

Current status in the management of uterine corpus cancer in Korea

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Uterine corpus cancer has increased in prevalence in Korean women over the last decade. Recently, elegant studies have been reported from many institutes. To improve treatment strategies, a review of our own data is warranted. This work will discuss the risks and prognostic factors for uterine corpus cancer, and the radiologic evaluation, prediction of lymph node metastasis, systematic lymphadenectomy, minimally invasive surgery, ovarian-saving surgery, fertility-sparing treatment, and adjuvant treatment in women with uterine cancer.

Key Words: Uterine neoplasms, Review

INTRODUCTION

Uterine corpus cancer is one of the most common female genital tract malignancies in many developed countries and has become more prevalent in Korean women over the last decade.^{1,2} Uterine corpus cancer accounts for approximately 4% of all newly diagnosed cancers and approximately 1.7% of cancer deaths in women worldwide. In 2002, an estimated 199,000 new cases of uterine corpus cancer and 50,000 cases of cancer-related deaths were expected worldwide.³ The association between obesity and increased risk of uterine corpus cancer is more significant than any other obesity-related cancer in reviews based on Western populations.⁴⁻⁸ Considering that the obesity is on the rise and uterine corpus cancer has become more prevalent, accounting for 3.7% of all newly diagnosed cancers in Korean women in 2005,⁹ it is anticipated that uterine corpus cancer will become a more significant public health problem in the future in Korea.

Based on the American College of Obstetrics and Gynecologists (ACOG) recommendations and the newly revised surgical staging system by the International Federation of Gynecology

and Obstetrics (FIGO), the cornerstone of treatment for uterine corpus cancer patients is surgery, including peritoneal cytology, hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy, and complete resection of all extrauterine disease.^{10,11} Nevertheless, debate continues regarding surgical staging procedures, especially in terms of the role of, candidates for, and extent of lymphadenectomy.

The data in support of treatment strategies of uterine corpus cancer are conflicting. For example, several retrospective studies have suggested a therapeutic benefit associated with lymphadenectomy in early stage uterine corpus cancer,^{12,13} but recent randomized trials have failed to prove a survival advantage.^{14,15} Moreover, several randomized trials have shown no evidence of benefit for adjuvant radiation for early stage uterine corpus cancer in terms of overall survival.^{16,17} Thus, we are still at chaos with the limited randomized controlled trials and sometimes, contradictory treatment guidelines for uterine corpus cancer.

Considering the ethnic and epidemiologic difference in the susceptibility to uterine corpus cancer, and the relatively low incidence of uterine corpus cancer compared to cervical cancer, we need to analyze and understand the results of Korean studies. Recently, the interest of Korean researchers in uterine corpus cancer has increased and there have been many clinically meaningful results. Thus, this article reviews the current status of the management of uterine corpus cancer in Korea based on the recently published results.

RISK FACTORS

Nulliparity, obesity, unopposed estrogen use, late menopause, and diabetes are the well-established clinical risk fac-

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tors for the development of uterine corpus cancer.¹⁸ Most of these risk factors are primarily associated with prolonged exposure to unopposed estrogen. Obesity is an important risk factor for uterine corpus cancer. In Western populations, obesity has been associated with a 2- to 5-fold increase in endometrial cancer risk in both pre- and post-menopausal women, because extra-ovarian estrogen derived from androgens aromatized in adipose tissue plays an important role in the development of uterine corpus cancer.⁴ In Korea, Jeong et al.¹⁹ studied the effect of obesity on uterine corpus cancer risk in an age-matched case-control study, and found that both obese ($\text{BMI} \geq 25 \text{ kg/m}^2$) and overweight ($23 \text{ kg/m}^2 \leq \text{BMI} < 25 \text{ kg/m}^2$) women had a significantly increased risk for endometrioid uterine cancer compared to non-obese women ($\text{BMI} < 23 \text{ kg/m}^2$).

Recently, antioxidant micronutrients have received attention as an environmental and lifestyle risk factor for uterine corpus cancer.^{20,21} Two small Korean case-control studies have reported that plasma levels of β -carotene, lycopene, folate, and vitamin B12 are inversely associated with uterine corpus cancer risk;^{22,23} however, they failed to prove an association between the intake of folic acid and vitamin B12 and disease risk.²³

Studies involving genetic single nucleotide polymorphisms (SNPs) for uterine corpus cancer have helped to explain the modest risk and differences in individual cancer susceptibility. Candidate genes may be involved in DNA damage repair, estrogen metabolism, carcinogen metabolism, cell-cycle control, apoptosis, and steroid receptor activation pathways.²⁴ In this way, several results have indicated common genetic polymorphisms in Korean women that augment the effects of risk-factor exposure, such as p53, p21, CCND1, ERCC1, and HER-2 genes; the results are summarized in Table 1.²⁵⁻²⁹ p53, which is one of the representative tumor suppressor genes, and p21, which is a downstream mediator of p53, were examined by Roh et al.²⁶ They found that the p53 genotypes containing the Pro allele at codon 72 and homozygous carriers of the p21 Ser allele at codon 31 were significantly associated with an increased risk of uterine corpus cancer. CCND1 is known as the gene involved in the normal cell cycle (the product of CCND1 is cyclin D1). An increased risk of uterine corpus cancer for

the AA genotype of the G870A SNP in CCND1 was described by Kang et al.²⁷ One study involving the C1900T SNP of excision repair cross-complementing group 1 (ERCC1) showed no evidence of an association with uterine corpus cancer risk.²⁸ Two interesting studies reported that HER-2 SNPs did not significantly affect the risk for uterine corpus cancer and these results were repeated with an additional analysis in relation to body mass index and patient age.^{25,29}

