Gynecologic Oncology 135 (2014) 518–524

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

The cost-effectiveness of selective lymphadenectomy based on a preoperative prediction model in patients with endometrial cancer: Insights from the US and Korean healthcare systems ☆

Jung-Yun Lee [a], David E. Cohn [b], Younhee Kim [c], Tae-Jin Lee [d], Jason C. Barnett [e], Jae-Weon Kim [a,*], Yong Woo Jeon [f], Kidong Kim [g], Sang Min Park [h], Sokbom Kang [i]

[a] Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, Republic of Korea
[b] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Ohio State University College of Medicine, Columbus, OH, USA
[c] Institute of Health and Environment, Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea
[d] Department of Health Policy and Management, Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea
[e] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, San Antonio Military Medical Center, Fort Sam, Houston, TX, USA
[f] Korean Health Promotion Foundation, Seoul, Republic of Korea
[g] Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Gyonggi-do, Republic of Korea
[h] Department of Family Medicine, Seoul National University, College of Medicine, Seoul, Republic of Korea
[i] Center for Uterine Cancer, National Cancer Center, Goyang, Gyeonggi-do, Republic of Korea

HIGHLIGHTS

- We evaluated the cost-effectiveness of selective lymphadenectomy in early-stage endometrial cancer in the US and Korea.
- Selective lymphadenectomy was more cost-effective than routine lymphadenectomy over a reasonable range of variables.

ARTICLE INFO

Article history:
Received 25 August 2014
Accepted 28 September 2014
Available online 29 October 2014

Keywords:
Endometrial cancer
Selective lymphadenectomy
Cost-effectiveness
Preoperative prediction

ABSTRACT

Objective. The aim of this study was to determine the cost-effectiveness of selective lymphadenectomy using a preoperative prediction model compared to routine lymphadenectomy for patients undergoing surgery for endometrial cancer in the US and Korea.

Methods. We used a modified Markov model to estimate clinical and economic outcomes for newly diagnosed, apparent early-stage endometrial cancer patients under two different strategies: (1) selective lymphadenectomy, where patients classified as low risk based on the preoperative prediction model did not undergo complete surgical staging, and (2) routine lymphadenectomy, where all patients underwent complete surgical staging. Published data were used to estimate the rates of adjuvant therapy and survival. Costs were calculated from the perspective of US or Korean payers. Cost-effectiveness ratios were analyzed separately using data from each country.

Results. Base-case analysis indicated that selective lymphadenectomy was less costly ($6454 vs. $7079 in Korea; $23,995 vs. $26,318 in the US) and more effective (6.91 quality-adjusted life years (QALYs) vs. 6.85 QALYs in Korea; 6.87 QALYs vs. 6.81 QALYs in the US) than routine lymphadenectomy in both countries. This result was robust in a deterministic sensitivity analysis, with the exception of when the utility scores for patients with lymphedema were varied. So long as a modest preference for avoiding lymphedema (disutility of 0.04) was obtained, selective lymphadenectomy remained the dominant strategy.

Conclusions. A selective lymphadenectomy strategy based on a preoperative prediction model was shown to be more cost-effective than routine lymphadenectomy for endometrial cancer patients in the US and Korea.

Introduction

Until recently, a full standard lymphadenectomy, including pelvic and paraaortic lymph node dissection, was recommended for all patients with endometrial cancer. While selective lymphadenectomy has gained visibility, debate on the value of routine lymphadenectomy

☆ Featured poster presented at the 45th Annual Meeting of the Society of Gynecologic Oncologists, Tampa, FL, March 22–25, 2014.

* Corresponding author at: Department of Obstetrics and Gynecology, Seoul National University, College of Medicine, 101 Daehak-ro, Jongno-gu, 110-744 Seoul, Republic of Korea. Fax: +82 2 762 3599.
E-mail address: kjwksh@snu.ac.kr (J.-W. Kim).

http://dx.doi.org/10.1016/j.ygyno.2014.09.020
0090-8258/

continues. Two large randomized controlled trials (RCTs) have demonstrated that comprehensive surgical staging does not improve progression-free or overall survival [1,2]. Current guidelines recommend a more selective and tailored lymphadenectomy approach in early-stage endometrial cancer [3]. The extent of surgical staging can be determined based on preoperative and intraoperative findings. In an effort to balance the risks and benefits of lymphadenectomy, prediction models have been developed to identify patients that might benefit from lymphadenectomy. Although no consensus exists on the definition of a "low-risk" patient for lymph node metastasis, several researchers have shown that the prevalence of nodal metastasis in this low-risk group is negligible [4–6].

The cost-effectiveness of various strategies for lymphadenectomy has been evaluated [7,8]. Clements et al. demonstrated that a strategy of selective lymphadenectomy based on intraoperative risk factors was less cost-effective than routine lymphadenectomy [7]. In addition, Cohn et al. suggested that surgical staging in all patients was the most cost-effective strategy compared to no staging and staging based on frozen sections following hysterectomy [8]. However, a prospective study has shown that lymphadenectomy increased morbidity and the cost of care without increasing survival rates in patients with low-risk endometrial cancer as defined by Mayo Clinic criteria: Type I histology, Grade 1 or 2, myometrial invasion $\leq$50%, and tumor diameter $\leq$2 cm [9]. When using a triage algorithm, the accuracy of the prediction model may be the key issue. Recently, the Korean Gynecologic Oncology Group (KGOG) proposed a preoperative prediction model for lymph node metastasis using serum CA-125 levels and MRI parameters [5]. A KGOG model showed good discrimination (area under the receiver operating characteristic curve = 0.85) and a low false negative rate of 1.3% (95% CI, 0.5–3.3%) with assumed prevalence of nodal metastasis of 10%. The strong performance of this model was also reproducible in a Japanese cohort [10].

