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Physics Contribution

Individualized Positron Emission Tomography–Based Isotoxic Accelerated Radiation Therapy Is Cost-Effective Compared With Conventional Radiation Therapy: A Model-Based Evaluation

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Summary

Although there are strong indications that PET-based isotoxic accelerated radiation therapy treatment (PET-ART) is beneficial for short-term outcomes, the survival, quality of life, and cost outcomes were never evaluated. In this study we evaluated the long-term health effects, costs, and cost-effectiveness of PET-ART compared with conventional CT-based

Purpose: To evaluate long-term health effects, costs, and cost-effectiveness of positron emission tomography (PET)-based isotoxic accelerated radiation therapy treatment (PET-ART) compared with conventional fixed-dose CT-based radiation therapy treatment (CRT) in non-small cell lung cancer (NSCLC).

Methods and Materials: Our analysis uses a validated decision model, based on data of 200 NSCLC patients with inoperable stage I-IIIB. Clinical outcomes, resource use, costs, and utilities were obtained from the Maastro Clinic and the literature. Primary model outcomes were the difference in life-years (LYs), quality-adjusted life-years (QALYs), costs, and the incremental cost-effectiveness and cost/utility ratio (ICER and ICUR) of PET-ART versus CRT. Model outcomes were obtained from averaging the predictions for 50,000 simulated patients. A probabilistic sensitivity analysis and scenario analyses were carried out.

Results: The average incremental costs per patient of PET-ART were €569 (95% confidence interval [CI] €−5327-€6936) for 0.42 incremental LYs (95% CI 0.19-0.61) and 0.33 QALYs gained (95% CI 0.13-0.49). The base-case scenario resulted in an ICER of €1360 per LY gained and an ICUR of €1744 per QALY gained. The probabilistic analysis

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radiation therapy treatment. We used a model-based approach, accounting for patient heterogeneity and parameter uncertainty. The results indicate that, according to the available data, PET-ART for non-small cell lung cancer seems to be cost-effective compared with conventional radiation therapy.

gave a 36% probability that PET-ART improves health outcomes at reduced costs and a 64% probability that PET-ART is more effective at slightly higher costs.
Conclusion: On the basis of the available data, individualized PET-ART for NSCLC seems to be cost-effective compared with CRT.

Introduction

The treatment paradigm in cancer care is "individualized" treatment, tailoring the treatment to the specific features of the patient and the tumor. The challenge is how to integrate clinical, molecular, and imaging information in a quantitative way to obtain clinical predictions that accurately estimate patient outcomes (1). In the field of health technology assessment, this means that for a proper evaluation of long-term costs and effects of individualized strategies, cost-effectiveness models need to incorporate patient and tumor features that may affect treatment decisions, disease progression, survival, adverse events, and quality of life.

An example of individualized treatment in non-small cell lung cancer (NSCLC) is the possibility to tailor radiation therapy treatment to the disease spread of an individual patient as observed on positron emission tomography (PET)-CT (2). PET-CT imaging for staging is standard in the diagnostic workup for NSCLC. However, the technical requirements for using PET-CT in radiation therapy planning are different from those for diagnosis and staging. An additional PET-CT scan in treatment planning allows for selective lymph node irradiation. In addition, on the basis of this PET-CT scan isotoxic therapy can be administrated, whereby doses of radiation therapy are individualized according to the constraints of the organs at risk. Individualizing therapy through isotoxic treatment planning improves tumor coverage, decreases the isolated nodal failure rate, and reduces the volume of healthy tissues irradiated compared with CT alone (3, 4). It is therefore justified to order a dedicated PET-CT scan for radiation therapy purposes, according to stringent technical specifications.

Further optimization of treatment can be obtained by hyperfractionated and accelerated radiation schemes, whereby patients receive lower-dose grays per fraction (hyperfractionated) twice daily, in a shorter overall treatment time (accelerated) (5). The 8-hour treatment interval between doses allows the healthy tissue to recover, thereby decreasing toxicity. Accelerated schemes have shown small reductions in mortality (5) and were shown to be more effective but also more costly than conventional radiation therapy (6).

