doi:10.1510/icvts.2010.233189

INTERACTIVE CARDIOVASCULAR AND THORACIC SURGERY

Interactive CardioVascular and Thoracic Surgery 10 (2010) 1015–1021

www.icvts.org

Best evidence topic - Thoracic oncologic

In elderly patients with lung cancer is resection justified in terms of morbidity, mortality and residual quality of life?

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Received 19 January 2010; received in revised form 28 February 2010; accepted 8 March 2010

Summary

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was: In [patients over 70 years of age with lung cancer] is [lung resection] when compared with [non-surgical treatment] justified in terms of [postoperative morbidity, mortality and quality of life]? Altogether more than 297 papers were found using the reported search, of which 12 represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. We conclude that patients over 70 years of age undergoing anatomical lung resection respond as well as younger patients in terms of morbidity, mortality and residual quality of life (QoL). Collective analysis of the papers reveals no significant difference in five-year survival rates following surgery for early stage disease (stage I non-small cell lung cancer: $<$70 years; 69–77%, $>$70 years; 59–78%), although, elderly patients currently receive far higher rates of palliative care (30–47% in patients 65–70 years vs. 8% in patients under 65 years). Additionally, 30-day mortality rates (5.7% $<$70 years vs. 1.3–3.3% $>$70 years), length of hospital stay [1.3 days vs. 1 day (video-assisted mini-thoracotomy) and 4.6 vs. 4.9–5.2 days (thoracotomy) for $<$70 years vs. $>$70 years, respectively] and postoperative lung function tests (FEV_1 decrease; 13% $<$70 years vs. 18% $>$70 years $P=0.34$, functional vital capacity decrease; 9% $<$70 years vs. 14% $>$70 years $P=0.31$) are equivalent between the two age groups. Residual QoL following lobectomy (evaluated by patient self-assessment) showed decreased social ($P<0.001$) and role ($P<0.001$) functioning but less pain at discharge ($P<0.001$) in those over 70 years. Global QoL, however, was not influenced by age (global QoL; $<$70 years 22.2 ± 25.3 vs. $>$70 years 17.6 ± 22.9). Pneumonectomy showed statistically significant decreases in physical functioning [six months postoperatively (MPO) $P=0.045$], role functioning (3 MPO $P=0.035$), social functioning (6 MPO $P=0.006$, 12 MPO $P=0.001$) and general pain (6 MPO $P=0.037$), but showed no age related differences ($<$70 years; 81.9 ± 19.1, $>$70 years; 78.0 ± 22.8).

Keywords: Pulmonary surgical procedures; Pneumonectomy; Mortality; Survival; Quality of life

1. Introduction

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

2. Three-part question

In [patients over 70 years of age with lung cancer] is [lung resection] when compared with [non-surgical treatment] justified in terms of [postoperative morbidity, mortality and quality of life]?

3. Clinical scenario

An 84-year-old man is on your ward having being referred from clinic following symptoms leading to a diagnosis of stage I non-small cell lung cancer (NSCLC) although otherwise in good health with no other cardiopulmonary disease. You decide a lobectomy would be potentially curative but are aware of the risks associated with operating on elderly patients and wonder if these outweigh the long-term benefits in terms of prolonging the quality and duration of the patient's life. You carry out a literature search for the evidence.

4. Search strategy

[exp pneumonectomy OR exp pulmonary surgical procedures/OR lobectomy.mp OR lung resection.mp] AND [exp mortality/OR exp survival rate/OR exp quality of life/] AND [elderly.mp OR exp aged]

Medline 1950–December 2009 using OVID interface.

5. Search outcome

Two hundred and ninety-seven papers were found using the reported search. From these, 12 were identified that provided the best evidence to answer the question. These are presented in Table 1.

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Table 1
Best evidence papers

