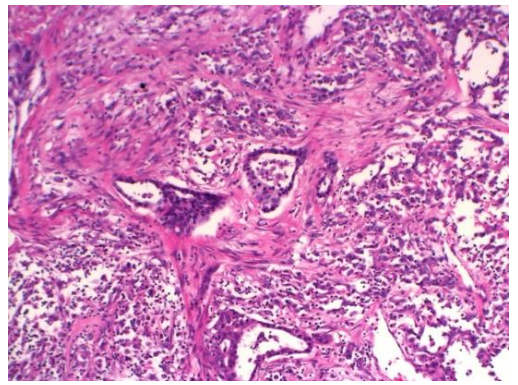




Stump smear

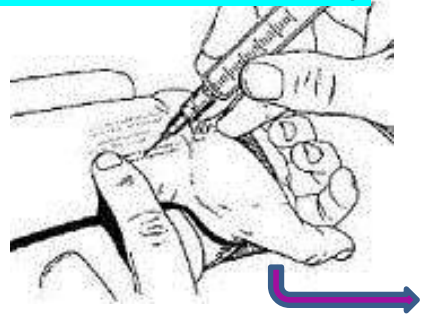


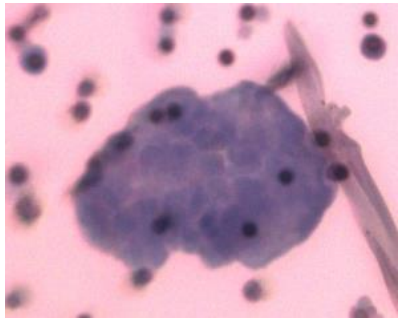




Just before Surg. No CTC

Post lobectomy

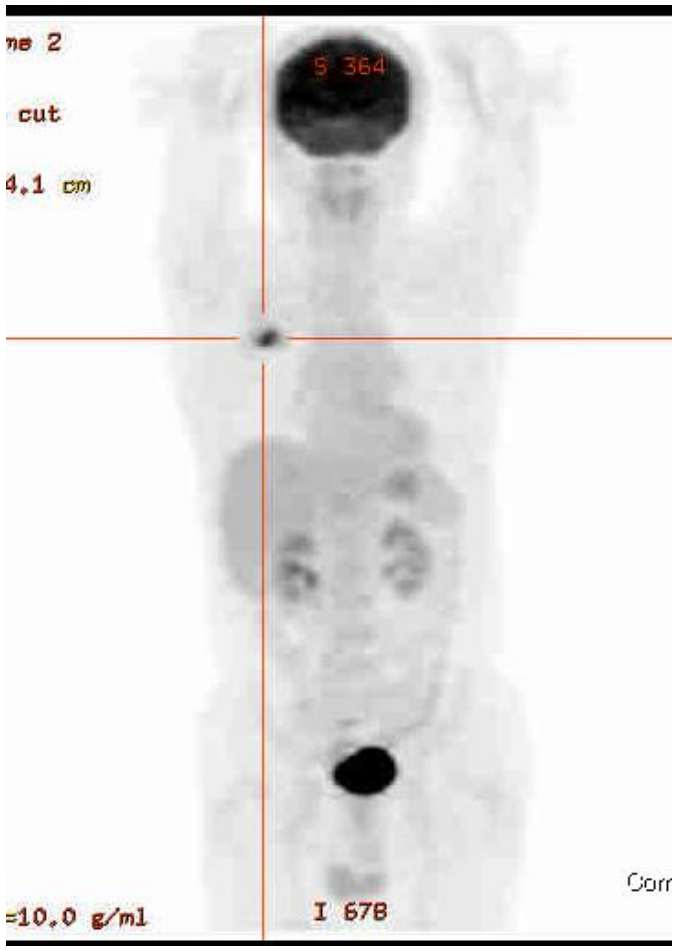




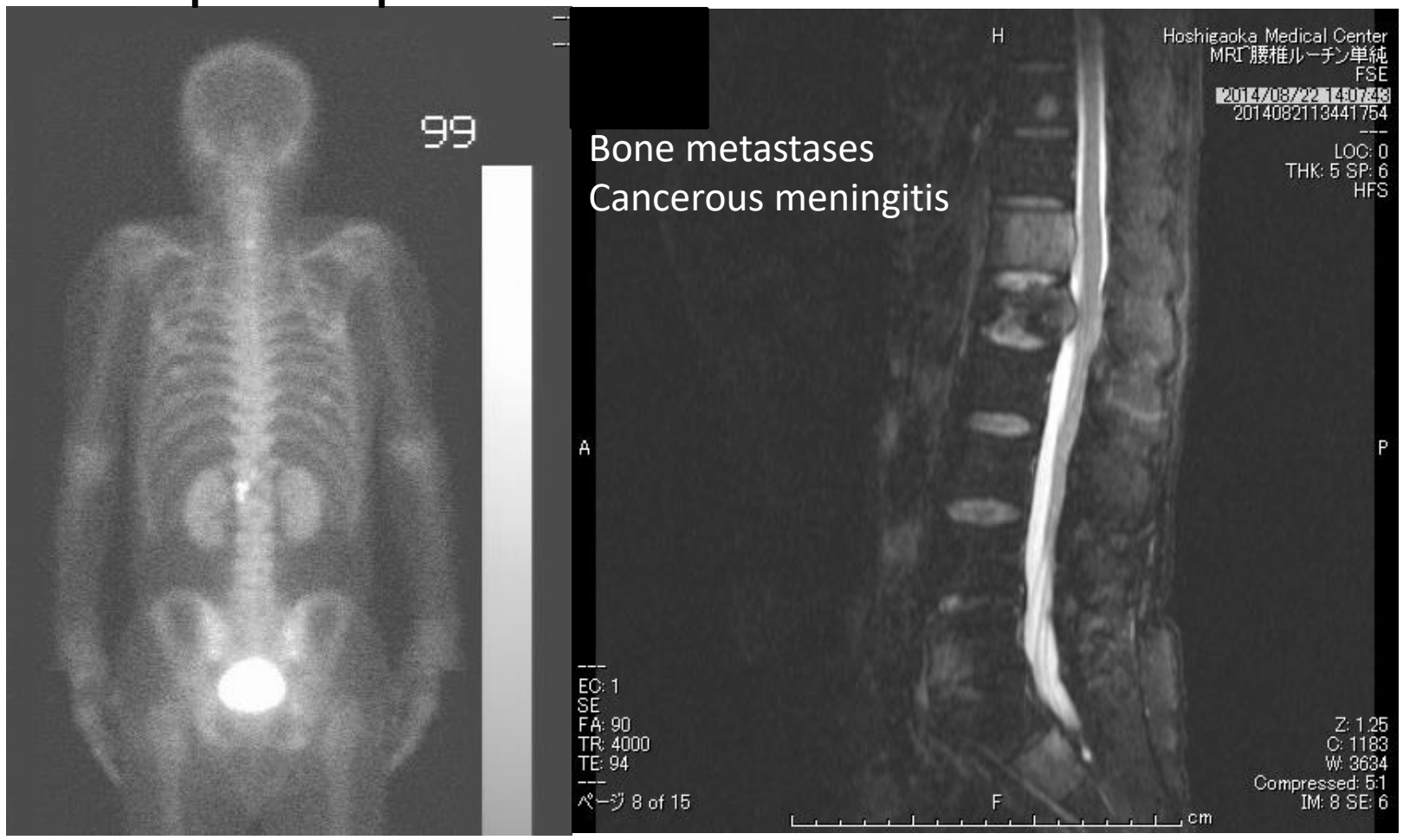
Adapted from Watanabe et al. Anticancer Research 2020;40

