

Is computed tomography follow-up of patients after lobectomy for non-small cell lung cancer of benefit in terms of survival?

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Abstract

A best evidence topic in cardiothoracic surgery was written according to a structured protocol. The question addressed was whether following up patients after lobectomy for non-small cell lung cancer (NSCLC) with computed tomography (CT) scanning is of benefit in terms of survival. Altogether, 448 papers were found using the reported search, of which five represented the best evidence to answer the clinical question and three provided supporting evidence. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. There is no general consensus in the literature. From the limited number of papers that address the effect of CT follow-up on survival following surgery for NSCLC, three showed that CT scanning may improve the survival of patients by detecting local and distant recurrences at an earlier stage when the patient is asymptomatic. One paper showed that detection by the use of low-dose CT or simultaneous chest CT plus positron emission tomography-CT led to a longer duration of survival compared with detection by clinical suspicion (2.1 ± 0.3 vs 3.6 ± 0.2 years, $p = 0.002$). However, two papers broadly showed that follow-up with CT does not improve survival outcomes regardless of the site of recurrence. One such study showed that there was no clinically significant difference in survival whether patients were followed up using a strict CT protocol compared with a symptom-based follow-up (median survival after recurrence: strict 7.9 months, symptom-based 6.6 months, $p = 0.219$). The remaining papers supported the use of CT as a screening tool for recurrence but did not comment directly on survival. Owing to the limited and contradictory evidence, there is a need for a randomized controlled trial to assess the survival outcomes of patients followed up with a CT screening protocol vs a symptom-based follow-up.

Keywords: Non-small cell lung cancer • Lobectomy • Computed tomography • Recurrence • Follow-up

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

THREE-PART QUESTION

In [patients who have undergone lobectomy for non-small cell lung cancer (NSCLC)] will [follow-up computed tomography (CT) scanning] improve [survival rates]?

CLINICAL SCENARIO

You have under your care a 62-year old patient who had a lobectomy for NSCLC 12 months ago. He has been scheduled for a routine chest X-ray (CXR) to detect recurrence of the cancer. During the consultation, he mentions a friend of his with colorectal cancer being followed up by CT scan. He asks whether the X-ray is more likely to detect recurrence than CT scans of his chest, whether this may have survival benefit and which parts of

his body might require CT. You resolve to check the literature yourself in order to help him make an informed decision.

SEARCH STRATEGY

Medline 1948 to March 2012 using PubMed interface: (Lung cancer[Ti] OR lobectomy[Ti] OR Pneumonectomy[Ti]) AND (CT [Ti] or computed tomography[Ti]) AND (recurrence[ti] OR follow*[ti] OR scan*[ti] OR surveil*[ti] OR screening[Ti] or postoperat*[ti]).

Additionally, the following were also searched for further relevant studies: references of all resulting papers and Cochrane Review Database.

SEARCH OUTCOME

Four hundred and forty-eight papers were found using the reported Medline search. Major inclusion criteria included surgical management of NSCLC and CT follow-up. Major exclusion criteria included exclusive use of non-surgical management of NSCLC and exclusive use of positron emission tomography

