Cost Effectiveness of Modified Fractionation Radiotherapy versus Conventional Radiotherapy for Unresected Non–Small-Cell Lung Cancer Patients

Bram L.T. Ramaekers, MSc,† Manuela A. Joore, PhD,*† Béranger Lueza, MSc,‡ Julia Bonastre, PhD,‡ Audrey Mauguen, MSc,‡ Jean-Pierre Pignon, MD, PhD,‡ Cecile Le Pechoux, MD,§ Dirk K.M. De Ruysscher, MD, PhD,‖¶ MAR-LC Collaborative Group,# and Janneke P.C. Grutters, PhD***

Introduction: Modified fractionation radiotherapy (RT), delivering multiple fractions per day or shortening the overall treatment time, improves overall survival for non -small-cell lung cancer (NSCLC) patients compared with conventional fractionation RT (CRT). However, its cost effectiveness is unknown. Therefore, we aimed to examine and compare the cost effectiveness of different modified RT schemes and CRT in the curative treatment of unresected NSCLC patients.

Methods: A probabilistic Markov model was developed based on individual patient data from the meta-analysis of radiotherapy in lung cancer (N = 2000). Dutch health care costs, quality-adjusted life years (QALYs), and net monetary benefits (NMBs) were compared between two accelerated schemes (very accelerated RT [VART] and moderately accelerated RT [MART]), two hyperfractionated schemes (using an identical (HRT^{I}) or higher (HRT^{H}) total treatment dose than CRT) and CRT.

Results: All modified fractionations were more effective and costlier than CRT (1.12 QALYs, €24,360). VART and MART were most effective (1.30 and 1.32 QALYs) and cost €25,746 and €26,208, respectively. HRT^{I} and HRT^{H} yielded less QALYs than the accelerated schemes (1.27 and 1.14 QALYs), and cost €26,199 and €29,683, respectively. MART had the highest NMB (€79,322; 95% confidence interval [CI], €35,478-€133,648) and was the most cost-effective treatment followed by VART (€78,347; 95% CI, €64,635-€92,526). CRT had an NMB of €65,125 (95% CI, €54,663-€75,537). MART had the highest probability of being cost effective (43%), followed by VART (31%), HRT^{I} (24%), HRT^{H} (2%), and CRT (0%).

Conclusion: Implementing accelerated RT is almost certainly more efficient than current practice CRT and should be recommended as standard RT for the curative treatment of unresected NSCLC patients not receiving concurrent chemo-radiotherapy.

Key Words: Radiotherapy, Dose fractionation, Non–small-cell lung cancer, Cost–benefit analysis, Markov chain.

(*J Thorac Oncol* 2013;8:1295–1307)

Non–small-cell lung cancer (NSCLC) comprises 85% of all lung cancer, which is the third most diagnosed form of cancer and causes the greatest number of cancer deaths.[1,2] Radiotherapy (RT) with or without chemotherapy is increasingly being used in the curative treatment for unresected NSCLC.[3] The therapeutic effect of radiation alone in lung cancer follows a clear dose–response relationship (i.e., higher biological doses lead to better local tumor control).[4–6] Hence, as recently shown by an individual patient meta-analysis,[7] modified fractionation RT schemes, with increased biological dose, have the ability to improve overall survival (OS) compared with conventional RT schedules (hazard ratio [HR], 0.88). Additionally, modified RT increased the risk of acute esophageal toxicity.[7]

With regard to the scarcity of resources and accelerating costs of cancer care, it is increasingly important to consider the cost–benefit ratio of (new) treatments to guide decision making.[8,9] Economic evaluations are frequently performed using decision-analytic modeling to synthesize different sources of evidence (e.g., effectiveness, patient-reported outcomes and costs), compare the cost effectiveness of competing interventions and support decision making under uncertainty.[9] As cost-effectiveness estimates are inevitably surrounded by uncertainty, it is essential to characterize uncertainty in economic evaluations.[9] Although parameter uncertainty (as exact estimates for parameters such as effectiveness are often unknown) is frequently acknowledged in decision-analytic modeling, patient heterogeneity is often ignored.[10,11] The objective of the present study is to perform a cost-effectiveness analysis comparing multiple modified fractionation RT

*Department of Health Services Research, CAPHRI-School for Public Health and Primary Care, Maastricht University, Maastricht, The Netherlands; †Department of Clinical Epidemiology and Medical Technology Assessment (KEMTA), Maastricht University Medical Center, Maastricht, The Netherlands; ‡Service Biostatistique et Epidémiologie, and §Département d'Oncologie et de Radiothérapie, Gustave Roussy, Villejuif, France; ‖Department of Radiation Oncology (MAASTRO), GROW-School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, The Netherlands; ¶Department of Radiation Oncology, University Hospital Leuven/KU Leuven, Leuven, Belgium; #List of the members of Meta-Analysis of Radiotherapy in Lung Cancer Collaborative Group is given at the end of the acknowledgments; and **Department of Epidemiology, Biostatistics and HTA, University Medical Center, St. Radboud, Nijmegen, The Netherlands.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Bram L.T. Ramaekers, MSc, Maastricht University Medical Center, Box 5800, 6202 AZ Maastricht, The Netherlands. E-mail: bram.ramaekers@mumc.nl

ISSN: 1556-0864/13/0810-1295

schemes with conventional fractionation RT (CRT) in the curative treatment of unresected NSCLC while taking into account both parameter uncertainty and patient heterogeneity.

MATERIALS AND METHODS

Meta-Analysis of RT in Lung Cancer

The Meta-Analysis of Radiotherapy in Lung Cancer (MAR-LC) database was used as the primary data source. This database consists of individual patient data from 12 randomized clinical trials (RCTs) that compared conventional and modified fractionated RTs.[7] The 10 RCTs with a population of unresected NSCLC patients were selected for the present study. These RCTs accrued a total of 2000 patients between 1989 and 2006 (median follow-up, 6.9 years). In four trials, the same chemotherapy was administered in both arms either concomitantly with RT (2 trials) or as induction chemotherapy (2 trials). No chemotherapy was given in the other RTCs. Most patients were men (75%), aged 60 to 69 years (42%), and had squamous cell carcinoma (SCC; 60%) and stage III disease (83%). Performance status was good (Eastern Cooperative Oncology Group performance status = 0) for 43% of the patients.

Markov Model Description

A probabilistic decision-analytic Markov cohort model was developed. To compare competing interventions, this model aims to reflect the course of a disease using a hypothetical cohort of patients who transit between mutually exclusive health states.[9] These health states were based on whether patients were alive and presence of toxicity (Fig. 1). Subsequently, the expected costs and effects were estimated for conventional fractionated RT and four types of modified fractionation RT. These modified fractionation schemes are based on two types of modified fractionation and their combination: (1) *accelerated* RT schemes, which consist of a reduced overall treatment time (OTT) compared with conventional fractionation and (2) *hyperfractionated* RT schemes, which consist of a higher number of fractions with a smaller dose per fraction compared with conventional RT. Five schemes were compared using the MAR-LC database (Appendix 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A451):

1. *CRT (10 trials; N = 944)*: five weekly fractions of 1.8 to 2.0 Gy, accumulating to a total treatment dose (TTD) of 60 to 70 Gy.
2. *Very accelerated RT (VART; 6 trials; N = 700)*: reduced OTT with more than or equal to 50%, using an identical (±5%) or lower (5%–10%) TTD compared with CRT (OS HR, 0.88 [95% confidence interval (CI) 0.78–0.98] versus CRT).[7]
3. *Moderately accelerated RT (MART; 1 trial; N = 29)*: reduced OTT with 14% to 49%, using a TTD identical (±5%) to CRT (OS HR, 0.90 (95% CI, 0.52–1.54) versus CRT).[7]
4. *Hyperfractionated RT using identical TTD (HRT[I]; 2 trials, N = 164)*: the average dose per fraction is decreased to 1.75 Gy or lesser, using a TTD identical (±5%) to CRT (OS HR: 0.87 (95% CI, 0.69–1.10) versus CRT).[7]
5. *Hyperfractionated RT using higher TTD (HRT[H]; 1 trial; N = 163)*: the average dose per fraction is decreased to 1.75 Gy or lesser, using a higher (5%–15%) TTD than CRT (OS HR, 0.92 [95% CI, 0.74–1.15] versus CRT).[7]

A lifetime time horizon and a cycle time of 1 month were used. Additionally, a half-cycle correction was applied. Future costs and effects were discounted by rates of 4.0% and 1.5%, respectively, according to the Dutch pharmaco-economic guideline.

