Survival of NSCLC Patients WITHOUT Treatment

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호흡기알레르기내과

엄중섭

Contents

Introduction

THE NATURAL HISTORY OF UNTREATED LUNG CANCER

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The natural history of a deep-seated tumor is difficult to study because the symptoms are commonly insidious and become manifest relatively late in the course of development. Furthermore the determination of malignant tumor presence usually leads to a therapeutic interruption of the course of events. The disease evolution cannot be well understood at the autopsy table, this usually being an end stage. Nor can it be delineated at surgery since this is rarely done at a very early stage in the process and represents only a single point of time in the tumor history.

The natural history of untreated lung cancer can be adequately studied by means of serial roentgen chest examinations. The roentgenogram presents a vivid picture of the lung tumor pathological anatomy and the pathological physiology produced by it. If repeated films at intervals are available, a brilliant illumination of the course of events can be obtained. Since, under favorable conditions lesions as small as 3 mm. in diameter can be found, the opportunity to observe the evolution of lung cancer from its early beginnings is apparent. Such studies must be largely retrospective, because the observation of a lung abnormality usually leads to interruption of the natural course of events. Because routine chest films of apparently well individuals are now made so commonly and failure either to observe a lesion, to interpret it correctly, or to manage it properly is so frequent, it is possible to find cases in which accurate observations over a period of many years can be made. I have now collected 122 cases of proven lung carcinoma, selected only because, fortuitously, chest roentgenograms had been made from six months to 15 years before the definitive diagnosis and, in which, some or all of the previous roentgenograms became available for my own interpretation.

There is one obvious fallibility in this thesis; namely, the assumption that a shadow seen in the same lung segment in which years later, cancer is proved to be present, is necessarily a cancer at the earlier time. This is impossible to prove beyond contention, since if the lesion had been biopsied when first observed, the course of events would have been interrupted. However, the observation of regular, steady changes in the shadow from its original appearance to its final development gives reasonable credence to the validity of the assumption.

Since about 1947, I have been collecting cases of the type described above and first reported some of the results of these observations in 1949.[1] In 1953, O'Loughlin, Tucker, and I[2] reported the long duration of lung cancer based upon further studies of the same type. In 1955[3] and finally in 1957[4] certain other conclusions were recorded, notably that the majority of lung cancers arose in the periphery and grew centrally. Confirmation of both theses has since been reported by a number of authors.[5-7] Similar retrospective studies using roentgenograms have been made by Emerson *et al.*[8] There are, of course, many other reports on the natural history of lung carcinoma, but these are largely based upon symptoms.

The method of approach which I have used is illustrated by the following case:

In October 1963, a 74-year-old woman with minor complaints of cough and chest pain starting several months before, presented with a roentgenogram of the chest (FIGURE 1) exhibiting a five cm. mass in the left upper lung field; it was well defined, dense, homogeneous and apparently retracting from the chest wall toward the hilum. Lobectomy was done and the lesion proved to

later incorporated into the tumor mass. In 1960 the nodule measured 40 mm., in 1963 50 mm., in its widest diameter.

Thus we can observe the gradual development of a cancer over a period of almost 12 years. Since the lesion had grown very slowly the past three years and was only five cm. in diameter at the time of surgery, it is obvious that more years might have passed before it caused the patient's death.

While this is the longest period that I have been able to trace backward in any case, I have seen one other dating back at least nine years and a substantial number over five years in duration from the first roentgen sign. In fact, the time from the tumor incipiency must of necessity be far longer since the smallest lesion which can be distinguished in a roentgenogram is three mm. in diameter, and thus represents a fairly well developed neoplasm.

Collins and his associates[9] proposed an original and ingenious idea for measuring the interval of time from the first cancer cell to the final surgical removal of

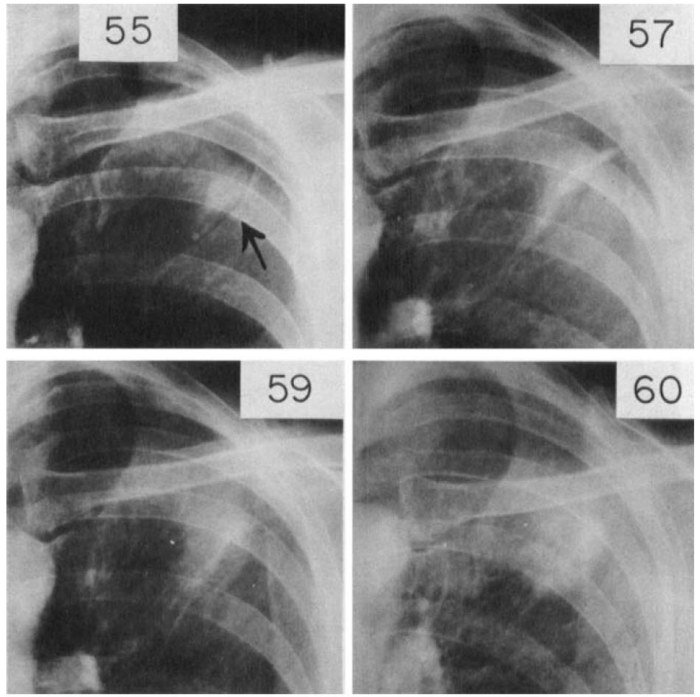


FIGURE 3. Same case as in FIGURES 1 and 2. (*a*) 1955. Increase in size of shadow. (*b*) 1957. Note the beginning linear area of atelectasis associated with the tumor mass. (*c*) 1959. Atelectasis is more prominent and the mass has grown considerably in size. (*d*) 1960. Mass now measures 40 mm. in one diameter with minor increase in size in past year.

Ann N Y Acad Sci. 1964 Apr 2;114:755-66.

Importance of understating the natural history

- ✓ Expectation of survival
- ✓ Avoiding the optimism bias
- ✓ Evidence of decisions for the treatment, supportive care and resource allocation

J Clin Epidemiol. 2021 Sep;137:265.
J Natl Cancer Inst. 2012 Apr 18;104(8):590-8.

Appropriate evidences?

- ✓ Best way? Cohort study of untreated patients?

  → Unethical and logistically challenging

- ✓ Prognosis from retrospective lung cancer registries
- ✓ Control arm of RCTs − Active treatment *vs*. BSC
- ✓ Case series

BMJ. 2009 Feb 23;338:b375.
CEBM Levels of Evidence. https://www.cebm.net

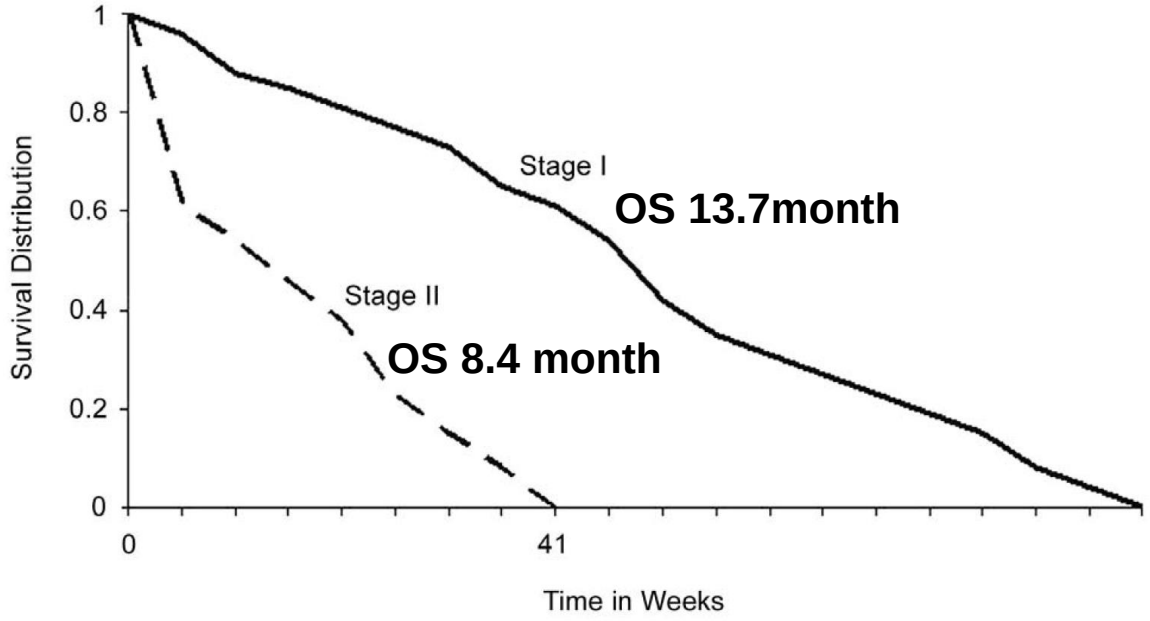
Retrospective lung cancer registries

ANTICANCER RESEARCH *25*: 3517-3520 (2005)

Survival in Untreated Early Stage Non-small Cell Lung Cancer

AMANDEEP S. CHADHA[1], APAR KISHOR GANTI[2],
JAIDEEP S. SOHI[1], ABE E. SAHMOUN[1] and SYED A. MEHDI[3]

[1]Department of Internal Medicine and [3]Department of Hematology/Oncology,
University of North Dakota School of Medicine, Fargo, ND 58102;
[2]Section of Oncology-Hematology, Department of Internal Medicine,
University of Nebraska Medical Center, Omaha, NE, U.S.A.



Anticancer Res. 2005 Sep-Oct;25(5):3517-20.

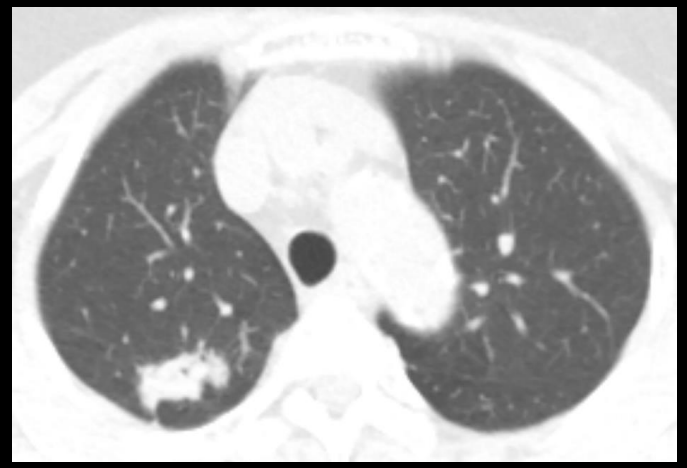
Case

- Female, 75 years old
- Incidental lung mass in the right upper lobe
- Asthma, Goiter, Hypertension, Diabetes
- ECOG 2

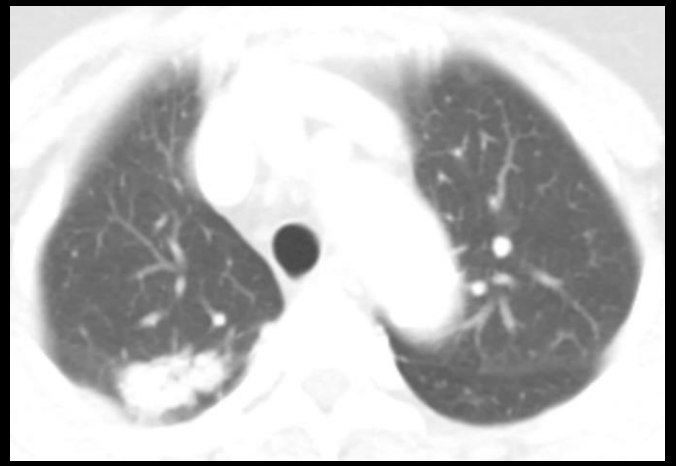
Adenocarcinoma, Stage I

- **Selection bias**
  - ✓ Older age
  - ✓ Lots of comorbidities
  - ✓ Psychologic problem
  - ✓ Socioeconomic issues