Author, date and country Study type (level of evidence)	Patient group	Outcomes	Key results		Comments
Burfeind et al., (2008), J Thorac Cardiovasc Surg, USA, [2] Prospective longitudinal cohort study (level 1b)	422 patients were prospectively assessed preoperatively and 3, 6, and 12 months after lobectomy. Outcomes were analysed with respect to age (group 1: <70 years and group 2: ≥70 years)		Group 1 ($n=256$)	Group 2 ($n=166$)	These results suggest quality of life (QoL) reduces transiently in both younger and older patients but returns to baseline after 12 months. Median survival rates appear different on the median survival curve separation but there was no overall survival discrepancy analysed by the log-rank test
		Physical functioning	81.9	78.0	
		Role functioning	79.0	80.4	
		Emotional functioning	78.5	82.4	
		Cognitive functioning	82.6	87.8	
		Social functioning	16.7	23.1	
		Global QoL	22.2	17.6	
		Pain in chest	33.0	32.7	
		Survival (median)	73.1	56.7	
Schulte et al., (2009), Lung Cancer, Germany, [3] Prospective cohort study (level 1b)	31 patients with non-small cell lung cancer (NSCLC) underwent surgical resection (lobectomy or bilobectomy) between January 1998 and December 2004 and were enrolled in our prospective study. The patients' QoL and clinical data were assessed prior to resection and for up to 24 months after surgery		Aged <70 years	Aged >70 years	While significant results where found for social and role functioning at 24 months postoperatively, global QoL was equivalent for the two groups with those >70 years experiencing less pain
		Physical functioning	82.6	75.7	
		Role functioning	72.0	83.9	
		Social functioning	68.2	80.6	
		Global QoL	56.4	56.9	
		Pain	23.1	21.1	
Balduyck et al., (2009), Eur J Cardiothorac Surg, Belgium, [4] Prospective cohort study (level 1b)	QoL was prospectively recorded in 60 consecutive septuagenarians of which 49 were undergoing lobectomies and 11 pneumonectomies. Questionnaires were administered before surgery and 1, 3, 6 and 12 months postoperatively		Months postoperatively (MPO)		Patients were not randomised and 23% of the cohort were lost to follow-up after 1 year, however, significant differences were seen in the reported areas postoperatively indicating a clear preference for lobectomy in septuagenarians
		Physical functioning	6 MPO $P=0.045$ Significant in favour of lobectomy		
		Role functioning	3 MPO $P=0.035$ Significant in favour of lobectomy		
		Social functioning	6 MPO $P=0.006$ 12 MPO $P=0.001$ Significant in favour of lobectomy		
		General pain	6 MPO $P=0.037$ Significant in favour of lobectomy		
		Postoperative coughing	1 MPO $P=0.049$ 3 MPO $P=0.012$ 12 MPO $P=0.022$ Significant in favour of pneumonectomy		
		5-year survival rate	Lobectomy 0.62 ± 0.12 NS Pneumonectomy 0.36 ± 0.16 NS		
Salati et al., (2009), Interact CardioVasc Thorac Surg, Italy, [5] Prospective cohort study (level 1b)	218 patients, 85 of whom were elderly (>70 years), had complete preoperative and postoperative (3 months) QoL measures. Additionally, in those over 70 years	Subjective preoperative and postoperative status as pointed out by the 10 different domains of the SF-36v2	The elderly group had significant lower physical component summary (PCS) ($P=0.03$) and physical functioning ($P=0.009$) but higher mental component summary (MCS) ($P=0.08$) and mental health ($P=0.02$)		Results indicate elderly patients experience a level of postoperative individual physical, emotional and social well-being comparable to the mean of a general population. The short

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Table 1 *(Continued)*

Author, date and country Study type (level of evidence)	Patient group	Outcomes	Key results				Comments
	they compared the preoperative with the postoperative measures of PCS and MCS scores between high-risk patients and low-risk counterparts		No significant differences were found between high- and low-risk elderly patients in any of the SF-36 v2 domains nor in the composite scores				follow-up period limits the interpretation of these, however, results do minimise drop-out rate frequently seen in these form of studies
Owonikoko et al., (2007), J Clin Oncol, USA, [6] Retrospective population study (level 2b)	316,682 patients from the national surveillance, epidemiology, and end results database were analysed for lung cancer outcomes during the period 1988–2003. A comparison was carried out between patients with lung cancer 80 years and older, 70–79 years, and younger than 70 years for demographics; stage distribution; 5-year relative survival; and survival based on histology, sex, race, stage, and treatment		Relative 5-year survival rate %				Poor survival rates seen with increasing age may be explained in part by a consistently lower for surgery and radiation therapy with increasing years. (80% of younger patients received active therapy compared with 70% of septuagenarians and 50% of very elderly within 4 months of diagnosis)
		NSCLC therapy	Age <70 years	Age 70–79 years	Age ≥80 years	*P*-value	
		Radiation 1998–2003	10.4	8.5	8.5	<0.0001; 0.001 (70–79 years vs. ≥80 years)	
		Surgery 1998–2003	63.2	58.4	61.4	<0.0001; 0.129 (70–79 years vs. ≥80 years)	
		Radiation and surgery 1998–2003	38.1	33.6	29.2	<0.0001	
		No therapy 1998–2003	5.3	3.9	3.3	<0.0001	
Sigel et al., (2009), Ann Surg Oncol, USA, [7] Retrospective population study (level 2a)	Survival rates (Resected 5-year) (Unresected 2-year)	Treatment type %	Age <60 years	Age 61–70 years	Age 71–80 years	Age ≥80 years	*P*-value	The results indicate that the relative effect of surgery on stage 1 lung cancer is similar across all ages and moreover if not treated, the majority of deaths are attributable to the lung cancer. This suggest elderly patients should be treated aggressively if medically fit for surgery
		Surgery	95	93	90	79	<0.001	
		No surgery	5	7	10	21	<0.001	
		Resected (Relative survival rates %) [confidence interval (CI)]						
		Males	69.2 (66.7–71.6)	66.0 (63.9–68.1)	62.8 (60.4–65.2)	63.5 (56.6–70.4)		
		Females	78.5 (76.4–80.6)	75.6 (73.5–77.6)	71.2 (69.0–73.5)	78.1 (72.0–84.2)		
		Unresected (Relative survival rates %) (CI)						
		Males	53.4 (45.2–61.7)	54.6 (49.4–59.8)	48.5 (44.4–52.6)	51.1 (45.1–57.3)		
		Females	55.4 (45.1–65.7)	58.3 (52.9–63.8)	55.9 (51.5–60.3)	59.6 (53.8–65.4)		
Peake et al., (2003), Age Ageing, USA, [8] Retrospective multicentre population study (level 2b)	1652 patients from 48 hospital trusts identified and followed through to 6 months postdiagnosis		Age <65 years	Age 65–74 years		Age 75+ years		Results indicate that the elderly are largely under-treated nationwide which may reflect the poor survival rates seen with increasing age
		Potentially operable	214 (43%)	324 (47%)		254 (54%)		
		Treatment type (% receiving) NSCLC-surgery						

