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Original Article

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Conditional relative survival of patients with endometrial cancer: a Korean National Cancer Registry study

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ABSTRACT

Objective: The purpose of this study was to estimate 5-year conditional relative survival (5Y CRS) rates of endometrial cancer (EC) in Korea accounting for time already survived. Subgroup-specific estimates stratified by various patient characteristics were also presented.
Methods: Using the data from the Korean Central Cancer Registry, 5Y CRS rates were calculated in patients who were diagnosed with EC between 1998 and 2017. The CRS rates were presented by year of diagnosis, age at diagnosis, histology, cancer stage, and treatment received.
Results: The 5-year relative survival rate at the time of diagnosis was 89.0% for all cases. The probability of surviving an additional 5 years (i.e., 5Y CRS), if the patient survived 1, 2, 3, 4, and 5 years after diagnosis was 91.8%, 94.1%, 95.6%, 96.5%, and 97.3%, respectively. Patients with poor initial prognoses, i.e., those who were older, had non-endometrioid histology, and high stage, showed the largest improvements in 5Y CRS, reaching >90% for most subgroups, except those with serous histology (88.4%) and distant stage (77.7%). Patients aged ≥70 years had the highest probability of death in the 1st and 2nd years after diagnosis (13.8 and 11.0%), but the conditional probability of death in the 3rd, 4th, and 5th years declined rapidly to 7.3%, 4.5%, and 3.7%, respectively.
Conclusion: The CRS rates for patients with EC improved with increased time elapsed from diagnosis. The greatest improvements in 5Y CRS were observed among patients who were older, those with non-endometrioid histology, and those with more advanced disease.

Keywords: Endometrial Cancer; Survival Rate; Conditional Survival; Korea

Synopsis

There is paucity of research which estimated the conditional relative survival (CRS) rates for patients with endometrial cancer, and the Asian population is underrepresented in these studies, despite that Asian patients have different age and histologic distribution. CRS rates were presented by year of diagnosis, age at diagnosis, histology, cancer stage, and treatment received. Such estimates based on patient's evolving risk profile will provide updated prognostic information useful for both patients and healthcare providers.

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

Author Contributions
Conceptualization: S.D.W., B.J., J.K.W.; Data curation: J.K.W., H.J.; Formal analysis: B.J., J.K.W., H.J.; Funding acquisition: J.K.W.; Investigation: S.D.W., H.J.; Methodology: S.D.W., B.J., H.J.; Project administration: S.D.W.; Supervision: B.J., J.K.W.; Writing - original draft: S.D.W.; Writing - review & editing: S.D.W.

INTRODUCTION

Endometrial cancer (EC) is the 2nd most common cancer of the female reproductive system and 6th most common female cancer worldwide [1]. In 2018, an estimated 382,000 women were diagnosed with EC, 90,000 of whom died of the disease. The incidence rates are relatively higher in North America and Europe (15–25 per 100,000 women) [2]; for example, in the US, EC is the second most prevalent female cancer [3]. In East Asian countries, while it is lower than that in western countries (around 6 per 100,000) [2], the incidence of EC has rapidly increased [4-6]. In Korea, EC comprises around 2.7% of all cancer in women, with an estimated 3,200 new cases in 2020 [7].

EC are generally regarded as having favorable prognosis, with a 5-year overall survival (5Y OS) reaching 80%, mainly because many patients are diagnosed at an early stage and are cured by surgery alone. However, some patients have higher risk of recurrence and poor prognosis, comprising those with older age, histology other than endometrioid, higher tumor grade, lymphovascular space involvement, and peritoneal carcinomatosis [8,9].

Prognostic information is of critical importance to patients, their families, and clinicians in terms of shared decision making on medical and life issues. Currently, OS, disease-free survival, and relative survival (RS), calculated from the time since diagnosis or surgery, are usually available statistical estimates. Such estimates are useful in guiding clinicians to make decisions on optimal treatment strategy, such as adjuvant therapy. However, as the probability of ongoing survival generally improves with time after diagnosis [10], a more relevant indicator is conditional survival, which describes the probability of surviving an additional amount of time (often 5 years) at various points after cancer diagnosis. RS is the relative ratio of observed survival in cancer patients to expected survival of the general population, and conditional RS (CRS) rate it can provide dynamic prognostic information compared to age- and sex-matched peers.

There is a paucity of research on conditional survival after EC diagnosis. Several cancer registries have reported conditional survival rates for major types of cancers [11-16]. While some studies did not report results for EC [14,15]. Others provided only brief results that were not stratified at all [11] or stratified only by age group [12,16] or cancer stage [13]. These data are often outdated and do not provide current estimates. One US Surveillance, Epidemiology, and End Results (SEER) study involving 78,147 EC patients diagnosed during 2000-2008 estimated the CRS rate according to factors such as age, race, marital status, stage, and grade [17]. However, that study did not consider histologic types. One recent study updated SEER data with 183,153 patients, and included histologic types in their analyses [18]. To date, no study has reported conditional survival of EC in Korea. Asian EC patients are diagnosed at younger age (mean age 52.2 in Korea [19] vs. 62 in the US [3,20]), have different histologic distribution [21], and show slightly longer survival than white patients [20].