PET-based treatment planning for selective lymph node irradiation is the preferred treatment strategy for patients eligible for radiation therapy according to the European guidelines (7). It is generally believed that treatment patterns vary over hospitals and regions, owing to differences in guidelines implementation (8). Specifically, it is not clear to what extent advanced imaging and modified radiation therapy schemes are implemented in standard care. Because new technologies in personalized care are often expensive, hospitals may be apprehensive to implement these technologies as standard care.

In this study we evaluated the long-term health effects, costs, and the cost-effectiveness of PET-CT−based isotoxic accelerated radiation therapy treatment (PET-ART) compared with conventional CT-based radiation therapy treatment (CRT) in NSCLC patients, using a previously developed and validated micro-simulation model (9).

Methods and Materials

Model description

The micro-simulation model used in this analysis simulates the disease progression and death of individual lung cancer patients until they are deceased or have reached a prespecified time-horizon of 3 years. Figure 1 presents the structure of the model, consisting of 4 health states. All patients start in state "Alive," where they are assumed to receive radiation therapy treatment. Over time, they can develop a local recurrence ("LR" [transition 1]), a distant metastasis ("DM" [transition 2]), or they can die without the detection of an LR or DM ("Death" [transition 3]). After they move to LR or DM, they are again at risk for Death (transitions 4 and 5, respectively). In addition to the 4 health states, the model keeps track of the occurrence of the adverse events "Dyspnea" and "Dysphagia."

Individual patients were simulated by repeatedly sampling a patient profile consisting of patient and tumor characteristics (World Health Organization [WHO] performance status, gross tumor volume, and number of lymph nodes affected) that are randomly drawn from prespecified

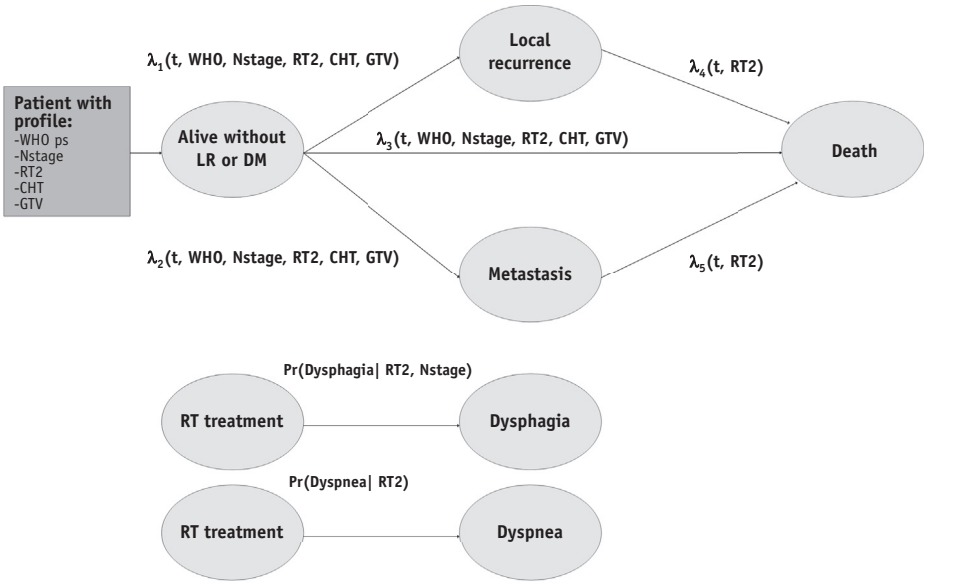

Fig. 1. Model structure of the micro-simulation model. From the health state "Alive" patients can develop Dysphagia or Dyspnea during or shortly after radiation therapy treatment.

correlated distributions. Once a specific individual patient profile is drawn, the disease progression after radiation therapy treatment is simulated for that individual. Transition rates between health states and the probability of acquiring toxicity depend on the patient profile and the type of treatment planning.