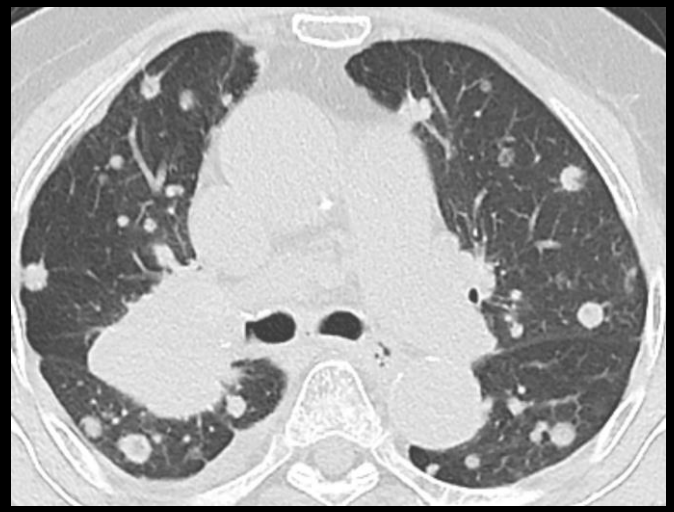
2015년 5월, 초진
75세



2016년 11월, 18개월
76세

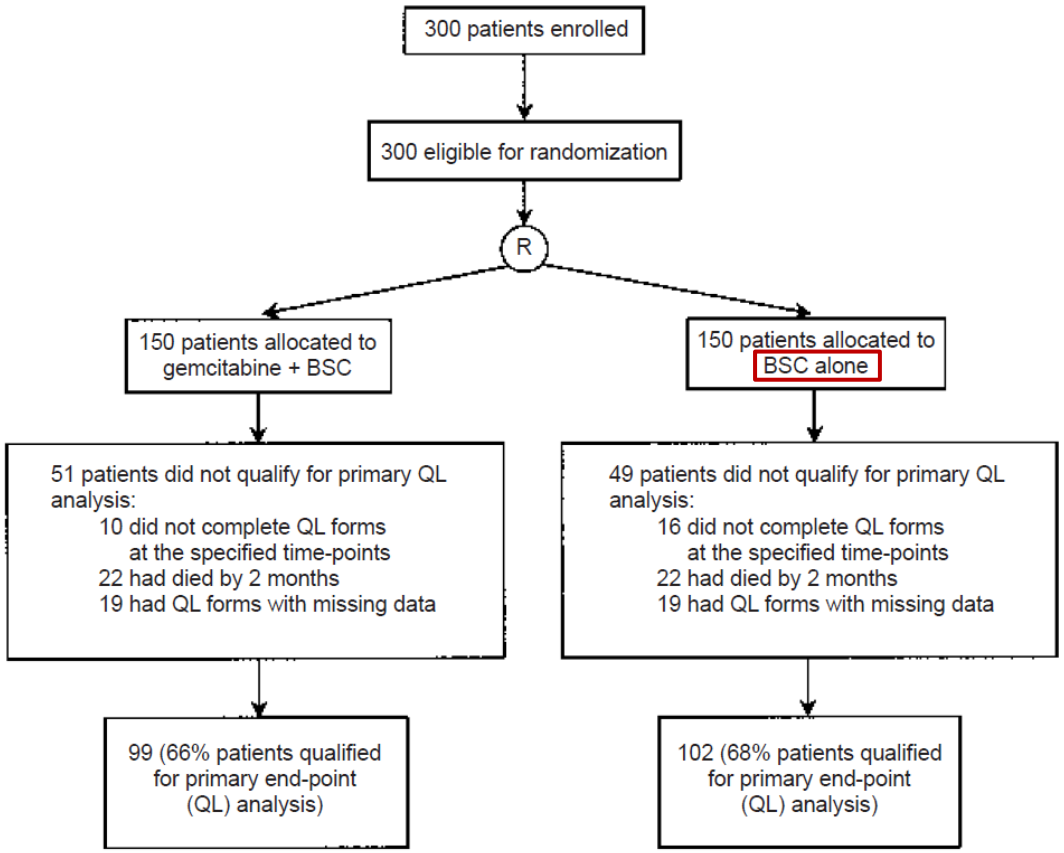


2017년 9월, 26개월
78세

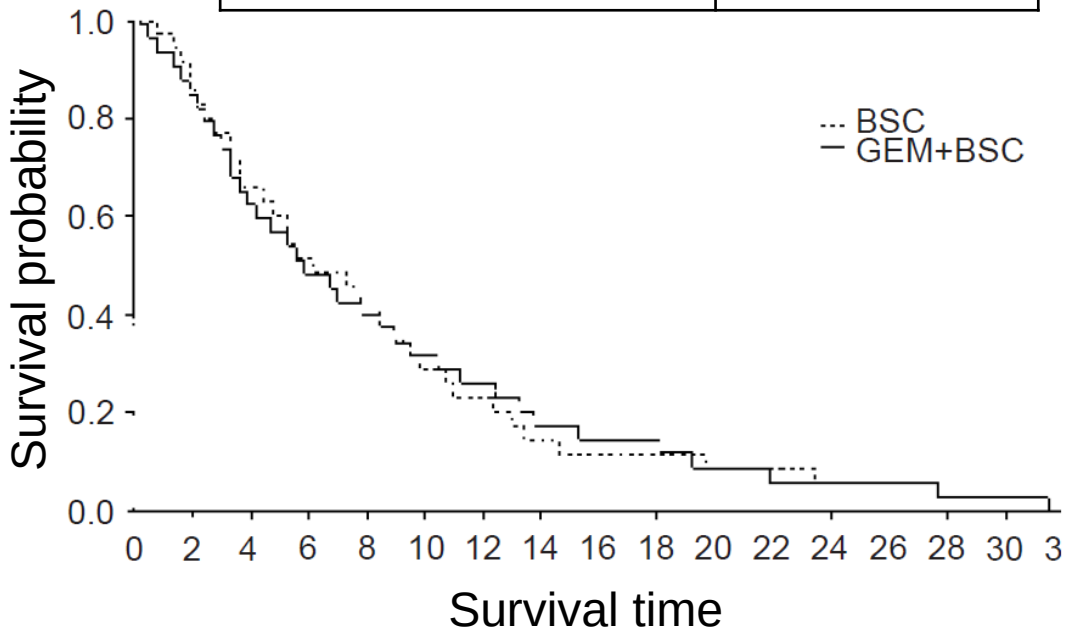


2022년 5월, 7년
82세

RCTs – Active treatment *vs.* BSC



Overall survival	
Gemcitabine + BSC	5.7 months
BSC	5.9 months



Br J Cancer. 2000 Aug;83(4):447-53.

Subject enrollment: 1994-1996

British Journal of Cancer (2000) **83**(4), 447–453

doi: 10.1054/ bjoc.2000.1307, available online at http://www.idealibrary.com on IDEAL®

Gemcitabine plus best supportive care (BSC) vs BSC in inoperable non-small cell lung cancer – a randomized trial with quality of life as the primary outcome

H Anderson[1], P Hopwood[2], RJ Stephens[3], N Thatcher[4], B Cottier[5], M Nicholson[6], R Milroy[7], TS Maughan[8], SJ Falk[9], MG Bond[10], PA Burt[11], CK Connolly[12], MB McIllmurray[13] and J Carmichael[14] on behalf of the UK NSCLC Gemcitabine Group

[1]Wythenshawe Hospital, Manchester; [2]CRC Psychological Medicine Group, Christie Hospital NHS Trust, Manchester; [3]Cancer Division, MRC Clinical Trials Unit, London; [4]Department of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester; [5]Clatterbridge Hospital, Bebbington, Liverpool; [6]Aberdeen Royal Infirmary, Aberdeen; [7]Stobhill NHS Trust, Glasgow; [8]Velindre Hospital, Whitchurch, Cardiff; [9]Bristol Oncology Centre, Bristol; [10]Cookridge Hospital, Leeds; [11]Christie Hospital NHS Trust, Manchester; [12]Darlington Memorial Hospital, Darlington; [13]Lancaster Royal Infirmary, Lancaster; [14]City Hospital, Nottingham, UK

Would it be the same now?

- ✓ Advances in the supportive case
- ✓ Improvement of living environment → Improved performance
- ✓ Trends for the early detection even in the same stage → Less tumor burden

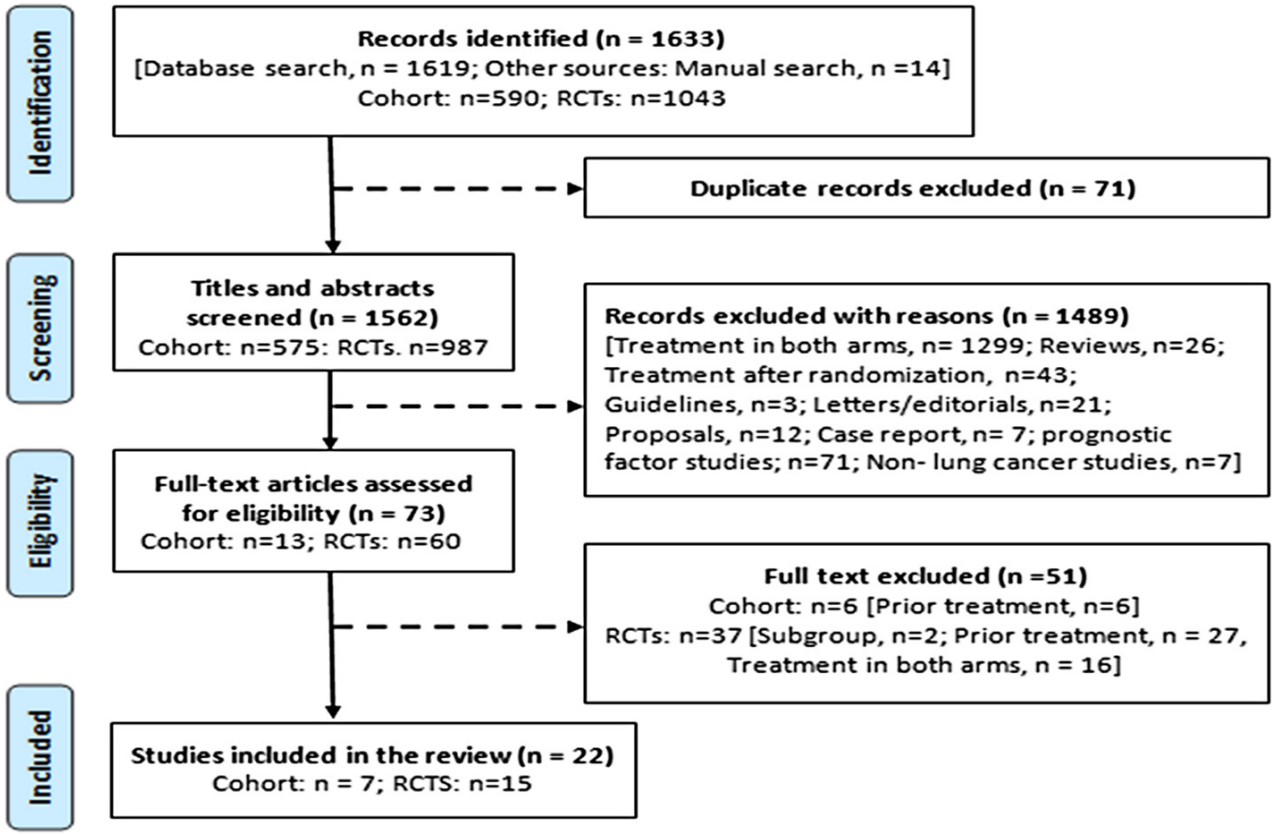
Br J Cancer. 2000 Aug;83(4):447-53.

