Turning Gray: The Natural History of Lung Cancer Over Time

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Abstract: As newer therapies for lung cancer are being explored it becomes more important to understand the natural history of lung cancer. A systematic review of the data shows that untreated lung cancer is almost uniformly rapidly fatal, even if it is stage I. Analysis of data regarding tumor volume doubling times shows that conventionally detected lung cancers have short mean doubling times, and only a small proportion with very long doubling times. Lung cancers found during the course of a CT screening program have markedly longer mean doubling times and a substantially greater proportion with very long doubling times (>400 days). Models of tumor growth, however, are not understood well enough to use the observed doubling time to predict length of survival without treatment.

Key Words: Natural history, Lung cancer, Doubling time, Screening.

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Many things are changing in the field of lung cancer, including newer treatments (sublobar resection, radiofrequency ablation, cyberknife, and stereotactic radiosurgery) and different methods of presentation (incidental detection on computed tomography (CT) in an asymptomatic patient).[1,2] Results for such interventions have been reported in many nonrandomized studies. The implied argument is generally that the results substantiate the value of the intervention because the outcome is better than if nothing had been done. This calls into question how well we actually know what would have happened if nothing was done to treat a lung cancer. This article seeks to carefully and systematically review the available data regarding the natural history of lung cancer. The primary focus is on early stage (I, II) non-small cell lung cancer (NSCLC), as these patients are the primary focus of most of the newer treatment methods.

Natural history is defined as patient survival in the absence of any active treatment for the cancer. Supportive care measures that palliate specific symptoms are allowed, but not a treatment intended to affect the growth of cancer cells. This may be somewhat ambiguous at times, for example in the case of radiotherapy that is given to shrink a particular focus of tumor blocking an airway or in the brain (while such treatments are given primarily to relieve symptoms, they can significantly affect the length of survival). However, there is general agreement that supportive care measures are permissible when evaluating the natural history of a tumor. Supportive care measures include pain medications, lower dose radiotherapy (<50 Gy) intended to palliate a particular symptom or a surgical procedure intended to palliate a symptom or a local problem. Active treatment is not allowed, such as surgical resection, chemotherapy, and radiotherapy given at higher doses with curative intent.

There are two main ways to assess the natural history. The most obvious is to follow the outcomes of patients who were not treated with any therapeutic intervention (other than basic supportive care). Direct measurement of the natural history is simple but may be difficult to generalize. Those patients who choose or are chosen not to receive any active treatment may be quite different from those receiving treatments, because of comorbidities, psychologic or social issues, all of which have been shown to affect survival.[3,4] The differences in the characteristics of treated and untreated patients are perhaps most marked in patients with early stage lung cancer, in whom definition of the natural history is most important.

Another way to estimate survival without treatment is based on observation of the tumor over a period of time, after which an intervention is (usually) undertaken. Estimation of the natural history from a period of observation is probably much more representative of the broad patient population with lung cancer. A period of observation may be more likely to have occurred in patients with slow growing tumors, although it is likely that this selection bias is relatively low. This suppositive is based on the high frequency of missed lesions seen retrospectively on chest radiographs and the frequency of an inherent period of observation of CT-detected lesions (e.g., interval between screening CT and diagnostic CT). However, there is uncertainty about how well the behavior during the period of observation can be extrapolated throughout the life of the tumor.[5]

METHODS

This review was prepared by following, as closely as possible, published criteria for a systematic review, even though no widely endorsed standard exists.[6,7] The purpose of

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the project was to define the natural history of untreated lung cancer, and to define growth rates on lung cancer during a period of observation. Specific questions were whether the natural history or growth rates were related to the years included, the histologic cancer type, gender, radiographic appearance, geographic location, the type of study (registry, institutional series etc.) or the method of detection.

The search was designed to find all articles providing data on the natural history and growth rates of NSCLC. We searched three electronic databases (MEDLINE, EMBASE, and the Cochrane Library) for original studies published between 1960 and 2007 that provided data on either the natural history of lung cancer or on the growth rate of untreated NSCLC. We also manually searched the reference sections of all studies identified electronically. The search strategies are available on request from the author. The search was limited to articles published in English. No source of funding was available for this study.

We included articles reporting data on the natural history of untreated patients with NSCLC or on tumor growth rates in the absence of treatment. Both prospective and retrospective study designs were included. Studies providing data on fewer than 20 patients were excluded, as were studies that reported primarily on cases of small-cell lung cancer. No unpublished data were considered. We considered all duplicate publications, but did not list data pertaining to the same cohort of patients twice in the tables (we included cohorts involving some overlapping patients). We excluded articles that reported on only a particular sample or selected patients (e.g., studies using a selected group merely to assess the reliability of measurements of tumor size). No articles were excluded for any other reasons.

Our search strategies yielded 527 studies, which were narrowed to 77 by reviewing the abstracts. These were then reviewed in detail for eligibility for inclusion, and 22 studies were chosen for analysis. In addition, manual search yielded another 13 articles, for a total of 35 that contained data relevant to this study. Primary outcome measures were death, death from lung cancer, and tumor growth. The characteristics of the patients included in the studies were recorded, according to the specific questions to be addressed by our review.

No formal analysis of study quality or publication bias was possible among these retrospective studies. We included data only on patients that met the definitions outlined in this article for natural history, with a few exceptions when it was evident that the outcomes would be similar to those meeting the strict criteria. We included data from studies in which most of patients (≥90%) were untreated. In some instances data was not included in the calculations because the end point or patient cohort was thought to be too dissimilar, but is nevertheless depicted in the tables so the readers can judge the appropriateness of the decision for themselves. In the situations where deviations from the defined end points occurred details of the particular circumstance are provided in the footnotes of the respective table. Quantitative synthesis of the results was limited to simple calculation of averages among the relevant studies. So many factors were poorly

