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Mortality patterns of synchronous uterine and ovarian cancers: a SEER registry analysis

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Abstract

Background—The degree to which uterine cancer metastatic to the ovary is misdiagnosed as synchronous stage I uterine and ovarian cancers is unclear. We sought to determine whether patients with synchronous cancers had mortality patterns similar to either stage IIIA uterine, stage I uterine, or stage I ovarian cancers alone.

Methods—The Surveillance, Epidemiology, and End Results database was used to compare mortality of patients with synchronous stage I uterine and stage I ovarian cancers versus those with stage IIIA uterine, stage I uterine, or stage I ovarian cancers alone. We calculated age-adjusted mortality hazard ratios (HR) and 95% confidence intervals (CI) accounting for calendar year and grade, adjuvant treatment, grade 1 endometrioid cancers, grade 3 endometrioid cancers, and stage IA cancers.

Results—Among the 9,321 patients, we observed lower age-adjusted mortality in patients with stage I synchronous cancers (n=937) compared to those with stage IIIA uterine (n=531; HR=0.45 95%CI 0.35–0.58), stage I uterine (n=6,919 HR=0.74; 95%CI 0.60–0.91), and stage I ovarian cancers (n=934; HR=0.52 95%CI 0.41–0.67). Results were similar after taking into account diagnosis year and grade, and limiting to those receiving adjuvant therapy, grade 1 or grade 3 endometrioid cancers, or stage IA cancers.

Conclusions—We observed lower mortality for synchronous stage I uterine and ovarian cancers, which was not explained by younger age, earlier stage, lower grade, histology type, or adjuvant therapy.

Impact—The possible misdiagnosis associated with clinicopathologic of synchronous uterine and ovarian cancers does not appear to worsen survival on a population level.

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This study was conducted using de-identified publicly available data and was exempt from IRB review.

Keywords

multiple primary; uterus neoplasm; ovarian neoplasm; diagnosis; misdiagnosis; antineoplastic agents; radiotherapy

Introduction

Uterine cancer is the most common gynecologic malignancy with an estimated lifetime risk approaching 4%(1). Uterine cancer is typically diagnosed at an early stage with a corresponding favorable prognosis. Among all patients with uterine cancer, approximately 2% will be diagnosed with a separate, synchronous ovarian cancer at the time of surgery for their uterine cancer(2), 50% of which are diagnosed incidentally on final pathology(3). Conversely, 2–4% of patients with a primary ovarian cancer will be diagnosed with a synchronous uterine cancer. In the subset of uterine cancer cases diagnosed in premenopausal, younger patients, the proportion of those with synchronous ovarian cancer is substantially higher, with a range of 11–29%(4,5). In some estimates, in 46–85% of synchronous cases, the histology is endometrioid adenocarcinoma in both the uterine and the ovarian tumor, and 42–67% are stage I cancers and treated independently(2,6).

Due to this commonly concordant histology type and lack of tumor beyond the uterus and ovary with two stage I cancers, synchronous tumors pose a diagnostic challenge to pathologists and oncologists. It is difficult to distinguish between two separate primary uterine and ovarian cancers versus a uterine cancer that has isolated metastases to the ovary (a stage IIIA uterine cancer). The converse, an isolated metastasis of an ovarian cancer to the endometrium, is not typically seen. To distinguish synchronous stage I uterine and stage I ovarian cancers from a metastatic uterine cancer, pathologic criteria were established by Ulbright and Roth, summarized by Scully et. Al. in 1998(7) (Table 1). However, the criteria to distinguish synchronous cancers versus a metastatic uterine cancer are mostly subjective and the question remains whether misdiagnosis could still occur, potentially adversely affecting receipt of appropriate treatment, and survival.

Stage I low grade uterine and stage I low grade ovarian tumors can often be managed with surgery alone and subsequent observation without the need for adjuvant radiation or chemotherapy. Conversely, all stage IIIA uterine cancers with ovarian metastases have a high risk of recurrence and require adjuvant radiation and/or chemotherapy to improve progression free and overall survival. Multiple small studies have evaluated different immunohistochemical tumor staining techniques(8), microsatellite instability status(9), and genome wide whole exome sequencing(10,11),12,(13) to address the possibility of misdiagnosis by demonstrating evidence of tumor clonality in selected tumor sets. Though these studies suggest that misclassification or misdiagnosis occurs, they did not attempt to assess the magnitude of misdiagnosis on survival on a population basis, nor if it has impact on survival in the population of patients diagnosed with these cancers. Also, prior studies have investigated survival of patients with synchronous tumors compared to those with non-synchronous stage I tumors and reported more favorable survival in those with

synchronous tumors, and no difference in survival after adjusting for typical factors such as age, but did not separately control for tumor grade, histology, or extent of invasion(2,14).

The goal of this study was to investigate the potential misdiagnosis of patients with an aggressive, metastatic stage IIIA uterine cancer as a synchronous stage I uterine and stage I ovarian cancer on a population level. We hypothesized that if such misdiagnosis was common among patients diagnosed with synchronous stage I uterine and ovarian tumors, they would have higher mortality than those with non-synchronous stage I uterine or stage I ovarian cancers, and mortality closer to that of patients with stage IIIA uterine cancers, after accounting for various patient and tumor characteristics.

