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Lung cancer • 7: Management of lung cancer in elderly patients

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Denying the elderly important advances in the treatment of lung cancer on prejudice alone is no longer justified. The fit elderly person with adequate organ function should be offered similar treatment to younger patients. Other elderly patients should ideally be included in randomised trials to provide an evidence base.

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The peak incidence of lung cancer in the UK is between 75 and 80 years of age, reported at 751 per 100 000 in men over 75 years,[1] with over half of 500 000 patients diagnosed annually worldwide being over the age of 70.[2 3] It is therefore an enormous health burden on our ageing populations and will, in the medium term, pose a significant challenge to health services worldwide as the age distribution of the population skews towards the octogenarian. Sufferers of lung cancer can expect a high symptom burden, particularly from fatigue and breathlessness,[4 5] together with the highest rates of co-morbidities found among all tumours[6 7]—including cardiovascular disease (23%), chronic obstructive airways disease (COPD) (22%), and other malignancies (15%).[7] Indeed, the prevalence of co-morbidity among lung cancer sufferers is significantly higher in patients aged >70 years, together with a proportionate increase in the number of co-morbidities per patient.[7 8] In patients with stage IV non-small cell lung cancer (NSCLC), increasing co-morbidity is associated with a reduction in the percentage of patients receiving chemotherapy.[9] The most frequent co-morbid combinations were COPD with cardiovascular disease (17%), COPD with other malignancy (13%), and COPD with hypertension (11%).[7] In a recent review of 966 patients with lung cancer and median age 70 years, COPD and combined cardiac and cerebrovascular disease were diagnosed in 7.6% and 26.3%, respectively, each correlating adversely with survival ($p=0.0275$ and $p=0.0466$, respectively, compared with performance status and stage, both $p<0.0001$).[10 11] Interestingly, over 70% of these patients were of Eastern Cooperative Oncology Group (ECOG) performance status 0–1.

Several factors are important when considering the treatment options, including an accurate diagnosis and tumour staging, knowledge of related symptoms, co-morbidities, and performance status. It is clear that, despite the rising incidence of lung cancer with age, discrimination on the basis of age is a frequent occurrence. The elderly obtain lower histological confirmation rates,[1 12] less accurate staging,[7] and lower rates of definitive treatments, yet patients aged >65 years account for over 50% of lung cancer sufferers with an excellent or good performance status.[1 13] The use of surgery and chemotherapy in patients with NSCLC was 18% and 21%, respectively, of patients aged <65 years compared with 2.1% and 0% for patients aged >75 years. Similarly, in small cell lung cancer (SCLC) 79% of patients aged <65 years and 41% of those aged >75 years received chemotherapy, differences in treatment persisting for both groups even after allowing for performance status and review by a chest physician.[1] In a population based study of 3864 patients with lung cancer, increasing age and the presence of co-morbidity adversely affected the use of surgery for localised NSCLC ($p=0.0001$ and $p=0.002$, respectively) while increasing age alone was adversely associated with chemotherapy for SCLC ($p=0.0001$).[7] Performance status and clinical stage of disease did not differ greatly in a review of 5404 lung cancer patients according to age >50 or <50 years, although highly significant differences exist in treatment allocation in favour of younger patients across all modalities (chemotherapy, surgery, surgery + chemotherapy or radiotherapy, all $p<0.001$).[14] Older patients received symptomatic treatment only ($p<0.001$) while younger patients derived a significant survival advantage ($p=0.011$).[14]

It is therefore clear that a significant proportion of elderly patients are not referred or do not receive treatment comparable to younger patients, and may as a consequence obtain inferior survival and palliation. However, this does not necessarily mean that the elderly will obtain equivalent benefit from modern diagnostic and therapeutic modalities as elderly patients possess, despite correction for performance status, age related decrements in cardiac, renal, and hepatic physiology.[15] It is therefore important to determine whether or not the elderly (>65 years) would indeed benefit from the same standards of management as their younger counterparts.

DIAGNOSTIC TECHNIQUES

Histological confirmation rates in the elderly are significantly worse than in younger patients and may impact on the subsequent correct management of lung cancer patients. This is presumed to be related to perceived fitness of the patient to withstand bronchoscopy, CT guided biopsy, other invasive techniques and treatment.