TABLE 1. Natural History of Untreated Advanced Stage NSCLC

Study		N	How Found	Clinical Stage	Environment	Comments	Overall Survival				Death Due to Ca
							MST (mo)	% 1-yr	% 2-yr	% 5-yr	
[a]Hyde et al.[62]	58–62	138	Routine	I–IIIb	VA	All men	(4)[b]	(13)[b]	(2)[b]	(0)[b,c]	—
[a]Roswit et al.[63]	~58–66	246	Routine	I–III	VA	All men	5	14	0	0	—
[a]Hyde et al.[64]	58–72	293	Routine	I–IIIb	VA	All men	—	—	(4)[b]	—	—
Zelen et al.[65]	57–73	193	Routine	III	VA	All men	4[d]	14[d]	—	—	—
Paul et al.[66]	60–82	50	Routine	III	Canada	—	5	12	0	0	—
Reinfuss et al.[67]	83–90	162	Routine	III	Poland	—	4	9	0	0	100
Vrdoljak et al.[68]	80–87	17	Routine	IIIa	Croatia	—	9	19	0	0	—
Leung et al.[69]	84–88	57	Routine	III	China	—	9	30	5	0	—
[e]Raz et al.[36]	89–03	1,306	Routine	IIIa	Calif	Registry	4	23	9	2	—
[e]Raz et al.[36]	89–03	7,248	Routine	IIIb	Calif	Registry	2	12	5	0	—
[f]**Average**							**5**	**17**	**3**	**0**	
[a]Hyde et al.[62]	58–62	328	Routine	IV	VA	All men	(2)[b]	(6)[b]	(1)[b]	(0)[b,c]	—
[a]Hyde et al.[64]	58–72	775	Routine	IV	VA	All men	—	—	(1)[b]	—	—
Zelen et al.[65]	57–73	522	Routine	IV	VA	All men	2[d]	6[a,d]	1	—	—
Vrdoljak et al.[68]	80–87	65	Routine	IV	Croatia	—	5	13	0	0	—
[e]Raz et al.[36]	89–03	12,840	Routine	IV	Calif	Registry	2	8	4	0	—
[f]**Average**							**3**	**9**	**2**	**0**	

Inclusion criteria: studies of ≥20 patients reporting the natural history of untreated non-small cell lung cancer.
[a] Estimated from indirect data provided.
[b] Crude survival.
[c] 4-year survival.
[d] Average of squamous carcinoma, adenocarcinoma, and large cell.
[e] Untreated during the 1st 6 mo after diagnosis.
[f] Excluding values in parentheses.
Ca, cancer; Calif, California; mo, months; MST, median survival time (in months); VA, veterans administration hospitals (USA).

described in these retrospective reports that a more sophisticated quantitative analysis appeared inappropriate. Whenever possible we tried to include details of the patient's characteristics and all of the results for the individual studies so that the reader could assess the consistency of the results and the appropriateness of combining the results for themselves.

DIRECT MEASUREMENT

Data on the survival of patients with untreated lung cancer is summarized in Tables 1 and 2. These studies have primarily involved lung cancers detected as part of the routine practice of medicine. Many of these patients presented because of symptoms, although some lung cancers were likely found incidentally on a chest radiograph taken for unrelated reasons (especially among patients with stage I tumors). The data demonstrates that survival of untreated patients is distinctively poor. For clinical stages I/II, III, and IV, respectively, the median survival time (MST) is 10, 5, and 3 months; the 1-year survival 39, 17, and 9%; and the 5-year survival only 2%, 0, and 0. Although there is a slight trend to better long-term survival of patients with earlier stages of disease, the effect is not pronounced, is related to lead time (at least in part) and long-term survivors are rare. A small trend can perhaps be perceived towards slightly better survival in more recent series among stage I/II and III patients compared with older patient cohorts, but the effect is marginal. The survival is shown graphically in Figure 1 from one of the largest series, involving almost 23,000 patients from the California cancer registry.

In older series, dating back 40 and 50 years, it seems to have been more acceptable to observe patients with lung cancer without administering any active treatment. Therefore, it may be that the patients in older series are more representative of patients in general. On the other hand, the relevance of such old data to the current situation is questionable. Besides the studies cited in Table 1 that reported specifically on untreated patients, a comparison group is available from studies of patients with advanced NSCLC who were randomized to either chemotherapy or basic supportive care during the last 20 years. Two systematic reviews of such studies

TABLE 2. Natural History of Untreated Early Stage NSCLC

Study	Accrual Years	N	How Found	Clinical Stage	Environment	Comments	Overall Survival MST (mo)	% 1-yr	% 2-yr	% 5-yr	Death Due to Ca
Vrdoljak et al.[68]	80–87	50	Routine	cI, II	Croatia	—	13	56	13	0	—
Chadha et al.[70]	90–01	39	Routine	cI, II	USA	Registry	12	26	0	0	49
Kyasa et al.[71]	91–98	70	Routine	cI, II	VA	—	11	44	17	0	86
[a]Wisnivesky et al.[20]	91–99	1,052	Routine	cI, II	SEER	M > 65 yr	6	30	14	3	~90[b]
[a]Wisnivesky et al.[20]	91–99	1,292	Routine	cI, II	SEER	F > 65 yr	9	40	19	5	~90[b]
Average			**Routine**	**cI, II**			**10**	**39**	**13**	**2**	**~80**
[a]Henschke et al.[72]	88–94	131	Routine	cIa	SEER	6–15 mm diam	(24)[c]	(81)[c]	(48)[c]	(39)[c]	—
[a]Raz et al.[36]	89–03	571	Routine	cIa	USA	Registry	13	53	33	9	—
Sobue et al.[13]	82–84	27	Routine	cI	Japan	Matched[d]	13	50	30	4	81
[a]Raz et al.[36]	89–03	1,432	Routine	cI	USA	Registry	9	42	24	7	84
[a]Wisnivesky et al.[73]	88–04	1,468	Routine	cI	SEER	—	(14)[c]	(57)[c]	(32)[c]	(14)[c]	73
Chadha et al.[70]	90–01	26	Routine	cI	USA	Registry	10	39	0	0	~50[b]
McGarry et al.[35]	94–99	49	Routine	cI[e]	VA	All M	14	62	38	—	53
[f]Motohiro et al.[14]	82–91	584	Routine	cI	Japan	—	(17)[b,f]	(69)[b,f]	(36)[b,f]	(14)[b,f]	—
Vrdoljak et al.[68]	80–87	19	Routine	cIb	Croatia	—	17	80	20	0	—
[a]Raz et al.[36]	89–03	861	Routine	cIb	USA	Registry	8	46	18	5	—
[a]Raz et al.[36]]	89–03	128	Routine	cII	USA	Registry	5	33	13	3	—
[a]Wisnivesky et al.[73]	88–04	140	Routine	cII	SEER	—	(14)[c]	(37)[c]	(20)[c]	(10)[c]	78
Vrdoljak et al.[68]	80–87	31	Routine	cIIb	Croatia	—	11	40	8	0	—
[g]**Average**			**Routine**	**cI, cII**			**11**	**49**	**22**	**4**	**70**
[h]Flehinger et al.[15]	73–78	29	CXR screen	cI	USA	—	(25)[c,h]	(88)[c,h]	(57)[c,h]	(9)[c,h]	—
Sobue et al.[13]	82–84	42	CXR screen	cI	Japan	—	25	76	48	14	80
[f]Motohiro et al.[14]	82–91	215	CXR screen	cI	Japan	—	(27)[f]	(80)[f]	(56)[f]	(24)[f]	—
[g]**Average**			**CXR screen**	**cI**			**25**	**76**	**48**	**14**	**80**