Therefore, the objectives of this study were to estimate 5-year CRS (5Y CRS) rates of EC in Korea accounting for time already survived. Subgroup-specific estimates were also presented stratified by age, stage at diagnosis, histology, year of diagnosis, level of social deprivation, and treatment received.

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MATERIALS AND METHODS

1. Data source and study population

Analyses of this study are based on the Korean Central Cancer Registry (KCCR), which is a nationwide, population-based cancer registry run by the Ministry of Health and Welfare in Korea. The completeness (>98% of all incident cases) and data quality of the KCCR are well documented [6]. The KCCR collects data on patient age; date of diagnosis; primary tumor site; histology according to the International Classification of Disease for Oncology, Third Edition (ICD-O-3) [22]; and SEER stage (collected since 2005). This KCCR database is used for official statistics [7,23], as well as studies on gynecological cancers in Korea [24,25].

This study comprised 22,131 women who were diagnosed with EC as their first primary cancer during the 1998–2017 period. Their vital status information through December 31, 2018, was obtained from the National Statistical Office of Korea through routine data linkage. Ethical approval for the research protocol was provided by the Institutional Review Board of the National Cancer Center, Goyang, Korea (NCC2020-0280). As this study is based on secondary data analysis with fully anonymized data, informed consent was waived.

2. Variables

Patient age at diagnosis was categorized into 5 groups: <40, 40–49, 50–59, 60–69, and ≥70 years. The histology of EC was categorized as endometrioid, serous, mucinous, clear cell, carcinosarcoma, or others by ICD-O-3 morphology code [21]. The stages at diagnosis were classified according to SEER summary staging categories (localized, regional, distant, or unknown). The year of diagnosis was classified into 5-year intervals: 1998–2002, 2003–2007, 2008–2012, and 2013–2017. Area-level social deprivation was calculated based on the Carstair method [26], and was categorized into 5 quintiles (the 1st quintile indicating the wealthiest area). Treatment during the first 4 months after diagnosis, including surgery, chemotherapy, and radiotherapy, is available in KCCR data. However, treatment details (e.g., brachytherapy vs. external beam radiotherapy) and intent (adjuvant vs. palliative) cannot be identified, and treatment received after 4 months is not recorded.

3. Statistical analysis

Observed survival, cause-specific survival and RS were calculated. RS is calculated as the observed survival among cancer patients divided by the expected survival of the general population of the same period, age, and sex, using the population lifetables [27].

The CRS rate, which is the likelihood of surviving an additional y years for a patient who has already survived x years, was calculated by dividing the RS at (x + y) years by the RS at x years:

$$\mathrm{CRS}\ (y|x) = \frac{\mathrm{RS}\ (x+y)}{\mathrm{RS}\ (x)}$$

In this study, 5Y CRS rates conditioned on 1–5 years of survival after diagnosis were calculated. Survival estimates were presented by age group, histological type, SEER stage at diagnosis, year of diagnosis, deprivation index, and treatment received.

Multivariate analyses were performed to estimate the relative excess risk (RER) to examine the relative effects of patient demographic and clinical characteristics on survival at baseline and at 2 and 5 years. Those who were diagnosed after 2005 were included in this analysis as

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stage information was available. Treatment received was not included as a predictor variable, because it is largely determined by other characteristics, such as cancer stage and histology, and its inclusion can create a multicollinearity problem.

All analyses were conducted using Stata version 15.0 (StataCorp LP, College Station, TX, USA) or SAS 9.4 (SAS Institute Inc, Cary, NC, USA). All statistical tests were 2-tailed, and p-values <0.05 were considered significant.

RESULTS

1. Baseline characteristics

Baseline characteristics of patients for calculation of RS and CRS at baseline and after 2 and 5 years are shown in **Table 1**. A total of 22,131 patients was diagnosed with EC between 1998

Table 1. Baseline characteristics of Korean endometrial cancer patients, 1998–2017

Variables	No. of patients (%)	Patients available for CRS calculation	
		After 2 years	After 5 years
Total	22,131 (100.0)	18,302	12,217
Year of diagnosis			
1998–2002	1,796 (8.1)	1,591	1,459
2003–2007	4,000 (18.1)	3,690	3,437
2008–2012	6,650 (30.0)	6,177	5,843
2013–2017	9,685 (43.8)	6,844	1,478
Age (yr)			
<40	2,541 (11.5)	2,215	1,566
40–49	5,057 (22.9)	4,388	3,162
50–59	8,694 (39.3)	7,426	4,966
60–69	4,067 (18.4)	3,113	1,915
≥70	1,772 (8.0)	1,160	608
Histology (ICD-O-3)			
Endometrioid	18,799 (84.9)	16,005	10,827
Serous	1,054 (4.8)	696	381
Mucinous	423 (1.9)	373	283
Clear cell	379 (1.7)	285	153
Carcinosarcoma	1,007 (4.6)	593	333
Others	469 (2.1)	350	240
Stage at diagnosis (since 2005, n=18,993)			
Localized	13,522 (71.2)	11,492	7,208
Regional	3,392 (17.9)	2,665	1,569
Distant	1,063 (5.6)	479	209
Unknown	1,016 (5.3)	849	628
Social deprivation index			
1 (wealthiest)	9,803 (44.3)	8,197	5,519
2	6,301 (28.5)	5,173	3,420
3	2,860 (12.9)	2,352	1,551
4	1,841 (8.3)	1,518	1,023
5 (poorest)	1,326 (6.0)	1,062	704
Treatment received within 4 months after diagnosis			
Surgery only	14,150 (63.9)	12,210	8,289
Surgery + Chemo	2,551 (11.5)	1,861	1,113
Surgery + RT	2,177 (9.8)	1,795	1,210
Surgery + Chemo + RT	1,276 (5.8)	975	599
RT only/Chemo only/Chemo + RT	430 (1.9)	238	133
No treatment	1,547 (7.0)	1,223	873