2 months after surgery; bone metastasis

Pre operation

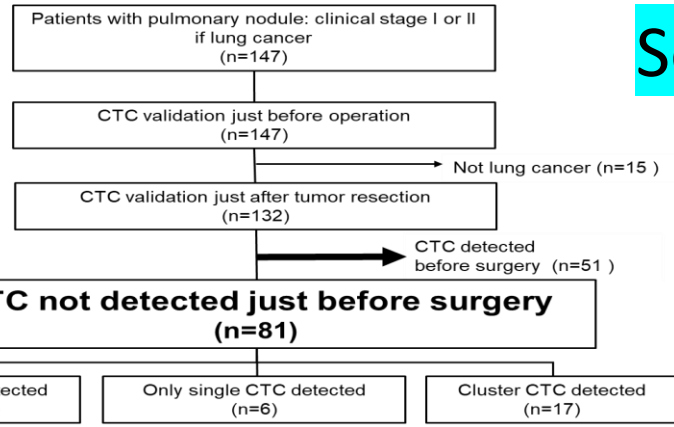


2Ms post operation→11Ms cancer death

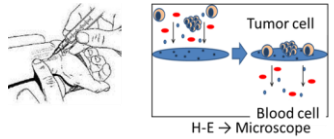


Adapted from Watanabe et al. Anticancer Research 2020;40

手術によって引き起こされるクラスター化CTCの臨床的意義は? クラスター化 CTC: 遠隔転移の予測変数

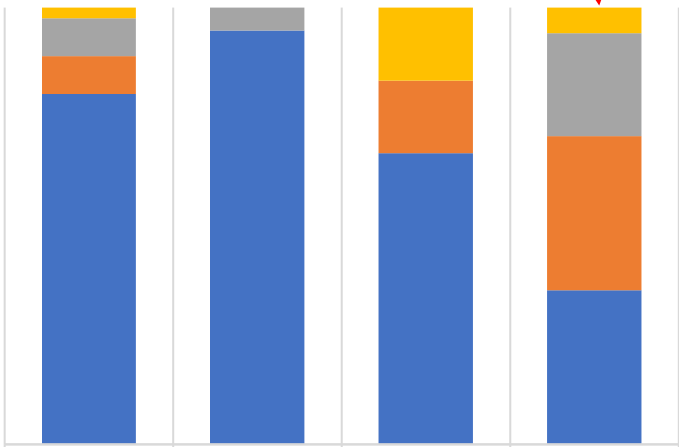


ScreenCell®

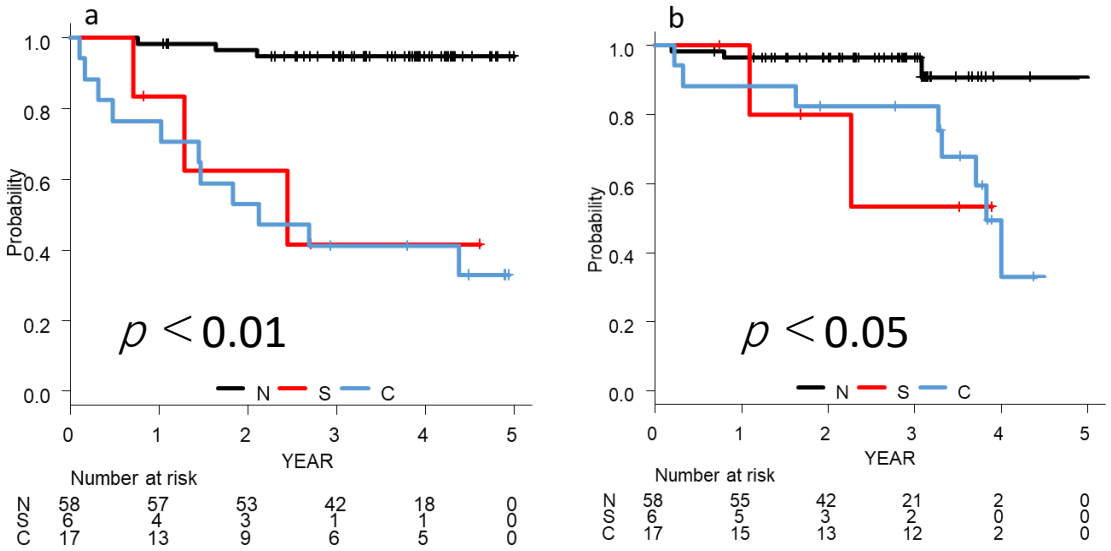


PREVARENCE OF RECURRENCE

$p < 0.01$



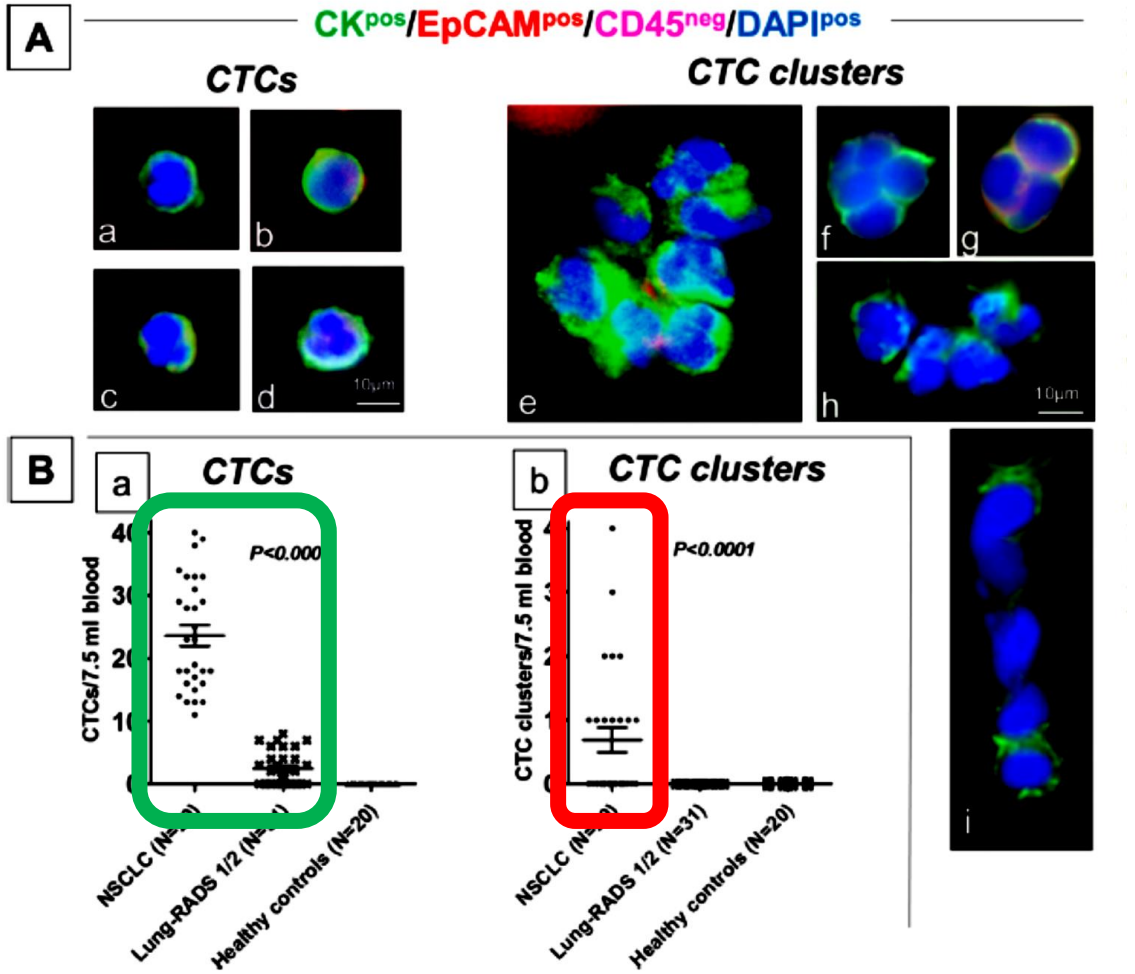
	Total	N	S	C
Margin local	2	0	1	1
Local	7	3	0	4
Distant	7	0	1	6
No recurrence	65	55	4	6