Fibreoptic bronchoscopy

In its summary of recommendations on diagnostic flexible bronchoscopy the British Thoracic Society does not consider age to be a barrier to the

application of this technique.[16] It is evident from a prospective study of patients undergoing flexible bronchoscopy that tolerance to the procedure was independent of age,[17] and two retrospective studies in the 1980s also support this view specifically in the elderly,[18 19] even in the presence of marked ventilatory impairment. In addition, a recent review of flexible bronchoscopy in the elderly found no evidence to suggest that age affects performance or outcome from this procedure.[20] However, COPD is a common co-morbidity in lung cancer sufferers and in the presence of severe disease may increase the complication rate.[21] A lower threshold to spirometry and/or arterial gas analysis may be justified. Similarly, care with the use of lignocaine and midazolam has been recommended in the elderly, given the possibility of occult hepatic or cardiac impairment.[16] Complication rates are otherwise extremely low with a morbidity of <1% and 0% mortality.[22]

CT guided thoracic biopsy

Little information is available specifically in the elderly about the tolerability of image guided biopsy of pulmonary lesions. In a prospective study of transthoracic fine needle biopsy in over 500 patients the complication rate was not adversely affected, despite the inclusion of patients up to 94 years of age, with over 60% showing varying degrees of emphysema radiologically. Procedural tolerance was also good, allowing discharge after 30 minutes without appreciable morbidity and mortality.[23] A cutting needle biopsy offers little additional information where the clinical picture suggests lung cancer although, in solitary pulmonary nodules or less clearcut cases, lymphoma and benign lesions can be diagnosed with greater confidence with cutting needle biopsy without recourse to surgical intervention[24] and is preferable regardless of age. Similarly, in a series of patients with mediastinal tumours aged up to 82 years, percutaneous cutting needle biopsy produced a tissue specific diagnosis in over 90% of biopsy specimens with minimal morbidity.[25]

Endoscopic ultrasound guided fine needle aspiration (EU-FNA) promises to improve the staging of lung cancer in all patients and may, as a consequence of tolerance, be of particular use in the elderly. A prospective study evaluated EU-FNA on 86 patients with mediastinal lymphadenopathy and was able to distinguish benign from malignant nodes with a negative and positive predictive value of 94% and 100%, respectively. Of particular importance was the change to non-surgical management in 80% of patients.[26] Specific data on the tolerance of transthoracic biopsy in the elderly come from a retrospective analysis of patients with suspected malignancy aged 70–90 years, indicating that transthoracic needle biopsy has equivalent safety and procedural tolerance to that reported for younger patients and can be performed as a day case in the majority of cases.[27]

Staging

All patients with suspected lung cancer should undergo a thoracic staging CT scan as accurate staging ensures correct treatment decisions and appropriate counselling. As mentioned above, accurate staging is often omitted in the elderly,[7] presumably a reflection of the low referral rates for non-surgical treatments. However, while encouraging referral of elderly patients for treatment, particularly surgical or radical radiotherapy, it is important that unnecessary morbidity is avoided. F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is capable of enhancing conventional staging (downstaging 10% of patients and upstaging 33%), affecting the intent of treatment in a significant proportion of cases—that is, curative to palliative in 22% of patients and palliative to curative in 4% of patients. There is also a significant enhanced prognostic stratification compared with conventional staging—for example, conventional staging is significantly inferior to PET staging ($p=0.013$ *v* $p<0.0001$) with respect to survival.[28] In addition, high rates of unsuspected distant metastases were found in patients with stage I–III NSCLC who would otherwise have been candidates for surgery, radical chemo/radiotherapy, or radical radiotherapy. PET scanning increased the detection of metastatic disease in CT evaluated patients with stage I disease by 7.5%, increasing to 24% in CT evaluated patients with stage III disease.[29] In addition, a prospective study of PET scanning noted a change in the CT evaluated stage of resectable NSCLC patients in 60.7% of cases, concluding that improved detection of local and distant metastases was possible.[30] Given that most lung cancer sufferers are aged >65 years, this has important implications for the effective management of this disease in the elderly, causing unnecessary morbidity, treatment delay, and incorrect choice of modality.[31] Unfortunately, F-18 FDG-PET is not widely available. Alternative conventional strategies aimed at detecting occult metastases in otherwise resectable disease do not appear able to reduce unnecessary surgical intervention in early stage disease.[32]

TREATMENT STRATEGIES FOR NON-SMALL CELL LUNG CANCER (NSCLC)