Inclusion criteria: studies of ≥20 patients reporting the natural history of untreated non-small cell lung cancer.
[a] Classified as untreated if no treatment for 6 mo, does not account for later treatment.
[b] Estimated from indirect data provided.
[c] Disease free survival.
[d] Matched by gender and age with CXR screen detected cases.
[e] Included 9% stage II tumors.
[f] Various non-surgical treatments used, none of which demonstrated a significant effect on survival.
[g] Excluding values in parentheses.
[h] 24% of patients received RT (either palliative or curative intent).
Ca, cancer; CXR, chest radiograph; Diam, diameter; F, women; M, men; mo, months; MST, median survival time (in months); RT, radiotherapy; SEER, surveillance, epidemiology, and end results registry (USA); VA, veterans administration hospitals (USA); yr, years old (patient age).

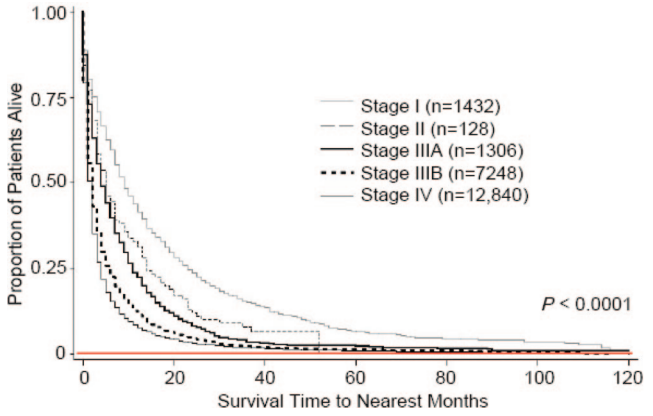

FIGURE 1. Survival of 23,954 patients with NSCLC who did not receive surgical resection, chemotherapy or radiotherapy.[36]

revealed little difference in MST (3.7 and 4.1 months) compared with the data in Table 1.[8,9] Taken together, the data among predominantly stage IV patients suggests a slight trend to better survival in more recent times (a gain of approximately 2 weeks for each decade since the 1960s).

Series of patients with early stage NSCLC who are not treated, suffer from the criticism that these patients are highly selected by negative factors and should therefore be expected to exhibit poor survival. Countering this is the observation that the majority of patients, in fact, died of lung cancer in those series in which this data was recorded. Although the suspicion has been raised that there is an inherent bias to attribute any death in a cancer patient to the cancer (sticky diagnosis or attribution bias), formal analysis has demonstrated that this is relatively infrequent.[10–12] Furthermore, this is probably even less prevalent in patients with severe comorbidities, in whom the comorbidities seemed to overshadow the importance of treating a lung cancer (particularly for stage I).

A trend to better survival is suggested among patients with lung cancer that participated in mass screening programs using chest radiographs (Table 2). This is based primarily on one study from Japan, which found a MST of 25 months and a 5-year overall survival of 14%.[13] This is corroborated by another study from Japan, which, however, included patients who received a variety of nonsurgical treatments (none of which significantly affected survival).[14] A third study from the Memorial Sloan Kettering chest radiograph (CXR) and sputum screening project conducted a decade earlier reported only disease free survival.[15] Although it is more difficult to compare, it seems that short- and intermediate-term survival was similar, whereas 5-year survival was worse than in the Japanese series. Furthermore, the patient cohort is not "clean" in that 24% received radiotherapy, although it is not clear at what dose and whether this was intended as curative or palliative treatment. Nevertheless, when all of the data is viewed as a whole, there is at least a suggestion that the natural history of lung cancer detected as part of a CXR screening program may be better than for patients presenting in a more routine fashion). Of course, this apparently longer natural history in screen detected cases includes the effects of lead time bias, and does not necessarily imply a difference in tumor biology. No data is available on the natural history of patients with lung cancer detected as a result of mass screening using CT.

ESTIMATION FROM TUMOR GROWTH

Mean Tumor Doubling Time

Several studies have retrospectively analyzed previous imaging studies to measure tumor volume doubling time (VDT). These are summarized in Table 3. The mean VDT is approximately 135 days for patients diagnosed during routine medical care, 150 days in screening studies involving chest radiographs, and 480 days in screening studies involving CT (Figure 2). This data is fairly consistent among studies involving a particular method of detection (routine care, CXR or CT screening), and thus is quite convincing that CT screening in particular identifies a different patient group. No real trend is apparent in more recent studies compared with older series. The VDT does not seem to be influenced by the reason for the interval between imaging studies, the length of the interval, the years involved or the geographic location of the study.

A more detailed analysis reveals that women consistently have longer mean doubling times than men by a factor of approximately 2 (range 1.4–2.9).[16–19] This gender difference seems to hold true within each method of detection (VDT of approximately 250 versus 125 days in women versus men with detection by CXR screening and 600 versus 350 days in CT screen detected, respectively). A survival advantage for women over men was seen for each cell type except squamous carcinoma in a large SEER database study of treated and untreated patients more than 65-year-old with cI, II NSCLC.[20] This suggests that the better survival in women is not merely because of a greater proportion of adenocarcinoma or bronchoalveolar carcinoma (BAC), but reflects a gender-specific difference in biological behavior.