Sawabata N et al J Thorac Dis 2020;12:4623-4632

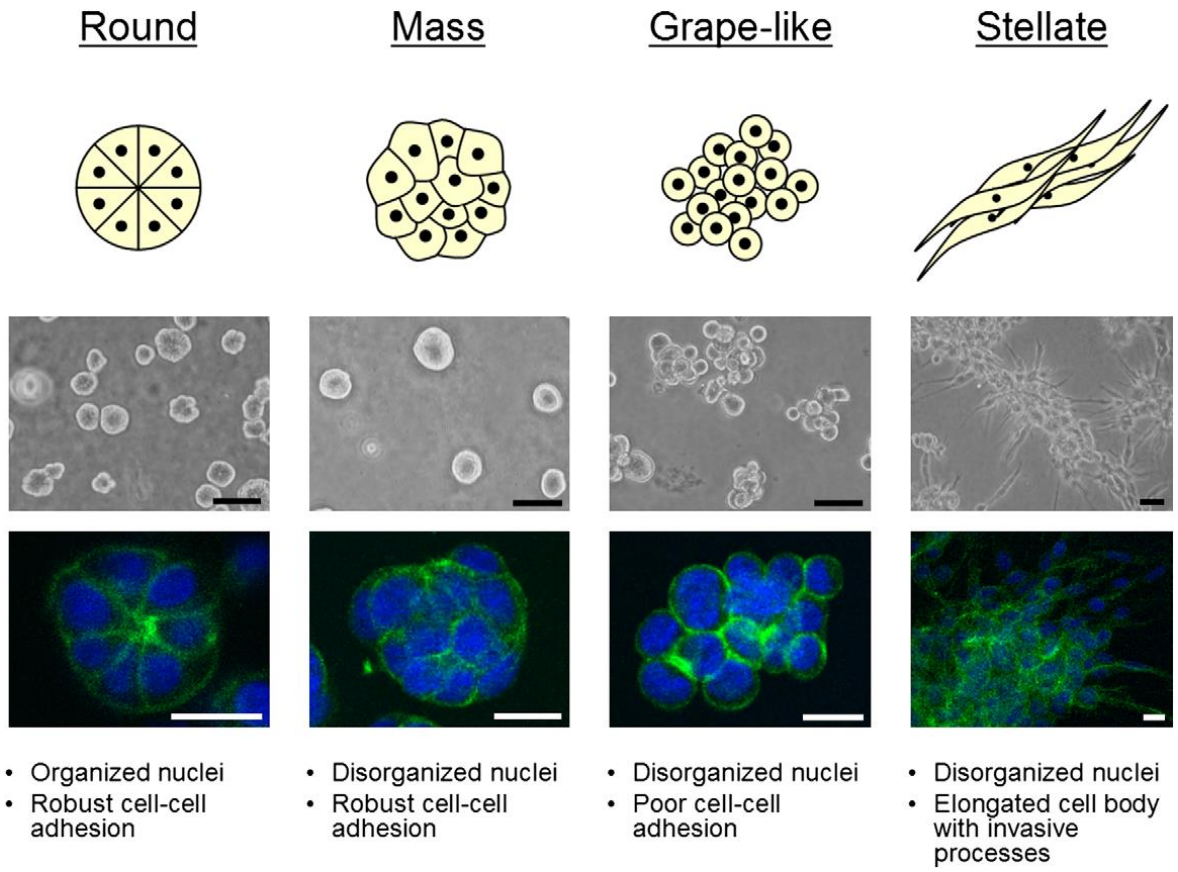
肺癌では、単発 CTC は担癌、非担癌でも検出
CTC clusters は担癌のみで検出

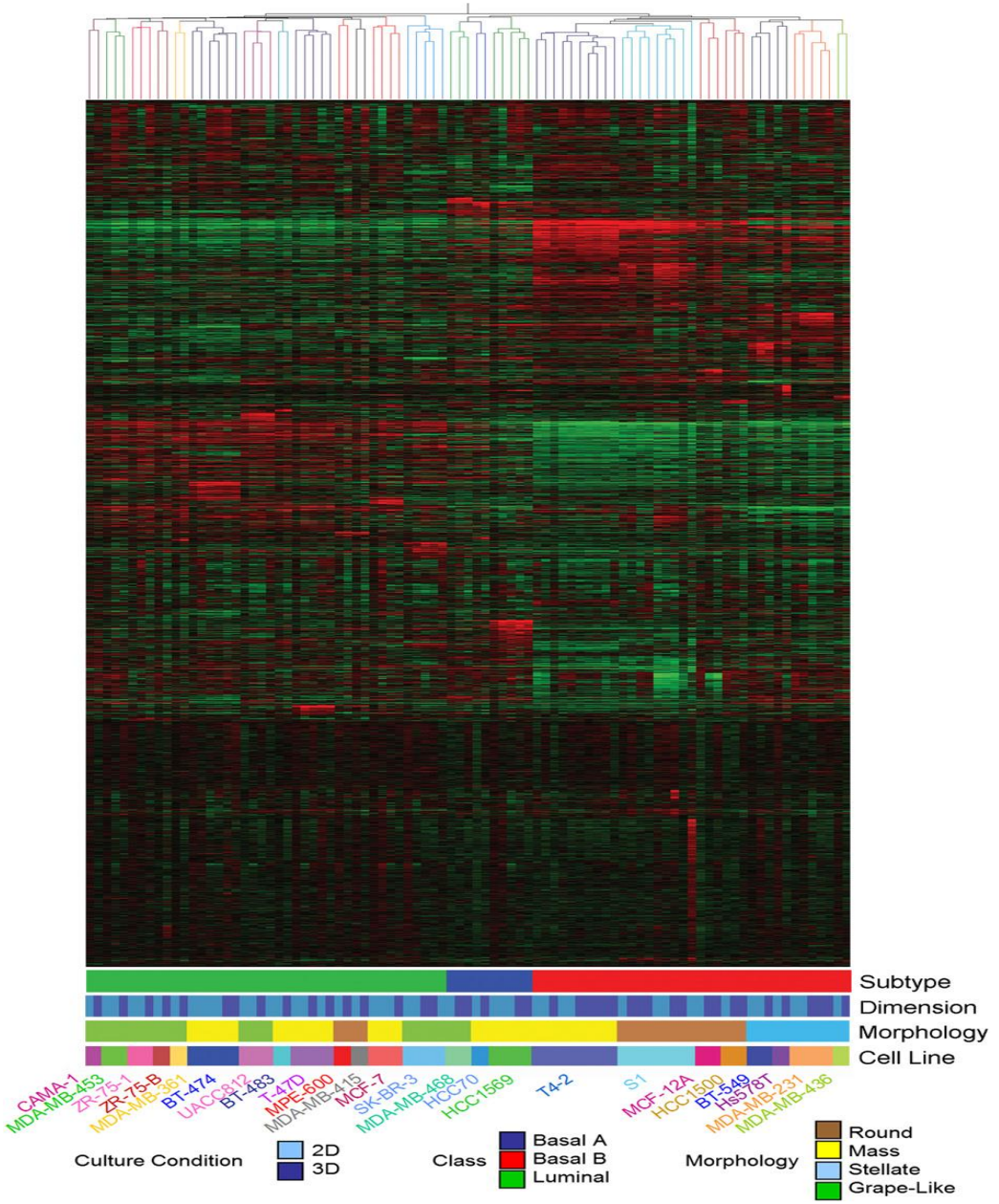
- Design
  - Prospective observational
- Inclusion criterion
  - A) Lung cancer
  - B) U.S. Preventive Services Task Force recommends (grade B evidence): 55–80 years, ≥30 pack-year smoking history, current smokers or quit within last 15 years.
  - C) Healthy controls were never-smoking volunteers.
- Exclusion criterion
  - Concurrent/past history of cancer
- CTC detection/isolation
  - Size selection method