These studies were characterized by a single ethnicity, hospital-based case-control design, relatively small sample size, selection of hospital controls, and adjustment of clinical variables (eg, age, body mass index, reproductive history, and exogenous hormone use). Therefore, these findings remain to be confirmed by an additional population-based study.

PREDICTION OF LYMPH NODE METASTASIS

Lymph node (LN) metastasis, one of the most significant prognostic factors, was observed in approximately 13% of patients with uterine corpus cancer in a multicenter Korean study.³⁰ Prediction of LN metastasis represents critical steps for planning the extent of surgery. To avoid unnecessary LN dissection and the associated surgical morbidity, several modalities, such as CT, MRI, PET/CT, and serum CA-125 levels, have been suggested for the prediction of LN metastasis (Table 2).³¹⁻³⁷

Selman et al.³⁸ conducted a meta-analysis to evaluate the accuracy of radiologic imaging to predict LN metastases, and found that MRI and sentinel node biopsy were more accurate than CT scanning. Similarly, there have been several efforts involving the performance of MRI for prediction of LN metastasis and deep myometrial invasion. Considering the clinical significance of LN metastasis, the tests to predict LN metastasis should have a high sensitivity and negative predictive value. The sensitivity and negative predictive value of MRI for LN metastasis were reported as 45-78% and 91-95%, respectively (Table 2). This uncertainty might be caused by difficulty in differentiating metastatic nodes from hyperplastic nodes.³⁹ Thus, we suggest that MRI shows unsatisfactory results in the prediction of LN metastasis and cannot replace surgical staging. This error with respect to LN metastasis was also ob-

Table 1. Association of genetic polymorphisms with uterine corpus cancer risk in Korean women

Author, year	Cases (n)	Controls (n)	Gene, position	Genotype	OR (95% CI)
Roh (2004) ²⁶	95	285	p53, P72R	Arg/Pro+Pro/Pro vs. Arg/Arg	3.56 (2.10-6.04)
			p21, S31R	Ser/Ser vs. Arg/Arg+Arg/Ser	2.68 (1.59-4.51)
Kang (2005) ²⁷	77	154	cyclin D1, G870A	AA vs. GG+AG	2.63 (1.04-2.66)
Jo (2007) ²⁸	102	302	ERCC1, C1900T	CT+TT vs. CC	0.91 (0.57-1.44)
Tong (2009) ²⁹	125	302	HER-2, rs1801200	GA vs. AA	1.13 (0.59-2.16)
			HER-2, rs1810132	TT vs. CC	0.97 (0.44-2.14)
			HER-2, rs2517951	TT vs. CC	1.40 (0.67-2.00)
			HER-2, rs1058808	GG vs. CC	1.39 (0.68-2.87)

OR: odds ratio, CI: confidence interval, ERCC1: excision repair cross-complementing group 1.

served in clinical stage I disease (45.0% sensitivity, n=166), thus some investigators warned that an incorrect decision might be made for a number of patients based on a pre-operative MRI.³⁵ MRI was not effective in the detection of para-aortic node metastasis as well. Park et al.³² described that 1 of 7 positive para-aortic LN areas were detected by MRI (sensitivity, 14.3%), compared to 5 of 6 pelvic node areas (sensitivity, 83%).³² Yoo et al.³³ reported that MRI failed to detect any of 3 positive para-aortic nodes among 99 patients. On the other hand, Park et al.³² compared PET/CT with MRI for accuracy in detecting retroperitoneal metastasis in 53 women, and found that PET/CT had a higher sensitivity than MRI in detecting para-aortic or pelvic node metastasis, although the difference was insignificant (69.2% vs. 46.2%, $p=0.250$).

The sensitivity of CA-125 had a wide range of variation (Table 2). Nevertheless, CA-125 was suggested as an additive tool to predict LN metastasis. Han et al.³⁴ examined the following 6 pre-operative factors to predict LN metastasis: age ≥ 55 years; serum CA-125 level (≥ 20 U/mL if < 50 years of age; ≥ 28 U/mL if ≥ 50 years of age); non-endometrioid histology; grade 3; metastatic LN assessed by pelvic MRI or CT; and deep myometrial invasion assessed by pelvic MRI only. In an analysis of 300 women, they reported 100% sensitivity and neg-

ative predictive value combining the 6 pre-operative tests.