All participants are Korean ethnicity.
Chemo, chemotherapy; CRS, conditional relative survival; ICD-O-3, International Classification of Disease for Oncology, Third Edition; RT, radiotherapy.

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and 2017. The number of EC cases increased very rapidly during the study period: from 1,796 cases in 1998-2002 to 9,685 cases in 2013-2017. Women were most frequently diagnosed with EC in their 50's (39.3%), followed by 40's (22.9%) and 60's (18.4%).

Endometrioid type accounted for most cases (84.9%), followed by serous (4.8%), carcinosarcoma (4.6%), mucinous (1.9%), and clear cell (1.7%). SEER stage information was available for women diagnosed since 2005 (n=18.993), and those with localized, regional, and distant stage represented 71.2%, 17.9%, and 5.6% of the total, respectively. Two-thirds (63.9%) of patients received surgery only, while 11.5%, 9.8%, and 5.8% received chemotherapy, radiotherapy, or both in addition to surgical treatment, respectively.

2. Cumulative observed and cause-specific survival

Cumulative survival curve for overall and EC-specific cause are depicted in **Fig. 1**. 5Y OS was87.1%, and 5Y EC-specific survival was 90.5%.

3. RS and CRS

For all EC, the 5-year and 10-year RS values at the time of diagnosis were 89.0% and 86.2%, respectively. The probability of surviving an additional 5 years (i.e., 5Y CRS) if the patient survived 1, 2, 3, 4, and 5 years after diagnosis was 91.8%, 94.1%, 95.6%, 96.5%, and 97.3%, respectively (**Fig. 2A**). The 5Y CRS rates for all EC patients according to year of diagnosis, age group, histology, stage at diagnosis, and treatment are displayed in **Fig. 2** and in **Table 2**.

The 5Y RS increased with year of diagnosis: from 83.5% for those diagnosed in 1998–2002 to 90.2% for those diagnosed in 2013–2017. However, after 2–3 years of survival, the values were similar (**Fig. 2B**). Younger patients had a higher 5Y RS, at 95.2, 94.1, 91.6, 80.7, and 69.1% for women at <40, 40-49, 50-59, 60-69, and ≥70 years, respectively. The 5Y CRS in older women increased rapidly with longer survival, but the difference in 5Y CRS between older and younger women remained significant even after 5 years (**Fig. 2C**).

At diagnosis, 5Y RS was highest for endometrioid (93.2%) and mucinous cancer (90.0%), followed by clear cell (84.8%), serous (60.5%), and carcinosarcoma (51.5%) in that order. The 5Y CRS increased for each histologic type over time and exceeded 90% at 5 years after

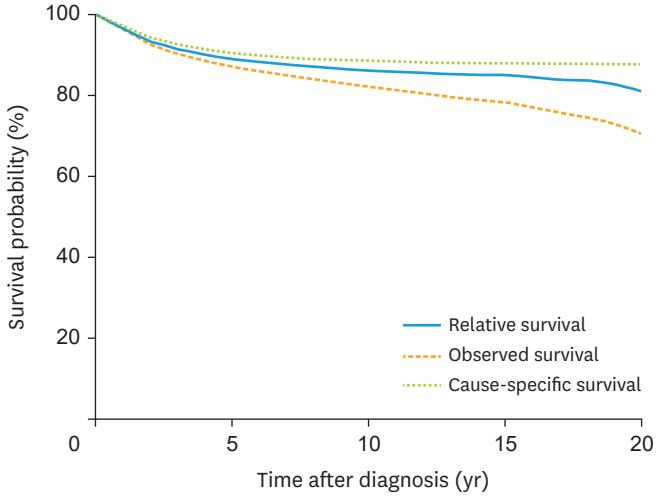

Fig. 1. Cumulative observed and cause-specific survival of endometrial cancer patients.

