Cost-effectiveness of prophylactic cranial irradiation in stage III non-small cell lung cancer

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Original Article

Cost-effectiveness of prophylactic cranial irradiation in stage III non-small cell lung cancer

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ABSTRACT

Introduction: In stage III non-small cell lung cancer (NSCLC), prophylactic cranial irradiation (PCI) reduces the brain metastases incidence and prolongs the progression-free survival without improving overall survival. PCI increases the risk of toxicity and is currently not adopted in routine care. Our objective was to assess the cost-effectiveness of PCI compared with no PCI in stage III NSCLC from a Dutch societal perspective.

Methods: A cohort partitioned survival model was developed based on individual patient data from three randomized phase III trials ($N = 670$). Quality-adjusted life years (QALYs) and costs were estimated over a lifetime time horizon. A willingness-to-pay (WTP) threshold of €80,000 per QALY was adopted. Sensitivity and scenario analyses were performed to address parameter uncertainty and to explore what parameters had the greatest impact on the cost-effectiveness results.

Results: PCI was more effective and costly (0.443 QALYs, €10,123) than no PCI, resulting in an incremental cost-effectiveness ratio (ICER) of €22,843 per QALY gained. The probability of PCI being cost-effective at a WTP threshold of €80,000 per QALY was 93%. The probability of PCI gaining three and six additional months of life were 76% and 56%. The scenario analysis adding durvalumab increased the ICER to €35,159 per QALY gained. Using alternative survival distributions had little impact on the ICER. Assuming fewer PCI fractions and excluding indirect costs decreased the ICER to €18,263 and €5554 per QALY gained.

Conclusion: PCI is cost-effective compared to no PCI in stage III NSCLC, and could therefore, from a cost-effectiveness perspective, be considered in routine care.

Lung cancer is the leading cause of cancer death worldwide, making up almost 25% of all cancer deaths. In 2020, 2.2 million new lung cancer cases were reported globally [1]. Non-small cell lung cancer (NSCLC) accounts for about 84% of all lung cancers [2].

Patients with resectable stage III NSCLC are treated with surgery followed by (neo)adjuvant chemotherapy [3]. Chemoradiotherapy remains the cornerstone of treatment for patients with unresectable stage III NSCLC. For fit patients, standard is concurrent chemoradiotherapy. For patients that cannot tolerate concurrent chemoradiotherapy, sequential chemoradiotherapy represent a valid and effective alternative [4]. Although adjuvant durvalumab was recently added to concurrent chemoradiotherapy for patients with unresectable stage III NSCLC whose disease had not pro-

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gressed after chemoradiotherapy [3], durvalumab was not considered part of the treatment pathway for stage III NSCLC in this study. Despite these treatments, approximately 30% of stage III NSCLC patients treated with concurrent chemoradiotherapy develop brain metastases (BM) in the first two years after diagnosis, which has a devastating impact on the prognosis as well as the health-related quality of life [5–7].

A recent individual patient data (IPD) meta-analysis in stage III NSCLC showed that prophylactic cranial irradiation (PCI) reduces the BM incidence and prolongs the progression-free survival (PFS) and brain metastases-free survival (BMFS). However, no statistically significant overall survival (OS) improvement was observed and PCI is therefore currently not adopted in routine care [8].

In addition to the clinical effectiveness, given that health resources are finite, economic evaluations are performed to consider the cost-effectiveness of treatments to inform decision making. Decision-analytic models can be used to compare the cost-effectiveness of a new treatment to existing treatments [9]. The objective of this study is to perform a cost-effectiveness analysis comparing PCI to no PCI in stage III NSCLC.