Methods

The Surveillance, Epidemiology, and End Results (SEER) database, a representative US population-based sample of 20 cancer registries with complete histology, stage, and survival data, was used for this study. This study was conducted using de-identified publicly available data and was exempt for IRB review, and is compliant with SEER reporting guidelines. Adjuvant treatment data (radiation and chemotherapy) was only available after 2004, so this study was restricted to diagnoses between 2004 and 2015 (years with complete survival information), with follow-up until 2018, accessed February 2020(15). All patients with any SEER stage I uterine, stage IIIA uterine, or stage I ovarian cancer, with a minimum survival of 4 months from index cancer diagnosis were included in the study. These stages were chosen to compare those which represent localized uterine cancers, localized ovarian cancers, and uterine cancers with isolated metastases to the ovary without lymph node involvement. Consistent with prior studies, synchronous stage I uterine and ovarian cancer was defined as diagnosis of the two cancers within 4 months of each other. Because the synchronous cancers were included with the second cancer diagnosed up to 4 months after the first cancer, follow-up for all groups started 4 months after the date of diagnosis of the primary cancer (first primary for synchronous) to avoid immortal time bias(16). Baseline demographic characteristics included age at diagnosis (mean and 10-year interval), year of diagnosis (reported by 5-year intervals), race and ethnicity (Hispanic ethnicity from all race categories grouped together, and non-Hispanic race categories reported separately), marital status at diagnosis (married, divorced, or never married), SEER region (Alaska, East, Northeast Plains, Pacific Coast, Southwest). Some categories were grouped to maintain anonymity and we did not report groups with fewer than 11 patients in accordance with SEER reporting guidelines. Stage was reported using standardized SEER stage based on the American Joint Committee on Cancer stages (IA noninvasive, IB <50% invasive, IC >50% invasive) rather than the most recent International Federation of Gynecology and Obstetrics (FIGO) staging in order to delineate noninvasive cancers for planned sensitivity analyses, and to account for changing FIGO stage definitions over the study period. Grade (1, 2, 3) and histology for each respective tumor was reported. We reported on receipt of surgery (yes/no), and initial receipt of adjuvant radiation or chemotherapy (yes/no) as binary variables due to consistency limitations of the SEER data over the study period regarding surgical details (i.e. lymphadenectomy) and specific chemotherapy regimens. Finally, status at end of observation period (alive or death from cancer or other cause) was also reported.

Differences in unadjusted mortality between synchronous, stage I ovary, stage I uterine, and stage IIIA uterine cancers were examined using Kaplan-Meier survival curves and a log-rank test. Cox proportional hazards models were then used to estimate the relative risk of death (mortality hazard ratio [HR]). Age adjusted HRs were calculated for patients with synchronous stage I uterine and stage I ovarian cancers compared to each of the other groups: patients with stage I ovary; stage I uterine; or stage IIIA uterine cancers. Additional age-adjusted sensitivity analyses were conducted to account for differences in treatment and tumor characteristics as follows: 1) adjusted for continuous calendar year of diagnosis to account for differences in year of diagnosis and improved ovarian cancer survival over time; 2) adjusted for grade given differences in survival by grade; 3) restricted to those receiving any adjuvant therapy given differences in application rates by stage; 4) restricted to endometrioid histology (the lowest risk and more common in synchronous tumors); 5) restricted to grade 1 endometrioid tumors (lowest possible risk type and unlikely to receive adjuvant therapy); 6) restricted to grade 3 endometrioid tumors (most common histology but highest risk grade); 7) stage I tumors restricted to SEER stage IA uterine and ovarian tumors (confined to the endometrium, or within one ovary without surface involvement or tumor rupture, respectively, to take possible differences in incidental diagnoses at time of surgery into account and control for different adjuvant therapies for sub-stages). We assumed covariates were missing at random and patients were dropped from specific analyses if the variable or covariate of interest was missing for that specific analysis.

Data availability Statement

The publicly available data analyzed in this study were obtained from National Cancer Institute Surveillance, Epidemiology, and End Results Program available at seer.cancer.gov/seerstat.

Results

Demographics

A total of 9,382 individuals were initially included in the analysis. After applying the 4-month minimum survival criteria we excluded 11 synchronous stage I uterine and ovarian, 7 stage IIIA uterine, 36 stage I uterine, and 7 stage I ovarian cancer patients from the analysis. A total of 9,321 patients were ultimately included in this analysis (Table 2), including 937 patients with synchronous stage I uterine and ovarian cancers, 531 with stage IIIA uterine cancers, 6,919 with stage I uterine cancers, and 934 with stage I ovarian cancers. Among patients with synchronous cancers, 582 (62%) of second cancers were diagnosed in the same month as the primary cancer, 233 (24%) within one month, 80 (8.5%) within two months, 27 (2.9%) within three months, and the remaining within four months of diagnosis of the primary cancer. Median follow-up time was 7.58 years (interquartile range [IQR]= 4.58–10.08). A slightly higher proportion of patients with synchronous uterine and ovarian tumors were diagnosed later in the study period (2010–2015, 52.8%) while those with stage IIIA uterine, stage I uterine, and stage I ovarian cancers were more likely to be diagnosed earlier in the study period (2004–2009, 54.0%, 59.4%, 61.2%, respectively, Table 2). Compared to patients with stage IIIA uterine, stage I uterine, and stage I ovarian cancers alone, those with

synchronous uterine and ovarian cancers were younger at diagnosis (mean age, 52.5 vs 64.3, 63.5, and 56.8 years, respectively), had the highest proportion of those of non-Hispanic Asian or Pacific Islander descent (10.2% vs 7.5%, 6.5% and 8.5%, respectively) and the lowest proportion of non-Hispanic Black individuals (3.3% vs 8.5%, 7.1% and 5.7%, respectively). The majority (75%) of patient were alive at the end of the study period.

