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Cost-effectiveness analysis of [18F]FDG PET-CT compared to contrast-enhanced CT at first response evaluation in stage IV NSCLC patients with a PD-L1 expression of ≥ 50% treated with immunotherapy

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Introduction

In 2020, lung cancer was a leading cause of cancer-related mortality in the Netherlands, with 13.910 new cases reported (Sosse E Klarenbeek, 2023). 9623 Of these new cases were non-small cell lung cancers (NSCLC) (Incidentie longkanker, 2021). When patients are first diagnosed, the NSCLC has in 50% of cases, NSCLC has already progressed to a metastatic disease (stage IV) (Vansteenkiste, 2019). In stage IV NSCLC, the cancer often spreads to distant sites such as the pleura, liver, brain, bones, or adrenal glands, or leads to malignant pleural or pericardial effusions (Vansteenkiste, 2019). The five-year survival of patients with stage IV NSCLC is only 3% (Overlevingscijfers van niet-kleincellige longkanker, 2021).

Patient with non-small cell lung cancer stage IV with a programmed death ligand (PD-L1) expression of ≥ 50% qualify for first-line treatment with immunotherapy (Vansteenkiste, 2019). According to the current Dutch Guideline these patients are treated with immunotherapy with Pembrolizumab as active ingredient regardless of the histologic subtype (squamous and non-squamous, respectively) (Eerstelijnsbehandeling met immunotherapie bij NSCLC, 2020). Pembrolizumab is an immune checkpoint inhibitor (ICI) that blocks the interaction between programmed cell death (PD-1) and programmed death ligand (PD-L1) to restore the immune surveillance against malignant cells (Castello, 2020). The current Dutch Guideline recommends a treatment period of 2 years and refers to the Keynote 189- and keynote 407 studies which showed significant improvements in survival outcomes and durable responses over a treatment period of 2 years (Leena Gandhi, 2018; Luis Paz-Ares, 2018; Eerstelijnsbehandeling met immunotherapie bij NSCLC, 2020).

In some patients, pembrolizumab may not be effective, necessitating the decision to discontinue treatment. To inform decisions on continuing or discontinuing the immunotherapy, in current best practice contrast-enhanced CT response evaluation is performed (Martin Reck, 2016). However, at first contrast-enhanced CT response evaluation after 6 to 9 weeks of treatment, perceived progression could, in fact, be pseudo-progression (Francesco Facchinetti, 2019). Typically, in treatments with immunotherapy, pseudo-progression occurs in the first few months of treatment. CT-based response evaluation primarily relies on observed growth of lesions, which in case of immunotherapy could be observed due to local inflammatory response causing the presence of oedema and haemorrhage (Wang, 2018; Wenxiao Jia, 2019; M. Mayorala, 2019). If progression is observed on CT-scan, but there is clinical improvement, immunotherapy is continued for an additional 6 to 9 weeks (Planchard et al., 2018). Continuing ineffective immunotherapy increases the risk of severe side effects, such as pneumonitis, fatigue, colitis, hepatitis, and severe skin reactions, while delaying potentially beneficial second line chemotherapy (Natasha B Leighl, 2019).

[^{18}F]FDG PET-CT could inform decisions on discontinuation at the time of first response evaluation, while with CT, the decision is often postponed (Martin Reck, 2016) to rule out pseudo-progression. After discontinuation, decisions to initiate second line treatment often depends on the patient's clinical condition and the time elapsed since first-line treatment (J-P. Sculier, 2009). Early discontinuation of treatment in non-responsive patients leads to cost savings on Pembrolizumab expenses treatment and improvements in health outcomes from the early to switch to a potentially beneficial second line treatment. While [18F]FDG PET-CT incurs higher initial imaging costs compared to contrast-enhanced CT, it can be cost-effective when the savings from avoided unnecessary treatments and health gain from timely switch to second line therapy outweigh the additional imaging expenses. This approach optimizes resource allocation and improves the efficiency of care while maximizing patient benefit.

By implementing an early switch strategy, patients may avoid prolonged exposure to pembrolizumab, thereby reducing the risk of experiencing severe side effects that could adversely impact their quality of life and overall treatment outcomes. This approach not only prioritizes patient safety but also ensures that individuals receive timely and appropriate therapies that may be more effective in managing their disease.

The aim of this study is to perform a cost-effectiveness analysis in which [^{18}F]FDG PET-CT is compared to contrast-enhanced CT for early response assessment in patients with stage IV NSCLC treated with immunotherapy to inform decisions on early discontinuation and switch to potentially beneficial second line treatment. This analysis can be used to inform recommendations regarding the prioritisation of [^{18}F]FDG PET-CT over CT in the early response assessment for patients with stage IV NSCLC with a PD-L1 expression of ≥ 50% that qualify for first-line treatment with immunotherapy.

Methods

Model structure

The Markov cohort model simulated a cohort of 10000 patients with stage IV NSCLC with a PD-L1 expression of ≥ 50%, who receive the immune checkpoint inhibitor monotherapy with Pembrolizumab as a first-line treatment. If first-line treatment is discontinued due to diagnosed progression or severe side effects, patients may receive second line Chemotherapy regimens if they are fit enough.

The difference between [18F]FDG PET-CT early response evaluation and contrast-enhanced CT response evaluation, which is currently the standard practice, during first response evaluation was modelled. This difference is expressed in the probability and timing of discontinuing immunotherapy during first response evaluation of both response assessments and was based on the studies by Park, et al. and Goldfarb, et al. (Sohyun Park, 2020; Lucas Goldfarb, 2019). Both studies investigated the effectiveness of [18F]FDG PET-CT in evaluating the response to immunotherapy in NSCLC patients. They described how many patients could discontinue treatment based on [18F]FDG PET-CT evaluation criteria during early response assessment. To demonstrate the added value of [18F]FDG PET-CT, these studies compared outcomes with those of contrast-enhanced response evaluation.

The time horizon for this study was five years with a cycle length of 6 weeks, allowing for transitions states. The model inputs are based on literature research on available evidence.

Strategies

The cost-effectiveness of [^{18}F]FDG PET-CT early response evaluation (PET-based evaluation) was compared to contrast-enhanced CT response evaluation (CT-based evaluation) and patients were categorized to continue or discontinue treatment during first response assessment. The distribution among these categories significantly impacts the occupancy of health states, thereby influencing the cost-effectiveness outcomes. After this initial response evaluation, subsequent evaluations for both strategies are conducted using contrast-enhanced CT alone.

