

Clinical Investigation: Head and Neck Cancer

Protons in Head-and-Neck Cancer: Bridging the Gap of Evidence

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Summary

Comparative effectiveness research is often scarcely available for innovative radiation therapy techniques, making it challenging to examine (cost-)effectiveness. Combining normal tissue complication probability models and planning studies with data on costs and quality of life is proposed as feasible and informative to bridge this gap of evidence. When assuming equal survival among both

Purpose: To use Normal Tissue Complication Probability (NTCP) models and comparative planning studies to explore the (cost-)effectiveness of swallowing sparing intensity modulated proton radiotherapy (IMPT) compared with swallowing sparing intensity modulated radiotherapy with photons (IMRT) in head and neck cancer (HNC).

Methods and Materials: A Markov model was constructed to examine and compare the costs and quality-adjusted life years (QALYs) of the following strategies: (1) IMPT for all patients; (2) IMRT for all patients; and (3) IMPT if efficient. The assumption of equal survival for IMPT and IMRT in the base case analysis was relaxed in a sensitivity analysis.

Results: Intensity modulated proton radiation therapy and IMRT for all patients yielded 6.620 and 6.520 QALYs and cost €50,989 and €41,038, respectively. Intensity modulated proton radiation therapy if efficient yielded 6.563 QALYs and cost €43,650. The incremental cost-effectiveness ratio of IMPT if efficient versus IMRT for all patients was €60,278 per QALY gained. In the sensitivity analysis, IMRT was more effective (0.967 QALYs) and less expensive (€8218) and thus dominated IMPT for all patients.

Conclusions: Cost-effectiveness analysis based on normal tissue complication probability models and planning studies proved feasible and informative and enables the analysis of individualized strategies. The increased effectiveness of IMPT does not seem to outweigh the higher costs for all head-and-neck cancer patients. However, when assuming equal survival among both

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modalities, intensity modulated proton radiation therapy is expected to be cost-effective compared with intensity modulated photon radiation therapy for selected patients.

modalities, there seems to be value in identifying those patients for whom IMPT is cost-effective.

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Introduction

The costs of cancer care are expected to accelerate owing to the aging population and costly new treatments, such as proton radiation therapy (1, 2). Because resources are scarce, it is important to consider the (cost-)effectiveness of new technologies (2). Economic evaluations are often performed using decision-analytic modeling to examine the cost-effectiveness ratio and guide evidence-based decision making under uncertainty (3). Economic evaluations frequently rely on comparative effectiveness research to estimate the effectiveness, patient-reported outcomes, and resource use. However, comparative effectiveness research is sparsely available for proton radiation therapy (4). Normal tissue complication probability (NTCP) models combined with comparative planning studies might be informative to bridge this gap of evidence. Normal tissue complication probability models estimate the probability of toxicity according to the expected radiation dose to healthy tissues. Comparative planning studies compare the dose distributions in patients for different radiation therapy techniques. Hence, NTCP models and comparative planning studies can be used in economic evaluations to estimate the expected benefit of innovative radiation therapy techniques. To explore this methodology, we examine the cost-effectiveness of intensity modulated proton radiation therapy (IMPT) as opposed to the current standard: intensity modulated radiation therapy with photons (IMRT) in head-and-neck cancer (HNC).

After radiation therapy for HNC, treatment-related toxicities like xerostomia and dysphagia substantially affect patients' health-related quality of life (5). Planning studies suggest that proton radiation therapy, with its favorable in-depth dose distribution, has the ability to reduce the radiation dose to healthy tissues and hence the occurrence of toxicity compared with photons (6). However, there is no clinical evidence that supports these theoretical benefits of protons (4, 6). Therefore, we aimed to combine NTCP models and comparative planning data in a model-based economic evaluation to explore the (cost-)effectiveness of swallowing-sparing IMPT (scanned) compared with swallowing-sparing IMRT for HNC patients. Swallowing-sparing techniques have the ability to reduce the dose to swallowing structures with similar dose to the parotid and submandibular glands compared with standard techniques. Consequently, swallowing-sparing techniques may reduce the occurrence of dysphagia and hence limit the impact of treatment on quality of life (5, 7). These swallowing-sparing techniques can be considered the best available IMRT and IMPT treatments. It is expected that not all HNC patients have an equal expected benefit from IMPT. Therefore, we will also examine an individualized strategy wherein IMPT is only administered to patients for whom IMPT is expected to be cost-effective.