Evidences

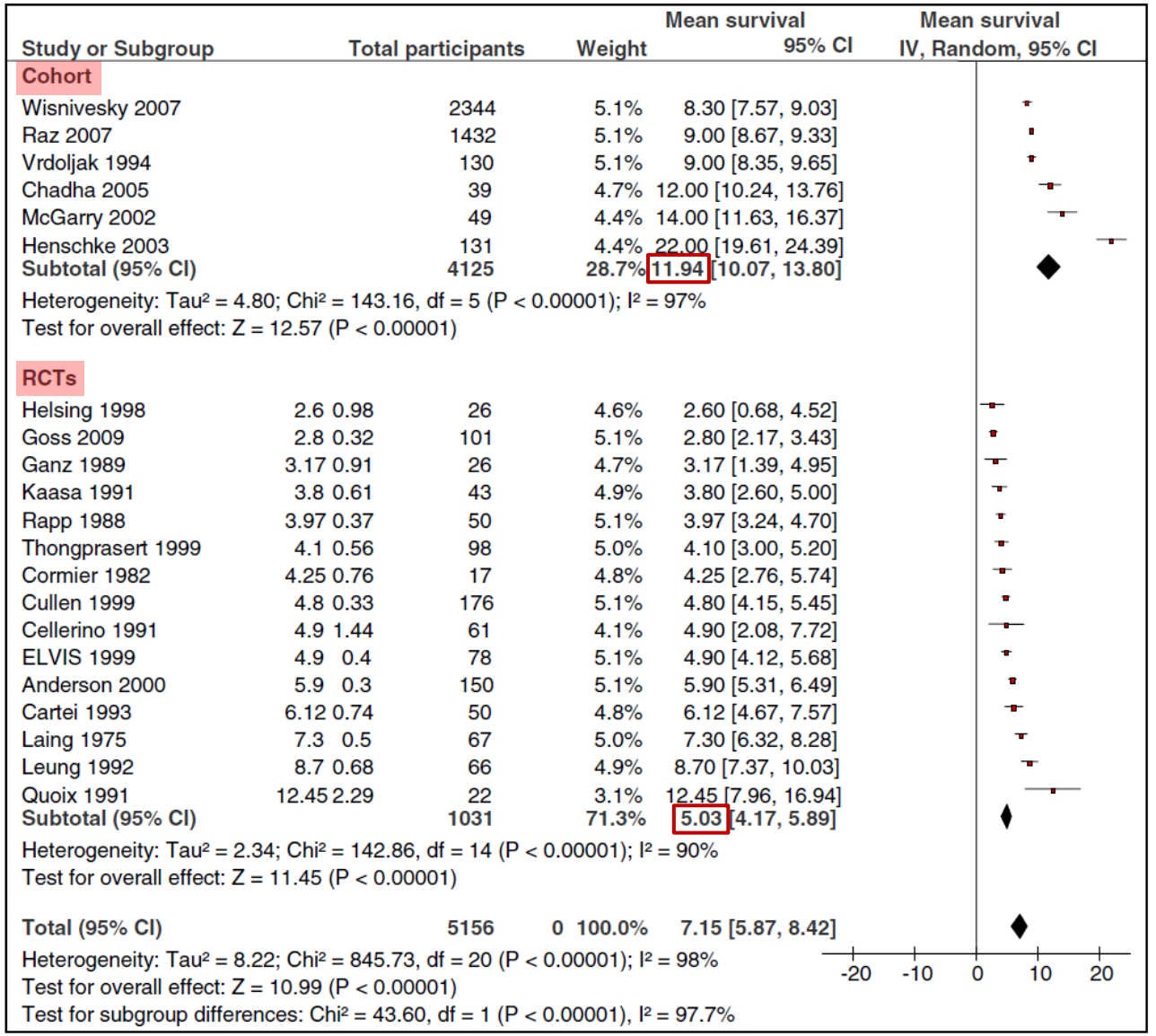
RESEARCH Open Access

Survival of patients with non-small cell lung cancer without treatment: a systematic review and meta-analysis

Hesborn Wao[1,2], Rahul Mhaskar[1,2], Ambuj Kumar[1,2,3*], Branko Miladinovic[1,2] and Benjamin Djulbegovic[1,2,3]

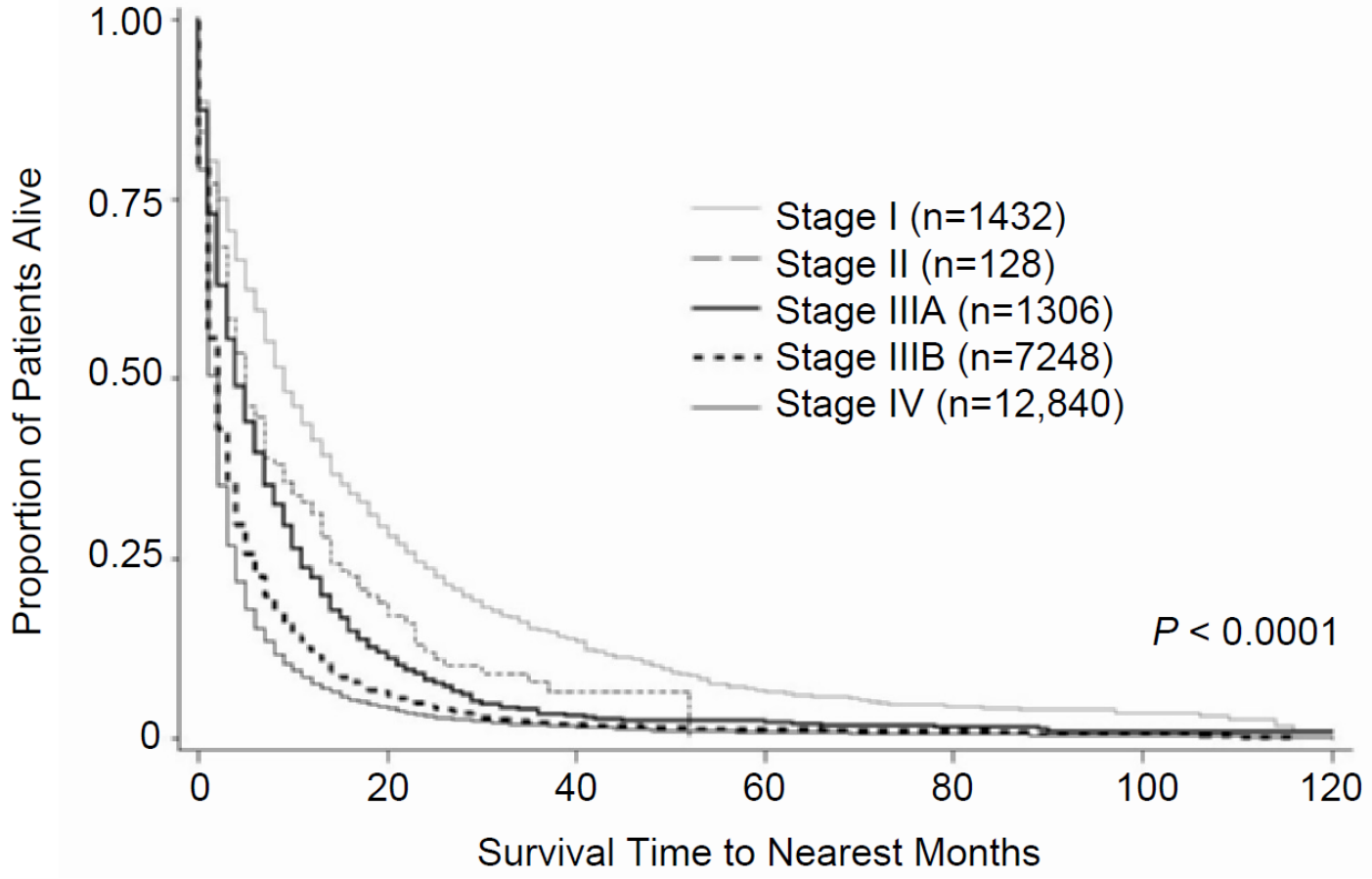


Syst Rev. 2013 Feb 4;2:10.



Syst Rev. 2013 Feb 4;2:10.

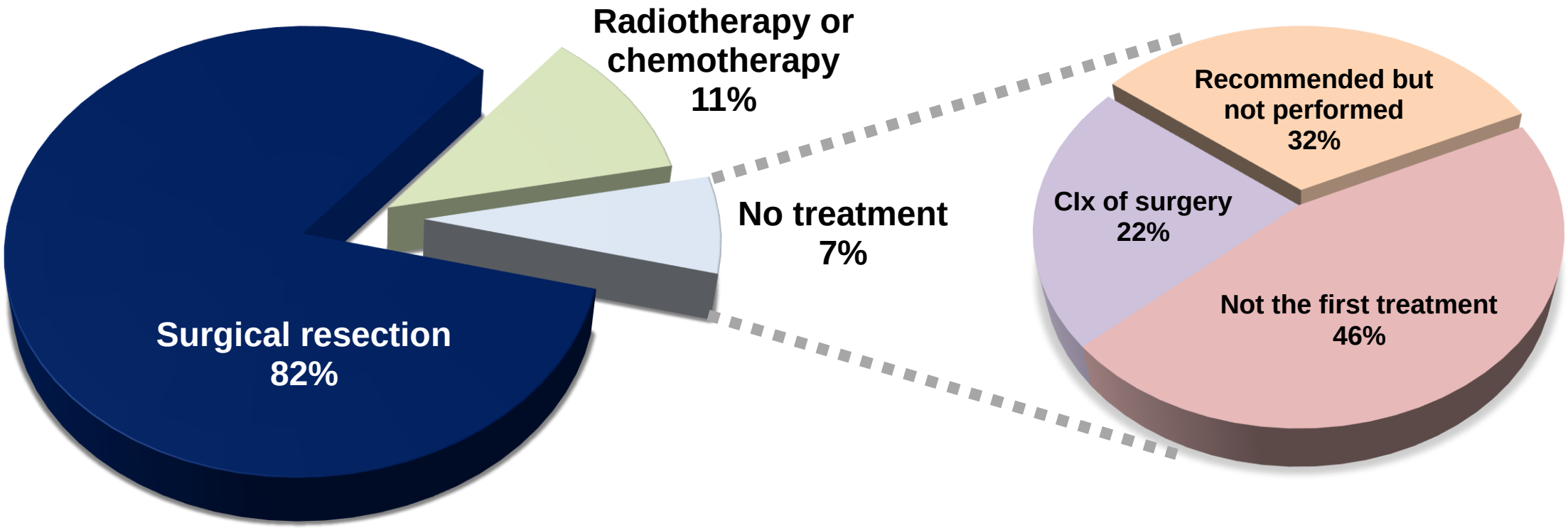
Natural History of untreated NSCLC



California Cancer Registry between 1989 and 2003

Chest. 2007 Jul;132(1):193-9.

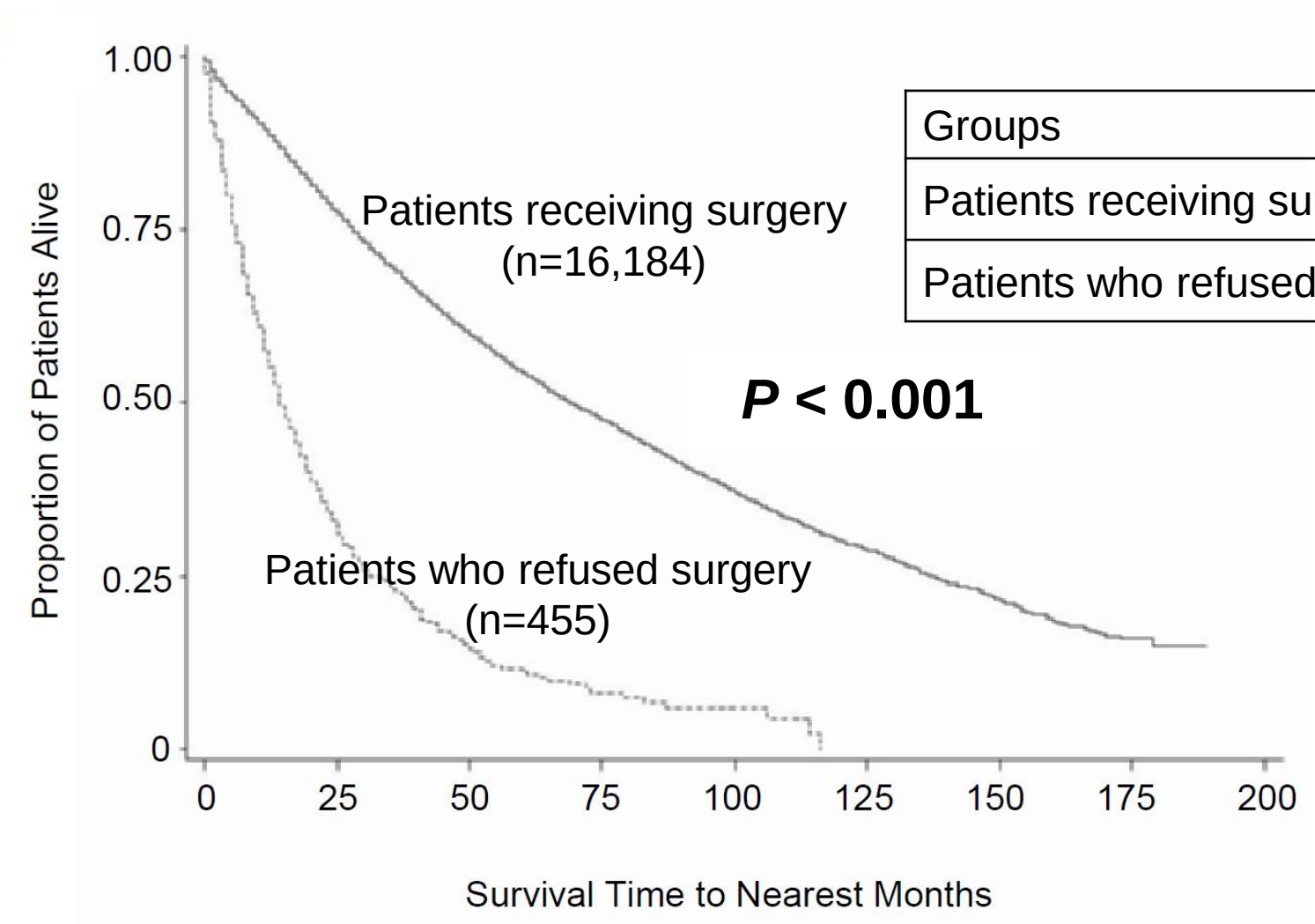
Natural History of Stage I NSCLC



Treatment of stage I NSCLC in California Cancer Registry between 1989 and 2003

Chest. 2007 Jul;132(1):193-9.

