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Meta-analysis

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Janneke P.C. Grutters [a,*], Alfons G.H. Kessels [b], Madelon Pijls-Johannesma [a], Dirk De Ruysscher [a], Manuela A. Joore [b,1], Philippe Lambin [a,1]

[a] Department of Radiation Oncology (MAASTRO Clinic), Maastricht University Medical Centre, The Netherlands
[b] Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, The Netherlands

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ABSTRACT

Purpose: To provide a comparison between radiotherapy with photons, protons and carbon-ions in the treatment of Non-Small-Cell Lung Cancer (NSCLC), performing a meta-analysis of observational studies. *Methods:* Eligible studies on conventional radiotherapy (CRT), stereotactic radiotherapy (SBRT), concurrent chemoradiation (CCR), proton therapy and carbon-ion therapy were searched through a systematic review. To obtain pooled estimates of 2- and 5-year disease-specific and overall survival and the occurrence of severe adverse events for each treatment modality, a random effects meta-analysis was carried out. Pooled estimates were corrected for effect modifiers. *Results:* Corrected pooled estimates for 2-year overall survival in stage I inoperable NSCLC ranged from 53% for CRT to 74% for carbon-ion therapy. Five-year overall survival for CRT (20%) was statistically significantly lower than that for SBRT (42%), proton therapy (40%) and carbon-ion therapy (42%). However, caution is warranted due to the limited number of patients and limited length of follow-up of the particle studies. *Conclusion:* Survival rates for particle therapy were higher than those for CRT, but similar to SBRT in stage I inoperable NSCLC. Particle therapy may be more beneficial in stage III NSCLC, especially in reducing adverse events.

Particle therapy (both protons and carbon-ions) has a better dose distribution compared to photons. This physical advantage of particle therapy can be used to reduce radiotherapy-induced adverse events by sparing normal tissue using similar dosage or to improve tumor control by giving a higher dose to the tumor but a similar dose to the normal tissue. Because of this theoretical advantage particle therapy gained increasing attention in the last decade.

Several papers were recently published that reviewed the effectiveness of particle therapy [1–5]. The main conclusion of these reviews was that there are almost no randomized clinical trials (RCTs) comparing particle therapy with conventional photon therapy. The lack of RCTs makes it difficult to draw firm conclusions about the clinical benefit of particle therapy. This resulted in an ongoing discussion about whether or not RCTs are required before particle therapy can become the treatment of choice for different types of cancer [6–12]. While it is acknowledged that implementation of new technologies should be evidence-based, it is questioned whether it is ethical to randomize patients to a radiotherapy delivery technique that has an obvious inferior dose distribution to normal tissue. The societal impact of this controversial topic is illustrated by the fact that also patients intervened in this discussion, stressing the importance of a meticulous consideration of all possible pros and cons [13].

For non-small cell lung cancer (NSCLC) only observational studies on particle therapy are published, mostly on stage I inoperable disease [4]. Although the results seem promising in comparison with conventional radiotherapy, stereotactic body radiotherapy (SBRT) also shows good results for these patients, comparable with the results of surgery [14]. Unfortunately, the available studies are difficult to compare as the study populations are often divergent. For example, the studies report on a mix of medically inoperable patients and patients who refused surgery. Medically inoperable patients are not sufficiently fit for surgery because of their poor condition. The difference in the percentage of medically inoperable patients between study populations may thus influence the study outcome, and hamper the comparison between different treatment modalities.

Even less data are available on the effectiveness of particle therapy in advanced NSCLC. Most patients with advanced NSCLC are poor in general health and concurrent chemotherapy can only be applied in combination with small irradiation target volumes. Because of its potential of sparing normal tissue, particle therapy may be especially beneficial in advanced stage NSCLC.

* Corresponding author. Address: Maastricht University, Dept. of Health Organization, Policy and Economics, P.O. Box 616, 6200 MD Maastricht, The Netherlands.
E-mail address: janneke.grutters@maastro.nl (J.P.C. Grutters).
[1] These authors contributed equally to this work.

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Despite the lack of randomized trials, decisions need to be made, and the single-arm studies are all the evidence that is currently available. The purpose of this paper is therefore to provide a comparison between radiotherapy with photons, protons and carbon-ions in the treatment of NSCLC, performing a meta-analysis based on published observational studies.

Methods

This meta-analysis was performed according to the guidelines proposed by the Meta-Analysis of Observational Studies in Epidemiology group [15].

Search strategy and selection criteria

A recent systematic literature review on particle therapy in lung cancer [4] was updated until August 2008 to identify the studies on the effectiveness of particle therapy. Since for CCR an extensive Cochrane review and meta-analysis on individual patient data were already performed, we decided to use the results from these studies for CCR [16,17]. The studies on the effectiveness of conventional radiotherapy alone (CRT), including hyperfractionated radiation schedules, and SBRT were identified through a predefined search. The following electronic databases were used: the Cochrane library, PubMed and MEDLINE, over the last 15 years (1994 to August 2008). The search included the following terms: ('lung cancer' or 'NSCLC') and ('Lung neoplasms/radiotherapy'[MESH terms] or 'Carcinoma, Non-Small-Cell Lung/radiotherapy'[MESH terms]) and 'survival'. Additional references were searched through manual searches of the reference lists and specialist journals.