Methods and Materials

Markov model description

The study population consisted of locally advanced (stage III-IV) HNC patients (oral cavity, laryngeal, and pharyngeal cancer), aged on average 61 years at start of radiation therapy and pretreatment Radiation Therapy Oncology Group (RTOG) grade <2 dysphagia and xerostomia. A decision-analytic Markov cohort model was constructed to estimate the expected costs and effects of 3 treatment strategies: (1) *IMPT for all patients*; (2) *IMRT for all patients*; and (3) *IMPT if efficient*: patients for whom IMPT is expected to be cost-effective receive IMPT, the remaining patients receive IMRT.

Our analysis focuses on the question what type of radiotherapy should be provided if radiotherapy is the therapy of choice. Because surgery is complementary to radiation therapy, it is not considered as comparator.

Through transiting a hypothetical cohort of patients between mutually exclusive health states, a Markov model aims to reflect the course of a disease to compare outcomes for competing interventions (3). The Markov model consisted of 7 health states (as illustrated in Fig. 1): (a) disease free without toxicity; (b) disease free with xerostomia RTOG grade ≥ 2 ; (c) disease free with xerostomia and dysphagia RTOG grade ≥ 2 ; (d) disease free with dysphagia RTOG grade ≥ 2 ; (e) locoregional recurrence; (f) distant metastasis; and (g) death.

To incorporate the reversibility of acute toxicity during the first 6 months after radiation therapy, a cycle time of 6 months was used in the first year; afterward the cycle time was 1 year. A lifetime time horizon was used.

Markov model assumptions

The main assumption was that disease progression (including radiation-induced cancer) and thus survival were equal for the comparators. This was assumed because the tumor dose in the planning studies used to estimate toxicity was similar for both modalities, and available clinical evidence does not show statistically significant differences in survival (6). Second, toxicity occurring in the first 6 months was (partly) acute toxicity and thus (partly) reversible. Patients can for instance transit from disease free with xerostomia to disease free without toxicity after the first 6 months. Thereafter, toxicity was assumed to be irreversible.

Markov model input

Transition probabilities

The occurrence of xerostomia and/or dysphagia was estimated according to 2 available NTCP models (8, 9). Mean radiation dose to