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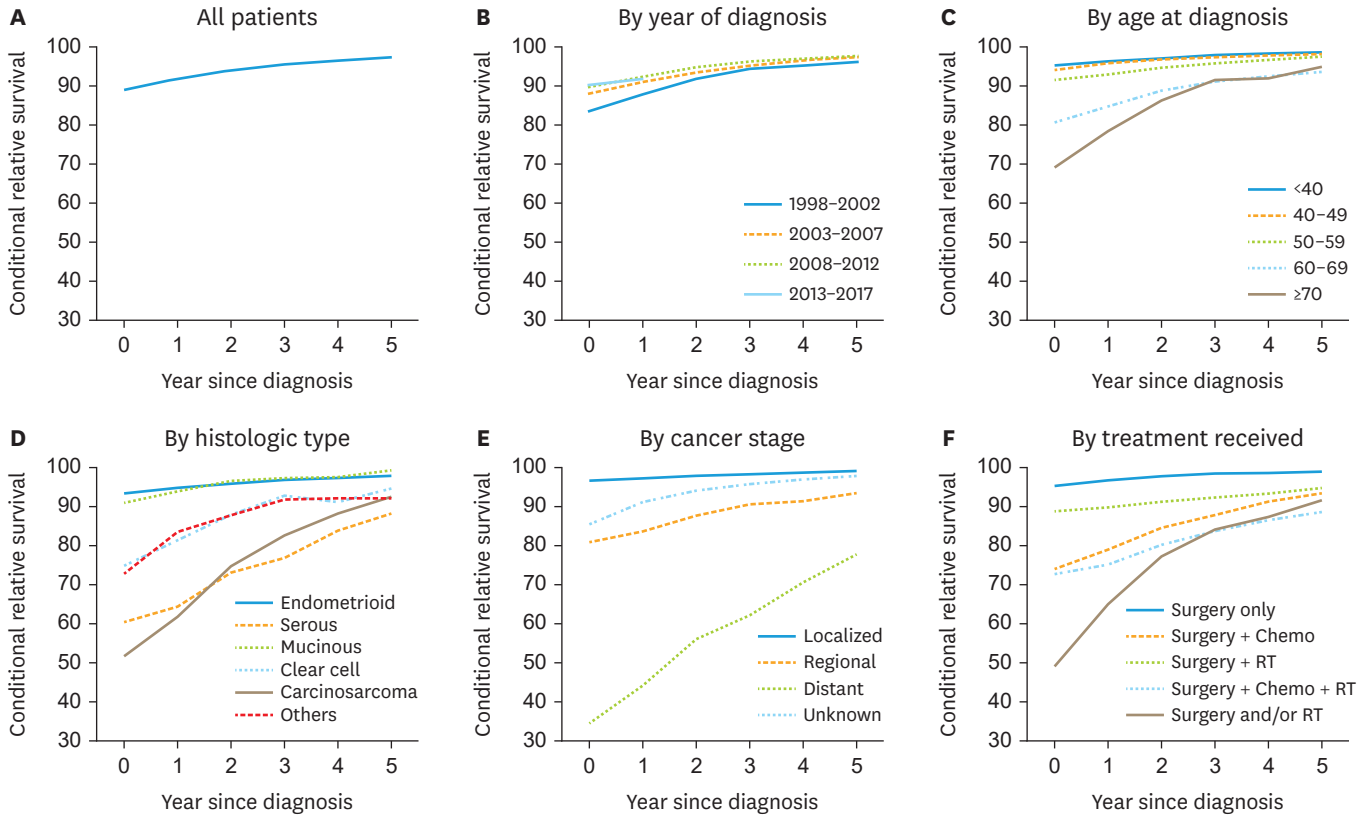

Fig. 2. Five-year conditional survival rates of endometrial cancer patients according to patient characteristics. (A) All patients, (B) by age at diagnosis, (C) by age at diagnosis, (D) by histologic type, (E) by cancer stage, (F) by treatment received.

diagnosis in all but serous type (88.4%) (**Fig. 2D**). There were large differences by stage at baseline (96.6%, 80.9%, and 34.5% for localized, regional, and distant stage, respectively), but the difference largely decreased after 5 years (99.1%, 93.5%, and 77.7%, respectively (**Fig. 2E**). Patients who received surgery showed high 5Y RS at the time of diagnosis (95.2%). Those who had radiation therapy and chemotherapy in addition to surgery showed 5Y RS values of 88.0 and 74.0 at diagnosis, respectively, which increased to >90% after 2 and 4 years. Those who received radiation and/or chemotherapy without surgery showed low survival at diagnosis (49.1%), but survival reached >90% if they survived for 5 years (**Fig. 2F**).

4. Conditional probability of death

Fig. 3 and **Table S1** shows the conditional probability of death according to age group and years since diagnosis. Older patients had a higher risk of death at the time of diagnosis, but it declined rapidly over time; patients ≥70 years of age had a 13.8% of probability of death in the first year, but the probability declined rapidly in the following years (11.0, 7.3, 4.5, and 3.7% in the 2nd, 3rd, 4th, and 5th years, respectively.

5. Effects of baseline characteristics on mortality according to survival time since diagnosis

Older patients showed consistently higher mortality with similar RERs based on time since diagnosis. There was no difference in RER at diagnosis, but diagnosis later in the study period was associated with low RER after 2 years of survival.