Table 1: Best evidence papers discussing survival outcomes

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments	
Westeel <i>et al.</i> , (2000), Ann Thorac Surg, France [2] Single centre prospective cohort study (level IIa)	192 patients who underwent complete resection of NSCLC between 1980 and 1993 Follow-up involved a four monthly CXR, history and examination as well as an annual CT	Recurrences			Asymptomatic recurrences had significantly better survival rates than for the 100 symptomatic recurrences The majority of recurrences that could be treated with curative intent were diagnosed by chest CT or bronchoscopy The authors concluded that a more intensive policy of follow-up can improve the outcome and is cost-effective It should be noted that the results focus solely on recurrences and do not include detection of second primary tumours (22 new malignancies occurred in these 192 patients)
		Total recurrences	136/192 (76%)		
		Scheduled procedure	85/192 (63%)		
		Non-scheduled visit (due to symptoms)	51/192 (37%)		
		Of scheduled procedures:			
		Number of asymptomatic	35/192 (26%)		
		Number of symptomatic	50/192 (37%)		
		Recurrence detected by CT	30/136 (22%)		
			5/50 (10%) in symptomatic patients		
			13/35 (37%) in asymptomatic patients		
	Median survival from date of operation	24 months (range 1–198 months)			
	from date of recurrence	7 months (range 0–164 months)			
	3-year survival from recurrence (95% CI)				
	all patients with recurrence asymptomatic, scheduled (n = 35)	13% (7–19%)			
	symptomatic, scheduled (n = 50)	31% (16–46%)			
	unscheduled (asymptomatic n = 1, symptomatic; n = 50)	10% (2–18%)			
	Cost per year of life gained due to thoracic CT and bronchoscopy	4% (0–9%)	\$12 902–\$13 415		
Lamont <i>et al.</i> , 2002, Arch Surg, USA [3] Single centre retrospective cohort study (level IIb)	124 patients who presented for follow-up between January 1996 and December 2000 after complete resection for NSCLC	SPLC picked up on CT	19 of 124 (15.3%) (all patients were asymptomatic)	Systematic follow-up of NSCLC, including annual CT, detects SPLC at an early stage (IA) that is potentially resectable Early detection of LRLC is also possible, but patients have poorer prognosis and shorter disease-free survival. Surgical treatment options are less affected by early detection Authors state that CT surveillance must be performed in a controlled setting by experienced personnel because many small benign pulmonary lesions are identified Careful adherence to a defined protocol is needed to avoid unnecessary interventions	
			In 11 of 19 cases (57.8%), SPLC picked up first by CT		
			16 of 19 (84.2%) detected at stage 1A		
			18 of 19 (94.7%) patients had potentially resectable SPLC		
		Probability of developing SPLC	2.1% per patient per year		
		LRLC picked up on CT	9 patients diagnosed with LRLC		
			CT first identified LRLC in 5 of 9 patients (55.6%)		
		Median disease-free survival	SPLC: 35 months LRLC: 2 months p = 0.02		

Continued

Table 1: (Continued)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Yokoi <i>et al.</i> , 1996, Ann Thorac Surg, Japan [4] Single centre prospective cohort study (level IIa)	128 patients with primary NSCLC underwent surgical resection at this centre between January 1989 and September 1992	Follow-up	Median 39 months Range 4–77 months	Brain metastases are a common cause of initial treatment failure after resection of NSCLC
		Recurrence	60 patients (47%) 11 patients (9%) with brain metastases	Many of these patients are asymptomatic and would present late without intensive follow-up
		Presence of neurological symptoms	7 of 11 (64%) were neurologically asymptomatic	The authors conclude that intensive follow-up with CT facilitates early detection and effective treatment of brain metastases in patients with completely resected lung cancer
		Median and 5-year survival of patients with brain metastasis	For all 11 patients: Median 10 months and 5-year, 24% In the 7 asymptomatic patients: Median 25 months and 5 year, 38%	
Choi <i>et al.</i> , 2011, Ann Thorac Surg, Korea [5] Single centre prospective cohort study (level IIa)	From January 2005 to June 2008, a total of 358 consecutive patients were enrolled in the study and underwent complete resections for NSCLC	Disease recurrence	111/358 (31%)	PET-CT detected more recurrences than conventional CT alone. 19 were missed by conventional CT of which 7 were extrathoracic, which would not have been found by chest CT
		How recurrence was detected	25 clinical suspicion 35 low-dose chest CT 51 simultaneous integrated PET-CT and low-dose chest CT 19 of 51 (37.3%) were detected only with PET-CT	However, there are hypometabolic lesions that were not detected with PET-CT but which were detected with chest CT
			26 of 51 (51.0%) detected with both PET-CT and chest CT 6 of 51 (11.8%) confirmed only by chest CT, with PET-CT not detecting the recurrence	Patients with recurrences detected by PET-CT and conventional CT had a longer survival than did those whose recurrences were detected by clinical suspicion or chest CT alone
		Duration of survival according to the method of detecting recurrence	Detection by clinical suspicion (2.1 ± 0.3 years) vs detection by imaging (3.6 ± 0.2 years) (<i>p</i> = 0.002) Detection with simultaneous PET-CT and chest CT (3.8 ± 0.2 years) vs detection with clinical suspicion or low-dose CT (2.9 ± 0.3 years) (<i>p</i> = 0.012) Detection with simultaneous PET-CT and chest CT (3.8 ± 0.2 years) vs detection with low-dose CT (3.3 ± 0.3 years) (<i>p</i> = 0.179)	However, when comparing chest CT alone with PET-CT plus chest CT in terms of survival, there was no statistically significant difference between the two methods (<i>p</i> = 0.179). This may have been related to the small sample size in this comparison