Materials and methods

Individual patient data meta-analysis of PCI in stage III NSCLC

IPD of four randomized controlled trials [10–13] (RCTs), which were previously used in a meta-analysis of Witlox et al. [8], were used as the primary data source for the economic model. Due to considerable inter-trial heterogeneity between the SWOG8300 trial [10] and the other trials, only the three most recent RCTs [11–13] were selected for the economic model. Between 2002 and 2015, these trials accrued a total of 670 patients (median follow-up 97 months, 95% CI [73–108]), treated with combinations of radiotherapy and chemotherapy with or without surgery. Administered PCI fractionation schedules varied across the trials (30 Gy in 15 and 10 fractions in respectively the RTOG0214 and the Guangzhou2005 trials, 36 Gy in 18 fractions or 30 Gy in 12 or 10 fractions in the NVALT-11 trial). Overall, most patients were men (65%), older than 60 years (55%), had non-squamous disease (68%) and an Eastern Cooperative Oncology Group performance status of 1 (51%).

Model structure, discounting, outcomes and assumptions

A cohort partitioned survival model was developed, comparing PCI to no PCI using a hypothetical cohort of patients. Five mutually exclusive health states (progression-free, brain metastases, extracranial metastases, both brain and extracranial metastases and death) were used to reflect the course of disease. These health states were based on whether patients were alive and whether disease progression (of different types) occurred or not (Fig. 1). OS was defined as the time from model entrance until death from any cause. PFS, BMFS and extracranial metastases-free survival (EMFS) were defined as the time from model entrance until death or first progression, first occurrence of BM and first occurrence of extracranial metastases (EM) respectively. All patients started in the progression-free health state and transitioned to other health states if disease progression or death occurred. The expected effects and costs per health state were estimated over a lifetime time horizon with a one month cycle time. Future effects and costs were discounted according to the Dutch pharmaco-economic guidelines by rates of respectively 1.5% and 4.0%. Expected life years (LYs), quality-adjusted life years (QALYs) and costs were calculated for current practice with and without PCI. A willingness-to-pay (WTP) threshold of €80,000 was adopted. The incremental

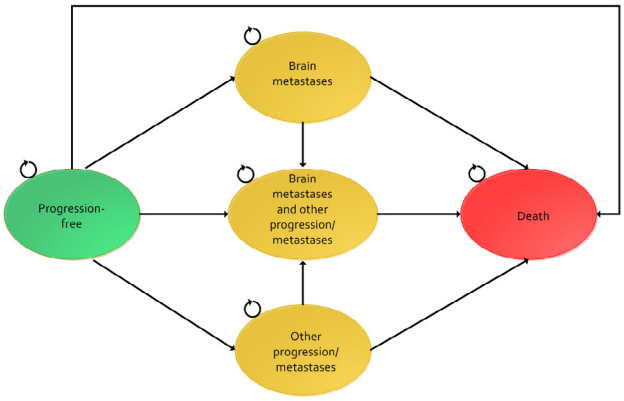

Fig. 1. Model structure.

costs were divided by the incremental QALYs to calculated the incremental cost-effectiveness ratio (ICER). The economic model was built and analysed in R version 3.6.2.

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

- After a progression event, patients could not return to the progression-free health state.
- PCI was assumed to be delivered in 15 fractions of 2 Gy. A different schedule (10 fractions of 3 Gy) was explored in a scenario analysis.
- No adverse event (AE) disutilities were applied to the model to capture negative health effects of AEs, because these were assumed to be incorporated through the treatment covariate in the mixed effects model that was used to estimate health state utilities.
- Costs of AEs were applied as a one-off cost in the first model cycle.

Model input parameters

Input parameters to populate the economic model are listed in Table 1.

Clinical effectiveness data

Effectiveness data from the PCI IPD meta-analysis were used to inform the economic model. The observed time-to-event data were fitted to parametric survival models (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalized gamma) to extrapolate the OS, PFS, BMFS and EMFS over the time horizon. To preserve randomization within the trials, the regression analyses for the parametric survival models were first estimated stratified by trial and subsequently the regression outcome parameters were pooled. Based on statistical testing (Akaike information criterion, Bayesian information criterion, supplementary appendix 1 Table 1), visual inspection of the curves and validation of the extrapolated data using external data (i.e. expert opinion), the log-normal distribution was selected for OS, PFS, BMS and EMFS (Fig. 2, supplementary appendix 1 Table 2).

