A preoperative risk-scoring system to predict lymph node metastasis in endometrial cancer and stratify patients for lymphadenectomy

CrossMark

Kazuaki Imai [a,*], Hisamori Kato [a], Kayoko Katayama [b], Kazuho Nakanishi [a], Aiko Kawano [a], Ayaka Iura [a], Katsuyuki Konnai [a], Ryo Onose [a], Fumiki Hirahara [c], Etsuko Miyagi [c]

[a] Department of Gynecology, Kanagawa Cancer Center, Yokohama, Kanagawa, Japan
[b] Cancer Prevention and Cancer Control Division, Kanagawa Cancer Center Research Institute, Yokohama, Kanagawa, Japan
[c] Department of Obstetrics and Gynecology, Yokohama City University Hospital, Minami-ku, Yokohama, Japan

HIGHLIGHTS

- Our preoperative scoring system can accurately predict rate of lymph node metastasis in endometrial cancer.
- Lymphadenectomy can be safely omitted for endometrial cancer patients with no risk of lymph node metastasis.
- Our scoring system can determine extent of lymphadenectomy for patients with risk of lymph node metastasis.

ARTICLE INFO

ABSTRACT

Objective. This study aimed to validate the preoperative scoring system adopted in the Kanagawa Cancer Center (KCC) to stratify endometrial cancer patients for lymphadenectomy according to the risk of developing lymph node metastasis (LNM).

Methods. The records of 432 and 221 uterine cancer patients treated in the KCC and Yokohama City University (YCU), respectively, were retrospectively analyzed. The KCC classified patients for LNM risk based on tumor volume, myometrial invasion, histological grade, and serum CA125 levels, while YCU used only myometrial invasion. Lymphadenectomy was omitted for 156 patients with 0 LNM risk, while pelvic lymphadenectomy (PLX) or PLX with para-aortic lymphadenectomy (PLAX) were performed for those with low and high LNM risk, respectively. The predicted and actual LNM rates were compared between the KCC and YCU patients, and cancer recurrence and overall survival were analyzed.

Results. There was no difference in survival between patients with LNM score 0 who were or were not treated with lymphadenectomy. None (0%) developed LNM and only 1 (0.6%) had recurrence. Patients who underwent PLX but not PLAX (low LNM score) had a low tumor recurrence rate in the para-aortic nodes (1.3%). The KCC scoring system was significantly more accurate than the YCU system in predicting LNM in the high-risk group (P < 0.05) and demonstrated that PLAX was unnecessary in almost 50% of the YCU cases.

Conclusion. The KCC preoperative scoring system is useful to predict LNM risk, and thereby prevent unnecessary lymphadenectomy or to determine its extent in endometrial cancer patients.

© 2016 Elsevier Inc. All rights reserved.

1. Introduction

Endometrial cancer is the most frequently occurring gynecologic malignancy in the world and has the top fifth mortality among cancers affecting women in Japan [1]. According to the International Federation of Gynecology and Obstetrics (FIGO) system, in 2007 in Japan, the five-year survival rates of uterine cancer patients with FIGO stages I, II, and III were 95.3%, 89.8%, and 75.6%, respectively, but have been decreasing thereafter. Patients with early stage cancer have relatively good prognosis due to timely surgical treatment [2], which includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, and, frequently, pelvic lymphadenectomy (PLX) and/or retroperitoneal, i.e., para-aortic, lymphadenectomy (PLAX). Lymph nodes (pelvic lymph node and para-aortic lymph node) are the most common sites of tumor spread in endometrial cancer; therefore, the FIGO recommends that lymphadenectomy should be performed for all patients to ensure accurate staging and determine appropriate postoperative treatment. However, lymphadenectomy may cause complications such as postoperative

* Corresponding author at: Kanagawa Cancer Center, 2-3-2, Nakao, Asahi-ku, Yokohama 241-8515, Japan.
E-mail address: wing-of-kazu-kun@excite.co.jp (K. Imai).

deep vein thrombosis or leg lymphedema, and an increasing number of studies have reported that it may be omitted for patients with a low risk of lymph node metastasis (LNM) [3–5]. On the other hand, patients with a high LNM risk benefit from lymphadenectomy, including PLAX, which has been shown to contribute to prognosis improvement [6].

Pelvic lymphadenectomy in uterine cancer has diagnostic significance, but its therapeutic impact has not been yet established. The results of a randomized comparative study conducted in Italy and the UK indicated that PLX significantly improved surgical staging, but did not increase disease-free or overall survival [7,8]. A multicenter questionnaire survey conducted by the Japanese Gynecologic Oncology Group (JGOG) in 2005 revealed that the majority of institutions (72%) performed PLX; however, PLAX or para-aortic lymph node biopsy was performed in 20% and 12% of institutions, respectively [9]. At the same time, a questionnaire survey conducted among gynecological tumor specialists in the United States showed that 69% of institutions performed PLAX [10]. These data indicate that there is no global consensus on the clinical significance and extent of lymphadenectomy in uterine cancer. In view of this, a recent study has proposed personalized treatment of uterine cancer based on a risk-scoring system predicting lymphatic metastasis after hysterectomy in endometrial carcinoma, which is to be used to identify patients with low and high risks of LNM and to determine the extent of lymphadenectomy [11]. Ideally, only the patients requiring extended surgery should undergo lymphadenectomy, while for the others it can be omitted to avoid unnecessary operation-associated risks because lymphadenectomy, PLAX in particular, prolongs surgery duration and increases intraoperative bleeding, postoperative complications, and costs of care [12]. Therefore, it is very important to establish a standard preoperative risk classification system in endometrial cancer to predict LNM preoperatively.

