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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.

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