Adverse events

AE rates were based on the NVALT-11 trial, as this was the only study reporting AE rates for both trial arms. Any grade of neurological and non-neurological AEs were included if it occurred in at least 5% of either arm. Serious (grade $\geq$ 3) neurological and non-

Table 1
Model input parameters.

Parameter	Value	Standard error	Distribution
Model			
Time horizon	40 years	–	Fixed
Cycle length	1 month	–	Fixed
Costs discount	4.0%	–	Fixed
Effects discount	1.5%	–	Fixed
Cost and resource use			
Number of fractions of PCI	15	–	Fixed
Price per fraction of PCI	€287	–	Fixed
Cost of PCI	€4305	–	Fixed
BM subsequent treatment volume per cycle	0.269	0.063	Gamma
EM subsequent treatment volume per cycle	0.147	0.014	Gamma
BM + EM subsequent treatment volume per cycle	0.101	0.022	Gamma
Price subsequent treatment BM per cycle	€617	5.856	Gamma
Price subsequent treatment EM per cycle	€12,708	10.422	Gamma
Price subsequent treatment BM + EM per cycle	€7781	18.807	Gamma
Price follow-up visit	€56	–	Fixed
Number of visits for progression-free patients	Year 1: 5 Year 2: 2 Next years: 1	–	Fixed
Number of visits for progressed patients	4 per year	–	Fixed
Indirect costs PCI	€129,284	–	Fixed
Indirect costs no PCI	€114,729	–	Fixed
Price durvalumab per model cycle (scenario analysis)	€7613	–	Fixed
Number of cycles of durvalumab (scenario analysis)	12	–	Fixed
Adverse event costs			
Total AE costs PCI	€3112[1]	–	Fixed[2]
Total AE costs no PCI	€1701[1]	–	Fixed[2]
Utilities			
Progression-free PCI	0.780	0.018	Normal[3]
Progression-free no PCI	0.787	0.018	Normal[3]
BM PCI	0.691	0.056	Normal[3]
BM no PCI	0.697	0.056	Normal[3]
EM PCI	0.717	0.019	Normal[3]
EM no PCI	0.724	0.019	Normal[3]
BM + EM PCI	0.550	0.051	Normal[3]
BM + EM no PCI	0.556	0.051	Normal[3]

[1] Cost and volume per adverse event reported in supplementary appendix 1 Table 3.
[2] Costs of the individual adverse events were included in the probabilistic sensitivity analysis using a beta distribution.
[3] The regression coefficients of the utility estimates rather than the actual health state utility values were varied in a normal distribution.

neurological AEs were included if it occurred in at least 2% of either arm. AE's that, irrespective of occurrence or grade, were expected to have a significant impact on costs (based on expert opinion) were also included in the economic model.

Utilities

Euroqol-5D utility scores were used to measure treatment benefits. Utility is a single score measure for generic health-related quality of life ranging from <0 (worse than death), through 0 (death) to 1 (full health). Utility scores based on the Dutch tariff were derived from the NVALT-11 trial, which is the only phase III trial that used the Euroqol-5D instrument. A linear mixed effects model (to account for multiple observations nested within patients), including treatment and progression status as covariates, was used to estimate health state utility values. No AE disutilities were applied to the model, because negative health effects of AEs were expected to be incorporated through the treatment covariate in the mixed effects model. Quality-adjusted life years (QALYs) were calculated by multiplying the estimated utility scores with life expectancy.

Costs

Costs were calculated using the Dutch health care perspective and converted to the 2020 price level, based on prices indices of Statistics Netherlands (CBS). The costs included in the model were treatment costs, disease management and monitoring costs, AE costs, and indirect costs.

Treatment costs

The cost of one fraction of PCI was €287 and the recommended and most commonly applied fractionation dose/schedule was a total of 30 Gy in 15 fractions of 2 Gy. PCI was assumed to be applied in the first 3 weeks of the model and PCI-related costs were therefore applied to the first model cycle only. Other treatment costs included in the model were related to subsequent treatments after disease progression. Prospective cohort data of the ARCTIC trial [14] including patients with stage III NSCLC that received radical intent treatment (N = 156), were used to calculate the average resource use per model cycle and per type of disease progression for subsequent treatments.