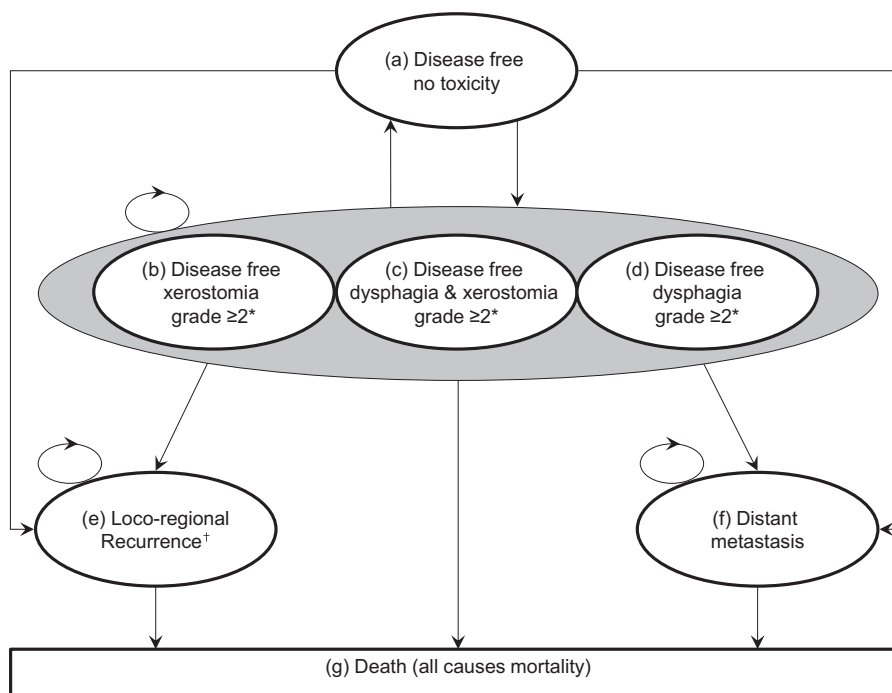


Fig. 1. Diagrammatic representation of the model structure. Toxicity that occurred in the first 6 months was (partly) reversible. Therefore, patients are allowed to move between health states a, b, c, and d 6 months after radiation therapy. Thereafter, toxicity was assumed to be irreversible. *Toxicity was defined according to the presence of Radiation Therapy Oncology Group grade 2 or higher. [†]There was no transition from locoregional recurrence to death via distant metastasis. This was done first because patients who develop distant metastasis are expected to die within 1 year (Appendix 3). If we would add the transition from locoregional recurrence to death via distant metastasis, it will last 1 year or more before patients die due to distant metastasis. Second, the intermediate step to distant metastasis was already included in the probabilities used to calculate death after locoregional recurrence (Appendix 3).

the parotis ipsilateral and parotis contralateral were used to predict xerostomia RTOG grade 2 at 6 and 12 months after radiotherapy (8). Mean dose to the pharyngeal constrictor muscle superior and the supraglottic area predicted dysphagia RTOG grade ≥ 2 at 6 and 12 months after radiation therapy (Appendix 1, available online) (9). The required dose parameters were retrieved from a planning study (n=25) comparing swallowing-sparing IMRT and swallowing-sparing IMPT (7). Subsequently, the individual dose parameters and NTCP models were used to calculate individual IMPT/IMRT toxicity probabilities. These individual probabilities were averaged

to obtain the average probabilities. The toxicity probabilities for *IMPT if efficient* were obtained by first determining which treatment (IMPT/IMRT) was expected to be cost-effective for each individual patient. This was done by using the individual dose parameters and toxicity probabilities to calculate individual cost-effectiveness. Second, in patients for whom IMPT was expected to be cost-effective the IMPT probabilities were used, whereas the IMRT probabilities were used in the remaining patients. Third, the obtained individual probabilities were averaged (calculation is illustrated in Table 1).

Table 1 Method to calculate toxicity for the *IMPT if efficient* strategy: Illustrated for xerostomia 6 months after radiation therapy

Patient	Probability of xerostomia (%)		ICER IMPT vs IMRT (€)	Preferred IMPT/IMRT	Probability of xerostomia (%) <i>IMPT if efficient</i> *
	IMPT	IMRT			
1	25.5	41.3	93,302	IMRT	41.3
2	18.9	36.6	169,448	IMRT	36.6
3	23.6	55.2	44,358	IMPT	23.6
4	26.7	37.2	150,041	IMRT	37.2
↓	↓	↓	↓	↓	↓
25	25.8	45.1	89,593	IMRT	45.1
Mean probability of xerostomia for the <i>IMPT if efficient</i> strategy					37.1%

Abbreviations: ICER = incremental cost-effectiveness ratio; IMPT = intensity modulated proton radiation therapy; IMRT = intensity modulated radiation therapy with photons.

* Patients will only receive IMPT in this scenario if IMPT is expected to be cost-effective compared with IMRT (grey fields), thus if the ICER is below the threshold of 80,000 per QALY gained.

The proportion of patients who had both xerostomia and dysphagia was calculated using conditional toxicity probabilities from a cross-sectional survey (Appendixes 1 and 2) (5).

Disease progression for all comparators was based on a meta-analysis that compared radiation therapy with and without chemotherapy in curatively treated nonmetastatic HNC (10). These probabilities were extracted from the concomitant chemotherapy arm (current standard treatment for advanced HNC). Age-dependent background mortality was used for disease-free patients. An increased mortality probability was used for patients who had locoregional recurrence or distant metastases (Appendix 3).

Effects and costs

Quality of life in terms of utility scores was used as outcome measure. Utility scores provide a single index value for health status, ranging from 0 (death) to 1 (full health). Utility scores were derived from a cross-sectional study (n=396) using the Euroqol-5D questionnaire in Dutch HNC patients (Appendix 3) (5). Utility scores were combined with life expectancy to calculate quality-adjusted life years (QALYs).