Two studies reported progressively longer VDT for solid, semisolid, and ground glass opacity (GGO) lesions detected by means of CT screening (approximately 150, 475, and 850 days respectively).[16,18] However, another study found little difference among these radiographic categories (approximately 500, 570, and 470 days, respectively, p = NS).[17]

Several studies (Table 4) have consistently documented progressively longer mean VDT by histologic types: squamous carcinoma < adenocarcinoma < BAC < atypical alveolar hyperplasia. This progressive trend seems to be consistent within several methods of detection. The trend to a longer mean VDT is not limited only to BAC, but is seen with adenocarcinoma as well. However, this data is of limited use to the clinician because the histologic type is generally not known until after resection has been accomplished. It is noteworthy that CT screen detected cases as compared with routinely detected cases have a markedly longer VDT for

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**

Inclusion criteria: studies of ≥20 patients reporting tumor doubling times among patients with non-small cell lung cancer.
[a] In most patients.
[b] Patients detected as part of unrelated medical care or because of symptoms of lung cancer.
[c] Estimated by combining patients detected incidentally and because of symptoms.
[d] Pathologic stage I patients, seen on a CT scan (but not through a CT screening program).
[e] Median.
[f] Excluding values in parentheses.
[g] Included patients with atypical alveolar hyperplasia (15%).
[h] Data only for the 56% that increased in size over a mean of 93 d between scans (42–120 d); rest were stable.
CT, computed tomography scan; CXR, chest radiograph; Diam, diameter; Dx obs, diagnostic period of observation; Eu, europe; M, men; MLP, Mayo lung project; mo, months; MSK, memorial Sloan Kettering study; VDT, volume doubling time; w/u, delay due to work up.

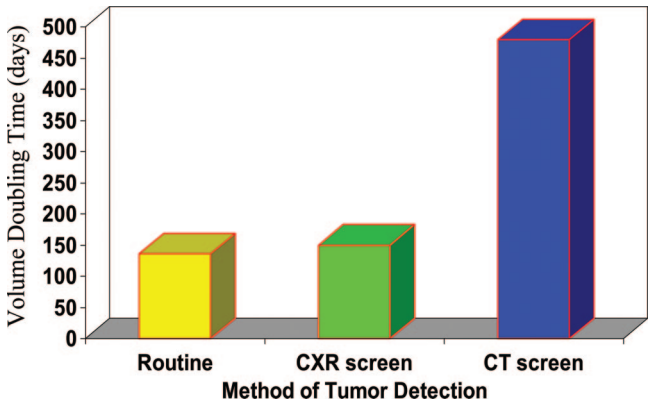

FIGURE 2. Mean doubling times observed among human non-small cell lung cancers, by the method of detection.

BAC and adenocarcinoma, but there is little difference in patients with squamous carcinoma. It is possible that CT screening has little impact on tumors arising in the airways, (i.e., squamous carcinoma) because of poor visualization of these areas on CT.

Distribution of Tumor Doubling Times

The data on mean tumor doubling times suggests that the growth rate varies according to the method of detection, and other factors such as gender, histologic type, and possibly the radiographic appearance. These mean values, however, obscure the broad spectrum of doubling times, which are summarized in Table 5. This data clearly demonstrates that there is a broad distribution of tumor doubling times. Furthermore, a marked trend in the distribution of VDT is seen according to the method of detection. In patients undergoing routine care and in CXR screening studies most of tumors have a relatively short VDT (<250 days), whereas in CT screening studies a much broader distribution is seen extending to a very long (>400 days) VDT (Figure 3). The study by Winer-Muram et al., is somewhat of an outlier, with a substantial portion (26%) of routine care detected patients having a VDT of more than 400 days.[21] A closer look, however, discloses that the patients in this study were limited to stage I lung cancers seen on a CT scan (although not part of a CT screening program). The decision to exclude this study can be challenged; if it is included the percentages become 41, 42, 11, and 7% for VDT categories of less than 100, 100 to 249, 250 to 399 and ≥400 days, respectively.

Factors other than the method of detection do not seem to influence the VDT distribution. The time period over which patients were enrolled in the studies does not seem to influence the VDT distribution. Differences exist between lung cancers seen in different parts of the world (e.g., a high proportion of squamous cell cancer in Europe, adenocar-

TABLE 4. Mean Doubling Time by Histologic Type

Study	n AAH/ BAC/Ad/Sq	Years of Accrual	How Detected	Location	Volume Doubling Time (d) AAH	BAC	Ad	Sq
Spratt et al.[25]	–/–/8/13	40–61		USA	—	—	118	70
Garland et al.[74]	–/–/7/22	~55–61	Routine	USA	—	—	222	128
Geddes et al.[34]	–/–/60/111	~60–75	Routine	Eu/USA	—	—	161	88
Mizuno et al.[33]	–/–/23/22	~75–80	Routine	Japan	—	—	178	103
[a]Jennings et al.[59]	–/19/51/48	96–04	Routine	USA	—	250	166	132
Average			**Routine**			**250**	**169**	**104**
Usuda et al.[19]	–/–/86/67	85–86	CXR screen[b]	Japan	—	—	223	105
Average			**CXR screen**				**223**	**105**
Hasegawa et al.[16]	–/–/49/8	96–98	CT screen	Japan	—	—	533	129
Sone et al.[18]	–/13/23/4	96–98	CT screen	Japan	—	747	448	(134)[c]
Lindell et al.[17]	–/9/22/8	99–03	CT screen	USA	—	780	746	103
[d]Takashima et al.[57]	3/8/6/3	96–98	CT screen	Japan	(988)[c,d]	(567)[d]	(384)[d]	(122)[d]
[e]**Average**			**CT screen**			**764**	**576**	**122**

Inclusion criteria: studies of ≥20 patients reporting tumor doubling times and histologic types of non-small cell lung cancer.
[a] Clinical stage I patients, found by CT scan (but not in a CT screening program).
[b] 75% of patients were enrolled in a screening study.
[c] Less than 5 patients in this category.
[d] Data only for the 56% that increased in size over a mean of 93 d between scans (42–120 d); rest were stable.
[e] Excluding values in parentheses.
AAH, atypical alveolar hyperplasia; Ad, adenocarcinoma; BAC, bronchioloalveolar carcinoma; CT, computed tomography scan; CXR, chest radiograph; Eu, europe; Sq, squamous cell carcinoma.