Continued

Table 1: (Continued)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Younes <i>et al.</i> , 1999, Chest, Brazil [6]	130 patients who underwent both operative and pathological complete resection of NSCLC between 1983 and 1993	Follow-up period	At least 2 years after operation	Early detection of recurrent disease does not translate into better control or longer survival for the patients
Single centre retrospective study (level IIb)	67 patients received strict follow-up with a routine CT scan every 6 months (strict CT group)	Recurrent cancer diagnosed using CT in: - strict group - symptom group	4/67 (5.97%) 3/63 (4.76%)	The rate of detection by routine CT scans in the follow-up routine setting at this service was not cost-effective for their patients
	63 patients were seen at hospital on a symptom oriented basis (symptom group)	Cost of CT (US\$): - strict group - symptom group	737.31 ± 200.63 117.46 ± 122.52 $p < 0.001$	
		Median survival after recurrence - strict group - symptom group	7.9 months 6.6 months $p = 0.219$	

CT: computed tomography; CXR: chest X-ray; LRLC: local recurrence of lung cancer; NSCLC: non-small cell lung cancer; PET-CT: positron emission tomography-computed tomography; SPLC: second primary lung cancer; US: United States.

(PET)-CT. From the search, five papers were identified that provided evidence addressing the specific question. These are presented in Table 1. Three papers provided supporting evidence, but did not directly assess survival outcomes and these are presented in Table 2.

RESULTS

Westeel *et al.* [2] studied the feasibility of an intensive surveillance programme, which included six monthly CTs and their influence on patient survival. They found that the 35 asymptomatic recurrences found on scheduled visits had significantly better survival rates (3-year survival, 31%) than the 50 symptomatic recurrences (3-year survival, 10%). However, the asymptomatic group accounted for only 26% of the recurrences detected. Within this group, an equal number were picked up by bronchoscopy as with chest CT, and a higher number by physical examination or CXR. The majority of recurrences that could be treated with curative intent, however, were diagnosed by chest CT scan or bronchoscopy, rather than physical examination and chest radiography. They concluded that this more intensive policy of follow-up improved the survival outcome.

Lamont *et al.* [3] showed that follow-up of patients with surgically resected NSCLC, including annual CT, detects second primary lung cancer (SPLC) at an early stage (IA) that is potentially resectable. Fifteen percent of patients, all of whom were asymptomatic, were diagnosed with SPLC. Of these, 84% were detected at stage IA. Fifty-eight percent were first picked up on CT scanning and 95% were potentially resectable. Although local recurrence of lung cancer (LRLC) can also be detected early, the

prognosis for these patients is poor, and surgical treatment options are less likely to be affected by early detection. The median disease-free survival for patients with SPLC was significantly higher than that for patients with LRLC ($P < 0.001$).

Yokoi *et al.* [4] studied the detection of brain metastases after lung resection on an intensive CT follow-up regime. Of 128 patients prospectively followed up for a median time of 39 months postoperatively, they found that 60 patients had recurrence, of which 11 had brain metastasis. For these 11 patients, the median survival was 10 months with a 5-year survival rate of 24%. Seven of these 11 patients were neurologically asymptomatic at detection. For these seven asymptomatic patients, the median survival was 25 months with a higher 5-year survival of 38%. They concluded that intensive follow-up with CT facilitated early detection and effective treatment of brain metastases in patients with completely resected lung cancer.