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Table 1 *(Continued)*

Author, date and country Study type (level of evidence)	Patient group	Outcomes	Key results			Comments
		All patients	19% 95% CI 15–24	12% 95% CI 9–16	6% 95% CI 4–9	
		Ps = 0.1, no COPD, potentially operable	37% 95% CI 28–47	24% 95% CI 17–31	15% 95% CI 8–24	
		SCLC-chemotherapy				
		All patients	77% 95% CI 69–86	66% 95% CI 58–74	48% 95% CI 34–62	
		Ps = 0.1, no COPD, potentially operable	82% 95% CI 72–90	75% 95% CI 64–83	59% 95% CI 41–75	
		Radiotherapy				
		All patients	45% 95% CI 41–50	47% 95% CI 43–50	39% 95% CI 35–44	
		Ps = 0.1	47% 95% CI 42–50	49% 95% CI 45–54	45% 95% CI 39–51	
		Mortality (within 6 months of bronchoscopy)				
		All patients	42% 95% CI 38–47	47% 95% CI 43–51	58% 95% CI 53–63	
		Ps = 0.1, no COPD, potentially	23% 95% CI 17–30	31% 95% CI 25–37	41% 95% CI 32–49	
Cangemi et al., (1996), Tumori, Italy, [9] Prospective cohort study (level 2b)	Compare the incidence and the prognostic effect of the parameters characterizing 283 resected patients with NSCLC when stratified by age of which 12% were aged >70 years	Hazard risk (indicator of poor prognostic risk)	Epidermoid carcinoma = 5.77 Multiple tumour nodules = 7.33			When multivariate analysis was performed in all early stage patients, only lymph node involvement and multiple tumour nodules were independently related to survival (hazard risk, 1.82 and 3.76, respectively) and had a poor prognosis
		Previous cancer	In comparing the older and younger groups, a higher incidence of previous primary neoplastic disease ($P = 0.001$), epidermoid carcinoma ($P < 0.05$) and multiple tumour nodules ($P < 0.001$) was observed in the elderly			
		Survival rates	Postoperative death was similar (3% vs. 4.8%) in the younger and older groups, respectively, as was survival expectancy when stratified by stage			These results indicate advanced age is not a risk factor in pulmonary resection
			Univariate analysis showed that epidermoid carcinoma ($P = 0.001$) and pneumonectomy ($P = 0.00001$) had a worse outcome in the older early stage subset than in the younger group			
Ciriaco et al., (1998), Int Surg, Italy, [10]	76 patients aged >70 years (67 men, 9 women) entered and analysed for	Postoperative complications	19.7%			Mortality at 12 months was not related to stage of disease, histology or lobectomy vs. wedge
		30-day mortality	1.3%			

