Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable): a systematic review

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Abstract

Objectives—To determine the effectiveness of radical radiotherapy in medically inoperable stage I/II non-small cell lung cancer (NSCLC) and the extent of treatment related morbidity.

Methods—Randomised trials were sought by electronically searching the Cochrane Clinical Trials Register, and both randomised and non-randomised trials were sought by searching Medline and Excerpta Medica (Embase). Further studies were identified from references cited in those papers already identified by electronic searching. The studies included were those of patients of any age with stage I/II NSCLC receiving radiotherapy at a dose of >40 Gy in 20 fractions over 4 weeks or its radiobiological equivalent.

Results—Two randomised and 35 non-randomised studies were identified. One randomised and nine non-randomised studies did not meet the selection criteria, leaving one randomised and 26 non-randomised studies for analysis. In the randomised trial 2 year survival was higher following continuous hyperfractionated accelerated radiotherapy (CHART; 37%) than following 60 Gy in 30 fractions over 6 weeks (24%). An estimated 2003 patients were included in the 26 non-randomised studies; overall survival was 22–72% at 2 years, 17–55% at 3 years, and 0–42% at 5 years. Following treatment, 11–43% of patients died from causes other than cancer. Cancer specific survival was 54–93% at 2 years, 22–56% at 3 years, and 13–39% at 5 years. Complete response rates were 33–61% and local failure rates were 6–70%. Distant metastases developed in approximately 25% of patients. Better response rates and survival were seen in those with smaller tumours and in those receiving higher doses although the reasons for prescribing higher doses were not clearly stated. The outcome was worse in those with prior weight loss or poor performance status. Assessment of treatment related morbidity and effects on quality of life and symptom control were inconclusive because of the lack of prospective evaluation and paucity of data.

Conclusions—No randomised trials compared a policy of immediate radical radiotherapy with palliative radiotherapy given

when patients develop symptoms. In the absence of such trials, radical radiotherapy appears to result in a better survival than might be expected had treatment not been given. A substantial, though variable, proportion of patients died during follow up from causes other than cancer. The optimal radiation dose and treatment technique (particularly with respect to mediastinal irradiation) remain uncertain.

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Keywords: radiotherapy; lung cancer; dosage; review

Background

In general, surgery is believed to offer the best prospects for cure for early stage non-small cell lung cancer (NSCLC). In spite of the intention to consider all patients with stage I/II disease for surgery, there are those who, although technically operable, either refuse surgery or are considered inoperable because of insufficient respiratory reserve, cardiovascular disease, or general frailty. This group may therefore be considered “medically inoperable”. Some respiratory physicians refer these patients for radical radiotherapy while others believe that radiotherapy has little to offer and adopt a watch policy, referring patients for palliative radiotherapy only when they become symptomatic.

Although there is no evidence from randomised trials to support the use of radical radiotherapy for stage I/II NSCLC, it is the perception of most clinical oncologists (radiotherapists) that patients should receive radical, as opposed to palliative, treatment.¹

The revised International System for Staging Lung Cancer² is based on outcomes in a series of over 5000 patients. Five year survival in T1N0 (stage IA) and T2N0 (stage IB) pathologically (surgically) staged tumours was 67% and 57%, respectively, while 5 year survival in clinically staged T1N0 and T2N0 tumours was 61% and 38%, respectively. For those with involvement of hilar nodes (stage IIA), 5 year survival was 55% and 39% for pathologically staged T1N1 and T2N1 tumours but 34% and 24% for those clinically staged. Five year survival for T3N0 (stage IIB) tumours was 38% when pathologically staged and 22% when clinically staged. The significance of the two sets of outcomes is that surgical patients are, by definition, pathologically staged while patients receiving radical radiotherapy are almost entirely clinically staged—

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that is, without mediastinoscopy or thoracotomy.

These results contrast with an untreated group of 50 patients with stage I/II disease in which all had died by the end of the third year.³ Although the survival following radical radiotherapy is thought to lie somewhere between that of untreated patients and patients treated surgically, outcome is also determined by the presence of other medical conditions, principally chronic obstructive pulmonary disease and coronary artery disease, which rendered the majority of individual patients inoperable.

Although current UK guidelines¹ recommend radical radiotherapy for this group of patients, factors influencing the decision to refer patients for radiotherapy include uncertainty as to whether radiotherapy can alter the natural history of NSCLC and anxieties about the safety of radiotherapy in the presence of poor lung function. The purpose of this review is to summarise the evidence on treatment effectiveness and morbidity to assist those involved in making treatment decisions. The effectiveness of (external beam) radical radiotherapy for stage I/II medically inoperable NSCLC is determined and, where possible, the extent of morbidity resulting from it. Endobronchial brachytherapy or the additional use of chemotherapy are beyond the scope of this review.

Methods

CRITERIA FOR CONSIDERING STUDIES IN THIS REVIEW

Criteria for inclusion of studies in this review were established prospectively.

Types of studies

Evidence from randomised controlled trials was sought in the first instance. Where this was not available, results were reported from non-randomised studies, bearing in mind that such evidence is prone to bias.

Types of participants

Patients of any age with T1–2N0–1M0 (now defined as stage I/IIA) or T3N0M0 (now defined as stage IIB) NSCLC,² either considered not sufficiently fit for or declining surgery.

Types of intervention

External beam radiotherapy given with radical intent (defined as an intended dose of at least 40 Gy delivered in 20 daily fractions or its radiobiological equivalent).

Types of outcome measures

Outcome measures included overall and cancer specific survival, local failure rate, response rate (both complete response and combined complete and partial response), deaths from intercurrent illness, and treatment morbidity (with particular respect to spinal cord and lung toxicity).

