

第60回関西胸部外科学会学術集会教育講演 胸部外科この10年の進歩：肺悪性腫瘍 EL 7-2:大腸癌肺転移手術の最近の話題

関西医科大学 呼吸器外科講座
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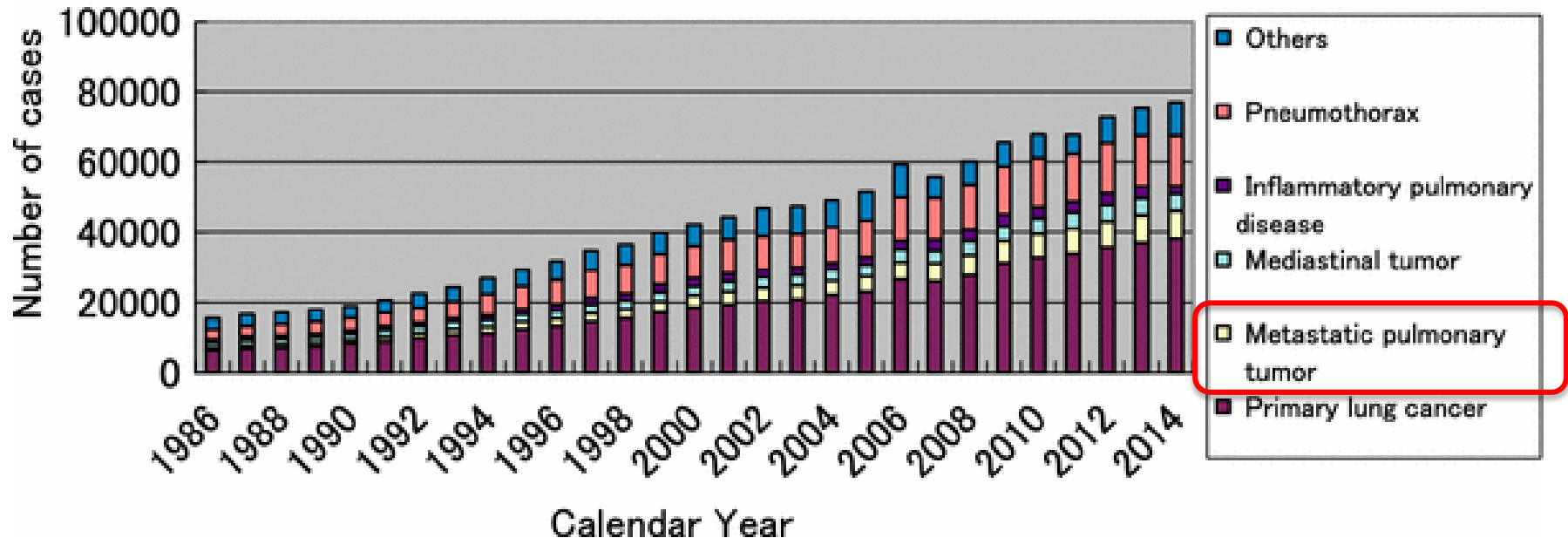


本邦での転移性肺腫瘍手術件数推移

日本胸部外科学会年次集計

- Thoracic and cardiovascular surgery in Japan during 2014 : Annual report by The Japanese Association for Thoracic Surgery. [1]
 - Gen Thorac Cardiovasc Surg. 2016 Nov;64(11):665-697.
- Metastatic pulmonary tumor:8057 cases (colo-rectal cancer 3902 cases)

General Thoracic Surgery



ガイドライン

Thomfordらによる転移性肺腫瘍切除の原則

- The surgical treatment of metastatic tumors in the lungs. [2]
 - Thomford NR, Woolner LB, Clagett OT.
 - J Thorac Cardiovasc Surg. 1965;49:357-63.
 - ❖ The patient must be a good risk for surgical intervention.
 - ❖ The primary malignancy is controlled.
 - ❖ There is no evidence of metastatic disease elsewhere in the body.
 - ❖ Roentgenologic evidence of pulmonary metastasis is limited to one lung

McCormackらによる転移性肺腫瘍切除基準

- Pulmonary Resection in Metastatic Carcinoma.
[3]
 - McCormack PM, Bains MS, Beattie EJ Jr, Martini N.
 - Chest 1978;73(2):163-6.
 - ❖ Primary site controlled or controllable
 - ❖ No extrapulmonary metastatic sites demonstrable
 - ❖ Good surgical risk
 - ❖ No effective treatment available by nonsurgical means

ガイドライン

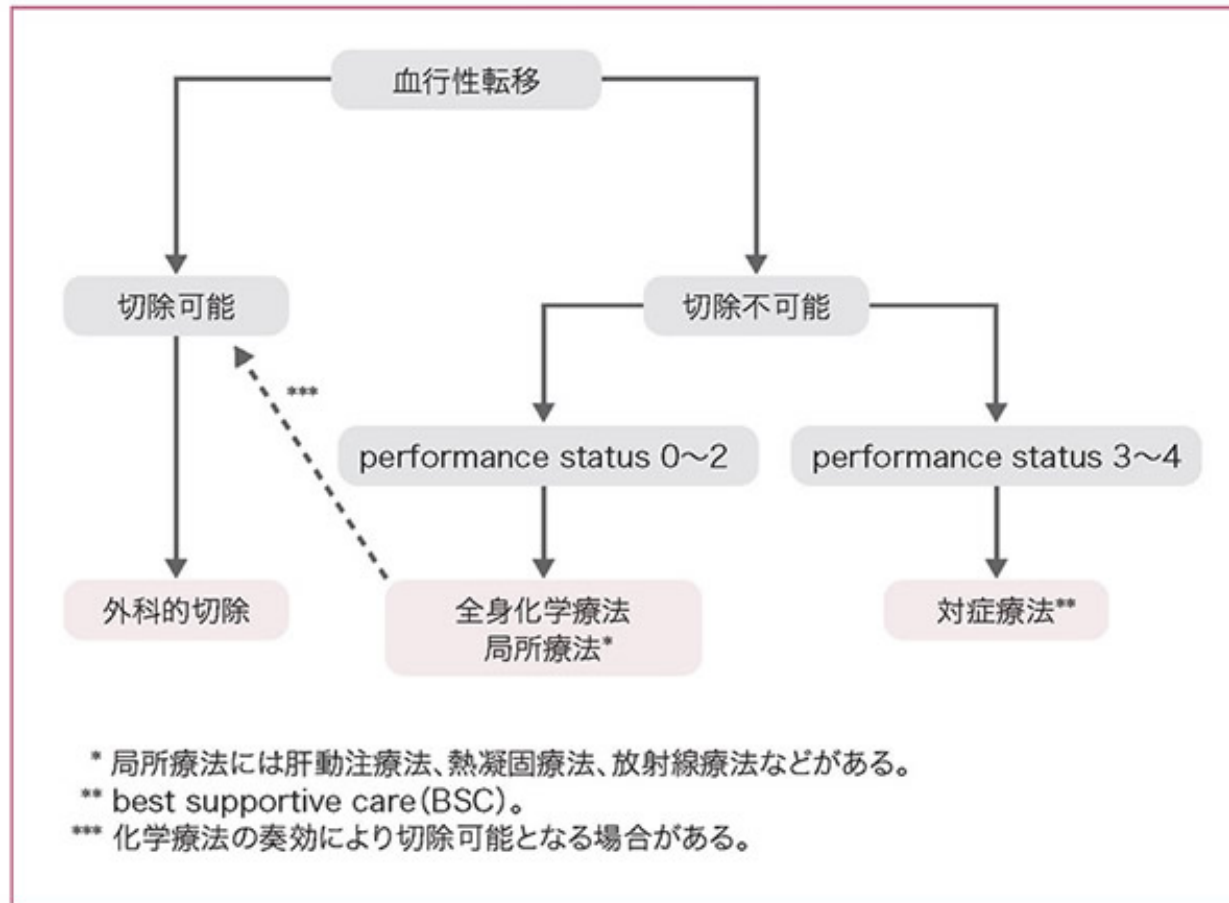
- 日本癌治療学会 <http://jsco-cpg.jp/guideline/13.html#IV-2>
 - がん診療ガイドライン [4]
 - 大腸がん
 - 血行性転移の治療方針
 - 2) 肺転移の治療方針
- 大腸癌研究会 <http://www.jscrc.jp/guideline/2014/particular.html#no3>
 - 大腸癌治療ガイドライン [5]
 - 4. 血行性転移の治療方針

大腸癌肺転移の治療方針

- 肺転移の治療には、肺切除と全身化学療法、放射線療法がある。
- 肺転移巣の切除が可能であれば肺切除を考慮する。
- 肺切除には系統的切除と部分（非系統的）切除がある。

血行性転移治療方針アルゴリズム [6]