Additionally, LN metastasis is highly correlated with the depth of myometrial invasion,^{30,40} and commonly used for the assessment of the risk of LN metastasis (Table 3).^{31,33-35,41-44} Prediction of myometrial invasion is also crucial in decisions as to whether conservative treatment should be administered to uterine corpus cancer patients. In this case, MRI is the preferred imaging modality in the prediction of myometrial invasion (Table 3). However, the sensitivity (36-90%) and negative predictive values (83-94%) of MRI in the detection of deep myometrial invasion was not satisfactory. Underestimation of myometrial invasion was associated with an isointense junctional zone-to-myometrium ($p<0.001$), and the presence of polypoid tumors ($p=0.037$) on MRI.³¹ In particular, false-positive cases were frequently found in the detection of any degree of myometrial invasion, and these results gives us attention in performing fertility-sparing treatment as the primary therapy of uterine corpus cancer.⁴⁴

As a result, previous results for the prediction of LN metastasis and myometrial invasion are not sufficiently reliable, thus leaving room for further study. On the other hand, the risk of LN metastasis based on pathological findings, such as myometrial invasion and tumor grade in 834 Korean patients

Table 2. Performance of magnetic resonance imaging (MRI), positron emission tomography/computed tomography (PET/CT), and CA-125 in prediction of lymph node metastasis

Author, year	Modality	Cases (n)	Se (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy (%)
Chung (2007) ³¹	MRI	120	68.8	97.1	78.6	95.3	93.3
Yoo (2009) ³³	MRI*	99	77.7	85.6	35.0	94.7	-
Han (2010) ³⁴	MRI or CT	297	53.3	92.9	45.7	94.7	-
Cho (2010) ³⁵	MRI	166	45.0	80.8	24.3	91.4	-
Park (2008) ³²	MRI	53	46.2	87.9	28.6	94.0	83.9
	PET/CT	53	69.2	90.3	42.9	96.6	88.3
Choi (2005) ³⁶	CA-125 [†]	42	100	87.2	37.5	100	-
Chung (2006) ³⁷	CA-125 [‡]	92	61.5	94.9	-	-	-
Han (2010) ³⁴	CA-125 [§]	219	78.6	78.0	34.4	96.1	-

Se: sensitivity, Sp: specificity, PPV: positive predictive value, NPV: negative predictive value.

*Only pelvic nodes were included. [†]The cut-off value was determined to be 50 U/mL. [‡]The cut-off value was determined to be 28.5 U/mL.

[§]The cut-off value was determined to be 28 U/mL (if ≥ 50 years of age) and 20 U/mL (if ≤ 49 years of age).

Table 3. Performance of magnetic resonance imaging (MRI) in prediction of myometrial invasion

Author, year	Modality	Cases (n)	Se (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy (%)
Kim (1995) ⁴¹	MRI	26	90	88	-	-	89
Ahn (2006) ⁴²	MRI	43	87.5	85.7	58.3	96.8	-
Chung (2007) ³¹	MRI	120*	50.6	89.2	91.3	44.6	62.5
Yoo (2009) ³³	MRI	99	46.6	84.5	35	89.8	-
Hwang (2009) ⁴³	MRI	53	50.0	89.7	63.6	83.3	79.2
Suh (2009) ⁴⁴	MRI	301*	68.8	74.4	86.9	49.2	59.2
	MRI	301	55.9	92.4	50.0	93.9	88.0
Han (2010) ³⁴	MRI	219	36.4	88.3	25.8	93.6	-
Cho (2010) ³⁵	MRI	182	66.7	95.2	77.4	92.1	-

Se: sensitivity, Sp: specificity, PPV: positive predictive value, NPV: negative predictive value.

*Both deep and superficial myometrial invasion was considered; others only included deep myometrial invasion.

with endometrioid uterine cancers, were analyzed by Lee et al.³⁰ Of the 215 patients with no myometrial invasion and tumor grade I/II, only 1 patient (0.5%) had LN metastasis and the other patients had significant risk, that is, at least more than 3.5%. Therefore, all uterine corpus cancers, except endometrioid uterine cancers with no myometrial invasion and tumor grade 1-2, would require complete pelvic and para-aortic lymphadenectomy for surgical staging.

ROLE OF SYSTEMATIC LYMPHADENECTOMY

Systematic lymphadenectomy has been reported to have an important role in the surgical staging of uterine corpus cancer.⁴⁵ It is used as a prognostic indicator and suggests guidance for adjuvant treatment. Retrospective studies have reported that more extensive lymphadenectomy is associated with improved survival in patients with uterine corpus cancer, including high-risk, early-stage disease.^{13,46} However, the therapeutic value of systematic lymphadenectomy for stage I uterine cancer is not evident in all studies. Data from the Surveillance, Epidemiology, and End Results (SEER) program also showed that lymphadenectomy is associated with an improved disease-specific survival in stage I disease with tumor grade 3.⁴⁷ On the other hand, systematic lymphadenectomy was not recommended as a routine procedure for therapeutic purposes in patients with stage I disease in the A Study in the Treatment of Endometrial Cancer (ASTEC) trial.¹⁵ The negative results from this trial may be caused by the fact that all histologic subtypes were included, para-aortic LN dissection was optional and inconsistently harvested, an inadequate number of LNs was retrieved in 1/3 of patients, and most patients were in the low-risk group.^{48,49}