Cancer specific survival rates (defined as the survival rate calculated after exclusion of those patients known to have died from causes other than cancer) are as quoted in individual studies. Local failure was defined as persistent

or recurrent disease at the primary site. Regional failure was defined as persistent or recurrent disease at the hilum or within the mediastinum or supraclavicular fossae. Locoregional failure was defined as failure in either local or regional sites. Complete and partial response rates were defined according to standard UICC criteria.⁴

SEARCH STRATEGY

Randomised trials were sought by electronically searching the Cochrane Clinical Trials Register and both randomised and non-randomised trials were sought by searching Medline and Excerpta Medica (Embase). Further studies were identified from references cited in those papers already identified by electronic searching. Searches were updated during July 2000.

METHODS OF THE REVIEW

Each study identified by the search strategy was categorised as either randomised or non-randomised and assessed independently by both reviewers to determine whether it met the inclusion criteria. Any disagreements were resolved by discussion, involving a third party where necessary.

DESCRIPTION OF THE STUDIES

Two randomised trials were identified, one comparing surgery with radiotherapy⁵ and the other comparing two radiotherapy fractionation schedules (continuous hyperfractionated accelerated radiotherapy (CHART) versus conventionally fractionated radiotherapy).⁶ The surgery versus radiotherapy trial was excluded as a proportion of patients were thought to have had involvement of mediastinal nodes. The CHART trial only met the inclusion criteria with subsequent publication of a subgroup analysis giving survival data for patients with stage I/IIA disease.⁷

Forty two references to non-randomised studies were identified.^{8–49} Several studies reported the results of treatment with a wide range of radiation doses. In some cases it was not clear whether doses lower than 40 Gy were used intentionally or were the result of treatment being discontinued before the prescribed dose had been delivered. Studies in which the majority of the patients had received doses greater than 40 Gy were included. Some studies included patients with stage III disease; these were included if sufficient data relevant only to patients with stage I/II were reported. Some studies included patients without a pathological confirmation of the diagnosis; while confirmation of the diagnosis is generally considered to be preferable, it is recognised that a proportion of patients have insufficient respiratory reserve to tolerate a pneumothorax following a CT guided lung biopsy. Studies were considered eligible if the proportion without pathological confirmation did not exceed 10%.

Thirty two references to 26 non-randomised studies^{8–39} form the basis of this review (table 1). Nine studies (10 references) were excluded. The reasons for exclusion were: stage not stated,^{40–41} radiation dose less than 40 Gy,^{42–47}

Table 1 Pretreatment characteristics of patients

Reference	n	Mean/median age (range)	Mediastinoscopy (%)	Staged with CT (%)	Declined surgery (n)	Unfit for surgery (n)
Stage I (T1–2N0)						
Haffty (1988) ⁸	43	64 (51–83)	4	9	6	37
Noordijk (1988) ^{9 a}	50					
Sandler (1990) ¹⁰	77	72 (44–80+)		16	13	64
Ono (1991) ¹¹	38	Not stated		24	4	34
Kaskowitz (1993) ¹²	53	73 (44–86)	8	All	10	43
Slotman (1994) ^{13 b}	47	75 (57–93)		55	3	44
Gauden (1995) ¹⁴	347	70 (34–90)		87	Not stated	Not stated
Park (1995) ¹⁵	15	66		Not stated	2	13
Krol (1996) ¹⁶	108	74 (56–88)		86	6	102
Slotman (1996) ^{17 b}	31	75 (54–85)		All	2	29
Morita (1997) ^{18 b}	149	74 (50–89)		All	26	123
Jeremic (1997) ¹⁹	49	63 (51–70)		All	20	29
Nguyen-Tan (1998) ^{20 c}	41	69 (53–81)	36	All	4	37
Sibley (1998) ²¹	141	70 (46–95)	1	90	2	139
Hayakawa (1999) ^{22 b}	36	>70		67	4	32
Stage IIA (T1–2N1)						
Salloom (1990) ²³	61	69 ^d		Some	Not stated	Not stated
Rosenthal (1992) ²⁴	62	68 (46–82)		Some	Not stated	Not stated
Stage I & IIA (T1–2N0–1)						
Zhang (1989) ²⁵	42	57 (37–70) ^d		0	12	32
Hayakawa (1992) ^{26 a}	64					
Schildge (1993) ²⁷	67	66 (not stated)	All earlier patients	Later patients only	Not stated	Not stated
Graham (1995) ²⁸	103	67 (43–89)	3	76	Not stated	Not stated
Koukourakis (1995) ²⁹	64	67 ^d (not stated)		All	Not stated	Not stated
Furuta (1996) ^{30 b}	32	79 (75–86)		Most	2	30
Hayakawa (1996) ³¹	84	>70		Some	5	79
Hayakawa (1996) ^{32 c}	84					
King (1996) ^{33 a}	11					
Saunders (1999),^e Bentzen (2000)⁷	169	Not stated		All	Not stated	Not stated
Anderson (2000) ³⁴	36	68 (46–82)		All	Not stated	Not stated
Stage I & IIB (T1–3N0)						
Talton (1990) ³⁵	77	65 (not stated)	Some	20	Not stated	Not stated
Dosoretz (1992), ³⁶ (1993) ^{37 a}	152	74 (51–88)		Most	Not stated	Not stated
Dosoretz (1996) ³⁸	245	Not stated			27	218
Kupelian (1996) ³⁹	59	Not stated		All	Not stated	Not stated

Data from individual studies have not been included in the table when these data have been included in a subsequent or duplicate series. Data from randomised trial shown in bold.