CT-based evaluation

In strategy A, first response evaluation is based on CT-criteria for response evaluation in patients treated with immunotherapy. In strategy A, first evaluation is performed 2-3 cycles after initiation of treatment according to CT-based criteria for the evaluation of treatment with immunotherapy. When patients are diagnosed with progressive disease at first evaluation, due to the inability to differentiate between pseudo-progression and true progression, immunotherapy is continued for an additional 2-3 cycles of immunotherapy. After this first response evaluation, conform protocol, every 2-3 cycles of immunotherapy treatment, a CT-scan and clinical consult informs decisions to continue or discontinue treatment.

PET-based evaluation

In strategy B, patients receive [^{18}F]FDG PET-CT for response evaluation 2-3 cycles after initiation of treatment according to PET-based criteria for the evaluation of treatment with immunotherapy to inform decisions to continue or discontinue treatment. After this first response evaluation, conform protocol, after every 2-3 cycles of immunotherapy treatment, a CT-scan and clinical consult inform decisions to continue or discontinue treatment.

States

In this Markov Model, patients move between 10 mutually exclusive health states, describing the patient journey for this disease domain. At each time cycle, patients can transition to another state or stay in their current state. Figure 1 shows the transitions between states. Patients can be in one state at a time. Transitions to the ‘Best Supportive Care’ state and the ‘Death’ can occur from every other state but are not explicitly included as arrows to enhance visual clarity. The ‘Death’ state is an absorbing state where patients stay in.

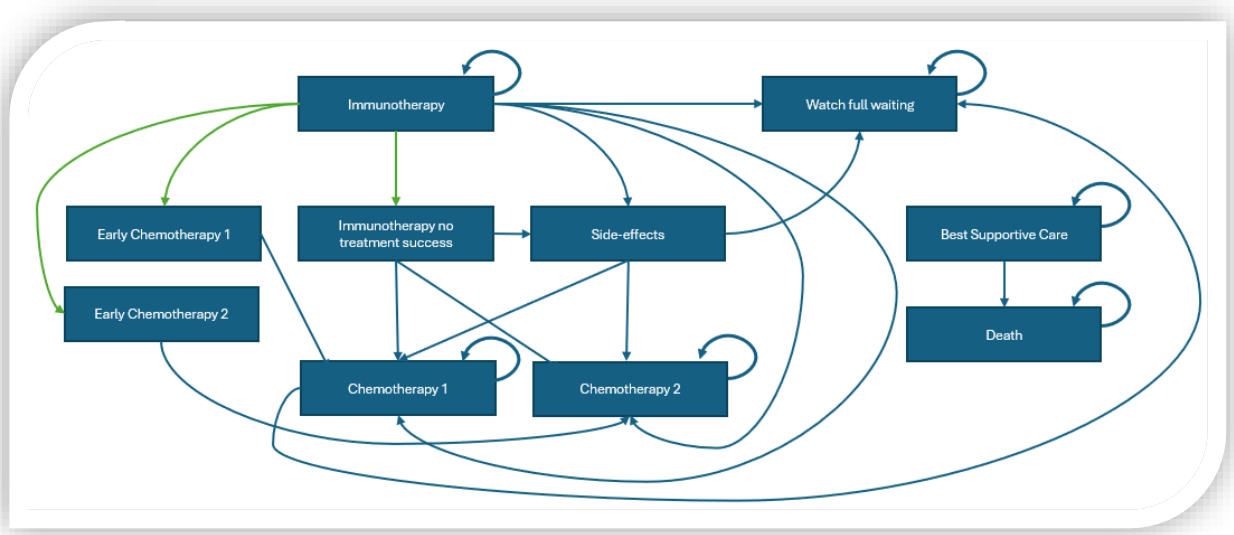

Figure 1. State transition diagram of the Markov model. Boxes represent health states, and arrows indicate possible transitions between states. Green arrows indicate transitions that are only possible in the PET-based evaluation – Strategy B. For visual clarity, transitions to the 'Best Supportive Care' state and the 'Death' state, which are possible from all health states, are not shown.

Immunotherapy

The 'immunotherapy state' includes patients with stage IV NSCLC with a PD-L1 expression of ≥ 50%, that qualify for first-line treatment with immunotherapy. These patients receive Pembrolizumab as first-line treatment regardless of their histological subtype: squamous, and non-squamous, respectively At start of the simulation all patients in the cohort start in the 'Immunotherapy state' with associated health outcomes and costs for treatment and imaging depending on the strategy.

Immunotherapy without treatment success

Patients in the 'Immunotherapy without treatment success' state are patients in the CT-based response evaluation strategy, who receive immunotherapy while not benefiting from this treatment due to earlier occurred progression. Because of the inability of distinguishing between true progression and pseudo-progression, all patients continue a second time cycle of treatment (also in patients who actually do have progression). While these patients don't benefit from the overall survival- and progression free survival outcomes of treatment with pembrolizumab, they may experience non- severe treatment related side effects.

Severe side effects of immunotherapy treatment

The downside of immunotherapy treatment lies in its potential side effects. Some of these side effects are so severe that discontinuing the treatment becomes necessary. The health state "Severe side effects immunotherapy treatment" leads patients to stop immunotherapy treatment, resulting in no further benefits from it. Additionally, they also experience the drawbacks (in reduced quality of life) of these side effects.

Chemotherapy - squamous type

After first-line treatment with Pembrolizumab, second line treatment consists of Chemotherapy regimens. In this Markov model, chemotherapy is administered when immunotherapy is no longer viable. This occurs if the immunotherapy treatment proves ineffective or if it needs to be halted due to side effects.

The choice of second line chemotherapy depends on the histological subtype of NSCLC, which is crucial for accurate clinical management and outcomes. The model differentiates between two distinct health states:

Squamous Type NSCLC

For patients with stage 4 squamous NSCLC who have progressed after first-line treatment, the recommended second line regimen is platinum-based chemotherapy combined with gemcitabine (J. Remon, 2021). Treatment typically continues for 6 cycles, as per standard practice.

Non-Squamous Type NSCLC

For patients with non-squamous NSCLC progressing after first-line treatment, pemetrexed plus platinum-based chemotherapy is the recommended second line option1. Chemotherapy treatment continues until progression or side effects emerge.

Both health states represent patients with stage 4 NSCLC receiving second line chemotherapy, but the specific regimens differ based on the histological subtype to reflect the distinct clinical approaches for each.