The studies were included if they were written in English or Dutch, and if they reported original data and 2- or 5-year (disease-specific) survival results for one or more disease stage(s) separately. In accordance with the previous review on particle therapy [4], only the studies with more than 20 patients were included.

Data extraction

Two investigators (J.G. and M.P.J.) independently extracted relevant data from the studies. General characteristics were recorded from each study: first author, year of publication, study design, treatment type, sample size, dose per fraction, number of fractions, total dose, overall treatment time (OTT), study population (age, percentage of medically inoperable patients, percentage of patients with tumors smaller than 3 cm) and follow-up period. To compare the total doses we calculated the biological equivalent dose for tumor in 2 Gy fractions, corrected for the overall treatment time, using the formula $EQD_{2,T} = D * [(d + (\alpha/\beta))/(2 + (\alpha/\beta))] - [(T - T_{ref}) * D_{prolif}]$ [18]. In this formula D represents the total radiation dose, d the dose per fraction and T the overall treatment time. An α/β ratio of 10 Gy was used for tumor tissue [18]. The value for T_{ref} was chosen at 21 days (3 weeks). Before day 21 repopulation was assumed to be zero, while after day 21 the dose recovered per day in 2 Gy equivalent fractions (D_{prolif}) was assumed to be 0.6 Gy [18].

The 2- and 5-year overall and disease-specific survival rates were extracted from each study, as well as the occurrence of grade 3/4 pneumonitis, grade 3/4 oesophagitis, grade 3/4 irreversible dyspnoea and grade 5 adverse events (treatment-related death). Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 [19].

Data analysis

To obtain pooled estimates of the effectiveness of the different treatment modalities, a meta-analysis was used to determine weighted summary statistics for each of the treatments. If between-study variation was present, a random effect model was used to take this heterogeneity into account [20].

Since differences between the characteristics of the study populations may influence the effectiveness of different treatment modalities, we explored whether such effect modifiers were present. We did this by including each characteristic (age, percentage of tumors smaller than 3 cm, percentage of medically inoperable patients and follow-up period) in the regression model separately. The characteristics that had a statistically significant influence on the regression model were defined as effect modifiers. We corrected for these effect modifiers in the final meta-analysis by estimating the models for the overall mean value of that characteristic. We did this by calculating for each study how much the characteristic deviated from the overall mean for all studies. This difference was incorporated as an independent variable in the meta-regression model.

Missing data on the characteristics of the studies were handled using multiple imputation. Instead of filling in a single value for each missing value, Rubin's multiple imputation procedure generates m datasets, each of which replaces each missing value with a plausible value, that represent the uncertainty about the right value to impute [21]. With regression models the missing value of a specific variable is predicted using the other variables, i.e. the covariates and outcome. In the multiple imputation method the imputed variables are drawn from the density function as generated by the regression model [22]. This results in statistically valid inferences that properly reflect the uncertainty due to missing values. We created five datasets ($m = 5$).

Meta-analyses were performed to obtain pooled estimates for 2- and 5-year overall and disease-specific survival, as well as the occurrence of adverse events for each treatment modality. The data were managed in SPSS 15.0 and analyzed using STATA 9.

Results

Selected articles and characteristics

Regarding the search on CRT and SBRT, on the basis of the keywords, 1711 articles were found. Excluding papers with review as publication type left 1289, of which another 1102 were excluded based on the screening of the titles. Most excluded references were papers on chemoradiation, advanced stage NSCLC or planning studies. Of the remaining 187 references the abstracts were screened and, if necessary, the papers were retrieved and the data were analyzed. Of these 187 references another 159 were excluded based on the exclusion criteria. One additional reference on SBRT was retrieved through manual searches of the reference lists [23]. As two SBRT papers reported on patients in a Japanese multi-institutional study [24,25], only the most recent paper was included [25]. An earlier version of the paper as well as other studies from participating institutions was excluded, to prevent duplication [24,26–30]. Two other studies reported on the same patient population [23,31]. We chose to include the study by Hoyer et al. [23] as this was a prospective study with a stronger focus on survival and all patients received the same fractionation schedule, as opposed to the divergent fractionation schedules analyzed retrospectively by Baumann et al. [31]. Ultimately, 22 studies that met the inclusion criteria were identified: 11 studies on CRT [32–42] and 11 studies on SBRT [23,25,43–51].

The particle therapy review resulted in five studies on proton therapy [52–56] and three studies on carbon-ion therapy [57–59]. No additional references were found since the previous search [4]. The search on both particle therapy and photon therapy is illustrated in a flow diagram in Appendix 1.

All studies on particle therapy, CRT and SBRT reported results for stage I NSCLC separately. The results for stage II NSCLC were

only reported by two SBRT studies (n = 27) [47,51]. The results for stage III NSCLC were reported by two proton studies, each reporting on only 8 patients [52,56]. Due to the lack of the data for particle therapy on advanced stage NSCLC we decided not to include these patient groups in the meta-analysis.