Surgery

The British Thoracic Society, in its guidelines on the selection of patients for lung cancer surgery, recommends that all patients should have equal access to lung cancer services regardless of age.[33] Whether age is a risk factor for lung cancer surgery remains controversial. In a review of over 1000 patients undergoing thoracotomy for lung cancer between 1977 and 1996, the mode of presentation was similar across all age groups (<60 years, 60–69 years, >70 years), although younger patients presented with more advanced disease. The rates of exploratory thoracotomy and pneumonectomy were, however, higher in those aged <70 years, together with higher rates of lobectomy and "lesser resection" in those aged >70 years. The mortality for lesser resections was of borderline significance with increasing age, although not for pneumonectomy.[34] A retrospective review of elderly patients showed a non-significant difference in operative mortality for patients aged <69 years, 70–79 years, and >80 years of 1.6%, 4.2% and 2.8%, respectively. However, pneumonectomy was significantly associated with mortality in the elderly. Abnormal pulmonary function or positive cardiac history did not correlate with increased overall or specific risk.[35] Other retrospective reviews of lung cancer surgery in the elderly (age >70 years) highlight a postoperative mortality rate of 3.1–21% and morbidity of 34–42%. Higher mortality rates are evident for more extensive resections (pneumonectomy/bilobectomy), for reviews with a higher proportion of patients with stage II/III disease, and in patients with co-morbidity (table 1). Two additional large retrospective reviews noted increasing morbidity and mortality in patients aged >65 years, together with shorter overall survival compared with younger patients.[36–38] Multivariate analyses have generally concluded, however, that age is not important for long term survival.[36 39–41] In addition to conventional factors such as stage, long term survival correlates with the nature (lobectomy *v* pneumonectomy) and mode (thoracoscopic *v* thoracotomy) of resection.[42] Licker *et al*[43] showed that age >70 years was a predictor of complications on univariate analysis although on multivariate analysis only prolonged surgery and the extent of surgery was significant. In support of this is the age related intolerance of pneumonectomy, with several studies confirming older age to be a significant predictor of operative mortality, survival, and morbidity.[44 45] Of particular interest is the high mortality rate in the elderly following a right pneumonectomy in the presence of ischaemic heart disease, which should be regarded as a relative contraindication to pneumonectomy.[46] Also of interest is the lack of impact on mortality of other co-morbid conditions such as diabetes, hypertension, peripheral vascular

Table 1 Operative mortality of patients with stage I–III non-small cell lung cancer

Reference	Overall mortality (%)	Mortality (%)						
		Pneumonectomy		Bilobectomy	Lobectomy	Lesser resection††	Morbidity	
		<60	>70				<70	>70
34	–	6.5	13.7	–	–	–	–	–
35	–	–	12.5	–	–	–	25	34
39	7.4	–	8	11.8	7.6	0	–	–
40	3.1	–	9.1**	–	–	–	–	–
46†	21	–	R=37, L=6	–	–	–	–	–
73*	3.7	–	–	–	–	–	42	
148	7.2	–	10	–	6.6	–	–	–
149†	–	16.2 ‡	27.5 ‡	–	–	–	26.3 ‡	34.1 ‡
150	Age 50–69: 4.4 Age >70: 6.9	Age 50–69: 6.2 Age >70: 9.1		–	Age 50–69: 1.9 Age >70: 4.7	–	–	–

*Patients >80 years; †predominantly stage II and III patients; ‡age <65 and >65 years, respectively; †† includes wedge resection, segmentectomy; results not significant unless**.
R=right; L=left.

disease, and cerebrovascular disease in this age group.[46] Encouragingly, there has been an increase in the mean age of patients undergoing surgery over the last two decades in combination with an increase in 5 year survival and lower operative mortality.[47] Changes in mortality were also reported in a series of 385 elderly patients, with mortality from pneumonectomy falling from 11.1% in 1971–82 to 2.6% in 1983–94; the latter was not dissimilar to the reported control group.[35] Evidence to date would support that the elderly do as well as younger patients (table 2) and, indeed, with modern surgical practice elderly patients may derive further benefit.

The increasing age of patients undergoing surgery together with acceptable morbidity and mortality is presumably a reflection of case selection involving detailed pulmonary and cardiac assessment, improved anaesthetic care, pain relief, postoperative facilities, and modern surgical techniques. The BTS guidelines provide detailed evidence based recommendations on selecting patients for lung cancer surgery.[33] However, it concluded that the use of video assisted thoracoscopic surgery (VATS) is too early in its development to draw firm conclusions and less than 2% of UK thoracic surgeons use this technique.[48] Nonetheless, the results of thoracoscopic techniques and the employment of limited resection may have a significant role to play in increasing the number of elderly patients undergoing potentially curative resection, as this technique may be able to accommodate the accrued excess of co-morbid conditions in this patient group. Particular advantages of this technique include reduced surgical trauma, minimal postoperative pain, shorter hospital stays, and a rapid resumption of normal activities[49] with a consequent reduction in costs. Mediastinal staging and diagnosis can be adequately performed using VATS,[50] and decreases the rate of exploratory thoracotomy.[51]

VATS has been performed easily and safely in the resection of pulmonary nodules up to 5 cm in size,[52–54] although the complication rate may increase with lesions >2 cm. Retrospective evaluation of VATS lobectomy for stage I–IIIA NSCLC can achieve 3 and 4 year survival rates of 90% and 70%, respectively, together with low postoperative complications (10–12.8%), shorter or equivalent hospital stays to thoracotomy, and a 6–10% conversion rate to thoracotomy.[55–57] In a series of 171 major pulmonary thoracoscopic resections (165 lobectomies, six pneumonectomies) no perioperative mortality was recorded and 90% had an uneventful postoperative course, although 15 elderly patients had prolonged air leaks.[58] Prospective studies comparing VATS lobectomy with thoracotomy have also concluded that VATS lobectomy is comparable to thoracotomy although intraoperative blood loss, postoperative pain, in-hospital stay, and postoperative pulmonary function are all significantly better with VATS lobectomy[59–61]; prospective data on 5 year survival are, however, lacking. VATS lobectomy performed on an elderly population is also associated with superior cardiac dynamics which, unlike conventional thoracotomy, extend into the postoperative period.[62] Similarly, a limited thoracotomy or video assisted minithoracotomy may limit the operation time and improve postoperative pulmonary function and morbidity compared with conventional thoracotomy.[63 64] In elderly patients with impaired respiratory reserve, limited resection should be considered.[65]