Early Chemotherapy – PET-based evaluation benefits

The model includes two health states that represent the advantages of PET-based early response assessment compared to CT-based evaluation for both squamous and non-squamous NSCLC types. These states reflect the potential health gains from early recognition of non-beneficial first-line treatment and timely transition to potentially beneficial second line therapy.

Squamous Type NSCLC

Patients with squamous type NSCLC who undergo PET-based evaluation can enter the "Early Chemotherapy Squamous type NSCLC" state. This state offers improved health outcomes compared to the standard "Chemotherapy Squamous type NSCLC" state. Patients may discontinue therapy due to intolerable side effects, disease progression, or lack of meaningful response. If treatment continues, patients transition to the standard chemotherapy state after one time cycle.

Non-Squamous Type NSCLC

Similarly, patients with non-squamous NSCLC benefit from the "Early Chemotherapy Non-Squamous type NSCLC" state. This state also provides better health outcomes than the standard chemotherapy state for non-squamous NSCLC2. The conditions for treatment discontinuation and transition to the standard chemotherapy state are the same as for the squamous type.

Both early chemotherapy states emphasize the potential advantages of PET-based evaluation in facilitating timely treatment adjustments and improving patient outcomes for stage IV NSCLC patients.

Best supportive care

This health state is where patients move to when there are no more treatment options available, and cancer progression is evident This state aims to provide the best possible care and involves the management of disease-related symptoms and pain management to ensure the highest quality of life. From this health state, patients can only die and move to the death state.

Watchful waiting

In this health state, patients show no progression and do not receive any treatment. Patients enter this state after completing 24 months of Immunotherapy treatment. In addition, patients who complete 6 cycles in the “Chemotherapy Squamous Type NSCLC” state, as per standard practice, and show no disease progression, could enter the “Watchful waiting” state including €3.005 imaging surveillance per six-week time cycle. Patients in the “Chemotherapy Non-Squamous Type NSCLC” state, do not transition to this state, as per standard practice, they proceed treatment until progression after which they transition to the “ Best Supportive Care” state. Furthermore, patients can enter this stage after being in the ‘Severe side effects’ state, where they experienced side effects but no progression. Patients remain in this state until progression occurs, or death occurs.

Model input

The transition probabilities shown in Table 1 represent the likelihood of patients moving between health states in each cycle of the model.

Transition	Probability	Resource
Receiving immunotherapy without treatment success during CT-based first response evaluation*	0.452	(Sohyun Park, 2020 (Lucas Goldfarb, 2019))
Progress from immunotherapy during early PET-based first response evaluation*	0.452	(Sohyun Park, 2020 (Lucas Goldfarb, 2019))
Being eligible for second line treatment after discontinuation of first line treatment due to progression or severe side effects**	0.36	(Alessio Cortellini, 2021)
Percentage Squamous Type NSCLC**	0.195	(Alessio Cortellini, 2021)
Percentage Non-Squamous Type NSCLC**	0.805	(Alessio Cortellini, 2021)
Death during immunotherapy with no treatment success**	0.0831	(Huiru Guo, 2021)
Getting severe side effects**	0.0049	(Natasha B Leighl, 2019)
Death in immunotherapy**	0.0455	(Martin Reck, 2016)
Death during severe side effects**	0.91	(Martin Reck, 2016)
Progress during immunotherapy during treatment after first response evaluation**	0.0515	(Martin Reck, 2016)
Having progression while in chemotherapy Squamous Type NSCLC state**	0.114	(Yaniss Belaroussi, 2023)
Death during chemotherapy Squamous Type NSCLC**	0.063448	(Martin Reck, 2016)
Having progression while in Chemotherapy Non-Squamous Type NSCLC state**	0.114	(Yaniss Belaroussi, 2023)
Death during Chemotherapy Non-Squamous Type NSCLC**	0.063448	(Martin Reck, 2016)
Progression during Watchful waiting**	0.0099	(Tony S K Mok, 2019)
Death during Watchful waiting**	0.0273	(Ayse Ece Cali Daylan, 2023)
Death during Best supportive care**	0.0831	(Huiru Guo, 2021)

Table 1. Transition probabilities. *Transitions that are applied only once. **Transitions that are applied per 6-week time cycle.

Costs per state

Table 2 shows the cost inputs used in the model, originally denominated in various currencies, were converted to euros (€). The conversion was carried out using the prevailing exchange rates at the time of data publication to ensure accuracy and consistency.

Subsequently, the converted euro amounts were indexed to the price level of the year 2024. This indexation was based on the tariff adjustments published by the Dutch Healthcare Authority (Nederlandse Zorgautoriteit, NZA). The NZA tariff indexations reflect the most recent updates and adjustments in healthcare pricing, ensuring that the cost data used in the model are adjusted for inflation and reflect the current economic conditions.

State	Costs in Euros	Resource
Immunotherapy state during CT-based first response evaluation	€19.660	(Mohamed Ismail Abdul Aziz, 2020)
Immunotherapy state during PET-based first response evaluation	€20.282	(Mohamed Ismail Abdul Aziz, 2020)
Immunotherapy state after first response evaluation	€19.660	(Mohamed Ismail Abdul Aziz, 2020)
Severe side effects immunotherapy	€6.798	(Yan Li, 2022)
Immunotherapy without treatment success	€19.660	(Mohamed Ismail Abdul Aziz, 2020)
Chemotherapy Squamous Type NSCLC	€ 8.663	(Mohamed Ismail Abdul Aziz, 2020)
Chemotherapy Non-Squamous Type NSCLC	€ 8.663	(Mohamed Ismail Abdul Aziz, 2020)
Best supportive care	€5.352	(Mohamed Ismail Abdul Aziz, 2020)
Watchful waiting	€3.005	(Yan Li, 2022)

Table 2. Costs in Euros per 6-week time cycle

Utilities per state

Table 3 presents the health state utilities used in the Markov model for advanced NSCLC. These utilities represent the quality of life associated with each health state, ranging from 0 (death) to 1 (perfect health). The values were derived from published literature and reflect the impact of disease progression and treatment-related factors on patients' quality of life.