TABLE 5. Tumor Doubling Time Distribution

Study	N	How Detected	Years Studied	Other Charac.	Location	% with Volume Doubling Time of (in d) <100	100–249	250–399	400–799		>800
Garland et al.[74]	40	Routine	~55–61	—	USA	48	38	8	4		2
Weiss et al.[77]	91	Routine	59–62	—	USA	48	40	7	3		1
Steele et al.[24]	67	Routine	~59–62	VA	USA	33	52	10	5		0
Weiss et al.[26]	47	Routine	59–65	—	USA	30	55	13	2		0
Kerr et al.[78]	23	Routine	~77–83	—	England	61	26	13	0		0
[a]Winer–Muram et al.[21]	50	Routine	96–01	VA	USA	(26)[a]	(36)[a]	(12)[a]	(8)[a]		(18)[a]
Average		**Routine**				**44**	**42**	**10**	**3**	**— 3 —**	**1**
Arai et al.[75]	237	CXR screen[b]	~89	—	Japan	37[c]	29[c]	22[d]	10[d,e]		4[e]
Usuda et al.[19]	159	CXR screen[b]	85–86	—	Japan	47	37	6	7		3
Yankelowitz et al.[76]	44	CXR screen	71–76	MLP, all M	USA	48	45[f]	5[f]	—	2	—
Yankelowitz et al.[76]	43	CXR screen	74–78	MSK, all M	USA	23	56[f]	14[f]	—	7	—
Average		**CXR screen**				**39**		**12**	**195**	**8**	**195**
Hasegawa et al.[16]	61	CT screen	96–98	—	Japan	24	31	19	21		5
Sone et al.[18]	45	CT screen	96–98	—	Japan	18	20	18	27		18
Lindell et al.[17]	48	CT screen	99–03	—	USA	33	40	—	—	27	—
Average		**CT screen**				**29**	**31**	**19**	**—**	**— 27 —**	**—**

Inclusion criteria: studies of ≥20 patients reporting a distribution of doubling times among patients with non-small cell lung cancer.
[a] Pathologic stage I patients, seen on a CT scan (but not through a CT screening program).
[b] 60–75% of patients were enrolled in a screening study.
[c] Threshold of 120 d.
[d] Threshold of 480 d.
[e] Threshold of 960 d.
[f] Estimated from indirect data reported.
CT, computed tomography scan; CXR, chest radiograph; M, men; MLP, Mayo lung project; MSK, memorial Sloan Kettering study; VA, veterans administration hospital system.

cinoma in North America, a higher proportion of BAC and epidermal growth factor receptor (EGFR) mutations in Japan). However, there does not seem to be a correlation of VDT distribution with geographic location.

The proportion of patients with a long VDT (>400 days) seems to be particularly large in women (59 and 37% in two studies) in CT screening studies (versus 36 and 11% in men).[17,18] The proportion with long VDT is dramatically

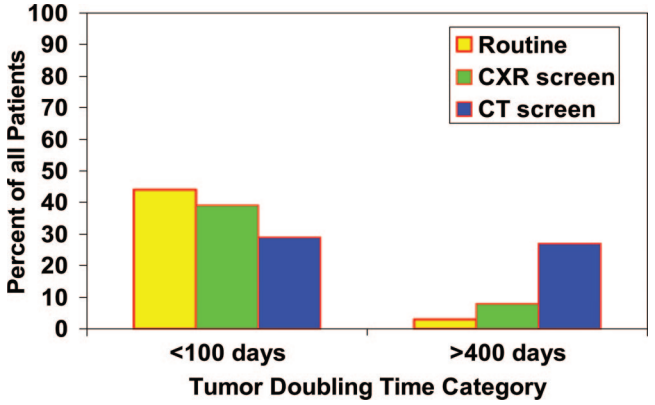

FIGURE 3. Proportion of patients with very short (<100 days) or very long (≥400 days) tumor doubling times according to the method of lung cancer detection.

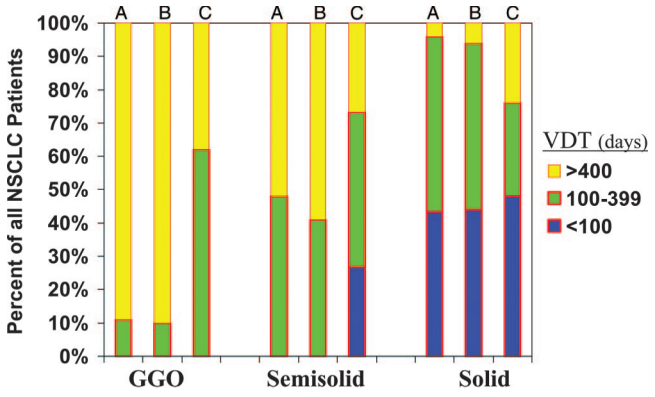

FIGURE 4. Proportion of tumor doubling time categories by radiographic appearance among CT screen detected cancers. *A,* Hasegawa M, et al. *Br J Radiol* 2000;73:1252–59;[16] *B,* Sone S, et al. *Lung Cancer* 2007;58:329–41;[18] *C,* Lindell RM, et al. *Radiology* 2007;242:555–62;[17] VDT: volume doubling time.

increased for GGO lesions with a corresponding decrease in the percent with a short (<100 days) VDT (Figure 4).[16–18] In fact approximately 50% of lung cancers that had a GGO appearance had a VDT of more than 800 days (2.2 years) in two CT screening studies.[16,18] Semisolid lesions also have a substantial portion (approximately 45%) with long VDT (>400 days), but include some rapidly growing tumors (approximately 10%). In contrast, solid lesions rarely grow slowly (approximately 10%), and many have short VDT (approximately 45%).[16–18]

There is no evidence that older patients have more slowly growing tumors in the only study providing data regarding this (involving CT screening).[18] In fact, the opposite seems to be true, with an increase in the proportion with short (<100 days) VDT in older patients (0, 18, and 36% of patients aged <60, 60–69, and >70, respectively) and arguably a decreasing proportion with long (>400 days) VDT (42, 59, and 18% of patients aged <60, 60–69, and >70, respectively).[18] It is unknown how characteristics such as risk factors (e.g., smoking) or willingness to participate in screening study may have influenced these results.