Because a model is a simplified representation of reality, assumptions about reality are inherent to modeling. The main assumptions were:

1. On the basis of an analysis of the Radiation Therapy Oncology Group database, acute toxicity was assumed to increase from start of radiotherapy up to 3 months after start of radiotherapy and to reverse afterwards for

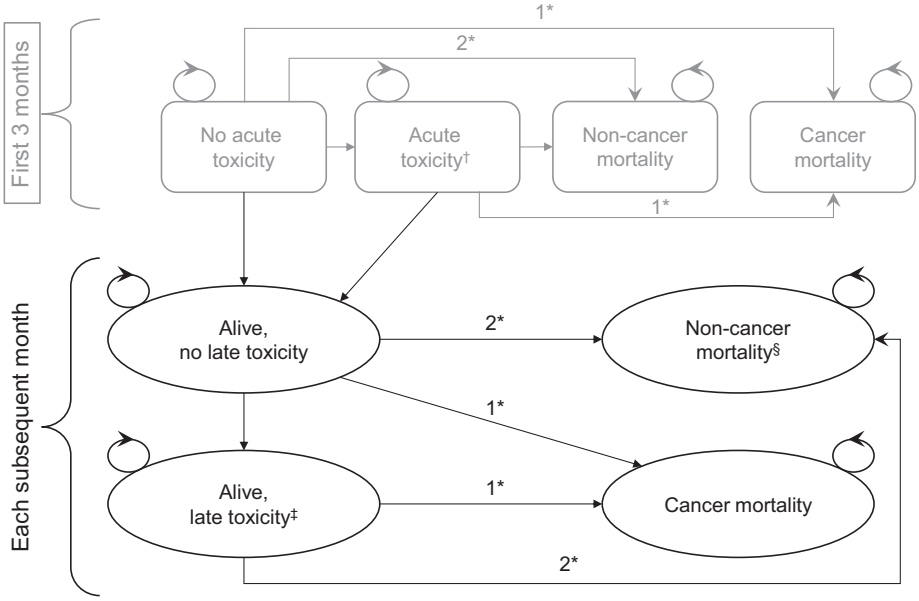


FIGURE 1. Diagrammatical representation of the Markov model structure. *The numbers (1 and 2) next to the arrows correspond to the Weibull models in Appendix 2 (Supplemental Digital Content 1, http://links.lww.com/JTO/A451). †Acute toxicity included grade 3 or higher pulmonary toxicity, esophageal toxicity, and hematological toxicity (see Appendix 3 [Supplemental Digital Content 1, http://links.lww.com/JTO/A451] for the corresponding logistic regression models). ‡Late toxicity included grade 3 or higher pulmonary toxicity and esophageal toxicity (Table 1). §Noncancer mortality was defined as deaths resulting from causes other than cancer and not occurring after disease progression.

TABLE 1. Input Parameters: Probabilities and Health State Utility

Parameter		Estimated Value	SE	Distribution	Source
Probabilities					
Probability of noncancer mortality		Dependent on time and patient characteristics Appendix 2			
Probability of cancer mortality		Dependent on time and patient characteristics Appendix 2			
Probability of acute pulmonary toxicity		Dependent on patient characteristics Appendix 3			
Probability of acute esophageal toxicity		Dependent on patient characteristics Appendix 3			
Probability of acute hematological toxicity		Dependent on patient characteristics Appendix 3			
Probability of late pulmonary toxicity[a]		15.4%	1.2%	Beta	MAR-LC
Probability of late esophageal toxicity[a]		3.3%	0.6%	Beta	MAR-LC
Health state utility					
No recurrence	No toxicity	0.800	0.029	Beta	[16]
	Acute hematological toxicity[b]	0.710			[16,33]
	Acute pulmonary toxicity[c]	0.493	0.075	Beta	[16]
	Acute esophageal toxicity[c]	0.493	0.075	Beta	[16]
	Late pulmonary toxicity[c]	0.493	0.075	Beta	[16]
	Late esophageal toxicity[c]	0.493	0.075	Beta	[16]
Recurrence	No toxicity	0.794	0.038	Beta	[16]
	Acute hematological toxicity[b]	0.704			[16,33]
	Acute pulmonary toxicity[c]	0.129	0.061	Beta	[16]
	Acute esophageal toxicity[c]	0.129	0.061	Beta	[16]
	Late pulmonary toxicity[c]	0.129	0.061	Beta	[16]
	Late esophageal toxicity[c]	0.129	0.061	Beta	[16]

[a]It was assumed that late toxicity increases from 3 months after start radiotherapy up to 18 months after start of radiotherapy to the total probability. The monthly probability was then calculated from the total probability using the following formula:[9]

$$p\ (1\ \text{month}) = 1 - e^{(\ln(1-p\ (\text{total}))\ \times\ 1/15)}.$$

[b]This health state utility was calculated based the utilities without toxicity, as given by Grutters et al.,[16] and a disutility from the study by Nafees et al.[33]

[c]It was assumed that patients with acute or late esophageal or pulmonary toxicity had the same utility scores.

NSCLC, non–small-cell lung cancer; MAR-LC, Meta-Analysis of Radiotherapy in Lung Cancer.

all patients.[12] Late toxicity was assumed to be irreversible, to begin 3 months after start of RT and to increase in frequency up to 1.5 years, with the assumption that it had plateaued.[12]

2. There is no overlap between toxicities, that is, a patient can only have one toxicity and not, for example, both pulmonary and esophageal toxicities concurrently. However, one patient can have different acute and late toxicities. No overlap between toxicities was assumed because there was only limited overlap in the MAR-LC database (3.1% for acute and 0.1% for late toxicity). Incorporating overlapping toxicities would unnecessarily increase the complexity and hence decrease the transparency of the model.
3. As mentioned above, modified RT may reduce noncancer mortality (most likely because of differences in treatment-related death).[7] Nevertheless, we conservatively assumed that there is no difference in noncancer mortality between the RT schemes. This was assumed because noncancer mortality, which included treatment-related deaths, was not reported for MART.

Transition Probabilities

Time-dependent survival probabilities were estimated by means of parametric survival models, using a Weibull distribution (Appendix 2, Supplemental Digital Content 1, http://links.lww.com/JTO/A451).[13] Separate Weibull regression models were developed for noncancer mortality and cancer mortality. Logistic regression models were developed to estimate acute toxicity (grade ≥3) probabilities, separately for acute pulmonary, esophageal, and hematological toxicity (Appendix 3, Supplemental Digital Content 1, http://links.lww.com/JTO/A451). All regression models were stratified by trial to preserve randomization and obtain unbiased estimates.[14] Potential heterogeneity in baseline risks was acknowledged through these regression models using the following covariates: treatment arm (CRT; VART; MART; HRT^{I}; HRT^{H}), sex (male; female), age (≤59 years; 60–69 years; ≥70 years), performance status (mild; good), histology (SCC; non-SCC), and disease stage (I/II; IIIA; IIIB). All variables were included in the initial model as categorical variables. Selection of covariates was performed as described by Hosmer et al.[15] except for the treatment arm variable. The treatment arm variable was not included in the Weibull model to predict noncancer mortality, and was always included in the Weibull regression model that predicts cancer mortality. Individual characteristics were needed to calculate the acute toxicity probabilities, using the logistic regression models. For this purpose, a hypothetical cohort of individual patients was replicated based on average characteristics and their correlations from the MAR-LC database

(Appendix 3, Supplemental Digital Content 1, http://links.lww.com/JTO/A451).

To estimate late pulmonary and esophageal toxicity (grade ≥3), the proportions from the MAR-LC database were used. Consistent with the meta-analysis, late toxicity was assumed to be equal for all comparators (Table 1).[7] All parameters retrieved from the MAR-LC database were computed in the Department of Biostatistics and Epidemiology of Institut de Cancérologie Gustave-Roussy by Lueza and Ramaekers.

Effects and Costs

Utility scores were used as effect measure. Utility is a single score measure for generic health-related quality of life and ranges from 0 (death) to 1 (full health). These utility scores were combined with life expectancy to calculate quality-adjusted life years (QALYs). Utility scores were derived from a Dutch cross-sectional study ($n = 260$),[16] which used the Euroqol-5D[17] questionnaire. Patients with unresected NSCLC ($n = 85$) were selected from this study (Table 1).

Patients who died because of NSCLC in the Markov model were assigned a disutility. This was the average disutility for recurrent disease (0.152) multiplied by the average life expectancy after recurrent disease (6 months in the MAR-LC database).

Costs were calculated using the Dutch health care perspective and converted to the 2011 price level, based on price indices from Statistics Netherlands (CBS). Resource use and unit prices are reported in Table 2.

Markov Model Analysis

Expected life years (LYs), QALYs, costs and net monetary benefit (NMB) were estimated for all comparators. The NMB was calculated by multiplying the number of QALYs with the ceiling ratio and subtracting the total costs. The treatment strategy with the highest NMB is considered as most cost effective. We adopted a ceiling ratio of €80,000, because this is the informal ceiling ratio for a high burden of disease in The Netherlands.[18] The incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental costs by the incremental QALYs. The ICER represents the costs of an additional QALY gained and was used to estimate the cost effectiveness of a treatment (1) opposed to CRT and (2) opposed to the next best alternative. A treatment is deemed cost effective when its ICER is below the ceiling ratio.