Manjunath Y, et al. Lung Cancer. 2019;134:147-150.

Cluster morphology & gene expression





Kenny PA, et al. Mol Oncol. 2007;1:84-96.

Clustered CTC: 肺癌症例における高悪性腫瘍の予測因子

ARTICLE

1. **Clustered Circulating Tumor Cells in Lung Adenocarcinoma: Implications of Test Results of Continuous Variables.**
   - Watanabe T, et al. Anticancer Res. 2020;40:7089-7094.
2. **Circulating tumor cells detected only after surgery for non-small cell lung cancer: is it a predictor of recurrence?**
   - Sawabata N, et al. J Thorac Dis. 2020;12:4623-4632.
3. **Cluster circulating tumor cells in surgical cases of lung cancer.**
   - Sawabata N, et al. Gen Thorac Cardiovasc Surg. 2020 Sep;68(9):975-983.
4. **Poor Prognosis Indicated by Venous Circulating Tumor Cell Clusters in Early-Stage Lung Cancers.**
   - Murlidhar V, et al. Cancer Res. 2017 Sep 15;77(18):5194-5206
5. **Perioperative circulating tumor cells in surgical patients with non-small cell lung cancer: does surgical manipulation dislodge cancer cells thus allowing them to pass into the peripheral blood?**
   - Sawabata N, et al. Surg Today. 2016 Dec;46(12):1402-1409.
6. Prevalence and number of circulating tumour cells and microemboli at diagnosis of advanced NSCLC.
   - Mascalchi M, et al. J Cancer Res Clin Oncol. 2016 Jan;142(1):195-200.
7. **Novel approach for detection of isolated tumor cells in pulmonary vein using negative selection method: morphological classification and clinical implications.**
   - Funaki S, et al. Eur J Cardiothorac Surg. 2011 Aug;40(2):322-7.
8. Detection of circulating tumour cells with a hybrid (epithelial/mesenchymal) phenotype in patients with metastatic non-small cell lung cancer.
   - Lecharpentier A, et al. Br J Cancer. 2011 Oct 25;105(9):1338-41.

Post-operation; Pre-operation; Non-surgical cases

TNM分類（8版，2017年）

T ― 原発腫瘍

TX：原発腫瘍の存在が判定できない，あるいは喀痰または気管支洗浄液細胞診でのみ陽性で画像診断や気管支鏡では観察できない

T0：原発腫瘍を認めないTis：上皮内癌（carcinoma in situ）：肺野型の場合は，充実成分径0cmかつ病変全体径≦3 cm

T1：腫瘍の充実成分径≦3cm，肺または臓側胸膜に覆われている，葉気管支より中枢への浸潤が気管支鏡上認められない（すなわち主気管支に及んでいない）

T1mi：微少浸潤性腺癌：部分充実型を示し，充実成分径≦0.5cmかつ病変全体径≦3 cm

T1a：充実成分径≦1cmでかつTis・T1miには相当しない

T1b：充実成分径＞1cmでかつ≦2cm

T1c：充実成分径＞2cmでかつ≦3cm

T2：充実成分径＞3cmでかつ≦5cm，または充実成分径≦3cmでも以下のいずれかであるもの

- 主気管支に及ぶが気管分岐部には及ばない
- 臓側胸膜に浸潤
- 肺門まで連続する部分的または一側全体の無気肺か閉塞性肺炎がある

T2a：充実成分径＞3cmでかつ≦4cm

T2b：充実成分径＞4cmでかつ≦5cm

T3：充実成分径＞5cmでかつ≦7cm，または充実成分径≦5cmでも以下のいずれかであるもの

- 壁側胸膜，胸壁（superior sulcus tumorを含む），横隔神経，心膜のいずれかに直接浸潤
- 同一葉内の不連続な副腫瘍結節

T4：充実成分径＞7cm，または大きさを問わず横隔膜，縦隔，心臓，大血管，気管，反回神経，食道，椎体，気管分岐部への浸潤，あるいは同側の異なった肺葉内の副腫瘍結節

N ― 所属リンパ節

NX：所属リンパ節評価不能

N0：所属リンパ節転移なし

N1：同側の気管支周囲かつ/または同側肺門，肺内リンパ節への転移で原発腫瘍の直接浸潤を含める

N2：同側縦隔かつ/または気管分岐下リンパ節への転移

N3：対側縦隔，対側肺門，同側あるいは対側の前斜角筋，鎖骨上窩リンパ節への転移

M ― 遠隔転移

M0：遠隔転移なし

M1：遠隔転移がある

M1a：対側肺内の副腫瘍結節，胸膜または心膜の結節，悪性胸水（同側・対側），悪性心嚢水

M1b：肺以外の一臓器への単発遠隔転移がある

M1c：肺以外の一臓器または多臓器への多発遠隔転移がある

液状検体；末梢血循環血液と同様

日本肺癌学会編：肺癌取扱い規約第8版（2017）．金原出版から改定

肺癌の病期分類（TNM分類）

8版，2017年		N0	N1	N2	N3	M1a	M1b 単発 遠隔転移	M1c 多発 遠隔転移
T1	T1a（≦1cm）	ⅠA1	ⅡB	ⅢA	ⅢB	ⅣA	ⅣA	ⅣB
	T1b（1-2cm）	ⅠA2	ⅡB	ⅢA	ⅢB	ⅣA	ⅣA	ⅣB
	T1c（2-3cm）	ⅠA3	ⅡB	ⅢA	ⅢB	ⅣA	ⅣA	ⅣB
T2	T2a（3-4cm）	ⅠB	ⅡB	ⅢA	ⅢB	ⅣA	ⅣA	ⅣB
	T2b（4-5cm）	ⅡA	ⅡB	ⅢA	ⅢB	ⅣA	ⅣA	ⅣB
T3	T3（5-7cm）	ⅡB	ⅢA	ⅢB	ⅢC	ⅣA	ⅣA	ⅣB
T4	T4（>7cm）	ⅢA	ⅢA	ⅢB	ⅢC	ⅣA	ⅣA	ⅣB