^aUpdated series: patients from Noordijk (1988)⁹ were included in Krol (1996),¹⁶ from Hayakawa (1992)²⁶ in Hayakawa (1996),³¹ from Dosoretz (1992)³⁶ and (1993)³⁷ in Dosoretz (1996),³⁸ and from King (1996)³³ in Sibley (1998).²¹

^bOverlapping series: some patients reported by Hayakawa (1996)³¹ and Furuta (1996)³⁰ were included in a series with stage I tumours reported by Morita (1997)¹⁸ and in a series of peripheral stage I tumours reported by Hayakawa (1999).²² Some patients reported in Hayakawa (1996)³¹ were included in a subset of elderly patients with stage I/IIA tumours reported by Furuta (1996).³⁰ Slotman (1984)¹³ and (1987)¹⁷ reported patients from overlapping time periods.

^cPublished data supplemented by data from authors (Nguyen-Tan, personal communication).

^dAge ranges are those of a larger group which included a proportion of patients with stage III tumours.

^eDuplicate series: Hayakawa (1996)³² reported the same results as Hayakawa (1996).³¹

inclusion of patients with small cell lung cancer,^{40 41 43 44} more than 10% of patients without cytological or histological confirmation,^{43 44} studies of patients with stages I–III but insufficient outcome data relating solely to those with stage I/II.^{44–49}

METHODOLOGICAL QUALITY OF INCLUDED STUDIES

The randomised (CHART) trial⁶ was a multi-centre study with randomisation performed by the method of minimisation by telephone call to a central trials office; data analysis was performed on an intention-to-treat basis and exclusions were solely on the basis of ineligibility—that is, failing to meet the entry criteria with regard to pathological diagnosis or performance status. The 26 non-randomised studies were all retrospective reviews (table 1).^{8–39}

Duplicate reporting

The extent of duplicate reporting was uncertain as some authors did not cite previous reports which included patients from the same centre over the same or an overlapping time period. As far as possible, these are identified in table 1.

Patient characteristics

Most of the non-randomised studies recorded details of age, stage, the use of CT imaging and mediastinoscopy for staging, and numbers of patients declining or considered insufficiently fit for surgery (table 1). Only those patients with WHO performance status 0–1 were eligible for the CHART trial.⁶ Data on performance status and weight loss were included in 16 and five non-randomised studies, respectively (table 2).

End points

A range of end points was used and in several studies the end points sought by this review were not reported. Different definitions of local and locoregional failure were used or were not defined. For example, it was not always clear whether in-field recurrences were local or regional or whether intrathoracic recurrences were in fact local, regional, or distant.

Adverse event reporting

The CHART trial⁶ recorded treatment morbidity prospectively using 4- or 5-point scales. While almost all the non-randomised studies appeared to report major morbidity, the reporting of treatment morbidity was, in general, poor. There was grading of morbidity

Table 2 Patient characteristics

Reference	Performance status	Weight loss
Saunders (1999),⁶ Bentzen (2000)⁷	All 0–1	–
Sandler (1990) ¹⁰	63% 0–1	–
Kaskowitz (1993) ¹²	91% 70–100	>5% in 32%
Slotman (1994) ¹³	64% 70–80; 32% 90–100	–
Gauden (1995) ¹⁴	74% 0–1	–
Park (1995) ¹⁵	13% 0–1	–
Krol (1996) ¹⁶	All 70–100	–
Slotman (1996) ¹⁷	65% 70–80; 23% 90–100	–
Jeremic (1997) ¹⁹	27% 70–80; 73% 90–100	>5% in 16%
Sibley (1998) ²¹	–	Present in 26%
Hayakawa (1999) ²²	97% 0–1	–
Rosenthal (1992) ²⁴	66% 0–1	>5% in 40%
Graham (1995) ²⁸	87% 0–1	Present in 33%
Koukourakis (1995) ²⁹	All 70–100	–
Furuta (1996) ³⁰	81% 0–1	–
Hayakawa (1996) ³¹	63% 0–1	–
Anderson (2000) ³⁴	56% 0–1	–
Kupelian (1996) ³⁹	57% 70–100	–

Performance status is graded by either the ECOG/WHO or Karnofsky scales; good performance status patients are those with ECOG/WHO 0–1 or Karnofsky scores of 70–100. Randomised trial shown in bold.

Table 3 Radiotherapy details

Reference	Radiation dose (Gy/no of fractions (F))	Mediastinum included (% patients)
Haffty (1988) ⁸	<i>Continuous:</i> median 59 Gy in 2 Gy fractions or <i>Split:</i> median 54 Gy in median 2.75 Gy fractions	88%
Sandler (1990) ¹⁰	Median 60 Gy/30F/6 weeks	90%
Ono (1991) ¹¹	60–70 Gy/30–35F split over 8–10 weeks	32%
Kaskowitz (1993) ¹²	40–79 Gy (median 63 Gy)	89%
Slotman (1994) ¹³	32 Gy/6F twice weekly, 40 Gy/10F split, 48 Gy/12F daily or 56 Gy/20F daily.	71%
Gauden (1995) ¹⁴	50 Gy/20F/4 weeks	100%
Park (1995) ¹⁵	60 Gy/30F	Not stated
Krol (1996) ¹⁶	60 Gy/20F split over 7 weeks or 65 Gy/26F daily	0%
Slotman (1996) ¹⁷	48 Gy/12F daily	0%
Morita (1997) ¹⁸	55–74 Gy mostly in 2 Gy fractions	44%
Jeremic (1997) ¹⁹	69.6 Gy/58F treatment twice daily	Hilum included
Nguyen-Tan (1998) ²⁰	40 Gy/10F split—64 Gy/32F	Not stated
Sibley (1998) ²¹	50–80 Gy in 1.2–3 Gy fractions; 15 patients treated twice daily	73%
Hayakawa (1999) ²²	48–81 Gy in 2 Gy daily fractions	28%
Salloum (1990) ²³	15–66 Gy (71% ≥50 Gy; 25% split course)	Not stated
Rosenthal (1992) ²⁴	18–65 Gy (median 60 Gy)	100%
Zhang (1989) ²⁵	55–70 Gy in 6–7 weeks	100%
Schildge (1993) ²⁷	60 Gy/30F	Not stated
Graham (1995) ²⁸	Median 60 Gy/30F daily (range 18–60 Gy)	80%
Koukourakis (1995) ²⁹	NTD 48–64 Gy in 2–4 Gy fractions over 3–10 weeks	100%
Furuta (1996) ³⁰	60–80 Gy/6–8 weeks	81%
Hayakawa (1996) ³¹	60–74 Gy in 2 Gy fractions; 10 patients received 80–90 Gy	85%
Saunders (1999),⁶ Bentzen (2000)⁷	60 Gy/30F daily or 54 Gy/36F/12 days (CHART)	100%
Anderson (2000) ³⁴	45–55 Gy/15–16F daily	Not stated
Talton (1990) ³⁵	60 Gy/30F/6 weeks	100%
Dosoretz (1992), ³⁶ (1993), ³⁷ (1996) ³⁸	45–75 Gy in 1.8–2 Gy fractions	Most
Kupelian (1996) ³⁹	Median 63 Gy	72%