〔血行性転移の治療方針〕



http://www.jscr.jp/guideline/2014/img/algorithm_hematogenous_metastases.jpg

大腸癌肺転移：肺切除適応基準

- 耐術可能。
- 原発巣が制御されているか，制御可能。
- 肺転移巣を遺残なく切除可能。
- 肺外転移がないか，制御可能。
- 十分な残肺機能。

大腸癌肺転移：肺切除適応基準 付記

- 切除不能肺転移で全身状態が一定以上に保たれる場合は、全身化学療法を考慮する。
- 耐術不能な場合でも、原発巣と肺外転移が制御されているか、制御可能で、5 cm 以内の肺転移個数が3個以内であれば体幹部定位放射線治療も考慮する
- 全身状態が不良な場合は適切なBSCを行う。

大腸癌肺転移切除例予後因子

症例の蓄積から得られた知見

The International Registry of Lung Metastases

- Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. [7]
 - Pastorino U, Buyse M, Friedel G, Ginsberg RJ, Girard P, Goldstraw P, Johnston M, McCormack P, Pass H, Putnam JB Jr; International Registry of Lung Metastases.
 - J Thorac Cardiovasc Surg. 1997 Jan;113(1):37-49.
- ❖ Factors affecting prognosis
 - Resectability
 - Disease-free interval
 - Number of metastases
 - Type of primary tumor (bowel [645 cases], RR: 0.831, 95% CI: 0.721-0.959)

Possible Prognostic factors

- Risk Factors for Survival after Lung Metastasectomy in Colorectal Cancer Patients: A Systematic Review and Meta-Analysis [8]
 - Gonzalez M, Poncet A, Combescure C, Robert J, Ris HB, Gervaz P.
 - Ann Surg Oncol 2013;20:572–579.
 - 25 studies including a total of 2925 pts
 - 4 parameters associated with poor prognosis

variables	HR	95% CI
Short DFI	1.59	1.27-1.98
multiple lung metastases	2.04	1.72-2.41
positive hilar and/or mediastinal LN	1.65	1.35-2.02
elevated pre-thoracotomy CEA	1.91	1.57-2.32

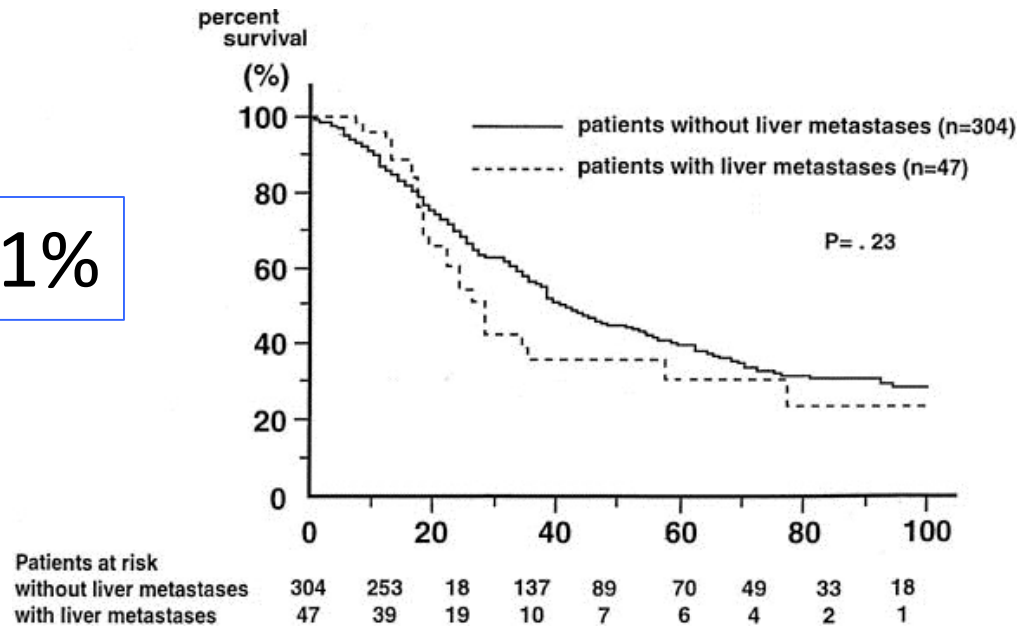
Possible Prognostic factors

- Surgical Resection of Pulmonary Metastases From Colorectal Cancer: A Systematic Review of Published Series. [9]
 - Pfannschmidt J, Dienemann H, Hoffmann H
 - Ann Thorac Surg 2007;84(1):324-338.
 - ❖ “YES”, “NO”, or “Nonreporting”
 - Stage of the primary tumor, Liver resection, DFI, CEA, Age, Histology of the primary tumor, Lung resection, R0 vs R1/2, Number of lesions, Thoracic lymph node involvement, Maximum tumor size
 - ❖ “YES” or “Nonreporting”
 - Aerogenous spread with floating cancer cell, Bcl-2+, Galectin-3, CEA-associated structural entropy
 - ❖ “NO” or “Nonreporting”
 - Distribution, Repeat pulmonary resection, ChemoRx

Metastatic Lung Tumor Study Group of Japan (関東)

- Surgical treatment for both pulmonary and hepatic metastases from colorectal cancer. [10]
 - Kobayashi K, et al. J Thorac Cardiovasc Surg. 1999;118:1090-6.
- Prognostic factors for OS: single metastasis/ few hepatic metastases

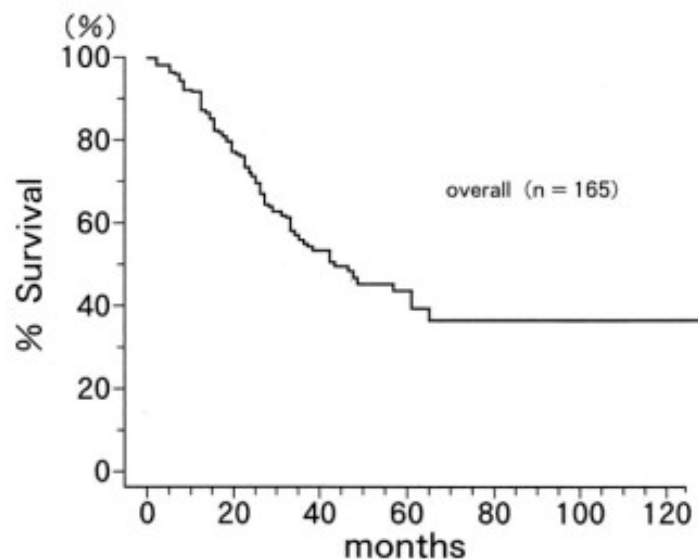
OS@5y:31%



Kansai Clinical Oncology Group (関西)

- Pulmonary metastasectomy for 165 patients with colorectal carcinoma: A prognostic assessment. [11]
 - Saito Y, et al. J Thorac Cardiovasc Surg. 2002;124:1007-13
- Prognostic factors for OS: LN metastasis/ preoperative CEA

OS@5y:40%

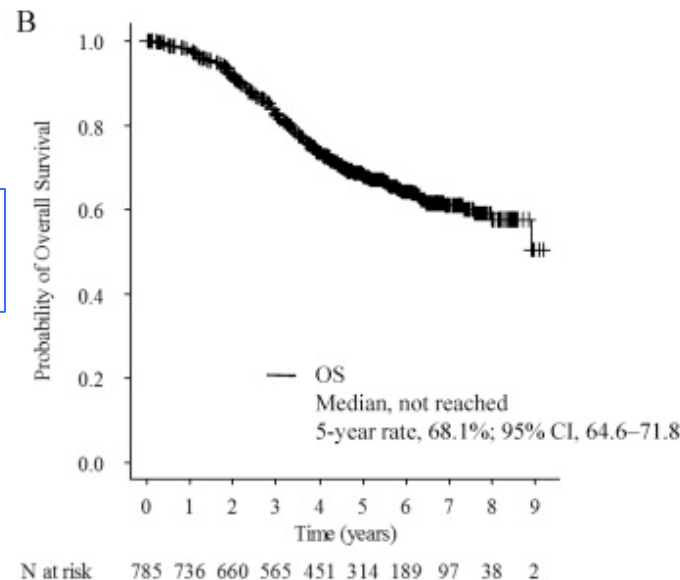


Japanese nationwide retrospective study of resected pulmonary metastases from colorectal cancer

46 institutions, 2004-2008

- Surgical Outcome and Prognostic Stratification for Pulmonary Metastasis from Colorectal Cancer. [12]
 - Okumura T, et al. Ann Thorac Surg 2017 [Epub ahead of print]
- Prognostic factors for OS: age \geq 70, DFI $<$ 2 year, extra-thoracic metastasis, abnormal CEA, number \geq 3