The micro-simulation model is programmed in Excel 2003 (Microsoft, Redmond, WA) and Visual Basic Editor 2003 (Microsoft, Redmond, WA).

Data used for model quantification and radiation therapy treatment strategies

Data on patient and tumor characteristics, toxicity, and follow-up were available for 200 NSCLC patients with inoperable stage I-IIIB receiving curative sequential chemoradiation or radiation therapy alone. The Maastro Clinic collected data on patients who were referred to their hospital between 2002 and 2009, according to a treatment protocol that described treatment regimen and data collection (10-12).

In detail, both radiation therapy treatment strategies are as follows. With CRT, patients received a radiation dose of either 70 Gy (stage I-II) or 60 Gy (stage III), in daily 2-Gy fractions in a mean overall treatment time of 42 days. With PET-ART, patients received a radiation dose of 54.0-79.2 Gy, delivered in 1.8-Gy fractions, twice daily, depending on the mean lung dose or spinal cord dose constraint. The mean overall treatment time was 25 days.

All patients received a diagnostic PET scan at baseline. Patients who received PET-ART received an additional PET-CT scan for treatment planning in the treatment position. Baseline characteristics are presented in Table E1 (available online at www.redjournal.com).

Parameters of the disease model

The distribution of baseline clinical features and tumor features, used to draw a hypothetical patient in the model, correspond to the distribution of these features in the general NSCLC population. Although the cohort of patients was separately drawn for both treatment strategies, baseline characteristics were similarly distributed to eliminate the bias due to different baseline characteristics (Table E2, available online at www.redjournal.com). The transitioning of patients between health states is governed by personalized hazard rates. These hazard rates consist of a baseline time-dependent hazard that is the same for each individual, and a personal time-independent hazard rate ratio (HR) that varies according to the features of the patient and the tumor and the treatment given. Parameter values are given in Table 1. Estimation of the model parameters has been described elaborately in the Supplementary Material (available online at www.redjournal.com). Model predictions for each transition of the model, for overall survival, and for toxicity were internally and externally validated (9).

Costs and health-related quality of life

A hospital perspective was taken in this study. Resource use estimates were based on the data of the Maastro Clinic and the literature (13-15). Costs were based on the Dutch Manual for Costing in Economic Evaluations, the Dutch

Table 1 List of input parameters for health effects, resource use, and unit costs

Parameter	Point estimate (HR, OR, probability)	SE (α, β)	Distribution	Reference (year)
Multistate model (HRs)			Lognormal	9, 10
Transition 1				
WHO PS	2.34	0.50		
N stage	0.75	0.43		
RT2	0.47	0.41		
Chemotherapy	2.37	0.00		
GTV (per 10 cm^3)	1.01	0.47		
Transition 2				
WHO PS	2.31	0.32		
N stage	1.51	0.27		
RT2	0.10	0.37		
Chemotherapy	3.21	0.00		
GTV (per 10 cm^3)	1.02	0.34		
Transition 3				
WHO PS	1.72	0.45		
N stage	2.98	0.35		
RT2	0.40	0.33		
Chemotherapy	0.60	0.00		
GTV (per 10 cm^3)	1.03	0.34		
Transition 4				
RT2	0.70	0.44		
Transition 5				
RT2	0.87	0.23		
Toxicities				
Dysphagia (ORs)			Normal	9, 10
RT2	0.80	0.23		
N stage	1.27	0.23		
Intercept for dysphagia = 2	2.06	0.24		
Intercept for dysphagia ≥3	4.18	0.32		
Dyspnea (probabilities)			Dirichlet*	9, 10
CRT grade <2	0.63	(12; 7)		
CRT grade 2	0.32	(6; 1)		
CRT grade ≥3	0.05	†		
PET-ART grade <2	0.74	(148; 52)	Dirichlet*	9, 10
PET-ART grade 2	0.16	(32; 20)		
PET-ART grade ≥3	0.10	†		
Probability of irreversible dyspnea	0.71	(5; 2)	Gamma	27
Resource use				
Radiation therapy				
No. of fractions CRT	31	1.89	Normal	10
No. of fractions PET-ART	36	5.71	Normal	
Adverse events				
Days of medication with dysphagia	30		Fixed	19
Days of hospital admission with dysphagia	2	(13.33; 0.15)	Gamma	15
Days of tube feeding with dysphagia	22	(220.50; 0.10)	Gamma	15
Days of irreversible dyspnea	Lifelong			
Outpatient visits				
Year 1	4		Fixed	14
Year 2	2			
Year 3	1			
Unit costs (€)				
Treatment				
Radiation therapy per fraction	244	16.95	Lognormal	14 (2010)
PET-scan	1325		Fixed	18 (2012)
Outpatient visits	60		Fixed	17 (2010)