NTD = nominal total dose.

Randomised trial shown in bold.

using RTOG scales in only two studies^{13 22} and using a descriptive scale in a third.¹⁰ In these three it was not stated whether morbidity had been scored prospectively or retrospectively.

Results

RANDOMISED TRIALS

The CHART trial compared two radiotherapy schedules and randomised 563 patients with stage I–IIIB NSCLC to receive either CHART (54 Gy in 36 fractions over 12 days) or conventionally fractionated radiotherapy (60 Gy in 30 fractions over 6 weeks).⁶ In the group as a whole CHART improved 2 year survival from 20% to 29% with hazard ratios showing no significant difference by stage. Subsequent publication of a subgroup analysis⁷

relating to the 169 patients with stage I/IIA disease showed a similar degree of benefit with 2 year survival improving from 24% for conventional radiotherapy to 37% with CHART. Four year survival improved from 12% to 18%. Most of the patients (130/169, 77%) had T2N0 tumours; 33 (20%) were T1N0 and only six (4%) were stage IIA. A two phase technique was used with elective mediastinal irradiation in the first phase.

NON-RANDOMISED STUDIES

Patient characteristics

Allowing for duplicate reporting, an estimated 2003 patients were included in 26 non-randomised studies (table 1).^{8–39} Individual studies were of varying size, ranging from 15 to 347 patients (median study size 60 patients). In two studies there were nine of 108¹⁶ and four of 103²⁸ without pathological confirmation of the diagnosis.

Age: the patients had a wide age range (34–95 years; table 1). Some studies reported median age while others reported the mean age. Taken together, median/mean ages in individual studies ranged from 57 to 79 years (median 70).

Staging: in the series reported before 1992 less than a quarter of patients had had CT imaging whereas, in those reported since, CT imaging had been performed in most (table 1). Mediastinoscopy was mentioned as being used in seven studies.

Location of stage I tumours: two studies included only peripheral tumours^{16 22} and, in a further study, 87% were located peripherally.¹⁷

Performance status and weight loss: most of the patients were of good performance status (ECOG/WHO 0–1, range 13–97% but >50% in all but one study; Karnofsky 70–100, range 57–100%; table 2). Ten studies did not report performance status. The presence of weight loss was noted in only five studies (>5% of body mass in three studies but undefined in two) and was reported by 16–40% of patients (table 2).

Proportion declining surgery *v* those considered not sufficiently fit: this was reported in 17 studies (n=1233 patients, table 1) in which 148 (12%) had declined surgery. Reasons for inoperability were given for 1003 patients and included pulmonary disease in 45%, cardiac disease in 13%, other unspecified medical problems in 20%, poor general condition in 9%, age in 11%, and other cancer in 1%.

Comorbidity: this was recorded separately from reasons for inoperability in two studies,^{13 28} in one of which²⁸ only 13 of 103 patients had no comorbidity. A better outcome was reported in those with normal cardiorespiratory function.²⁷

Treatment details: details of radiotherapy fractionation and whether the mediastinum was included in the treated volume are shown in table 3.

Survival

Overall survival: overall survival in the studies was 50–93% at 1 year, 22–72% at 2 years, 17–55% at 3 years, and 0–42% at 5 years. Median survival varied from 15 to 33 months