A Korean multi-center retrospective study involving 758 patients surgically treated for early-stage endometrioid uterine cancer, with a median follow-up of 35 months, reported that systematic lymphadenectomy did not provide a therapeutic benefit in terms of overall survival in all of the patients, while the systematic lymphadenectomy group showed improved overall survival in high-risk patients.⁵⁰ In a retrospective analysis of 303 women with stage I disease, Seo et al.⁵¹ concluded that complete surgical staging, including lymphadenectomy, did not improve overall survival significantly. For non-endometrioid uterine cancer, 112 patients who underwent surgical staging were retrospectively reviewed. The systematic lymphadenectomy group did not have improved overall survival and distant failure was the prominent pattern of disease spread irrespective of systematic lymphadenectomy.⁵⁰

To evaluate a therapeutic role for para-aortic lymphadenectomy, Chang et al.⁵² compared 85 women who underwent surgical staging with pelvic and para-aortic lymphadenectomy with 75 women who received surgical staging with pelvic lymphadenectomy alone in stage I-III uterine cancer. They proposed that patients who underwent para-aortic lymphadenectomy had improved 5-year disease-free survival and overall

survival in patients with intermediate- and high-risk uterine cancer. However, a consensus has not been reached regarding the issue of whether to perform para-aortic lymphadenectomy on intermediate- and high-risk patients.⁵³

Therefore, we suggest that systematic lymphadenectomy is effective in detecting micro or occult LN metastasis, and thus improve surgical staging, and make it possible to accurately predict the prognosis in patients with uterine corpus cancer.

ROLE OF MINIMALLY INVASIVE SURGERY

Since laparoscopy was first proposed as an option for apparently early-stage uterine corpus cancer in 1993,⁵⁴ several Korean researchers have published their experience on the feasibility of this approach (Table 4).⁵⁵⁻⁵⁸ These results collectively suggest that laparoscopic staging is as feasible and effective as laparotomy. Recently, the laparoscopic approach has been more commonly used in Korea. According to results of the Korean Gynecologic Oncology Group (KGOG) survey in 2009,⁵⁹ laparoscopic staging was routinely performed by about one-half of Korean gynecologic oncologists. This trend was more common in young surgeons with 10 years of experience or less.

Cho et al.⁵⁸ retrospectively analyzed 388 women with clinical stage I-II treated by laparoscopy or laparotomy between 1997 and 2006. Compared with laparotomy, the laparoscopy group had shorter hospital stays and fewer complications, and had no difference in operative time and number of harvested LNs. Nevertheless, most intra-operative complications, including injuries to the great vessels, bladder, ureters, and bowel serosa were more frequent in the laparoscopy group; most intra-operative complications were repaired by laparoscopic methods. Post-operative complications, such as wound problems, intra-abdominal abscesses, ileus, and thromboembolic events were more common in the laparotomy group. They found that the survival outcome and recurrence rate after laparoscopy was also similar to the laparotomy group (Table 5). In another retrospective study involving stage I-III disease, there was better survival in the laparoscopy group, but the results were limited because of favorable tumor characteristics in the laparoscopy group.⁵⁶

Although laparoscopic staging has become an accepted alternative to traditional laparotomy, it has not been determined whether laparoscopic staging using a uterine manipulator is associated with positive peritoneal cytology or not. Regarding this issue, it has been suggested that laparoscopic staging using a uterine manipulator with a balloon might be associated with positive cytologic conversion.⁶⁰ They showed that 2 of 46 patients had positive cytology conversion after the insertion of a uterine manipulator, but neither of the 2 women had recurrences.

On the other hand, robotic surgery using the da Vinci system (Intuitive Surgical Inc., Sunnyvale, CA, USA) has received attention as a new surgical option for the treatment of uterine

Table 4. Feasibility of laparoscopy for the management of uterine corpus cancer

Author, year	Subjects (n)	Stage	No. harvested LNs		Freq. of complications		Operating time (min)	Hospital stay (days)
			Pelvic	PA	IOC (%)	POC (%)		
Laparoscopy								
Cho (2007) ^{58*}	165	I-II	26	5	6 (3.6)	10 (6.1)	155	10
Lee (2008) ⁵⁷	35	I-III	22	7	1 (2.9)	3 (8.6)	150	8
Hahn (2010) ⁵⁶	140	I-III	28	13	NA	23 (16.4)	160	10
Jung (2010) ⁵⁵	25	I	18	4	0	2 (8.0)	165	8
Robotic surgery								
Jung (2010) ⁵⁵	28	I	21	8	0	2 (7.1)	193	8

LNs: lymph nodes, PA: para-aortic, IOC: intra-operative complication, POC: post-operative complication, EBL: estimated blood loss, NA: not applicable.