(*continued on next page*)

Table 1 (*continued*)

Parameter	Point estimate (HR, OR, probability)	SE (α, β)	Distribution	Reference (year)
Total costs in state LR and DM per year (mean, median)	33,220, 22,992			13 (2005)
Daily costs used for base-case scenario (mean)	91			
Breakdown of total costs in state LR and DM (median)				
Hospitalization	12,428	16,808	Lognormal	
Outpatient visits	2168	3753	Lognormal	
Chemotherapy	5016	963	Lognormal	
Diagnostic tests	245	723	Lognormal	
Lab	3135	3070	Lognormal	
End-of-life care costs in cancer per year (palliative care only)	6603	737	Lognormal	16 (2000)
Toxicity				
Medication dysphagia per day	2.80		Fixed	19 (2012)
Treatment irreversible dyspnea per year	1140	112	Gamma	14 (2000)
Hospital admission per day	462		Fixed	17 (2010)
Replacing/removing tube	105		Fixed	17 (2009)
Tube feeding per day	25		Fixed	15 (2009)
Utilities				
No progression (reference value)‡	0.825	0.067	Beta	20
Disutility any adverse event	0.353	0.05	Beta	15
Disutility local recurrence	0.053	0.034	Beta	20
Disutility metastatic disease	0.252	0.032	Beta	20

Abbreviations: CHT = chemotherapy; CRT = conventional CT-based radiation therapy treatment; DM = distant metastasis; GTV = gross tumor volume; HR = hazard ratio; LR = local recurrence; N stage = number of lymph nodes affected; OR = odds ratio; PET-ART = positron emission therapy–based isotoxic accelerated radiation therapy treatment; RT2 = effect of PET-ART versus CRT; WHO PS = World Health Organization performance status.

* Dirichlet distributions were based on a series of conditional β distribution for probabilities of dyspnea grade <2 (p1) and dyspnea grade 2 (p2).

† The probability of dyspnea grade ≥3 was estimated by 1-p1-p2.

‡ "No progression" is the reference utility. Utilities for the states LR and DM are obtained by subtracting corresponding disutility.

Healthcare Board, or the Pharmacotherapeutical Compass, and the literature (16-19). All costs were reported in euros. Price indices were used to convert costs to the 2012 price level.

Each health state in the model is associated with a specific utility, reflecting the quality of life in that health state. The utility estimates for the model are obtained from a meta-analysis of 23 studies of utilities in NSCLC patients (20) and from a cost-effectiveness study (15).

Resource use estimates, costs, and utility values are presented in Table 1. The Supplementary Material (available online at www.redjournal.com) describes cost calculations and utility values in more detail.

Base-case analysis

In the base-case analysis, model predictions for both radiation therapy strategies were obtained by simulating the health trajectories of a cohort of 50,000 patients from the moment they start radiation therapy until they die or have reached the time-horizon of 3 years. This time horizon was chosen because it was deemed appropriate to cover the health benefits and costs of radiation therapy in NSCLC.