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Table 2. Relative and conditional survival rates (%), 1997–2016 (n=25,859)

Characteristic	Relative survival (95% CI)		Conditional 5-year relative survival (95% CI)				
	5-year	10-year	1-year	2-year	3-year	4-year	5-year
Total	89.0 (88.5–89.4)	86.2 (85.5–86.8)	91.8 (91.3–92.2)	94.1 (93.7–94.6)	95.6 (95.1–96.1)	96.5 (96.0–97.0)	97.3 (96.8–97.8)
Year of diagnosis							
1998–2002	83.5 (81.6–85.3)	79.9 (77.7–82.0)	87.9 (86.0–89.5)	91.8 (90.1–93.3)	94.4 (92.8–95.7)	95.2 (93.7–96.5)	96.2 (94.7–97.4)
2003–2007	88.0 (86.8–89.0)	85.3 (84.0–86.5)	91.0 (89.9–92.0)	93.5 (92.5–94.4)	95.2 (94.2–96.0)	96.6 (95.7–97.4)	97.4 (96.6–98.1)
2008–2012	89.6 (88.8–90.4)	87.3 (86.2–88.3)	92.3 (91.5–93.0)	94.8 (94.1–95.4)	96.3 (95.6–96.9)	97.0 (96.2–97.6)	97.7 (96.9–98.5)
2013–2017	90.2 (89.3–91.1)	-	91.9 (90.6–93.2)	-	-	-	-
Age (yr)							
<40	95.2 (94.2–96.0)	93.8 (92.5–94.8)	96.2 (95.2–97.0)	97.0 (96.0–97.8)	97.8 (96.9–98.5)	98.3 (97.4–99.0)	98.6 (97.6–99.2)
40–49	94.1 (93.4–94.8)	92.4 (91.4–93.3)	95.9 (95.2–96.5)	97.0 (96.2–97.6)	97.4 (96.7–98.0)	97.9 (97.2–98.5)	98.3 (97.6–98.9)
50–59	91.6 (90.9–92.2)	89.1 (88.2–90.0)	93.0 (92.3–93.7)	94.7 (94.0–95.3)	95.9 (95.2–96.5)	96.8 (96.1–97.4)	97.6 (96.9–98.2)
60–69	80.7 (79.2–82.1)	75.1 (73.0–77.1)	84.8 (83.3–86.2)	88.9 (87.3–90.3)	91.3 (89.6–92.8)	92.5 (90.7–94.1)	93.7 (91.7–95.5)
≥70	69.1 (66.1–71.9)	63.5 (58.7–68.2)	78.3 (74.8–81.5)	86.3 (82.3–89.9)	91.6 (87.0–95.7)	92.1 (86.6–97.0)	95.0 (88.7–100.5)
Histology							
Endometrioid	93.2 (92.7–93.6)	90.9 (90.2–91.5)	94.8 (94.3–95.2)	95.9 (95.5–96.4)	96.9 (96.4–97.3)	97.4 (96.9–97.8)	97.9 (97.3–98.4)
Serous	60.5 (57.0–63.8)	53.2 (49.1–57.1)	64.4 (60.6–68.1)	73.2 (68.9–77.0)	77.0 (72.3–81.1)	84.0 (79.2–88.0)	88.4 (83.4–92.3)
Mucinous	90.9 (87.3–93.8)	89.9 (85.4–93.4)	93.9 (90.3–96.5)	96.5 (93.0–98.8)	97.3 (93.6–99.5)	97.6 (93.9–99.9)	99.3 (95.6–101.4)
Clear cell	74.8 (69.2–79.6)	70.0 (62.7–76.6)	81.3 (75.3–86.4)	87.9 (81.4–92.8)	92.9 (86.1–97.7)	91.1 (83.1–96.8)	94.7 (86.3–100.1)
Carcinosarcoma	51.5 (48.0–54.9)	47.4 (43.5–51.1)	61.6 (57.5–65.4)	74.7 (70.2–78.7)	82.6 (77.9–86.6)	88.3 (83.4–92.2)	92.5 (87.7–96.1)
Others	72.6 (67.8–76.8)	66.2 (60.6–71.5)	83.4 (78.5–87.4)	87.8 (82.7–91.8)	91.8 (86.8–95.6)	92.1 (86.8–96.0)	92.1 (86.2–96.3)
Stage at diagnosis							
Localized	96.6 (96.2–97.0)	95.3 (94.6–96.0)	97.2 (96.7–97.6)	97.8 (97.4–98.3)	98.3 (97.8–98.8)	98.7 (98.1–99.2)	99.1 (98.4–99.6)
Regional	80.9 (79.3–82.4)	75.3 (73.2–77.4)	83.7 (82.0–85.2)	87.7 (86.0–89.3)	90.6 (88.8–92.2)	91.4 (89.4–93.2)	93.5 (91.4–95.3)
Distant	34.5 (31.3–37.7)	26.8 (23.2–30.5)	44.2 (39.8–48.4)	56.0 (50.4–61.2)	62.2 (55.6–68.3)	70.6 (63.2–77.0)	77.7 (69.0–84.5)
Unknown	85.5 (82.8–87.8)	83.3 (80.2–86.1)	91.2 (88.8–93.3)	94.1 (91.7–96.0)	95.8 (93.4–97.6)	97.0 (94.7–98.8)	97.9 (95.5–99.6)
Treatment received							
Surgery only	95.2 (94.7–95.6)	93.8 (93.1–94.4)	96.6 (96.1–97.0)	97.7 (97.2–98.1)	98.4 (97.9–98.8)	98.5 (98.0–99.0)	98.9 (98.4–99.4)
Surgery + Chemo	74.0 (72.0–75.9)	68.9 (66.4–71.2)	79.0 (76.9–80.9)	84.5 (82.4–86.5)	87.8 (85.6–89.8)	91.3 (89.0–93.2)	93.4 (91.1–95.3)
Surgery + RT	88.8 (87.1–90.3)	83.6 (81.3–85.8)	89.8 (88.1–91.4)	91.2 (89.4–92.8)	92.2 (90.3–93.9)	93.3 (91.3–95.0)	94.7 (92.6–96.4)
Surgery + Chemo + RT	72.7 (69.8–75.3)	64.2 (60.6–67.6)	75.2 (72.2–77.9)	80.2 (77.0–83.0)	83.7 (80.3–86.6)	86.5 (82.9–89.5)	88.6 (84.8–91.7)
RT only/Chemo only/Chemo + RT	49.1 (43.8–54.2)	44.5 (38.6–50.3)	65.0 (58.3–71.0)	77.2 (69.7–83.4)	83.9 (76.2–89.8)	87.2 (79.1–93.1)	91.5 (82.7–97.4)
No treatment	81.3 (79.0–83.4)	78.6 (75.9–81.1)	88.1 (85.9–90.1)	92.3 (90.2–94.0)	95.3 (93.3–96.9)	96.7 (94.7–98.2)	97.2 (95.0–98.8)