Tumor characteristics

Patients with synchronous stage I uterine and ovarian cancers were more likely to have stage IA uterine tumors compared to those with stage I uterine cancers alone (44% vs 31%), but less likely to have stage IA ovarian cancers compared to those with stage I ovarian cancers alone (53% vs 61%). They were also more likely to have grade 1 tumors than other patients (Table 3).

Ninety percent of uterine cancers diagnosed as synchronous stage I uterine and ovarian cancers were endometrioid, compared to 87% of stage I, and 72% of stage IIIA uterine cancers alone. A high proportion (66%) of ovarian cancers diagnosed as synchronous stage I uterine and ovarian cancers were endometrioid, compared to only 25% of stage I ovarian cancers alone. The majority (n=593, 63%) of the synchronous stage I uterine and ovarian cancers were concordant for endometrioid histology (Figure 1).

More than half (55%) of patients with synchronous uterine and ovarian cancers received any adjuvant therapy, slightly more than those with stage I ovarian cancer alone (45%), and much more than stage I uterine cancer alone (23%), but fewer than those with metastatic stage IIIA non-synchronous uterine cancer (67%).

Mortality analyses

In unadjusted analyses, mortality differed between cancer types (log-rank p-value<0.001); patients with synchronous stage I uterine and ovarian cancers had the lowest mortality, and those with stage IIIA uterine cancer had the highest mortality (Figure 2). Given that age at diagnosis differed across the groups, the subsequent mortality comparisons were adjusted for age at diagnosis. In age-adjusted analyses, patients with stage I synchronous uterine and ovarian cancers had lower mortality compared to patients with metastatic stage IIIA uterine cancers (HR 0.45, 95%CI 0.35–0.58); stage I uterine cancer alone (HR 0.74, 95%CI 0.60–0.91); and stage I ovarian cancer alone (HR 0.52, 95%CI 0.41–0.67) (Figure 3).

The observed lower mortality among those with synchronous stage I cancers compared to those with stage I uterine or stage I ovarian cancer alone also remained after adjusting for calendar year of diagnosis (HR 0.72 95% CI 0.59–0.89 and HR 0.51 95% CI 0.40–0.65, respectively), and grade (HR 0.68 95% CI 0.51–0.90 and HR 0.47 95% CI 0.34–0.65, respectively). In analyses restricted to patients who received any adjuvant therapy (for either cancer type), we observed mortality patterns similar to the main age-adjusted analyses for those with synchronous stage I cancers compared to those with stage IIIA uterine cancer (HR 0.51, 95%CI 0.36–0.73), stage I uterine cancer alone (HR 0.65, 95%CI 0.48–0.89), and stage I ovarian cancer alone (HR 0.60, 95%CI 0.42–0.86). Similar patterns were also observed in analyses restricted to endometrioid uterine and/or ovarian cancers (of any grade), those restricted to grade 1 (any histology), and those restricted to grade 3 (any

histology, Figure 3), though the estimates for grade 1 endometrioid tumors were imprecise due to smaller sample size (Figure 3). Analyses restricted to stage IA uterine and/or ovarian cancers were also similar.

Discussion

In this population-based SEER registry analysis, we found that patients with synchronous stage I uterine and ovarian cancers had lower mortality compared to those with non-synchronous stage IIIA uterine cancers, stage I uterine cancers, and stage I ovarian cancers. These patterns persisted across analyses accounting for age, calendar year of diagnosis, and grade, and after restricting by receipt of adjuvant therapy, endometrioid histology and grade, and earliest stage (IA). Our findings support that the misdiagnoses of stage IIIA uterine cancers as synchronous ovarian/uterine cancers is either infrequent or is not associated with large mortality differences.

Previous population-based studies of synchronous uterine and ovarian cancer patients from earlier diagnosis years (1973–2005(5), 1973–2013(2,14), and 2001–2011(17)) reported similar patterns of mortality, and a higher proportion of endometrioid uterine and ovarian histologies when compared with all uterine or ovarian cancers. However, these studies did not compare patients with synchronous stage I uterine and ovarian cancers to stage IIIA uterine, stage I uterine, and stage I ovarian cancers as presented here, or consistently investigate the role of age at diagnosis, stage, histology, grade and adjuvant treatment. In the current study, we adjusted for age, restricted to those who received adjuvant treatment, and those with endometrioid histologies, but the patterns of association were similar across all of these analyses. We also evaluated whether the distribution of sub-stage (IA versus IB or IC) at diagnosis might explain some of the survival differences between cancer types based on earlier incidental diagnoses. However, patients with synchronous stage I uterine and ovarian cancers had a larger proportion of stage IA uterine cancers than those with stage I uterine cancer alone, but a smaller proportion of stage IA ovarian cancers than those with stage I ovarian cancer alone. The results from sensitivity analyses restricted to stage IA cancers were similar to those in the primary analysis.