Additionally, in the base-case analysis the following assumptions were made. (*1*) The type of radiation therapy treatment strategy affects all transitions, and this effect is different for each transition; (*2*) Patients in both treatment groups have similar resource use after the end of radiation therapy treatment, until their transitioning to the next event; (*3*) The risk to develop a DM after an LR is implicitly incorporated in the risk of death after LR; (*4*) Patients with an LR and patients with a DM have similar costs per unit of time, independent of their history; and (*5*) All deaths within the time horizon are caused by cancer.

For both radiation therapy strategies, we determined the proportion of patients experiencing LR or DM, the proportion of deaths, the proportion and grade of both adverse events, the average total costs, the average life-years lived (LYs), and the average quality-adjusted life-years (QALYs). To obtain the QALY estimates per patient, we multiplied the time in a health state by the utility of that state and subsequently summed over all health states that are visited until death. Costs and LYs were discounted at 3%. We computed the incremental cost-effectiveness ratio (ICER) of PET-ART compared with CRT by dividing the difference in costs by the difference in LYs. The incremental cost utility ratio (ICUR) of PET-ART compared

with CRT was obtained by dividing the difference in costs by the difference in QALYs.

Uncertainty analysis

For the probabilistic analysis, we assigned distributions to all the model input parameters (Table 1). We randomly created 1000 parameter sets, and for each set of parameters, 50,000 patients were simulated. Model predictions for the difference in costs and LYs between PET-ART and CRT, and for the difference in costs and QALYs were represented on a cost-effectiveness plane.

For the HRs that were used to calculate the profile-specific transition rates between the health states in the model, normal distributions were assumed. By means of Cholesky decomposition of the covariance matrix, correlated draws for all the HRs were obtained (21). The same was done to obtain correlated random draws for the parameters of the regression model for dysphagia. The probabilities of dyspnea grade 2 and grade 3 or higher were varied according to Dirichlet distributions (21).

To draw conclusions regarding cost-effectiveness of PET-ART compared with CRT, a cost-effectiveness acceptability curve was obtained, which presents the probability that PET-ART is cost-effective compared with CRT according to the simulation results for the 1000 parameter sets, for different threshold values for 1 unit in health gain. According to the WHO, a strategy is considered highly cost-effective if the ICUR does not exceed the value of once the gross domestic product (GDP) per capita purchasing power parity of a country (22). This means a threshold value of €25,982 per QALY in Europe and €31,594 in the United States, which has the highest GDP worldwide (23). To explicitly explore the sensitivity of the ICER and ICUR of PET-ART versus CRT to the model assumptions, we carried out scenario analyses for health effects, costs, and utilities (see Supplementary Material, available online at www.redjournal.com).

Results

Table 2 shows the results of the base-case analysis. For PET-ART, the proportions of LR, DM, and death after three years were smaller than for CRT. However, proportions of severe toxicity were smaller for CRT. Incremental life years and incremental QALYs were 0.42 and 0.33 in favor of PET-ART. PET-ART was slightly more expensive; incremental costs of PET-ART compared with CRT were €569. The incremental costs and effects resulted in an ICER of €1360/LY and an ICUR of €1744/QALY. The model predictions of the base-case analysis for progression-free and overall survival are presented in Supplementary Figure 1 (available online at www.redjournal.com).

Uncertainty analyses

Figure 2A and B show the results of the probabilistic sensitivity analysis for LYs gained and QALYs gained in 2 cost-effectiveness planes. The grey dots correspond to the 1000 parameter sets, each parameter set representing the simulated results of 50,000 patients. The black dot and the black horizontal and vertical lines in each plane correspond with the point estimates and their 95% confidence intervals (CIs) for the difference in LYs, QALYs, and costs as shown in Table 2.