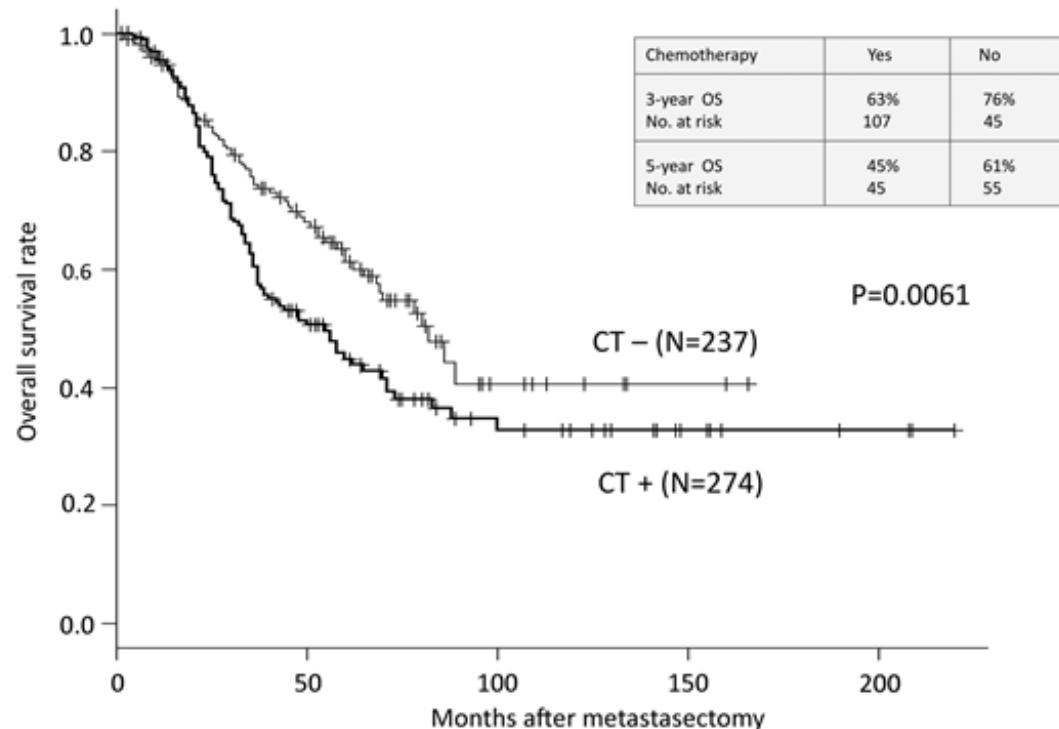
OS@5y:68%



Metastatic Lung Tumor Study Group of Japan (関東)

26 institutions, 1990-2007

- Recent improvement of survival prognosis after pulmonary metastasectomy and advanced chemotherapy for patients with colorectal cancer. [13]
 - Nakajima J, et al. Eur J Cardiothorac Surg. 2017 May 1;51(5):869-873



(素朴な)疑問

- 転移性肺腫瘍を局所病変のように扱い、局所療法 (resection, ablation, radiation, など) を行うことは適切であるか？
- 肺切除は非手術療法に勝る生存に対する利益があるか？

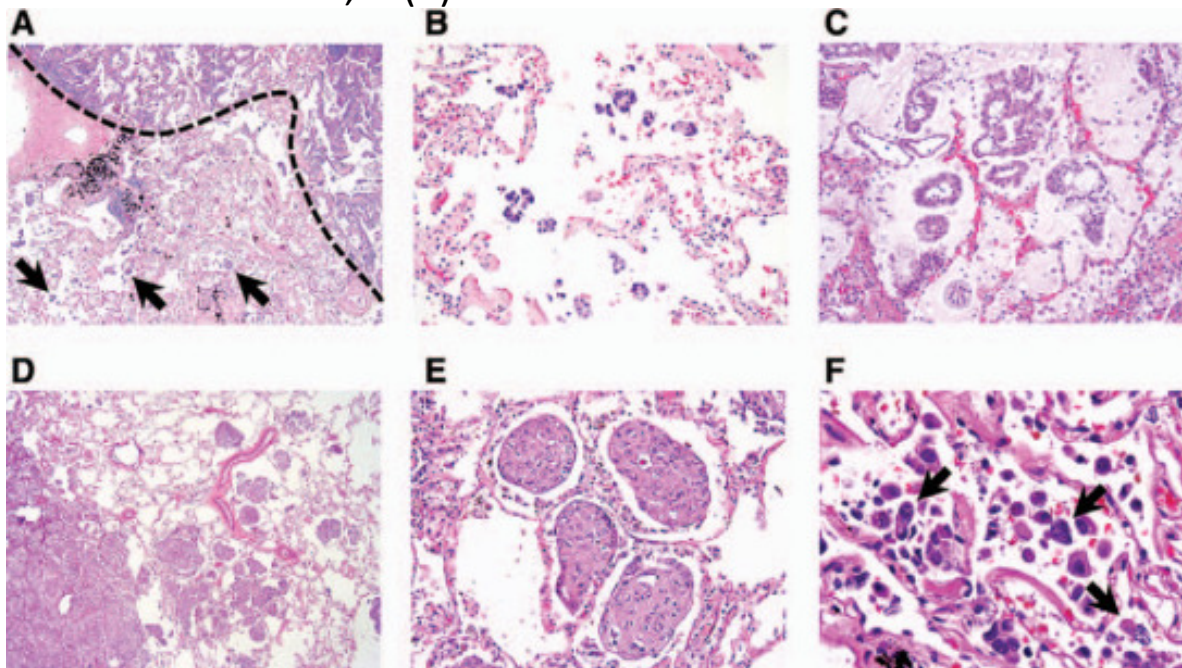
Possible Prognostic factors

- Surgical Resection of Pulmonary Metastases From Colorectal Cancer: A Systematic Review of Published Series. [9]
 - Pfannschmidt J, Dienemann H, Hoffmann H
 - Ann Thorac Surg 2007;84(1):324-338.
 - ❖ “YES”, “NO”, or “Nonreporting”
 - Stage of the primary tumor, Liver resection, DFI, CEA, Age, Histology of the primary tumor, Lung resection, R0 vs R1/2, Number of lesions, Thoracic lymph node involvement, Maximum tumor size
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 - Distribution, Repeat pulmonary resection, ChemoRx

肺癌の気腔散布

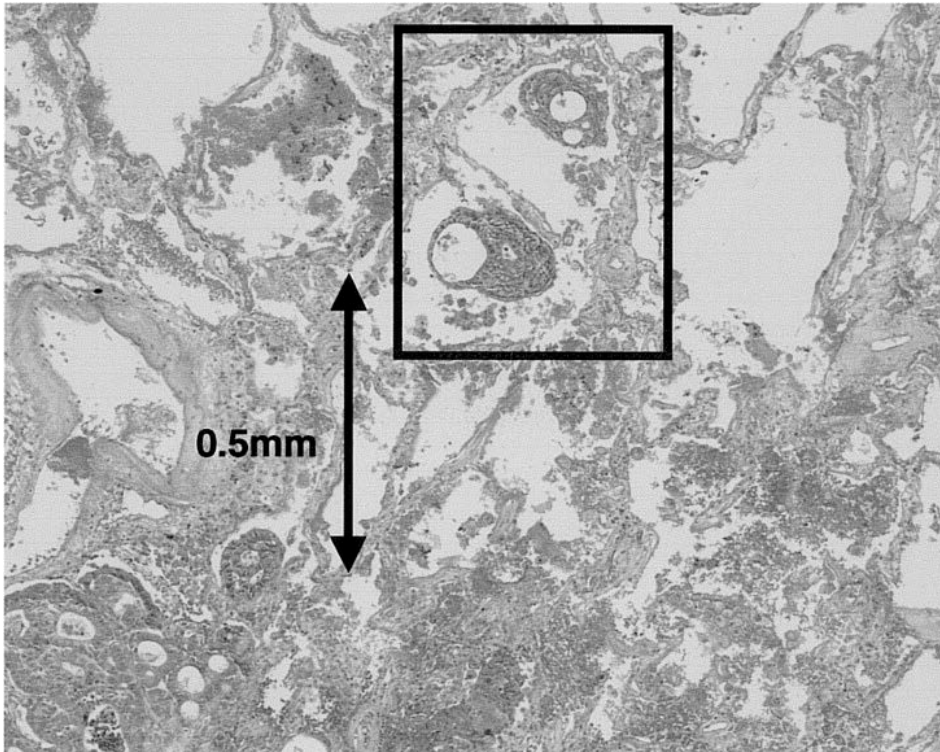
Tumor Spread through Air Space (Tumor STAS)

- Tumor Spread through Air Spaces is an Important Pattern of Invasion and Impacts the Frequency and Location of Recurrences after Limited Resection for Small Stage I Lung Adenocarcinomas. [14]
 - Kadota K, Nitadori J, Sima CS, Ujiie H, Rizk NP, Jones DR, Adusumilli PS, Travis WD.
 - J Thorac Oncol 2015;10(5):806-14.