Matsuo et.al.(2) noted that the diagnosis of synchronous uterine and ovarian cancers relative to all uterine cancers decreased between 1985 and 2013, but increased relative to all ovarian cancers. Our study reported absolute numbers of cancer cases over a narrower time window (2004–2015), and observed a slightly lower proportion of synchronous cases in 2004–2009 compared to 2010–2015, whereas there were fewer cases of stage IIIA uterine, stage I uterine, and stage I ovarian cancer diagnosed in the latter study period. When examining absolute numbers of cases by year, it is clear that the number of synchronous cancers is relatively stable over time, but the numbers of stage IIIA uterine, stage I uterine, and stage I ovarian cancers are decreasing over time (Supplemental Table 1). This may partially explain why the median follow-up time was shorter for synchronous cancers compared to the other cancer types. Despite these differences, adjusting for diagnosis year did not alter the magnitude of the HRs for mortality for synchronous cancers compared to those for the other cancer types.

Case series with fewer than 150 patients with synchronous uterine and ovarian cancers have also reported that patients with synchronous uterine and ovarian cancers tend to be younger, with lower grade cancers and more endometrioid histologies compared to historical controls of all uterine or ovarian cancers(3,6,18,19). These studies were able to include more granular information on patient and clinicopathologic features, elucidating that the majority of patients with synchronous tumors were premenopausal, that 50% of the ovarian malignances were incidental, and that recurrence and survival were predicted by uterine cancer lymphovascular space invasion, uterine cancer stage, and ovarian cancer histology. In an analysis comparing 14 synchronous cancers to 49 stage III uterine cancers, Oranratanaphan et. al.(4) reported that patients with synchronous tumors had a favorable survival compared to those with stage III tumors. They were unable to adjust for covariates as performed in our analaysis due to smaller sample size.

This study did not include a centralized pathology review to assess the degree to which the Scully and Roth criteria were applied, which would have been ideal. However, the population-based nature of the study is a major strength, assessing overall survival to evaluate the magnitude and/or outcomes-level consequence of such misclassification, which was not seen after multiple adjustments. The lack of specific adjuvant therapy details and inability to analyze a reliably untreated group stand as a weakness to the SEER anayslsis which does not allow analysis of an untreated group by reporting guidelines; however HRs restricted to those receiving adjuvant treatment were unchanged.

Strengths of this study include the use of population-based cancer registry data to investigate this population of synchronous cancers compared to non-synchronous cancers, and its use of the most patient-centered outcome: overall survival. Due to it being a large study of a rare tumor type, we are able to perform multiple sensitivity analyses to investigate different biases or confounders to attempt to explain the survival difference for patients with synchronous cancers.

Notably absent from this and most other investigations is the consideration of Lynch, BRCA, or other genetic cancer syndromes which may be more or less prevalent among patients with synchronous cancers and explain differing outcomes in populations undergoing increased surveillance. Signorelli et. al.(18) indeed noted that 10 of 18 deaths among patients with synchronous uterine and ovarian cancers were from unrelated colon, breast, and brain cancers (of increased risk in Lynch, BRCA 1 or 2 and BRCA 2, respectively) rather than their gynecologic cancer, but did not have specific testing for these cancer syndromes, and did not compare these cancer specific mortalities to another population. However, Soliman et.al. investigated Lynch syndrome specifically and found a prevalence of 7% among their cohort of patients with synchronous uterine and ovarian cancers, falling within most estimates of the prevalence among patients with endometrial cancer(20).

Lynch syndrome is not the only biological marker absent from this and other investigations; the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) classification by Levine et.al.(21) has not been used to categorize a population-based sampling of uterine tumors in this synchronous population. The MSI-high, POLE mutated, copy number high and copy number low groups are highly correlated with survival and response to therapies.

Anglesio et. al.(11) investigated molecular markers of synchronous uterine and ovarian tumors and found that the majority of tumors had evidence of clonality, suggesting that metastatic (stage IIIA uterine cancers) may be commonly misdiagnosed as synchronous primaries if clinicopathologic criteria alone are used. Ishikawa et. al(12) and Reijnen et. al.(13) also found evidence of clonality in their synchronous tumor samples, and did find a higher proportion of lower risk PRoMISE subclassification of tumors compared to the general TCGA cohort of non-synchronous tumors. These studies used select cases; our population-based study would suggest that this possible misclassification is either not widespread, or does not have clinical implications on survival.