The aim of our study was to evaluate the cost-effectiveness of a selective lymphadenectomy strategy using a preoperative prediction model compared to routine lymphadenectomy in endometrial cancer patients. The results of the cost-effectiveness analysis should be interpreted with caution as economic studies conducted in one country may not transfer well to other countries: As healthcare utilization and costs differ between societies, what is cost-effective in one country is not necessarily cost-effective in another. The US is one of the few industrialized countries where the federal government is not the primary payer for healthcare services. Korea implemented the National Health Insurance (NHI) system, which is currently a single-payer program, in 1989. In 2007, 96% of the Korean population was covered by the NHI program and the remaining 4% was covered by Medicaid, which is a public assistance program for those with very low incomes [11]. For this reason, we also set out to determine whether selective lymphadenectomy using a model based on the KGOG criteria was cost-effective from the perspectives of both healthcare systems.

Methods

The costs and outcomes of the two strategies were evaluated using a modified Markov model constructed using commercially available software (TreeAge Pro Suite, Williamstown, MA). The primary decision analysis model compared two strategies for the management of newly diagnosed, apparent early-stage endometrial cancer (Fig. 1): (1) selective lymphadenectomy based on a preoperative prediction model that used serum CA-125 levels and MRI parameters and (2) routine lymphadenectomy. Markov states included "disease-free without lymphedema," "disease-free with lymphedema," "cancer survivor without lymphedema," "cancer survivor with lymphedema," and "death." From years one to five, patients in the "disease-free" state either remained in the same Markov state or were reclassified as "death" with each transitional probability. After a post-treatment period of five years all patients who remained alive became "cancer survivors." Patients in the "cancer survivor" state could also remain in that state or be reclassified as "death." The cycle length was one year and the time horizon, 10 years. For the base model, patients entered the model at 60 years old. We defined "apparent early-stage disease" as no clinically apparent spread beyond the uterus based on preoperative physical examination [12]. Costs and outcomes were discounted by 5% each year.

Strategy 1

All patients underwent preoperative assessment using serum CA-125 levels and MRI. A patient was classified as having a low risk of lymph node metastasis and advanced to "hysterectomy without lymphadenectomy" if all of the followings condition were met: (1) preoperative MRI image with myometrial invasion less than half the depth of the myometrium, no enlarged lymph node(s), and no evidence of extrauterine spread of disease; (2) serum CA-125 level less than 35 IU/ml; and (3) preoperative biopsy showing endometrioid subtype. If the assessment did not indicate a low risk of lymph node metastasis, patients advanced to "hysterectomy with complete surgical staging." In the base case, the sensitivity and specificity of the test were estimated at 0.927 and 0.570, respectively, based on external validation results of KGOG prediction model [10].

Strategy 2

Under Strategy 2 all patients underwent pelvic and paraaortic lymphadenectomy at the time of hysterectomy.

Clinical estimates

All medical variables used in the decision trees and their origins are listed in Table 1. The prevalence of patients with metastatic disease in the retroperitoneal lymph nodes was set at 10% for cases of apparent early-stage disease [13].

For "disease-free" state, we used the transitional probability of mortality in endometrial cancer patients that Havrilesky et al. estimated based on results from the SEER database [12,14,15]. They categorized patients into three cohorts to estimate outcomes: (1) Cohort 1, patients with Stage III or IV endometrial cancer with metastatic nodes, fully staged; (2) Cohort 2, those with Stage III or IV disease, unstaged; and (3) Cohort 3, those with Stage I or II endometrial cancer, fully staged. For "cancer survivor" state, we assumed that they have probability of death from the cause other than endometrial cancer. For the nonendometrial cancer mortality rate, we used age- and sex-specific mortality rates from the general population. For Korean cancer survivors we used the age- and sex-specific mortality rates from 2012 reported by the Korean National Statistical Office [16]. For US cancer survivors we extracted mortality rates from the US National Vital Statistics Reports [17].

Under Strategy 1, the sensitivity, specificity, and false positive and negative rates of prediction model were estimated based on validated results from Japanese cohorts (Table 1) [5]. The performance of the KGOG preoperative prediction model indicated four possible scenarios: true positive, true negative, false positive, and false negative. Overall survival was modeled as follows: true positive, Cohort 1; false negative, Cohort 2; and true negative and false positive, Cohort 3. Under Strategy 2 (routine lymphadenectomy), the model was as follows: patients with nodal metastases who were fully staged, Cohort 1; and patients with nodal metastasis who had negative nodes, Cohort 3.

We assumed the same conditions for the rates of adjuvant radiotherapy and chemotherapy as suggested by Havrilesky et al. [12]. The rate of lymphedema after lymph node dissection for endometrial cancer patients varies in the literature [18–20]. Based on two randomized controlled trials, a Cochrane Review indicated that the rate of lymphedema was 6.7% [21]. However, considering the low number of lymph nodes removed in