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Treatment strategies for stage IB cervical cancer: A cost-effectiveness analysis from Korean, Canadian and US perspectives

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HIGHLIGHTS

- We performed a cost-effectiveness analysis for stage IB cervical cancer.
- A cost-effectiveness analysis was performed using data from US, Canada, and Korea.
- MRI-based triage strategy was cost-effective in all countries.

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ABSTRACT

Objectives. To assess the cost-effectiveness of two commonly used strategies and an alternative triage strategy for patients with Stage IB cervical cancer in the US, Canada, and Korea.

Methods. A Markov state-transition model was constructed to compare three strategies: (1) radical hysterectomy followed by tailored adjuvant therapy (primary surgery), (2) primary chemoradiation, and (3) an MRI-based triage strategy, in which patients without risk factors in preoperative MRI undergo primary surgery and those with risk factors undergo primary chemoradiation. All relevant literature was identified to extract the probability data. Cost data were calculated from the perspective of US, Canadian, and Korean payers. Strategies were compared using an incremental cost-effectiveness ratio (ICER). Cost-effectiveness ratios were analyzed separately using data from each country.

Results. Base case analysis showed that the triage strategy was the most cost-effective of the three strategies in all countries at usual willingness-to-pay threshold (Korea: $30,000 per quality-adjusted life year (QALY), Canada and US: $100,000 per QALY). Monte Carlo simulation acceptability curves from Korea indicated that at a willingness-to-pay threshold of $30,000/QALY, triage strategy was the treatment of choice in 71% of simulations. Monte Carlo simulation acceptability curves from US and Canada indicated that at a willingness-to-pay threshold of $100,000/QALY, triage strategy was the treatment of choice in more than half of simulations.

Conclusions. An MRI-based triage strategy was shown to be more cost-effective than primary surgery or primary chemoradiation in the US, Canada, and Korea.

1. Introduction

Cervical cancer remains a major global health problem that creates a substantial burden in terms of morbidity, mortality, and healthcare costs. Approximately 450,000 cases of cervical cancer are diagnosed annually, and the World Health Organization (WHO) reports that 250,000 women die of this disease each year [1].

To date, a single randomized controlled trial has compared the outcomes of primary surgery and primary radiotherapy for Stage IB cervical cancer [2]. Landoni et al. did not find greater survival rates for either treatment modality; however, an increase in toxicity was observed following the combined use of radical hysterectomy and adjuvant radiation. As there have not been any randomized comparisons of primary radical surgery and primary chemoradiation, the choice of primary treatment option depends on various factors, including available resources, cost, patient characteristics, and physician preferences. Current

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National Comprehensive Cancer Network (NCCN) guidelines recommend basing the primary treatment option on tumor size for stage IB cervical cancer. Surgery is the preferred option for patients with stage IB1 disease, whereas primary chemoradiation is the most appropriate option for those with stage IB2 disease [3]. However, surgery is the preferred option and most frequently employed primary treatment modality in practice [4–6]. Therefore, a considerable proportion of patients with Stage IB cervical cancer undergo surgery followed by postoperative adjuvant therapy, raising concerns over the additional cost and morbidity resulting from multimodality therapy [2,7,8]. Selection of an appropriate primary treatment is crucial. Although it is not accepted as part of the formal staging procedure, the use of advanced imaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET)-CT, has been suggested as a means of guiding treatment options and design for cervical cancer patients. The inclusion of MRI or PET-CT in the decision-making process for primary treatment modality could have reduced the number of patients requiring multimodality therapy in a significant percentage of women with Stage IB cervical cancer [9,10].

Before conducting conclusive randomized controlled trials to compare the outcomes of surgery and primary chemoradiation, it is important to identify the most cost-effective strategy based on the best available evidence and circumstances in each country. There have been several cost-effectiveness studies for Stage IB cervical cancer to identify the most appropriate treatment option [7,8,11], and radical hysterectomy followed by tailored adjuvant therapy has been suggested as the most cost-effective strategy. However, Katanyoo et al. showed that this strategy was only cost-effective for patients who did not require adjuvant treatment after surgery [8].

We suggest an alternative triage strategy based on preoperative MRI and demonstrate the efficacy of reducing the rate of multimodality therapy while maintaining the proportion of patients who could be treated using surgery alone [10]. The aim of this study was to evaluate the cost-effectiveness of two commonly used strategies (primary surgery and primary chemoradiation) and an alternative triage strategy for Stage IB cervical cancer.