Models of Tumor Growth

To apply the data on observed doubling times to predict the natural history of lung cancer, a review of some concepts of tumor growth is necessary. The two main models of tumor growth are reviewed, and some of the general implications and pitfalls of estimating the natural history.

Exponential Growth

Early laboratory studies included a classic series of elegant experiments involving a murine leukemia model known as L1210.[22] In this murine model essentially all of these tumor cells were actively dividing at a constant rate, and could be traced back to a single malignant cell of origin. This led to the widespread adoption of the concept of exponential growth, a model of tumor growth that is still often used today.[23] This model fit extremely well with the observed proliferation of leukemia cells in the mouse L1210 model. Early observations of primary lung cancers and metastatic pulmonary nodules on serial CXR were consistent with exponential growth, although the period of observation was limited.[24–26]

The exponential model postulates that all of the cells are in a growth phase and dividing at a constant rate throughout the life of the tumor. With each doubling time the volume of the tumor doubles; simple mathematics correlates each doubling of volume with an increase in the diameter of approximately 1.26 (the cube root of 2). Assuming the initial tumor cell has a diameter of 10 μm, it would take 30 doublings to reach a diameter of 1 cm, 35 doublings to reach 3 cm, and 40 doublings to reach a diameter of 10 cm (and a weight of ~1 kg). A tumor of this size in the chest is likely to cause significant life-threatening effects, and therefore the usually accepted time of death is estimated to be at about 40 to 41 doubling times (Figure 5).

Gompertzian Growth Model

Another model, known as the Gompertzian model, stems from an actuarial model that has been applied to tumor

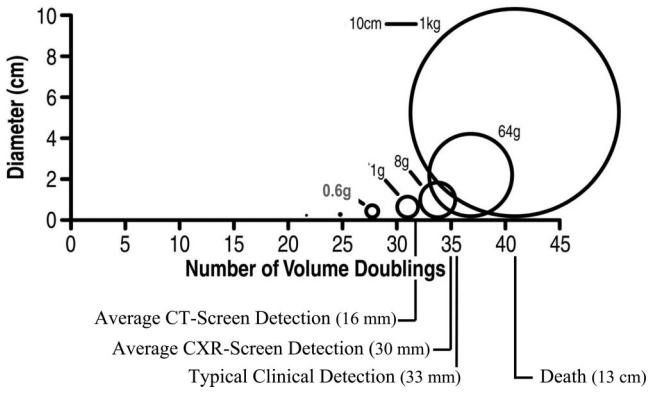

FIGURE 5. Schematic of exponential growth of a cancer, with time expressed as number of volume doublings. (From Geddes DM. *Br J Dis Chest* 1979;73:1–17.[34])

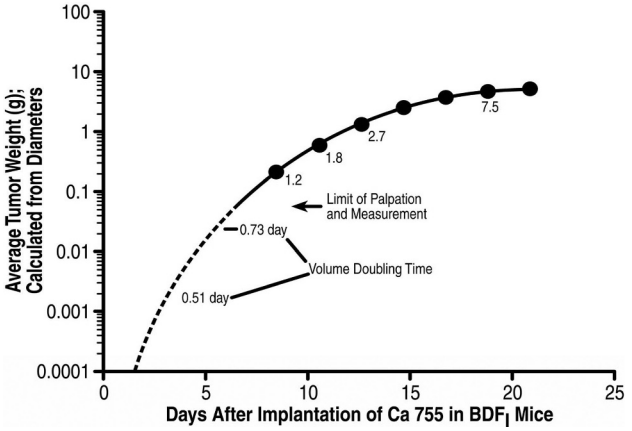

FIGURE 6. Gomperztian growth curve demonstrated by observed average growth rates in 100 mice after implantation of adenocarcinoma. The solid and dotted line represents a best-fit Gompertz function. (From Schabel FM. *Cancer* 1975;35:15–24.[28])

growth. This model also assumes that rate of tumor cells division is constant, which has been demonstrated to be the case.[27] However, the fraction of tumor cells that is in a growth phase decreases over time. This might be due to the tumor outstripping its blood and nutrient supply, excess excretory products, contact inhibition, or simple crowding.[28] This model predicts a progressively longer VDT as the tumor size increases. Mathematically the Gompertz equation states that tumor growth at each instant is exponential, but with a growth constant (growth fraction) that is simultaneously decreasing exponentially.[28]

Clinical observations over longer periods have shown that most human tumors follow a Gompertzian growth curve, in which growth slows as the tumor gets larger (with the possible exception of Burkitt's lymphoma which follows a more exponential growth curve).[27,29] In fact, Gompertzian growth is also observed in most animal models (Figure 6).[28,30,31] The maximum growth rate occurs when the tumor is approximately one-third of its maximal size.[27] The Gompertzian model predicts a shorter period of preclinical growth than the exponential model, and longer survival after diagnosis.[29]

Phases in the Life of a Cancer

It is often assumed that a cancer starts with malignant transformation of a single cell. This cell grows, but has a prolonged period during which the developing tumor is so small it is undetectable by all means. At some point, the tumor is sufficiently large to be detectable if an imaging study is done (i.e., CT or positron emission tomography), but it is still too small to cause any clinical symptoms. Eventually a change in the patient's well-being prompts medical attention and a diagnosis is made. The time from the initial malignant transformation to clinical detection is the preclinical phase, and generally is at least ¾ of the entire life of the tumor. If a diagnosis is made by an intercurrent imaging study before the onset of symptoms, the time between this incidental diagnosis and the usual diagnosis at clinical presentation represents the lead time. The time between the diagnosis and the patient's death is the survival time. Obviously, if diagnosis is made earlier, the survival time will be longer (even without any active treatment) because of the lead time.