Choi *et al.* [5] showed that using chest CT or PET-CT for the detection of recurrence improved the duration of survival compared with detection by clinical suspicion (3.6 ± 0.2 vs 2.1 ± 0.3 years, $p = 0.002$). PET-CT was better than chest CT alone for detecting recurrences of NSCLC. Of 51 recurrences detected by simultaneous PET-CT and chest CT, 19 were missed by conventional CT. However, because of the possibility of PET-CT failing to detect small or hypometabolic recurrences, they recommended that it be performed along with low-dose chest CT during annual surveillance. Despite this, there was no statistically significant difference in the duration of survival between detection with simultaneous PET-CT and chest CT (3.8 ± 0.2 years) vs detection with low-dose CT (3.3 ± 0.3 years, $p = 0.179$).

Younes *et al.* [6] compared the influence of strict routine follow-up, including CT scanning, after lung cancer resection on

Table 2: Best evidence papers providing supporting evidence

Author, date and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Chiu <i>et al.</i> , 2003, J Thorac Cardiovasc Surg, Taiwan [7] Single centre prospective cohort study (level IIa)	Part 1: 30 patients who underwent surgical resection of NSCLC subjected to CXR, LDCT, and SDCT to verify the diagnostic accuracy of LDCT Part 2: 43 patients were prospectively enrolled and followed up regularly after complete resection of NSCLC	Recurrent case-detection rates compared with SDCT	SDCT: 7 cases detected (100%) LDCT: 6 of 7 cases detected (85.7%) CXR: 2 of 7 cases detected (28.6%)	Authors state that postoperative follow-up of NSCLC patients with LDCT every 3 months in the first 2 years may be of considerable value in early detection of recurrent disease
		Follow-up time (median months and range)	15.5 months (3.1–23.5)	However, the study did not directly comment on survival
		Recurrent case-detection rate using low-dose CT	78.6% (11 of 14 patients)	
		Recurrent site-detection rate using low-dose CT	57.9% (11 of 19 sites)	
Korst <i>et al.</i> , 2005, J Thorac Cardiovasc Surg, USA [8] Single centre retrospective cohort study (level IIb)	A retrospective analysis was performed in 140 patients who presented for follow-up in 2002 after complete resection for NSCLC	Recurrence	32 of 105 (30%) of abnormal scans were suspicious for recurrence Further workup showed recurrent or new primary lung cancer in 16 of 32 patients	Authors concluded that surveillance CT is frequently abnormal after complete resection for NSCLC; however, the majority of these abnormalities are not clinically suspicious
			Scans that were abnormal but not deemed suspicious (73 of 105 scans in 60 patients) revealed five additional recurrences	Only 30% of abnormal scans were deemed suspicious. This raises the obvious question as to the significance of the findings on the remaining 73 unsuspecting scans read as abnormal by the radiologists
				Although these patients have been followed into 2004, a clear weakness of this study is its cross-sectional nature, with lack of longer-term follow-up
Korst <i>et al.</i> , 2006, Ann Thorac Surg, USA [9] Single centre retrospective cohort study (level IIb)	92 patients with previously resected NSCLC who underwent 105 surveillance CT scans of the chest and upper abdomen in 2002 that were read as abnormal by the radiologist	Follow-up results in the 60 patients with 73 abnormal but non-suspicious scans	Recurrence in 7 Alive without recurrence in 49 Died without recurrence in 4	In this study the surgeon utilizing surveillance CT rarely missed recurrent NSCLC, but a significant number of negative investigations were generated by its use
			None of the 60 patients with non-suspicious abnormal scans had recurrent or new primary lung cancer in the area read as abnormal by the radiologist in 2002	Focus is on the surgeon's accuracy in interpreting CT abnormality over the radiologist detection of CT findings
		Accuracy of CT when used by thoracic surgeon	Sensitivity: 94.1% Specificity: 86.7% NPV: 99% PPV: 53%	Important to note that only 77 of the 92 patients had lobectomies. Others underwent other anatomic resections

CT: computed tomography; CXR: chest X-ray; LDCT: low-dose computed tomography; NPV: negative predictive value; NSCLC: non-small cell lung cancer; PET-CT: positron emission tomography-computed tomography; PPV: positive predictive value; SDCT: standard-dose computed tomography.

the outcome of patients with NSCLC, with symptom-oriented follow-up. There was no clinically significant difference in median survival after recurrence ($p = 0.219$).