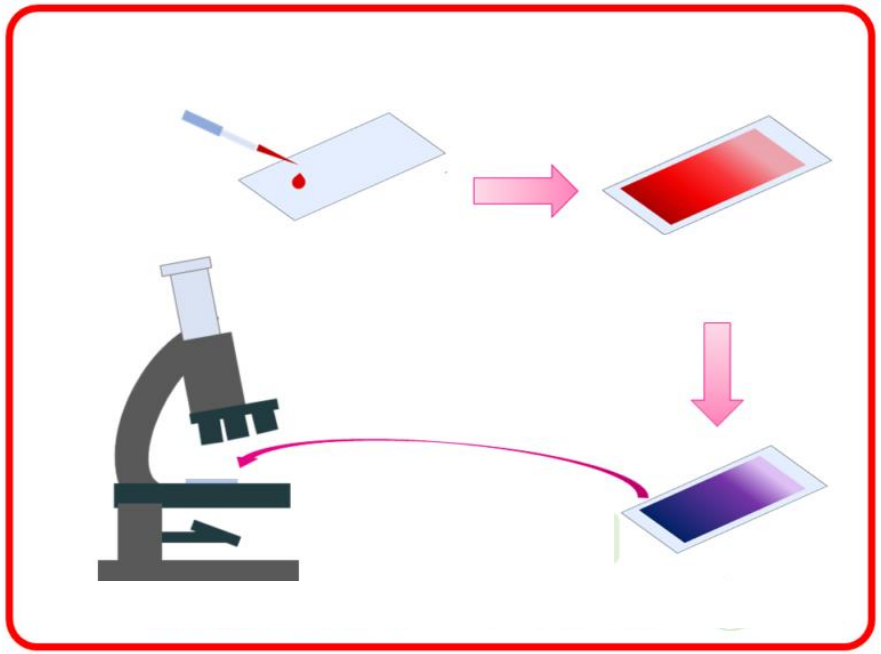
日本肺癌学会編：肺癌取扱い規約第8版（p6，2017）．金原出版より作成

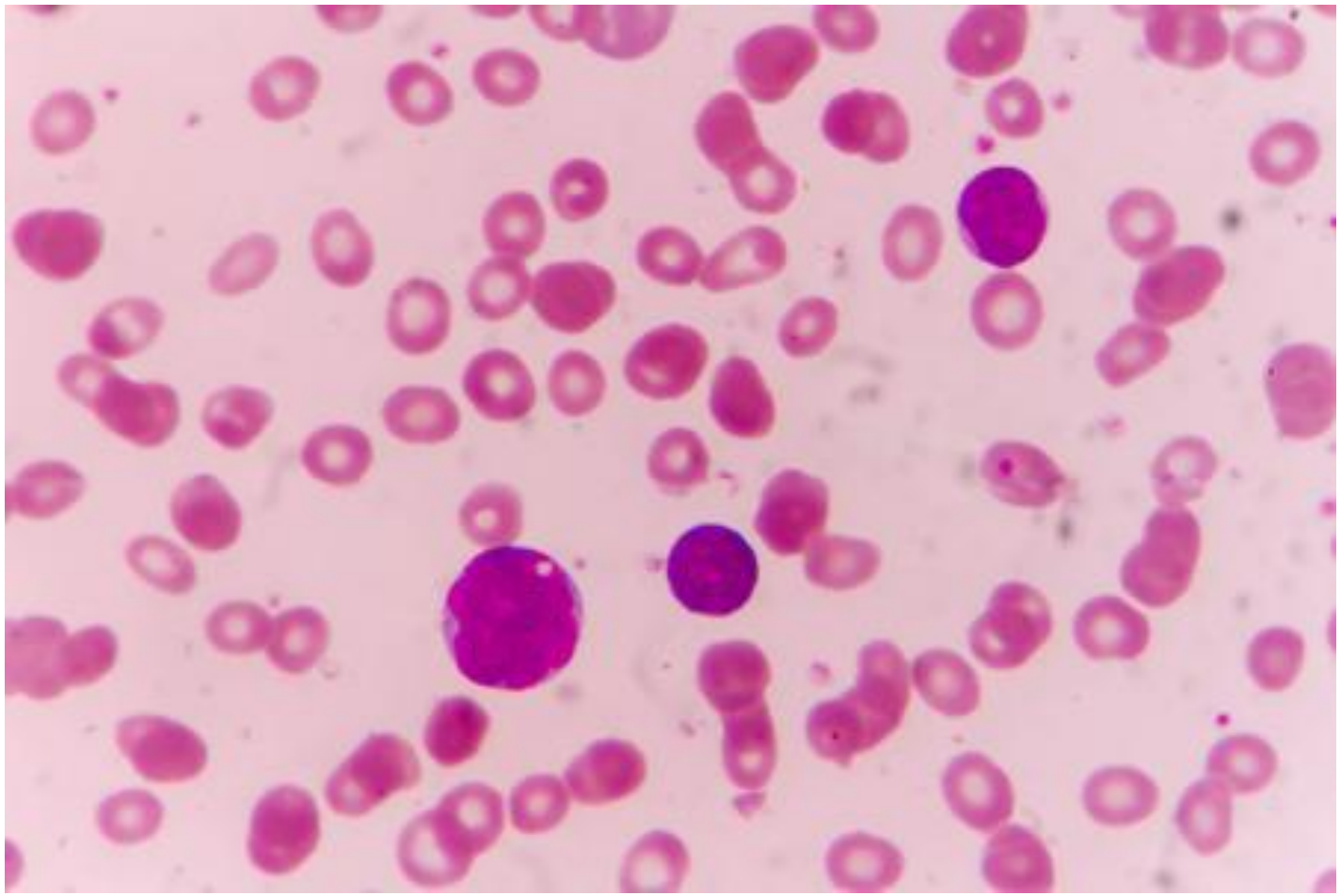
目次

- □肺癌手術の実際
- □肺癌手術症例における遊離腫瘍細胞(ITC)の含意
- **□肺癌手術症例における末梢血循環腫瘍細胞(CTC)の含意**
  - CTCとは?
  - CTCの肺癌手術症例における特徴
  - **CTC抽出法**
  - CTCをターゲットとしたLiquid biopsy

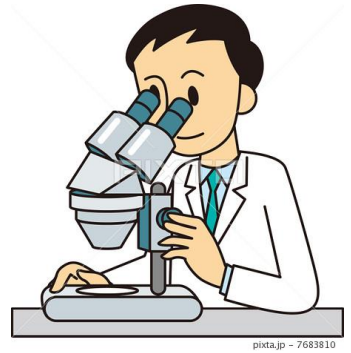
https://jp.freepik.com/premium-vector/samurai-sword_6696687.htm#page=1&query=samurai&position=35