The Markov model was analyzed in Microsoft Excel 2003 (computer software; Microsoft Corporation, Redmond, WA). The analyses required to retrieve the input parameters were performed in SAS version 9.2 (SAS Institute, Cary, NC), except the Weibull analysis, which was performed in R version 2.13.1 (open-source computer software; R Foundation, Vienna, Austria), as SAS did not support stratification by trial in this analysis.

Parameter Uncertainty

To explore the impact of parameter uncertainty on the estimated (cost) effectiveness, probabilistic sensitivity analysis was performed using Monte Carlo simulation (15,000 iterations).[9] For this purpose, a distribution was assigned to the input parameters (Tables 1 and 2). The Weibull and logistic regression models were included using Cholesky decompositions.[9] Cost-effectiveness acceptability curves were created to show for different ceiling ratios the probability that a treatment is most cost effective.[9]

Because the estimated cost effectiveness is surrounded by uncertainty it is possible that based on current information, the *wrong* decision is being made. The expected value of perfect information (EVPI) analysis quantifies the costs of this decision uncertainty. It estimates the value of further research to gain knowledge of the *true* parameter values.[9] Thus, the EVPI represents the upper limit that society should be willing to pay to reduce decision uncertainty and inform the decision in the future.[9] The EVPI per patient was multiplied by the effective population in the next 5 years (expected lifespan of the technology) and discounted by a rate of 4% to calculate the population EVPI. The effective population was calculated based on a yearly incidence of 8661 NSCLC patients in The Netherlands (Dutch Cancer Registration, 2010) minus the estimated proportion of resected NSCLC patients (20%) and the estimated proportion with metastatic disease among unresected patients (40%), this resulted in an annual population of 4157 patients. To identify the most valuable research topics, the expected value of partial perfect information (EVPPI) for (groups of) parameters was calculated.

Heterogeneity

The expected value of individualized care (EVIC) was calculated to examine the impact of patient heterogeneity on cost effectiveness.[19,20] The EVIC estimates the value of providing the optimal treatment for each individual instead of the average best treatment for all patients. The same hypothetical cohort of individual patients as for the logistic regressions was used for this calculation (Appendix 3, Supplemental Digital Content 1, http://links.lww.com/JTO/A451). The EVIC per patient was estimated by calculating (1) the NMB of the optimal treatment per patient ($NMB_{patient\_max}$); (2) the NMB of the average best treatment ($NMB_{average\_max}$); (3) $EVIC_{patient} = NMB_{patient\_max} - NMB_{average\_max}$ for all individual patients; and (4) calculating the average $EVIC_{patient}$ and multiplying it by the effective population.

RESULTS

Expected survival ranged from 20 months for CRT (1.63 LYs) and HRT^H (1.66 LYs) to 22 months for HRT^I (1.83 LYs), up to 23 months for VART (1.88 LYs) and MART (1.90 LYs). MART was also the most effective treatment (1.32 QALYs) in terms of QALYs, followed by VART (1.30 QALYs), HRT^I (1.27 QALYs), HRT^H (1.14 QALYs), and CRT (1.12 QALYs).

HRT^H was most costly (€29,683), followed by MART (€26,208), HRT^I (€26,199), VART (€25,746), and CRT (€24,360). Costs differences were mainly because of differences in the number of fractions leading to differences in primary treatment costs.

CRT was both the least effective and least expensive treatment. Compared with CRT, all comparators except HRT^H (ICER: €228,852) were cost effective, with ICERs ranging between €7,592 (VART) and €12,379 (HRT^I).

TABLE 2. Input Parameters: Resource Use and Costs

Parameter	Estimated Value	SE/Range	Distribution	Source
Primary treatment costs				
Time per fraction of radiotherapy (min)	10	8–18	Beta PERT	EO
Costs per 10 min of radiotherapy	€233	€194–€291	Beta PERT	[34]
Number of fractions for CRT	30	0.2	Gamma	MAR-LC
Costs of CRT	€6,940			
Number of fractions for VART	36	0.2	Gamma	MAR-LC
Costs of VART	€8,290			
Number of fractions for MART[a]	38	0.2	Gamma	MAR-LC
Costs of MART	€8,940			
Number of fractions for HRT^{I}[a]	38	0.2	Gamma	MAR-LC
Costs of HRT^{I}	€8,940			
Number of fractions for HRT^{H}	53	1.1	Gamma	MAR-LC
Costs of HRT^{H}	€12,237			
Event costs				
Acute pulmonary toxicity costs (≥grade 3)				
Probability of hospitalization (%)	2.5	0.3	Beta	EO
Days of hospital admission	11	2.0	Gamma	[35]
Costs of hospital admission (per day)	€463	Fixed		[36]
Medication costs	€22	Fixed		CvZ
Acute pulmonary toxicity costs	€147			
Acute esophageal toxicity costs (≥grade 3)				
Days of hospital admission	2	0.3	Gamma	EO
Costs of hospital admission (per day)	€463	Fixed		[36]
Days of tube feeding when hospitalized	21	2.0	Gamma	EO
Costs of tube nutrition per day	€18	Fixed		MP
Costs of placing and removing tube	€269	Fixed		NZa
Medication costs for acute esophageal toxicity	€31	Fixed		CvZ
Acute esophageal toxicity costs	€1,604			
Acute hematological toxicity costs (≥grade 3)				
Costs of an episode of febrile neutropenia	€3,754	€1241	Gamma	[37]
Mortality costs (costs of last life-year before dying)				
Cancer mortality	€22,793	€2000[b]	Gamma	[38]
Noncancer mortality	€16,246	€2000[b]	Gamma	[38]
Health state costs				
Follow-up costs				
Costs per follow-up visit	€73	Fixed		[36]
Number of follow-up visits in first year	4	Fixed		NSCLC guideline
Monthly costs of follow-up first year	€24			
Number of follow-up visits in second year	2	Fixed		NSCLC guideline
Monthly costs of follow-up second year	€12			
Number of follow-up visits after second year	1	Fixed		NSCLC guideline
Monthly costs of follow-up after second year	€6			
Late toxicity costs				
Yearly costs of irreversible dyspnea ≥ grade 3	€1099	€100[b]		[35]
Monthly costs of irreversible dyspnea ≥ grade 3	€92			

[a]Because of a lack of data, the number of fractions was assumed to be 96% of the theoretical number of fractions (as observed on average for the other comparators) and the SE from very accelerated radiotherapy was used.

[b]SE was based on expert opinion.

EO, expert opinion; MP, market price; NZa, Nederlands Zorg Authoriteit/Dutch Healthcare Authority; CvZ, College voor Zorgverzekeringen/Health Care Insurance Board; CRT, conventional fractionation radiotherapy; MAR-LC, Meta-Analysis of Radiotherapy in Lung Cancer; VART, very accelerated radiotherapy; MART, moderately accelerated radiotherapy; HRT^{I}, identical hyperfractionated radiotherapy; HRT^{H}, higher hyperfractionated radiotherapy; NSCLC, non–small-cell lung cancer.

TABLE 3. Incremental Analyses (Sorted by QALY)

	Expected Outcomes (95% CI)[a]			Compared with CRT (95% CI)[a]			Compared with Next Cost-Effective Strategy (95% CI)[a]			
Treatment	QALYs	Costs	NMB	Incremental QALYs	Incremental Costs	ICER Costs/ QALY	Comparator	Incremental QALYs	Incremental Costs	ICER Costs/ QALY
CRT	1.12 (1.00–1.24)	€24,360 (€21,173–€28,110)	€65,125 (€54,663–€75,537)	—	—	—	—	—	—	—
HRT^{H}	1.14 (0.90–1.42)	€ 29,683 (€25,536–€35,208)	€61,663 (€40,967–€84,360)	0.02 (−0.20 -0.28)	€5,323 (€3,907–€7,533)	€228,852	CRT	0.02 (−0.20 -0.28)	€5,323 (€3,907–€7,533)	€228,852
HRT^{I}	1.27 (1.00–1.57)	€26,199 (€22,714–€30,523)	€75,170 (€53,320–€99,989)	0.15 (−0.11 -0.44)	€1,839 (€1,212–€2,699)	€12,379	CRT	0.15 (−0.11 -0.44)	€1,839 (€1,212–€2,699)	€12,379
VART	1.30 (1.14–1.47)	€25,746 (€22,370–€29,861)	€78,347 (€64,635–€92,526)	0.18 (0.05–0.32)	€1,386 (€957–€1,982)	€7,592	HRT^{I}	0.03 (−0.29 -0.33)	−€453 (−€908 to −22)	Dominant
MART	1.32 (0.78–1.99)	€26,208 (€22,690–€30,571)	€79,322 (€35,478–€133,648)	0.20 (−0.35 to 0.87)	€1,848 (€895–€2,845)	€9,214	VART	0.02 (−0.55 -0.70)	€462 (−€347 to €1,168)	€25,716

[a]The mean and 95% CI were based on the probabilistic sensitivity analysis (see Appendix 4 for the cost-effectiveness planes corresponding to the comparisons).