Natural History of Stage I NSCLC

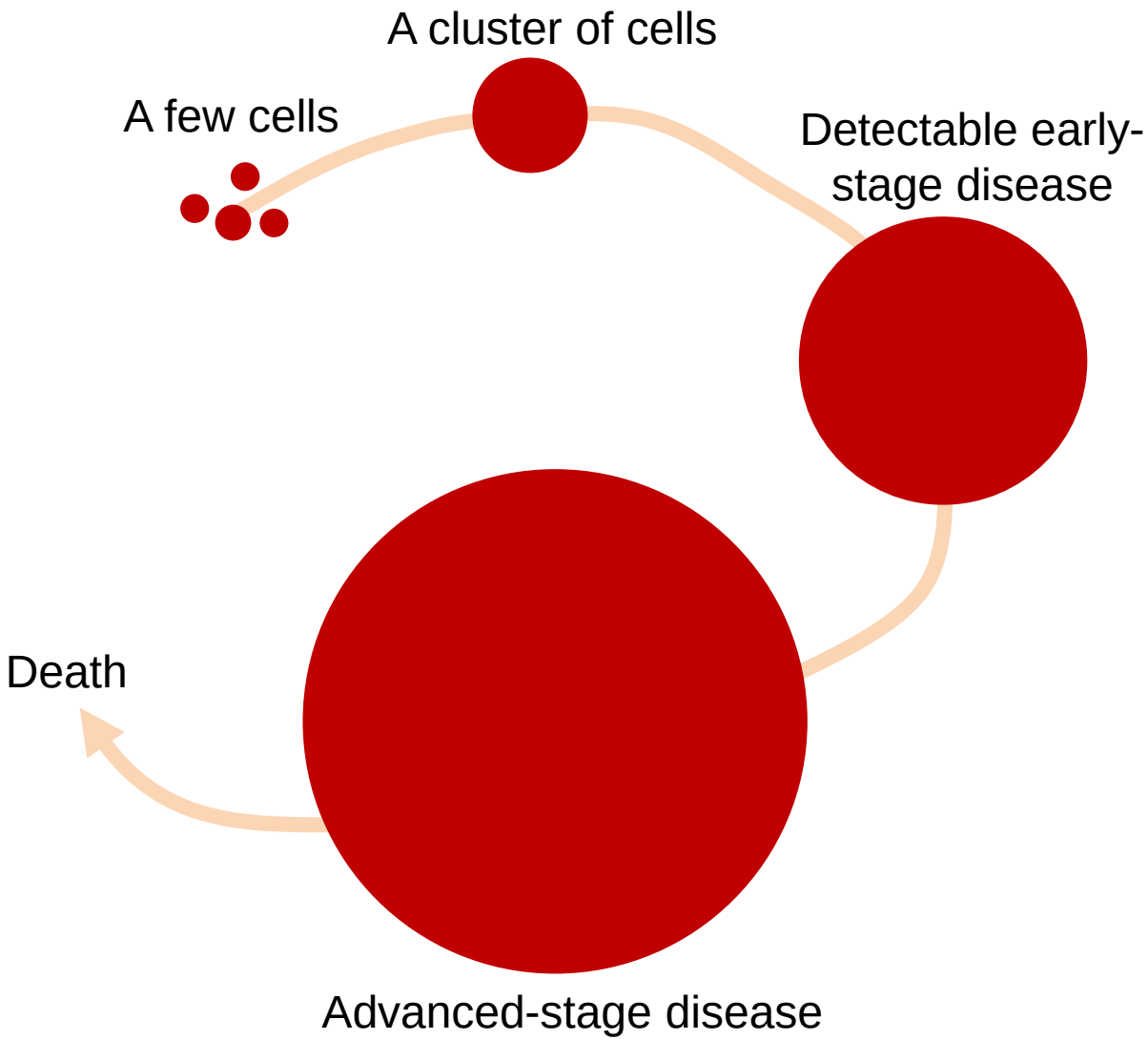


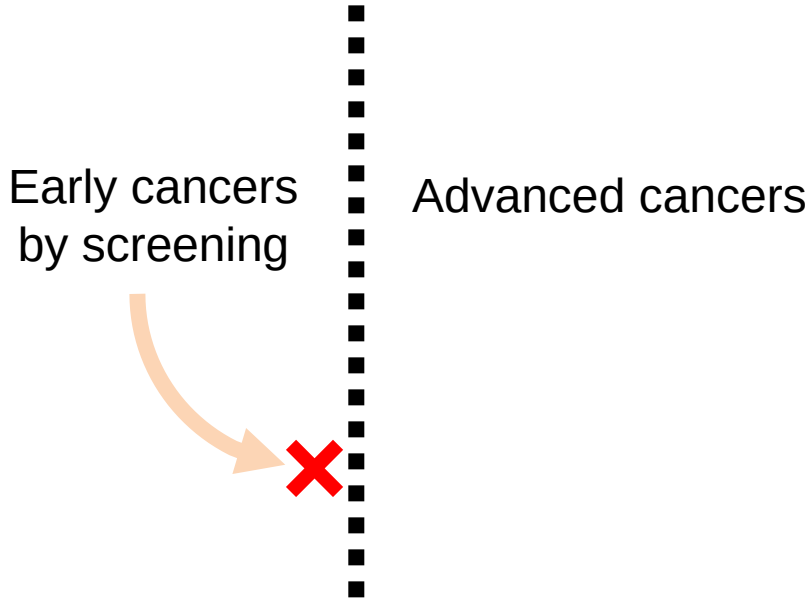
Groups	5YSR
Patients receiving surgery	53%
Patients who refused surgery	11%

Chest. 2007 Jul;132(1):193-9.

Two models of lung cancer

Natural-history model *vs.* Bipartite model





Evidence of Bipartite model – X-ray screening

	Number of patients	Early cancers, n	Advanced cancers, n	Early cancers in screened group compared with control group, n	Advanced cancers in screened group compared with control group, n
London					
Intervention (chest radiography every 6 months)	29 723	44	57	+22	+3
Control (chest radiography at end of 3 years)	25 311	22	54	..	..
Mayo Lung Project **F/U: 20 years**					
Intervention (chest radiography and sputum cytology every 4 months for 6 years)	4618	99	107	+48	−2
Control (advised to have chest radiography and sputum cytology annually)	4593	51	109	..	..
Czech **F/U: 15 years**					
Intervention (chest radiography and sputum cytology every 6 months)	3172	20	19	+10	+2
Control (chest radiography and sputum cytology at end of 3 years)	3174	10	17	..	..

Lancet Oncol. 2008 Jul;9(7):693-7.

Evidence of Bipartite model – CT screening

	Number of patients	Early cancers detected/ expected, n	Advanced cancers detected/ expected, n	Additional early cancers in screened group compared with number expected, n	Additional advanced cancers in screened group compared with number expected, n
Istituto Tumori	977	25/3	11/9	22	2
Mayo Clinic	1439	48/5	18/15	43	3
Moffitt Cancer Center	830	29/3	13/10	26	3

Lancet Oncol. 2008 Jul;9(7):693-7.

Case

- Female, 60 years old
- Incidental lung nodule (routine checkup)
- No previous medical history
- ECOG 0

Adenocarcinoma, Stage I

2019년 6월, 초진
60세

2019년 10월, 4개월
60세

2020년 12월, 18개월
61세

2022년 6월, 36개월
63세

문화·라이프 > 건강

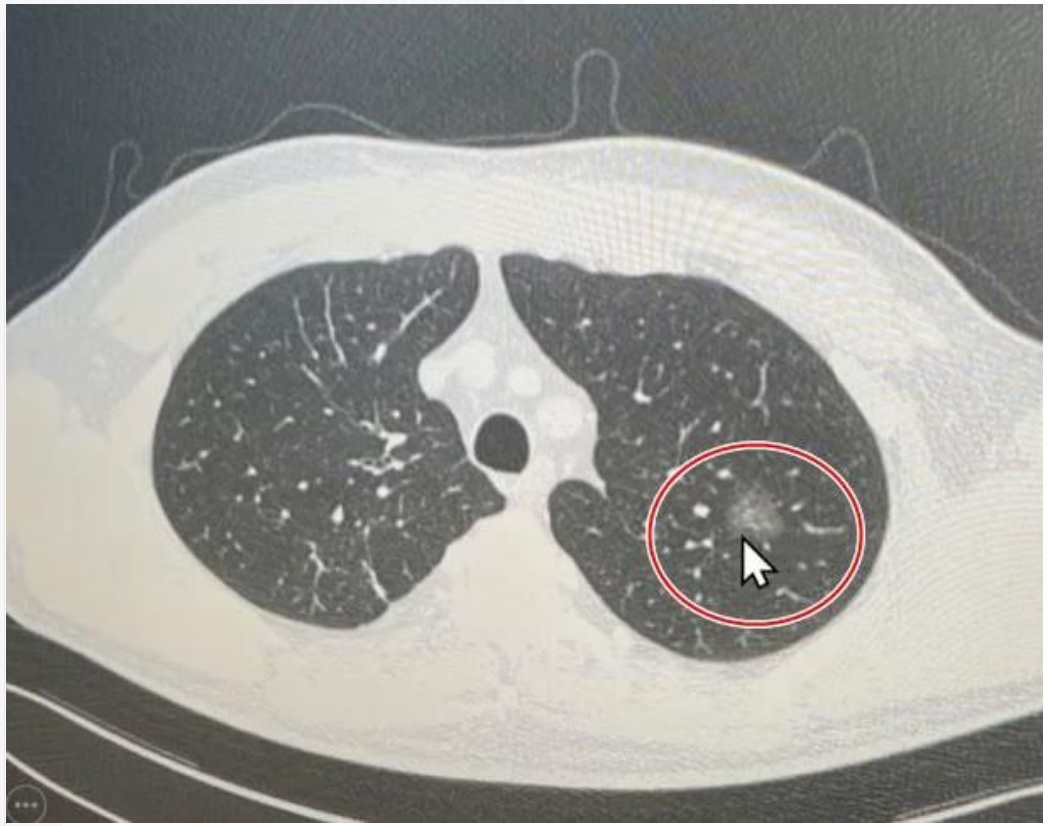
홍혜걸, 폐암 투병기...“30년간 담배 피워, 폐 절반 떼어냈다”