大腸癌肺転移の気腔散布

- Predictive factors for local recurrence of resected colorectal lung metastases. [15]
 - Shiono S, Ishii G, Nagai K, Yoshida J, Nishimura M, Murata Y, Tsuta K, Kim YH, Nishiwaki Y, Kodama T, Iwasaki M, Ochiai A.
 - Ann Thorac Surg. 2005 Sep;80(3):1040-5.
- Histopathologic prognostic factors in resected colorectal lung metastases. [16]
 - Shiono S, Ishii G, Nagai K, Yoshida J, Nishimura M, Murata Y, Tsuta K, Nishiwaki Y, Kodama T, Ochiai A.
 - Ann Thorac Surg. 2005 Jan;79(1):278-82;

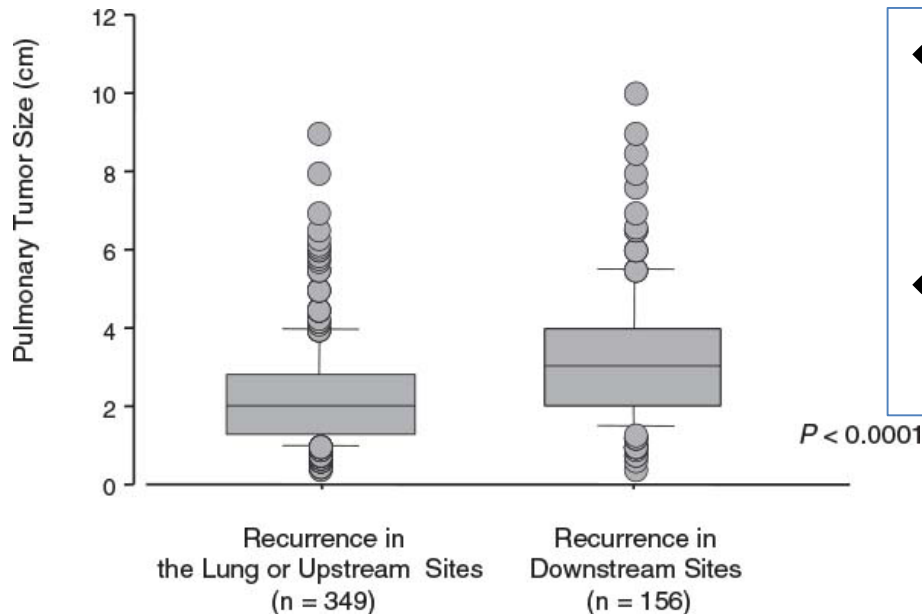


“Aerogenous spreads with floating cancer cell clusters around the main tumor”

Concept of “semi-local disease”

the lung as a filter organ

- Prognostic factors after pulmonary metastasectomy for colorectal cancer and rationale for determining surgical indications: a retrospective analysis. [17]
 - Iida T, Nomori H, Shiba M, Nakajima J, Okumura S, Horio H, Matsuguma H, Ikeda N, Yoshino I, Ozeki Y, Takagi K, Goya T, Kawamura M, Hamada C, Kobayashi K; Metastatic Lung Tumor Study Group of Japan.
 - Ann Surg 2013;257(6):1059-64.



- ❖ Upstream from the lung:
loco-regional sites or the liver
- ❖ Downstream from the lung:
the brain, bone, and so on

切除のタイミング

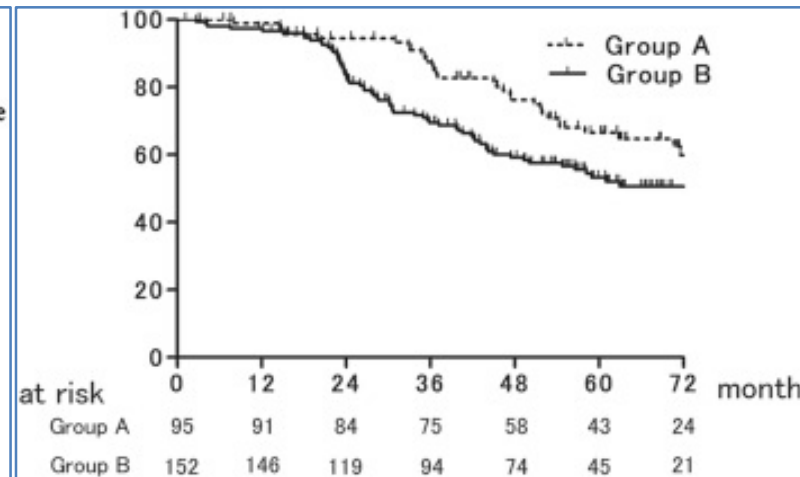
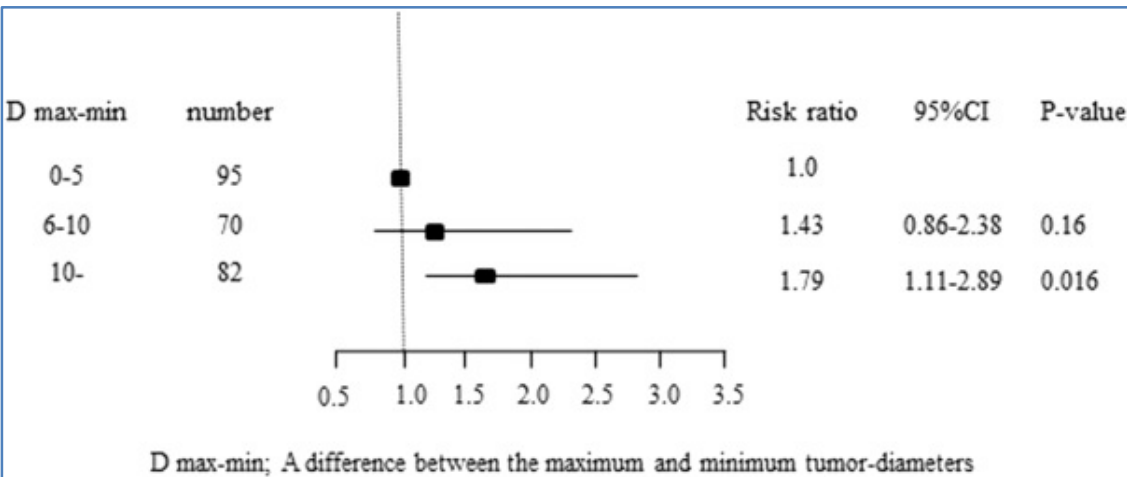
- Optimal timing of pulmonary metastasectomy--is a delayed operation beneficial or counterproductive? [18]
 - Krüger M, Schmitto JD, Wiegmann B, Rajab TK, Haverich A.
 - Eur J Surg Oncol 2014;40(9):1049-55.
- ❖ “There is no evidence that a delayed operation, for example after re-staging following an interval of 3 months, provides a benefit.”
- ❖ “A delayed operation seems justified if the indication for resection is questionable due to a high risk of early multilocal recurrence.”

切除のタイミング

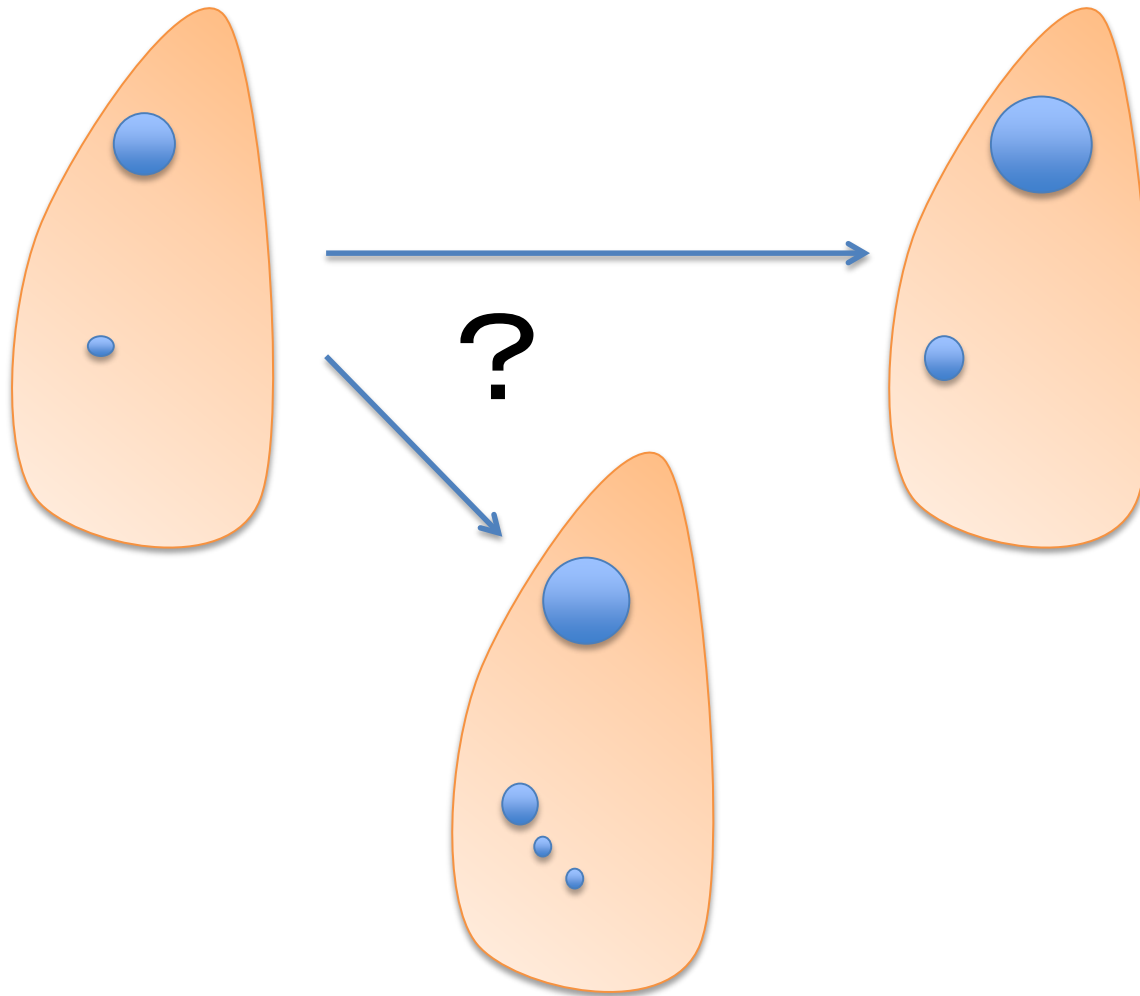
- The optimal timing to resect pulmonary metastasis. [19]
 - Tanaka Y, Maniwa Y, Nishio W, Yoshimura M, Okita Y.
 - Eur J Cardiothorac Surg. 2008 Jun;33(6):1135-8.
- ❖ “Performing metastasectomy at least three months after detection of pulmonary metastasis may significantly improve the prognosis of patients.”

