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Metformin is associated with improved survival in endometrial cancer

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HIGHLIGHTS

- Metformin use is associated with improved all-cause mortality in diabetic endometrial cancer patients.
- The role of metformin in improving endometrial cancer recurrence remains unclear.
- Metformin in endometrial cancer should be further investigated, given the high prevalence of comorbidities such as diabetes.

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ABSTRACT

Objective. Preclinical evidence suggests that metformin exhibits anti-tumorigenic effects in endometrial cancer. We sought to investigate the association of metformin on endometrial cancer outcomes.

Methods. A multi-institutional IRB-approved retrospective cohort analysis was conducted comparing endometrial cancer patients with diabetes mellitus who used metformin (based on medication review at the time of diagnosis) to those who did not use metformin from 2005 to 2010. Metformin use on treatment related outcomes (TTR: time to recurrence; RFS: recurrence free survival; OS: overall survival) were evaluated using univariate and multivariate modeling.

Results. 24% (363/1495) endometrial cancer patients were diabetic, of whom 54% used metformin. Metformin users were younger and heavier than non-users, though nearly all were postmenopausal and obese. 75% of both groups had endometrioid histology. Stage, grade, and adjuvant therapy distributions were similar. Metformin users had improved RFS and OS. Non-metformin users had 1.8 times worse RFS (95% CI: 1.1–2.9, $p = 0.02$) and 2.3 times worse OS (95% CI: 1.3–4.2, $p = 0.005$) after adjusting for age, stage, grade, histology and adjuvant treatment. Metformin use was not associated with TTR.

Conclusion. Metformin use was associated with improved RFS and OS but not TTR, most likely due to improving all-cause mortality. Its role in modifying cancer recurrence remains unclear. Prospective studies that capture metformin exposure prior to, during and post endometrial cancer treatment may help define the role of metformin upon cancer specific and overall health outcomes.

Introduction

Endometrial cancer is the most common cancer of the female genital tract and an estimated 49,560 new cases will be diagnosed in 2013 in the United States, with 8190 cancer related deaths [1]. Endometrial cancer has been closely linked to obesity and diabetes, both of which are increasing at alarming rates in the United States [2–4]. The relative risk of endometrial cancer increases by 1.59 (95% CI: 1.50–1.68) for each 5 point increase in BMI [5,6]. A recent metaanalysis revealed that diabetes mellitus is associated with over two times the risk of developing endometrial cancer (RR: 2.10, 95% CI: 1.75–2.53) [7]. Some evidence also suggests that obesity and diabetes may worsen endometrial cancer outcomes, although the inter-relationship between these entities is complex and often difficult to unravel [8–10].

Unfortunately while many women with endometrial cancer will be cured, a significant portion will still suffer from a recurrence of their disease. Up to one-fourth of patients diagnosed with local disease and one-half of patients diagnosed with advanced disease will die of their endometrial cancer [11]. Researchers are continuing to search for

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novel therapeutic targets to decrease the morbidity and mortality of endometrial cancer.

Metformin, classically used as an anti-diabetic medication, may serve as a new therapeutic agent for endometrial cancer. Metformin is a biguanide drug that was approved in the United States in 1994 and is currently used as the first line treatment for type II diabetes mellitus [12]. Population based studies have suggested a protective role for metformin in the prevention of solid tumor malignancies in diabetic patients [13] and some evidence of decreased mortality following cancer diagnosis [14,15]. Laboratory studies have also demonstrated anti-neoplastic effects in several cancer cell lines including breast, colon and endometrial cancer [16,17]. Metformin likely exerts its anti-tumorigenic effects, through a combination of indirect mechanisms via increasing insulin sensitivity, inhibiting liver gluconeogenesis, and reducing hyperglycemia and insulin levels [18]; and direct mechanisms via activating AMP-activated protein kinase (AMPK). Activation of AMPK leads to regulation of multiple signaling pathways involved in the control of cellular proliferation and metabolism, including inhibition of the mammalian target of rapamycin (mTOR) pathway [19].

To date there is very little clinical evidence of the effect of metformin on endometrial cancer related outcomes. In one population based study, diabetic women diagnosed with ovarian or endometrial cancer who were taking metformin at the time of diagnosis had half the risk of dying (of all causes) compared to non-metformin users (HR: 0.48, 95% CI: 0.28–0.81) [20]. However, these results did not account for cancer pathology, stage, or treatment, which are important factors to consider given the biologic heterogeneity of endometrial cancer subtypes. Another retrospective study reported improved overall survival in diabetics on metformin with non-endometrioid type cancers compared to non-metformin users and non-diabetics; however they did not report on cancer specific recurrence or progression [21]. Therefore, we sought to investigate the association of metformin use with endometrial cancer-specific and all-cause mortality outcomes.