Of 1000 ICER and ICUR replicates, 36% of the replicates are in the lower right quadrant, indicating that PET-ART both improves outcomes and reduces costs. The remaining 64% is located in the upper right quadrant,

Table 2 Base-case scenario: Model predictions for CRT and PET-ART over a 3-year time horizon (n = 50,000)

Parameter	No discounting		Discounted at 3%		Δ (PET-ART −CRT)	95% CI for Δ	ICER (€/LY)	ICUR (€/QALY)
	CRT	PET-ART	CRT	PET-ART				
Proportion LR			0.14	0.11	−0.03			
Proportion M			0.49	0.38	−0.11			
Proportion death overall			0.82	0.65	−0.17			
Dysphagia (proportions)								
0-1			0.77	0.61	−0.16			
2			0.19	0.31	0.12			
3+			0.04	0.08	0.04			
Dyspnea (proportions)								
0-1			0.63	0.74	0.11			
2			0.32	0.16	−0.16			
3+			0.05	0.10	0.05			
Total LYs	1.39	1.82	1.38*	1.79*	0.42	0.19, 0.61		
Total QALYs	1.07	1.40	1.04*	1.38*	0.33	0.13, 0.49		
Total costs (€)	25,186	25,720	24,879*	25,449*	569	−5327, 6936	1360	1744

Abbreviations: CI = confidence interval; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; LYs = life years; M = metastasis; QALYs = quality-adjusted life years. Other abbreviations as in Table 1.

* Numbers are rounded.

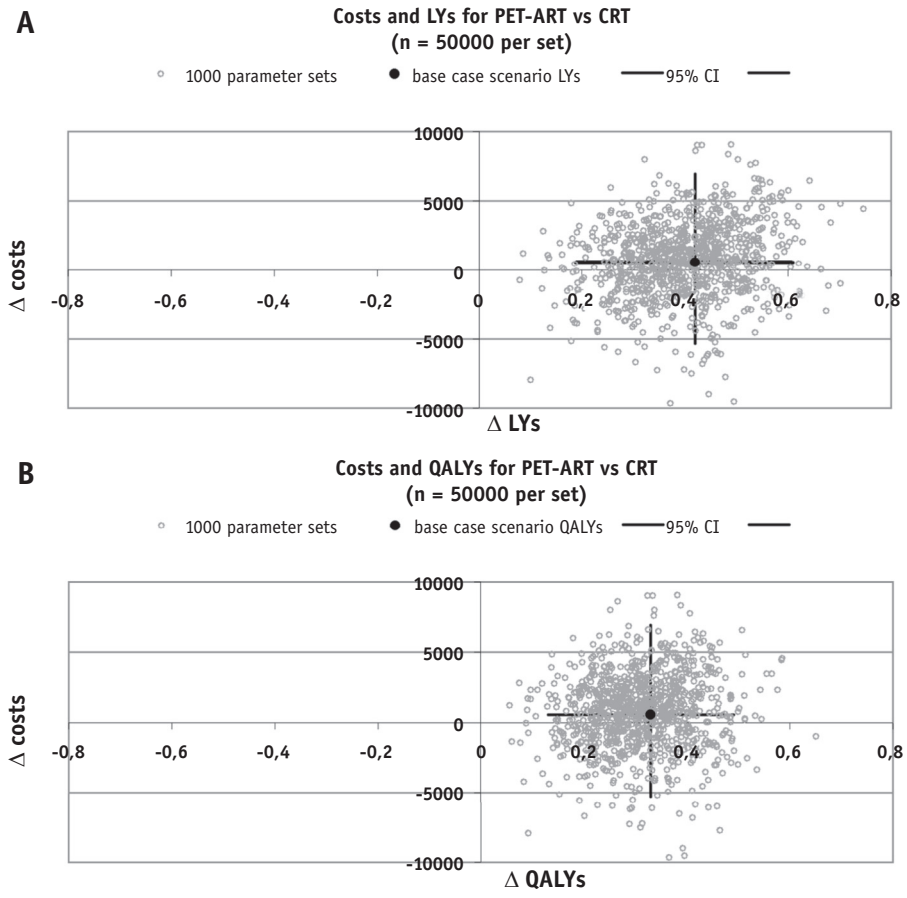

Fig. 2. Results of the probabilistic sensitivity analysis showing incremental costs and incremental life years (LYs) (A) and quality-adjusted life-years (QALYs) (B) for positron emission tomography—based isotoxic accelerated radiation therapy treatment (PET-ART) compared with conventional CT-based radiation therapy treatment (CRT).