QALYs, quality-adjusted life years; NMB, net monetary benefit; ICER, incremental cost-effectiveness ratio; CI, confidence interval; CRT, conventional fractionation radiotherapy; HRT^{I}, identical hyperfractionated radiotherapy; HRT^{H}, higher hyperfractionated radiotherapy; VART, very accelerated radiotherapy; MART, moderately accelerated radiotherapy.

HRT^{H} was both more effective (0.02 QALYs) and expensive (€5,323) than CRT. This resulted in an ICER of €228,852. Given the ceiling ratio of €80,000 per QALY gained, HRT^{H} was not cost effective opposed to CRT. HRT^{I} was also more effective (0.15 QALYs) and expensive (€1,839) than CRT, leading to an ICER below the ceiling ratio (€12,379). HRT^{I} was thus cost effective opposed to CRT. VART was more effective (0.03 QALYs) and less expensive (€453) and thus dominated HRT^{I}. MART was more effective (0.02 QALYs) and more expensive (€462) than VART. The calculated ICER (€25,716) was below the ceiling ratio. Thus, MART is the most cost-effective RT scheme (Table 3).

Figure 2 and Appendix 4 (Supplemental Digital Content 1, http://links.lww.com/JTO/A451) show the uncertainty surrounding the results. Taking into account this uncertainty, MART had the highest probability of being cost effective (43%), followed by VART (31%), HRT^{I} (24%), HRT^{H} (2%), and CRT (0%; Fig. 2). Additionally, the estimated EVPI was €228 million (Fig. 3). More specifically, the EVPPI indicated that further research would be most valuable for the primary treatment costs of MART (€8.2 million) and cancer mortality after VART (€6.7 million) and MART (€5.4 million). The EVIC showed a value of individualizing care of €0.1 million (Fig. 3).

DISCUSSION

All modified RT schemes were more effective and costlier than CRT. Although MART was the most cost-effective treatment strategy, the differences between comparators were small, and all CIs for the incremental costs and effects were overlapping (Table 3). Therefore, it is uncertain which modified fractionation strategy is most cost effective. Moreover, estimated survival after MART was based on only one study with a small number of patients (n = 58). Despite this uncertainty, modified fractionation RT in general is likely (>99%) cost-effective compared with CRT, and accelerated schemes are likely to be the most effective and cost-effective modified fractionation schemes. However, it is unclear which accelerated fractionation scheme is deemed optimal. The comparison of MART versus VART resulted in a 51% probability for MART and 49% probability for VART of being cost effective (Appendix 4, Supplemental Digital Content 1, http://links.lww.com/JTO/A451). Additionally, in the individual patient meta-analysis, heterogeneity in the relative treatment effect between the different RT schemes was not demonstrated.[7] In this article we examined patient heterogeneity based on differences in baseline risk, and found that there was relatively little value to individualize care (i.e., to provide different treatments to different patients). Instead, it would be more valuable to perform further research to reduce parameter uncertainty, specifically for primary treatment costs of MART and cancer mortality after VART and MART.

Our study was the first to assess the cost effectiveness of several modified RT schemes in NSCLC. In one prior analysis, which also used a Markov model, an ICER of €11,576 was estimated for continuous hyperfractionation accelerated radiotherapy (CHART) compared with CRT; thus leading to the conclusion that CHART is likely cost effective in Belgium.[21] This CHART trial was included in the VART arm in our study. The comparison in our study of VART and CRT would result in a slightly more beneficial ICER for VART of €7,592.

The limitations of present study were, first, that the health care perspective was used instead of the societal perspective. Therefore, productivity losses at work were not incorporated. Because 48% of the study population was above the Dutch pensionable age at the beginning of the treatment, no large differences between the perspectives are expected. Second, all MAR-LC trials compare modified RT and CRT (Appendix 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A451). Hence, the comparisons between different modified fractionated RT

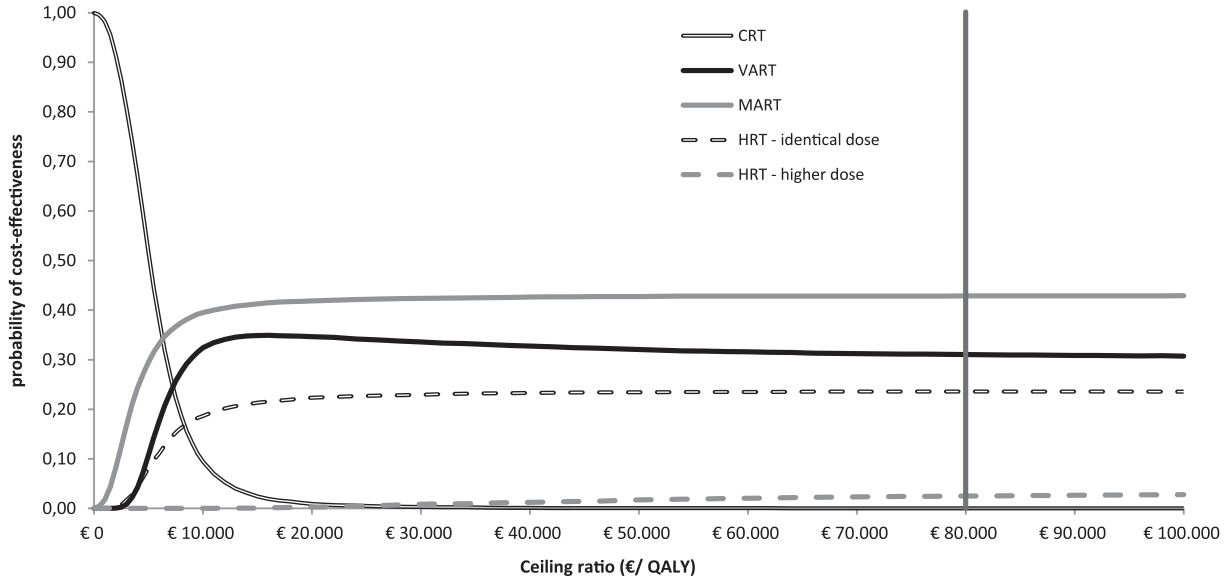


FIGURE 2. Cost effectiveness acceptability curves. The vertical line represents the ceiling ratio that was adopted in our analyses (€80,000 per QALY gained). CRT, conventional fractionation radiotherapy; VART, very accelerated radiotherapy; MART, moderately accelerated radiotherapy; HRT, hyperfractionated radiotherapy.

schemes are based on indirect evidence. Although synthesis of head-to-head comparisons of RCTs provides the most valid evidence of treatment effectiveness, it has been recommended that indirect treatment comparisons should be considered if direct evidence is unavailable.[22,23] The comparisons were stratified by trial, comparing patients only within each trial (preserving randomization), to obtain unbiased estimates.[14] Third, concomitant chemo-radiotherapy is the current standard although this was administered in only two of the ten included trials. Only one study (NCCTG 94242) used cisplatin-doublet chemotherapy during RT, which is at present considered to be the standard concurrent schedule. We were therefore unable to examine