Methods

A multi-institutional retrospective cohort analysis was performed, comparing endometrial cancer patients who were diabetic and using metformin at the time of their cancer diagnosis to those who were diabetic and not using metformin. We included all patients who were diagnosed with endometrioid, serous, clear cell, and carcinosarcoma endometrial cancers at two tertiary care NCI and NCCN designated academic institutions between 2005 and 2010. Institutional Review Boards approval was granted at both institutions. Patients underwent routine care, which primarily consisted of a hysterectomy and staging surgery by gynecologic oncologists. We designated the primary cohort as diabetic metformin users and the comparator group as diabetics who did not use metformin. For a sub analysis, we created a third cohort of women diagnosed with endometrial cancer but who did not have diabetes.

Demographic, biometric, surgical, pathologic and oncologic data were obtained via electronic medical records. Medication use including metformin, insulin, sulfonamide and thiazolidinedione at the time of cancer diagnosis was recorded. Body mass index was calculated using height and weight at the time of cancer diagnosis. Pathologic review of cases occurred at the weekly tumor board conferences, and cases were reviewed by a gynecologic pathologist. The last follow-up visit was designated as any visit to each of the two respective hospitals. Recurrence data was captured from physician notes, laboratory data and imaging reports. Death data was captured from electronic medical records and from the Social Security Death Index (http://www.genealogybank.com/gbnk/ssdi/). Causes of death were not reliably available for the majority of patients, and therefore point estimates based on death due to disease (endometrial cancer) were not performed.

Cox regression modeling was used to explore associations of selected covariates of interest on the time-to event outcomes of time to time to recurrence (TTR), recurrence free survival (RFS) and overall survival (OS). TTR was defined as the time from the hysterectomy date (or date of cancer diagnosis by biopsy if hysterectomy was not performed) to documented disease recurrence, and therefore deaths occurring in the absence of proven endometrial cancer were censored. RFS was defined as the time from the hysterectomy date (or biopsy date if no hysterectomy) to the date of disease recurrence or death from any cause. OS was defined as the time from the hysterectomy date (or biopsy date if no hysterectomy) to death from any cause. Thus, deaths were counted as events in the RFS and OS estimates, but were treated as a censoring condition for TTR. The Kaplan–Meier method was used to estimate TTR, RFS, and OS curves. The log-rank test was used to test for differences between curve estimates. Fisher's exact test was used to test two-group and/or nominal categorical variable comparisons. The nonparametric Jonckheere–Terpstra method was used to test for significant differences across ordered categories for contingency tables where at least one of the variables was ordinal. The Wilcoxon rank-sum test (using normal scores) was used for continuous variables undergoing two-group comparisons. For Cox proportional hazards modeling estimates, candidate models were pre-specified before analyses based on the effective sample size for each outcome (ten events for each covariate to be included in a model) and clinical relevance. Selection of final models was based on best fit according to information criteria (BIC). Covariates of interest included age, race, BMI (kg/m^2), grade, histology, stage, and adjuvant treatment. Both SAS (v 9.2) and R statistical software were used.

Results

363 women were diagnosed with endometrial cancer and diabetes mellitus, which accounted for 24% of our entire endometrial cancer population (n = 1495). 55% (200/363) patients used metformin. 34% of metformin users were also using sulfonylureas, 18% thiazolidinediones, 15% insulin, and 7% other anti-diabetic agents. Of the non-metformin users, nearly one third (29%) used insulin based regimens (Table 1).

Table 1
Demographic features of endometrial cancer patients with diabetes who were metformin users versus non-metformin users.

	No metformin	Metformin	p-Value
	n = 163	n = 200	
Age (median, IQR)	64.8 (59–73)	62.2 (54–70)	.01
BMI (median, IQR)	36 (31–42)	38 (33–46)	0.004
Race			
Caucasian	96 (59)	137 (69)	0.03
African-American	61 (37)	50 (25)	
Other	6 (4)	13 (7)	
Grade			
I	70 (43)	84 (42)	0.72
II	35 (21)	54 (27)	
III	58 (36)	62 (31)	
Histology			
Endometrioid	127 (78)	153 (77)	0.03
Serous	16 (9)	29 (15)	
Clear cell	6 (4)	8 (4)	
Serous-clear	3 (2)	0 (0)	
Carcinosarcoma	11 (7)	10 (1)	
Stage			
I	133 (82)	153 (76)	0.23
II	6 (4)	7 (4)	
III	18 (11)	31 (16)	
IV	6 (4)	9 (5)	
Adjuvant treatment			
Chemotherapy	31 (20)	46 (25)	0.36
Radiation	42 (27)	58 (31)	0.47
Other diabetes medication			
Sulfonylurea	49 (30)	68 (34)	0.43
TZD	21 (13)	36 (18)	0.19
Insulin	48 (29)	30 (15)	0.001
Other	8 (7)	14 (10)	0.50