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Cost-effectiveness of adjuvant intravaginal brachytherapy in high-intermediate risk endometrial carcinoma

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ABSTRACT

PURPOSE: We assessed the cost-effectiveness of adjuvant intravaginal brachytherapy (IVBT) vs. observation after total hysterectomy and bilateral salpingo-oophorectomy (TH/BSO) for high-intermediate risk (HIR) endometrial carcinoma.

METHODS AND MATERIALS: A Markov model was used to assess the cost-effectiveness of IVBT by comparing average cumulative costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) between patients allocated to (*1*) 'observation' or (*2*) 'IVBT' after TH/BSO. We used a prototype Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)—defined HIR patient in the base case analysis. We calibrated the model to match the outcomes reported in the PORTEC-1 and PORTEC-2 trials. Utilities were obtained from published estimates, and costs were calculated based on Medicare reimbursement ($5445 for IVBT). The societal willingness-to-pay threshold was set at $100,000 per QALY. The time horizon was 5 years.

RESULTS: IVBT was associated with a net increase of 0.094 QALYs (4.512 vs. 4.418) as well as an increase in mean cost ($17,453 vs. $15,620) relative to observation. The ICER for IVBT was $19,500 per QALY. On one-way sensitivity analysis, IVBT remained cost-effective when its cost was less than $12,937. If the probability of vaginal recurrence in the observation arm was increased or decreased by 25%, the ICER became $1335 per QALY and $87,925 per QALY, respectively. Probabilistic sensitivity analysis revealed that IVBT was the preferred management option in 86% of simulations.

CONCLUSIONS: IVBT is cost-effective compared with observation after TH/BSO for HIR endometrial carcinoma by commonly accepted willingness-to-pay thresholds.

Keywords: Cost-effectiveness; Markov model; Endometrial carcinoma; High-intermediate risk; Intravaginal brachytherapy

Introduction

Adjuvant radiotherapy (RT) has been shown to improve local control in early-stage endometrial carcinoma (EC) patients after total hysterectomy and bilateral salpingo-oophorectomy (TH/BSO) in multiple randomized trials (1−3). These trials have not observed an overall survival benefit from adjuvant RT, which may be attributable to salvage options after local failure, competing risks of mortality, and/or designs lacking sufficient power to detect such a difference. Although recent retrospective data suggest a possible survival benefit to adjuvant RT (4), it is not recommended in all early-stage EC patients. For adequately low-risk patients, observation can be used as an alternative to upfront adjuvant RT.

The Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) 1 and 2 trials examined the benefit of adjuvant RT in patients with intermediate risk EC. The PORTEC-1 trial identified a high-intermediate risk (HIR)

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subgroup of patients who appeared to benefit most from adjuvant RT (1). Given that the most common site of recurrence in the absence of adjuvant RT was the vaginal cuff in PORTEC-1, the PORTEC-2 trial showed that intravaginal brachytherapy (IVBT) was noninferior to whole-pelvic external beam radiotherapy (EBRT) for vaginal control in the HIR subgroup with the added benefit of reduced toxicity (5). Consequently, national guidelines recommend that adjuvant IVBT be considered for patients with HIR EC after surgery (6).

Evidence-based allocation decisions are important to optimize the efficiency of a health-care system. Cost-effectiveness analysis (CEA) calculates the ratio of net health-care costs to benefits (both monetary and quality of life) and can be used to set priorities. As such, we assessed the cost-effectiveness of IVBT in HIR EC after surgery and compared it to common societal willingness-to-pay (WTP) thresholds using a Markov model based on the results from PORTEC-2. Results from PORTEC-1 were needed to estimate clinical outcomes in the hypothetical observation arm, therefore inclusion criteria for data modeling the two competing management approaches were not identical.

Methods and materials

A Markov-state transition cost-effectiveness model was created using TreeAge Pro (Version 2017, TreeAge Software, Inc., Williamstown, MA) to estimate the quality-adjusted life years (QALYs) and cumulative costs of adjuvant IVBT vs. observation in a hypothetical cohort of patients with PORTEC-defined HIR EC after TH/BSO without lymphadenectomy in the base case analysis. The difference in cost between these two management approaches divided by the difference in their effectiveness was used to calculate the incremental cost-effectiveness ratios (ICERs) if there was no dominant strategy. The treatment strategy was deemed to be cost-effective if the ICER value was found to be less than previously described societal WTP thresholds (defined as $100,000 per QALY in the base case) (7).

Initial treatment and patient cohort

The hypothetical cohort included patients who would have qualified for the PORTEC-2 (IVBT vs. EBRT) and PORTEC-1 (EBRT vs. observation) trials after undergoing TH/BSO for early-stage EC. Patients qualifying for PORTEC-2 had two of three HIR factors (age $>$ 60 years, greater than 50% myometrial invasion [MMI] on pathology, and International Federation of Gynecology and Obstetrics histological grade 3). Patients in the PORTEC-1 trial were accrued prior to proposal of the HIR definition, and thus 54.3% of patients in this study could be classified as HIR, though all were deemed intermediate risk (any age, grade 1 with $\geq$50% MMI, grade 3 with $<$50% MMI, and grade 2 with any invasion). The PORTEC-1 observation arm was chosen for comparison with the PORTEC-2 IVBT arm because it is the largest population of HIR patients randomized to observation without surgical staging. Patients entered the model at age 60 for the purpose of calculating competing risk of mortality using Centers for Disease Control and Prevention death data (8). This age was chosen given its approximation of the median age of EC diagnosis.

Markov model

At the initiation of the model (Fig. 1), patients who had received TH/BSO without residual disease were allocated to either adjuvant IVBT or observation. From this state, patients were passed through the model with 1-year cycles for a total of 5 years where they remained at risk for recurrence (vaginal, pelvic, and distant), salvage, complications related to upfront or salvage therapy, cancer-related death, and intercurrent death. A time horizon of 5 years was felt to encompass the majority of relevant disease and treatment-related events. The choice of salvage therapy depended on the adjuvant management allocation and the location of the recurrence. Costs and utilities were assessed at the end of each 1-year cycle.

Model inputs

Model parameters were derived from the published literature with high quality, randomized phase III data preferred where available (Table 1). The model was calibrated to match the 5-year recurrence rates of the adjuvant IVBT arm from the PORTEC-2 trial, while those from the observation arm were derived from the PORTEC-1 trial. For the adjuvant IVBT cohort, the 5-year rate of vaginal recurrence was estimated at 1.8% and the probability of successful salvage was 20.5%. Successful salvage was defined as freedom from disease progression at 5 years. For the observation cohort, the 5-year rate of vaginal recurrence was estimated at 10.2% and the probability of successful salvage was 59.5% (based on an average value from eight retrospective studies (11–18)). Of note, the estimates of cancer-related outcomes from the PORTEC-1 observation arm required inclusion of low-intermediate risk patients and potentially underestimates the true risk of recurrence. This conservative estimate was felt to minimally bias the data toward the null hypothesis that adjuvant IVBT was not cost-effective. Complications were defined as those treatment-related secondary effects requiring surgical management (Common Terminology Criteria for Adverse Events grade three or four). Risk of death annually from metastatic cancer was estimated from patients with FIGO stage IVB EC (10). Risk of death from intercurrent disease was determined from the National Vital Statistics Report for a woman between the ages of 60 and 65 years.

Utilities and costs

Utilities for each health state (Table 2) were obtained from published estimates (23) based on surveys of nine oncologists