State	Utilities	Resource
Immunotherapy state	0.087	(Mohamed Ismail Abdul Aziz, 2020)
Severe side effects immunotherapy	0.074	(Mohamed Ismail Abdul Aziz, 2020)
Immunotherapy without treatment success	0.019	(Yan Li, 2022)
Chemotherapy Squamous Type NSCLC	0.075	(Xiaohan Hu, 2018)
Early Chemotherapy Squamous Type NSCLC	0.075	Assumption for it being equal to or higher than the Chemotherapy 1 state and lower than the Immunotherapy state
Chemotherapy Non-Squamous Type NSCLC	0.075	(Xiaohan Hu, 2018)
Early Chemotherapy Non-Squamous Type NSCLC	0.075	Assumption for it being equal to or higher than the Chemotherapy 1 state and lower than the Immunotherapy state
Best supportive care	0.021	(Yan Li, 2022)
Watchful waiting	0.093	(Mohamed Ismail Abdul Aziz, 2020)

Table 3.State utilities per 6 week time cycle

Base-case analysis

For the base-case analysis, the difference was modelled between CT-based and PET-based response evaluation strategies in determining treatment discontinuation. The analysis assessed several key outcomes, including overall survival, which encompasses both five-year survival rates and survival curves. Additionally, we evaluated state occupancy probabilities over time and intermediate outcomes after one cycle.

The cost analysis included total costs and a detailed breakdown by health state, alongside the total quality-adjusted life years (QALYs) gained over the time horizon. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental costs by the incremental effectiveness (ΔCost/ΔQALY). For the cost-effectiveness assessment, we utilized the Dutch willingness-to-pay threshold of €80.000 per QALY gained.

Results

The simulation results demonstrate a notable difference in the distribution of patients across health states over time between the PET-based evaluation strategy and the CT-based evaluation strategy, as illustrated in Tables 1, 2 and 3 in the Appendix.

In both strategies 9.91% (991/10.000) patients completed the full 2 years of immunotherapy treatment. At the end of the time-horizon, after five years, the overall survival was similar for the CT-based and PET-based evaluation strategy (i.e., 4.63% (463/10.000) for the CT-based evaluation strategy and 4.67% (467/10000) for the PET-based evaluation strategy). Figure 2 shows the survival curve of both strategies over the time horizon of five years.

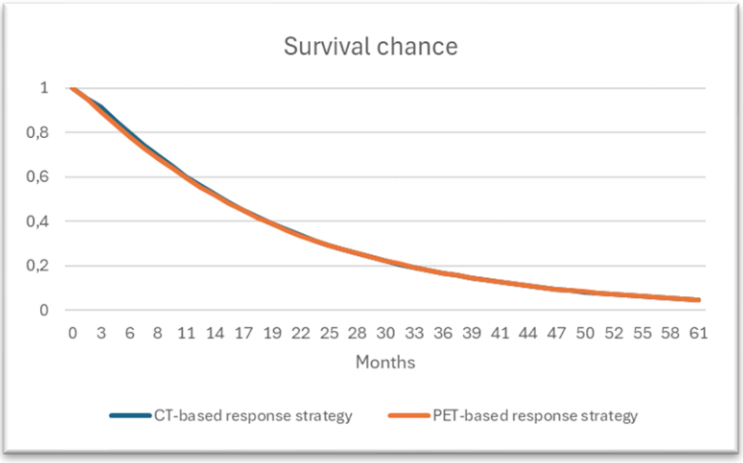

Figure 2. Survival curve of CT-based evaluation strategy and PET-based evaluation strategy

In the CT-based strategy at first response evaluation after one time cycle, 50 patients discontinued immunotherapy because of severe side effects and 9.495 patients continue treatment of which 4.520 patients receive immunotherapy without treatment success. In contrast, in the PET-based evaluation strategy in total 5.025 of 10.000 patients discontinue immunotherapy treatment, 1627 patients were eligible for second line treatment after progression, 2893 patients received best supportive care after progression, 455 patients died and, compliant with the CT-based strategy, 50 patients discontinued immunotherapy because of severe toxicity (i.e., imaging does not affect the probability of experiencing severe side effects). 4.975 Patients continued immunotherapy treatment. Consequently, 4.520 patients are avoided to receive further immunotherapy without treatment success. After the second cycle of immunotherapy, the number of patients receiving treatment becomes equal between the CT-based and PET-based strategies. This alignment is expected, as PET primarily influences the decision-making process after the first cycle. It's important to note that this model assumes no difference in sensitivity or specificity between PET and CT for subsequent evaluations.

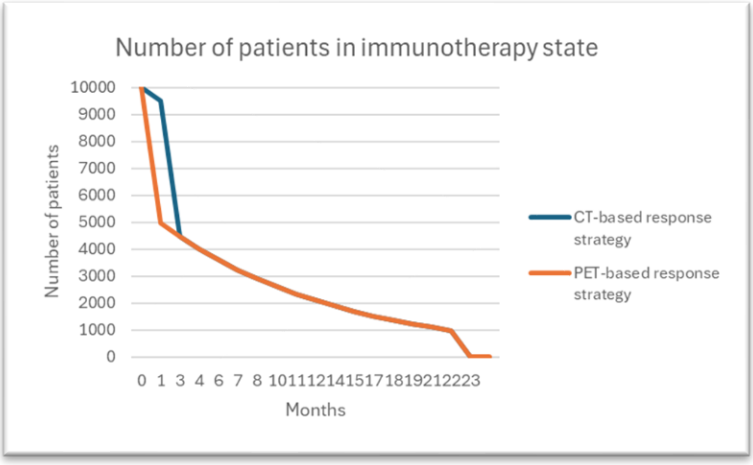

Figure 3. Number of patients in immunotherapy state per month

Figure 4 shows the mean costs per patient per health state for both the PET-based evaluation strategy and the CT-based evaluation strategy. This figure shows that during first response evaluation the PET-based evaluation strategy has higher mean costs per patient than the CT-based evaluation strategy. The mean costs per patient for second line treatment chemotherapy and for Watchful Waiting is higher for the PET-based evaluation strategy than for the CT-based evaluation strategy. In addition, the mean costs per patient for best supportive care are higher for the CT-based evaluation strategy than for the PET-based evaluation strategy.