On the other hand, malignant tumors lead to death not only because of growth of the primary tumor mass, but because of the capacity of tumors to metastasize to distant sites. The historical concept has been abandoned that distant metastases only occurs when the local lymphatics have become overwhelmed and can no longer contain the tumor. The question "When do tumor cells reach the bloodstream? " has given way to the question "What gives a circulating tumor cell the ability to successfully implant and grow? " Sensitive analyses have shown that circulating tumor cells are common, even in early stage cancers. For example, circulating tumor cells were detected by reverse transcription-polymerase chain reaction in 40% of 71 patients with NSCLC and 30% of 15 patients with small cell lung cancer patients.[32] The presence of circulating tumor cells was unrelated to tumor stage. An acquired genetic change in the tumor cells (i.e., an angiogenesis factor) may be what determines how and when circulating cells develop the ability to form actively growing metastases. Alternatively, it may be changes in the host immune system or microenvironment (i.e., chemokines) that are the key. An understanding of these factors has implications on the ability to predict natural history from observation of the tumor doubling time during a limited period.

Predictions on the Natural History from Doubling Times

It is possible, using the tumor diameter and the observed doubling time, to calculate for an individual patient what the natural history would be if the tumor followed an exponential growth pattern. One study has directly compared actual survival in individual patients with that predicted from the observed doubling time, and found remarkable correlation among nonresected patients with survival time as predicted by the exponential model ($r = 0.88$, $p < 0.01$).[33] These were patients diagnosed with lung cancer during routine medical care (no screening involved) in whom prior chest radiographs were available. It is not clear why there was a delay in diagnosis (or treatment). Surgical resection resulted in markedly better survival than predicted by the model, but other treatments (given to 24 of 26 nonresected patients) seemed to have little benefit, which is perhaps not surprising given the state of affairs around 1980. Thus this study provides fairly direct data in support of the exponential growth model, although the data is not "clean" (i.e., involving truly untreated patients).

One can attempt to validate growth models in general terms by comparing predictions based on average tumor sizes, average doubling times with average observed survival. Studies have reported an average tumor diameter of 33 mm among cancers detected during routine care,[33–37] 30 mm in patients undergoing CXR screening,[38–40] and 16 mm in patients undergoing CT screening (all scans).[1,16,17,37,38,41–45] For patients detected purely by an incidence scan during the course of CT screening the average size is approximately 13 mm.[1,42,44]

TABLE 6. Estimated Relevant Clinical Intervals Based on Tumor Doubling Time[a]

How Detected	Mean VDT (d)	Mean Diam (mm)	# DT Elapsed	# DT Left	Mean Survival Time (in Years, Untreated)		
					1st Cell to Detection	Detection to Death	1st Cell to Death
Routine	136	33	35	6	13	**2.2**	15
CXR screen	150	30	34.5	6.5	14	**2.7**	17
CT screen	480	16	32	9	42	**12**	54

[a] Survival times over 3 yr rounded to nearest integer. Calculations made based on the classic assumptions of the exponential growth model: a cell diameter of 10 μm, spherical cells, a constant growth rate and death at a diameter of 13 cm (41 doublings).

CT, computed tomography scan; CXR, chest radiograph; Diam, diameter; # DT elapsed, number of doubling times elapsed between development of the 1st malignant cell and clinical detection (calculated by average size at detection); # DT left, number of doubling times left from detection to death (assuming death at 41 total doublings); VDT, volume doubling time.

Table 6 tabulates results of calculations based on reported average tumor sizes and doubling times according to the method of detection using the exponential growth model. The calculated survival time based on mean size and mean doubling time is approximately 2.2, 2.7, and 12 years for routine, CXR-screen and CT-screen detected NSCLC, respectively. This is markedly longer than what has been reported in Tables 1 and 2 for routine detection cases, although it is similar for stage I CXR screen detected cases. Furthermore, the estimate of the entire life of the tumor is 15, 17, and 54 years. Even 15 years is difficult to believe, and 54 years seems practically impossible. Thus these estimates call into question the validity of predictions about the survival time based on observed doubling times and the exponential model (including the assumption that death occurs on average after 40–41 doublings).

Predicting growth over the entire life of a tumor using the Gompertzian model is more complex. This is in part because the doubling time varies depending upon the size of the tumor. Thus the applicability of the observed doubling time must be estimated by taking into account the tumor size during the period of observation. In general terms, however, the Gompertzian model would predict that the growth rate before clinical detection would be more rapid than the exponential model, and slower afterward. Thus the survival times after clinical detection would likely be two to three times longer than predicted by the exponential model. These predictions do not fit the observed survival times for lung cancers detected by routine care or by CXR screening (no observations exist with which to correlate survival of CT detected lung cancers).

IMPLICATIONS OF NATURAL HISTORY ON PATIENT MANAGEMENT

The observed survival of untreated patients in whom lung cancer is detected as part of routine care is uniformly poor, suggesting that these patients should be managed aggressively and expeditiously. The median survival of patients with routinely detected clinical stage I, II tumors is only about 10 months if untreated. A brief trial of antibiotics to differentiate between infection and malignancy may sometimes be justified. However, in many instances such a "diagnostic delay" is not justified because the radiographic appearance so clearly suggests lung cancer and not infection (discrete, solid, spiculated mass). Unless the radiographic appearance is strongly suggestive of scar, a period of delay to observe growth does not seem to be warranted. Furthermore, a prolonged sequential work-up involving a battery of imaging tests and biopsy procedures often takes many weeks to complete. Prompt referral to a specialist appears to result in a more rapid and streamlined evaluation and initiation of treatment. This has led the relevant medical organizations in several countries (Great Britain, Canada, France, Sweden) to either mandate or strongly recommend through guidelines that patients with a suspicion of lung cancer be referred and seen promptly (within 1–2 weeks) by a thoracic specialist, in general in conjunction with a multidisciplinary team. However, the amount of benefit that is realized from rapid evaluation and initiation of treatment is unclear.[46] It is suggested that the patient be seen in an organized multidisciplinary program,[47,48] because of data suggesting that this promotes the delivery of evidence-based care and improves outcomes.[49–53]

The data regarding the distribution of tumor doubling times shows that lung cancers involve a wide spectrum of growth rates. A broader appreciation of this fact is warranted, because CT imaging in particular appears to affect the spectrum of disease that is encountered. The presence of CT screening programs and the increased prevalence of CT imaging (outside of a CT screening program) makes this observation particularly important at this time. Direct natural history data to corroborate this observation, however, is not available. Nevertheless, the increasingly broad spectrum of disease leads to speculation that with a better understanding it may be possible to match the aggressiveness of the treatment to the aggressiveness of the particular tumor. Obviously, this will require not only methods to define average characteristics of types of tumors, but confidence that one can define the aggressiveness of the tumor of an individual patient.