Chiu *et al.* [7] followed up 43 patients with a complete resection of NSCLC, which included low-dose CT every 3 months in the first 2 years post-operatively until tumour recurrence. Low-dose CT detected 79% of cases with tumour recurrence and 58% of all tumour recurrence sites. This study did not comment on survival.

Korst *et al.* [8] showed that surveillance CT is frequently abnormal post-resection but the majority of the abnormalities are not suspicious for recurrence. A retrospective analysis showed 105 abnormal CT findings in 92 patients 6 months or 1 year or yearly post-resection. Of these, 32 scans of 32 patients were suspicious for recurrence and further work-up showed recurrence or new malignancy in 16 of 32 patients. Of the 73 abnormal but unsuspecting scans, five patients had recurrence. Nine patients had interval lung cancers detected independently of surveillance CT scanning.

Korst *et al.* [9] then followed up the previously identified 92 patients for an average of 3.2 years. Of the 60 patients with the 73 abnormal but unsuspecting scans, 7 developed recurrent lung cancer during the follow-up period. Of the 16 patients with abnormal CT scans that were deemed suspicious but were found to have no further malignancy, 3 developed a recurrence during this follow-up period. The surgeon utilizing surveillance CT rarely missed recurrent NSCLC but a low-positive predictive value generated a significant number of negative and sometimes invasive investigations.

CLINICAL BOTTOM LINE

From the limited number of papers that address the effect of CT follow-up on survival following lobectomy for NSCLC, three [2, 4, 5] showed that CT scanning may improve the survival of patients by detecting local and distant recurrences at an earlier stage when the patient is asymptomatic, therefore allowing earlier interventions to take place. However, this may also require CT head in addition to CT chest [4] and we must also take into account lead-time bias when interpreting these results. Furthermore, it is important for doctors to explain the radiation implications of CT scanning to their patients.

Two papers [3, 6] broadly showed that follow-up with CT does not improve survival outcomes regardless of the site of recurrence. Owing to the limited and contradictory evidence, a randomized controlled trial to assess the survival outcomes of patients followed up with a CT screening protocol vs a symptom-based follow-up would be required to definitively comment on whether a survival benefit is present. The remaining papers [7–9] supported the use of CT as a screening tool for recurrence, although they did not directly comment on survival. It should be noted that ongoing studies are looking at the role of CT scanning in detecting lung cancers in high-risk individuals (current or former smokers) who have not had lung cancer. Two prominent trials [10, 11] have shown that CT screening for lung cancer increases the detection of early stage lung cancer but no reduction in mortality has been observed.

Conflict of interest: none declared.

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eComment. Computed tomography surveillance of lung cancer survivors: The jury is still out

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Srikantharajah *et al.*'s review of five single centre studies concludes that the existing evidence for a survival benefit from routine computed tomography (CT) surveillance of non-small cell lung (NSCLC) cancer survivors following an anatomical resection is equivocal and conflicting. Hence they plead for a randomized control trial [1]. In fact this patient subgroup have been largely excluded from prospective analysis by most trial designs.

The multi-centre prospective phase III North American National Lung Screening Trial (NLST) reported a lung cancer-specific 20% mortality risk reduction with (three annual) low-dose (LD) CT scans for lung cancer screening in 'at risk' individuals (aged 55–74 years with a minimum 30 pack year history of tobacco exposure), although two other contemporary trials failed to demonstrate a similar survival benefit [2–4].

More recently, the American Association for Thoracic Surgery (AATS) published guidelines recommending annual LDCT be performed each year from such individuals age 55–79 years and not just three screening scans in the lifetime of the patient [5]. This is based in part on the peak age of incidence of lung cancer in the USA and average life expectancy, at 70 years and 78.6 years respectively, and the age-related linear increase in NSCLC incidence. Additionally, the AATS has issued a recommendation for annual LDCT screening to be offered to all surgically treated NSCLC survivors who have completed 4 years of radiologic surveillance without evidence of recurrence. Such patients should be initially followed-up with a high