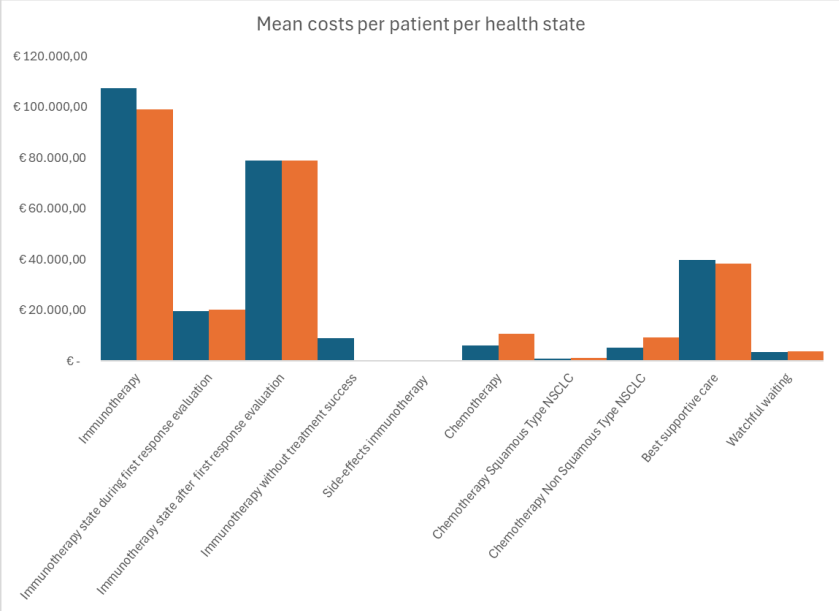

Figure 4. Mean costs per patient per health state for the CT-based evaluation strategy and the PET-based evaluation strategy.

Figure 5 shows the mean quality-adjusted life years (QALYs) gained per patient per health state based on state occupancy for both the PET-based evaluation strategy and the CT-based evaluation strategy. The mean QALYs per patient gained for second line treatment chemotherapy and for Watchful Waiting is higher for the PET-based evaluation strategy than for the CT-based evaluation strategy. In addition, the mean QALYs per patient gained for Immunotherapy without treatment success and Best Supportive Care are higher for the CT-based evaluation strategy than for the PET-based evaluation strategy.

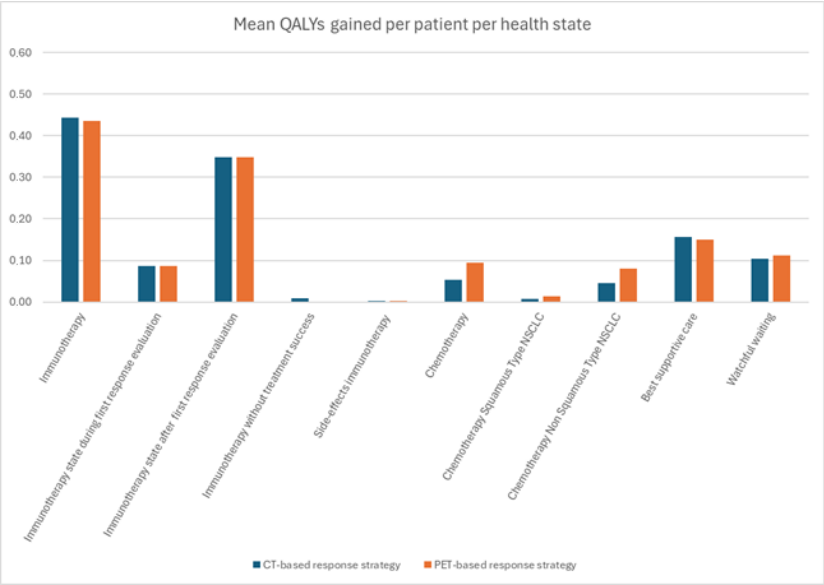

Figure 5. Mean QALYs gained per patient per health state for the CT-based evaluation strategy and the PET-based evaluation strategy.

Within the PET-based evaluation strategy, the mean costs per patient for Immunotherapy state during first response evaluation is higher than for the CT-based evaluation strategy. This difference is primarily attributed to the additional cost of the PET scan performed in the PET-based strategy. However, these additional costs do not outweigh the additional costs in the Immunotherapy without treatment success state. Furthermore, the PET-based strategy leads to earlier identification of non-responders, resulting in more patients transitioning to second-line chemotherapy sooner. This earlier transition increases costs in the chemotherapy state for the PET-based strategy compared to the CT-based strategy. In the CT-based evaluation strategy, patients in the immunotherapy state without treatment success are not identified as having progressed and consequently transition to Best Supportive Care at a later stage.

The distribution of mean QALYs gained per patient between health states after discontinuation of immunotherapy[1] differs between the PET-based evaluation strategy and the CT-based evaluation strategy. Within the PET-based strategy, earlier identification of non-responders, results in more patients transitioning to second-line chemotherapy sooner with a higher mean QALYs gained per patient. In comparison, within the CT-based strategy, non-responders transition to the Immunotherapy without treatment success state with lower mean QALYs gained per patient. The mean QALYs gained per patient over all health states after discontinuation of immunotherapy[2] is similar between the PET-based evaluation strategy and the CT-based evaluation strategy.

The model predicted that patients under the CT-based evaluation strategy would experience an average of 1.70 life years (LY) and an average of 0.76 quality-adjusted life years (QALYs) at a cost of €156.685 per patient. In comparison, patients under the PET-based evaluation strategy would experience an average of 1.68 LY and an average of 0.79 QALYs at a cost of €151.924 per patient.

The incremental cost-effectiveness ratio (ICER) was €-140.385 per QALY gained. The PET-based evaluation strategy cost €140.385 less for each additional quality-adjusted life year (QALY) gained compared to the CT-based evaluation strategy. Therefore, the PET-based evaluation strategy dominates the CT-based evaluation strategy. Furthermore, the ICER of the PET-based versus the CT-based evaluation strategy lies below the Dutch willingness-to-pay threshold of high burden diseases of €80.000 per QALY (Figure 6).