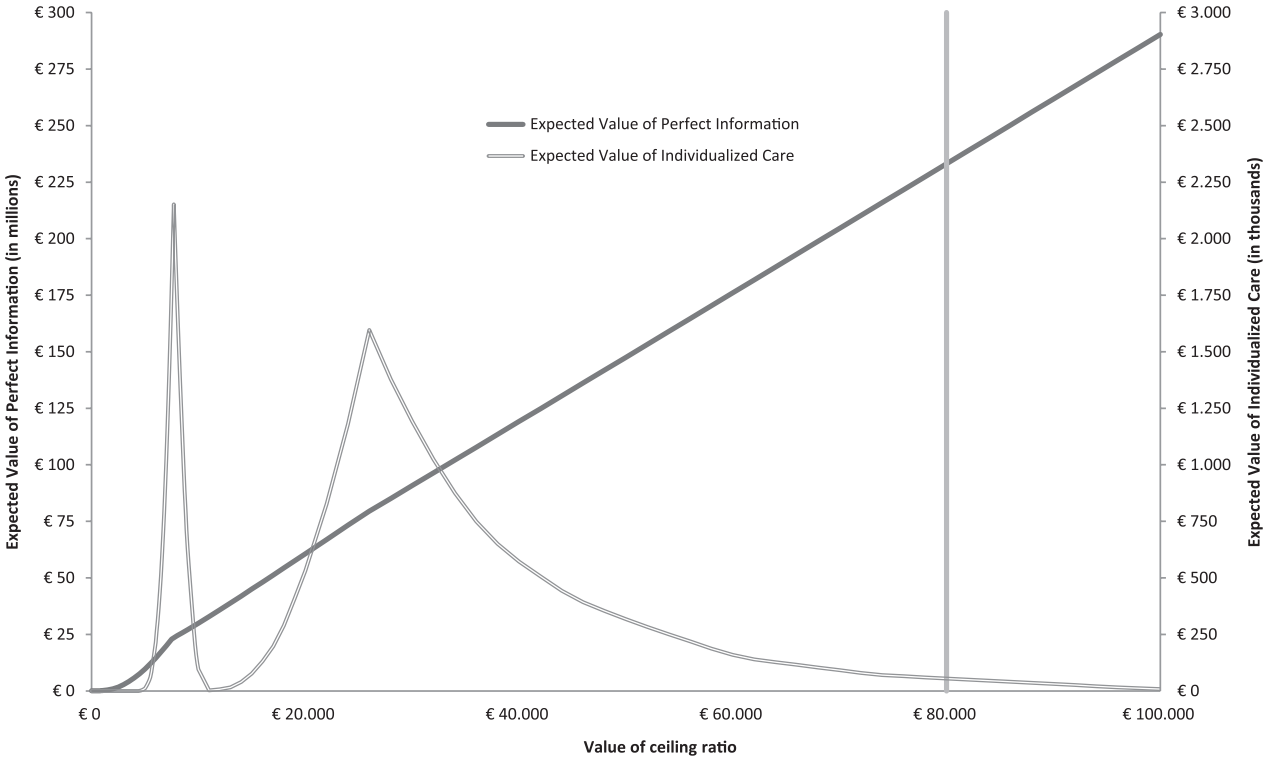


FIGURE 3. Expected value of individualized care and expected value of perfect information. The vertical line represents the ceiling ratio that was adopted in our analyses (€80,000 per quality-adjusted life year gained).

the impact of concomitant chemo-radiotherapy. Nevertheless, compared with CRT the benefit of modified RT with chemotherapy on OS (HR = 0.92; 95% CI, 0.77–1.10) was not significantly (interaction $p = 0.57$) lower than for modified RT without chemotherapy (HR = 0.87; 95% CI, 0.78–0.97).[7] Additionally, although this was not observed in a recent phase II study,[24] modified RT delivered concurrently with chemotherapy may increase acute side effects in comparison with concurrent chemotherapy with conventional RT. In case of increased toxicity when providing concomitant chemo-radiotherapy, the incremental costs for modified RT compared with CRT might on the one hand increase because of potentially increased toxicity management costs. On the other hand, it might result in lower incremental costs, for instance because of interruption and stopping of both chemotherapy and RT (before finishing all chemotherapy cycles and RT fractions). Thus, if chemotherapy is added to all included trials, the incremental effects can be expected to be similar and the impact on incremental costs would be unclear. This issue should be addressed in future (economic) studies. Fourth, to avoid unnecessary complexity in the model, it was decided not to incorporate overlapping toxicities (as described in the Model Description section). Despite this simplification of the model, the total occurrence of the acute and late toxicities in the present model would be equal to a more complex model incorporating *overlap* between toxicities. Also, as described in the Methods section, overlap between available toxicities in the MAR-LC database was small. Therefore, considering this low proportion of overlap between toxicities and the equivalence between total occurrence of toxicity, this model assumption is unlikely to have a large impact on the study results. Finally, the applied survival of 6 months after recurrence, to calculate the disutility for cancer mortality, could be criticized in view of the median survival of 10 to 12 months in newly diagnosed stage IV NSCLC.[25] Nevertheless, this was a conservative assumption, that is, longer survival after recurrence, and thus a higher disutility, will favor the modified RT treatments because these have less NSCLC deaths (and thus fewer disutilities).

It is likely that with recent advancements in RT techniques, the same level of acceleration can be given safely in fewer fractions, that is, 24 fractions instead of 38 fractions (as for VART and MART).[26,27] This could reduce the costs (because of the lower number of fractions) while maintaining the survival benefit of accelerated RT. HRT[1], the third most cost-effective option in our analysis, applies split-course RT. Although this was not observed in the individual patient meta-analysis,[7] it is widely believed to be less efficient than continued RT schemes. As a result, split-course RT is rarely used nowadays.[28] Also, concurrent chemotherapy and CRT is nowadays the treatment of choice for good performance status patients with locally advanced NSCLC.[29] However, as many patients are not eligible for concomitant chemo-radiotherapy treatment,[30] sequential chemotherapy and accelerated RT seems a promising treatment option. In the present analysis we were unable to examine the role of chemotherapy in combination with modified fractionation RT. Although the benefit of modified RT with and without chemotherapy did not differ significantly,[7] the results of RTOG 9410 and RTOG 0617 caution against assuming that modifying conventional concomitant chemo-radiotherapy will improve the therapeutic ratio.[31,32] For sequential chemotherapy and RT, there are no indications that there would be an interaction between both modalities for toxicity. Hence, the present study results are probably most applicable to patients not receiving concomitant chemo-radiotherapy. Studies examining the role of modified fractionation RT combined with concomitant chemotherapy are warranted. This includes examining for instance whether it is safe to provide chemotherapy concurrently with accelerated RT, whether the benefits of modified fractionation are preserved in case of concurrent chemo-radiotherapy, and whether other well-studied[27] types of accelerated once-daily high-dose RT are cost effective.

In conclusion, it remains uncertain which modified scheme is most cost effective and it is unclear whether the study results can be extrapolated to modified RT combined with concomitant chemotherapy. Hence, further research comparing the cost effectiveness of different types of modified RT and examining the role of chemotherapy might be valuable. Nevertheless, implementing accelerated RT is almost certainly more cost effective than current practice (CRT) for patients treated with sequential chemo-radiotherapy or RT alone. Hence, waiting for more evidence before implementing accelerated RT (without concomitant chemotherapy) would lead to health benefits forgone. In addition, if future evidence would show that accelerated RT is not the most cost-effective RT type, the forgone implementation costs (sunk costs) are expected to be low. Therefore, despite available uncertainty, it is encouraged to adopt accelerated RT for the curative treatment of unresected NSCLC patients who do not receive concurrent chemo-radiotherapy and examine its role in the context of concurrent chemo-radiotherapy.

ACKNOWLEDGMENTS

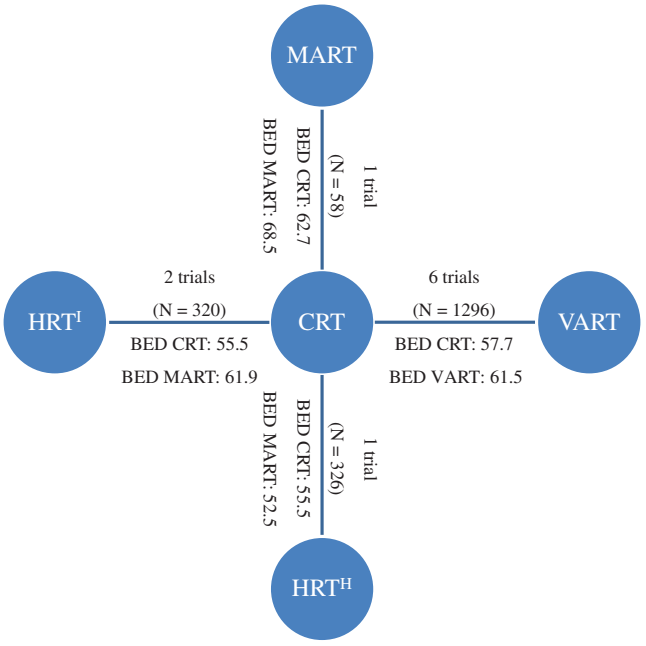
The authors sincerely thank the following research groups who agreed to share their data: Arbeitsgemeinschaft Radioonkologie der Deutschen Krebsgesellschaft, Eastern Cooperative Oncology Group, Medical Research Council, North Central Cancer Treatment Group, and Radiation Therapy Oncology Group. The contents of this publication and methods used are solely the responsibility of the authors. This study was supported by an unrestricted research grant (No. 152002021) from the Dutch Organization of Health Research and Development (ZonMw) and the French National League against Cancer. ZonMw and the French National League against Cancer had no influence on the study design, data analyses, data interpretation, article writing, or the decision to submit the article for publication.