The health care perspective was used to calculate costs using activity-based costing. Unit prices and resource use were based on guidelines, a cross-sectional survey (5), or if necessary expert opinion (Appendixes 4 and 5).

The primary treatment costs for IMPT were calculated by multiplying treatment costs for IMRT with a cost ratio of 2.1 (1, 11). For *IMPT if efficient*, both IMPT and IMRT treatment plans were made to compare individual dose distributions and decide upon the most efficient treatment per patient. Therefore, costs of an extra treatment plan (€88) were added for this strategy.

A half-cycle correction was applied for QALYs and costs (12). Future QALYs and costs were discounted by rates of 1.5% and 4.0%, respectively (13). All costs were converted to the 2010 price level.

Markov model analyses

Expected mean costs, occurrence of toxicity, disease- and toxicity-free life years (DTFLYs) and QALYs were estimated for all comparators. Subsequently, the incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental costs by the incremental QALYs. The ICER represents the costs of an additional QALY gained when comparing 2 strategies. Whether a treatment strategy is considered cost-effective depends on how much society is willing to pay per gained QALY, which is referred to as the ceiling ratio. We adopted a ceiling ratio of €80,000, because this is the informal ceiling ratio for a high burden of disease in The Netherlands.

Sensitivity analyses

The assumption of equal disease progression for IMPT and IMRT was relaxed in a sensitivity analysis. The probabilities used in this analysis were based on a synthesis (6) of available clinical studies for oropharyngeal carcinomas (Appendix 3).

Probabilistic sensitivity analyses were performed to reflect the uncertainty in the input parameters and its impact on the estimated (cost-)effectiveness (3). This was done by assigning a distribution to the input parameters (Appendixes 1-4) and subsequently drawing random values from these distributions using Monte Carlo simulation (20,000 iterations). The results of the

probabilistic sensitivity analyses were presented using cost-effectiveness acceptability curves. For different ceiling ratios this curve shows the probability that a treatment strategy is cost-effective (3).

Value of information analyses

Because the results are surrounded by uncertainty, chances are that the wrong decision is being made when implementing the most cost-effective strategy. The expected value of perfect information (EVPI) analysis assesses the expected costs of this decision uncertainty. Hence, the EVPI places a maximum that society should be willing to pay for further evidence to reduce this uncertainty (3).

The population EVPI was calculated by multiplying the EVPI per patient by the effective population in the next 10 years (expected life span of the technology) and discounted by a rate of 4% (13). The effective population was calculated according to a yearly incidence of 2265 HNC patients in The Netherlands (Dutch cancer registry 2008), of which 2063 were expected to receive radiation therapy, minus the estimated proportions of patients with early-stage HNC (33%) and/or pretreatment dysphagia and/or xerostomia grade ≥ 2 (36%).

To identify the most valuable research topics, the EVPI for (groups of) parameters was calculated for the NTCP models, disease progression, utility scores, and costs. All analyses were performed in Microsoft Office Excel (Microsoft, Redmond, WA).

Results

The estimated occurrence of xerostomia and dysphagia at 12 months was lowest for *IMPT for all patients* (22% and 18%), followed by *IMPT if efficient* (36% and 21%) and *IMRT for all patients* (44% and 23%) (Appendix 1).

IMPT for all patients was the most effective (6.620 QALYs, 5.800 DTFLYs) and most expensive (€50,989) strategy (Table 2). *IMRT for all patients* was the least effective (6.520 QALYs, 4.197 DTFLYs) and least expensive (€41,038) strategy. The difference in costs between these 2 strategies was mainly due to higher primary treatment costs (€21,100 vs €10,048). For all 25 patients, IMPT resulted in more QALYs compared with IMRT. Restricting IMPT to the 7 patients (28%) for whom IMPT is expected to be cost-effective (*IMPT if efficient*) would yield 6.563 QALYs and 4.875 DTFLYs at an estimated cost of €43,650.