*They used mean values and the others used median values.

Table 5. Survival outcomes of Korean studies comparing laparoscopy with laparotomy for the management of uterine corpus cancer

Author, year	Study period	Stage	No. subjects		Follow-up periods (mo)		Survival outcome
			Laparoscopy	Laparotomy	Laparoscopy	Laparotomy	
Cho (2007) ⁵⁸	1997-2006	I-II	165	144	28 (1-98)	51 (1-113)	PFS, 95.5% vs. 96.5%
Hahn (2010) ⁵⁶	1996-2007	I-III	140	325	40 (1-145)	67 (1-149)	DFS, 97.7% vs. 90.8%

PFS: progression-free survival, DFS: disease-free survival.

corpus cancer. Robotic surgery has been proposed as an innovative technology that uses a three-dimensional visual system and laparoscopic instruments with wrist-like mechanisms. The feasibility of robotic surgery was investigated by one Korean comparative study.⁵⁵ They described that robotic surgery using three robotic arms is a feasible approach for the uterine corpus cancer because both the robotic surgery and laparoscopy groups had a similar number of harvested LNs, operative times, complications, and hospital stays.

ROLE OF OVARIAN-SAVING SURGERY

The incidence of ovarian metastasis in patients with uterine corpus cancer has been reported to be approximately 5%, and more infrequent in early-stage disease.^{40,61} Early-stage, well-differentiated uterine corpus cancer has been reported to be most commonly encountered in younger patients. Even though bilateral salpingo-oophorectomy is recommended as a part of surgical staging for the treatment of uterine corpus cancer, the issue of ovarian-saving surgery for early-stage uterine corpus cancer needs further consideration.^{59,62} In two case-control Korean studies regarding this issue, it was concluded that ovarian-saving surgery in early-stage disease did not affect disease-free survival and overall survival with a mean of 39 months follow-up⁶³ and recurrence.⁶⁴ They suggested young patients with a low pre-operative CA-125 and low tumor grade are considered as candidates for ovarian-saving surgery.⁶⁴

In a nationwide survey under the influence of the Korean Gynecologic Oncology Group, Lee et al.⁴⁸ analyzed outcomes

of 175 women undergoing ovarian-saving surgery. During a median follow-up of 55 months, recurrence-free survival and overall survival were 94.3% and 93.3%, respectively. All 7 recurrent cases had risk factors, including non-endometrioid histology (4/7), deep myometrial invasion (5/7), cervical stromal invasion (4/7), and inadequate adjuvant treatment (4/7). They proposed the indications of ovarian-saving surgery for uterine corpus cancer to be as follows: women who desire to retain ovarian function; no gross intra-operative extra-uterine spread; no gross abnormalities in bilateral ovaries, negative results of frozen biopsy for lymph nodes suspicious for metastasis; endometrioid-type histology on pre-operative biopsy; and women without a genetic predisposition to breast or ovarian cancer.

ROLE OF ADJUVANT THERAPY

Whereas adjuvant treatment in advanced-stage uterine corpus cancer is commonly accepted, the role of adjuvant radiation in early-stage uterine cancer is a matter of debate. Most trials have been able to show the same trend of adjuvant radiation to reduce locoregional recurrence, but have not been able to convert these results into improvement in overall survival.^{16,65-67} In an aforementioned Korean study involving 758 patients for early-stage endometrioid uterine cancer, the effect of adjuvant radiation on overall survival in 547 endometrioid uterine cancer patients who underwent systematic lymphadenectomy was analyzed.⁵⁰ The 5-year survival rate of the adjuvant radiation versus the no-adjuvant radiation group was similar and this result was repeated, even in the high-risk group. Therefore, it is

thought that adjuvant radiation is of limited value in controlling distant recurrences of uterine corpus cancer,⁶⁸ especially in systematic lymphadenectomized patients. In view of the limited value of adjuvant radiation in systematic lymphadenectomized patients, the role of adjuvant radiation should be re-evaluated based on the recurrence risk and disease spread pattern for early-stage endometrioid uterine cancer.

On the other hand, adjuvant chemotherapy or chemoradiation may be proposed as a reasonable option in these high-risk patients.^{69,70} There have been two Korean studies involving this issue.^{71,72} In an analysis of 46 patients with high-risk early disease, the adjuvant chemoradiation or chemotherapy group showed better disease-free survival than the adjuvant radiation group.⁷¹ Another study for stage I-IV disease suggested that adjuvant paclitaxel/platinum chemotherapy had a similar activity as adjuvant radiation and acceptable toxicity for the treatment of uterine corpus cancer.⁷²