The study characteristics for the included studies are tabulated in Table 1. We included both retrospective and prospective studies. One non-randomized study was found on proton therapy. In this study by Bush et al. the patients were assigned to the treatment arms based on cardiopulmonary function and the results were presented for the total group only [52]. All other included studies were single-arm studies.

The percentage of tumors smaller than 3 cm was very diverse, ranging from 19% to 100% in the studies on stage I disease. The percentage of medically inoperable patients ranged from 42% to 100%. The $EQD_{2,T}$ ranged from 32 to 176 Gy between the studies, and also ranged within the studies.

Exploration of influencing baseline characteristics

Entering age, percentage of small tumors (<3 cm) and median follow-up in the random effect meta-regression model did not influence the treatment coefficients and increased the variance of these coefficients. This indicates that these characteristics were not modifying the results and should not be corrected for. Only the percentage of medically inoperable patients was found to statistically significantly influence the coefficients and reduce the variance of the coefficients in the model. We therefore corrected the outcomes in the meta-analysis for differences in the percentage of medically inoperable patients only. This means that the corrected pooled estimates apply to a study population with 82% medically inoperable patients, which was the mean for all studies.

Survival for stage I NSCLC after two years

All but one [53] study reported 2-year overall survival (Fig. 1). The results of the random effect meta-analysis on 2-year overall survival are presented in Table 2. The corrected 2-year overall survival estimates and their 95% confidence intervals were 53% (46–60%) for CRT, 70% (63–77%) for SBRT, 61% (47–75%) for proton therapy and 74% (61–86%) for carbon-ion therapy. The uncorrected 2-year survival estimates were slightly lower than the corrected estimates for CRT and SBRT, while the uncorrected estimates were higher than the corrected estimates for protons and carbon-ions (Fig. 1). The corrected pooled 2-year overall survival for CRT was statistically significantly lower than that for SBRT (p-value <0.001) and carbon-ion therapy (p-value 0.006). SBRT, proton therapy and carbon-ion therapy did not have statistically significantly different 2-year overall survival rates.

Six CRT studies [33,35,37–39,41], six SBRT studies [23,43,45,46,48,51], three proton studies [53,54,56], and three carbon-ion studies [57–59] reported 2-year disease-specific survival. The corrected 2-year disease-specific survival estimates and their 95% confidence intervals were 67% (59–76%) for CRT, 83% (75–92%) for SBRT, 74% (61–87%) for proton therapy and 82% (70–93%) for carbon-ion therapy (Table 2). The pooled 2-year disease-specific survival rate for CRT was statistically significantly lower than that for SBRT (p-value 0.006). The differences in 2-year disease-specific survival between SBRT, proton therapy and carbon-ion therapy were not statistically significant.

Survival for stage I NSCLC after five years

Ten studies on CRT [32–38,40–42], five studies on SBRT [25,43,45,46,51], two studies on proton therapy [55,56] and all three studies on carbon-ion therapy [57–59] reported 5-year overall survival (Fig. 2). Because of the limited follow-up in both the SBRT and particle studies, 5-year outcomes should be interpreted with caution.

The corrected pooled estimates for 5-year overall survival and their 95% confidence intervals were 19% (15–24%) for CRT, 42% (34–50%) for SBRT, 40% (24–55%) for proton therapy and 42% (32–52%) for carbon-ion therapy (Table 3). Correcting for the percentage of medically inoperable patients in a study population increased the survival rate of CRT, but lowered the pooled estimates of SBRT, proton therapy and carbon-ion therapy (Fig. 2). The corrected pooled 5-year overall survival for CRT was statistically significantly lower than that for SBRT (p-value <0.001), proton therapy (p-value 0.014) and carbon-ion therapy (p-value <0.001). SBRT, proton therapy and carbon-ion therapy did not have statistically significantly different 5-year overall survival.

Five CRT studies [33,35,37,38,41], five SBRT studies [25,43,45,46,51], two proton studies [53,56], and three carbon-ion studies [57–59] reported 5-year disease-specific survival. The corrected pooled estimates for 5-year disease-specific survival ranged from 43% for CRT to 64% after carbon-ion therapy (Table 3). Five-year disease-specific survival for CRT (43%) was statistically significantly lower than that for SBRT (63%; p-value 0.045).

Occurrence of adverse events

In stage I NSCLC the occurrence of severe adverse events (CTCAE grade 3–5 [19]) was infrequent for all treatment modalities. The majority of studies reported zero adverse events. Combining studies with zero events is problematic because continuity corrections are needed, which can influence the results [60]. To avoid the use of continuity corrections we decided to add up the adverse events occurring for each treatment modality, instead of pooling the estimates using a meta-regression. The total occurrence of each adverse event per treatment modality, as well as the number of patients at risk, is listed in Table 4. Proportions and 95% confidence intervals were calculated using a binomial distribution. The number of patients at risk varies because not all studies reported all adverse events. In Table 4 we therefore also reported which studies were used to derive each figure.