At the outset, this study sought to investigate if a possible misdiagnosis of metastatic stage IIIA uterine cancers as synchronous uterine and ovarian cancers could be detected as worse survival outcomes for those diagnosed with synchronous tumors. The observed higher overall survival, even after taking into account age, year, stage, grade, histology, and adjuvant treatment does not support a need to change diagnosis or treatment guidelines; patients should receive adjuvant treatment in accordance with established guidelines for their pathologically-defined uterine and ovarian tumors independently.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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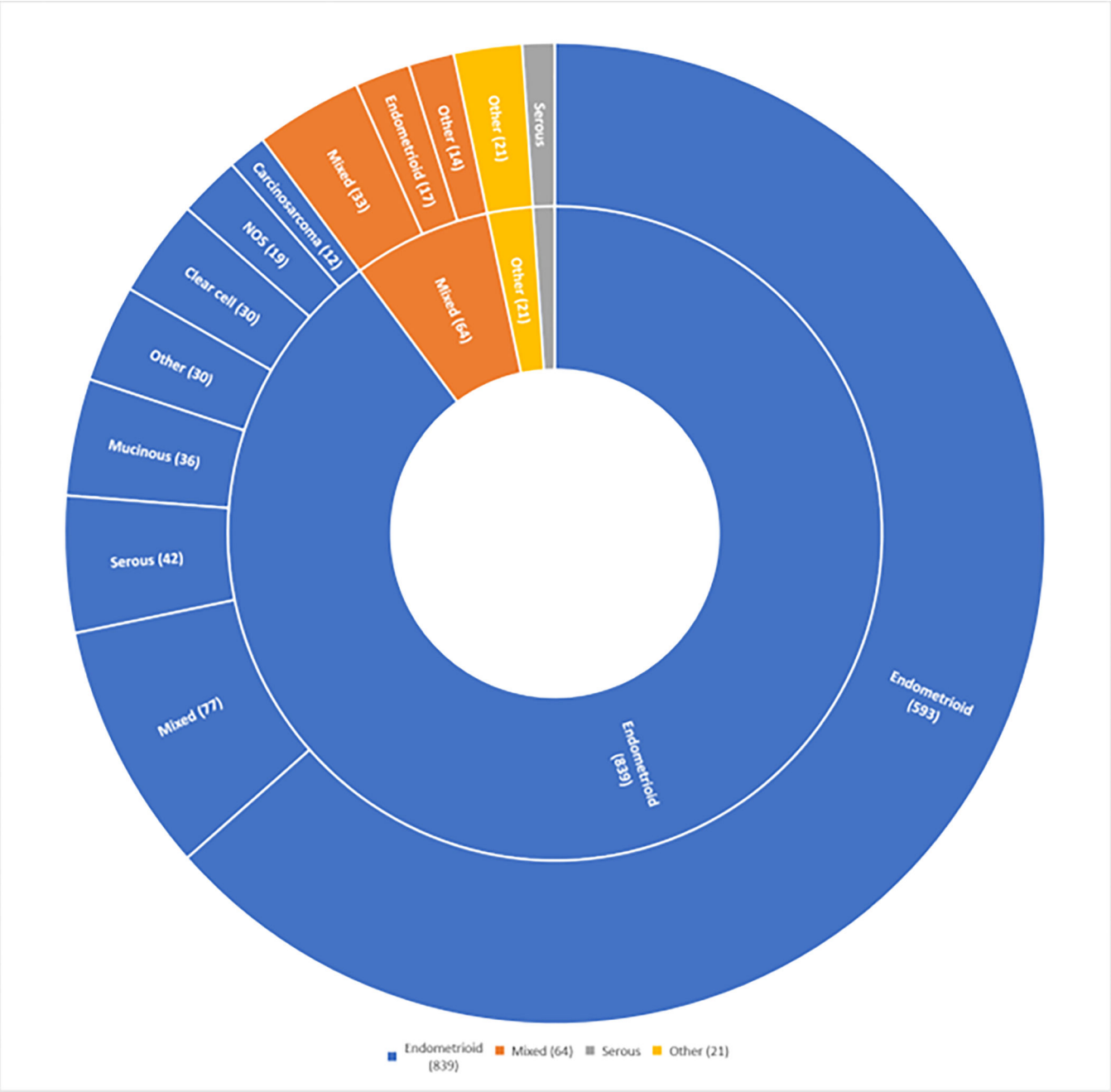

Figure 1:

Distribution of histologies for synchronous uterine and ovarian cancers, n=937.

The proportions of endometrioid, mixed, serous and other histologies are depicted for uterine cancers in the inner ring, and ovarian cancers in the outer ring, among patients with synchronous primaries.