List of the members of the MAR-LC Collaborative group: R. Arriagada (Institut Gustave-Roussy/Karolinska Institutet), K. Bae (Radiation Therapy Oncology Group), D. Ball (Peter MacCallum Cancer Centre and the University of Melbourne), M. Baumann (University of Dresden), K. Behrendt (Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology), C.P. Belani (Penn State Hershey Cancer Institute), J. Beresford (Peter MacCallum Cancer Centre), J. Bishop (Victorian Comprehensive Cancer Centre), J.A. Bonner (University of Alabama-Birmingham), H. Choy (The University of Texas Southwestern), S.E. Dahlberg (Dana-Farber Cancer Institute), D. De Ruysscher (University

Hospital Leuven and University Hospital Maastricht), S. Dische (Mount Vernon Hospital), P. Fournel (Institut de Cancérologie de la Loire), R. Koch (University of Dresden), C. Le Péchoux (Institut Gustave-Roussy), S.J. Mandrekar (Mayo Clinic), A. Mauguen (Institut Gustave-Roussy), F. Mornex (Centre Hospitalier Lyon Sud), M. Nankivell (MRC Clinical Trials Unit), G. Nelson (Mayo Clinic), M.K. Parmar (MRC Clinical Trials Unit), R. Paulus (Radiation Therapy Oncology Group), J.P. Pignon (Institut Gustave-Roussy), M.I. Saunders (Mount Vernon Hospital), W. Sause (Intermountain Medical Center), S.E. Schild (Mayo Clinic), A.T. Turrisi (Sinai Grace Hospital), A. Zajusz (Maria Sklodowska -Curie Memorial Cancer Center and Institute of Oncology).

APPENDIX 1. Classification of MAR-LC Trials

BED, biologic effective dose (average in case of multiple trials); CRT, conventional fractionation radiotherapy; MART, moderately accelerated radiotherapy; HRT^{I}, identical hyperfractionated radiotherapy; HRT^{H}, higher hyperfractionated radiotherapy; MAR-LC, Meta-Analysis of Radiotherapy in Lung Cancer.



APPENDIX 2. Input Parameters for Survival

The Weibull models were constructed according to the intention-to-treat principle using the following covariates: treatment arm (CRT; VART; MART; HRT^{I}; HRT^{H}), sex (male; female), age (≤59; 60–69; ≥70 years), performance status (mild; good), histology (SCC; non-SCC) and disease stage (I/II; IIIA; IIIB). All variables were included in the initial model as categorical variables. Selection of covariates was performed as described by Hosmer et al.,[1] except for the treatment arm variable. This variable was not included in the equation to predict noncancer mortality, and was always included in the model for cancer mortality. The parameterization of the Weibull model is as follows:

$$S(t) = e^{-\lambda t^{\alpha}} \quad (1)$$

Where S(t) = survival probability at time t. The shape parameter (α) could be retrieved from the analysis output. Lambda (λ), the event rate parameter, was calculated by the sum of all coefficients multiplied by the accompanying covariates (X):

$$\begin{aligned}\lambda &= \beta_{\text{Intercept}} + \beta_{\text{Treament arm}}\text{X}_{\text{Treatment arm}} \\ &+ \beta_{\text{Age 60-69}}\text{X}_{\text{Age 60-69}} + \beta_{\text{Age 70}} + \text{X}_{\text{Age 70+}} \\ &+ \beta_{\text{Female}}\text{X}_{\text{Female}} + \beta_{\text{Performance status good}}\text{X}_{\text{Performance status good}} \\ &+ \beta_{\text{Histology Squamous cell}}\text{X}_{\text{Histology Squamous cell}} \\ &+ \beta_{\text{Disease Stage IIIA}}\text{X}_{\text{Disease Stage IIIA}} + \beta_{\text{Disease Stage IIIB}}\text{X}_{\text{Disease Stage IIIB}}\end{aligned} \quad (2)$$

The coefficients (β) for all covariates were retrieved from the analysis output. The coefficient for the intercept was calculated based on the shape (α) and scale parameters from the R output:

$$\beta_{\text{Intercept}} = -\text{Ln}(\text{scale}) \times \text{shape} \quad (3)$$

One essential statistical technique when analyzing multiple trials is stratification by trial, which guarantees that patients are compared within each trial and not across trials.[2] The Weibull model was stratified by trial, which resulted in separate scale and shape parameters for each trial. The different scale and shape parameters were pooled using a random-effects model.[3] Subsequently, all coefficients were multiplied by the accompanying average covariates to calculate λ. For instance, the proportion of female patients X_{Female} was multiplied by the coefficient for female β_{Female}. The time-dependent transition probability between two cycles (between t_1 and t_2), was then calculated using the following formula (derived from Eq. 1):

$$S(t_2 - t_1) = e^{-\lambda(t_1^{\alpha} - t_2^{\alpha})} \quad (4)$$

Estimated Regression Coefficients for Survival Probabilities

	Equation 1: Probability of Cancer Mortality (1644 Events)		Equation 2: Probability of Noncancer Mortality (205 Events)	
Parameter	**Estimated Value**	**SE**	**Estimated Value**	**SE**
Model characteristics				
Model distribution	Weibull[a]		Weibull[a]	
Shape (α)	1.093	0.200	0.920	0.372
Ln(scale)	6.635	0.053	8.389	0.147
Intercept[b]	−7.252		−7.722	
Explanatory baseline characteristics[c]				
Treatment arm				
VART	−0.176	0.064		
MART	−0.169	0.276		
HRT^{I}	−0.137	0.128		
HRT^{H}	−0.022	0.119		
Age (yr)				

(*Continued*)

(*Continued*)

60–69	−0.123	0.061	0.378	0.219
70+	−0.149	0.070	0.688	0.223
Sex				
Female	−0.149	0.059	−0.372	0.188
Performance status				
Good	−0.237	0.053	−0.508	0.160
Disease stage				
IIIA	0.242	0.081		
IIIB	0.384	0.083		
Mean 2Y probability[d]				
CRT	62%		18%	
VART	56%		18%	
MART	56%		18%	
HRT^{I}	57%		18%	
HRT^{H}	61%		18%	
Source	MAR-LC		MAR-LC	

[a]Included in the probabilistic sensitivity analysis using a multivariate normal distribution which was constructed using Cholesky decompositions (multivariate normal distribution).[4]

[b]Calculated using the following formula: −Ln(scale) × shape.

[c]Histology was excluded (according to the purposeful selection of covariates algorithm by Hosmer and Lemeshow).[1,5]

[d]This probability represents the mean 2-yr probability for the separate Weibull models (not the 2-yr probability as in the Markov trace).

2Y = 2-yr; CRT, conventional fractionation radiotherapy; HRT^{I}, identical hyperfractionated radiotherapy; HRT^{H}, higher hyperfractionated radiotherapy; VART, very accelerated radiotherapy; MART, moderately accelerated radiotherapy; MAR-LC, Meta-Analysis of Radiotherapy in Lung Cancer.

APPENDIX 3. Input Parameters for Acute Toxicity

The included covariates and subsequent selection procedure were the same for acute pulmonary and esophageal toxicity as described for the Weibull models (Appendix 2). This was also the case for hematological toxicity, except that the treatment arm was excluded as covariate because it is caused by chemotherapy and independent of radiation fractionation scheme. The parameterization of the logistic model is as follows:

$$p = \frac{e^{z}}{1+e^{z}} \quad (1)$$

Where p is the toxicity probability and z was calculated by the sum of all coefficients multiplied by the accompanying covariates (X):

$$\begin{aligned} z &= \beta_{\text{Intercept}} + \beta_{\text{Treament arm}} X_{\text{Treatment arm}} \\ &+ \beta_{\text{Age 60–69}} X_{\text{Age 60–69}} + \beta_{\text{Age 70+}} X_{\text{Age 70+}} \\ &+ \beta_{\text{Female}} X_{\text{Female}} + \beta_{\text{Performance status good}} X_{\text{Performance status good}} \\ &+ \beta_{\text{Histology Squamous cell}} X_{\text{Histology Squamous cell}} \\ &+ \beta_{\text{Disease Stage IIIA}} X_{\text{Disease Stage IIIA}} + \beta_{\text{Disease Stage IIIB}} X_{\text{Disease Stage IIIB}} \end{aligned} \quad (2)$$

As for the Weibull models, the logistic regression models were stratified by trial. However, no coefficient for the intercept is given if the logistic regression models are stratified by trial in SAS, thus absolute toxicity probabilities based could not be calculated based on this logistic regression model. Therefore, separate logistic regression models were constructed for each trial using the covariates as selected in the above described logistic regression model stratified by trial. The obtained coefficients for each trial were pooled using a random-effects model.[3] To calculate the acute toxicity probabilities using the logistic regression models, individual characteristics were needed. For this purpose, a hypothetical cohort of individual patients with individual characteristics was replicated based on the average characteristics and their correlations from the MAR-LC-database. For each patient, the individual z values and toxicity probabilities were calculated. To obtain the toxicity probabilities for the whole cohort, the individual probabilities were averaged. This was done separately for each comparator.