Disease management and monitoring costs

In accordance with clinical guidelines and expert opinion, for patients in the progression-free health state five follow-up visits were assumed in the first year, two follow-up visits in the second year and one follow-up visit in every year thereafter. For patients who progressed, a follow-up visit once every three months was assumed.

AE costs

Costs related to the treatment of AEs were applied in the first treatment cycle and sourced from published literature (supplementary appendix 1 Table 3).

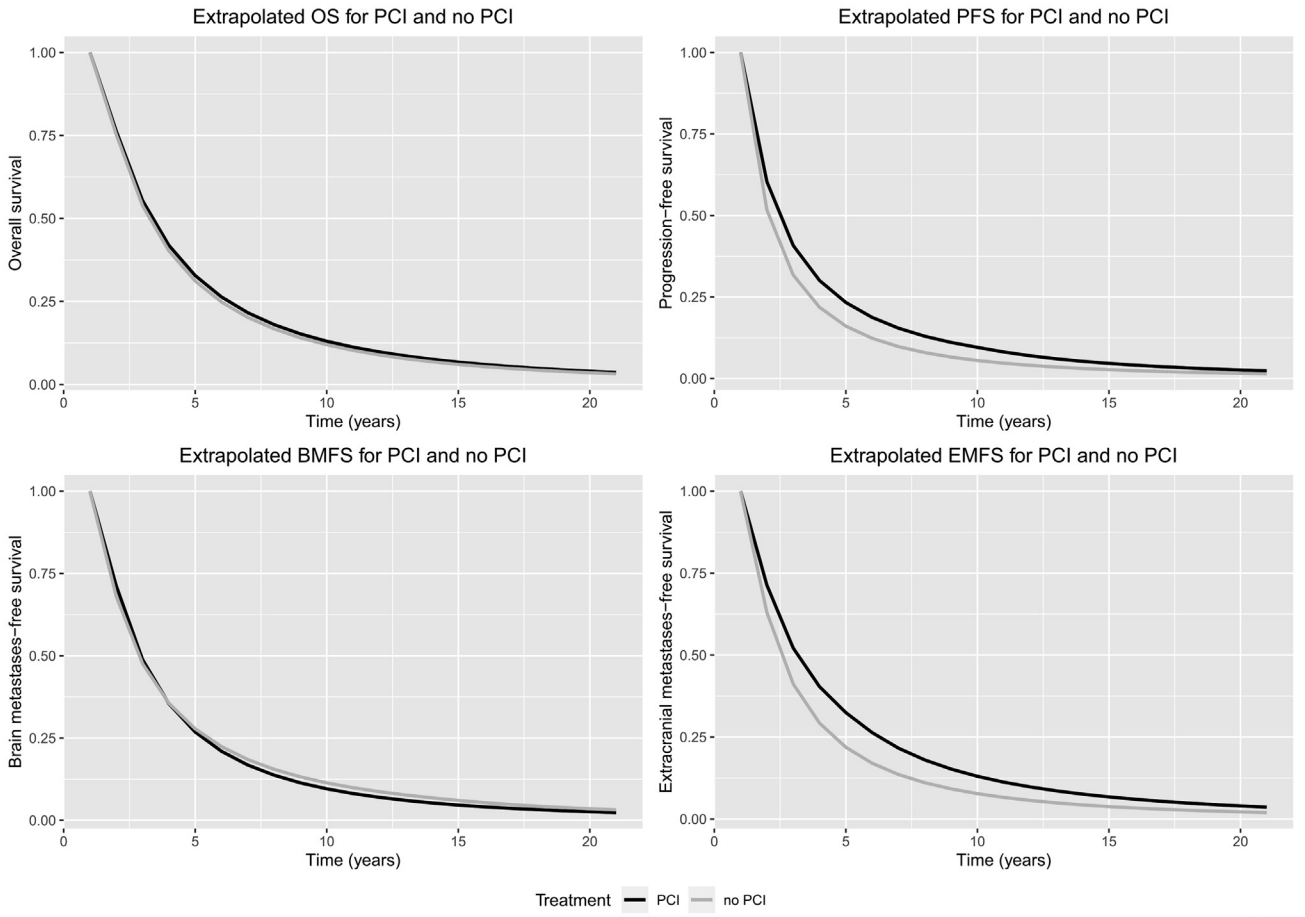

Fig. 2. extrapolated OS, PFS, BMFS and EMFS curves for PCI and no PCI.

Indirect costs

Indirect costs (costs in the last year of life, costs of unrelated diseases, and non-medical consumption costs) were estimated using the Practical Application to Include Disease Costs (PAID) tool [15].

Sensitivity analyses

Deterministic sensitivity analyses were conducted to explore what parameters had the greatest impact on the cost-effectiveness results. The 10 parameters with the greatest impact on the ICER were presented in tornado diagrams in descending order. Probabilistic sensitivity analyses (5,000 iterations) were performed (and plotted on a cost-effectiveness plane) to explore the impact of parameter uncertainty on the cost-effectiveness by assigning a distribution to the input parameters. The probability of PCI yielding a minimal clinically important difference (the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management [16]) at different LY and QALY thresholds was plotted using a survival probability curve. To illustrate the probability of PCI being cost-effective at different WTP thresholds, cost-effectiveness acceptability curves were used. In addition, expected loss curves were plotted to estimate the expected financial loss at different WTP thresholds. The population expected value of perfect information (EVPI) was calculated, assuming an annual