Possible Prognostic factors

- Heterogeneity of Tumor Sizes in Multiple Pulmonary Metastases of Colorectal Cancer as a Prognostic Factor. [20]
 - Maniwa T, Mori K, Ohde Y, Okumura T, Boku N, Hishida T, Sakao Y, Yoshiya K, Hyodo I, Kondo
 - Ann Thorac Surg. 2017 Jan;103(1):254-260.



切除のタイミングをどうする？



手術例の潜在的バイアス

大腸癌肺転移に対する肺切除の頻度

選択された症例

- Diagnosis of colorectal cancer: about 135,000 cases/year [21]
 - http://ganjoho.jp/reg_stat/statistics/stat/summary.html
- 1/2 cases with advanced stage [22]
 - http://ganjoho.jp/reg_stat/statistics/brochure/hosp_c_reg_surv.html

大腸癌肺転移に対する肺切除の頻度 [22]

選択された症例

がん診療連携拠点病院

院内がん登録

2007年生存率集計 報告書

国立がん研究センター がん対策情報センター
がん統計研究部 院内がん登録室

表 3-3-1 対象者の属性:大腸

	男性		女性		全体	
	対象者数	(%)	対象者数	(%)	対象者数	(%)
全体	12,453	100.0	8,843	100.0	21,296	100.0
年齢						
15-39歳	194	1.6	176	2.0	370	1.7
40歳代	490	3.9	432	4.9	922	4.3
50歳代	2,143	17.2	1,504	17.0	3,647	17.1
60歳代	3,797	30.5	2,184	24.7	5,981	28.1
70歳代	4,146	33.3	2,720	30.8	6,866	32.2
80歳以上	1,683	13.5	1,827	20.7	3,510	16.5
UICC TNM 分類治療前ステージ						
I期	3,526	28.3	2,306	26.1	5,832	27.4
II期	2,588	20.8	1,864	21.1	4,452	20.9
III期	3,135	25.2	2,445	27.6	5,580	26.2
IV期	2,252	18.1	1,611	18.2	3,863	18.1
不詳	826	6.6	522	5.9	1,348	6.3
空欄	126	1.0	95	1.1	221	1.0
観血的治療						
有	10,903	87.6	7,783	88.0	18,686	87.7
無	1,550	12.4	1,060	12.0	2,610	12.3
発見経緯						
がん検診	1,362	10.9	935	10.6	2,297	10.8
健康診断・人間ドック	1,189	9.5	650	7.4	1,839	8.6
他疾患経過観察中	2,600	20.9	1,553	17.6	4,153	19.5
その他・不明	7,302	58.6	5,705	64.5	13,007	61.1
部位						
結腸	7,251	58.2	6,006	67.9	13,257	62.3
直腸	5,202	41.8	2,837	32.1	8,039	37.7

大腸癌肺転移に対する肺切除の頻度

選択された症例

- 3,902 pulmonary resections for metastases from colorectal cancer/year
 - Thoracic and cardiovascular surgery in Japan during 2014. [1]
 - General Thoracic and Cardiovascular Surgery 2016:64(11);665-697.

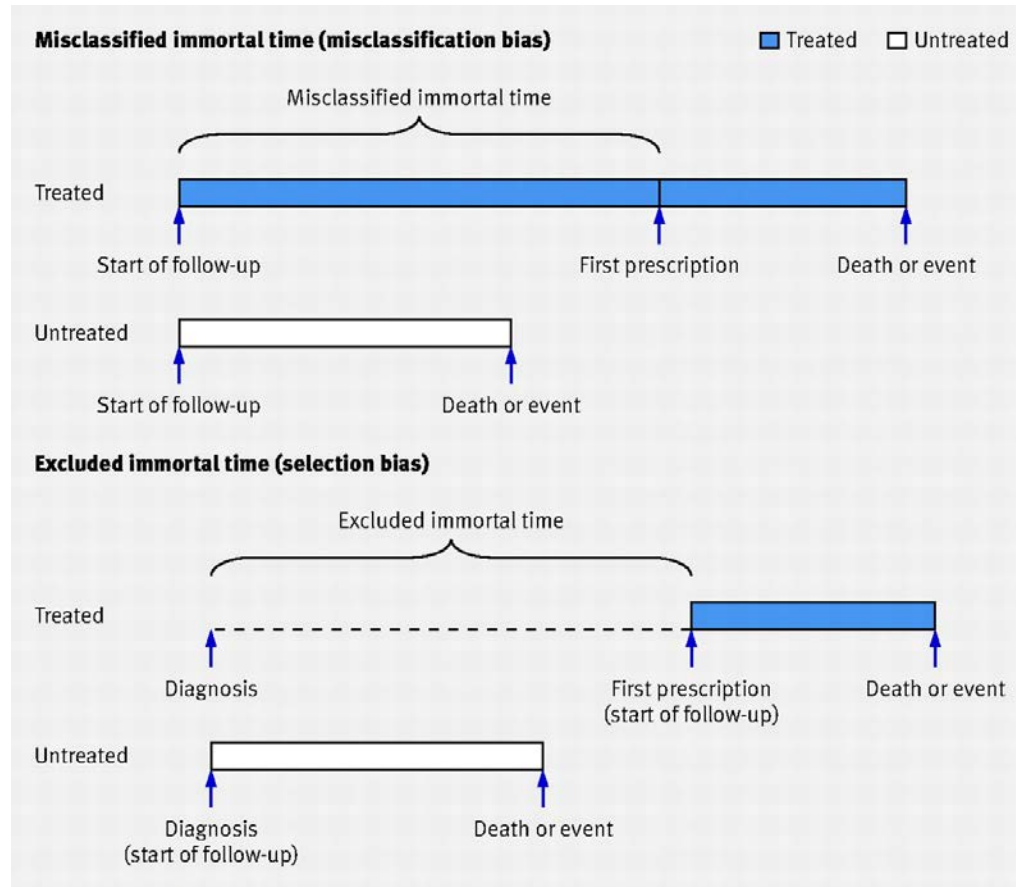
Immortal time bias

- Immortal Time Bias in Pharmacoepidemiology.
[23]
 - Suissa S.
 - Am J Epidemiol 2008;167: 492-499.
- ❖ “underestimate the rate ratio, thereby creating the false illusion that a medication is effective at reducing the rate of major disease outcomes”

Immortal time bias

- Examples identified to be affected by immortal time bias
 - ❖ Cardiac transplantation in man. VI. Prognosis of patients selected for cardiac transplantation. [24]
 - Clark DA, Stinson EB, Griepp RB, Schroeder JS, Shumway NE, Harrison DC.
 - Ann Intern Med 1971;75(1):15-21.
 - ❖ Survival-times after cardiac allografts. [25]
 - Messmer BJ, Nora JJ, Leachman RD, Cooley DA.
 - Lancet. 1969 May 10;1(7602):954-6.
 - ❖ Survival in Academy Award-winning actors and actresses. [26]
 - Redelmeier DA, Singh SM.
 - Ann Intern Med. 2001 May 15;134(10):955-62.