Estimated Regression Coefficients for Acute Toxicity (≥Grade 3) Probabilitiesa

Parameter	Equation 1: Probability of Acute Pulmonary Toxicity (77 Events)[b]		Equation 2: Probability of Acute Esophageal Toxicity (304 Events)		Equation 3: Probability of Acute Hematological Toxicity (202 Events)	
	Estimated Value	SE	Estimated Value	SE	Estimated Value	SE
Explanatory baseline characteristics[c]						
Intercept	−2.856	0.273	−2.429	0.268	−1.892	1.418
Trial arm						
VART	−0.625	0.324	1.281	0.216		
$MART/HRT^{H}$	0.086	0.405	0.428	0.539		
HRT^{I}	0.016	0.839	−0.157	0.314		
Age (yr)						
60–69	0.360	0.323			0.364	0.560
70+	0.737	0.354			1.033	0.374
Sex						
Female			0.672	0.204	0.963	0.313
Mean probability[d]						
CRT	7.8%		9.8%		24.7%[e]	
VART	4.4%		27.8%		24.7%[e]	
$MART/HRT^{H}$	8.5%		14.3%		24.7%[e]	
HRT^{I}	8.0%		8.6%		24.7%[e]	
Source	MAR-LC		MAR-LC		MAR-LC	

[a]Included in the probabilistic sensitivity analysis using a multivariate normal distribution which was constructed using Cholesky decompositions (multivariate normal distribution).[4]

[b]To handle the occurrence of zero events in 2 × 2 tables between dependent and independent variables (leading to quasicomplete separation), the Firth's penalized maximum likelihood estimation method[6,7] was used for four logistic regression models.

[c]A combined estimate was calculated for HRT^{H} and MART. This was done because acute toxicity was not reported in the MART trial and the overall treatment time and total treatment dose are similar for these two comparators In addition, performance status, histology and disease stage were excluded (according to the purposeful selection of covariates algorithm by Hosmer and Lemeshow).[1,5]

[d]It was assumed that acute toxicity increased from start radiotherapy to 3 months thereafter to the total probability (reported in the table). The monthly probability was then calculated from the total probability using the following formula:[4]

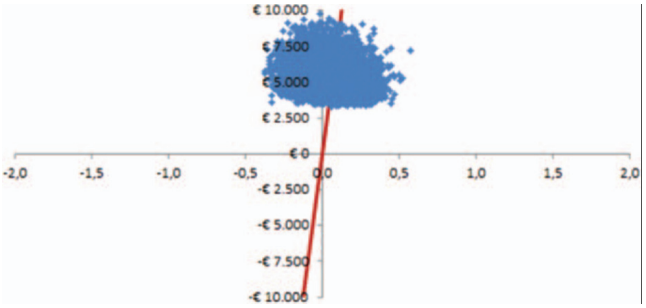
$$p(1\text{ month}) = 1 - e^{\left(\ln\left(1-p\,(\text{total})\right)\times 1/3\right)}$$

[e]Hematological toxicity is mainly caused by the administration of chemotherapy rather than the radiotherapy treatment scheme and was therefore assumed to be independent of the radiotherapy scheme (and thus equal for all comparators). The calculated probability (24.7%) was conditional on that patients received chemotherapy and has to be multiplied by the proportion of patients who received chemotherapy (29.5%; assumed equal among all comparators) to calculate the average probability of acute hematological toxicity per comparator (7.3%).

CRT, conventional fractionation radiotherapy; HRT^{I}, identical hyperfractionated radiotherapy; HRT^{H}, higher hyperfractionated radiotherapy; VART, very accelerated radiotherapy; MART, moderately accelerated radiotherapy; MAR-LC, Meta-Analysis of Radiotherapy in Lung Cancer.

APPENDIX 4. Cost-Effectiveness Planes Corresponding to the Comparison in Table 3

HRT^H versus CRT

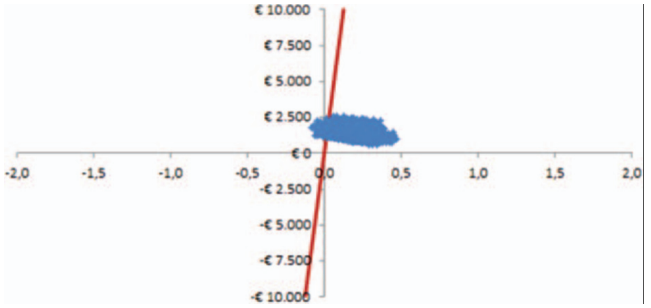


	% Simulations
North-west quadrant	44.0
North-east quadrant	56.0
South-west quadrant	0.0
South-east quadrant	0.0
HRT^H cost effective	35.2
CRT cost effective	64.8

The diagonal line represents the ceiling ratio which was adopted in our analyses (€80,000 per QALY gained).

HRT^H, hyperfractionated radiotherapy using higher total treatment dose as conventional radiotherapy; CRT, conventional fractionation radiotherapy.

VART versus CRT

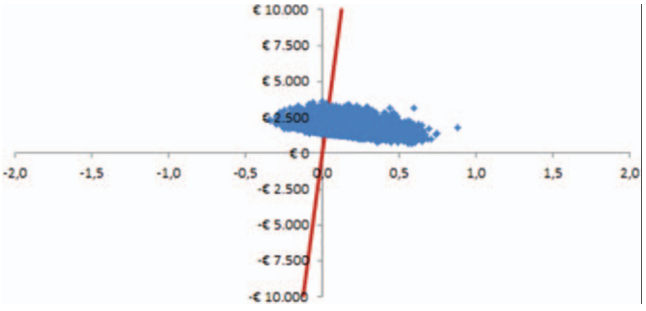


	% Simulations
North-west quadrant	0.4
North-east quadrant	99.6
South-west quadrant	0.0
South-east quadrant	0.0
VART cost effective	99.1
CRT cost effective	0.9

The diagonal line represents the ceiling ratio which was adopted in our analyses (€80,000 per QALY gained).

CRT, conventional fractionation radiotherapy; HRT^I, hyperfractionated radiotherapy using identical total treatment dose as conventional radiotherapy; VART, very accelerated radiotherapy.

HRT^I versus CRT

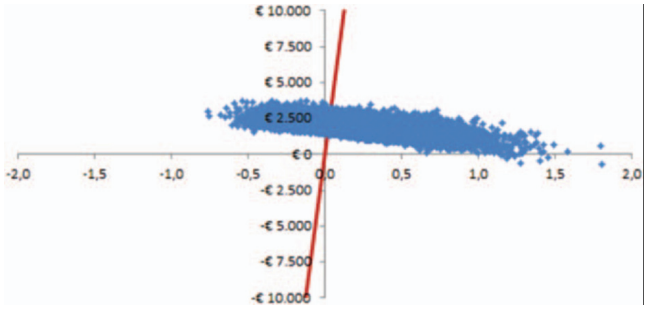


	% Simulations
North-west quadrant	14.5
North-east quadrant	85.5
South-west quadrant	0.0
South-east quadrant	0.0
HRT^I cost effective	80.7
CRT cost effective	19.3

The diagonal line represents the ceiling ratio which was adopted in our analyses (€80,000 per QALY gained).

CRT, conventional fractionation radiotherapy; HRT^I, identical hyperfractionated radiotherapy.

MART Versus CRT

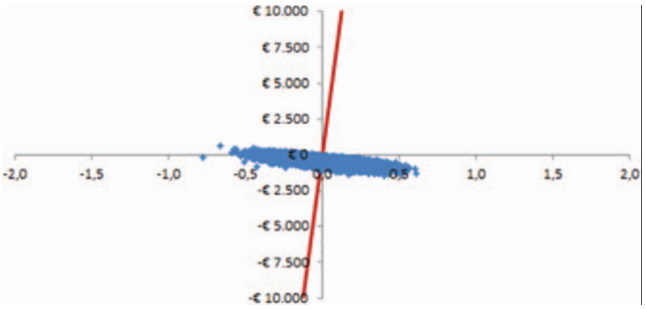


	% Simulations
North-west quadrant	27.3
North-east quadrant	82.6
South-west quadrant	0.0
South-east quadrant	0.1
MART cost effective	69.7
CRT cost effective	30.3

The diagonal line represents the ceiling ratio, which was adopted in our analyses (€80,000 per QALY gained).

CRT, conventional fractionation radiotherapy; MART, moderately accelerated radiotherapy.