김소정 기자

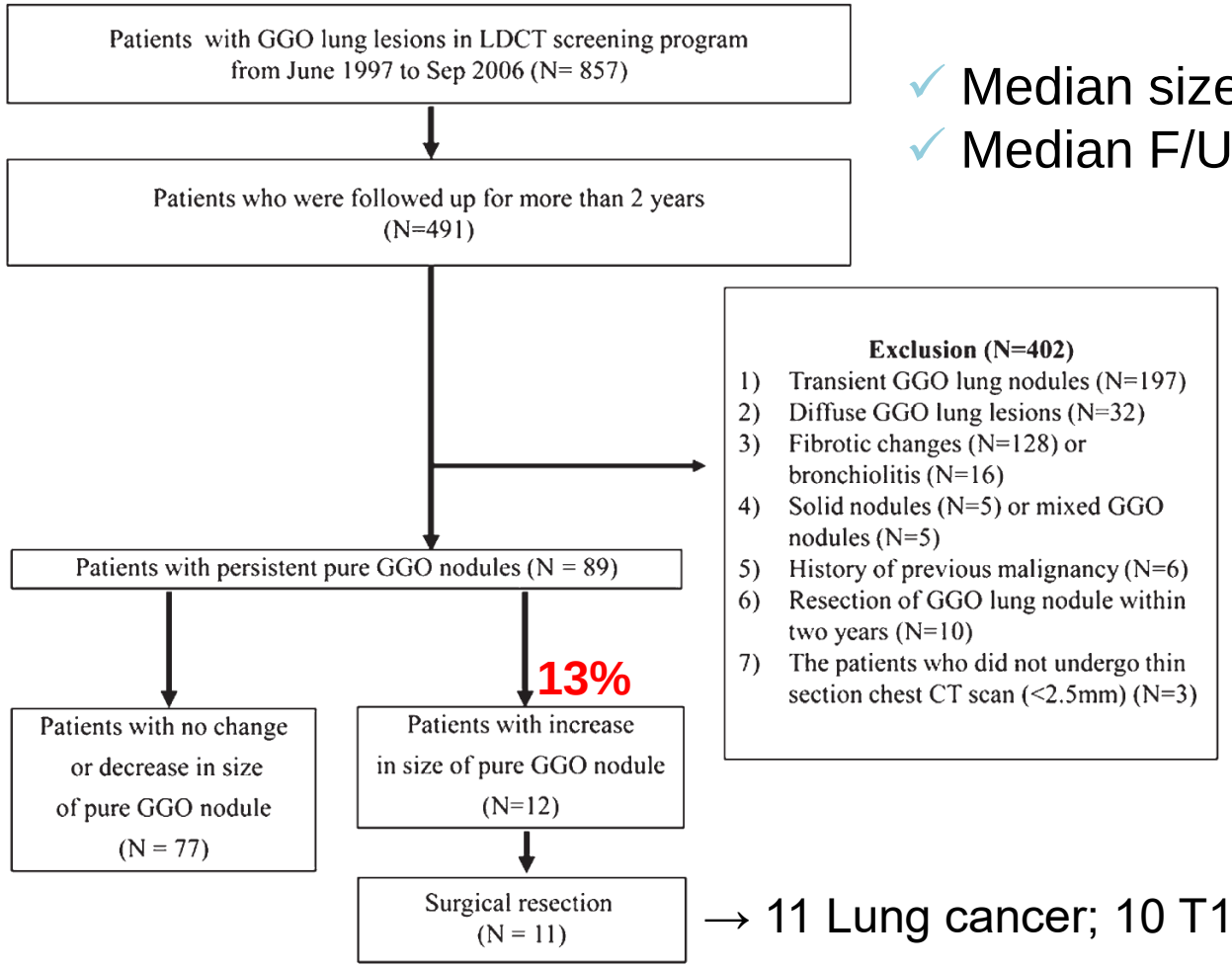
입력 2022.04.24 17:19

의사 출신 의학전문기자 홍혜걸(55)씨가 “공식적으로 폐암 환자가 됐다”고 밝혔다. 그는 최근 간유리음영으로 폐 수술을 받았다. 간유리음영은 흉부 CT에서 폐 조직이 유리를 갈아 놓은 것처럼 뿌옇게 보인다고 해서 붙여진 이름이다. 간유리음영은 제때 발견하지 못해 놔두면 폐암으로 진행된다. 홍씨 경우, 간유리음영의 크기가 점점 커져 수술을 결정했다고 한다.

최근 폐 수술을 받은 홍혜걸씨/유튜브 '의학채널 비온뒤'



Natural history of pure GGO nodules



- ✓ Median size: 5.5 mm (range, 3-20 mm)
- ✓ Median F/U: 59 months

→ 11 Lung cancer; 10 T1aN0 + 1 T2aN2

Chest. 2013 Jan;143(1):172-178.

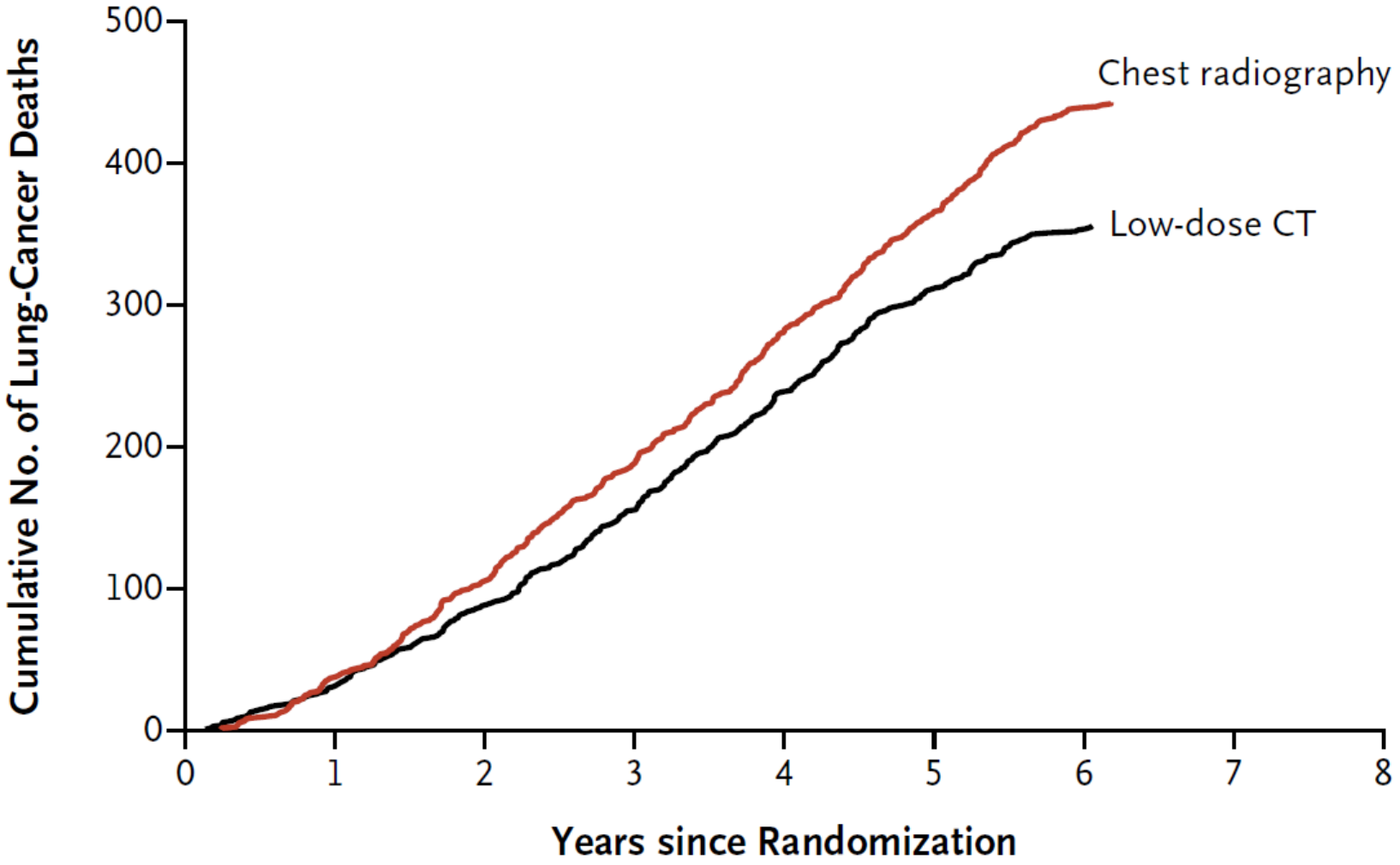
Case

- Male, 78 years old
- Incidental lung nodule (routine checkup)
- No previous medical history
- ECOG 1

2018년 8월, 초진
78세

2018년 11월, 3개월
78세

2020년 12월, 28개월
81세



N Engl J Med. 2011 Aug 4;365(5):395-409.

Estimated reduction in all-cause risk of death

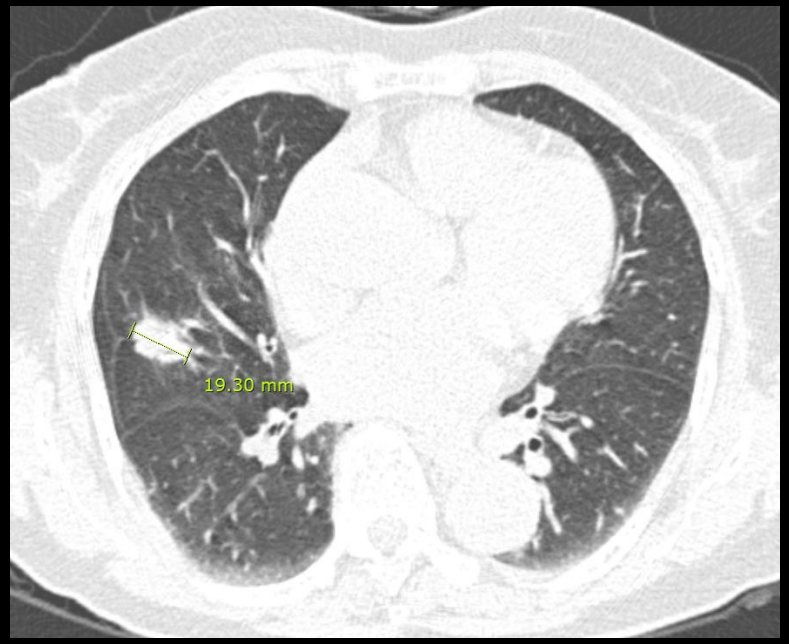
	All-cause risk of death in 10-year	
	Before correction of impact of LDCT screening	20% reduction in lung cancer mortality from LDCT screening
Mortality	**365/1000**	**347/1000**

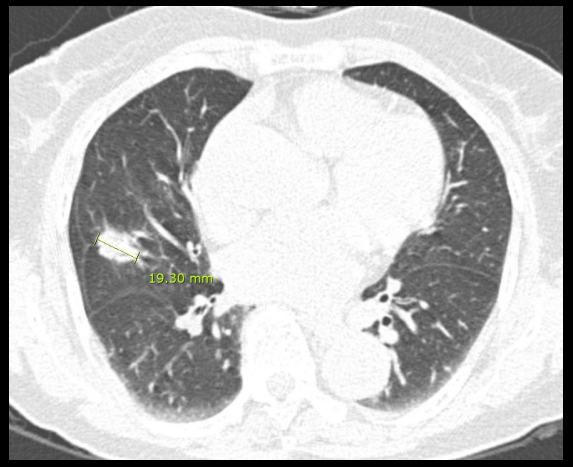
Death of 65-year-old male smoker in the United States

J Natl Cancer Inst. 2008 Jun 18;100(12):845-53.
Chest. 2006 Apr;129(4):1088-97.

Case

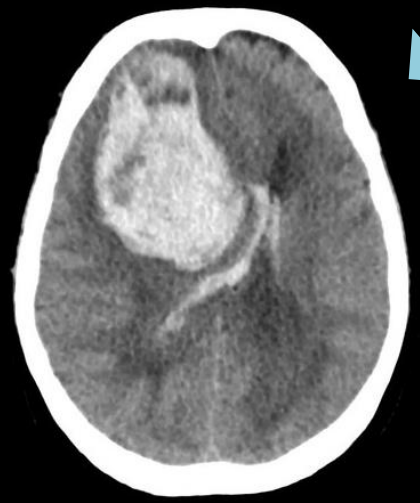
- Female, 82 years old
- Incidental lung nodule (routine checkup)
- Hypertension
- ECOG 0





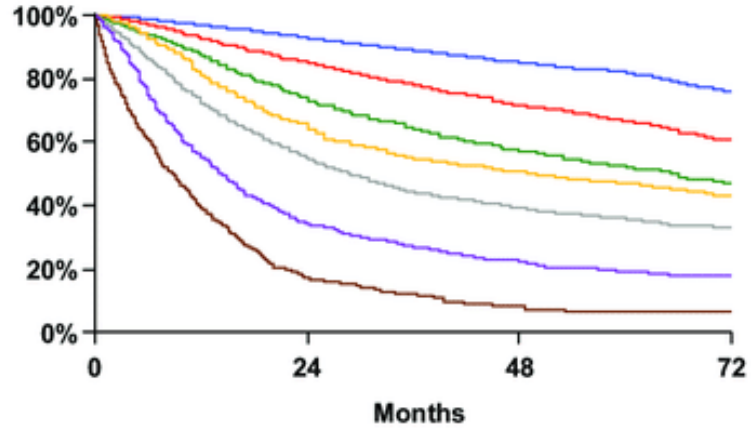
2013년 5월, 초진
82세

2017년 12월, 46개월
87세



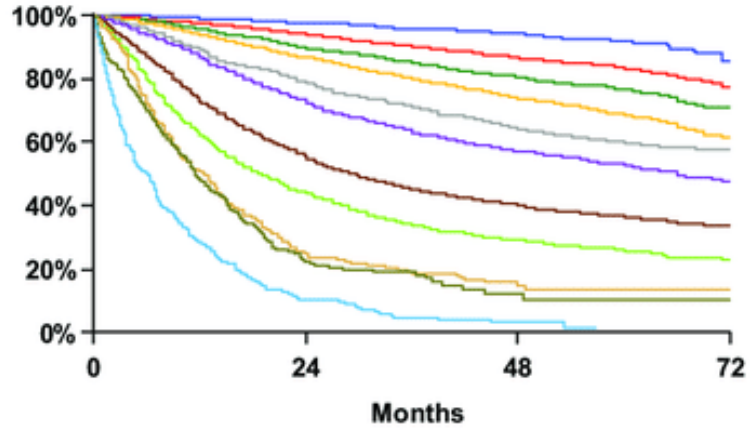
2019년 1월, 59개월
88세

A



7th Ed.	Events / N	MST	24 Month	60 Month
IA	1119 / 6303	NR	93%	82%
IB	768 / 2492	NR	85%	66%
IIA	424 / 1008	66.0	74%	52%
IIB	382 / 824	49.0	64%	47%
IIIA	2139 / 3344	29.0	55%	36%
IIIB	2101 / 2624	14.1	34%	19%
IV	664 / 882	8.8	17%	6%