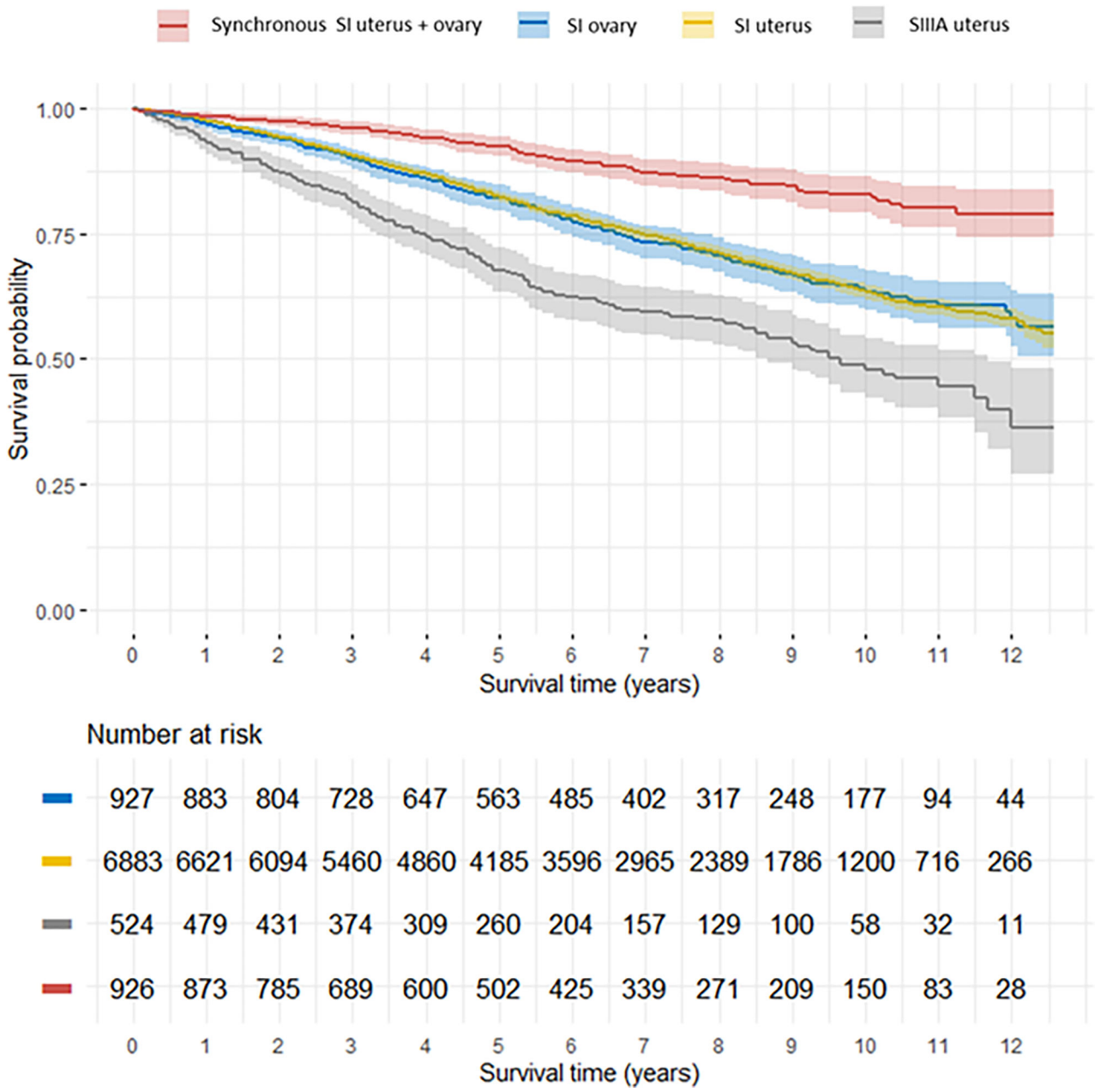

Figure 2:

Overall survival by cancer type.

This figure depicts unadjusted overall survival for patients with synchronous stage I (SI) uterine and SI ovarian, stage I ovarian, stage I uterine, and stage IIA (SIIIA) cancers, SEER 2004–2015.