indicating that PET-ART improves outcomes at increased costs compared with CRT. The cost-effectiveness acceptability curve (Fig. 3) shows that at a threshold value of €18,000 per QALY, there is a 95% probability that PET-ART is cost-effective. Considering the aforementioned WHO-based threshold value of €25,982 per QALY, the probability that PET-ART is cost-effective compared with CRT is 99%.

None of the scenario analyses resulted in an ICER or ICUR higher than the aforementioned WHO-based threshold values, which would have affected the treatment decision.

Discussion

In this study we showed that, given the available data, individualized PET-ART for NSCLC seems to be cost-effective compared with CRT. In our base-case analysis we found that patients receiving PET-ART have an average of 0.42 (95% CI 0.19-0.61) incremental LYs and 0.33 (95% CI 0.13-0.49) incremental QALYs over similar patients receiving CRT. One year of survival gain costs €1360, and a gain of 1 year in quality-adjusted survival costs €1744. In our probabilistic analysis, PET-ART was more effective than CRT in all simulations. The probability that PET-ART is not only more effective but also less costly than CRT was 36%.

In the present study we compared a more individualized strategy, PET-ART, with a less personalized treatment strategy, CRT. The PET-CT—based strategy is a way to improve the detection of lymph nodes affected with tumor activity and to individualize the dose of radiation therapy according to the constraints of the organs at risk (24). A wide variability of doses is the consequence. In addition, a modified accelerated scheme was used. The conventional radiation therapy treatment strategy refers to CT planning for affected lymph nodes based on anatomical visualization, and consequently a fixed dose is optimized according to the anatomy of the tumor and the organs at risk.

Ideally we would have included a number of other strategies in our evaluation, such as a purely hypothetical nonindividualized PET-CT—based planning strategy and an individualized CT-based planning strategy, with and without an accelerated radiation therapy scheme. However, no data for such alternative strategies were available.

A recent meta-analysis evaluated modified radiation therapy schemes, concluding that accelerated radiation

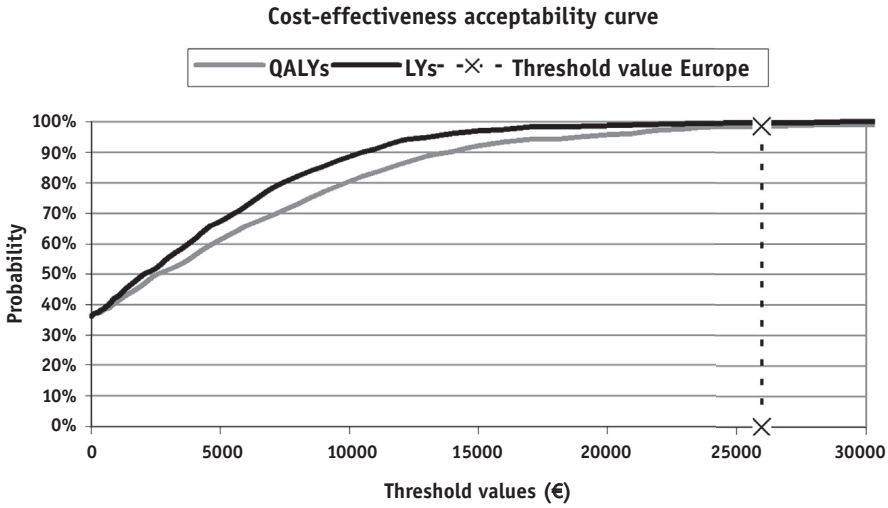

Fig. 3. Cost-effectiveness acceptability curve for quality-adjusted life-years (QALYs) and life years (LYs): The probability that positron emission tomography–based isotoxic accelerated radiation therapy treatment is cost-effective compared with conventional CT-based radiation therapy treatment for different threshold values.