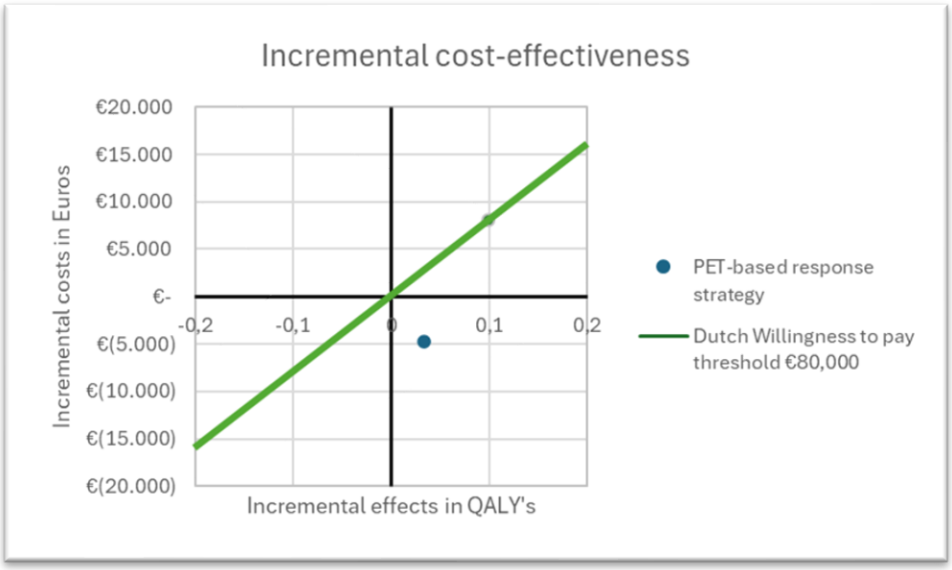

Figure 6. Incremental cost-effectiveness diagram

[1] Health states: Severe side-effects immunotherapy, Immunotherapy without treatment success, Chemotherapy, Best-supportive care and Watchful waiting

[2] Health states: Severe side-effects immunotherapy, Immunotherapy without treatment success, Chemotherapy, Best-supportive care and Watchful waiting

Discussion

In this study, both strategies had similar five-year overall survival rates. The overall five-year survival rate was slightly higher for the PET-based evaluation strategy than for the CT-based evaluation strategy, 4.67% versus 4.63% respectively. The survival curve showed similar survival rates and no worse outcomes for the PET-based evaluation strategy. Importantly, the PET based evaluation strategy demonstrated ad modest improvement in QALYs (0.79 vs. 0.76) despite a slight decrease in overall life years (1.68 vs. 1.70 LY). This suggests that the PET-based evaluation may enhance quality of life by avoiding unnecessary treatment-related side effects and enabling early transitions to potentially beneficial second line treatment. The PET-based strategy achieves large cost savings primarily by avoiding ineffective treatment early on, while maintaining similar long-term outcomes. While the PET-based evaluation strategy incurred higher initial evaluation costs and increased expenses in second line Chemotherapy and Watchful Waiting states, these were offset by reduced costs in ineffective immunotherapy. With an ICER of ICER of € -140.385 per QALY gained, the PET-based evaluation strategy dominates the CT-based evaluation strategy, providing greater health benefits at a lower cost.

Based on the outcomes of this study and supporting data that have indicated that PET-based response assessment is more effective in the early response evaluation of immunotherapy in comparison to contrast-enhanced CT (Castello, Rossi, Toschi, & Lopci, 2020; Rossi et al., 2020), timely switching to second line treatment could be beneficial. The model demonstrated that a PET-based evaluation strategy for immunotherapy in stage IV NSCLC patients with a PD-L1 expression ≥ 50% offers cost savings while maintaining comparable health outcomes to the CT-based evaluation strategy. Despite a substantial difference in early treatment discontinuation (50.25% for PET-based vs. 5.05% for CT-based), both strategies resulted in identical rates of patients completing the full two-year immunotherapy course (9.91%). In comparison to available literature, these results are in accordance with the study of Rittber, et al. describing 10.2% (72/718) of patients completing two years of immunotherapy, while the KEYNOTE-024 trial 25% (39/154) of patients completed 2 years of immunotherapy (Rebekah Rittberg, 2023) (Martin Reck, 2016). In patients who complete the 2 years of Pembrolizumab treatment, the overall five-year survival rate was 83% (Martin Reck, 2016). In comparison, patients with untreated stage IV NSCLC have an overall survival rate of 3% (Overlevingscijfers van niet-kleincellige longkanker, 2021).

In the base case analysis, assumptions were made about the transition probability of patients being eligible for second line treatment during first response assessment and for the utility improvement due to an early switch to second line treatment because of the early PET-based evaluation. It is important to note that after the first response evaluation, subsequent evaluations in both strategies are conducted using CT alone. This study assumes that the sensitivity and specificity of CT-based evaluations are identical for both the PET-based and CT-based strategies in these later assessments. In the analysis, conservative inputs were employed for the probability to be eligible for second line treatment and for the possible better health outcomes in the early chemotherapy health states than in later chemotherapy health states. These conservative inputs may not accurately reflect the health gains associated with an early switch to second line treatment. The same inputs were used within the PET-based evaluation strategy as within the CT-based evaluation strategy with a probability of 0.36 for being eligible for second line treatment and the utility of 0.75 for being in a chemotherapy state. Although, alternative inputs do not affect the dominance of PET-based evaluation over CT-based evaluation, the overall health gain could potentially be greater than what the conservative estimates suggest. This indicates that the true benefits of an early treatment switch may be underestimated in the model. Furthermore, there were no model input for the "Early Chemotherapy" states, indicating the benefits from the earlier start of second line treatment, therefore the assumption was made that health outcomes for this stage were better than in the Chemotherapy states starting at least 1 time cycle later, but as it is the second choice of treatment, health outcomes are not better than within the Immunotherapy states. Furthermore, the assumption was made that the probability of receiving second line treatment at the moment of first response evaluation would be at least the same or higher than the probability would be in later time cycles.

The CT-based evaluation strategy assumes that all patients with progression will continue treatment, given the possibility of pseudoprogression. However, it is possible that some patients may exhibit such clear signs of progression, that a second scan would be deemed unnecessary, and they would immediately discontinue treatment based on the first CT scan showing progression. According to Keynote-024 treatment with pembrolizumab can continue beyond disease progression if the patient is clinically stable and the investigator believes the patient is deriving clinical benefit (Rebekah Rittberg, 2023). By not accounting for this scenario, the model may overestimate the benefits of the PET-based evaluation strategy. However, this overestimation is likely

minimal, as immediate discontinuation after a single CT scan showing progression is rare. According to Keynote-024 most clinicians prefer to confirm progression with a second scan or continue treatment if the patient is clinically stable (Rebekah Rittberg, 2023).