A retrospective analysis of patients undergoing segmentectomy (a difficult operation) compared with lobectomy indicated no significant differences in operative mortality or complications although spirometric parameters improved in the segmentectomy group; this procedure is therefore potentially useful in patients with borderline respiratory function. Five year survival was not affected at 96.8%.[66] Wedge resection or segmentectomy for tumours <2 cm was evaluated prospectively and may prove an acceptable alternative to lobectomy.[67] However, concern exists regarding the local recurrence rate after limited resection and the impact that this may have on survival.[68] High rates of co-morbidity in the elderly, together with pressure from performance league tables,

Table 2 Long term survival following surgery in elderly patients with non-small cell lung cancer (NSCLC)

Reference	No of patients	Age	Stage	1 year survival (%)	5 year survival (%)
39	500	>70	OS	–	33.7
40	258	>70	I	–	73.6
			II	–	23.0
			II	–	8.9
46	70	>70	I	60	40
			II	63	33
			III	33	14
73	54	>80	OS	86	43
			I	97	57
148	223	>70	I	–	45.7
			II	–	36.3
			III	–	13.8
150	136	50–69	I/II/III	77/61/41*	66/53/25**
	43	>70	I/II/III	83/100/53*	75/83/40**

*2 year survival; **4 year survival; OS=overall survival. No significant differences were noted between the groups.

may deter the surgeon from undertaking operative intervention; cardiovascular disease remains an independent predictor of mortality in pneumonectomy[45] and perceived tolerance of poor respiratory reserve excludes many patients from consideration. However, in patients with mild to moderate COPD, pulmonary lobectomy did not impact upon operative or actuarial survival or postoperative complications. There was also a significant preservation of lung function at 6 months in patients with forced expiratory volume in 1 second (FEV_1) 40–80% of predicted.[69] Similarly, in a small series of elderly patients with severe COPD, surgical resection (either conventional or thoracoscopic) proved acceptable with no deterioration in pulmonary function. This was predicted to improve if the tumour site and scintigraphic perfusion defect corresponded.[70 71] In addition, patients with FEV_1 <60% and FEV_1/FVC ratio <60% were unlikely to lose additional ventilatory function following lobectomy.[72] The encouraging reports in octogenarians with lung cancer using limited thoracoscopic resection and including patients with poor cardiorespiratory reserve should stimulate us to ensure that age is not a valid exclusion criteria for selecting patients for surgery,[73–76] and to assess critically and transparently co-morbid conditions at multidisciplinary meetings.

It is clear from a Joint Working Party report of the British Thoracic Society and The Society of Cardiothoracic Surgeons of Great Britain and Ireland[77] that the provision of thoracic surgery in the UK is in crisis. Fewer than 10% of lung cancer cases are resected (less than half the rates of the US and Europe), and elderly patients in the UK are much less likely to receive operative intervention. Whether this is the result of inappropriate subconscious influences is open to question.[78] With only 2% of UK thoracic surgeons practising thoracoscopic procedures, rates in the elderly are unlikely to improve rapidly. The pressures on our surgical colleagues are immense, with inadequate consultant numbers and ever increasing pressures on time as a consequence of the recommendations of the Calman-Hine report and the reduction in junior doctors' hours. The report concludes that 50 extra thoracic surgeons are required to meet average European standards, together with a commensurate increase in beds and infrastructure and a radical review of training. This should encompass thoracoscopic techniques if the increasing numbers of elderly patients with lung cancer are to have equal access to services. Randomised trials of thoracoscopic resection in elderly patients together with limited resection (depending upon respiratory function) are now warranted to delineate the place of these techniques in lung cancer management. The role of additional local treatments after limited resection also requires clarification.