VART versus HRT[I]

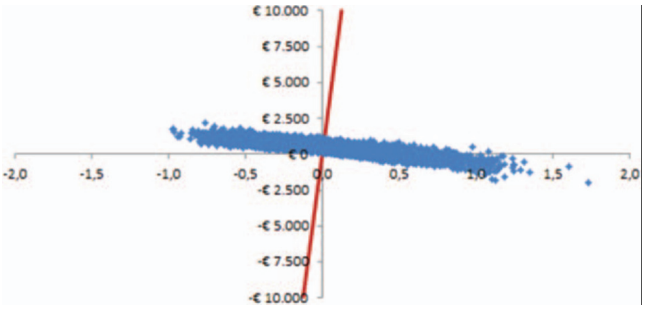


	% Simulations
North-west quadrant	2.1
North-east quadrant	0.0
South-west quadrant	38.5
South-east quadrant	59.4
VART cost effective	60.6
HRT[I] cost effective	39.4

The diagonal line represents the ceiling ratio which was adopted in our analyses (€80,000 per QALY gained).

VART, very accelerated radiotherapy; identical hyperfractionated radiotherapy.

MART versus VART



	% Simulations
North-west quadrant	50.3
North-east quadrant	39.0
South-west quadrant	0.0
South-east quadrant	10.7
MART cost effective	51.0
VART cost effective	49.0

The diagonal line represents the ceiling ratio which was adopted in our analyses (€80,000 per QALY gained).

MART, moderately accelerated radiotherapy; VART, very accelerated radiotherapy.

REFERENCES

1. Hosmer DW, Lemeshow S, May S. Applied Survival Analysis: Regression Modeling of Time to Event Data. New York: John Wiley & Sons, 2008.
2. Buyse M, Piedbois P, Piedbois Y, et al. Meta-analysis: methods, strengths, and weaknesses. *Oncology (Williston Park)* 2000;14:437–443; discussion 444, 447.
3. Whitehead A. Meta-analysis of Controlled Clinical Trials. New York: John Wiley & Sons, 2002.
4. Briggs A, Sculpher MJ, Claxton K. Decision Modelling for Health Economic Evaluation. Oxford: Oxford University Press, 2006.
5. Bursac Z, Gauss CH, Williams DK, et al. Purposeful selection of variables in logistic regression. *Source Code Biol Med* 2008;3:17.
6. Firth D. Bias Reduction of Maximum Likelihood Estimates. Biometrika 1993;80:27–38.
7. Allison PD. Statistics and Data Analysis Convergence Failures in Logistic Regression. SAS Global Forum 2008. Texas: 2008. Available at: http://www.mendeley.com/research/statistics-data-analysis-convergence-failures-logistic-regression/.

REFERENCES

1. Ferlay J, Shin HR, Bray F, et al. *Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10*. Available at: http://globocan.iarc.fr Accessed June 20, 2012.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;62:10–29.
3. Blackstock AW, Govindan R. Definitive chemoradiation for the treatment of locally advanced non small-cell lung cancer. *J Clin Oncol* 2007;25:4146–4152.
4. Belderbos JS, Heemsbergen WD, De Jaeger K, Baas P, Lebesque JV. Final results of a Phase I/II dose escalation trial in non-small-cell lung cancer using three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;66:126–134.
5. Kong FM, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys* 2005;63:324–333.
6. Willner J, Baier K, Caragiani E, Tschammler A, Flentje M. Dose, volume, and tumor control prediction in primary radiotherapy of non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002;52:382–389.
7. Mauguen A, Le Péchoux C, Saunders MI, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *J Clin Oncol* 2012;30:2788–2797.
8. Meropol NJ, Schrag D, Smith TJ, et al; American Society of Clinical Oncology. American Society of Clinical Oncology guidance statement: the cost of cancer care. *J Clin Oncol* 2009;27:3868–3874.
9. Briggs A, Sculpher MJ, Claxton K. *Decision Modelling for Health Economic Evaluation*. Oxford: Oxford University Press, 2006.
10. Grutters JP, Sculpher M, Briggs AH, et al. Acknowledging patient heterogeneity in economic evaluation: a systematic literature review. *Pharmacoeconomics* 2013;31:111–123.
11. Jain R, Grabner M, Onukwugha E. Sensitivity analysis in cost-effectiveness studies: from guidelines to practice. *Pharmacoeconomics* 2011;29:297–314.
12. Werner-Wasik M, Paulus R, Curran WJ Jr, Byhardt R. Acute esophagitis and late lung toxicity in concurrent chemoradiotherapy trials in patients with locally advanced non-small-cell lung cancer: analysis of the radiation therapy oncology group (RTOG) database. *Clin Lung Cancer* 2011;12:245–251.
13. Carroll KJ. On the use and utility of the Weibull model in the analysis of survival data. *Control Clin Trials* 2003;24:682–701.
14. Buyse M, Piedbois P, Piedbois Y, Carlson RW. Meta-analysis: methods, strengths, and weaknesses. *Oncol (Williston Park)* 2000;14:437–43; discussion 444, 447.
15. Hosmer DW, Lemeshow S, May S. *Applied Survival Analysis: Regression Modeling of Time to Event Data*. New York: John Wiley & Sons, 2008.
16. Grutters JP, Joore MA, Wiegman EM, et al. Health-related quality of life in patients surviving non-small cell lung cancer. *Thorax* 2010;65:903–907.
17. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy* 1990;16:199–208.
18. Council for Public Health and Health Care. *Sensible and sustainable care [in Dutch]. Zoetermeer: Council for Public Health and Health Care*, 2006. Available at: http://www.rvz.net/data/download/advies_Zinnige_zorg.pdf.
19. Basu A, Meltzer D. Value of information on preference heterogeneity and individualized care. *Med Decis Making* 2007;27:112–127.

20. van Gestel A, Grutters J, Schouten J, et al. The role of the expected value of individualized care in cost-effectiveness analyses and decision making. *Value Health* 2012;15:13–21.
21. Lievens Y, Kesteloot K, Van den Bogaert W. CHART in lung cancer: economic evaluation and incentives for implementation. *Radiother Oncol* 2005;75:171–178.
22. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;50:683–691.
23. National Institute for Health and Clinical Excellence. *Guide to the Methods of Technology Appraisal*. London: National Institute for Health and Clinical Excellence, 2008.
24. van Baardwijk A, Reymen B, Wanders S, et al. Mature results of a phase II trial on individualised accelerated radiotherapy based on normal tissue constraints in concurrent chemo-radiation for stage III non-small cell lung cancer. *Eur J Cancer* 2012;48:2339–2346.
25. Paz-Ares LG, Biesma B, Heigener D, et al; NSCLC [non–small-cell lung cancer] Research Experience Utilizing Sorafenib (NExUS) Investigators Study Group. Phase III, randomized, double-blind, placebo-controlled trial of gemcitabine/cisplatin alone or with sorafenib for the first-line treatment of advanced, nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2012;30:3084–3092.
26. van Elmpt W, De Ruysscher D, van der Salm A, et al. The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer. *Radiother Oncol* 2012;104:67–71.
27. Belderbos J, Uitterhoeve L, van Zandwijk N, et al; EORTC LCG and RT Group. Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973). *Eur J Cancer* 2007;43:114–121.
28. Dubben HH, Krüll A, Beck-Bornholdt HP. Split-course radiotherapy: where do we stand? *Strahlenther Onkol* 2001;177:227–239.
29. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:2181–2190.
30. De Ruysscher D, Botterweck A, Dirx M, et al. Eligibility for concurrent chemotherapy and radiotherapy of locally advanced lung cancer patients: a prospective, population-based study. *Ann Oncol* 2009;20:98–102.
31. Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst* 2011;103:1452–1460.
32. Bradley JD, Paulus R, Komaki R, et al. *A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy +/- cetuximab for stage IIIA/IIIB non-small cell lung cancer: preliminary findings on radiation dose in RTOG 0617*. Miami Beach: American Society for Radiation Oncology (ASTRO), 2011.
33. Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes*. 2008;6:84.
34. Peeters A, Grutters JP, Pijls-Johannesma M, et al. How costly is particle therapy? Cost analysis of external beam radiotherapy with carbon-ions, protons and photons. *Radiother Oncol*. 2010;95:45–53.
35. Hoogendoorn EJI, Feenstra TL, Rutten-van Molken MPMH. *Resource use and costs of care for treating asthma and COPD in the Netherlands [in Dutch]*. Bilthoven: National Institute for Public Health and the Environment 2004.
36. Hakkaart- van Roijen L, Tan SS, Bouwmans CAM. *Manual for costing research [in Dutch]*. Amstelveen: College voor Zorgverzekeringen 2010.
37. Timmer-Bonte JN, Adang EM, Smit HJ, et al. Cost-effectiveness of adding granulocyte colony-stimulating factor to primary prophylaxis with antibiotics in small-cell lung cancer. *J Clin Oncol*. 2006;24:2991–2997.
38. Kommer GJ, Slobbe LCJ, Polder JJ. Risicosolidariteit en zorgkosten: Council for Public Health and Health Care (RVZ) 2005.