Overall, the SBRT studies reported somewhat more adverse events than the CRT studies, mainly regarding pneumonitis and treatment-related death. However, the six treatment-related deaths after SBRT were all from a single study with a high biological equivalent dose and including peripherally located tumors [50]. This study also reported eight cases of grade 3/4 adverse events, but because they did not specify the types of adverse events, these were not incorporated in the count. The SBRT studies also reported more adverse events than the proton and carbon-ion studies, which is only partly attributable to the lower number of patients at risk in the particle therapy studies. Particle therapy resulted in no grade 3/4 oesophagitis, dyspnoea or treatment-related deaths, while only 4 out of 336 patients with stage I NSCLC treated with particle therapy had grade 3/4 pneumonitis.

Discussion

To the best of our knowledge, this meta-analysis was the first to pool the effectiveness of CRT, SBRT, proton therapy and carbon-ion therapy in the treatment of stage I NSCLC, to allow for a comparison between particle therapy and photon therapy. A total of 30 studies met the inclusion criteria and were used in the meta-analysis. Two- and five-year (disease-specific) survival rates, corrected for differences in the percentage of medically inoperable patients in the studies, were lower for CRT than for the other treatment modalities. The corrected survival rates for SBRT, proton therapy and carbon-ion therapy were comparable. Because of the limited follow-up in both the SBRT and particle studies, 5-year outcomes

Table 1
Study and population characteristics for studies on stage I NSCLC.

First author	Year	Study design	Treatment type	Sample size	Fraction dose (Gy)	Fraction number	Total dose (Gy)	OTT (weeks)	$EQD_{2,T}$	Median/*mean* age (range)	% tumors < 3 cm	% Medically inoperable	Median FU in months (range)
Gauden [30]	1995	R	CRT	347	2.5	20	50	4	48	70 (34–90)	48	64	22
Krol [36]	1996	R	CRT	108	2.5–3	20–26	60–65	5–7	51–57	*74* (56–88)	47	94	NR
Jeremic [40]	1997	P	CRT	49	1.2	58	70	6	54	63 (51–70)	51	59	NR
Morita [32]	1997	R	CRT	149	2	27–38	55–74	5–8	46–57	*74* (50–89)	40	83	91
Sibley [33]	1998	R	CRT	141	1.8–3	NR	50–80	4–10	NC	70 (46–95)	54	99	24 (7–132)
Hayakawa [35]	1999	R	CRT	36	2	30–40	60–81	6–8	47–59	NR	19	89	NR
Firat [34]	2002	R	CRT	50	NR	NR	31–77	NR	NC	69 (52–83)	50	NR	NR
Lagerwaard [31]	2002	R	CRT	113	2–2.5	28–35	60–72	5–7	47–60	74 (49–87)	58	90	29
Bradley [37]	2003	P	CRT	56	1.8–2	30–42	60–84	6–8	42–63	73 (52–90)	55	100	20 (15–72)
Fang [39]	2006	R	CRT	85	NR	NR	45–90	NR	NC	73	64	82	19 (2–77)
Din [38]	2008	P/R	CRT	192	1.5	36	54	2	57	71*	39	NR	Minimum 24
Uematsu [44]	2001	R	SBRT	50	5–12	5–10	50–60	1–2	63–110	71 (54–86)	48	42	36
Hoyer [21]	2006	II	SBRT	40	15	3	45	1	94	70 (46–80)	55	100	29 (13–58)
Nyman [43]	2006	P	SBRT	45	15	3	45	1	94	*74* (58–84)	40	100	43 (24–74)
Timmerman [48]	2006	II	SBRT	70	20–22	3	60–66	1–2	150–176	70 (51–86)	50	100	18 (1–44)
Zimmermann [46]	2006	I/II	SBRT	68	6–12.5	3–5	24–40	NR	32–50	*76* (59–92)	100	100	17 (3–44)
Xia [45]	2006	P	SBRT	25	7	10	70	2	99	*71* (44–88)*	42	100	27 (24–54)
Koto [41]	2007	II	SBRT	31	7.5–15	3–8	45–60	1–2	88–94	*77* (60–83)	61	65	32 (4–87)
Onishi [23]	2007	R	SBRT	257	4.4–35	1–14	30–84	NR	NC	74 (39–92)	64	61	38 (2–128)
Scorsetti [47]	2007	P	SBRT	43	7–10	2–4	20–32	NR	33–40	*74* (52–90)	67	100	14 (6–36)
Lagerwaard [42]	2008	P	SBRT	206	7.5–20	3–8	60	NR	90–150	73	59	81	12 (3–44)
Salazar [49]	2008	P	SBRT	60	13	4	52	3	100	*75* (53–93)*	75	100	38 (2–84)
Bush [50]	1999	P	Proton	26	1.8–5.1	10–41	51–74	2–5	64	*72* (54–87)*	44	NR	14 (3–44)
Shioyama [54]	2003	R	Proton	28	2–6	7–32	49–93	1.5–11	NC	74 (25–87)*	32	NR	30 (18–153)
Bush [51]	2004	II	Proton	68	5.1–6	10	51–60	2	64–80	*72* (52–87)	43	93	NR
Nihei [53]	2006	R	Proton	37	3.5–4.7	20	70–94	4–5	70–111	75 (63–87)	46	62	24 (3–62)
Hata [52]	2007	P	Proton	21	5–6	10	50–60	2	63–80	74 (51–85)	52	43	25 (10–54)
Miyamoto [57]	2003	I/II	Carbon-ion	81	3.3–8.8	9–18	59–95	3–6	53–124	*72* (47–85)	50	74	53
Miyamoto [56]	2007	II	Carbon-ion	50	8	9	72	3	108	*74* (61–84)	59	66	59 (6–83)
Miyamoto [55]	2007	I/II	Carbon-ion	79	13.2–15	4	53–60	1	102–125	*75* (47–88)	53	78	39 (3–72)