目視の末血象：ギムザ染色
Huge cell in blood smears ≒ CTC

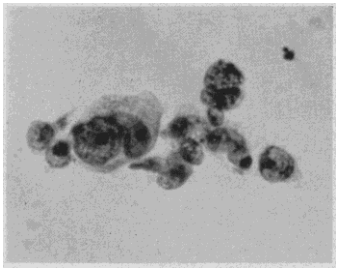




CTC: circulating tumor cell
Historical background



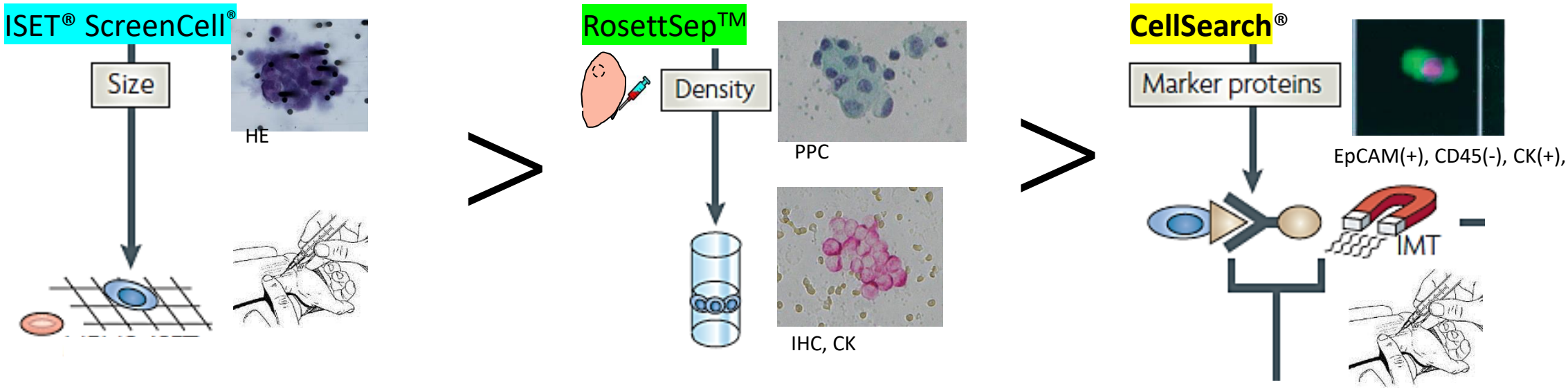
- Free cancer cells in the blood
  - Sanson M. Faint remarkable de diatheses cancereuse. Gaz Med de Paris;2:140 1834
- “Seed and soil”
  - Paget S. THE DISTRIBUTION OF SECONDARY GROWTHS IN CANCER OF THE BREAST.The Lancet 133:571-573 1889
- Cancer infection
  - Ryall C et al. The technique of cancer operations, with reference to the danger of cancer infection. BMJ;2:1005-8 1908
- CTC via cytology
  - 1950’s-1960’s



Stuart et al Arch of surg 1958

Clustered CTC を抽出するための利用可能な形態学的方法

Method		ISET®	ScreenCell®	RosettSepTM	CellSearch®
Selection		Size		Negative, Density	Positive, Antibody
Target		Large, **Cluster**	Large, **Cluster**	CD45(-)	EpCAM(+), CD45(-), CK(+),
Exclusive machine		Needed	**Not needed**	Not needed	Needed (FDA)
Cell collection	Rate	**Excellent**	**Excellent**	Fir (CTC)	Excellent
	Cluster	**Excellent**	**Excellent**	**Good**	**Fair**



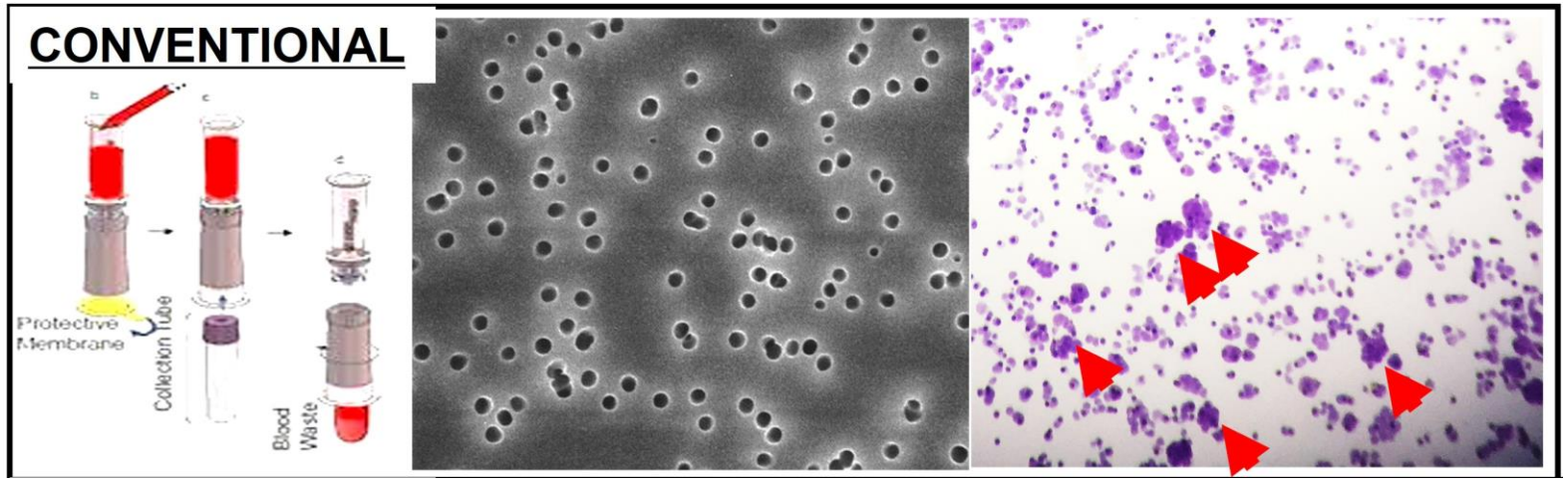
新製品：安くて簡単すぐできるCTC抽出フィルター

Brand new filter: US patent suspended

'TORAY'

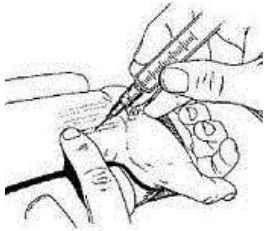
Innovation by Chemistry

COMFIDENTIAL

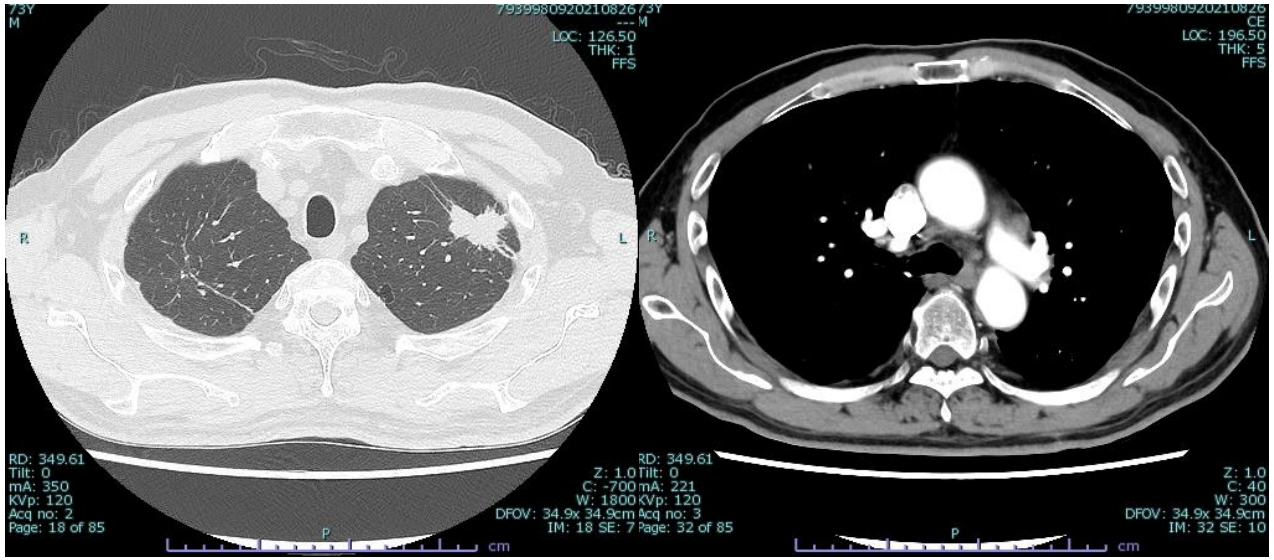


72才　男性　cT2aN2M0 stage IIIA

- 縦郭リンパ節：肺動脈に強固に浸潤癒着→試験開胸
- 原発巣のDebulking
- V(+), Ly(+), PL3



- 術前CTC(+)