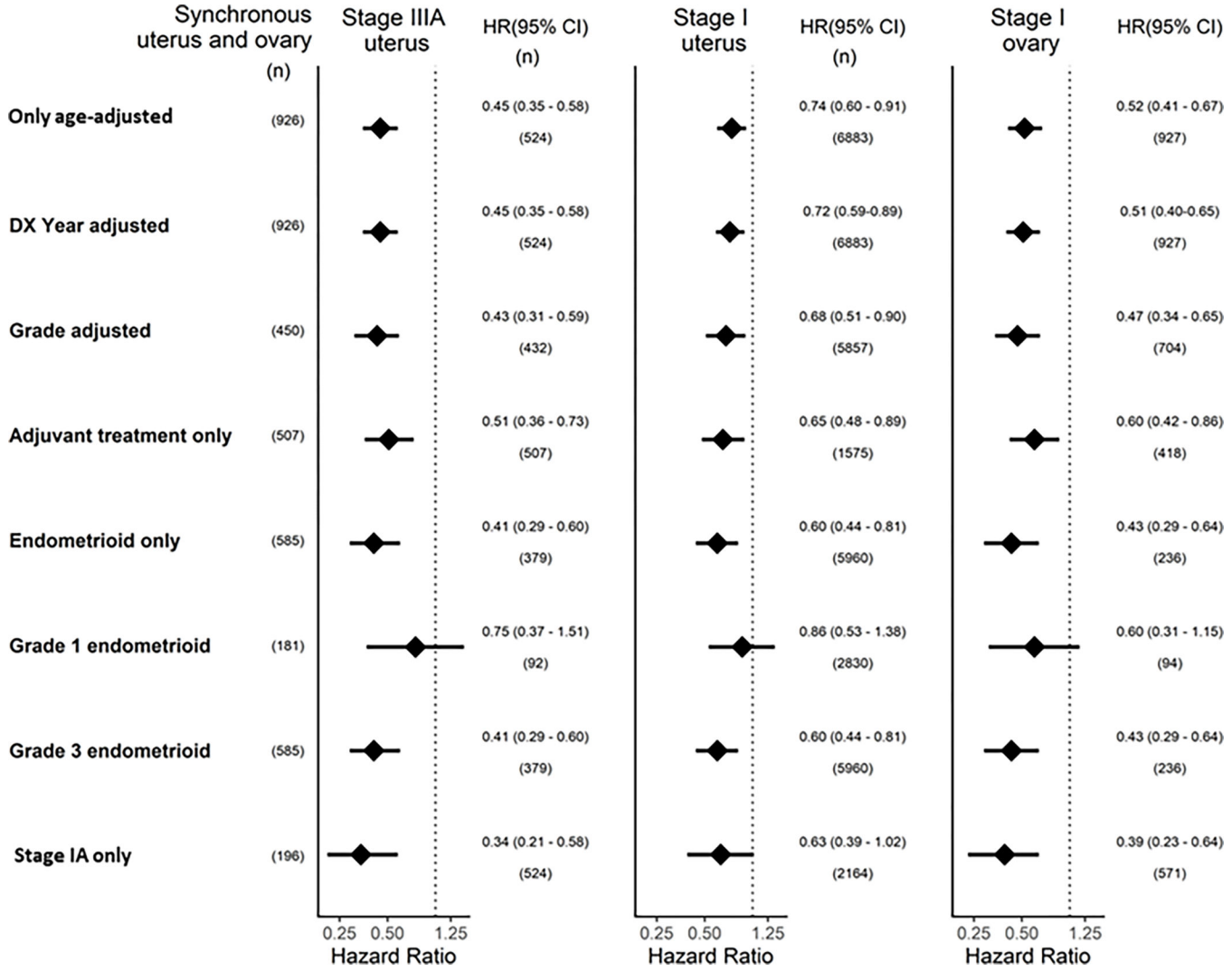

Figure 3:

Age-adjusted mortality HRs for synchronous uterine and ovarian cancers by non-synchronous cancer type, SEER 2004–2015.

Hazard ratios (diamonds) and 95% confidence intervals for each pair-wise comparison are depicted, with synchronous uterine and ovarian cancers compared to each of the other cancer types. Analyses include age-adjusted overall survival, diagnosis (DX) year adjusted, grade adjusted, and restricted to those receiving adjuvant therapy, endometrioid histology, grade 1 endometrioid histology, and grade 3 endometrioid histology, and stage IA uterine or ovarian cancers only (for all cancer types except for stage IIIA uterine cancers).

Table 1:

Ulbright and Roth criteria to distinguish between synchronous primary uterine and ovarian cancers, versus uterine cancer with ovarian metastasis

Synchronous stage I uterine and stage I ovarian primaries	Uterine cancer with ovarian metastases (Stage IIIA)
No direct or continuous connection between tumors No myometrial infiltration No lymphatic and intravascular infiltration Tumors mainly present on endometrium and the ovaries Tumor limited to the primary and only minor metastases Endometrial primary may be accompanied by hyperplasia Ovarian primary may be accompanied by endometriosis Concordant or discordant histologic types	Ovarian tumors <5 cm Bilateral ovarian invasion and multiple nodular lesions Deep myometrial infiltration of the uterine cancer Tumor infiltrating vessels Oviduct violation

Table 2:

Patient characteristics, for synchronous uterine and ovarian, stage IIIA uterine, stage I uterine, and stage I ovarian cancers, SEER 2004–2015

		Synchronous	Non-synchronous		
		Stage I uterus + Stage I ovary (n= 937)	**Stage IIIA uterus (n=531)**	**Stage I uterus (n=6,919)**	**Stage I ovary (n=934)**
Age, years no.[1] (%)	mean (SD[2])	52.5 (10.7)	64.3 (11.0)	63.5 (10.7)	56.8 (14.3)
	<=40	90 (9.6%)	<11 (NR)[3]	144 (2.1%)	121 (13.0%)
	41–50	333 (35.5%)	39 (7.3%)	552 (8.0%)	152 (16.3%)
	51–60	330 (35.2%)	151 (28.4%)	2033 (29.4%)	285 (30.5%)
	61–70	121 (12.9%)	181 (34.1%)	2416 (34.9%)	226 (24.2%)
	71–80	42 (4.5%)	114 (21.5%)	1345 (19.4%)	107 (11.5%)
	>80	21 (2.2%)	36 (6.8%)	429 (6.2%)	43 (4.6%)
Followup time in years, median (IQR[2])		6.0 (3.1–9.2)	7.1 (4.8–9.8)	7.8 (4.8–10.2)	7.8 (4.8–10.3)
Ethnicity and Race, no. (%)	Hispanic	92 (9.8%)	50 (9.4%)	628 (9.1%)	121 (13.0%)
	Non-Hispanic American Indian / Alaskan Native	<11 (NR)	<11 (NR)	47 (0.7%)	<11 (NR)
	Asian / Pacific Islander	96 (10.2%)	40 (7.5%)	451 (6.5%)	79 (8.5%)
	Black	31 (3.3%)	45 (8.5%)	489 (7.1%)	53 (5.7%)
	White	715 (76.3%)	392 (73.8%)	5,294 (76.5%)	675 (72.3%)
	Unknown	<11 (NR)	<11 (NR)	<11 (NR)	<11 (NR)
Year of diagnosis, no. (%)	2004–2009	442 (47.2%)	287 (54.0%)	4,109 (59.4%)	572 (61.2%)
	2010–2015	495 (52.8%)	244 (46.0%)	2,810 (40.6%)	362 (38.8%)
Marital status, no. (%)	Married	460 (49.1%)	261 (49.2%)	3,753 (54.2%)	473 (60.5%)
	Divorced	136 (14.5%)	142 (27.3%)	1,802 (26.0%)	214 (22.9%)
	Never Married	291 (31.1%)	103 (19.4%)	1,071 (15.5%)	212 (22.7%)
	Unknown	50 (5.3%)	25 (4.1%)	293 (4.2%)	35 (3.7%)
Region, no. (%)	Alaska	<11 (NR)	<11 (NR)	<11 (NR)	<11 (NR)
	East	321 (34.3%)	193 (36.3%)	2,515 (36.3%)	342 (36.6%)
	Northeast Plains	104 (11.1%)	45 (8.5%)	769 (11.1%)	105 (11.2%)
	Pacific Coast	473 (50.5%)	268 (50.5%)	3,327 (48.1%)	438 (46.9%)
	Southwest	39 (4.2%)	25 (4.7%)	300 (4.3%)	48 (5.1%)
Status	Alive	836 (89.2%)	319 (60.1%)	5,061 (73.1%)	679 (72.7%)