2. Methods

A modified Markov model was constructed using TreeAge Pro software (TreeAge Software Inc., Williamstown, MA). The model evaluated three strategies for managing patients with Stage IB cervical cancer: (1) radical hysterectomy with pelvic lymphadenectomy followed by tailored adjuvant therapy (primary surgery), (2) primary chemoradiation, and (3) an MRI-based triage strategy, in which patients without risk factors in preoperative MRI underwent primary surgery and those with risk factors underwent primary chemoradiation. Markov states included "disease-free without complications," "disease-free with chronic complications," and "death" (Fig. 1). The cycle length was one year and the time horizon, five years.

Patients were assumed to have been diagnosed and clinically staged by a gynecologic oncologist using patient history, a physical examination, and a cervical biopsy. In addition, each patient received a CT scan to exclude obvious advanced disease.

In the primary surgery strategy, patients had surgery (radical hysterectomy and pelvic lymphadenectomy) as the primary treatment modality. All patients were assumed to complete surgery. Therefore, we did not consider aborted surgery due to incidentally found parametrial involvement or lymph node metastasis based on intraoperative frozen section. Then, patients were assumed to receive postoperative adjuvant therapy according to pathologic risk factors. Patients had two possibilities: (1) no risk factors or (2) risk factor(s). For patients with no risk factors, adjuvant therapy was not assumed. Patients with risk factors were defined as either intermediate risk or high risk. High-risk patients who had at least one Category 1 risk factor (positive resection margin, lymph node metastasis (LNM), or parametrial involvement (PMI)) were assumed to receive postoperative chemoradiation. Intermediate-risk patients with two or more Category 2 risk factors based on Classic criteria (positive lymphovascular space invasion, deep stromal invasion, or large tumor size) were assumed to receive adjuvant radiotherapy [12]. Guideline adherence to adjuvant treatment was assumed to be 100%. For patients undergoing adjuvant chemoradiation, radiation was delivered at 1.8 Gy per fraction once per day for five days a week over six weeks, with a total median pelvic dose of 50.4 Gy. Six cycles of concomitant platinum-based chemotherapy were performed, with a cisplatin dose of 40 mg/m^2 per week.

In primary concurrent chemoradiation (CCRT), all patients were assumed to receive whole pelvic external-beam radiation (WPRT), six cycles of platinum-based chemotherapy, and additional vaginal cylinder brachytherapy. Radiation was delivered at 1.8 Gy per fraction once per day for five days a week over six weeks, with a total median pelvic dose of 50.4 Gy. Six cycles of concomitant platinum-based chemotherapy were performed, with a cisplatin dose of 40 mg/m^2 per week. After pelvic WPRT, patients received intracavitary radiation (ICR) therapy with a total dose of 25 Gy in five fractions to Point A.

In the MRI-based triage strategy, all patients underwent pelvic MRI, and the primary treatment modality was recommended according to these results. Patients were categorized into two groups according to MRI-based parameters: a low-risk group (no evidence of PMI or LNM in MRI) and a high-risk group (findings suggesting PMI and/or LNM in MRI). Low-risk patients were assumed to undergo primary radical surgery followed by tailored adjuvant therapy based on final pathology, and high-risk patients were assumed to undergo primary chemoradiation. Similar to the primary surgery strategy, there were two possibilities for patients who underwent primary radical surgery in the MRI-based triage strategy: (1) no risk factors and (2) risk factor(s).

The sensitivity and specificity of the MRI were incorporated into the model such that four possible scenarios resulted: true positive (high risk on MRI, patients underwent primary CCRT with risk factor), true negative (low risk on MRI, patients underwent primary surgery and no further treatment), false positive (high risk on MRI, patients underwent primary CCRT despite no risk factor) and false negative (low risk on MRI, patients underwent primary surgery and adjuvant treatment).

2.1. Model estimates

2.1.1. Clinical parameters: survival

Data from the literature review were used to define the five-year overall survival rates for each risk and treatment category (Table 1). We identified Phase III studies that evaluated the outcomes of Stage IB cervical cancer by performing a literature search of reports in PubMed. The overall search strategy included terms for cervical cancer and Phase III trials. We used the transitional probability of mortality in cervical cancer patients based on results from Phase III trials [2,13–15]. We categorized patients into four cohorts to estimate outcomes: (1) surgery with no risk factors [2], (2) surgery with risk factors (intermediate risk) followed by adjuvant radiotherapy [14], (3) surgery with risk factors (high risk) followed by adjuvant chemoradiation [13], and (4) primary chemoradiation [15].

2.1.2. Clinical parameters: probability

The probability of patients having the following outcomes after radical hysterectomy was estimated from previous reports (Table 1). We estimated that approximately 50% of patients would have no risk factors and would therefore require no adjuvant therapy after primary surgery. The alternative triage strategy using preoperative MRI results selects patients who are more likely to require primary surgery alone. Therefore, under this strategy, approximately 65.5% of patients would have no risk factors and would therefore require no adjuvant therapy when undergoing primary radical surgery based on preoperative MRI results. [10].