CI, confidence interval; Chemo, chemotherapy; RT, radiotherapy.

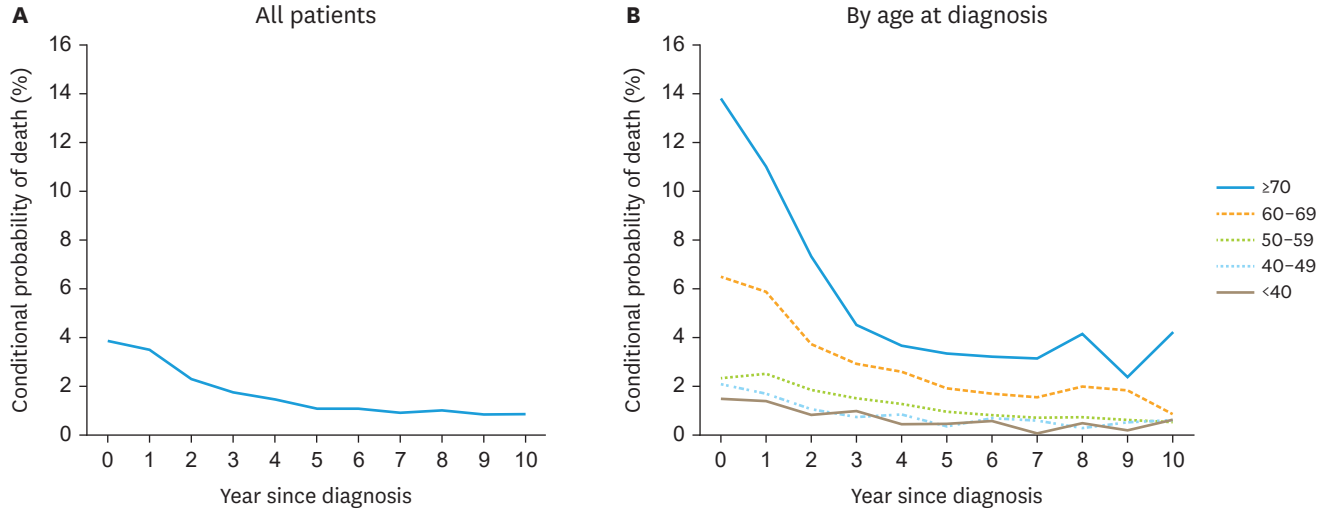

Fig. 3. Conditional probability of death according to years since diagnosis. (A) All patients, (B) by age at diagnosis.

The relative effect of histology on survival was consistent, with longer survival for most histologic types, but the RER increased with time for serous type histology (1.39 at diagnosis to 2.04 at 5 years after diagnosis). The RER for SEER stage decreased with time, especially

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Table 3. Factors associated with mortality according to survival time since diagnosis, 2005–2017 (n=18,993): multivariate analyses

