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Original Article

Impact of comorbidities on recurrence rates and survival in patients with endometrial cancer

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Abstract

Aim: Endometrial cancer (EC) is mostly seen in elderly population, the impact of comorbid conditions on clinical outcomes and survival of EC is a topic of increasing interest. The aim of this study was to determine the association of diabetes mellitus (DM), hypertension (HT) and metformin use with survival in patients with EC.

Material and Methods: Clinical and tumor characteristics of 410 patients who underwent surgery for EC in our institution between 2006 and 2012 were reviewed. Demographic features, histological subtypes, stage, type of surgery, comorbidities, treatment modalities and patient outcomes in terms of relapse-free survival (RFS) and overall survival (OS) were assessed.

Results: Median follow-up was 39 months. The presence of HT and DM were associated with overall survival after adjusted for age, disease stage and grade (HR for HT 2.88, p=0.055, HR for DM 2.01, p=0.045). Presence of either HT or DM (or both) was independently associated with lower rate of 5 years survival (HR 8.24, p=0.041). Metformin use was not associated with RFS or OS in whole patient population. However, among patients with diabetes, metformin use was associated with improved 5 years survival (p=0.024) but not with RFS (p=0.47).

Conclusion: Our study showed DM and HT to be associated with increased mortality in patients with EC but no link was shown between presence of DM/HT and disease recurrence. Metformin might be the treatment of choice in patients with DM and EC, but beneficial effects are probably through metabolic effects rather than anticancer efficacy.

Keywords: Endometrial cancer; diabetes mellitus; hypertension; survival

INTRODUCTION

Endometrial cancer (EC) is the most common gynecologic malignancy in western countries (1). While the vast majority of women with EC are diagnosed with early-stage tumors that are associated with an excellent prognosis, patients with advanced disease are at increased risk of relapse and death (2). Main predictors of overall and recurrence free survival are age, histological subtype, tumor grade, FIGO stage, and myometrial invasion (3). EC is mostly seen in elderly population, many of whom suffer from additional comorbidities. The contribution of comorbid conditions on clinical outcomes and survival of EC is a topic of increasing interest (4).

Previous studies have shown increased risk of EC in women with diabetes (5-7). Diabetes mellitus (DM) was also found to be associated with decreased survival in patients with EC (4,8-10), however a recent meta-analysis suggested no association between DM and EC mortality (11). The potential biological link between the two diseases is suggested to be related to hyperinsulinemia, hyperglycemia, insulin-like growth factor, and adipocytokines (9). Metformin, an oral antidiabetic drug, suppresses hepatic gluconeogenesis causing decreased serum levels of glucose and insulin. In vitro studies have revealed that the use of metformin may have anti-cancer effects and retrospective studies showed improved survival with metformin use but prospective data is lacking (12-16). The prognostic value of the presence of hypertension (HT) has been less clear in EC. Some studies suggested that HT is associated with decreased survival (4, 17), while others did not (18, 19).

The aim of this study was to determine the association of DM, HT and metformin use with survival in patients with EC treated in our institution.

MATERIAL and METHODS

This study was performed in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee of the university. Clinical and

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tumor characteristics of 410 patients who underwent surgery for primary endometrial cancer in our institution between 2006 and 2012 were retrospectively reviewed. Demographic features, histological subtypes, stage, type of surgery, comorbidities, treatment modalities and patient outcomes in terms of relapse-free survival (RFS) and overall survival (OS) were assessed. Mortality data were obtained from patient files and social security registry. Disease recurrence data were obtained also from patient files and by phone calls in patients who were followed up in other centers.

Descriptive analysis was performed for demographic and clinical characteristics of the patients. Student's t-test or Mann-Whitney U test was used for comparison of numeric variables between two groups. Chi-square test was used for comparison of ratios between the groups. Kaplan–Meier analysis was performed to examine the influence of predefined factors on survival, with the log-rank test used to compare strata. Cox regression analysis was used to conduct multivariate analysis of factors associated with OS and RFS. Entry into the multivariate model was conditional on a P value of <0.2. Statistical analysis was performed with SPSS software version 17.0 (SPSS Inc., Chicago, IL) and statistical significance was set at P less than 0.05.

RESULTS

Patient characteristics are shown in Table 1. Median age was 58. Most of the patients were post-menopausal (70%) and obese (56%), body mass index being >30 kg/m^2. Majority of the patients (97%) were initially treated surgically with comprehensive staging, i.e. total abdominal hysterectomy,bilateral salphingo-oopherectomy, bilateral pelvic and paraaortic lymph node dissection and omentectomy. Of the patients 317 (77%) were Stage I, 32 (8%) were stage II, 55 (13.5%) were stage III, 6 (1.5%) were stage IV. Median follow up was 39 months.

Treatment

Eighty-two patients received adjuvant chemotherapy (paclitaxel and carboplatin in 89 %), 40 patients' external radiotherapy and 35 patient's brachytherapy. Chemotherapy was utilized in 42% of the patients with stage I grade III disease, 47% of the patients with stage II grade III disease, 85% of the patients with stage III disease and all patients with stage IV disease. Variation of chemotherapy utilization was secondary to patient comorbidities, treatment in other oncology centers and variation in our treatment protocol particularly for stage I grade III disease, in which we previously did not use chemotherapy but we do since 2011.