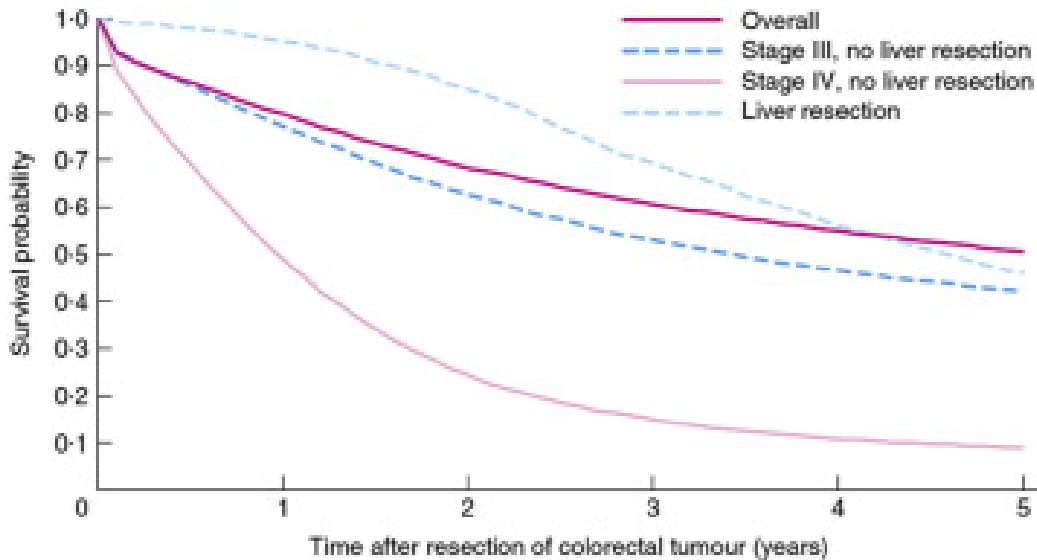
Immortal time bias



Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. Lévesque LE, Hanley JA, Kezouh A, Suissa S. *BMJ* 2010;12;340:b5087. [27]

Immortal time bias

- Survival is higher after repeat lung metastasectomy than after a first metastasectomy: Too good to be true? [28]
 - Treasure T, Mineo T, Ambrogi V, Fiorentino F.
 - J Thorac Cardiovasc Surg. 2015 May;149(5):1249-52

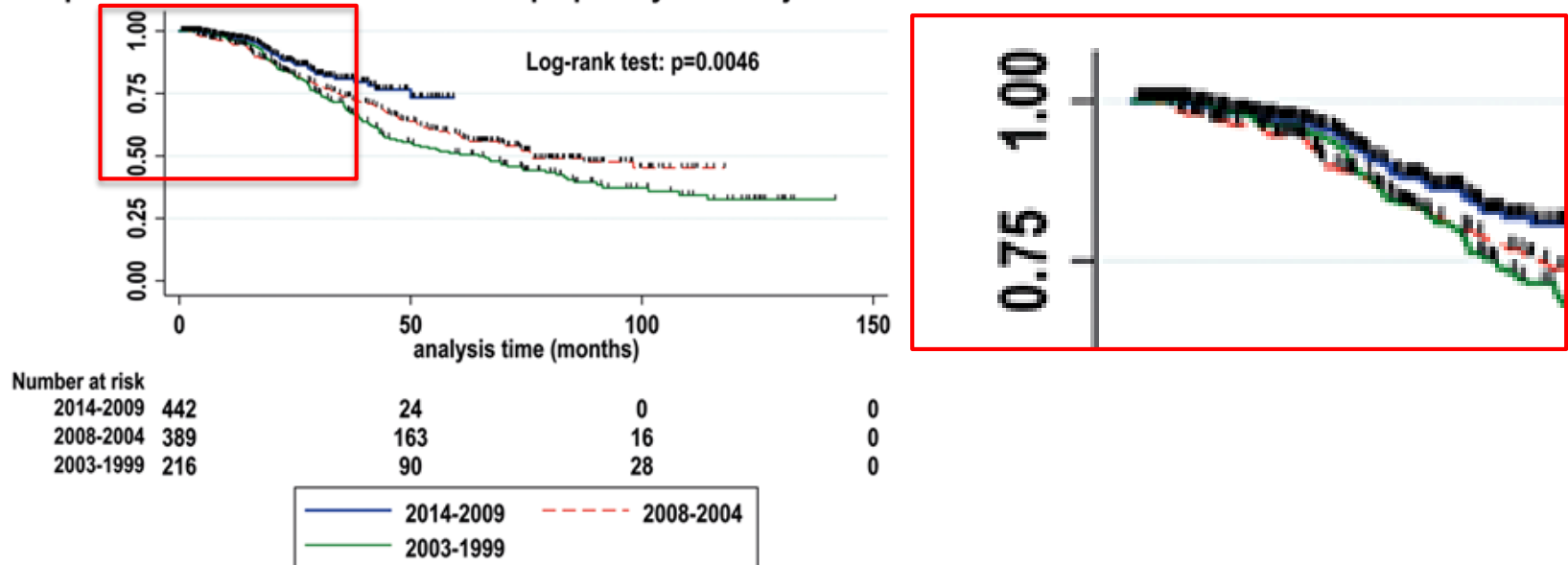


“conditional entry of patients judged clinically to be likely to survive for a reasonable time after operation”

Metastatic Lung Tumor Study Group of Japan (関東)

25 institutions, 1999-2014

Kaplan-Meier survival estimates before propensity-score adjustment



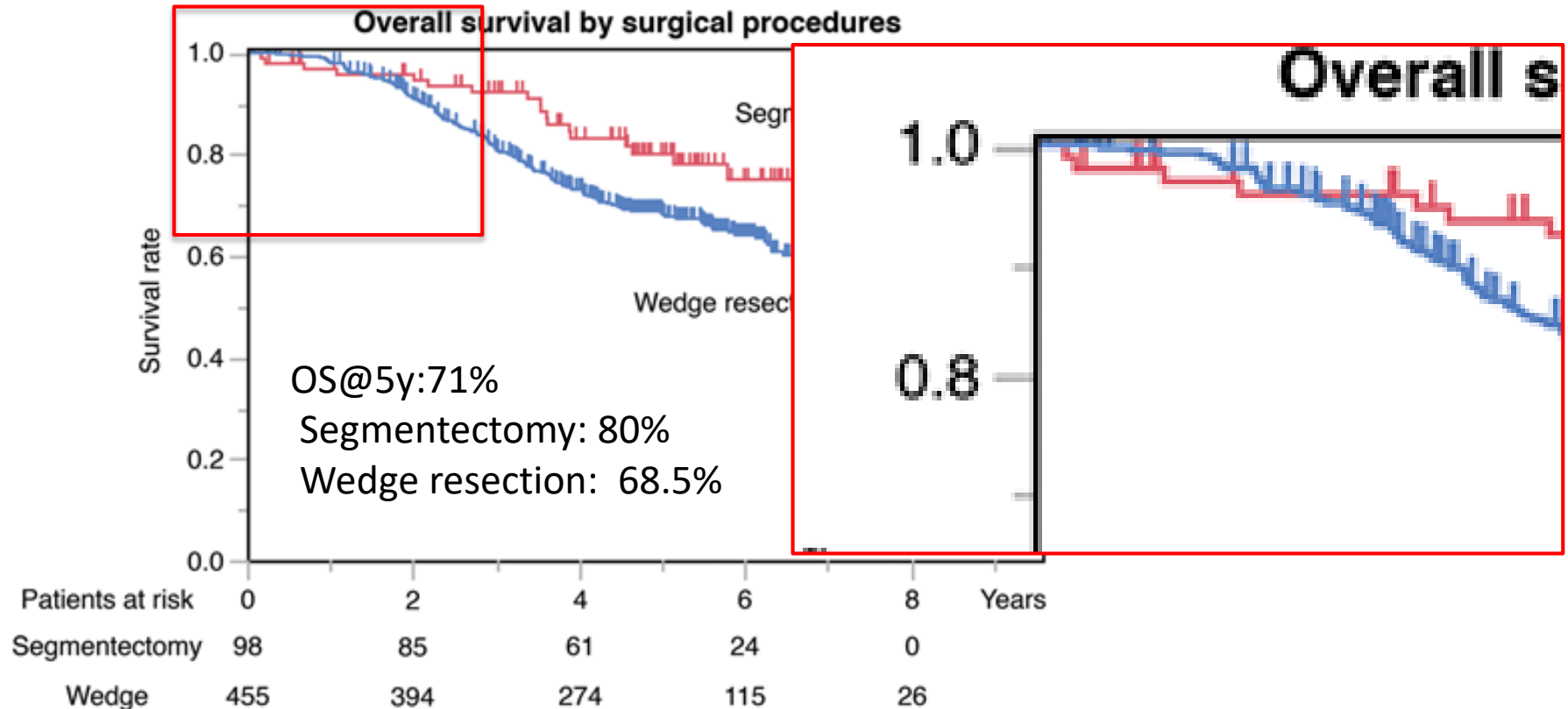
Thoracoscopic surgery versus open surgery for lung metastases of colorectal cancer: a multi-institutional retrospective analysis using propensity score adjustment. [29]

Murakawa T, Sato H, Okumura S, Nakajima J, Horio H, Ozeki Y, Asamura H, Ikeda N, Otsuka H, Matsuguma H, Yoshino I, Chida M, Nakayama M, Iizasa T, Okumura M, Shiono S, Kato R, Iida T, Matsutani N, Kawamura M, Sakao Y, Funai K, Furuyashiki G, Akiyama H, Sugiyama S, Kanauchi N, Shiraishi Y

Eur J Cardiothorac Surg. 2017 Jun 1;51(6):1157-1163

Japanese nationwide retrospective study of resected pulmonary metastases from colorectal cancer