Abbreviations: Gy, gray (for particle therapy gray equivalent (GyE) or cobalt gray equivalent (CGE)); $EQD_{2,T}$, biological equivalent dose for the tumor in 2 Gy fractions corrected for time (for SBRT studies when no OTT was reported we assumed an OTT < 21 days); OTT, overall treatment time; FU, follow-up; P, prospective; R, retrospective; I, Phase I; II, Phase II; CRT = conventional radiotherapy with photons; SBRT, stereotactic body radiotherapy with photons; NR, not reported; NC, not calculable.

* Population characteristics are for total study population, including other disease stages.

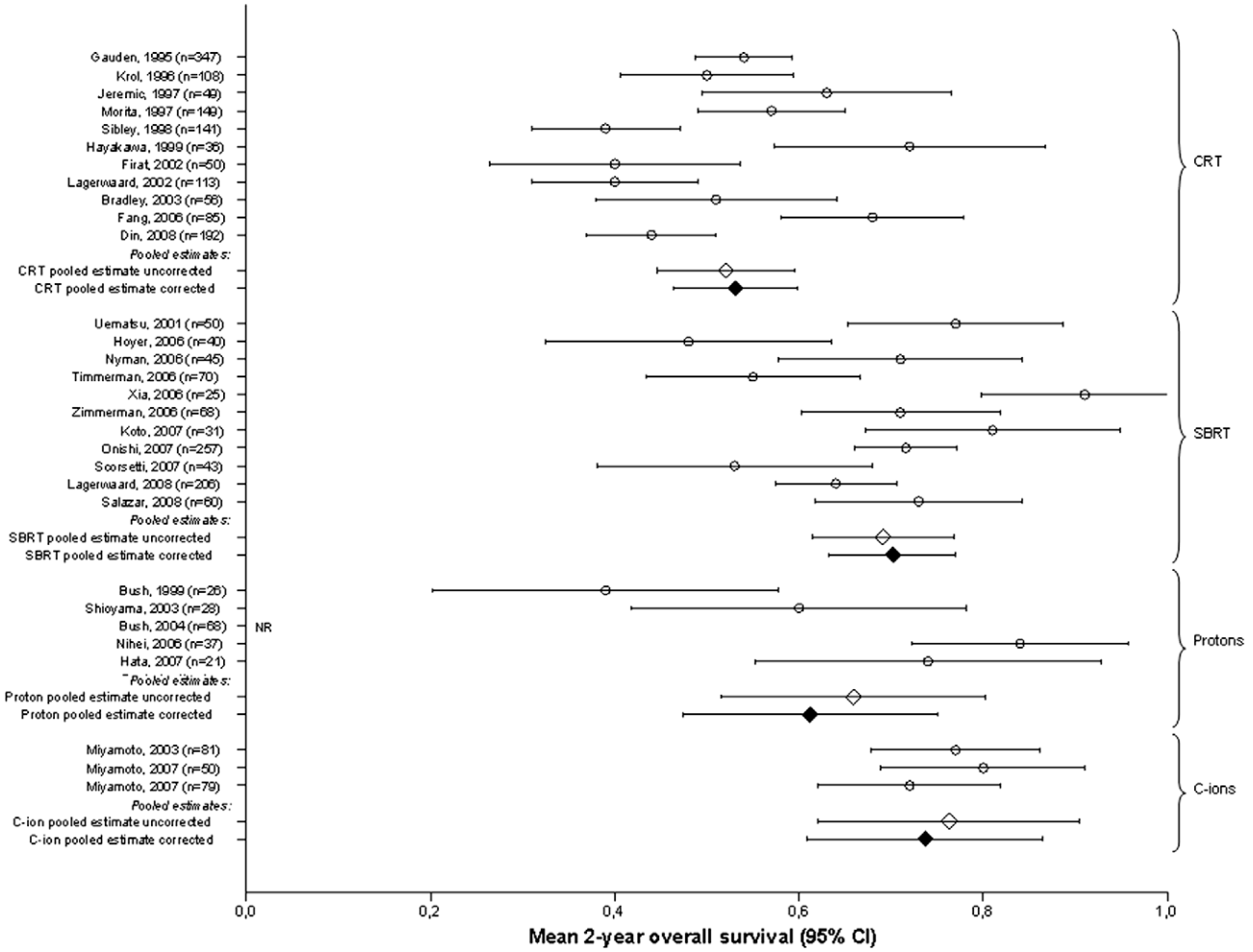

Fig. 1. Overview of 2-year overall survival and 95% confidence intervals for all studies and pooled estimates, uncorrected and corrected for percentage of medically inoperable patients, per treatment modality (NR, not reported).