Radical radiotherapy and NSCLC

In patients not sufficiently fit for surgery with stage I/II disease, radical radiotherapy is considered to be the treatment of choice. A recent systematic review highlighted the lack of high quality randomised trials involving radical radiotherapy and found only two randomised trials, only one of which met the selection criteria for analysis. It concluded that, in the absence of a phase III trial comparing immediate radical radiotherapy with palliative radiotherapy as symptoms develop, radical radiotherapy offers better survival than might be expected had treatment been deferred.[79] However, the optimal radiation dose and treatment technique remain undetermined. In elderly patients a retrospective study analysed 97 patients who had received high dose radiotherapy and who were either inoperable or unresectable. Subdivision into three groups based on age allowed comparison of outcomes (group I <75 years, group II 75–79 years, and group III >80 years) with 2 and 5 year survivals in groups I, II, and III of approximately 36% and 12%, 32% and 13%, and 28% and 4%, respectively, and no statistically significant difference between the three groups. Across these groups there was also no significant survival difference for stage I–II disease, although survival of octogenarians with stage III disease was inferior. Deterioration in performance status with treatment was seen in only a minority (group I, 5%; groups II/III, 8%).[80]

A prospective analysis of quality of life data obtained before and after radical radiotherapy noted good symptomatic control of haemoptysis, pain, and anorexia and challenged the widely held belief of cough relief, which was poorly alleviated, as were dyspnoea and fatigue. Physical and role functioning responded poorly, as did global quality of life. Social and cognitive functioning, however, achieved over a 50% response.[81] A retrospective review of 347 patients with stage I NSCLC concluded that a nihilistic approach to treatment of elderly patients unfit for or refusing surgery is no longer justified, given that 5 year survival of patients aged >70 years receiving radical radiotherapy is comparable to or better than younger age groups.[82] It is evident that more information is required regarding the optimal place of radical radiotherapy, although it does appear that radical radiotherapy is safe, efficacious and impacts minimally on performance status in elderly patients with limited disease. Symptom control is not, however, universal and quality of life is adversely affected across some domains. It remains to be seen whether elderly patients will choose survival over quality of life, particularly as overall and cancer specific survival rates differ with many patients dying prematurely but free from cancer (2 year survival: 22–72% *v* 54–93%; 3 year survival: 17–55% *v* 22–56%; and 5 year survival: 0–42% *v* 13–39%).[79] Evidence to date, although not specific to radical radiotherapy, would suggest that the elderly may favour quality of life over survival in contrast to their younger counterparts, although they are equally accepting of treatment.[83 84]

Chemoradiotherapy for stage III NSCLC

Combined modality treatment for locally advanced unresectable disease has been advocated following a meta-analysis comparing radiotherapy alone with chemotherapy plus radiotherapy which showed superior survival at 1 and 2 years for patients receiving chemotherapy, particularly platinum based.[85 86] Subsequently, a phase III study has confirmed the superiority of sequential conformal radiotherapy with platinum based combination chemotherapy without increasing the toxicity of treatment.[87] Combination platinum based concurrent chemoradiotherapy is superior to sequential chemoradiotherapy[88–90] and can be regarded as the standard of treatment, although alternative strategies may be required for elderly patients given the excess toxicity with concurrent regimens.[91] Interestingly, age ⩾60 years was a highly significant favourable prognostic factor on multivariate analysis in a randomised trial comparing concurrent hyperfractionated (HFX) radiotherapy plus platinum-etoposide chemotherapy versus HFX radiotherapy alone.[92] Dedicated studies are required using conformal fields and hyperfractionated regimens to clarify the tolerability of these regimens in the elderly.

Chemotherapy and NSCLC

A recent meta-analysis of 52 randomised trials found no evidence to suggest that groups specified by age did not derive equal benefit from chemotherapy,[86] and a subanalysis of the work of Cullen *et al*[93] showed no significant survival difference for patients aged >65 years. Despite this and other data, some health professionals—irrespective of their thoughts on age—still have to be convinced that chemotherapy in advanced NSCLC is of benefit. An analysis of the Survival, Epidemiology and End-Points Results (SEER) tumour registry concluded that chemotherapy in elderly patients with stage IV disease and in those with co-morbidity had similar efficacy to that seen in randomised trials.[94] Indeed, the results of randomised

Table 3 Randomised trials comparing chemotherapy in advanced NSCLC with best supportive care (1988–2001)

Reference	No of patients	Regime	Median (range) age	Quality of life	Survival	p value (survival)
93	351	MIP	62 (41–75)	+	+	0.03
95	207	D	59 (36–75)	+	+	0.026
96	191	VNR	74 (70–85)	+	+	0.02
151	251	PVd		NR	+	0.01
		CAP				0.05
152	63	PV		–	–	0.09
153	48	CbEt		+	+	NR
154	287	IEP	58 (36–73)	+	+	0.0003
		MVP	58 (28–76)			
155	157	T	65 (37–78)	+	+	0.037
156*	104	D	61 (37–76)	+	+	0.047
157	300	G	65 (37–82)	+	–	0.84

P = cisplatin; Vd = vindesine; C = cyclophosphamide; A = doxorubicin; V = vinblastine; I = ifosfamide; E = epirubicin; Et = etoposide; M = mitomycin; T = paclitaxel; D = docetaxel; VNR = vinorelbine; G = gemcitabine; Cb = carboplatin; + = statistically significant; – = not significant.
*Second line treatment.

controlled trials of chemotherapy in advanced NSCLC plus best supportive care versus best supportive care alone (a concept embracing palliative radiotherapy, psychosocial support, analgesics and other tumour related medication, and nutritional support) consistently favour the use of chemotherapy with significant improvements in quality of life and survival (table 3). The majority of patients entered into these trials were, however, of good performance status and perhaps less than 45% of patients were aged >65 years.[93 95] It is therefore difficult, given the altered physiology of the elderly,[3] to extrapolate these results, even if one allows for performance status.