incidence of 900 Dutch patients with stage III NSCLC expected to be eligible for PCI, and assuming 5 and 10 year time horizons of the technology (11,000 annual incidence in the Netherlands × 85% NSCLC × 30% stage III × 40% concurrent chemoradiotherapy or surgery × 80% fit enough for PCI ≈ 900).

Scenario analyses

A scenario analysis was performed to explore the impact of adding durvalumab (every four weeks, 12 months maximum) to the local treatment modalities (combinations of radiotherapy and chemotherapy with/without surgery) for both the PCI and no PCI strategy. This was done by incorporating the durvalumab costs and adjusting the estimated absolute OS and PFS to be in line with PACIFIC without modifying the parameters for the PCI treatment effect [17] (Table 1, supplementary appendix 1 Table 2). Although durvalumab in routine care is currently only given after concurrent chemoradiotherapy, to explore the maximum impact of adding durvalumab it was added to all patients, irrespective of their local treatment modality. In addition, scenario analyses were performed to explore different survival distributions (log logistic and generalized gamma, supplementary appendix 1 Table 2), to explore a different PCI fractionation schedule (10 fractions of 3 Gy), and to explore the impact of excluding indirect costs on the cost-effectiveness results.

Model validity

The economic model was validated using the Assessment of the Validation Status of Health-Economic decision Models (AdViSHE) checklist (supplementary appendix 2). The modelled OS, PFS, BMFS and EMFS were internally validated against the observed outcomes in the pooled trial data (supplementary appendix 1 Table 4).

Table 2
Average results of the probabilistic base-case cost-effectiveness analysis (5000 iterations).

Treatment	Life years	QALYs	Costs	Incr. life years	Incr. QALYs	Incr. costs (€)	ICER
No PCI	3.963	3.023	€108,773				
PCI	4.539	3.466	€118,896	0.576	0.443	€10,123	€22,843