IMPT if efficient as opposed to *IMRT for all patients* resulted in an ICER of €60,278 per QALY gained. *IMPT for all patients* compared with *IMPT if efficient* resulted in an ICER of €127,946 per QALY gained. *IMPT if efficient* can thus be regarded as the most cost-effective strategy (Table 2).

IMPT if efficient had the highest probability (62%) of being the most cost-effective strategy (Fig. 2). The value of further research was estimated to be €2.4 million for the total population. Further research focusing on utility scores after xerostomia (€0.7 million), NTCP models for dysphagia (€0.3 million), and for xerostomia (€0.1 million) is most worthwhile.

In the sensitivity analysis, *IMRT for all patients* yielded 1.493 more QALYs and was €8093 less expensive and thus dominated *IMPT for all patients* (Table 3). This was the case for all individual patients. The individualized strategy was thus equal to *IMRT for all patients* plus the costs of an extra treatment plan and is therefore not considered in the sensitivity analysis.

Table 2 Base case results of the cost-effectiveness analyses (sorted by QALY)

Treatment strategy	Expected outcomes (95% CI*)		Comparator	Increments (95% CI*)		ICER € per QALY/ DTFLY [†]
	QALY/DTFLY [†]	Costs (€)		Incremental QALY/DTFLY [†]	Incremental costs (€)	
IMRT for all patients	6.520 (5.781 to 7.018)	41,038 (38,878 to 44,158)				
IMPT if efficient	6.563 (5.818 to 7.059)	43,650 (41,523 to 46,949)	IMRT for all patients	0.043 (0.014 to 0.073)	2612 (2008 to 3306)	60,278
IMPT for all patients	6.620 (5.869 to 7.115)	50,989 (48,227 to 54,852)	IMPT if efficient	0.057 (0.016 to 0.102)	7339 (6001 to 8744)	127,946
IMRT for all patients	4.197 (3.198 to 4.964)	41,038 (38,878 to 44,158)				
IMPT if efficient	4.875 (3.761 to 5.630)	43,650 (41,523 to 46,949)	IMRT for all patients	0.678 (0.448 to 0.854)	2612 (2008 to 3306)	3854
IMPT for all patients	5.800 (4.536 to 6.594)	50,989 (48,227 to 54,852)	IMPT if efficient	0.925 (0.628 to 1.182)	7339 (6001 to 8744)	7936

Abbreviations: CI = confidence interval; DTFLY = disease and toxicity free life year; QALY = quality-adjusted life year. Other abbreviations as in Table 1.

* Confidence interval is based on probabilistic analysis.

[†] Values in lower 3 rows represent DTFLY.

IMRT for all patients had the highest probability (75%) of being cost-effective (Fig. 2).

Discussion

The original aspect of this assessment was that despite the lack of comparative effectiveness research, we were able to explore the cost-effectiveness of IMPT versus IMRT. The present study showed that using NTCP models combined with comparative planning studies into model-based economic evaluations is feasible and informative. Besides examining the (cost-)effectiveness, this methodology can potentially be used to identify patients for whom particular treatments are more or less (cost-)effective than for the whole group. If equal disease control is assumed, IMPT is more effective than IMRT for all HNC patients. Thus, on the basis of effectiveness, IMPT would be the treatment of choice for all patients. However, the increased effectiveness of IMPT does not outweigh its additional costs for all patients. Administering IMPT only to selected patients for whom it is expected to be cost-effective (*IMPT if efficient*) seems the most cost-effective treatment strategy. IMRT is the dominant strategy if disease progression is based on clinical evidence. The quality and quantity of available studies is, however, poor (6). Accordingly, it is possible that differences in disease progression found in these studies and thus the dominance of IMRT are not a reflection of actual differences.