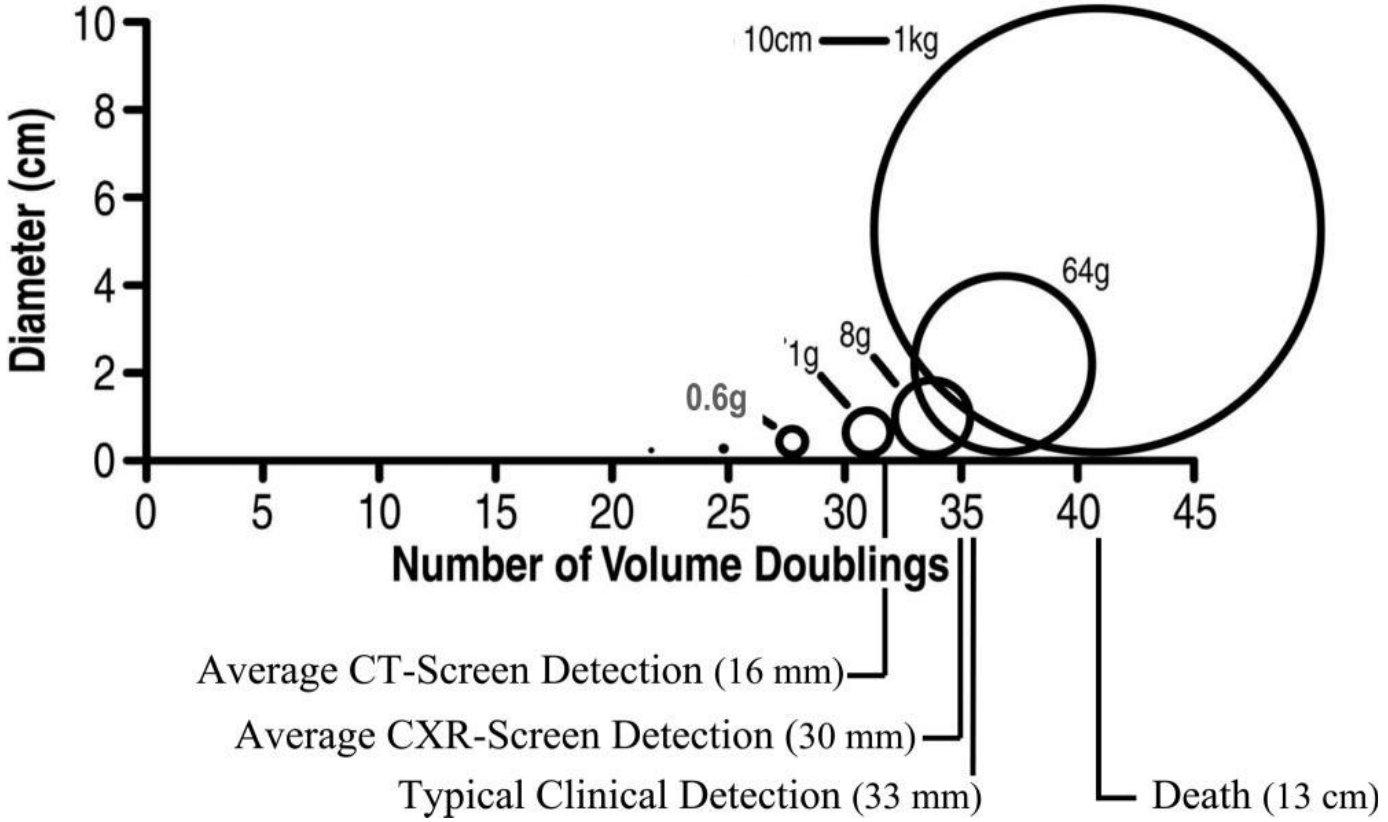
B



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

Growth patterns and Doubling time

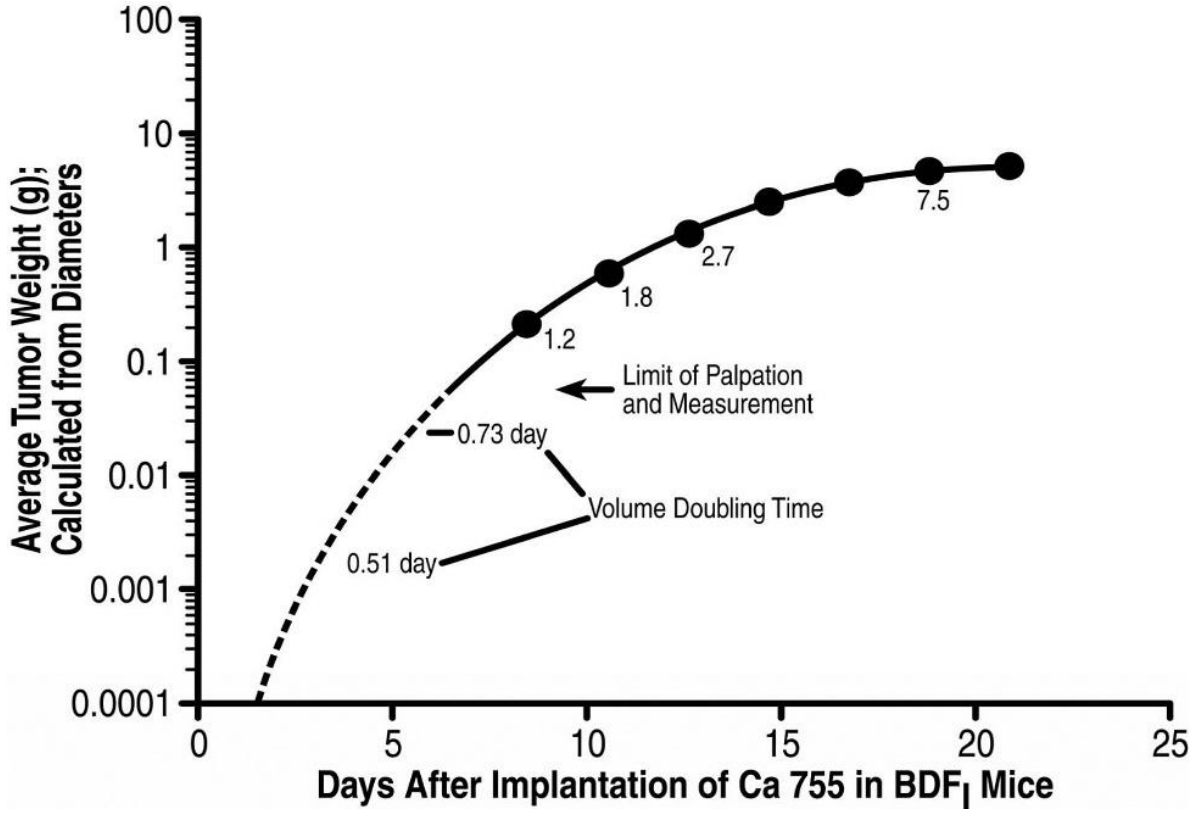
Exponential growth



Schematic of exponential growth of a cancer

Br J Dis Chest. 1979 Jan;73(1):1-17.

Gomperztian growth curve



Average growth rates in 100 mice after implantation of ADC

Cancer. 1975 Jan;35(1):15-24.

Modeling the Natural History

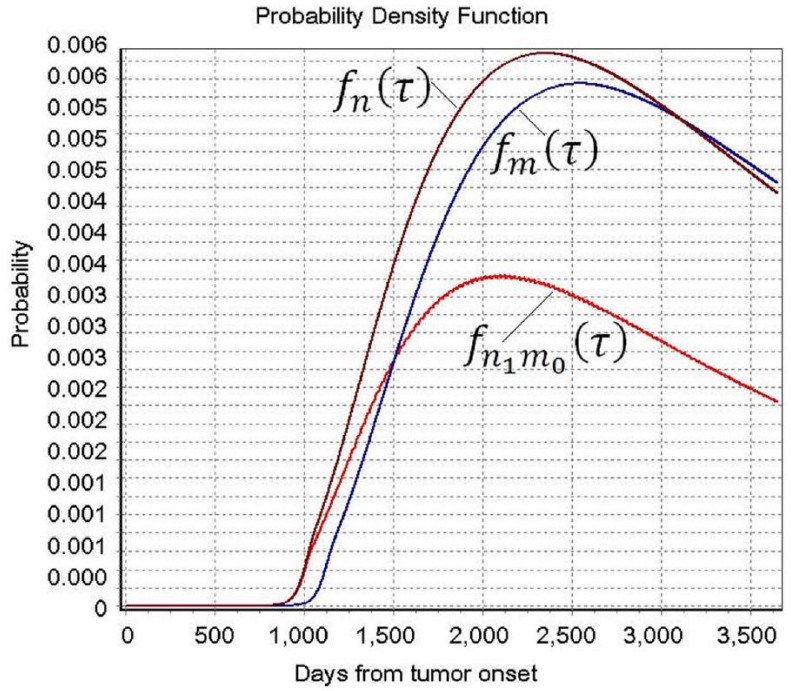


Figure 1. Probability density functions of nodal and distant metastases from the time of tumor onset, using the estimated parameters $\xi = 0.01$, $\mu_n = 8.05 \times 10^{-9}$, $\mu_m = 2.78 \times 10^{-9}$, $K = 3.80$ and $\theta = 1.15$.

The primary tumor size is calculated using the tumor growth model by giving the growing time t, with a constant growth rate λ. Thus, we rewrite $F_n(s), F_m(s)$ to $F_n(t,\lambda) = \int_0^t f_n(\tau,\lambda)d\tau$ and $F_m(t,\lambda) = \int_0^t f_m(\tau,\lambda)d\tau$, where $f_n(\tau,\lambda)$ and $f_m(\tau,\lambda)$ are the probability density functions (p.d.f.) of time that nodal and distant metastases happened in a group of patients with the same tumor growth rate λ. Then,

$$f_n(\tau) = \int f_n(\tau,\lambda) * \gamma(\lambda|k,\theta)d\lambda \; ; \; f_m(\tau) = \int f_m(\tau,\lambda) * \gamma(\lambda|k,\theta)d\lambda$$

where f_n and f_m are the p.d.f. of time that nodal and distant metastases occurred in patients with tumor growth rate having a Gamma distribution, and γ is the Gamma distribution function with parameters k and θ. Then,

$$f_{n_1 m_0}(\tau) = \int (f_n(\tau,\lambda) - f_m(\tau,\lambda)) * \gamma(\lambda|k,\theta)d\lambda$$

$$\Phi_n(s) = \frac{p(s,1,0)+p(s,1,1)}{p(s,0,0)+p(s,1,0)+p(s,0,1)+p(s,1,1)}$$

$$\Phi_m(s) = \frac{p(s,0,1)+p(s,1,1)}{p(s,0,0)+p(s,1,0)+p(s,0,1)+p(s,1,1)}$$

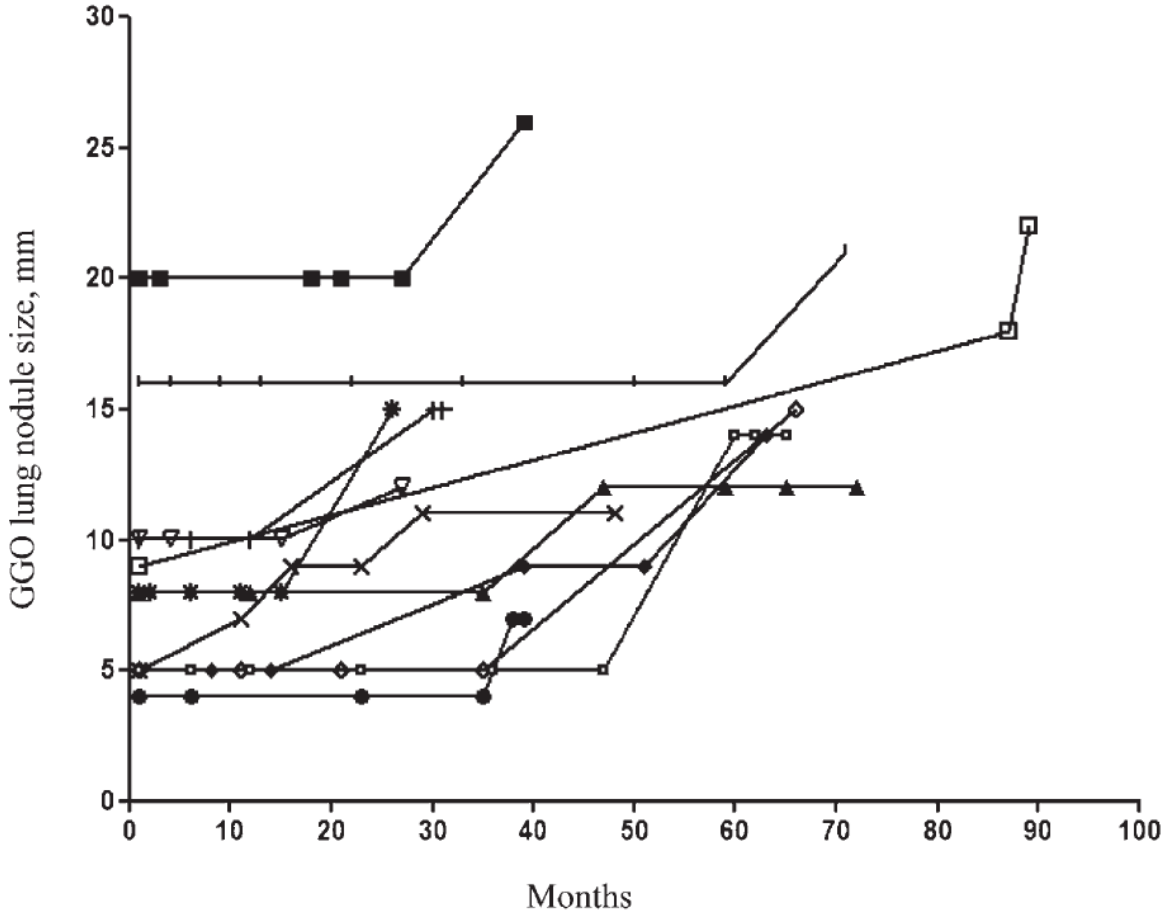
Substitute $p(s,n,m)$ with Z'_{nm}, F_n, and F_m we obtain:

$$F_n(s) = \frac{\Phi_m Z'_{00} Z'_{10} + (\Phi_n - \Phi_m) Z'_{00} Z'_{11}}{Z'_{11} Z'_{10} + \Phi_n (Z'_{00} - Z'_{10}) Z'_{11} + \Phi_m (Z'_{10} - Z'_{11}) Z'_{00}}$$

$$F_m(s) = \frac{\Phi_m Z'_{00} Z'_{10}}{Z'_{11} Z'_{10} + \Phi_n (Z'_{00} - Z'_{10}) Z'_{11} + \Phi_m (Z'_{10} - Z'_{11}) Z'_{00}}$$

PLoS One. 2014 Apr 4;9(4):e93430.

Growth patterns of pure GGO nodules



Chest. 2013 Jan;143(1):172-178.

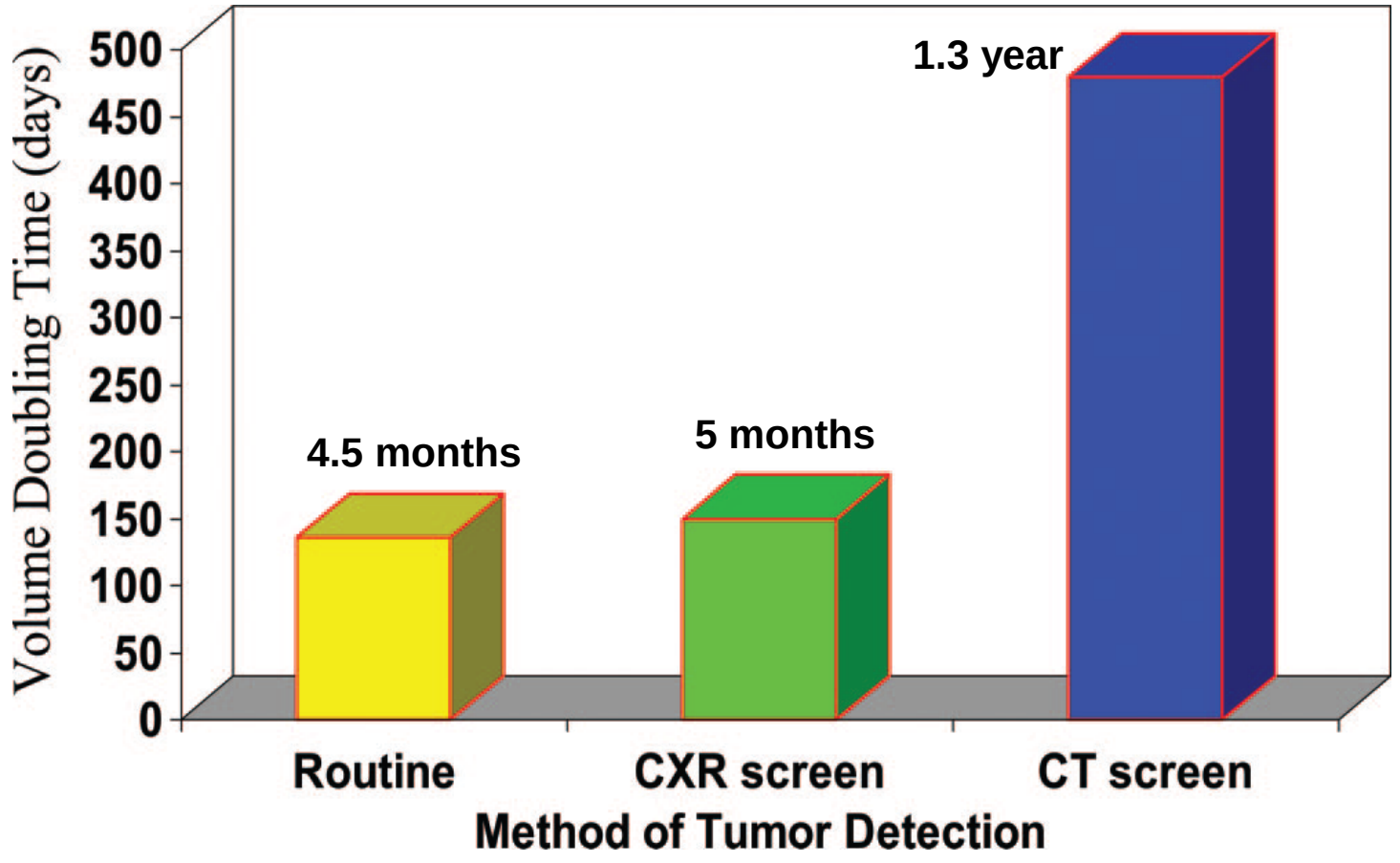
Doubling time and Detection modality

TABLE 3. Mean Doubling Time

Study	N	Years of Accrual	How Detected	Reason for Interval	Interval (mo)	Environment	Other Comments	Mean VDT (d)
Spratt et al.[25]	34	40–61	Routine	—	—	USA		88
Garland et al.[74]	41	~55–61	Routine	—	—	USA		162
Geddes et al.[34]	228	~60–75	Routine	—	—	Eu/USA		102
Mizuno et al.[33]	50	~75–80	Routine	—	—	Japan		136
Usuda et al.[19]	45	85–86	Routine	Missed[a]	3–12	Japan		167
Arai et al.[75]	96	~89	Routine[b]	Missed/Dx obs	>6[a]	Japan		139[c]
[d]Jennings et al.[59]	149	96–04	Routine	Various	4[e]	USA		(161)[d]
[g]**Average**			**Routine**					**136**
Yankelowitz et al.[76]	44	71–76	CXR screen	Missed	12	USA	MLP, all M	101
Yankelowitz et al.[76]	43	74–78	CXR screen	Missed	12	USA	MSK, all M	144
Usuda et al.[19]	129	85–86	CXR screen	Missed	3–12	Japan		163
Arai[75]	138	~89	CXR screen	Missed/Dx obs	>6[a]	Japan		190
Average			**CXR screen**					**150**
Hasegawa et al.[16]	61	96–98	CT screen	Missed[a]	5–15	Japan		452
Sone[18]	45	96–98	CT screen	Missed, w/u	—	Japan		470
[g]Takashima et al.[57]	20	96–98	CT screen	w/u	3	Japan	1–2 cm diam	(508)[h]
Lindell et al.[17]	48	99–03	CT screen	Dx obs	—	USA		518
[g]**Average**			**CT screen**					**480**

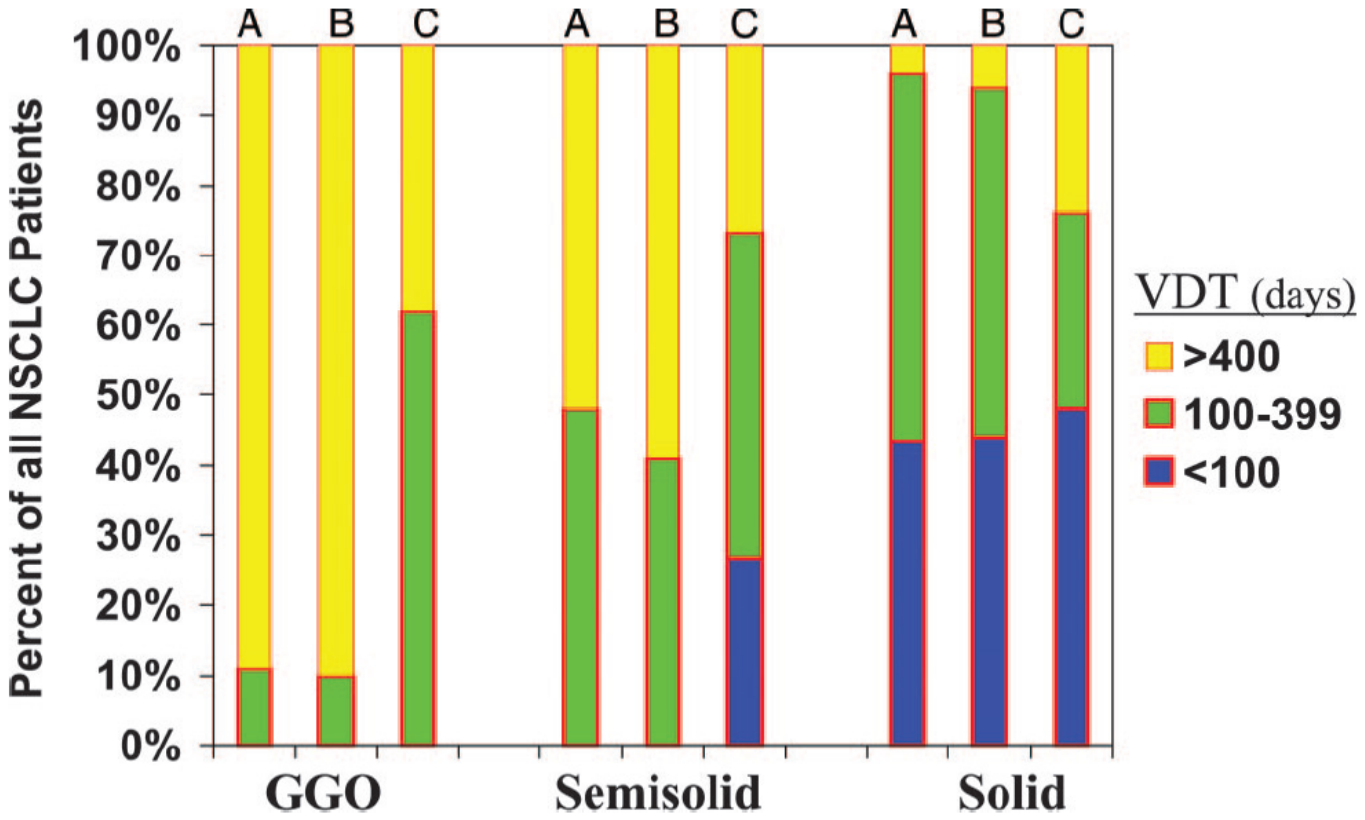
J Thorac Oncol. 2008 Jul;3(7):781-92.

Doubling time and Detection modality



J Thorac Oncol. 2008 Jul;3(7):781-92.

Doubling time and Radiologic appearance



Br J Radiol. 2000 Dec;73(876):1252-9.
Lung Cancer. 2007 Dec;58(3):329-41.
Radiology. 2007 Feb;242(2):555-62.

Doubling time in the elderly

Age	Short VDT (< 100 days)	Long VDT (> 400 days)
< 60	**0%**	**42%**
60-69	**18%**	**59%**
> 70	**36%**	**18%**

Lung Cancer. 2007 Dec;58(3):329-41.