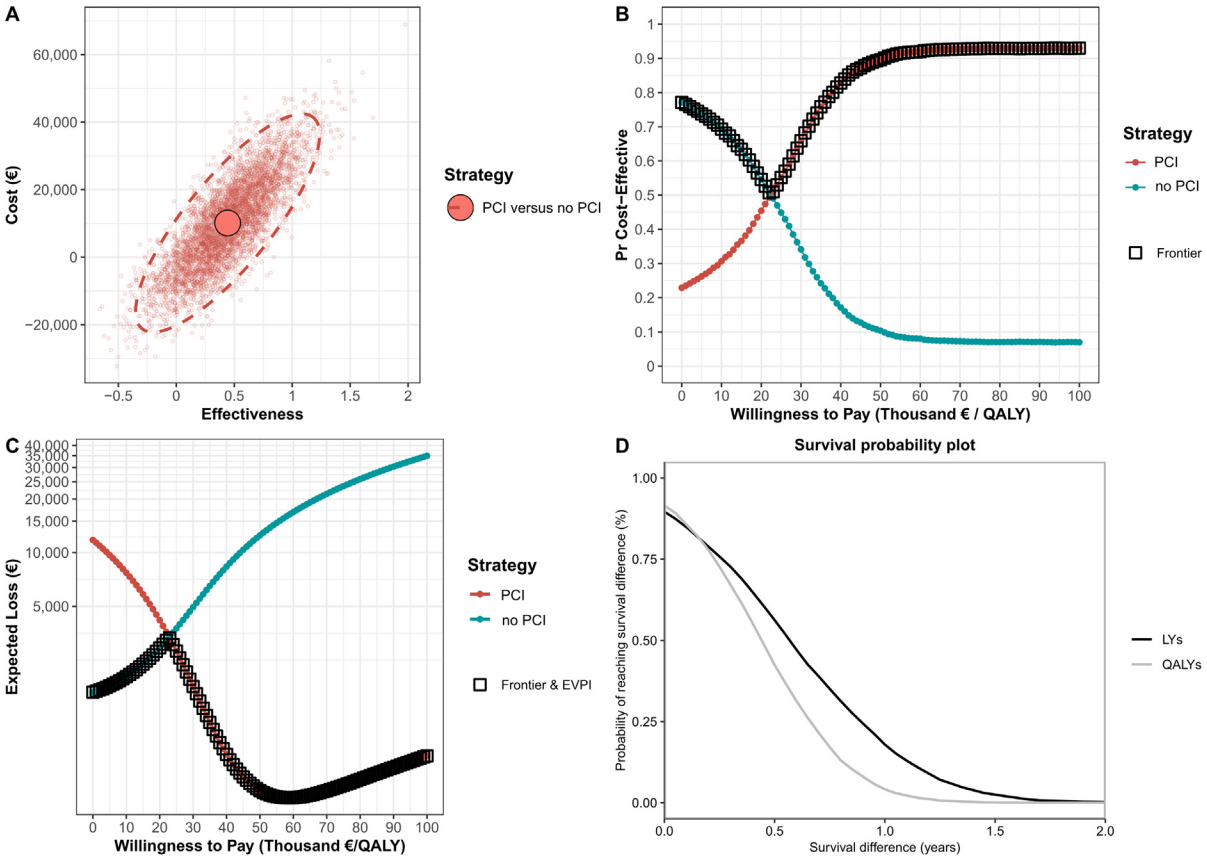

Fig. 3. cost-effectiveness plane (A), cost-effectiveness acceptability curves (B), expected loss curves (C), and survival probability curves (D).

Results

The mean probabilistic costs for PCI were €118,896 (95%CI €102,205–€139,255). Mean LYs and QALYs were 4.539 (95%CI 3.871–5.272) and 3.466 (95%CI 2.986–3.960) respectively. For no PCI, mean probabilistic costs were €108,773 (95%CI 92,683–126,630), and mean LYs and QALYs were 3.963 (95%CI 3.402–4.564) and 3.023 (95%CI 2.612–3.444) respectively. Mean incremental costs, LYs and QALYs amounted to €10,123, 0.576 and 0.443 respectively, which resulted in an ICER of €22,843 per QALY gained (Table 2, Fig. 3A). Incremental QALYs and costs were mainly driven through the progression-free health state.