Despite this, however, in the elderly vinorelbine has been found to have superior efficacy over best supportive care alone with significant survival gains and improved quality of life scores encompassing global health status, role, cognitive, social and physical functioning, fatigue and pain, and clearly establishes the potential of chemotherapy in this age group.[96] In addition, single agent gemcitabine has confirmed activity and a favourable toxicity profile in elderly patients with advanced NSCLC, with older patients tolerating the same dose intensity as younger ones, albeit with a higher incidence of grade 3–4 anaemia (table 4).[97–99] A combined analysis of four phase II trials showed that single agent gemcitabine was as efficacious in older patients as in younger ones, despite a significant increase in patients aged >65 years with stage IV disease.[100] Frasci *et al*[101] showed that the combination of gemcitabine with vinorelbine in the elderly was superior to vinorelbine alone with a projected 1 year survival rate of 30%, a clear delay in symptom progression, and preservation of quality of life. However, data from the MILES study which compared gemcitabine plus vinorelbine with vinorelbine alone or gemcitabine alone was not able to demonstrate superiority for any regimen.[102 103]

Platinum based combination chemotherapy has also been explored in the elderly (table 4). Cisplatin, using varying schedules, in combination with gemcitabine given every 3 or 4 weeks produced response rates of 15–53% and a median survival of 7.7–11 months[104–106] with no significant difference in

Table 4 Single and combination chemotherapy in the elderly: data from phase II studies

Reference	No of patients	Age	Regime	PS	ORR (%)	MS (months)	1 year survival
96†	78	70–86	BSC	ECOG 0–2	–	21 w	14
	76		VNR		19.7	28 w	32
98	32	70–81	G	KP >70	27	–	–
99	46	>70	G	ECOG 0–2	22.2	6.75	–
100	250	<65	G	NR	16	8	27
	105	>65	G		24	9	36
101†	120	>70	V	ECOG 0–2	15	18 w	13
			GV		22	29 w	30
102	98	>70	G	ECOG 0–2	18.4	32 w	37
			GV		18.4		
104	207	<70	PG		29	9.4	–
	53	>70	PG		15	7.7	–
105	19	>68	PG	WHO 0–2	53	–	–
106	30	70–79	P + G	ECOG 1–2	38	11	–
107	79	>70	G + Cb	ECOG 0–2	39.2	9.9	–
108	44	>70	P + VNR	KP ≥70	54	31 w	37
109	39	>65	D	ECOG 0–2	20	–	28
109	41	>65	DG	ECOG 0–2	29	–	–
110	35	>70	T	ECOG 0–3	23	10.3	45
158	19	>65	G	ECOG >2	31	–	43
159	71	<70	G + D	WHO 0–2	–	9	29
	24	>70				6.5	30

Abbreviations for chemotherapeutic agents defined as in table 3.
PS = performance status; KP = Karnofsky performance; ECOG = Eastern Cooperative Oncology Group; WHO = World Health Organisation; w = weeks; MS = median survival; ORR = objective response rate.
†Phase III.

outcome for patients younger or older than 70 years.[104] Similarly, gemcitabine plus carboplatin every 3 weeks achieved a response rate of 39.2% and median survival of 11 months.[107] The addition of vinorelbine to cisplatin 3 weekly produced a response rate of 54% and overall survival of 31 weeks.[108] The toxicity profiles of all of these regimes were acceptable and were mainly related to myelosuppression. In addition, single agent taxanes have been used in a phase II setting in the elderly on a weekly dosing schedule.[109 110] Interestingly, patients with performance status 0–1 and 2 attained equivalent 1 year survival rates with docetaxel (28%) and no serious haematological toxicity.[109] The addition of gemcitabine to docetaxel enhanced the overall response at the expense of myelotoxicity. Survival data are not yet available.[109] In a study of single agent paclitaxel in the elderly, including patients of performance status 2–3, median and 1 year survival of 10.3 months and 45%, respectively, was found.[110]

Chemotherapy in elderly patients with NSCLC is therefore currently indicated in those with advanced disease and performance status 0–2 using single agent vinorelbine or gemcitabine or combination platinum regimens. Emerging regimes require additional phase III analysis, but phase II studies are encouraging and both single agent and combination regimes need to be explored, not necessarily including platinum. Additional data on blood transfusions, antibiotic requirements, hospitalisation, and quality of life will also be required.