Reasons for refusing treatment

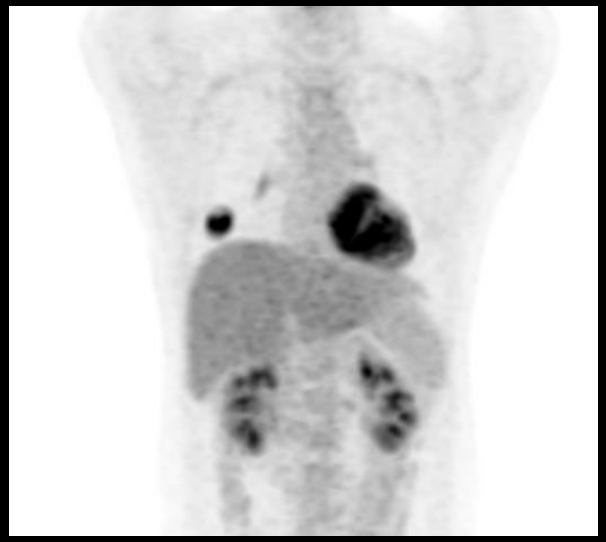
Refusal of medical treatment

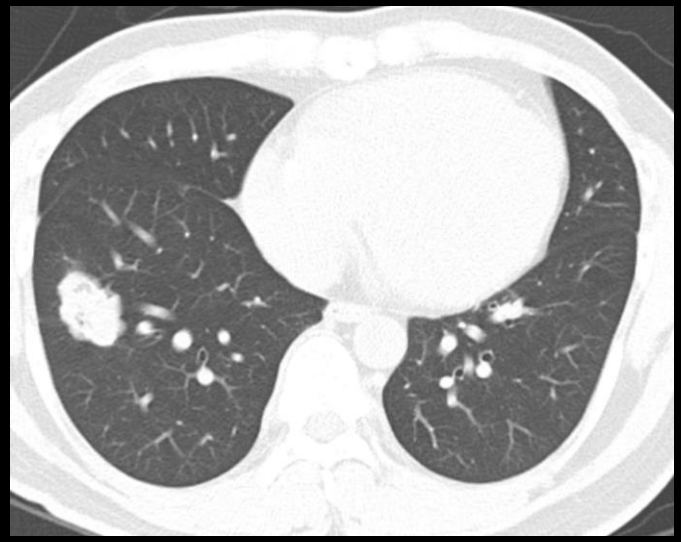
Socio-demographic factors	Clinical characteristics
✓ Being elderly	✓ Cancer stage III or IV
✓ Unmarried status	✓ Poor performance status
✓ Female gender	✓ Charlson comorbidity score >2
✓ Non-white race	
✓ Not having insurance	

Ann Palliat Med. 2021 Apr;10(4):4868-4877.

Case

- Male, 33 years old
- Incidental lung mass
- No previous medical history

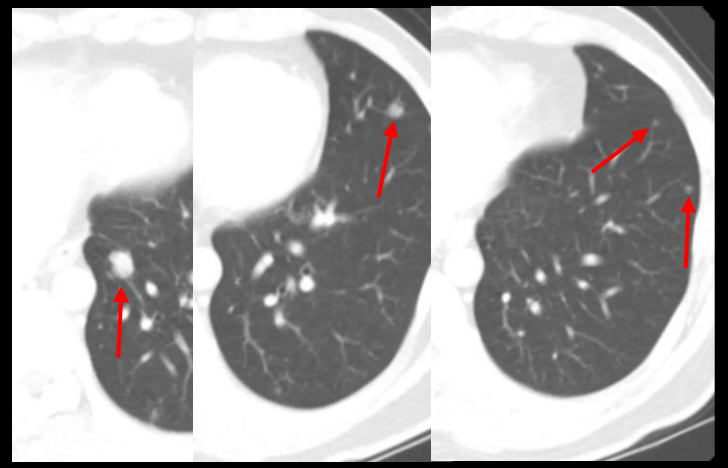




Early stage adenocarcinoma, ALK FISH+

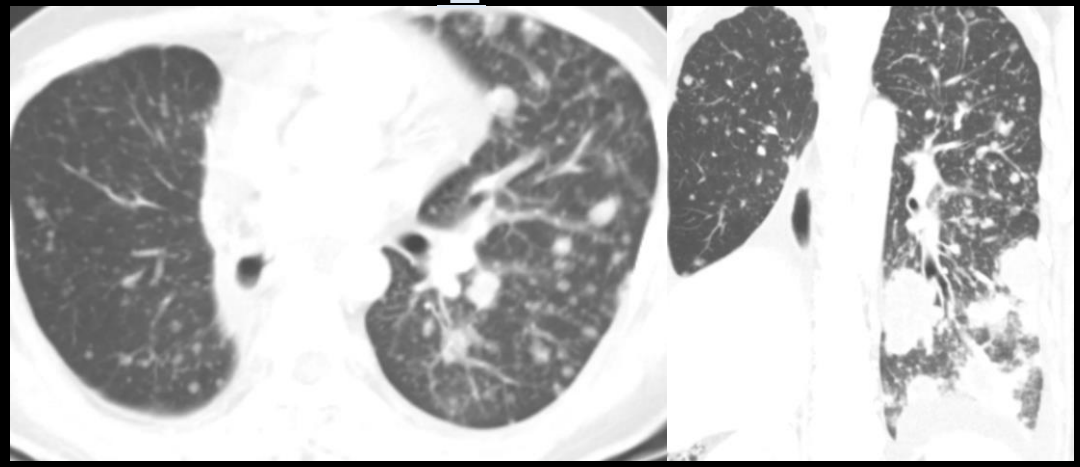
2015년 8월, **초진.** 33세.

- 수술 후 3기 확인.
- 보조 항암치료.
- 술 후 방사선치료.



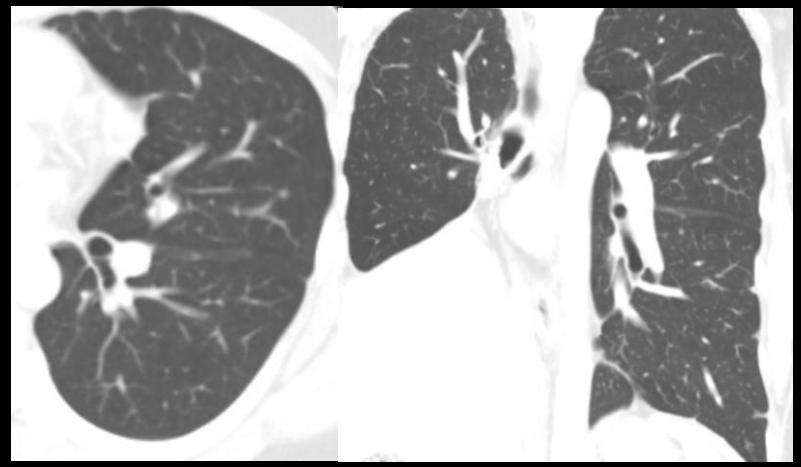
2017년 2월, **18개월.** 35세.

- F/U loss
- 완치를 위한 사설 면역요법



2018년 8월, **36개월.** 36세.

- Alectinib 복용



2022년 7월, **83개월.** 40세.

(주)세종바이오솔루션
Sejongbio Solution
Medical Care Service Platform

회사소개 | 중입자 치료 | 유전자캡슐 | 면역세포 | 동맥내 암 치료 | 토모테라피 | 메리디안 | 줄기세포 | 진단&검사 | 자문관 및 동역자 | 바이오인포매틱스

면역세포

- HITV요법 (수지상세포)
  - HITV요법 수지상세포
  - 적용과절차
  - 일본 사례
  - 하스미 백신
  - 연구소
  - 연혁
- 고농축 활성화 자기 림프구 치료법
- Naive-T7종 면역세포요법

세종바이오솔루션은 해외 병원에 연계해 주는 에이전시 회사입니다.

HITV 요법

Human Initiated Therapeutic Vaccine
; 인간 주도 치료백신

HITV 요법의 적용과 치료 계획
치유의 지름길은 계획적인 치료

치료의 적용요건은?

HITV 요법의 치료 대상이 되는 것은 "재발암", 혹은 의사가 "수술 불가능"이라고 보는 스테이지 IV(4기)의 환자입니다.
치료에는 아래의 4개의 적용 요건이 있습니다.

1. 암은 백신이 목표로 삼을 수 있도록 '덩어리'를 형성해야 합니다. 백혈병과 같은 혈액암은 적용되지 않습니다.
2. 암의 종류는 상관없지만, 체내의 암 부위가 5개 이내, 1개의 종양의 최고 직경이 3cm 이하인 것이 바람직합니다.
3. 종양에 방사선이나 항암제에 대한 감수성이 남아있어야 합니다.
4. 치료에 견딜 수 있는 기초체력이 필요합니다.

병변의 수 및 종양의 최대 지름에 대한 바람직한 범위가 있지만 이것은 절대적인 치료의 요구 사항은 아닙니다. 실제로 HITV 요법이 치유로 이끈 환자들 중에는 병변의 수가 40곳(악성림프종), 종양 직경이 10cm(폐암)을 넘는 분도 계셨습니다.

N 폐암

통합 | 이미지 | 뉴스 | VIEW | 지식iN | 인플루언서 | 동영상 | 쇼핑 | 어학사전 | 지도 | ...

파워링크 '폐암' 관련 광고입니다. 등록 안내

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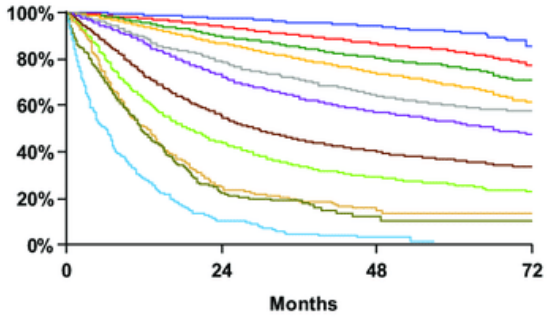
코로나19
확진현황 및 백신접종 정보

신속항원검사
내 주변 검사기관 찾기

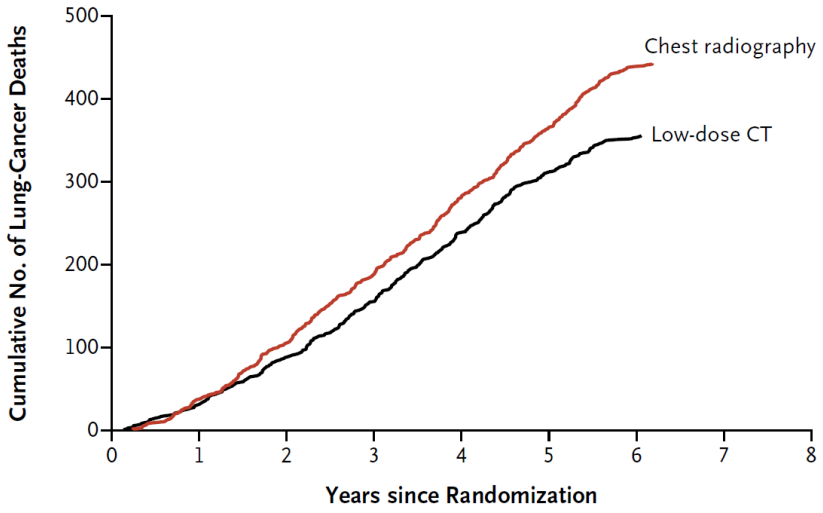
코로나19 팩트체크
코로나백신 결과 보기

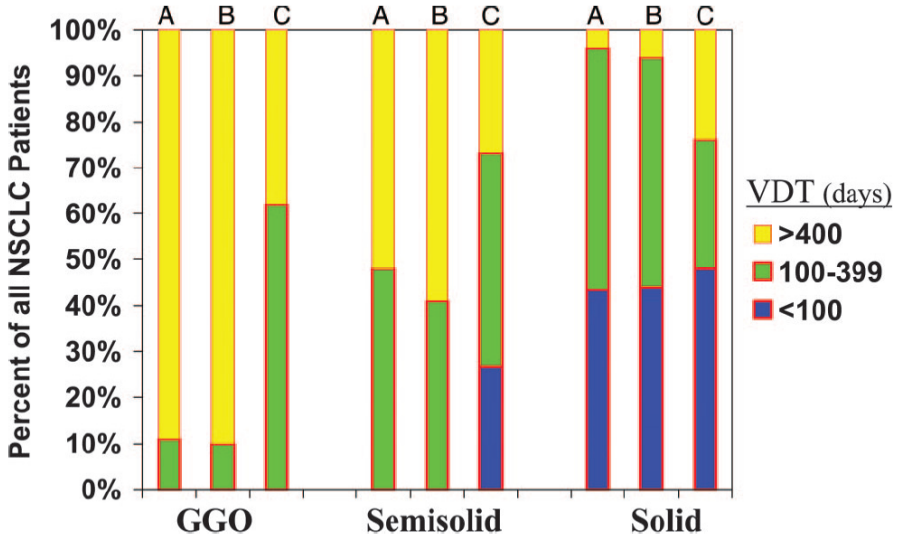
잔여백신예약
내 주변 잔여백신 찾기

Summary



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%





감사합니다.