Table 4 Overall and cancer specific survival

Reference	Intercurrent deaths (%)	n	Clinical subset	Median survival (months)	Overall survival (%)				Cancer specific survival (%)				Disease free survival (%)	
					1 year	2 year	3 year	5 year	1 year	2 year	3 year	5 year	2 year	5 year
Stage I (T1–2N0)														
Haffty (1998) ⁸	NS	43		28			36	21						
		11	Continuous	52				45						
		32	Split	27				12						
Sandler (1990) ¹⁰	13	77		20			17				22			
		25	<3 cm				25				30			
		41	3–6 cm				13				17			
		9	>6 cm				0				0			
Ono (1991) ¹¹	NS	38		NS	84	68	55	42						
Kaskowitz (1993) ¹²	25	53		21		43	19	6		54	33	13		
Slotman (1994) ¹³	43	47		20	70		33	15	90		53	32		
Gauden (1995) ¹⁴	12	347		28		54	40	27					41	23
		167	T1					32						
		180	T2					21						
Park (1995) ¹⁵	NS	15		15		22		0						
Krol (1996) ¹⁶	30	108		23	75	49	31	15	81	58	42	31		
		89	≤4 cm				35				40			
		19	>4 cm				11				13			
Slotman (1996) ¹⁷	42	31		33	81	72	42	8		93	76 ^a			
Morita (1997) ¹⁸	13	149		27	78		34	22						
			<4 cm					25						
			>4 cm					17						
Jeremic (1997) ¹⁹	12	49		33				30						41
		25	T1	40		76		37						
		24	T2	24		50		24						
Nguyen-Tan (1998) ²⁰	20	41		23		41								
		19	T1	26		63								
		22	T2	14		24								
Sibley (1998) ²¹	33	141		18		39		13		60		32		
Hayakawa (1999) ²²	NS	36		NS			42	23			56	39		
Stage IIA (T1–2N1)														
Salloum (1990) ²³	NS	61		18				22						
Rosenthal (1992) ²⁴	NS	62		18	70	33	20	12						
			PS 0–1	23	83	49	28							
			PS 2–3	6										
Stage I & IIA (T1–2N0–1)														
Zhang (1989) ²⁵	14	42		NS	93		52	31						
Schildge (1993) ²⁷	NS	67		17	55		19	5						
		35	NCRF		69		21	11						
Graham (1995) ²⁸	25	103		16		35		13						
		35	T1 ^b					29						
		68	T2 ^b					4						
Koukourakis (1995) ²⁹	NS	64	NTD	NS										
			56–64 Gy											30
			48–55 Gy											12
Furuta (1996) ³⁰	34	32		NS		40		16		57		36	43	23
Hayakawa (1996) ³¹	NS	84		NS										
		28	T1–2N0			74		31						
		56	T1–2N1			40		19						
		48	<5 cm					29						
		36	≥5 cm					14						
Saunders (1999), ⁶	NS	169	60 Gy	NS		24	12 ^a							
Bentzen (2000) ⁷			CHART			37	18 ^a							
Anderson (2000) ³⁴	NS	36		12	50	22		6						
Stage I & IIB (T1–3N0)														
Talton (1990) ³⁵	NS	77		18	56	37	21	17						
Dosoretz (1992), ³⁶ (1993) ³⁷	11	152				40								9
		44	T1	NR									55	
		63	T2	12									20	
		41	T3	12									25	
Dosoretz (1993) ³⁷			T1 60–65Gy										29 ^c	
			T1 >65 Gy										90 ^c	
Dosoretz (1996) ³⁸		245		16			7						28	9
			<3 cm										38	
			>5 cm										23	
Kupelian (1996) ³⁹	NS	19	T1	NS						49				
		26	T2							47				
		14	T3							26				

Intercurrent deaths are deaths known not to be due to cancer (where reported), shown as a percentage of the number of patients undergoing treatment.

NS = not stated; NR = not reached; NCRF = normal cardiorespiratory function.

^a4 year survival; ^bonly 10% of each subgroup had N1 disease; ^c3 year disease free survival.

Randomised trial shown in bold; results of subgroup analyses shown in italics.

(but was not stated in seven studies; table 4 without subgroup analysis).

Survival was better for T1 than for T2 tumours (range 29–37% v 4–24% at 5 years)^{12 14 19 20 28 36} and fell progressively as tumour size increased, although different studies used different cut off sizes.^{10 16 18 31 38} For those with involved hilar nodes, 5 year survival

ranged from 12% to 22%.^{23 24 31} Survival was unaffected by whether or not patients had had CT imaging performed as part of staging.^{10 24}

Survival appeared to be better in subgroups which received a higher dose in some studies^{12 28 29 37} but, in another,¹⁸ the complete response rate was improved with higher doses but survival appeared to be unaffected. In

contrast, the development of bronchial stenosis with doses higher than 80 Gy may have contributed to better survival with doses in the range 60–69 Gy.³¹

In some studies there was a trend in favour of better overall survival in those aged less than 70 years^{12 14 21} or less than 80 years,¹⁸ but not in others.^{10 13 16 17 24 28 31} The presence of comorbidity^{13 28} or weight loss^{19 28} affected survival adversely. There were striking differences in outcome according to performance status. Median survival times in the studies with data on performance status was 23–24 months for those with ECOG performance status 0–1 or Karnofsky scores of 90–100 compared with 6–13 months for those with ECOG ≥ 2 ^{24 31} or Karnofsky scores of 70–80.¹⁹ In contrast, in one study there was no difference in survival in those with Karnofsky scores ≥ 70 compared with < 70 ,¹² and in another survival was unaffected by the presence of weight loss.²⁴

Differences in survival by histological subtype (squamous, adenocarcinoma, or large cell carcinoma) were noted in only one study in which those with squamous carcinomas had a better outcome.²¹

Disease free survival: the disease free survival was 28–43% at 2 years and 9–41% at 5 years (table 4).^{14 19 30 38} A further study attempted to equate dose schedules that incorporated a range of total doses and fraction sizes or the use of split courses by quoting the nominal total dose (NTD) rather than the prescribed dose,

and demonstrated better disease free survival in those receiving a higher NTD.²⁹

Intercurrent deaths: intercurrent deaths, defined as the proportion of patients undergoing treatment who died from non-cancer causes during the follow up period, are shown in table 4. There was a wide range of intercurrent death rates (11–43%, median 25%). This is likely to be an underestimate as only those deaths known not to be due to cancer would have been reported.

Cancer specific survival: because of the varying proportions of intercurrent deaths, cancer specific survival may give a more reliable estimate of the effectiveness of treatment. Cancer specific survival in studies reporting data was 54–93% at 2 years, 22–56% at 3 years, and 13–39% at 5 years (table 4).