ROLE OF FERTILITY-SPARING TREATMENT

Since it has been proposed that young women (under 40 years of age) with endometrioid uterine cancer may be treated conservatively with progestin therapy,^{73,74} a few Korean studies have supported this hypothesis.⁷⁵⁻⁷⁸ Recently, Hahn et al.⁷⁷ demonstrated the efficacy of progestin therapy in early-stage, grade 1 endometrioid uterine cancer. They found that the efficacy of 250-1500 mg of medroxyprogesterone acetate (MPA) or 160 mg of megestrol for grade 1 endometrioid uterine cancer (35 cases) presumed to be stage IA was complete remission (CR) in 22 women (63%). However, 9 of the 22 patients (41%) with CR developed recurrent disease and the median time-to-recurrence was 12 months (range, 8 to 48 months). This result was comparable with one phase II trial by Ushijima et al.⁷⁴ showing 55% CR and 47% recurrence after CR. Thus, in spite of the proven efficacy of fertility-sparing treatment with high-dose of MPA, close follow-up is needed because of the substantial rate of recurrence, even in responders. For pregnancy outcomes, fertility-preserving therapy is considered a good option in women with early-stage uterine corpus cancer.

According to two retrospective Korean studies, approximately 80% of women who tried to conceive were successful with normal pregnancies, and 8 of 14 pregnancies resulted in live births.^{77,78}

POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY (PET/CT)

Recently, investigative work involving molecular imaging technologies has received much attention. PET uses the glucose analogue, 18-fluorodeoxyglucose (FDG), as a radioisotope and relies on increased metabolism of tumor cells, and thus increased glucose uptake.⁷⁹ PET/CT provides the synergistic benefits of morphologic and molecular imaging because of localization of increased FDG uptake with anatomical specificity.⁸⁰ Substantial evidence has now emerged documenting the role of PET/CT in the management of uterine corpus cancer patients, at the pre-operative evaluation as well as at the post-treatment surveillance (Table 6).^{32,80,81} Park et al.³² performed a retrospective comparison of surgical staging with PET/CT in 53 uterine corpus cancer patients. They showed that pre-operatively, PET/CT detected lymph node metastasis with 69% sensitivity and 90% specificity. According to other studies for the detection of recurrent disease,^{80,81} PET/CT had excellent performance with 100% sensitivity and 83-100% specificity. The use of PET/CT has been shown to detect recurrences even in asymptomatic women with 100% sensitivity and specificity,⁸¹ and can provide important prognostic information for women after primary treatment.

PROGNOSTIC FACTORS

The prognostic impact of age, histologic subtype, grade, and FIGO stage has been established in Western populations.⁸² However, according to a recent retrospective survey, uterine corpus cancer of Korean women is characterized by a younger age in peak incidence and less obesity compared to Western countries.¹⁹ Thus, the prognostic significance of the aforementioned factors in Korean patients with endometrioid ute-

Table 6. Performance of positron emission tomography/computed tomography (PET/CT) and PET for the evaluation of uterine corpus cancer

Author, year	Modality	No. of patients	Validity	Se	Sp	PPV	NPV	Accuracy
				(%)				
Park (2008) ³²	PET/CT	53	Primary lesion	90	51	93	38	85
			PALNM	57	88	57	88	81
			PLNM	83	91	36	99	88
			Total LNM	69	90	43	97	88
Chung (2008) ⁸⁰	PET/CT	31	Recurrent lesion	100	95	92	100	97
Park (2008) ⁸¹	PET/CT or PET	24*	Recurrent lesion	100	83	96	95	100
		64 [†]	Recurrent lesion	100	100	100	100	100

Se: sensitivity, Sp: specificity, PPV: positive predictive value, NPV: negative predictive value, PALNM: para-aortic lymph node metastasis, PLNM: pelvic lymph node metastasis, LNM: lymph node metastasis.

*Patients were suspected to have recurrence based on tumor markers or CT. [†]Patients were asymptomatic with no evidence of recurrence.

rine cancer is different. For example, FIGO stage (hazard ratios, 3.37; $p < 0.01$) and lymphovascular invasion (hazard ratios, 2.75; $p = 0.01$) were significant prognostic factors for overall survival, whereas age provided no significant impact in prognostic ability (Table 7). Even though age is well-known as one of the prognostic factors for uterine corpus cancer, this result did not show independent prognostic ability. This result may reflect the original characteristics of Korean women, i.e., Korean patients were younger compared to Western patients. Therefore, the prognostic effect of age could be lessened.

To further improve treatment and follow-up for uterine corpus cancers, a number of molecular markers have been extensively studied. DNA ploidy, hormone receptors, p53, bcl-2, and proliferation markers have already been shown with consistent results to be prognostic factors through retro-

spective studies.⁸² In Korea, there have been several efforts to define the molecular factors for uterine corpus cancer (Table 8).^{37,83-88} Whereas cyclooxygenase-2 (COX-2), mammalian target of rapamycin (mTOR), and microsatellite instability (MSI) have shown no prognostic ability, several other markers, including p53, pre-operative CA-125, and osteopontin, have been shown to have significance as prognostic factors for uterine corpus cancers.