46 institutions, 2004-2008



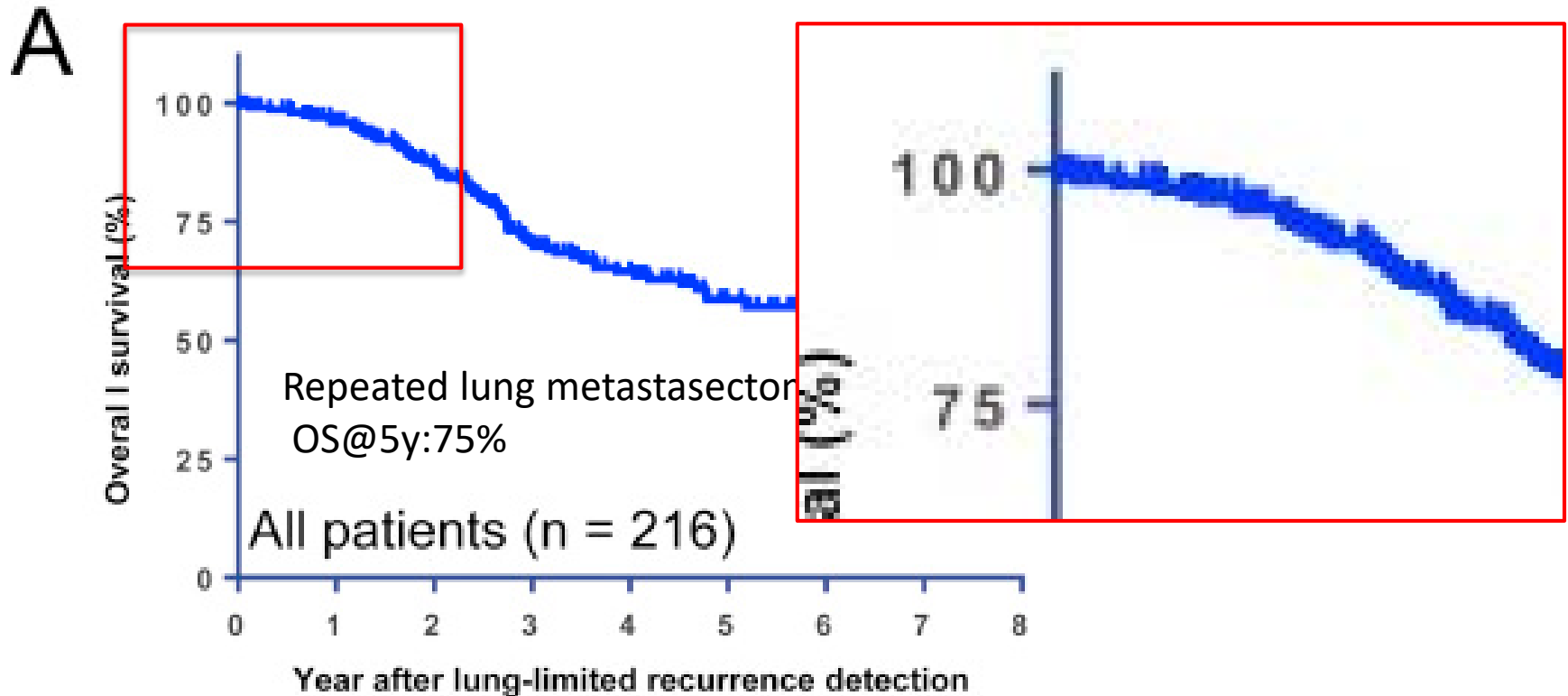
Outcomes of segmentectomy and wedge resection for pulmonary metastases from colorectal cancer.

[30]

Shiono S, Okumura T, Boku N, Hishida T, Ohde Y, Sakao Y, Yoshiya K, Hyodo I, Mori K, Kondo H.
Eur J Cardiothorac Surg. 2016 Oct 23. pii: ezw322. [Epub ahead of print]

Japanese nationwide retrospective study of resected pulmonary metastases from colorectal cancer

46 institutions, 2004-2008



Does Repeated Lung Resection Provide Long-Term Survival for Recurrent Pulmonary Metastases of Colorectal Cancer? Results of a Retrospective Japanese Multicenter Study. [31]

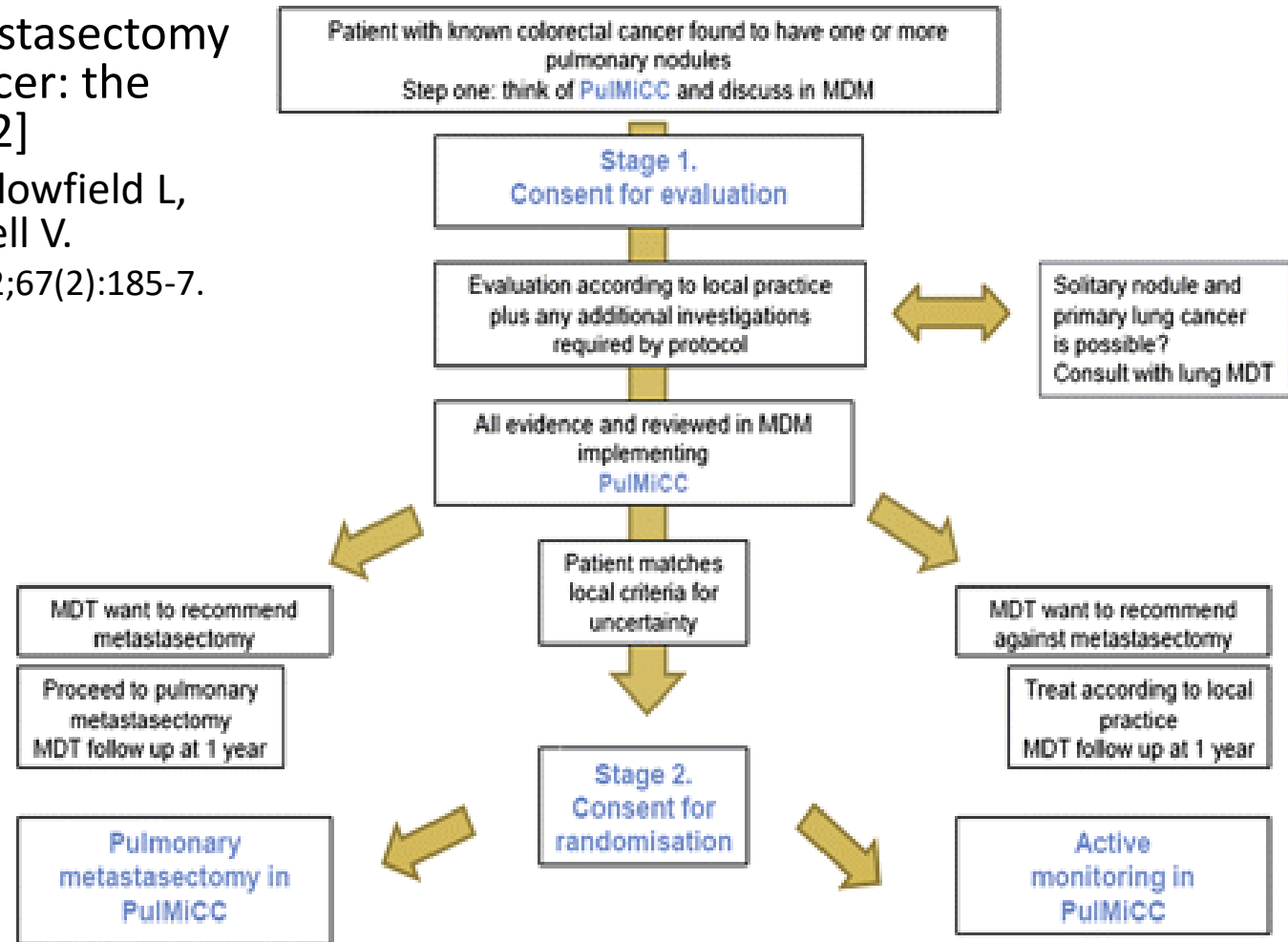
Hishida T, Tsuboi M, Okumura T, Boku N, Ohde Y, Sakao Y, Yoshiya K, Hyodo I, Mori K, Kondo H.

Ann Thorac Surg. 2017 Feb;103(2):399-405.

PulMiCC (Pulmonary Metastasectomy in Colorectal Cancer) Trial

March 2010~

- Pulmonary metastasectomy in colorectal cancer: the PulMiCC trial. [32]
 - Treasure T, Fallowfield L, Lees B, Farewell V.
 - Thorax 2012;67(2):185-7.



鏡視下手術の役割

Criticism

- Thoracoscopic approach may preclude
 - precise identification by palpation
 - sufficient surgical margin due to limited insertion angle of instruments

胸腔鏡手術の位置付け

- Role of video-assisted thoracic surgery in the treatment of pulmonary metastases: results of a prospective trial. [33]
 - McCormack PM, Bains MS, Begg CB, Burt ME, Downey RJ, Panicek DM, Rusch VW, Zakowski M, Ginsberg RJ.
 - Ann Thorac Surg. 1996 Jul;62(1):213-6.
- ❖ “We conclude that video-assisted thoracic surgery should be used only as a diagnostic tool in managing lung metastasis. A thoracotomy is required to achieve complete resection, which is the major survival prognosticator for satisfactory long-term results.”