Local control: complete tumour response rates overall were 33–61% with complete and partial response rates of 80–100%.^{11 15 16 18 19 24} Complete response rates declined with increasing tumour size, being 48–52% in tumours less than 4 cm in diameter and 20–21% for those over 4 cm.^{16 18} A complete response rate of 60% was observed in patients receiving 72 Gy compared with 32% after 60 Gy, although survival was unchanged.¹⁸ Local failure ranged from 6% to 70% and was related to the dose given^{12 21 25} and to tumour stage^{19 20 36 39} or size³¹ (table 5). In-field, local, or locoregional progression free survival at 3 years was 44–51%.^{10 12}

Table 5 Patterns of failure

Reference	Subset	Local failure (%)	Regional failure (%)		Locoregional failure (%)		Distant metastases (%)
		Any or first ^d	Isolated	Any	Isolated or first ^d	Any	Any or first ^d
<i>Stage I (T1–2N0)</i>							
Haffty (1988) ⁸						39	
Sandler (1990) ¹⁰						43 ^a	
Kaskowitz (1993) ¹²		63					40
	<65 Gy	50					
	>65 Gy	25					
Slotman (1994) ¹³					26 ^b		21
Krol (1996) ¹⁶		68	2	15			33
Slotman (1996) ¹⁷		6	3	6			16
Morita (1997) ¹⁸		44					
Jeremic (1997) ¹⁹		45	0	11			25
	T1	29					
	T2	62					
Nguyen-Tan (1998) ²⁰		41					22
	T1	32					
	T2	50					
Sibley (1998) ²¹		22	3	7			23
Hayakawa (1999) ²²		8	3	8		11	36
<i>Stage IIA (T1–2N1)</i>							
Rosenthal (1992) ²⁴					55 ^d		30
<i>Stage I & IIA (T1–2N0–I)</i>							
Schildge (1993) ²⁷				30			28
Furuta (1996) ³⁰		25 ^d					25 ^d
Hayakawa (1996) ³¹	Tumour <5cm				24 ^a		57
	Tumour >5cm				53 ^a		80
<i>Stage I & IIB (T1–3N0)</i>							
Dosoretz (1992) ³⁶		70					45
	T1	30 ^c					9 ^c
	T2	80 ^c					40 ^c
	T3	86 ^c					40 ^c
Kupelian (1996) ³⁹	T1	11					
	T2	39					
	T3	58					

Sites of failure according to whether noted to be the first site of relapse, an isolated site of relapse, or a site of relapse at any time during the course of the disease. Results of subgroup analyses are shown in *italics*.

^aIn-field recurrence rate; ^bintrathoracic failure rate; ^cactuarial 4 year risk; ^dsite of first relapse.

Mediastinal irradiation: isolated relapse in the hilum or mediastinum was uncommon (0–3%) in those studies of stage I tumours in which the mediastinum had not been irradiated^{16 17 19 21 22}; regional relapse occurred more commonly in association with local or distant failure (6–15%). In studies where the mediastinum had been included in a proportion of cases^{21 22 39} survival was not improved by the use of mediastinal irradiation, although this comparison could well be biased by the use of mediastinal irradiation in higher risk patients.

Locoregional relapse was significantly less likely in one study if those with stage II tumours had received at least 40 Gy to the mediastinum, although the effect on survival was of borderline significance.³¹ However, in patients with stage I tumours, survival appeared to be better if the mediastinum had been treated,¹⁸ although the complete response rate was higher in this group.

Distant metastases: the incidence of distant metastases ranged from 16% to 40% (median 24%) in studies reporting only stage I tumours and from 25% to over 50% in those which included stage IIA/B tumours (table 5). The highest incidence was reported in the study by Hayakawa³¹ where 57% of those with tumours less than 5 cm in diameter and 80% of those with tumours over 5 cm in diameter developed distant metastases. Distant metastases were observed more frequently (52% *v* 12%) when a complete response had not been obtained.¹⁶ The rising incidence of metastases with advancing T stage was no longer apparent if local control had not been achieved.³⁶

Quality of life: although not defined as end points within this review, information was sought about symptom control and quality of life. No study reported on the impact of treatment on symptoms, quality of life, or performance status.

Morbidity

Spinal cord damage: one patient in the study by Zhang *et al*²⁵ died from radiation myelopathy but no further details are given.

Lung damage: lung toxicity was reported in several studies with the highest incidence of pneumonitis or lung damage (not graded) being seven of 38 (18%).¹¹ In the two studies that used RTOG scales (also the two studies using hyperfractionation)^{19 21} there was grade 3 pneumonitis in 1–2% of patients and grade 3 late lung toxicity in 0–2% with one case of fatal pneumonitis. The use of doses in excess of 80 Gy (delivered in 2 Gy fractions) for central tumours resulted in four out of five patients developing bronchial stenosis.³¹ In the absence of prospective data recording, morbidity is likely to have been underestimated in a number of studies. Only one study reported pretreatment lung function tests (FEV₁).³³ Post-treatment FEV₁ was not reported.

Discussion

It is always preferable to base clinical decisions on the results of randomised trials. In the absence of these, one must look to results from observational studies although these represent

a lower level of evidence. While evidence from non-randomised studies may be subject to several types of bias, there is evidence that patients entered into randomised trials may not reflect patients at large (fewer patients with adverse prognostic factors may be recruited into trials). On the other hand, non-randomised studies may appear to overestimate the effect of treatment because of poorer results in “historical” control groups.⁵⁰ The result is that the magnitude of reported treatment effects tends to be fairly similar.⁵¹ This is borne out in this review where the 2 year survival rates in the two arms of the CHART trial (24–37%) lie in the range reported for the non-randomised studies (22–40%) of patients with stage I/IIA disease.