Immunohistochemical overexpression of p53, one of the most frequently detected tumor suppressor genes in human cancer, has a strong association with tumor aggressiveness.⁸³ Similarly, based on the results of 131 patients, 29.8% of patients had p53 alteration determined by p53 overexpression or exonal mutation, and p53 alteration was associated not only with aggressive tumor behavior, but with poor disease-free survival.⁸⁶

Table 7. Hazard ratios of endometrioid uterine cancer based on clinico-pathological variables in Korea

Variables			Univariate		Multivariate	
			HR (95% CI)	p-value	HR (95% CI)	p-value
BMI	<23.0	297	1.00		1.00	
	23.0-24.9	207	0.98 (0.42-2.27)	0.96	0.93 (0.37- 2.30)	0.87
	≥25.0	433	0.82 (0.40-1.66)	0.58	0.87 (0.41-1.83)	0.70
Age	≤50	376	1.00		1.00	
	>50	561	5.14 (2.01-13.11)	<0.01	2.66 (0.84-8.50)	0.10
Menopause	No	396	1.00		1.00	
	Yes	505	3.08 (1.41-6.73)	<0.01	1.51 (0.57-3.99)	0.41
Stage	I+II	777	1.00		1.00	
	III+IV	142	6.50 (3.50-12.09)	<0.01	3.37 (1.55-7.35)	<0.01
ADJTX	No	590	1.00		1.00	
	Yes	340	4.30 (2.22-8.34)	<0.01	1.30 (0.53-3.22)	0.57
Grade	I	644	1.00		1.00	
	II	199	2.20 (1.06-4.55)	0.03	1.46 (0.65-3.24)	0.36
	III	81	4.50 (1.92-10.57)	<0.01	1.96 (0.79-4.88)	0.15
LNM	No	629	1.00			
	Yes	80	6.30 (2.93-13.53)	<0.01		
TD	≤2 cm	299	1.00			
	>2 cm	485	2.02 (0.94-4.36)	0.07		
MI	No	273	1.00			
	Yes	639	3.81 (1.49-9.73)	0.01		
CE	No	816	1.00			
	Yes	107	3.05 (1.49-6.24)	<0.01		
LVSI	No	734	1.00		1.00	
	Yes	184	5.86 (3.11-11.0)	<0.01	2.75 (1.27-5.95)	0.01
AE	No	840	1.00			
	Yes	53	5.80 (2.74-12.26)	<0.01		
PPC	No	836	1.00			
	Yes	39	4.54 (1.89-10.91)	<0.01		
RS	ER –/PR –	91	1.00			
	ER +/PR –	30	0.60 (0.07-5.13)	0.64		
	ER –/PR +	63	0.38 (0.07-1.99)	0.25		
	ER +/PR +	213	0.68 (0.23-2.00)	0.49		

HR: hazard ratio, CI: confidence interval, BMI: body mass index, ADJTX: adjuvant treatment, LNM: lymph node metastasis, TD: tumor diameter, MI: myometrial invasion, CE: cervical extension, LVSI: lympho-vascular space invasion, AE: adnexal involvement, PPC: positive peritoneal cytology, RS: receptor status, ER: estrogen receptor, PR: progesterone receptor.

Table 8. Molecular prognosticators for uterine corpus cancer in Korea

Author, year	Target	Cases	Materials	Tool	Results	Outcome	Prognostic ability
Jeon (2004) ⁸³	COX-2	152	Paraffin-embedded tissue	IHC	17.8% of patients were COX-2 positive	Possible association with carcinogenesis during the postmenopausal period	Null
	p53	152	Paraffin-embedded tissue	IHC	20.4% of patients showed overexpression	Strong association with cancer aggressiveness	Null
Chung (2006) ³⁷	CA-125	92	Serum	RIA	DFS of patients with ≤ 28.5 IU/mL was worse prognosis than patients with > 28.5 IU/mL	Independent prognostic marker for DFS	DFS, log rank; $p=0.004$
An (2007) ⁸⁷	MSI	100	Paraffin-embedded tissue	TMA	MSI-high phenotype was related with LVSI, DMI, and higher clinical stages	Possible role as a prognostic factor	Null
Kim (2008) ⁸⁸	PTTG	43	Paraffin-embedded tissue	IHC	7.5% of patients had nuclear PTTG overexpression with a lower OS	Possible role as a prognostic factor	OS, log-rank; $p=0.04$
Cho (2009) ⁸⁵	Osteopontin	56	Frozen tissue, paraffin-embedded tissue, plasma	Real-time PCR, IHC, ELISA	62.1% of stage I patients were seropositive that were not detected by CA125; AUC 0.758 for plasma osteopontin levels	Useful diagnostic marker for uterine cancer, independent prognostic marker for DFS	DFS, HR=3.18; $p=0.0035$
No (2009) ⁸⁴	mTOR	141	Paraffin-embedded tissue	IHC	7.1% of patients showed overexpression	Association with COX-2 overexpression	Null
Lee (2010) ⁸⁶	p53	131	Paraffin-embedded tissue	PCR, IHC	29.8% of patients had p53 alteration with a lower DFS	Independent prognostic marker for DFS	DFS, HR=17.7; $p=0.027$

COX-2: cyclooxygenase-2, IHC: immunohistochemistry, RIA: radioimmunoassay, DFS: disease-free survival, MSI: microsatellite instability, TMA: tissue microarray, LVSI: lympho-vascular space invasion, DMI: deep myometrial invasion, PTTG: pituitary tumor-transforming gene, OS: overall survival, PCR: polymerase chain reaction, ELISA: enzyme-linked immunosorbent assay, HR: hazard ratio, mTOR: mammalian target of rapamycin.