therapy led to reduced mortality (5). The results of this meta-analysis were used in a cost-effectiveness study, showing increased effects and costs for all schemes other than conventional radiation therapy (6). The radiation therapy scheme evaluated in the present study was not only accelerated but isotoxic as well. This scheme is believed to be beneficial in terms of tumor coverage, the isolated nodal failure rate, and the volume of healthy tissues irradiated (3, 4). However, long-term effects on overall survival, progression-free survival, quality of life, and costs were never evaluated. Our results indicate that PET-ART also leads to better progression-free survival, overall survival, and quality of life.

Our study has a number of limitations. First, we were restricted to estimate the effect in patients who were treated with radiation therapy alone (with or without sequential chemotherapy) rather than concurrent chemoradiation therapy. It is important to note that at present, concurrent chemoradiation therapy remains the standard treatment option for stage III patients. However, this may change in the future as radiation therapy schemes are further optimized, because concurrent chemoradiation therapy is associated with a considerable patient burden. Indeed, because the improved survival of concurrent chemoradiation therapy over sequential chemoradiation therapy is due to improved local tumor control with a similar hazard for distant metastases (25), it may be hypothesized that optimized sequential chemoradiation therapy alone may lead to the same survival but with fewer side effects. In addition, the guideline recommendation for concurrent chemoradiation therapy is based on the results of a meta-analysis that included trials in which relatively fit patients with minimal comorbidities were included (25). These patients are not representative of the typical NSCLC patient population (7). Indeed, for many patients, sequential chemoradiation therapy or radiation therapy alone is considered the best treatment option. In case of stage I patients who are ineligible for surgery, stereotactic radiation therapy is currently standard treatment. A small proportion of the patients in our data had stage I disease (15%). However, these patients were not eligible for stereotactic treatment, nor for concurrent chemoradiation therapy, owing to their tumor location. They received sequential therapy instead. Because the patients in our data were not treated in a trial setting, but to their best treatment option available at the time, we believe that our results are representative and relevant for a real-life clinical setting.

Second, we used a time-horizon of 3 years instead of a lifelong time horizon. However, because in the data more than 80% of lung cancer deaths had already occurred within 3 years, this time-horizon seems appropriate for this patient group. Moreover, because only few events occurred after 3 years, the timing of events cannot be accurately predicted after 3 years.

Finally, our study was carried out in a Dutch health setting, using mainly Dutch sources for costs and resource use. However, although costs vary widely over countries, the results of the scenario analyses showed that varying cost and resource did not affect our main conclusion.

Evaluations of long-term health effects of novel radiation therapy strategies in randomized, controlled trials are scarce (26). To extrapolate short-term evidence to long-term predictions, we carried out a model-based evaluation. We have used the best available evidence to estimate all parameters of the model and validated the model both internally and externally. By using this micro-simulation model, we were able to assess the consequences of uncertainty in all health parameters of the model on model predictions, taking the correlations among input parameters into account. Patient heterogeneity is included in the model. As such, we were able to simulate a randomized, controlled trial, thereby eliminating bias due to differences in baseline

characteristics between the 2 treatment groups (9). We explicitly opted for a micro-simulation model to easily adjust the patient population for other decision problems in radiation therapy treatment for lung cancer. With these properties, the micro-simulation model provides a proxy for empirical evidence, while clearly presenting the uncertainty of the model and allowing for evaluations of other relevant scenarios. This model will be used to evaluate new developments in radiation therapy treatment, with both treatment strategies in the present study as reference strategies.

Conclusion

According to the available data, we found that PET-ART is likely to be more effective than CRT and seems to be cost-effective as well. There is a 64% probability that PET-ART is more costly, but the additional cost is limited. These findings can support decision makers to implement PET-ART schemes in radiation therapy treatment planning.

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