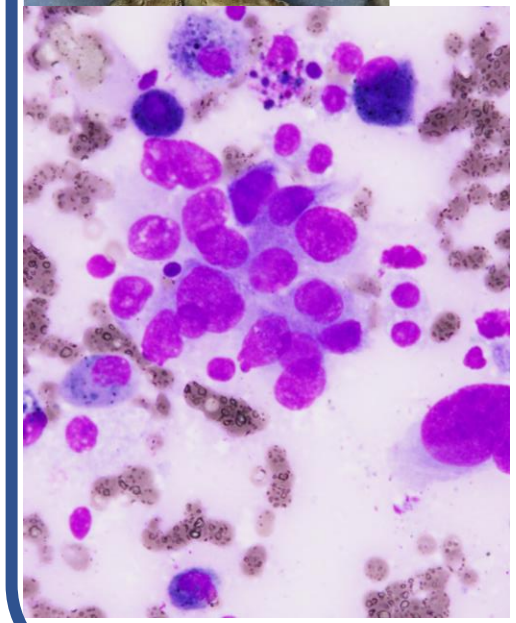


捺印細胞診と同じ形態

confidential

US patent suspended

腫瘍捺印



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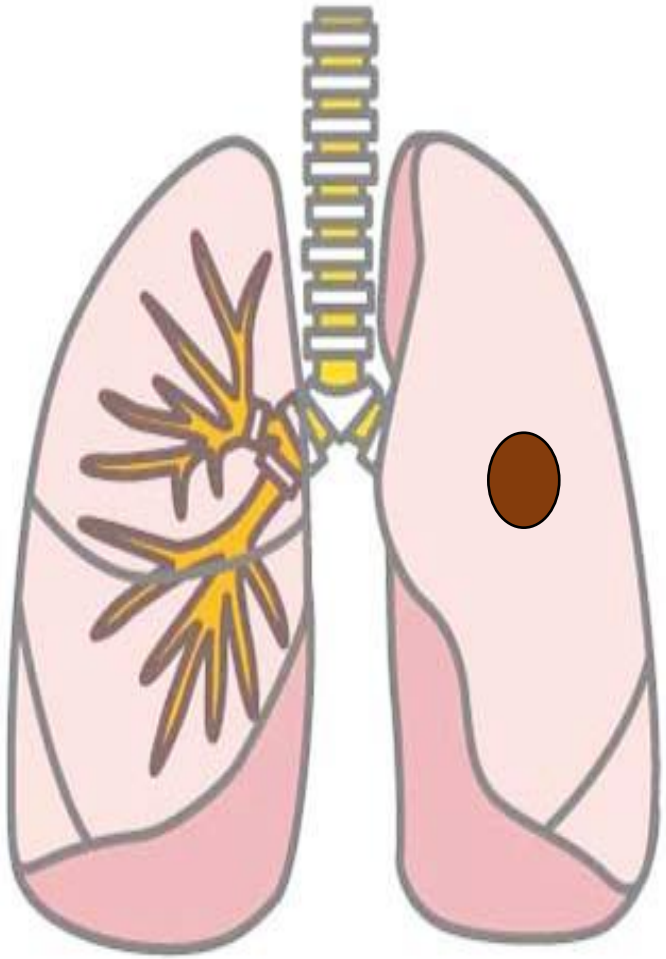
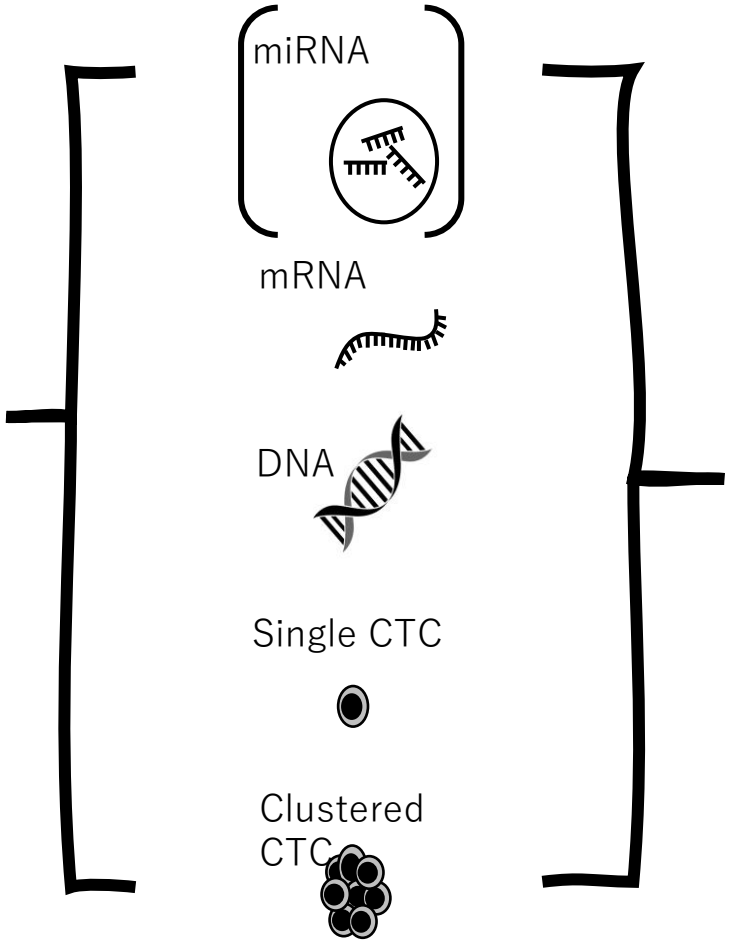
Liquid biopsy of peripheral blood; for clustered CTC