In the Kanagawa Cancer Center (KCC), we have been providing personalized treatment of uterine cancer since 1998 by using our preoperative scoring system that allows the identification of patients with a low risk of developing LNM based on tumor volume, myometrial invasion, histological type, and serum CA125 levels [13]. The KCC system enabled us to preoperatively identify patients at risk of developing cancer metastases to pelvic and para-aortic lymph nodes, and thus to decide who would benefit from lymphadenectomy and determine the anatomic extent of lymph node dissection (PLX only, or PLX and PLAX). Our hypothesis was that complete lymphadenectomy should not be routinely performed and that the KCC scoring system would be a clinically valid tool for preoperative patient stratification for surgery. The objective of this retrospective cohort study was to validate the KCC system by comparing it with that adopted in Yokohama City University (YCU), which used myometrial invasion as a single criterion of LNM risk.

2. Methods

2.1. Patients

A total of 485 and 262 uterine cancer patients who had undergone the initial surgery at the KCC and YCU, respectively, between January 2005 and December 2011 were screened. The inclusion criteria were as follows: endometrial cancer of FIGO stages I–III without ovarian cancer, histological type other than sarcoma, and no extrauterine spread. The exclusion criteria were as follows: FIGO stage IV, complication with sarcoma and/or ovarian cancer, death of another cancer, unknown follow-up prognosis, and/or cancer progression due to extrauterine metastasis. As a result, 432 KCC and 221 YCU patients were included in the study (Fig. 1).

2.2. KCC scoring system

In the KCC, we determine the surgical treatment for uterine cancer using our scoring system that classifies patients into three groups according to LNM risk (Table S1). Four criteria, each assigned 1 score,
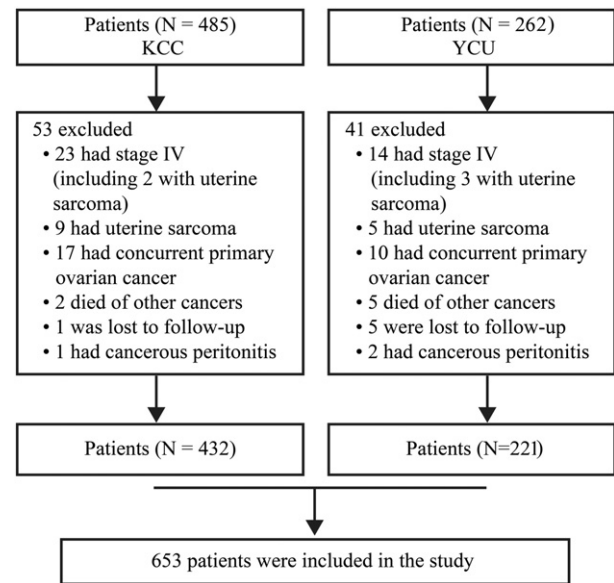

Fig. 1. Study design. KCC, Kanagawa Cancer Center; YCU, Yokohama City University.

were used: (1) tumor volume > 6 cm^3 (calculated based on three dimensions provided by the preoperative MRI test or intraoperative visual findings), (2) myometrial invasion above 50% (by preoperative MRI or intraoperative visual examination), (3) histological type other than G1 endometrioid adenocarcinoma on preoperative endometrial tissue examination, and (4) serum CA125 level higher than 70 U/ml for premenopausal and 25 U/ml for menopausal women; the cut-off values for tumor volume and serum CA125 value were based on previous studies by Nakayama et al. performed in the KCC [14,15]. Patients with no LNM risk (score 0) received only the standard therapy comprising abdominal total hysterectomy (ATH) and bilateral salpingo-oophorectomy (BSO) without lymphadenectomy, while those with moderate LNM risk (scores 1–2) were treated with ATH, BSO, and PLX, and those with high LNM risk (scores 3–4) had ATH, BSO, PLX, and PALX. In addition, if preoperative diagnostic imaging (CT and/or MRI) indicated swollen lymph nodes in patients with no LNM risk, PLX was added to the treatment. Patients with a high post-operative risk of cancer recurrence were treated with chemotherapy; the regimen consisted of paclitaxel (180 mg/m^2) plus carboplatin (AUC5) for not more than 3 months post-operatively. Patients who demonstrated strong symptoms of peripheral neuropathy were switched from paclitaxel to docetaxel (70 mg/m^2).

On the other hand, in YCU, all patients suspected of myometrial invasion prior to surgery underwent PLAX, and no standards were adopted for the dissection range, which was determined empirically.

2.3. Study design

The patients were divided into the lymphadenectomy and no-lymphadenectomy groups and the overall survival was compared. KCC and YCU patients in the lymphadenectomy group who scored 0 (i.e., for whom lymphadenectomy could be omitted) were analyzed for LNM rate, and KCC patients who scored 1–2 and underwent PLX were evaluated for the rate, pattern, and site of tumor recurrence in para-aortic lymph nodes (PAN). In addition, the accuracy of histological diagnosis of metastasis to pelvic lymph node (PEN) and PAN in the lymphadenectomy group was compared between the KCC and YCU cases. Moreover, given the difference in the preoperative criteria for lymphadenectomy between the two centers, the patients who underwent PLAX in the YCU were classified according to the KCC criteria to determine whether the application of the KCC system could assist in patient stratification for PALX and improve the accuracy of LNM