胸腔鏡手術の位置付け

McCormack PM, et al. Ann Thorac Surg. 1996 Jul;62(1):213-6.

[34]

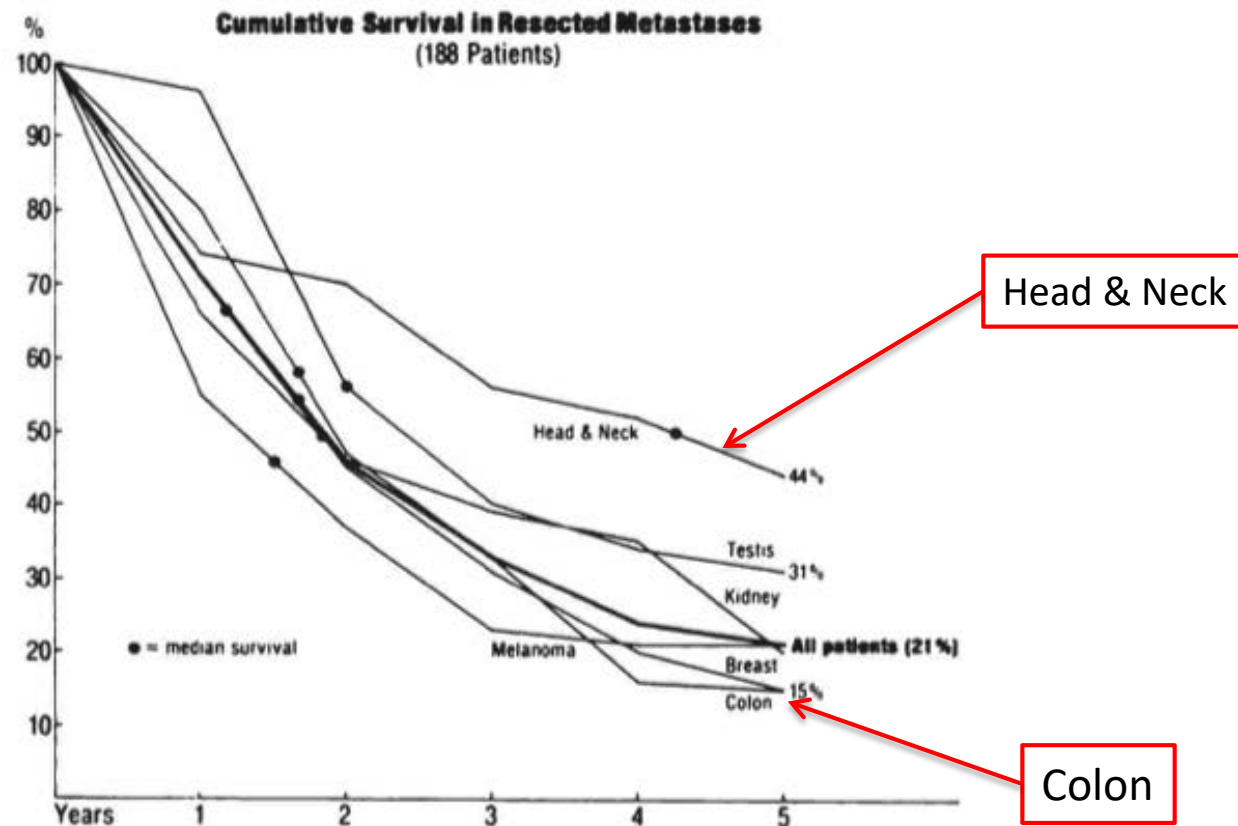


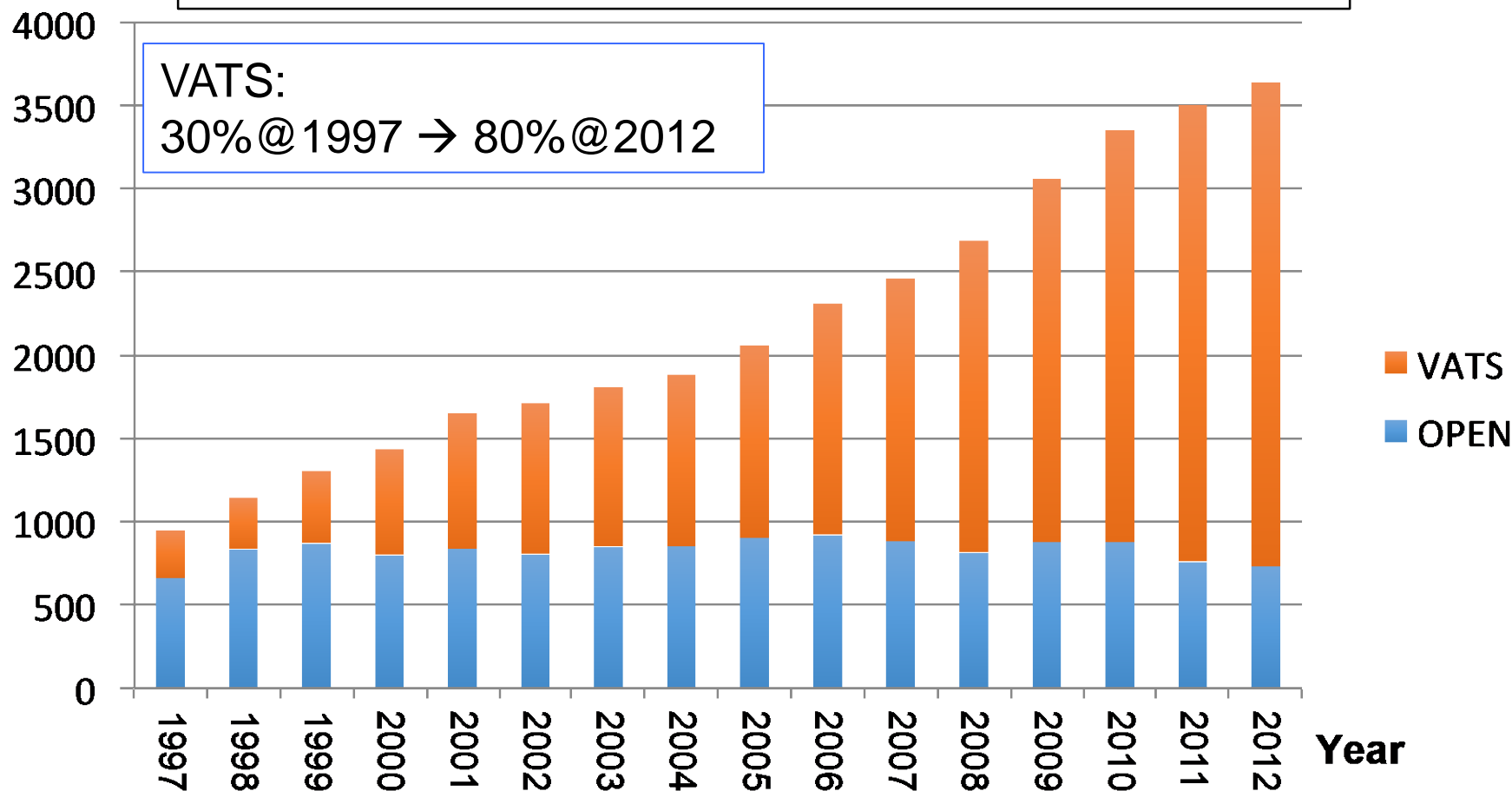
FIGURE 2. Curves for five-year survival from diagnosis and treatment of pulmonary metastases, as determined by actuarial method.

胸腔鏡手術の位置付け

- Thoracoscopic Versus Open Pulmonary Metastasectomy : A Prospective, Sequentially Controlled Study. [35]
 - Eckardt J, Licht PB
 - Chest 2012;142(6), 1598-1602
- A prospective study to determine the incidence of non-imaged malignant pulmonary nodules in patients who undergo metastasectomy by thoracotomy with lung palpation. [36]
 - Cerfolio RJ, Bryant AS, McCarty TP, Minnich DJ.
 - Ann Thorac Surg. 2011 Jun;91(6):1696-700.

Annual survey by the Japanese Association for Thoracic Surgery [37]

Surgery for pulmonary metastasis of colo-rectal cancer



Issue of tumor identification

Pulmonary nodule		Preoperative CT	
		detectable	not detectable
Intraoperative finger palpation	palpable	open: resectable vats: resecatable	open: resectable vats: may lost
	not palpable	open: resectable, but requires preoperative marking vats: resectable, but requires preoperative marking	open: not resectable vats: not resectable

まとめ

- **バイアスこみ**の結果ではあるが大腸癌肺転移例の中で、厳しく選択された症例には肺切除は有力な治療選択肢の一つといえる
- 画像診断・多彩な局在マーキング方法が存在する現在では、胸腔鏡アプローチは許容されると考えられる。