Preoperative serum CA-125 has been shown to be a significant prognostic factor.⁸⁹ According to Chung et al.,³⁷ patients with a serum CA-125 ≤ 28.5 U/mL have a significantly better 5-year disease-free survival than patients with a CA-125 > 28.5 U/mL (85.6% vs. 60.0%, $p=0.004$). Therefore, they suggested a preoperative CA-125 as a useful tool for optimal individualized cancer treatment.

Osteopontin, a kind of phosphoglycoprotein, is known as a mediator of tumor transformation and malignant progression in human cancers, and its overexpression in tissues or blood of cancer patients may indicate the presence of a tumor.⁹⁰ Cho et al.⁸⁵ investigated the diagnostic and prognostic role of osteopontin in uterine corpus cancer. They proved that osteopontin was seropositive in 62.1% of patients with stage I disease who were not detected by CA-125, and that osteopontin positivity was an independent prognosticator for disease-free survival in patients with uterine corpus cancer.

MANAGEMENT OF RECURRENT DISEASE

Most uterine corpus cancers are diagnosed at an early stage and have a favorable prognosis. However, a substantial number of patients undergo disease recurrence after primary treatment. According to one Korean retrospective study of 301 pa-

tients,⁹¹ approximately 26 (9%) of patients develop recurrent disease and the mean time-to-recurrence is 29 months. Among women with recurrences, 22 (85%) had distant failure and most women with recurrences presented at an advanced stage at the time of diagnosis. After diagnosing a recurrence, 18 women received systemic chemotherapy or chemoradiation, 2 women had radiation, and only one woman underwent surgical treatment. Among the 18 women with chemotherapy, the taxane-based group had a better median survival than the non-taxane group (22 vs. 15 months, $p=0.047$).⁹² In the planning for patients with recurrent disease, it is important to consider the site of recurrence, performance status of the patient, and prior therapy the patient has received. After specific considerations for each patient, combined modalities, as well as surgical cytoreduction, radiation therapy, hormonal treatment, systemic chemotherapy, and palliative therapy may be used. In this era, research should focus on developing new chemotherapeutic and molecular targets active against uterine corpus cancer.

HORMONE REPLACEMENT THERAPY

Because there has been no conclusive data to prove the benefit or safety of hormone replacement therapy in patients with

uterine corpus cancer, this question remains unanswered. To date, an overall lower recurrence rate or a non-significant difference in recurrence between hormone-users and -non-users has been noted in several retrospective studies⁹³⁻⁹⁶ and in one randomized controlled trial.⁹⁷ A retrospective Korean study which evaluated tibolone in patients with uterine corpus cancer also showed no significant difference in disease-free survival and overall survival between the two groups.⁹⁸ This finding should be used along with other information for counseling patients regarding the risks of hormone replacement therapy in uterine corpus cancer.

CONCLUSION

Like other malignancies, uterine corpus cancer must be affected by genetic differences. Thus, if possible, treatment guidelines should be individualized based on ethnic-specific treatment results. Even though there have been a number of advances in treatment strategies and research products for uterine corpus cancers in Korea, most of our data are characterized by retrospective design, small sample size, single institute experience, and insufficient follow-up. Thus, prospective multi-center trials should be performed to make more progress in the treatment of gynecologic cancer patients, including uterine corpus cancer. In addition, we also should be interested in primary and secondary prevention to improve cancer control, and in treatment-related symptom management, palliation, and end-of-life care to improve quality of life.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Standards for Different Types of Articles

Guidelines for six different types of articles have been adopted by the *Journal of Gynecologic Oncology*:

1. **CONSORT** (Consolidated Standards of Reporting Trials) standards for reporting randomized trials
2. **PRISMA** (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines for reporting systematic reviews and meta-analyses
3. **MOOSE** (Meta-analysis of Observational Studies in Epidemiology) guidelines for meta-analyses and systematic reviews of observational studies
4. **STROBE** (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for the reporting of observational studies
5. **STARD** (Standards for Reporting of Diagnostic Accuracy) standards for reporting studies of diagnostic accuracy
6. **REMARK** (Reporting of tumor Markers Studies) guidelines for reporting tumor marker prognostic studies

Investigators who are planning, conducting, or reporting randomized trials, meta-analyses of randomized trials, meta-analyses of observational studies, observational studies, studies of diagnostic accuracy, or tumor marker prognostic studies should be familiar with these sets of standards and follow these guidelines in articles submitted for publication.

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