Table 2
Results of meta-analysis for 2-year (disease-specific) survival.*

Treatment	2-year overall survival	(95% CI)	*p*-Value**		
			SBRT	Protons	Carbon-ions
CRT	0.531	(0.464–0.599)	<0.001	0.310	0.006
SBRT	0.702	(0.633–0.770)		0.262	0.638
Protons	0.612	(0.474–0.750)			0.180
Carbon-ions	0.737	(0.609–0.864)			
	2-year disease-specific survival				
CRT	0.674	(0.587–0.761)	0.006	0.430	0.065
SBRT	0.834	(0.751–0.917)		0.246	0.797
Protons	0.740	(0.607–0.874)			0.391
Carbon-ions	0.815	(0.700–0.930)			

Abbreviations: CI, confidence interval; CRT, conventional radiotherapy; SBRT, stereotactic body radiotherapy.
* Pooled estimates are based on a study population with 82% medically inoperable patients.
** *p*-Value for the difference between the treatments.

should however be interpreted with caution. Particle therapy and conventional radiotherapy appeared to result in less adverse events than SBRT, but adverse events were difficult to compare due to poor or incongruous reporting. Due to a lack of data no pooled estimates were derived for more advanced stages of NSCLC.

The application of formal meta-analytic methods to observational studies has been controversial [61]. One of the most important reasons for this is that the designs and populations of the studies are diverse, and that these differences may influence the pooled estimates. However, when no RCTs are available, as is the case for particle therapy in lung cancer, a meta-analysis of observational studies is one of the few methods for assessing efficacy and effectiveness [15]. Moreover, it represents the uncertainty surrounding the pooled estimates, and is a valuable method to inform the decision whether more evidence is needed, which is a timely discussion topic with regard to particle therapy [6–13]. When studies are well documented, a meta-analysis also allows to correct for potentially modifying differences between study populations or designs, as has been done in the current study. However, potential bias may have occurred because the CRT studies were overall older than the SBRT and particle