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Table 1 *(Continued)*

Author, date and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Prospective cohort study (level 1b)	postoperative complications and survival from surgery of NSCLC	54-month mortality rate	53%	resection but was higher in those patients who had postoperative cardiopulmonary complications. Results of preoperative spirometry, blood gas and cardiac status were predictive of mortality at 12 months ($P<0.05$)
Tovar, (2001), Eur J Cardiothorac Surg, USA, [11] Prospective cohort study (level 1b)	65 consecutive patients underwent major lung resections. 30 were 70 years of age or older (25 septuagenarians and 5 octogenarians; mean age, 75.7 years). 46 lobectomies, 8 bilobectomies, and 11 pneumonectomies were performed using a video-assisted muscle-sparing minithoracotomy. In the elderly group, 24 lobectomies, 3 bilobectomies, and 3 pneumonectomies were performed	Postoperative complications 30-day mortality Mean length of hospital stay	Younger 0 Elderly 0 Younger 2 patients Elderly 1 patient Younger 1.3 days Elderly 1 day	The results indicate that septuagenarians and octogenarians may undergo minimally invasive surgery and experience accelerated recovery in line with younger patients as a measure of functional ability being rapidly restored
Sullivan et al., (2005), Chest, USA, [12] Prospective cohort study (level 1b)	140 patients underwent lobectomy for NSCLC with a curative intent. Of those patients, 63 were able to be followed-up at 1 year postoperatively for PFTs and functional status assessment using KS comparing those <70 and >70 years of age	Functional vital capacity decrease Functional expiratory volume decrease Functional status [Karnofsky scores (KS) score dropping from 80 to 100% (normal activity without limitation) to 40–70% (unable to work, but able to care of self at home)]	Younger 14% Elderly 9% Younger 19% Elderly 13% Younger 24% Elderly 8%	Elderly patients ≥ 70 years of age undergoing lobectomy for NSCLC had similar pulmonary function test (PFT) results and functional status as younger patients <70 years of age 1 year after undergoing surgery. Curative resection should not be denied based on age alone
Cerfolio and Bryant, (2006), Ann Thorac Surg, USA, [13] Prospective cohort study (level 1b)	A prospective nested case-control study over a 5-year period ($n=6450$) of patients with NSCLC who underwent complete resection. Patients 70 years or older, 75 years or older, and 80 years or older were matched 1:1 to younger controls for stage, pulmonary function, performance status, and type of pulmonary resection	Controls / Stratified elderly group <70 years / 70–74 years / 75–79 years / 80+ years / *P*-value Hospital LOS (days): 4.6 / 4.9 / 5.2 / 5.0 / 0.54 % ICU admission: 3% / 1% / 2% / 1% / 0.61 Morbidity: 17% / 19% / 29% / 20% / 0.98 Major morbidity: 7.1% / 13% / 12% / 7% / 1.00 Operative mortality: 3.8% / 2.4% / 1.6% / 1.9% / 0.2 5-year survival: Elderly / Age <70 years	Elderly patients who received neoadjuvant therapy had three times the risk of developing major morbidity [odds ratio (OR) 2.8, 95% confidence interval (CI) 1.14–7.41]. There was a statistically significant better 5-year survival in elderly patients with stage I NSCLC (78% vs. 69%, $P=0.01$); however, survival was similar for all other stages

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Table 1 *(Continued)*

Author, date and country Study type (level of evidence)	Patient group	Outcomes		Key results	Comments
		Stage I	78%	69%	
		Stage II	47%	54%	
		Stage III 4-year mortality	23%	36%	

SCLC, small cell lung cancer; ICU, intensive care unit; NS, non-significant; Ps, performance status; COPD, chronic obstructive pulmonary disease; LOS, length of stay.

6. Results

The largest prospective longitudinal evaluation of quality of life (QoL) in elderly patients undergoing pulmonary resection was conducted by Burfeind et al. [2]. Patients of <70 years ($n=256$) or >70 years ($n=166$) experienced transient decreases in all QoL domains at three months which, bar physical conditioning (<70 years: 81.9 ± 19.1, >70 years: 78.0 ± 22.8) returned to baseline at 12 months. Additionally, mean survival was equivalent when matched for cancer stage [<70 years: 73.1 months vs. >70 years: 56.7 months, $P=$non-significant (NS)]. Schulte et al. [3] also found global QoL to be equivalent between those >70 years and <70 years although role functioning ($P<0.001$) and social functioning ($P<0.001$) were lower in those <70 years.

Balduyck et al. [4] prospectively studied QoL in 60 septuagenarians undergoing either lobectomy ($n=49$) or pneumonectomy ($n=11$). Significant differences in physical functioning [6 months postoperatively (MPO) (6 MPO, $P=0.045$), role functioning (3 MPO, $P=0.035$), social functioning (6 MPO, $P=0.006$, 12 MPO, $P=0.001$) and general pain (6 MPO, $P=0.037$)] were found in favour of lobectomy patients. Five-year survival rates were 0.62 ± 0.12 (analysed using the Kaplan–Meier estimator) in the lobectomy group and 0.36 ± 0.16 in the pneumonectomy group ($P=$NS).