Variables	At diagnosis	2 years after diagnosis	5 years after diagnosis
	RER (95% CI)	RER (95% CI)	RER (95% CI)
Age (yr)			
<40	1	1	1
40–49	1.24 (0.79–1.93)	1.13 (0.81–1.56)	1.05 (0.81–1.36)
50–59	1.18 (0.78–1.79)	1.19 (0.88–1.61)	1.24 (0.98–1.58)
60–69	2.11 (1.39–3.21)	2.16 (1.59–2.92)	2.23 (1.75–2.84)
≥70	3.66 (2.38–5.61)	3.64 (2.66–4.99)	3.56 (2.75–4.61)
Year of diagnosis			
2005–2010	1	1	1
2011–2016	0.99 (0.82–1.18)	0.83 (0.73–0.95)	0.83 (0.75–0.93)
Histology			
Endometrioid	1	1	1
Serous	1.39 (1.06–1.81)	1.85 (1.54–2.24)	2.04 (1.75–2.37)
Mucinous	1.22 (0.60–2.47)	1.40 (0.86–2.27)	1.19 (0.78–1.80)
Clear cell	1.54 (0.99–2.40)	1.72 (1.24–2.38)	1.54 (1.15–2.05)
Carcinosarcoma	3.60 (2.90–4.47)	4.04 (3.43–4.76)	3.88 (3.38–4.46)
Others	3.35 (2.35–4.79)	3.22 (2.42–4.27)	2.51 (1.93–3.27)
Stage at diagnosis			
Localized	1	1	1
Regional	6.69 (4.86–9.21)	5.88 (4.80–7.21)	5.36 (4.59–6.27)
Distant	37.37 (27.48–50.82)	27.17 (22.23–33.21)	22.67 (19.36–26.54)
Unknown	7.63 (5.12–11.38)	4.79 (3.58–6.39)	3.84 (3.03–4.85)
Deprivation index			
1 (wealthiest)	1	1	1
2	1.02 (0.83–1.26)	1.01 (0.86–1.17)	1.03 (0.90–1.16)
3	1.22 (0.95–1.57)	1.18 (0.98–1.42)	1.17 (1.00–1.36)
4	1.16 (0.85–1.58)	1.17 (0.93–1.46)	1.15 (0.95–1.40)
5 (poorest)	1.27 (0.94–1.73)	1.22 (0.97–1.54)	1.10 (0.90–1.35)

CI, confidence interval; RER, relative excess risk.

for distant stage, and was 37.37 at diagnosis and 22.67 at 5 years after diagnosis. Social deprivation was associated with higher mortality at diagnosis, but the significance was lost after 2 years (**Table 3**).

DISCUSSION

In this study using the nationwide cancer registry in Korea, 5Y CRS increased with each additional year survived after EC diagnosis, and patients who are older and who have more advanced disease or a non-endometrioid histology showed larger increases of CRS over time than other patients. The prognostic importance of SEER stage and social deprivation index decreases as survival time increases, whereas the prognostic importance of age and histology remains similar over time.

Overall, the 5Y RS of EC in Korea were similar to or slightly higher than estimates reported from other countries. The 5Y RS of all EC cases was 89.0% for women diagnosed in 1997–2016, which is comparable than that reported in the US (91%–96%, diagnosed in 2000–2017) [18,28] or Japan (≤80%, diagnosed in 1993–2011) [11]. Stage distribution was similar to that reported in the US [20]. The 5Y RS for localized, regional, and distant stage was 96.6%, 80.9%, and 34.5%, respectively. While direct comparisons could be misleading due to differences in study populations, study period, and clinical practice, the Korean patients showed higher conditional survival than US patients (95.3%, 67.8%, and 16.9%, most recent

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US SEER estimates) and European patients (>95%, 68%, and 17%) [3,13,18,29,30]. The 5Y CRS for each SEER stage (99.1%, 93.5%, and 77.8%) was similar to or slightly higher than in the US (98.3%, 89.2%, and 77.0%, respectively, most recent US SEER estimates) [13,17] (**Table S2**). It is possible that relatively younger age or Asian ethnicity contributed to better prognosis [31].

Multiple studies define 'cure' as CRS >90% or 95%. [12,16] Applying these definitions to this study, time to cure for EC in all patients was <1 year and <3 year, respectively. This is especially true for patients who are young or have endometrioid or mucinous type cancers of localized stage. The majority of ECs is diagnosed in early stage, requires only surgery, and has low risk of recurrence [32,33]. The 5Y OS or 5Y RS from the time of diagnosis in such patients is >95% [34]. Thus, care of this populations needs to focus more on general health management than oncological care, as EC is not a common cause of death in this group [21].

On the other hand, there are patients who have poorer prognosis at diagnosis, such as those with advanced stage disease or non-endometrioid histology. These patients might have higher risk or recurrence and feelings of uncertainty regarding their future. However, increase of the 5Y CRS in this study indicates that risk of death substantially decreases with time survived since diagnosis. As with many cancers, most recurrence (≤70%) occurs within 3 months for EC patients who underwent primary surgical treatment [8,9,35]. In line with that, this study showed that the greatest number of deaths occurred during the first 3 years following diagnosis, and 5Y CRS rate exceeds 90% for most patients at 3–5 years after EC diagnosis. This indicates that most patients do not experience significant excess mortality 3–5 years after cancer diagnosis compared to the general population. This is quite different from ongoing reduced survival expectations for ovarian cancer, for which 5Y CRS >90% is not achieved even at 5 years after diagnosis [12]. Therefore, providing such updated survival information to these patients could reduce their anxiety and help to plan their life after cancer treatment.

Year of diagnosis did not have a significant independent prognostic effect (i.e., RER=1) at the time of diagnosis. Advances in surgical techniques decreased patient morbidity and improved quality of life but have an uncertain effect on improvement of recurrence or survival outcomes [21,35]. This is consistent with the absence of substantial improvement in survival for EC since 1999 in a US study [21]. This suggest that the difference in CRS largely reflects younger age of onset in recent years, which also is observed in other countries, such as the US [20]. However, while difference in CRS decreased with time, RER became statistically significant only after several years of survival. This means that those who have survived several years in recent years have lower mortality than those in previous years. It is known that EC survivors, especially those who underwent chemotherapy, are at higher long-term risk of cardiovascular disease, including hypertensive heart disease, pulmonary heart disease, and congestive heart failure [18,36]. Increased interest in cardio-oncology and better management of cardiovascular risk factors explain the difference in CRS during the study period.