Some limitations should also be discussed. First, the presented methodology is not yet validated. As with any novel methodology, further research and application of the methodology in practice are needed to demonstrate its validity. Second, disease progression was based on a meta-analysis that included trials conducted before 2000. Because recent studies show more favorable results (10), disease progression might have been overestimated. Third, the health care perspective was used for cost calculation. The societal perspective, including productivity losses, might favor IMPT because less toxicity presumably reduces productivity losses. The preceding 2 limitations can be regarded as conservative toward

IMPT. Fourth, radiation-induced cancer was not incorporated, because evidence on the magnitude and direction of this effect is lacking (14). Additionally, given that radiation-induced cancer generally occurs years after radiation therapy, it is probably not an influential factor in this older population. Fifth, utility scores for the different health states were retrieved from a cross-sectional study (5). Preferably, these utility scores are based on a prospective study to correct for possible baseline differences. However, the occurrence of xerostomia and/or dysphagia is expectedly independent of baseline utility scores. Sixth, 2 available prediction models (8, 9) were used to predict the occurrence of toxicity. As with all prediction models, these models can possibly be optimized to achieve more accurate predictions. For the validity of the proposed methodology, it is of great importance to use valid prediction models. This uncertainty is incorporated in the probabilistic sensitivity analysis. Seventh, the analyses were based on swallowing-sparing radiation therapy techniques. Choice of these techniques most likely decreases the QALY gain for IMPT compared with IMRT owing to a smaller reduction of dysphagia (7). Hence, using swallowing-sparing techniques can be regarded as conservative toward IMPT. Those interested can use the interactive decision support tool (www.predictcancer.org) to examine the cost-effectiveness of IMPT versus IMRT for any other radiation therapy technique. Eighth, incorporating additional time points to estimate toxicity would lead to a more realistic representation of clinical practice. However, because this concerns both comparators, the impact on the difference in toxicity and consequently the difference in QALYs is probably small. Finally, to estimate the occurrence of toxicity, we used NTCP models validated with photons. It has been argued that using these NTCP models for protons possibly requires modification because photons and protons differ in low to intermediate dose distributions (15). At this moment, it is unknown to what degree NTCP models validated in photon studies can be used for protons.

One previous study (16) addressed the cost-effectiveness of proton radiation therapy in HNC and reported a substantially lower ICER of €3811 per QALY for proton versus photon radiation therapy than the present study. This discrepancy can be