Salati et al. [5] assessed lobectomy and pnemonectomy resections on residual QoL in patients <70 ($n=133$) and those over 70 ($n=85$), years. The physical component summary (PCS) (50.3 vs. 50, $P=0.7$) and mental component summary (MCS) (50.6 vs. 49, $P=0.2$) were equivalent. High-risk and low-risk elderly patients responded equally in residual QoL.

Owonikoko et al. [6] conducted a retrospective population study of 316,682 patients undergoing lung cancer therapy. Overall, five-year survival rate decreased with increasing age (<70, 70–79 or ≥80 years was 15.5%, 12.3% and 7.4%, respectively, $P<0.0001$) although local therapy (radiation or surgery) was offered to the elderly far less frequently (palliative care being 19%, 28% or 47%, respectively). In those offered surgery, five-year survival rates were comparable (63.2%, 58.4%, 61.4%, respectively).

Sigel et al. [7] retrospectively analysed 27,859 cases of confirmed, stage I NSCLC. Rates of surgical resections declined from 95% in patients <60 years to 79% in patients ≥80 years. Five-year relative survival rates were lower in males ≥80 years (63.5%) compared with those <60 years (69.2%), but similar in women or unresected patients, regardless of gender.

Peake et al. [8] conducted a retrospective study in 48 UK hospital trusts. Overall, 6% of all patients >75 years were offered surgery, rising to 15% in patients with early stage NSCLC and no chronic obstructive pulmonary disease (COPD) (19% and 33%, respectively, for those <65 years). In all patients, five-year mortality rates were 42% in <65 years and 58% >75 years for low-risk patients, this was 23% and 41%, respectively.

Cangemi et al. [9] showed that epidermoid carcinoma and multiple tumour nodules were poor prognostic factors and, in their cohort of 283 patients, were more common in the elderly [epidermoid carcinoma ($P<0.05$) and multiple tumour nodules ($P<0.001$)]. Additionally, pneumonectomy had a worse outcome ($P=0.00001$), and survival rates were similar between young and old.

Ciriaco et al. [10] looked prospectively at 76 patients aged >70 years, treated surgically for NSCLC. Postoperative complications arose in 15 cases (19.7%), 30-day operative mortality was 1.3% and 54-month survival rate was 53%. Twelve-month mortality was similar in all surgery types and stages of disease but correlated to severity of concomitant cardiopulmonary disease ($P<0.05$).

In 2001, Tovar [11] assessed video-assisted mini-thoracotomy for lung resection to determine whether elderly patients benefit from an accelerated recovery as those aged <70 years. Thirty-day mortality occurred in 5.7% (two patients; <70 years) and 3.3% (one patient; >70 years). Mean length of stay (LOS) was 1.3 days (<70 years) and one day in >70 years.

Sullivan et al. [12] addressed pulmonary function in young (62.6 ± 6.1 years) and elderly patients (74.5 ± 3.6 years) following lobectomy for early stage NSCLC. Postoperative complications occurred in 32% of young patients ($n=12$) and 48% of elderly patients ($n=12$). FEV_1 ($F_{1,59}=1.06$; $P=0.31$) and functional vital capacity (FVC) ($F_{1,59}=0.94$; $P=0.34$) were NS.

Cerfolio and Bryant [13] conducted a nested case control study of 726 patients (<70 years, $n=363$, >70 years, $n=363$) who underwent complete pulmonary resection for NSCLC. Length of hospital stay, operative mortality and morbidity were statistically equivalent, although neo-adjuvant therapy was a risk factor in the elderly [odds ratio

(OR) 2.8, 95% confidence interval (CI) 1.14–7.41]. Additionally, elderly patients had a better five-year survival rate with stage I NSCLC (78% vs. 69%, $P=0.01$), while all other stages were similar.

7. Clinical bottom line

In patients with early stage NSCLC, pulmonary resection provides the best form of treatment in terms of survival rate and residual QoL. Many surgeons, however, will not offer surgery to patients >70 years because of the additional risk associated with operating on this cohort, and limited long-term benefits they perceive this will offer. Here, several prospective and large population studies have shown unanimously, that patients >70 years of age respond as well as younger patients in all outcome measures pertaining to morbidity, mortality and QoL postoperatively, and should receive aggressive surgical management if considered fit for surgery, in accordance with the British Thoracic Society guidelines.

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