Peripheral blood

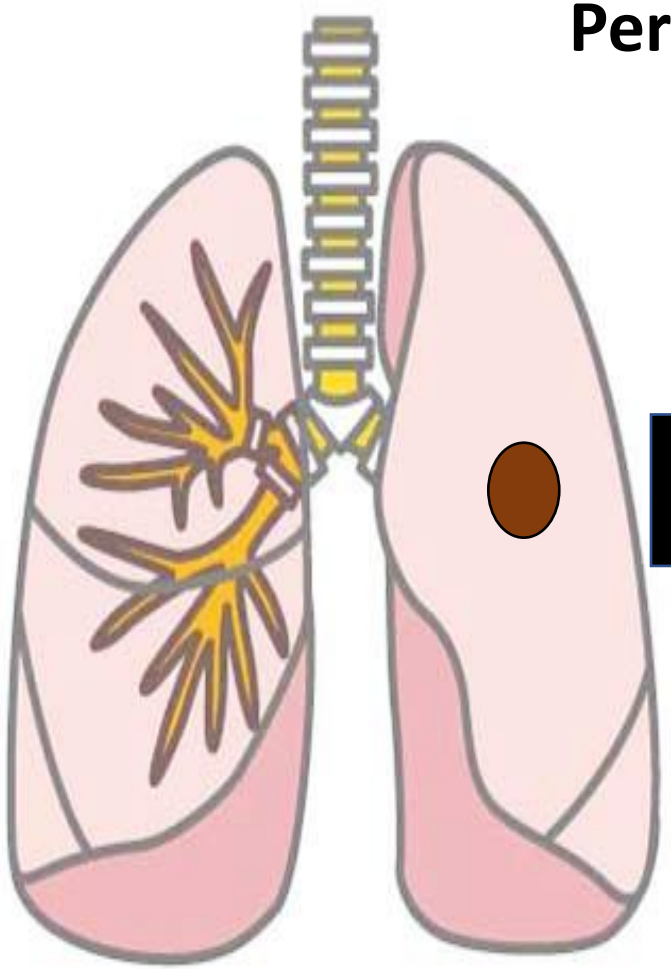


Pathological-molecular

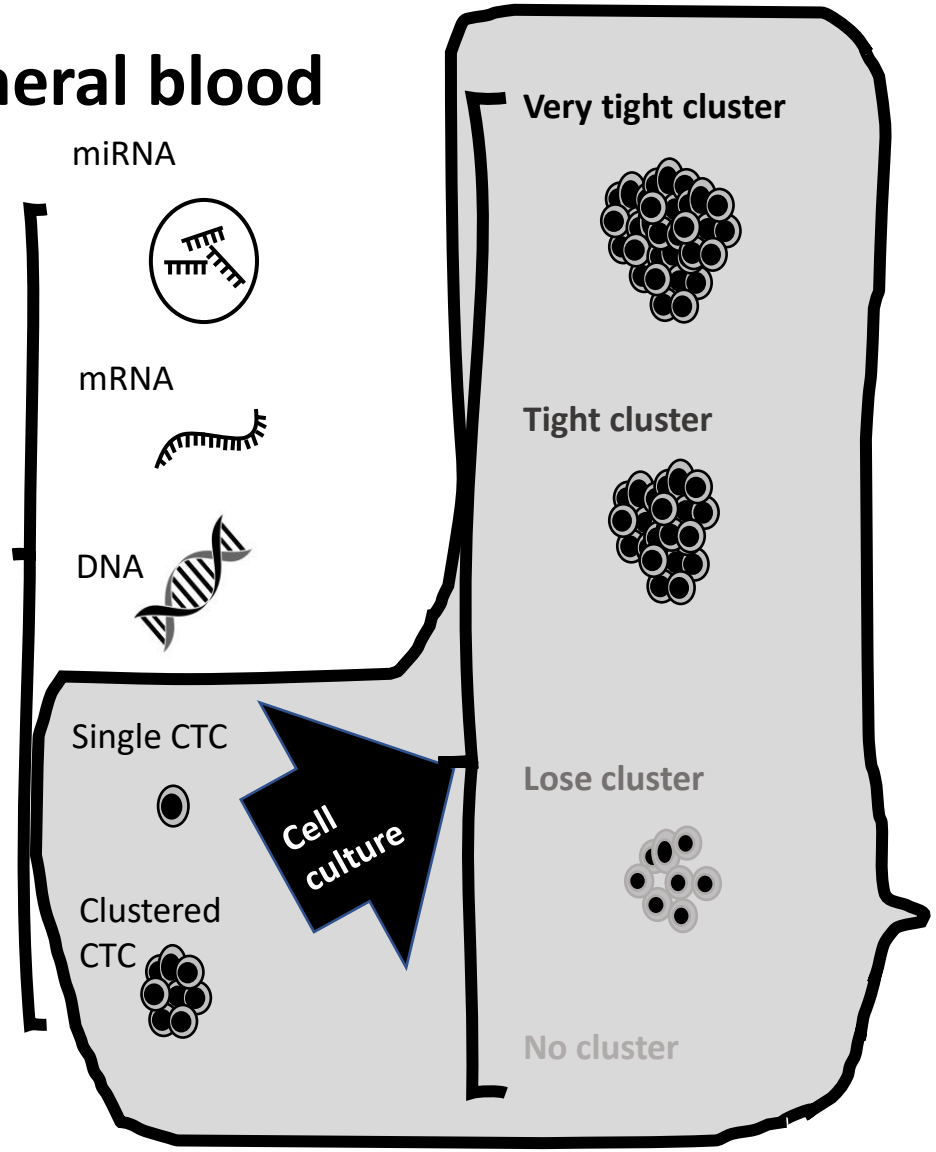
Tumor cells (Cytology)
Antigen (Ag) (PD-1, PD-L1, CTL-4, etc)
PCR (EGFR, ALK, ROS1, etc)
Tumor mutation burden: TMB
Next reneration sequencer NGS (Panel)
Cell culture/cell lines

■, available in CTC alone

CTC as liquid biopsy using Brand-new filter



Peripheral blood



Pathological and molecular biological diagnostics

Tumor cells (Cytology)
Antigen (Ag) (PD-1, PD-L1, CTL-4, etc)
PCR (EGFR, ALK, ROS1, etc)
Tumor mutation burden: TMB
Next reneration sequencer NGS (Panel)
Cell culture/cell lines

Demonstrated in cell-line cell

Future perspective

Lung cancer outlook

Measurements of the number of circulating tumour cells in the blood could help oncologists to determine the best treatment for their patients with lung cancer and improve survival times. By Benjamin Plackett

of treatment and warn of potential relapses.

we're still trying to pin it down," he says. "I can't promise it won't change in the coming years."

The results showed, unsurprisingly, that higher CTC levels both before and after treatment were significantly associated with an increased risk of relapse.

A second study[5] took blood samples from 104 surgical patients at an early stage of lung cancer. The results confirmed that high CTC levels correspond with a lower survival rate. Noriyoshi Sawabata, a thoracic surgeon at Nara Medical University in Kashihara, Japan, who led the study, says the findings mean that CTC monitoring has a clinical future. "I would like to see CTC tests become routine as they correspond with patient outcome," he says.

Tailored treatments

There is plenty of evidence that high levels of CTCs in lung cancer are an accurate predictor of worse outcomes. "The essential question

Noriyoshi Sawabata, a thoracic surgeon at Nara Medical University in Kashihara, Japan, says the findings mean that CTC monitoring has a clinical future. "CTC検査が患者の転帰に対応するので、CTC検査が日常的になることを望む," he says.

Take home message

1. 肺癌術後再発は術後の遺残癌細胞から起こる
2. 遺残癌細胞には微小転移、遊離癌細胞、末梢血循環癌細胞(CTC)などがある
3. 肺癌手術はCTCを誘発
4. クラスター化CTC は悪性度が高く、長期生存し、かつ回遊性がある
5. 周術期のCTCモニタリングは、クラスター化CTCに焦点を当てることによりより含意が高まる
6. CTCはliquate biopsyのターゲットになりうる
7. 簡単で安価なCTCを回収フィルターが利用可能になった

Thank you
for your attention