The DSA showed that the ICER was most sensitive to the utility of the progression-free health state and the number of administered PCI fractions. Nevertheless, for none of these parameters the ICER was above €31,000 per QALY gained (supplementary appendix 1 Fig. 1). The results of the PSA showed that, at a WTP threshold of €80,000 per QALY, the estimated probability of PCI being cost-effective was 93%. The expected loss at this WTP threshold was €534 for PCI and €25,863 for no PCI (Fig. 3B and C). Furthermore, the probability of PCI gaining three and six additional months of life were 76% and 56% respectively, and PCI gaining three and six months of life in perfect health were 73% and 42% (Fig. 3D). In addition, the estimated EVPI over time horizons of 5 and 10 years were 2.22 million and 4.05 million.

The scenario analysis exploring the impact of adding durvalumab to the local treatment modalities in the PCI and no PCI strategy resulted in an increased ICER of €35,159 per QALY gained (€21,424 in the deterministic base case). The scenario analyses using alternative survival distributions had little impact on the ICER. The scenarios of PCI given in fewer fractions and excluding indirect costs decreased the ICER to €18,263 and €5554 per QALY gained (Table 3).

Discussion

PCI after chemotherapy, radiotherapy and/or surgery was more effective (incremental QALYs 0.443), but also more costly than chemotherapy, radiotherapy and/or surgery alone (incremental costs €10,123). At a WTP of €80,000, PCI is very likely cost-effective (93%) compared to no PCI. The largest QALY gain for PCI was observed in the progression-free health state. This is in line with the results from the meta-analysis by Witlox et al. [8], which showed a statistically significant PFS benefit for PCI compared to no PCI. Incremental costs were also the largest in the progression-free health state, mainly driven by the cost of PCI and treating AEs. Nevertheless, the additional cost of PCI treatment (€4305) was relatively low.

Table 3
Results of the scenario analyses.

Treatment	Life years	QALYs	Costs	Incremental life years	Incremental QALYs	Incremental costs (€)	ICER
Deterministic base case							
No PCI	3.946	3.023	€108,439				
PCI	4.518	3.477	€118,164	0.572	0.454	€9725	€21,424
Scenario adding durvalumab to usual care in both arms							
No PCI	5.534	3.875	€205,804				
PCI	6.246	4.418	€224,888	0.712	0.543	€19,083	€35,159
Scenario alternative PCI fractionation schedule: 10 fractions of 3 Gy							
No PCI	3.946	3.023	€108,439				
PCI	4.518	3.477	€116,729	0.572	0.454	€8290	€18,263
Scenario alternative survival distribution for OS, PFS, BMFS and EMFS: log logistic							
No PCI	4.018	3.086	€109,067				
PCI	4.512	3.479	€117,586	0.493	0.393	€8519	€21,670
Scenario alternative survival distribution for OS, PFS, BMFS and EMFS: generalized gamma							
No PCI	4.044	3.111	€107,754				
PCI	4.751	3.668	€119,220	0.707	0.557	€11,466	€20,602
Scenario excluding indirect costs							
No PCI	3.946	3.023	€16,428				
PCI	4.518	3.477	€18,949	0.572	0.454	€2521	€5554

A strength of the current study is that we had access to the IPD of three recent RCTs that assessed PCI in stage III NSCLC. This allowed us to check and verify the published aggregate data and gave us detailed information about PCI-related side-effects. In addition, the ARCTIC dataset [14] included detailed information about the type of disease progression and subsequent treatments, and enabled us to very accurately estimate subsequent treatment costs and resource use.

One limitation of our study was that, although we included indirect costs using the PAID tool, we did not explicitly incorporate productivity losses in the economic model. However, 55% of the patient population was $\geq$ 60 years at model entrance, which is close to the Dutch pensionable age and productivity losses were therefore expected to be minor. Modelled OS was slightly better for PCI than no PCI, leading to higher indirect costs for the PCI strategy. The scenario analysis excluding indirect costs therefore decreased the ICER to €5554 per QALY gained. Another limitation was the potential heterogeneity (I^2 = 53%) between the included trials informing the economic model. Although the SWOG8300 trial was excluded because it was considerably older than the three other trials and likely used outdated imaging techniques and treatment methods (I^2 = 0%), trial differences were also observed in the remaining trials. Patients in the Guanghzou2005 trial, for example, all received surgery and chemotherapy, whereas most patients in the RTOG0214 and NVALT-11 trials were treated with concurrent chemoradiotherapy. In addition, PCI fractionation schedules were different between the trials (RTOG0214 30 Gy in 15 fractions, Guangzhou2005 30 Gy in 10 fractions, NVALT-11 36 Gy in 18 fractions or 30 Gy in 12 or 10 fractions).