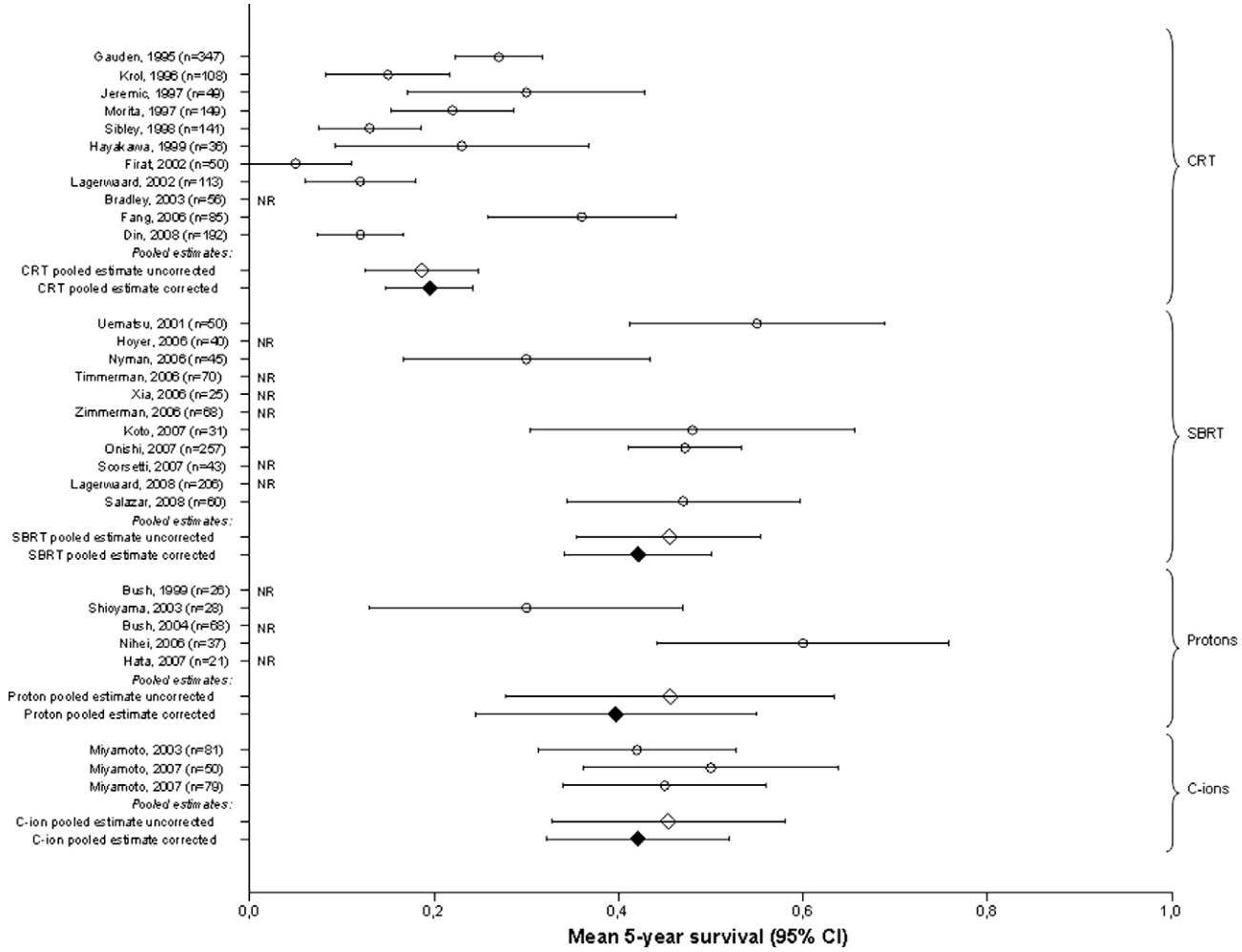

Fig. 2. Overview of 5-year overall survival and 95% confidence intervals for all studies and pooled estimates, uncorrected and corrected for percentage of medically inoperable patients, per treatment modality (NR, not reported).

Table 3
Results of meta-analysis for 5-year (disease-specific) survival.*

Treatment	5-year overall survival	(95% CI)	*p*-Value**		
			SBRT	Protons	Carbon-ions
CRT	0.195	(0.148–0.242)	<0.001	0.014	<0.001
SBRT	0.421	(0.341–0.501)		0.782	0.985
Protons	0.397	(0.245–0.550)			0.790
Carbon-ions	0.421	(0.322–0.520)			
	5-year disease-specific survival				
CRT	0.435	(0.311–0.559)	0.045	0.471	0.051
SBRT	0.627	(0.500–0.754)		0.389	0.999
Protons	0.521	(0.319–0.724)			0.353
Carbon-ions	0.643	(0.486–0.801)			

Abbreviations: CI, confidence interval; CRT, conventional radiotherapy; SBRT, stereotactic body radiotherapy.
* Pooled estimates are based on a study population with 82% medically inoperable patients.
** *p*-Value for the difference between the treatments.

studies. This may have underestimated the pooled estimates for CRT, since oncology care as well as disease staging for NSCLC has improved considerably in the last decade [62]. In the present analysis studies were included regardless of their follow-up period. This can be criticized, especially with regard to the 5-year outcomes. However, we feel that, although they are uncertain and should be handled carefully, the 5-year outcomes are of importance to the present study. We therefore decided to include all studies in the analyses that reported 5-year results, although we emphasize that the results of these analyses should be interpreted with caution.

Although meta-analyses of observational studies can be a solution when no RCTs are available, this method can only be used when sufficient observational data are available. We did not pool the occurrence of adverse events in a meta-regression due to the many studies with zero adverse events. Also, due to a lack of data we were unable to pool the effectiveness of proton and carbon-ion treatment for more advanced stages of NSCLC. Promising results for proton therapy in stage III disease were presented by Shioyama et al. [56], but these results were only based on 9 patients and are therefore excluded from the current analysis. Additionally, preli-

Table 4
Occurrence of adverse events grade 3–5* for each treatment modality in patients with stage I NSCLC.

Treatment	*N* events	*N* at risk	Proportion	(95% CI**)	Source	*N* events	*N* at risk	Proportion	(95% CI**)	Source
	Pneumonitis grade 3/4					*Oesophagitis grade* 3/4				
CRT	2	867	0.0023	(0.0003–0.0083)	[30,32,33,35–37,40]	1	831	0.0012	(0.0000–0.0067)	[30,32,33,35–37,40]
SBRT	16	800	0.0200	(0.0115–0.0323)	[21,23,41–44,46,47,49]	2	840	0.0024	(0.0003–0.0086)	[21,23,41–44,46–49]
Protons	1	126	0.0079	(0.0002–0.0434)	[51–53]	0	126	0.0000	(0.0290)	[51–53]
Carbon-ions	3	210	0.0143	(0.0030–0.0412)	[55–57]	nr	nr	-	-	
	Irreversible dyspnoea grade 3/4					*Treatment-related death* (*grade* 5)				
CRT	5	980	0.0051	(0.0017–0.0119)	[30–33,35–37,40]	1	980	0.0010	(0.0000–0.0057)	[30–33,35–37,40]
SBRT	6	769	0.0078	(0.0029–0.0169)	[21,23,42–44,46,47,49]	6	870	0.0069	(0.0025–0.0150)	[21,23,41–44,46–49]
Protons	0	58	0.0000	(0.0620)	[52,53]	0	126	0.0000	(0.0290)	[51–53]
Carbon-ions	0	210	0.0000	(0.0170)	[55–57]	0	210	0.0000	(0.0170)	[55–57]

Abbreviations: CRT, conventional radiotherapy; SBRT, stereotactic body radiotherapy; CI, confidence interval.
* Adverse events were graded in accordance with the CTCAE scoring system [19].
** When the number of events was 0, only the upper limit of the confidence interval was calculated.

minary results from conference presentations indicated that for stage III NSCLC proton therapy combined with chemotherapy results in less adverse events than IMRT and chemotherapy [63–65]. Unfortunately it will take a number of years before survival results can be derived from this study. Nevertheless, these preliminary results emphasize the potential clinical benefit of particle therapy in advanced NSCLC, being a reduction of adverse events and higher survival due to a higher radiation dose to the tumor.