TREATMENT STRATEGIES FOR SMALL CELL LUNG CANCER (SCLC)

Chemotherapy in SCLC

Chemotherapy is established in the management of SCLC. As a consequence of the significant median and overall survival gains seen with treatment over the last two decades,[12 111–113] the majority of elderly patients receive active treatment (surgery, chemotherapy, radiotherapy) in sharp contrast to elderly patients with NSCLC (age 75+: 78% *v* 42%).[1] This difference in referral exists after review by a chest physician and suggests that elderly patients in general are fit for chemotherapy and that non-referral is a function of perceived efficacy of treatment, perhaps an assumption of a "good innings" or paternalism. In one phase III study elderly patients had a significantly inferior overall survival rate and time to disease progression when high dose epirubicin/cisplatin was compared with cisplatin/etoposide.[114] Albain *et al* showed that age >70 years was a significant adverse prognostic indicator in both extensive (non-platinum containing regimes) and limited disease (platinum containing regimes).[115] However, a large French retrospective multivariate analysis of 787 patients using numerous regimes found no such correlation. Disease extent, participation in a clinical trial, type of chemotherapy, and use of mediastinal irradiation were, however, significant independent prognostic variables.[113] This raises the possibility that the type of chemotherapy may adversely affect survival in the elderly, perhaps in relation to tolerability. Elderly patients receive significantly less chemotherapy (total dose, cycle number, and dose intensity) with higher febrile neutropenia rates.[114] Consequently, reducing the impact of febrile neutropenia where the risk of fatal infection is greater in patients aged >60 years[116] or developing regimens with less haematological toxicity are viable approaches in the management of elderly patients with SCLC, particularly in those with a poor prognosis.

The incidence and effects of febrile neutropenia may be averted by the use of granulocyte colony stimulating factors (G-CSF) and prophylactic antibiotics. A randomised study comparing differing doses of G-CSF in elderly patients undergoing platinum based chemotherapy showed that a dose of 4 μg/kg G-CSF significantly reduced the duration of treatment and produced a shorter duration of grade 4 neutropenia and a higher neutrophil nadir. In addition, a significant reduction in the incidence of grade 4 neutropenia lasting >4 days occurred, together with removal of the need for antibiotics after chemotherapy (p=0.01).[117] Alternatively, the use of ciprofloxacin and roxithromycin on days 4–13 after chemotherapy with doxorubicin, cyclophosphamide and etoposide (ACE) (either standard doses or intensified treatment) significantly reduced the incidence of febrile neutropenia, the use of therapeutic antibiotics, infectious deaths, and hospital admissions for febrile neutropenia, together with reduced Gram negative, Gram positive, and clinically documented infections.[118]

Despite concerns over haematological toxicity, elderly patients with a good prognosis should be considered for aggressive treatment. Carboplatin-etoposide with accelerated hyperfractionated radiotherapy in elderly patients with limited stage disease may produce 2 and 5 year survival rates of 32% and 13%, respectively.[119] Cisplatin, doxorubicin, vincristine, and etoposide in combination in elderly patients has also shown good activity (92% response rate) and a 70 week median survival[120]; both require phase III evaluation. Similarly, 2 and 5 year survival rates of 47% and 26%, respectively, were achieved with cisplatin-etoposide given concurrently with twice daily radiotherapy, a significant improvement over a once daily radiotherapy regime.[121] Although not performed specifically on the elderly, 30–40% of the population was >65 years and a separate analysis concluded that elderly patients obtained similar responses and survival figures.[122] In patients with extensive disease the combination of cisplatin-etoposide-epidoxorubicin and cyclophosphamide up to age 75 years produced significantly greater response rates, time to disease progression, and survival than cisplatin-etoposide alone, with no statistically significant impact of age on these variables.[123] Other studies which have included patients with a median age of >65 years have shown a favourable response and survival data together with the suggestion of improved symptom control, less hospitalisation, and reduced risks of life threatening sepsis.[124–127] Most recently, the cisplatin-irinotecan combination has been shown to be more efficacious in extensive stage disease than cisplatin-etoposide, and this effect persisted despite adjustment for age (up to 70 years) and performance status.[128] Early reports of newer combinations are also emerging with encouraging response rates in phase II studies. Topotecan-etoposide, carboplatin-vinorelbine, cisplatin-etoposide-gemcitabine, and gemcitabine-carboplatin combinations have recently produced response rates of 54–76% with grade 4 neutropenia 25–60% in populations of median age ≥65 years.[129–132]

Elderly patients with a good prognosis, determined by pretreatment characteristics,[133] with limited stage SCLC require treatment with the aim of attaining long term survival. In patients with poorer prognoses palliative chemotherapy should be offered, remembering the high incidence of life threatening sepsis in these patients that can be ameliorated with prophylactic G-CSF or antibiotics.