While the model assumes perfect accuracy for [^{18}F]FDG PET-CT, a limitation of the current analysis is that it does not account for inaccuracy of [^{18}F]FDG PET-CT in first response evaluation. Evidence suggests that PET-CT can yield false results during early response assessment, as patients classified as non-responders during early response assessment would be reclassified as responders at later assessments (Lucas Goldfarb, 2019). This could be also due to the occurrence of pseudo-progression. However, it's important to note that pseudoprogression rates after PET assessment are expected to be significantly lower than in CT assessments. According to recent studies, PET-CT has shown superior performance in distinguishing pseudoprogression from true progression compared to conventional CT imaging (Egesta Lopci, 2023). This suggests that while PET-CT is not perfect, it is less limited by pseudoprogression issues than CT alone, potentially leading to more accurate early response evaluations in immunotherapy. Conversely, false positives could inform decisions on early response assessment would potentially lead to premature cessation of treatment for patients who might have benefited from continued therapy. Given these conflicting perspectives, further investigation is warranted to determine the extent of patients affected by inaccurate PET-CT results. Additionally, modelling this scenario in a cost-effectiveness analysis could provide valuable insights into the implications of early diagnostic strategies and their impact on treatment outcomes. Such research could help refine decision-making processes and optimize treatment pathways for patients with stage 4 NSCLC.

Patients in the watchful waiting state may experience further progression of their disease. Although this factor was not incorporated into the model, it is important to note that state occupancy of the watchful waiting state is similar for both strategies. As a result, this aspect is unlikely to have impacted the cost-effectiveness outcomes.

The cost per time cycle in this study is derived from existing cost-effectiveness studies. To ensure consistency with the time cycle framework employed in the research, these costs were adapted to match the specific time cycle used in this study. This adaptation process involved scaling and adjusting the reported costs to fit the model's time parameters. It is important to note that this method of cost adaptation may introduce some discrepancies between the actual costs for the time cycle and the costs used in the study. These discrepancies arise from the inherent differences in time cycle durations and cost reporting methods among various studies. Despite these potential variations, this approach allows for the integration of comprehensive and relevant cost data, facilitating a more robust economic analysis within the specified time framework.

Another limitation of the study is the simplification of side effects in the model. While a health state to represent treatment discontinuation due to severe side effects was included, there was not accounted for ongoing side effects during immunotherapy. This may lead to an overestimation of the utility in the immunotherapy state, as it doesn’t capture the potential decrease in quality of life due to manageable but still impactful side effects. In reality patients may experience a spectrum of side effects, with only the most severe leading to discontinuation. This simplification could affect cost-effectiveness results by not fully capturing side effects’ impact on quality of life. Future research should model side effects more comprehensively, including those during ongoing treatment. Collecting more precise utility data for patients in the immunotherapy state experiencing various side effects would enhance future models’ accuracy. Furthermore, the potential overestimation of mortality due to treatment side effects is a limitation of this study. The model's mortality rates, derived from a small patient cohort, may not accurately reflect the true incidence of fatal side effects in clinical practice. This could lead to a conservative estimate of patient outcomes by overstating treatment-related deaths. Future research should focus on collecting data from larger, more diverse populations and refining methodologies for capturing side effect-related mortality. While the model provides valuable insights, its mortality estimates should be interpreted cautiously due to the limited dataset used.

Furthermore, a limitation of the current study is the absence of probabilistic sensitivity analysis (PSA) and Value of Information (VOI) analysis. Incorporating PSA enhances the robustness of future cost-effectiveness analysis by quantifying uncertainty and providing a comprehensive understanding of how variability in model parameters affects outcomes, ultimately supporting more informed decision-making. In addition, VOI analysis can identify which parameters have the greatest impact on the model's outcomes. This insight allows researchers to focus on collecting more precise data for those critical parameters, ultimately improving the robustness of the analysis (Erpur Adalsteinsson, 2013).

While the results suggest potential benefits of a PET-based strategy, clinicians should exercise caution in immediately changing practice. The model's assumptions, particularly regarding PET-CT accuracy, may not fully reflect real-world conditions. Further data on the accuracy of PET-CT in early response assessment for immunotherapy, including rates of false positives and false negatives, is needed. In addition, real-world data on patient outcomes and quality of life under different evaluation strategies would also be valuable.

In conclusion, the study provides a promising economic argument for PET-based response evaluation in immunotherapy for advanced NSCLC. However, LUMC clinicians should view these results as a starting point for further investigation rather than definitive evidence. By pursuing targeted research to address the identified knowledge gaps, LUMC can contribute to optimizing response evaluation strategies and potentially improving both cost-effectiveness and patient outcomes in advanced NSCLC treatment.

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Appendix

0	10000	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
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2	0	0	4468	0	0	0	0	0	0	0	0	0	0	0	0	0	0	33	0	132	0	0	0	0	0	547	0	0	3957	2	862
3	0	0	0	4012	0	0	0	0	0	0	0	0	0	0	0	0	0	22	0	16	109	0	0	0	0	517	0	0	3854	3	1467
4	0	0	0	0	3603	0	0	0	0	0	0	0	0	0	0	0	0	20	0	15	13	90	0	0	0	485	0	0	3740	4	2031
5	0	0	0	0	0	3235	0	0	0	0	0	0	0	0	0	0	0	18	0	13	12	11	74	0	0	453	0	0	3617	4	2562
6	0	0	0	0	0	0	2905	0	0	0	0	0	0	0	0	0	0	16	0	12	11	10	9	61	0	421	0	0	3488	4	3062
7	0	0	0	0	0	0	0	2609	0	0	0	0	0	0	0	0	0	14	0	11	10	9	8	7	50	390	0	0	3355	5	3532
8	0	0	0	0	0	0	0	0	2343	0	0	0	0	0	0	0	0	13	0	9	9	8	7	7	6	360	0	0	3218	46	3974
9	0	0	0	0	0	0	0	0	0	2104	0	0	0	0	0	0	0	12	0	9	8	7	7	6	5	331	0	0	3077	48	4387
10	0	0	0	0	0	0	0	0	0	0	1889	0	0	0	0	0	0	10	0	8	7	6	6	5	5	304	0	0	2936	49	4774
11	0	0	0	0	0	0	0	0	0	0	0	1697	0	0	0	0	0	9	0	7	6	6	5	5	4	279	0	0	2796	50	5136
12	0	0	0	0	0	0	0	0	0	0	0	0	1524	0	0	0	0	8	0	6	6	5	5	4	4	255	0	0	2658	50	5476
13	0	0	0	0	0	0	0	0	0	0	0	0	0	1368	0	0	0	8	0	6	5	5	4	4	4	232	0	0	2523	49	5793
14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1229	0	0	7	0	5	5	4	4	4	3	212	0	0	2390	49	6090
15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1103	0	6	0	4	4	4	3	3	3	192	0	0	2262	48	6367
16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	991	5	0	4	4	3	3	3	3	175	0	0	2137	47	6625
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	4	3	3	3	3	2	159	0	0	2017	935	6867
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19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	2	2	107	0	0	1819	797	7267
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22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	60	0	0	1536	627	7776
23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	49	0	0	1448	579	7924
24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	40	0	0	1363	533	8063
25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	33	0	0	1282	491	8194
26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	27	0	0	1204	452	8316
27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	23	0	0	1131	417	8430
28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	19	0	0	1061	384	8537
29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	0	0	994	354	8637
30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	13	0	0	932	326	8730
31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	0	0	873	300	8817
32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	817	276	8898
33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	764	255	8974
34	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	714	235	9045
35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	668	216	9111
36	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	624	199	9173
37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	583	183	9231
38	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	544	169	9284
39	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	508	156	9334
40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	474	143	9381
41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	442	132	9424
42	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	412	122	9465
43	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	385	112	9502
44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	359	103	9537