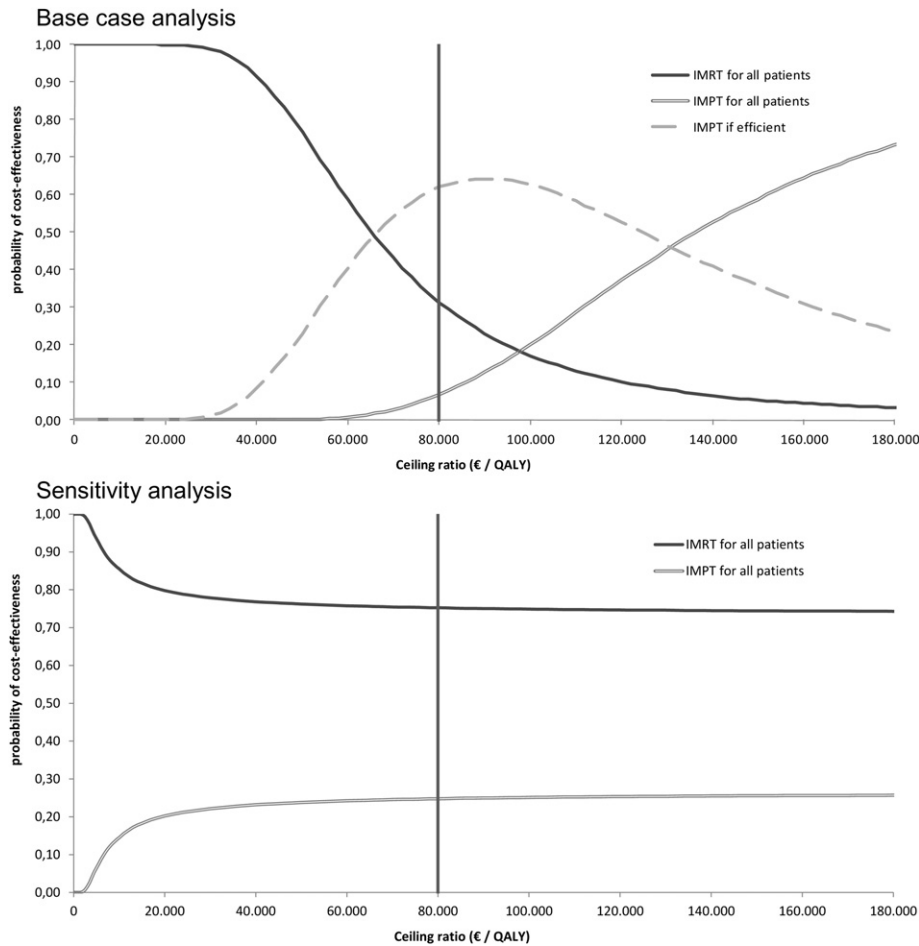


Fig. 2. Cost-effectiveness acceptability. The vertical line represents the ceiling ratio that was adopted in our analyses (€80,000 per quality-adjusted life year gained). IMPT = intensity modulated proton radiation therapy; IMRT = intensity modulated radiation therapy with photons.

explained by differences in assumptions. Our model assumed equal survival for both comparators, whereas Lundkvist et al (16) assumed a mortality risk reduction of 24% for proton radiation therapy.

To our knowledge, no other studies used NTCP models in economic evaluations. Konski et al (17) used dose-response data

to predict recurrences in an economic evaluation for proton radiation therapy in prostate cancer.

The main research implication is that the applied study method, possibly combined with dose-response data for disease progression (17), is feasible and informative to explore the potential (cost-)effectiveness of innovative radiation therapy

Table 3 Sensitivity analysis (sorted by QALY)

Treatment strategy	Expected outcomes (95% CI*)		Comparator	Increments (95% CI*)		ICER
	QALY/DTFly [†]	Costs (€)		Incremental QALY/DTFly [†]	Incremental costs (€)	€ per QALY/DTFly [†]
IMPT for all patients	6344 (3.729 to 10.581)	48,042 (44,372 to 54,416)				
IMRT for all patients	7.937 (6.309 to 9.741)	39,949 (36,445 to 45,273)	IMPT for all patients	1.493 (-2.953 to 4.786)	-8093 (-13,546 to -3478)	Dominant
IMPT for all patients	5.425 (2.677 to 9.917)	48,042 (44,372 to 54,416)				
IMRT for all patients	5.114 (3.608 to 6.774)	39,949 (36,445 to 45,273)	IMPT for all patients	-0.310 (-4.943 to 2.792)	-8093 (-13,546 to -3478)	26,094

Abbreviations: As in Tables 1 and 2.

* Confidence interval is based on probabilistic analysis.

† Lower two rows represent DTFly.

techniques if clinical evidence is lacking. Clinical data and especially comparative evidence is obviously superior to the proposed methodology. However, the proposed methodology offers a solution if clinical data are lacking and it is not desirable to wait or postpone decisions until clinical data become available. For proton radiation therapy this methodology may provide new insights to the debate considering pros and cons of clinical trials comparing proton and photon radiation therapy (4). It would be interesting for this debate to explore which radiation therapy technique is optimal and consider planning studies primarily focused on sparing other structures than the swallowing structures. Additionally, further research on utility scores after xerostomia and NTCP models seems most valuable to reduce decision uncertainty.

Our results showed that, on the basis of equal survival for IMPT and IMRT, IMPT is cost-effective for individually selected patients in The Netherlands. For clinical practice it is therefore recommended to make a trade-off between expected costs and benefits for each individual patient. The presented methodology can be used to make this individual trade-off. This is in line with recent policy recommendations (18). In these recommendations it is mentioned that a clinically significant reduction of complications is required for patients to be eligible for IMPT. However, it is not specified what can be considered as a clinically significant reduction. It is required to specify a threshold when patients are eligible for IMPT, either based on cost-effectiveness or solely on effectiveness. In our analyses, the reduction in complications was expressed in terms of QALYs. The adopted ceiling ratio of €80,000 per QALY gained enabled us to calculate which treatment is preferred according to cost-effectiveness.

In deciding which patients receive IMPT, the proposed methodology, if validated by clinical data, could act as a clinical decision support tool. Our tool is published online as example (www.predictcancer.org). Treatment allocation could then be based on individual patient data to ensure that IMPT is assigned to patients for whom it is expected to be worthwhile.

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