Radiotherapy and SCLC

Current standard practice supports the administration of prophylactic cranial irradiation (PCI) to patients with SCLC who achieve a complete response with chemotherapy.[134] The available data suggest that no subgroup, including the elderly, benefited more or less from PCI.[135] More contentious issues—such as the timing of PCI and the optimal dose required to reduce the incidence of cerebral metastases—are applicable to all patients regardless of age and still require more study. However, a review of 987 patients with SCLC in complete remission suggested trends for higher radiation doses and earlier administration of PCI to reduce the risk of brain metastases, although these did not affect survival.[135] In addition and perhaps of great relevance to the elderly was the lack of change in neuropsychological function between groups receiving PCI or not, although long term data are not available.

The tolerability and efficacy of thoracic irradiation in limited stage disease is more clearcut,[115 136 137] although

whether the elderly attain similar benefit to younger patients remains undecided.[115 136 138] A meta-analysis examining the place of thoracic radiotherapy suggested that survival may be superior in those under 55 years of age, while a review of 520 patients with limited stage SCLC and either early or late radiotherapy found little difference in survival between patients aged 65–75 years and those aged <65 years. However, patients aged >75 years exhibited a significantly inferior survival to patients <75 years.[136] Pignon *et al*[136] were unable to clarify whether early or late radiotherapy was better in their meta-analysis. The results from three randomised clinical trials indicate the survival benefit of early concurrent chemoradiotherapy compared with delayed concurrent chemoradiotherapy.[139–141] An older trial by Perry *et al*,[142 143] however, showed no advantage of early concurrent chemoradiotherapy compared with delayed treatment, and no significant benefit was seen for early compared with later chest irradiation and sequential chemotherapy.[144] Supporting data for early concurrent chemoradiotherapy, particularly with twice daily fractionation of radiotherapy, was reported by Turrissi *et al*[121] and multivariate analyses of a series of trials from the South West Oncology Group indicated that being treated with early concurrent chemoradiotherapy was a strong independent predictor of survival.[115] Consequently, early concurrent radiotherapy with platinum-etoposide chemotherapy can now be regarded as standard treatment.[141] In addition, patients aged >75 years may have an inferior survival compared with younger patients,[136] but elderly patients with limited SCLC (median age 72 years, ~40% of patients >75 years) may obtain favourable survival with abbreviated (2 cycles) platinum based chemotherapy and concurrent thoracic radiotherapy.[145]

Surgery and SCLC

The use of surgery in the management of SCLC is the subject of some ongoing debate and its exact place in management is not well defined.[146 147] The resection of early stage disease (stage I–II) followed by chemoradiotherapy or chemotherapy with surgical resection and subsequent radiotherapy/chemotherapy will pose a significant physiological challenge; it is likely therefore that only a few elderly patients will be candidates for this approach. Evidence from randomised controlled trials does not support this approach in preference to standard chemotherapy regimes with or without radiotherapy.

CONCLUSION

The elderly are a complex patient group with increasing co-morbidity and shrinking physiological reserve. Careful selection of individual patients through optimal work up and tailoring proposed treatments to accommodate co-morbidities and the likely prognosis can allow us to provide effective management of this challenging disease. Denying the elderly important advances in the treatment of lung cancer based on prejudice alone is no longer justified. Treatment for this disease is far from ideal; the challenge is to increase access to life enhancing treatments across all ages in a timely manner to provide efficacious palliation and improve survival. The advent of targeted treatment exploiting current knowledge has already led to novel agents directed at the epidermal growth factor receptor and farnesyl transferase, and may prove useful in the elderly either alone or in combination with current treatment modalities with further impact on survival. Important questions still require answers; the inclusion of elderly patients in randomised clinical trials will bring about advances and also provide a sound scientific basis for treatment decisions.

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LUNG ALERT

Lung volume reduction surgery for severe emphysema increases exercise capacity but not does not affect mortality

▲ National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;**348**:2059–73

This was a randomised multicentre trial comparing lung volume reduction surgery with continuing medical treatment in patients with severe emphysema (n=538 and 540, respectively, after exclusions). The primary outcomes were mortality and maximal exercise capacity 2 years after randomisation.

Overall mortality was similar in both groups (0.09 deaths per person-year for those undergoing surgery *v* 0.10 for those who did not). Exercise capacity after 24 months improved by more than 10 W in 16% of those undergoing surgery compared with 3% in the group receiving continuing medical treatment ($p<0.001$). In secondary analyses four subgroups were established, combining high or low exercise capacity with the presence or absence of predominantly upper lobe emphysema. In the patients with predominantly upper lobe emphysema and a low baseline exercise capacity, mortality was lower in the group who underwent surgery than in those who did not (death risk ratio 0.47, $p=0.005$); the converse was true in patients without predominantly upper lobe emphysema and a high exercise tolerance (risk ratio 2.06, $p=0.02$) and functional gain was negligible. There was no difference for the other subgroups.

Although this was a large, well conducted study with interesting results for physicians, the data should be interpreted with caution as mortality only differed in the secondary analysis. Perhaps, therefore, this study should serve to generate further hypotheses and future studies.

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