The 5Y RS at diagnosis of EC was markedly lower for older patients, consistent with previous studies [15,17,18,20]. This indicates that diagnosis of EC can have higher relative impact on survival in older patients than younger patients. Older women are diagnosed with more advanced stage with higher tumor grade and more frequent deep myometrial invasion than are younger women. In addition, less aggressive therapy, poor tolerance to toxic treatment, and more comorbidities might be responsible for the relatively poorer prognosis in older patients

with EC [17]. However, the difference in 5Y CRS between age groups became smaller over time, with a >90% CRS in the oldest age group, also consistent with previous studies [12,16].

Differences in CRS between the stages decreased over time. While women with distant stage showed marked improvement of 5Y CRS from 34.5 at diagnosis to 77.7% after 5 years, the criterion for 'cure' was not met for these patients. Analysis of RER in this study supported disease stage as a very strong factor determining prognosis even after 5 years, despite some decrease in RER by time since diagnosis. This suggests that delayed mortality after prolonged therapy (e.g., EC patients with serous histology) or late effects of radiation or chemotherapy can cause non-EC deaths in this population [37]. The latter would be important, as it can be avoided or better managed through cardio-oncological care [38] or shared care with primary care physician [39].

Difference in prognosis calculated from baseline (i.e., 5Y RS) was similar to reported estimates from previous studies.[21] Endometrioid and mucinous carcinoma had the most favorable prognosis: 5 YRSs were >90% from time of diagnosis and reached nearly 100% after 5 years. Rarer histological types had poorer prognosis, but there was some variation. Clear cell had intermediate prognosis and showed a 5Y CRS of ≤95% if the patient survived for 5 years. While carcinosarcoma has the poorest prognosis, CRS rapidly increased, reaching >90% at 5 years, which is similar to the recent US study [18]. The reason for this is unclear, but recurrence in carcinosarcoma tends to be local rather than hematogenous metastasis and may have better survival even if it recurs after several years. The 5Y CRS for serous carcinoma did not reach 90% even after 5 years, and serous histology was associated with relatively worsening prognosis over prolonged survival. This implies consistently high risk of relapse and death even with long-term disease-free survival or prolonged survival with long-term palliative chemotherapy. This is a unique finding of this study, as CRS estimates by EC histologic type have been reported only in one recent SEER registry study [18]. Interestingly, this pattern is quite similar to that found in ovarian cancer, in which serous histology has consistently poorer survival probability than mucinous, endometrioid, and clear cell cancers [24].

The 5Y CRS by treatment seemed to reflect treatment pattern by stage. For example, those who received surgery only had low risk of EC (e.g., International Federation of Gynecology and Obstetrics [FIGO] stage IA grade 1–3 or IB, grade 1,2). Those who underwent surgery + RT received vaginal brachytherapy for recurrence prevention (e.g., FIGO IA with myometrium invasion or lymphovascular space involvement). Those who received surgery + chemotherapy were likely to have stage II disease, and those who received surgery + chemotherapy + RT were likely to have stage III disease. Those who received chemotherapy or RT without surgical treatment were most likely to have stage IV disease. The results of current study showed that, while expected survival was poorer in patients who received treatment other than or in addition to surgery, the difference significantly decreased with survival time.

The strengths of this study are the use of national, whole-population data without selection bias, long follow-up time (up to 20 years), and stratification by various factors. Presentation of the results from a non-White population, which is currently rare [20], is another merit of the current research. However, this study also has several limitations. First, the KCCR does not contain histological information such as tumor grade, myometrial invasion, and lymphovascular space involvement, which are important predictors in clinical practice [8,20]. In addition, type I and type II endometrioid cancers, which have different prognoses, could not be distinguished using KCCR data. Second, as with most other cancer registry data, the

KCCR does not include information about recurrence, so conditional disease-free survival could not be calculated. Third, KCCR data do not contain information about other prognostic factors, such as marital status, income, educational status, smoking status, body mass index, or comorbidities [17,21]. Fourth, methods for RS estimates used in this study are possibly subject to the bias from the informative censoring. Finally, the findings from this study might not be generalizable to other healthcare settings. Korea offers a free national cervical cancer screening program [25,40], and most standard cancer treatment is well covered through a universal health insurance system.

In conclusion, 5Y RS of overall EC patients was as high as 89% from the time of diagnosis, and the CRS rates for patients improve over time, reaching no significant excess mortality risk at 1 to 3 years after diagnosis. Patients with poor initial prognoses, i.e., those who were older or had non-endometrioid histology or distant stage, showed the largest improvements in 5Y CRS, which reached >90% for most subgroups at 5 years after diagnosis, except for serous histology (88.4%) and distant stage (77.7%). Such estimates based on patient's evolving risk profile will provide updated prognostic information useful for both patients and healthcare providers.

SUPPLEMENTARY MATERIALS

Table S1

Conditional probability of death (%) by age group and years since diagnosis

Click here to view

Table S2

Five-year conditional survival rates: comparison of KCCR and the US SEER data

Click here to view

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