The spectrum of lung cancer detected as a result of CT screening is markedly different than that of patient diagnosed during routine medical care. Tumors found in CT screening programs have markedly longer doubling times, and a substantially greater proportion with very long (>400 days) doubling times. There is little difference between routine care detected tumors and CXR screen detected tumors, although a slight trend is apparent. Surprisingly, there is little difference

in routine care detected cancers currently compared with those detected decades ago. A minor trend towards less rapidly growing tumors in more recent times is suggested, perhaps related to a greater prevalence of imaging for individuals in general.

Several important implications follow from the observations that a spectrum of aggressiveness exists among lung cancers and that the proportion of patients along the spectrum is affected by the method of detection, and other characteristics such as the radiographic appearance (GGO versus semisolid versus solid). First, it is probably inappropriate to use data generated from routinely detected patients to make estimates about the outcomes of CT screen detected patients. This applies to an estimate of a potential mortality benefit as well as an assessment of cost-effectiveness. Similarly, we must be careful in the interpretation of phase II studies of novel treatment approaches such as Radiofrequency Ablation and Stereotactic radiosurgery. Second, evaluation of treatments for less aggressive tumors may require a prolonged period of follow-up before the true impact of the treatment can be assessed. Finally, the greater prevalence of indolent tumors raises the question that over-treatment and over-diagnosis may be a substantial risk in some settings.

Unfortunately, models of tumor growth do not seem to correlate well with estimations derived from observed doubling times. Thus predictions about the natural history made from doubling times are not currently accurate enough to justify not treating a diagnosed lung cancer in most clinical situations. Although observation alone may well turn out to be appropriate for some patients, this must be studied further. This conclusion is further strengthened by the lack of understanding of the relationship between (indolent) tumor growth and the development of distant metastases.

A particularly poignant issue is the management of patients with a GGO. The data regarding VDT suggests that this group has a high proportion of slow growing tumors (40–90% with VDT of >400 days among CT screen detected tumors). Several factors contribute to the difficulty in defining the appropriate management of a GGO. The correlation between radiographic characteristics and histologic diagnosis (atypical alveolar hyperplasia, BAC, or well differentiated adenocarcinoma) is unclear.[54–56] Furthermore, in a substantial portion of patients with a GGO the presence of a malignancy is associated with an increase in the density of the lesion without growth, or even with shrinkage of the lesion.[17,57–59] Thus a GGO may represent a benign lesion or a cancer, and growth alone does not always differentiate these.

The data cited in this review stems largely from formal screening studies, and an important question is how well this applies to patients who are not participating in a screening program, given the rapidly increasing number of CT scans that are done for unrelated reasons.[60] Recent studies among treated patients have suggested the same good prognosis among patients with a CXR screen detected lung cancer and one detected incidentally by a CXR done for other reasons during work-up of an unrelated medical condition—in contrast to a lung cancer detected by routine clinical presentation.[61] This observation held up even among stage pI tumors, suggesting that the method of detection, whether part of a formal screening program or not, selected patients with a different biological behavior.[61] No comparison is available between lung cancers detected incidentally by a CT scan and one detected in a CT screening program.

Many questions remain about the natural history of lung cancer, and insufficient and conflicting data exists in many areas. Nevertheless, two main concepts clearly emerge. First, untreated lung cancer as detected during routine clinical care is rapidly fatal, even among patients with stage I NSCLC. However, a second central concept is that the spectrum of growth rates of lung cancer seems to be changing significantly. The evidence is strong and consistent that CT screening identifies a somewhat different cohort of patients with lung cancer that includes many more patients with slow growing tumors. This phenomenon may also extend to GGOs that are discovered incidentally because of an increasing frequency of imaging in general. Thus our changing health care environment demands that we view lung cancer as a spectrum of shades of gray. It is important that we develop a thorough appreciation of the range of disease behavior, because it is crucial to appropriately evaluate data regarding practically every aspect of lung cancer—including screening, diagnosis, staging, and treatment.

CONCLUSIONS

Review of the data on the natural history of lung cancer leads to the following conclusions:

1. Lung cancer as diagnosed during routine medical care is rapidly fatal, even among clinical stage I tumors. Patients who are found to have a lesion suspicious for lung cancer should be referred promptly to a specialist for evaluation. A period of observation by the internist or family practitioner is not justified other than possibly for a brief period to exclude pneumonia. There is only a minimal trend to better survival in more recent years.
2. There is a wide variation in tumor growth rates. Lung cancer is a heterogeneous disease with a spectrum of growth characteristics.
3. The proportion of slowly growing tumors VDT (>400 days) is substantially increased in patients diagnosed as part of screening program (especially CT screening). It is inappropriate to apply data regarding the natural history of lung cancer from populations of patients detected during routine care to patients detected as part of a CT screening program.
4. The larger proportion of slowly growing tumors in CT screening programs suggests that over-treatment and over-diagnosis may exist.
5. Limited data suggests that the increase in indolent tumors seen in CT screening programs may also be present among tumors found by incidental (nonscreening) CT imaging.
6. Models of tumor growth are not sufficiently clear to allow accurate prediction of the natural course from knowledge of the VDT of the tumor.

7. Awareness of the changing spectrum of aggressiveness among lung cancers is needed to correctly interpret the results of non-randomized studies.

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