To our knowledge, this study was the first to examine the cost-effectiveness of PCI in stage III NSCLC. The clinical effectiveness of PCI was assessed in several RCTs [10–13,18–228] and the recently published IPD meta-analysis [8], concluding that PCI, despite statistically significantly improving PFS and BMFS, did not statistically significantly improve OS compared to no PCI in stage III NSCLC. From a clinical perspective, this lack of clear OS benefit in combination with the increased risk of PCI-related toxicity are the most important arguments why PCI is currently not adopted in routine care for NSCLC. There are, however, conceptual differences between the clinical and cost-effectiveness perspectives in the evaluation of PCI. For example, both perspectives use different endpoints for the evaluation of health benefits and harms (i.e. individual clinical endpoints such as OS and toxicity versus QALYs as a single endpoint). In addition, both perspectives differ regarding their conception of clinical relevance (i.e. a minimum OS benefit based on clinical guidelines versus assuming that any QALY gain is potentially valuable), and their statistical framework for decision-making (i.e. frequentist framework using a pre-defined significance level versus Bayesian framework using probabilities). Therefore, in contrast to the clinical effectiveness results from the IPD meta-analysis and the previous trials, the current study shows that PCI added to current practice has a probability of 93% to be cost-effective, and the survival probability curve showed that PCI had an 76% and 56% probability to give the patient three and six additional months of life. From a cost-effectiveness perspective, PCI could therefore be considered for routine care. Most importantly, patients should be informed about the full range of treatment options that could be beneficial for them and associated consequences (in terms of OS, PFS or quality of life) in a shared decision making process.

Recently, fit patients with unresectable stage III NSCLC are increasingly treated with concurrent chemoradiotherapy followed by durvalumab [3]. In the base case, however, we assessed the cost-effectiveness of PCI after chemotherapy, radiotherapy and/or surgery without durvalumab, as the RCTs used as the primary data source for this economic evaluation were conducted before the emergence of immunotherapy. A scenario analysis was conducted to explore the potential impact of adding durvalumab to the local treatment modalities of both strategies in the economic model. The ICER increased (€35,159 per QALY gained), but remained below the WTP threshold of €80,000 per QALY. This suggests that PCI is a cost-effective option, also in the current situation with the availability of durvalumab. This result, however, should be verified in future studies such as the NVALT28 trial (NCT04597671), in which a low dose of PCI will be added to concurrent chemoradiotherapy and durvalumab. Pre-clinical models showed that immunotherapy potentiates the effects of radiotherapy by on average a factor two [23–27]. This makes it interesting to evaluate whether the combination of low-dose PCI (i.e. half the normal dose) and immunotherapy can further decrease the percentage of BM as well as preserve organ function as a lower radiation dose can probably be used when combined with an anti-PD(L)-1. Then, future studies should focus on the cost-effectiveness of immunotherapies combined with low dose and/or hippocampal sparing PCI, as these combinations could play an important role in the treatment pathway of patients with stage III NSCLC.

In conclusion, our analyses showed that PCI resulted in a QALY gain and is cost-effective compared to no PCI in stage III NSCLC. PCI

could therefore, from a cost-effectiveness perspective, be considered in routine care in a shared decision process with the patient.

Disclosures

Dirk K.M. De Ruysscher, Willem J.A. Witlox, Benjamin Lacas, Mary Redman, Si-Yu Wang, Vincent van der Noort, Harm van Tinteren, and Manuela A. Joore have no relationship to disclose considering this trial.

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Appendix A. Supplementary data

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