This review has attempted to categorise the patient populations in these non-randomised studies in order to draw conclusions about outcome and prognostic factors. Many of these retrospective reviews are relatively small so that, when outcomes for individual subgroups are examined, tests for statistical significance become inappropriate. Inevitably, there are many possibilities for bias affecting these conclusions but, hopefully, this systematic review will help to identify key questions to be addressed in future randomised trials.

For stage I/II NSCLC the effectiveness of radiotherapy relative to surgery remains uncertain. The only comparison of surgery and radiotherapy comes from a single randomised trial⁵ performed 40 years ago when standards and techniques of staging and radiotherapy were very different. For patients considered “medically inoperable”, a comparison with surgery would be inappropriate and unrealistic as almost 90% had been considered not sufficiently fit for surgery.

There have, unfortunately, been no randomised trials that have addressed the key question of whether patients with medically inoperable NSCLC should receive immediate radical radiotherapy or be watched and only receive palliative radiotherapy when they develop symptoms warranting treatment. A randomised trial of immediate versus delayed palliative radiotherapy did not show a difference in symptom control or survival but included only patients with locally advanced disease.⁵² Indirect evidence supporting the use of radiotherapy (variation in survival according to radiotherapy technique and other subgroup analyses) has been sought.

PATIENT SELECTION

The proportion of patients declining surgery varied between studies. As these patients had been offered surgery, they probably had less comorbidity and better performance status than those considered unfit for surgery. As outcome is highly dependent on performance status, weight loss, and comorbidity, the size of this group of patients may have affected the outcome in individual series. The non-randomised study with the best survival rates was the one with the highest proportion of patients declining surgery and with Karnofsky scores of 90–100¹⁹; because of this it is difficult to gauge whether the use of hyperfractionation

in this study may have contributed to the results.

IMPACT OF CLINICAL V PATHOLOGICAL STAGING

Prior to the advent of CT imaging, 37% of patients were upstaged at surgery.⁵³ In a more recent randomised study of lobectomy versus limited resection in patients with T1N0 NSCLC,⁵⁴ 21% were found to have more advanced disease at surgery. This difference between clinical and pathological staging is recognised in the supporting evidence to the revised staging system.² For example, 5 year survival was 57% for pathologically staged T2N0 (stage IB) tumours but only 38% for those clinically staged. Awareness of these survival differences suggests that the gap between 5 year survival rates for surgery and radiotherapy may not be as wide as at first appears.

IMPACT OF COMORBIDITY

The “gap” in effectiveness between surgery and radiotherapy may be further narrowed when factors which make surgery ill advised such as coexistent medical conditions or general frailty are taken into consideration. In this review deaths from causes other than cancer occurred in approximately one quarter of all patients treated. In contrast, in a retrospective study of 289 resected patients there were 79 non-cancer deaths (27%),⁵⁵ and in the previously cited randomised trial of lobectomy versus limited resection 35 of the 247 patients (14%) died from causes other than cancer.⁵⁴ In this review poor respiratory function was the cause for inoperability in almost half of those judged not fit for surgery, and in a study of patients with chronic obstructive pulmonary disease (COPD) but without a diagnosis of cancer only 41% of those with an FEV₁ less than 50% of predicted were alive at 5 years.⁵⁶ It is therefore difficult to assess the impact of comorbidity in different studies, especially as retrospective studies may underestimate non-cancer deaths to a greater extent than prospective or randomised studies and as the proportion of non-cancer deaths is also related to duration of follow up.

TREATMENT OUTCOME

There is a difference of approximately 10–20% between overall and cancer specific survival at 5 years (table 3). Despite the poor overall survival of this group of patients, there are subgroups who may benefit to a greater degree and subgroups whose outcome is so poor that alternative approaches should be considered. The former group includes those with T1 tumours, of whom more than one third survive 5 years. The latter group includes those with significant weight loss or poor performance status for whom median survival times may be substantially less than 1 year.

Age alone did not appear to be a significant prognostic factor, although one might expect older patients to have a greater incidence of coexistent cardiorespiratory disease which, in turn, might mitigate against a better outcome.

Response rates have been reported as they may give some indication of treatment effectiveness. However, it is well recognised that assessment is more difficult for central than for peripheral tumours, where there is associated collapse or consolidation, and that assessment by plain radiography alone is less reliable than by CT imaging. The presence of adjacent pneumonitis or fibrosis frequently makes interpretation difficult. In this instance, local progression free survival would be a better measure of local control.

With respect to local failure, there is the need to distinguish between recurrence at the primary site, recurrences that are regional (that is, in hilar and mediastinal nodes), and recurrences elsewhere in the chest (which may be regarded as a category of systemic relapse). For locoregional failure it is important to know whether failure was within the radiation field, although this was not often stated. Reports tended to define local failure differently and table 4 may therefore have inadvertently included figures under the same category where there was a mixture of local and locoregional failure. Such data need to be collected prospectively, ideally within the context of a randomised trial.

RADIATION DOSE

The CHART trial clearly demonstrates the superiority of the accelerated and hyperfractionated CHART regime over conventionally fractionated radiotherapy to 60 Gy.⁶ However, most of the patients in the stage I/IIA subgroup analysis had T2N0 disease.⁷ The relative absence of patients with T1N0 disease may reflect the reluctance of clinical oncologists to employ a technique using elective mediastinal irradiation for small tumours, especially if peripheral.