Table 1. CT-based evaluation strategy's patient distribution over health states over a five-year time horizon

	IB	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12	I13	I14	I15	I16	I17	SI	INTS	CH1C1	CH1C2	CH1C3	CH1C4	CH1C5	CH1C6	CH2	ECH1C1	ECH2	BSC	WW	D
0	10000	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	0	4975	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	50	0	0	0	0	0	0	0	0	317	1310	2893	0	455
2	0	0	4468	0	0	0	0	0	0	0	0	0	0	0	0	0	0	25	0	18	261	0	0	0	0	1152	0	0	3004	2	1070
3	0	0	0	4012	0	0	0	0	0	0	0	0	0	0	0	0	0	22	0	16	15	215	0	0	0	1015	0	0	3065	3	1637
4	0	0	0	0	3603	0	0	0	0	0	0	0	0	0	0	0	0	20	0	15	13	12	177	0	0	895	0	0	3087	3	2174
5	0	0	0	0	0	3235	0	0	0	0	0	0	0	0	0	0	0	18	0	13	12	11	10	145	0	790	0	0	3077	4	2684
6	0	0	0	0	0	0	2905	0	0	0	0	0	0	0	0	0	0	16	0	12	11	10	9	8	119	699	0	0	3041	4	3165
7	0	0	0	0	0	0	0	2609	0	0	0	0	0	0	0	0	0	14	0	11	10	9	8	7	7	618	0	0	2984	103	3620
8	0	0	0	0	0	0	0	0	2343	0	0	0	0	0	0	0	0	13	0	9	9	8	7	7	6	548	0	0	2904	101	4045
9	0	0	0	0	0	0	0	0	0	2104	0	0	0	0	0	0	0	12	0	9	8	7	7	6	5	486	0	0	2813	98	4446
10	0	0	0	0	0	0	0	0	0	0	1889	0	0	0	0	0	0	10	0	8	7	6	6	5	5	431	0	0	2714	96	4822
11	0	0	0	0	0	0	0	0	0	0	0	1697	0	0	0	0	0	9	0	7	6	6	5	5	4	383	0	0	2610	93	5175
12	0	0	0	0	0	0	0	0	0	0	0	0	1524	0	0	0	0	8	0	6	6	5	5	4	4	340	0	0	2501	89	5507
13	0	0	0	0	0	0	0	0	0	0	0	0	0	1368	0	0	0	8	0	6	5	5	4	4	4	303	0	0	2391	86	5818
14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1229	0	0	7	0	5	5	4	4	4	3	270	0	0	2279	82	6109
15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1103	0	6	0	4	4	4	3	3	3	240	0	0	2168	79	6381
16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	991	5	0	4	4	3	3	3	3	214	0	0	2059	75	6636
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	4	3	3	3	3	2	191	0	0	1951	961	6874
18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	3	2	2	2	157	0	0	1862	888	7080
19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	2	2	129	0	0	1773	820	7270
20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	2	106	0	0	1683	756	7448
21	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	88	0	0	1595	698	7616
22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	72	0	0	1509	644	7773
23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	59	0	0	1425	595	7921
24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	49	0	0	1344	548	8059
25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	40	0	0	1266	505	8189
26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	33	0	0	1191	465	8311
27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	27	0	0	1120	428	8424
28	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	22	0	0	1052	395	8531
29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	18	0	0	988	363	8631
30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	15	0	0	926	335	8724
31	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	0	0	868	308	8811
32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	0	0	813	284	8892
33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	762	262	8968
34	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	713	241	9039
35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	667	222	9105
36	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	623	205	9167
37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	583	189	9225
38	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	544	174	9279
39	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	509	160	9329
40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	475	147	9376
41	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	443	136	9419
42	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	414	125	9460
43	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	386	115	9498
44	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	360	106	9533

Table 2. PET-based evaluation strategy’s patient distribution over health states over a five-year time horizon

	IB	I2	I3	I4	I5	I6	I7	I8	I9	I10	I11	I12	I13	I14	I15	I16	I17	SI	INTS	CH1C1	CH1C2	CH1C3	CH1C4	CH1C5	CH1C6	CH2	ECH1C1	ECH2	BSC	WW	D
0																															
1																			-4520								317	1310	2893		
2																		-8		-114	261					606			-953		208
3																					-94	215				498			-788		170
4																						-77	177			410			-652		143
5																							-64	145		337			-540		121
6																								-52	119	277			-447		103
7																									-43	228			-371	98	88
8																										188			-314	55	71
9																										154			-264	51	59
10																										127			-222	47	48
11																										104			-186	43	39
12																										86			-157	40	31
13																										71			-132	36	25
14																										58			-111	34	19
15																										48			-93	31	15
16																										39			-79	28	11
17																										32			-66	26	8
18																										27			-56	24	5
19																										22			-47	22	3
20																										18			-39	21	1
21																										15			-33	19	-1
22																										12			-27	17	-2
23																										10			-23	16	-3
24																										8			-19	15	-4
25																										7			-16	14	-5
26																										6			-13	13	-5
27																										5			-11	12	-6
28																										4			-9	11	-6
29																										3			-7	10	-6
30																										3			-5	9	-6
31																										2			-4	8	-6
32																										2			-3	8	-6
33																										1			-2	7	-6
34																										1			-2	7	-6
35																										1			-1	6	-6
36																										1			-1	6	-6
37																										1			0	5	-6
38																										1			0	5	-5
39																										0			1	4	-5
40																										0			1	4	-5
41																										0			1	4	-5
42																										0			1	3	-5
43																										0			1	3	-4
44																										0			1	3	-4

Table 3. PET-based evaluation- minus CT-based evaluation strategy’s patient distribution over health states over a five-year time horizon