		Synchronous	Non-synchronous		
		Stage I uterus + Stage I ovary (n= 937)	**Stage IIIA uterus (n=531)**	**Stage I uterus (n=6,919)**	**Stage I ovary (n=934)**
	Uterine cancer death	12 (1.3%)	72 (13.6%)	279 (4.0%)	-
	Ovarian cancer death	34 (3.6%)	-	-	67 (7.2%)
	Death from other cause	55 (5.9%)	140 (26.4%)	1579 (22.8%)	188 (20.1%)

[1] Number

[2] standard deviation

[3] Some categories reported as n<11 and percent not reported to maintain data anonymity in accordance with SEER reporting guidelines

[4] inter-quartile range

Table 3:

Clinical characteristics and outcomes for synchronous uterine and ovarian, stage IIIA uterine, stage I uterine, and stage I ovarian cancers, SEER 2004–2015

		Synchronous	Non-synchronous		
		Stage I uterus + Stage I ovary (n= 937)	**Stage IIIA uterus (n=531)**	**Stage I uterus (n=6,919)**	**Stage I ovary (n=934)**
Uterine Cancer stage[1] (SEER)	IA confined to endometrium	413 (44.1%)	-	2176 (31.4%)	-
	IB <50% myometrial invasion	450 (48.0%)	-	3421 (49.4%)	-
	IC >50% myometrial invasion	74 (7.9%)	-	1322 (19.1%)	-
	IIIA adnexal/ovarian spread	-	531 (100%)	-	-
Ovarian Cancer stage (SEER)	IA confined to 1 ovary	495 (52.8%)	-	-	573 (61.3%)
	IB confined to both ovaries	67 (7.2%)	-	-	41 (4.4%)
	IC surface involvement or spill	375 (40.0%)	-	-	320 (34.3%)
Uterine cancer histology	Carcinosarcoma	<11 (NR) [2]	2–3 (4.3%)	128 (1.8%)	-
	Clear cell	0 (0.0%)	63 (0.9%)	<11 (NR)	-
	Endometrioid	839 (89.5%)	381 (71.8%)	5,990 (86.6%)	-
	Leiomyosarcoma	<11 (NR)	<11 (NR)	29 (0.4%)	-
	Mixed	64 (6.8%)	45 (8.5%)	334 (4.8%)	-
	Serous	15 (1.6%)	60 (11.3%)	217 (3.1%)	-
	Other / Unknown	12 (1.3%)	<11 (NR)	158 (2.3%)	-
Ovarian cancer histology	Adenocarcinoma NOS[3]	22 (1.6%)	-	-	47 (5.0%)
	Carcinosarcoma	14 (1.5%)	-	-	12 (1.3%)
	Clear cell	35 (3.7%)	-	-	119 (12.7%)
	Endometrioid	621 (66.3%)	-	-	236 (25.3%)
	Mixed	112 (12.0%)	-	-	68 (7.3%)
	Mucinous	46 (4.9%)	-	-	151 (16.2%)
	Serous	55 (5.9%)	-	-	205 (21.9%)
	Other / Unknown	32 (3.4%)	-	-	96 (10.3%)
Uterine cancer grade	1 / Well differentiated	433 (46.2%)	99 (18.6%)	2973 (43%)	-
	2 / Moderately differentiated	262 (28.0%)	149 (28.1%)	1860 (26.9%)	-
	3 / Poorly differentiated	67 (7.2%)	144 (27.1%)	834 (12.1%)	-
	Undifferentiated	<11 (NR)	46 (8.7%)	222 (3.2%)	-
	Unknown	169 (18.0%)	93 (17.5%)	1030 (14.9%)	

		Synchronous	Non-synchronous		
		Stage I uterus + Stage I ovary (n= 937)	**Stage IIIA uterus (n=531)**	**Stage I uterus (n=6,919)**	**Stage I ovary (n=934)**
Ovarian cancer grade	1 / Well differentiated	333 (35.5%)	-	-	188 (20.1%)
	2 / Moderately differentiated	294 (31.4%)	-	-	216 (23.1%)
	3 / Poorly differentiated	105 (11.2%)	-	-	225 (24.1%)
	Undifferentiated	33 (3.5%)	-	-	77 (8.2%)
	Unknown	172 (18.4%)	-	-	228 (24.4)
Adjuvant therapy	Chemotherapy only	413 (44.1%)	116 (21.8%)	193 (2.8%)	408 (43.7%)
	Radiation only	37 (3.9%)	102 (19.2%	1168 (16.9%)	<11 (NR)
	Radiation + Chemotherapy	62 (6.6%)	136 (25.6%)	216 (3.1%)	<11 (NR)
	None / Unknown	425 (45.4%)	177 (33.3%)	5342 (77.2%)	515 (55.1%)

[1]Note that this study reports SEER stage which separates tumors confined to the endometrium as IA, rather than FIGO staging

[2]Some categories reported as n<11 and percent not reported to maintain data anonymity in accordance with SEER reporting guidelines

[3]Not otherwise specified.