Although radiation dose appeared to influence outcome in several non-randomised studies, factors leading to choice of dose were rarely stated. It is possible that less fit patients or those with more advanced disease received a lower dose. In one study³¹ those showing signs of response received a higher dose. However, the presence of a dose-response relationship has been clearly demonstrated in a large randomised study of inoperable disease,⁵⁷ so these observations may not be so lightly dismissed. A study of patients surviving at least 18 months following radiotherapy for stage I–III NSCLC found that there was a progressive fall in local failure rate with increasing dose such that, with a dose of >59 Gy, local failure occurred in only one of 20 patients.⁵⁸ Similarly, a multivariate analysis of patients undergoing high dose palliative or radical radiotherapy showed the radiation dose to be a significant determinant of outcome.⁴⁷

A recurring theme is that higher doses or more intensive regimes such as CHART may be associated with the best results. While CHART to 54 Gy is clearly superior to 60 Gy conventionally fractionated, one can only speculate on the possible benefits of dose escalation in both CHART and conventionally

fractionated regimes without elective mediastinal irradiation.

MEDIASTINAL IRRADIATION

Traditionally, the whole mediastinum (extending from suprasternal notch to 5 cm inferior to the carina) is treated to a dose of 40–50 Gy in an attempt to eradicate subclinical disease. Most of the studies included in this review followed this practice. However, for peripherally located stage I tumours, isolated regional relapse was uncommon when the mediastinum was intentionally not included. Subclinical hilar or mediastinal node involvement in stage I/II NSCLC was found in one study to be less frequent in tumours not evident at bronchoscopy (that is, peripheral),⁵⁹ and in a multivariate analysis tumour size was of only borderline significance. By not including the mediastinum, the mean lung dose will be lower and with it the risk of lung damage.⁶⁰ As patients with stage I tumours referred for radiotherapy are commonly those with poor lung function, this would seem a reasonable approach.

For stage II tumours there may be fewer regional relapses if the mediastinum is treated,³¹ although an effect on survival was not apparent. The value of mediastinal irradiation for stage II tumours remains uncertain.

DISTANT METASTASES

This review found that only about one quarter of patients with stage I/II disease develop metastatic disease after radiotherapy, whereas this figure is in the region of 60–80% for those treated for stage III disease. The importance of this observation is that the potential for improving survival by improving local control is much greater in earlier stage disease.

In one study¹⁶ distant metastases occurred more frequently if a complete tumour response had not been obtained. Dosoretz *et al*⁶⁰ reported that the incidence of distant metastases was related to tumour size only if there had been a complete response; without a complete response the relationship between tumour size and incidence of distant metastases was lost. While the biological properties of the tumour might predispose to both radioresistance and metastatic potential, these observations would also be consistent with persisting tumour continuing to act as a source of metastases.

TREATMENT MORBIDITY

In general, reporting of treatment side effects was inconsistent and mostly poor with little grading of adverse effects in retrospective studies. While there was prospective recording of morbidity in the CHART trial, data relating to patients with stage I/IIA disease have not been reported separately. There are therefore insufficient data to make a confident statement about treatment morbidity in this group.

USE OF CHEMOTHERAPY

Although the inclusion criteria for this review required that patients had been treated with radiotherapy alone rather than with a combination of radiotherapy and chemotherapy, in a

meta-analysis which included patients with stages I–IIIB NSCLC the addition of adjuvant chemotherapy to radical radiotherapy improved 2 year survival from 15% to 19% and 5 year survival from 5% to 7%.⁶¹ Synchronous chemoradiotherapy (the subject of a number of trials in patients with predominantly stage III disease) was not evaluated in this meta-analysis. Many medically inoperable patients in studies in this review were elderly and would not have been considered fit enough to receive chemotherapy. Whether synchronous chemoradiotherapy might offer any greater benefit without undue toxicity in this group has yet to be evaluated.

Conclusions

IMPLICATIONS FOR PRACTICE

As the majority of conclusions are based on the results of retrospective studies, the possibility of a significant degree of bias cannot be excluded.

- Radical radiotherapy offers the prospect of cure for a proportion of patients with medically inoperable NSCLC.
- Complete response rates are approximately 50% in tumours of <4 cm in diameter but only 20% for tumours with a diameter of >4 cm.^{16 18}
- Better outcome (overall survival) is seen in those with T1 tumours^{12 14 19 20 28 36} and may be achieved with CHART⁷ or, where not available, conventionally fractionated doses of 60 Gy or more.^{12 28 29 37}
- Worse outcome is seen in those with:
 - (a) performance status WHO/ECOG ≥ 2 ^{24 31} or Karnofsky score ≤ 80 ¹⁹; or
 - (b) weight loss of $\geq 5\%$ body weight.^{19 28}
- There is no evidence that age or histological subtype significantly affects outcome.
- The evidence does not support the use of mediastinal irradiation for peripheral stage I tumours.^{16 17 22}
- The benefits of mediastinal irradiation for centrally placed stage I tumours are uncertain.
- There is some evidence to support the use of mediastinal irradiation in stage II tumours.³¹

IMPLICATIONS FOR RESEARCH

- Randomised studies should help to determine the optimal dose and fractionation, in particular whether conventionally fractionated courses with dose escalation or CHART (or similar) with dose escalation offer benefits over CHART to 54 Gy.
- Studies are needed to determine the functional consequences of irradiating small fields in patients with poor lung function; this would help to establish evidence based criteria for eligibility for radical radiotherapy on the basis of lung function.
- Randomised studies are urgently needed to evaluate the practice of routine irradiation of clinically uninvolved sites within the mediastinum. In such a trial, patients with stage II or central stage I tumours (possibly with PET scanning to exclude mediastinal involvement) might be randomised to receive either radiotherapy to involved sites only or

a two phase treatment (to the same total dose) with the first phase treating the whole mediastinum. Recording the mean lung dose and careful monitoring of lung function would be an essential part of such a study.

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A version of this review has been published in the Cochrane Library. Cochrane systematic reviews are regularly updated to include new research and in response to comments and criticism from readers.

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