A number of literature reviews that separately addressed the effectiveness of CRT [66–69], SBRT [70] and particle therapy [1–5] were published recently. Although no actual meta-analysis of particle therapy in NSCLC has been published until now, there has been an attempt to calculate pooled estimates for the effectiveness of particle and photon therapy by Lodge et al. [2]. These estimates were on average lower than the pooled estimates presented in the current study. This difference can be explained by two main factors. First, Lodge et al. used a different method than our random effects meta-analysis and their estimates are unweighted. Second, the present review included more recent studies, and especially these newer studies tend to show better results.

Regarding potential effect modifiers, the present study found that the difference in the percentage of medically inoperable patients between the study populations significantly influenced the outcome. It was already shown in previous studies that operable patients who had refused surgery had better outcomes than medically inoperable patients [24,25,46]. The low percentage of medically inoperable patients in some particle studies may therefore overstate the effectiveness of particle therapy. In the present study we found that correcting for differences in the percentage of medically inoperable patients indeed resulted in lower pooled estimates for particle therapy. However, four studies did not report the percentage of medically inoperable patients in their study population. Although we tackled this using multiple imputation on our missing data, this emphasizes the importance that authors fully document the characteristics of the study populations in their papers. The difference in percentage of small (<3 cm) tumors between study populations was not found to influence the results of the meta-analysis. Although smaller stage I tumors are associated with higher expected survival [68], differences in the percentage of small tumors between the study populations were not modifying the results of the meta-analysis for stage I inoperable NSCLC.

Another possible source of bias is selection bias. SBRT and especially particle therapy are highly specialist treatments, only available to a limited number of patients. By examining and correcting for influencing characteristics we have tried to eliminate selection bias as much as possible.

In the SBRT and particle studies, higher doses are given to the tumor, which is likely to, at least partly, explain the higher survival for these treatments as opposed to conventional radiotherapy. Hence, if it were possible to give such higher doses to the tumor using conventional radiotherapy, CRT would probably show better survival results.

In stage I NSCLC, especially for proton therapy, large uncertainty exists on the effectiveness of particle therapy. While the two most recent proton studies showed promising results, the older studies showed lower survival results. This may be the result of improved fractionation schedules or techniques. For carbon-ion therapy there is less variation and thus uncertainty, presumably because all studies are from the institution in Chiba, Japan. For a long time Chiba was the only carbon ion institute in the world, but carbon-ion facilities are currently under construction in Italy and Germany. However, it obviously takes a number of years before survival data from these institutes will be published.

The present study shows that although RCTs generate the highest level of evidence, observational studies can also be used to compare the effectiveness of different treatment modalities. It is however important that the observational studies are well documented and present similar endpoints.

From the results of this meta-analysis of observational studies it is clear that particle therapy results in higher survival rates than CRT in stage I inoperable NSCLC patients. However, the survival rates of particle therapy are equal to those of SBRT in these patients. Based on the currently available data, although preliminary results show a trend towards less adverse events with particle therapy than with photon therapy, no firm conclusions can be drawn on the reduction of side effects after particle therapy. Particle therapy may be more beneficial in stage III NSCLC, where 2-year survival is only 26–36% with concurrent chemoradiation with photons, and severe adverse events occur more frequently. However, more evidence is needed on whether particle therapy is actually beneficial in advanced stage NSCLC.

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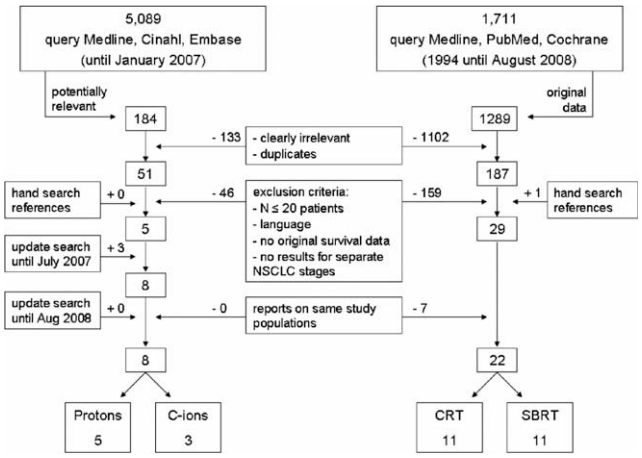
Appendix 1. Flow diagram of the search results for particle therapy (left) and photon therapy (right)



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