Overall survival

Five-year OS was 88%. Five-year OS was 94% for stage 1, 85% for stage 2, 55% for stages 3 and 4 patients. The presence of HT and DM were associated with overall survival after adjusted for age, disease stage and grade (HR for HT 2.88 (95% CI: 0.98-8.49) p=0.055; HR for DM 2.01 (95% CI: 1.02-4.18) p=0.045) (Figure 1, 2). As patients with DM and HT largely overlapped (85% of patients with

Table 1. Patients characteristics

	N (%)
Age, median (range)	58 (52-66)
BMI (kg/m^2)	31 (26-35)
Tumor size, cm. median (IQR)	3 (2-4)
Ca125 IU/mL median (IQR)	31 (26-35)
Comprehensive staging	397 (97%)
# of lymph nodes dissected, median (IQR)	37 (29-46)
Comorbid diseases	
Hypertension	231(56%)
Diabetes Mellitus	94 (23%)
Metformin use	58 (14%)
Stage	
IA	222 (54%)
IB	95 (23%)
II	32 (8%)
III	55 (13%)
IV	6 (1%)
Histological Type	
Endometrioid	340 (83%)
Serous	38 (9,3%)
Clear cell	5 (1,2%)
Other	27 (6.5%)
Chemotherapy	82 (20%)
Radiotherapy	40 (9,8%)
Brachytherapy	35 (8,5%)

Abbreviations: BMI, body mass index; IQR, interquartile range

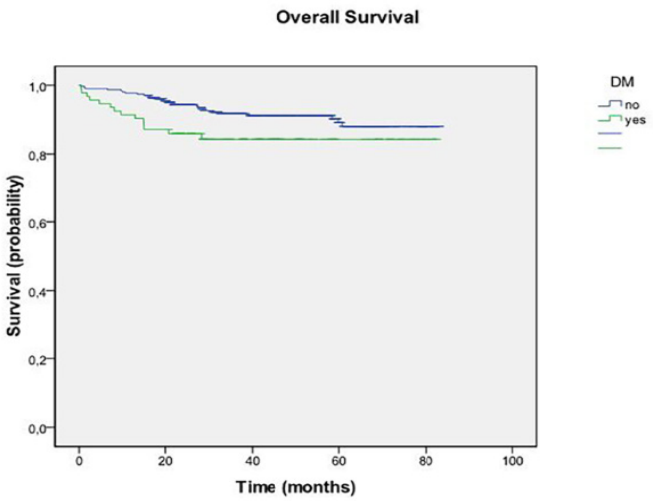

Figure 1. Kaplan-Meier estimates of overall survival, according to DM

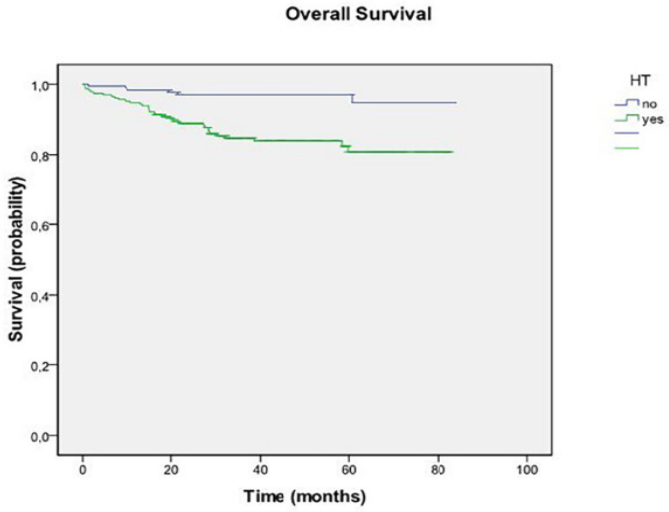

Figure 2. Kaplan-Meier estimates of overall survival, according to HT

Table 2. Multivariate Cox regression analysis of factors associated with overall and disease free survival

	5 yrs RFS (%)	Univariate P	Multivariate P	HR (95% CI)	5 yrs OS (%)	Univariate P	Multivariate P	HR (95% CI)
Age		**0.002**	**0.011**	**1.051 (1.011-1.093)**		**<0.001**	**0.001**	**1.08 (1.03-1.13)**
Stage		**<0.001**				**<0.001**		
I	**96**				**94**			
II	**83**		**0.024**	**5.500 (1.247-24.255)**	**85**		**0.014**	**5.15 (1.40-18.9)**
III-IV	**46**		**0.002**	**6.224 (1.910-20.275)**	**55**		**0.001**	**4.6 (1.85-11.45)**
Grade		<0.001	NS			<0.001	NS	
I-II	94				93			
III	71				74			
Lymphovascular invasion		**<0.001**	**0.042**	**3.639 (1.050-12.611)**		<0.001	NS	
Yes	**96**				92			
No	**67**				72			
CA-125		<0.001	NS			0.003	NS	
Normal	94				90			
High	74				78			
HT or DM		0.011						
Absent	94				**95**	**<0.001**	**0.041**	**8.24 (1.09-62.56)**
Present	85				**82**			
Metformin use		0.361	NS			0.81		
Yes	85				88			
No	89				91			

Abbreviations: HT, hypertension; DM, diabetes mellitus; RFS, relapse-free survival:; OS, overall survival; NS, not significant

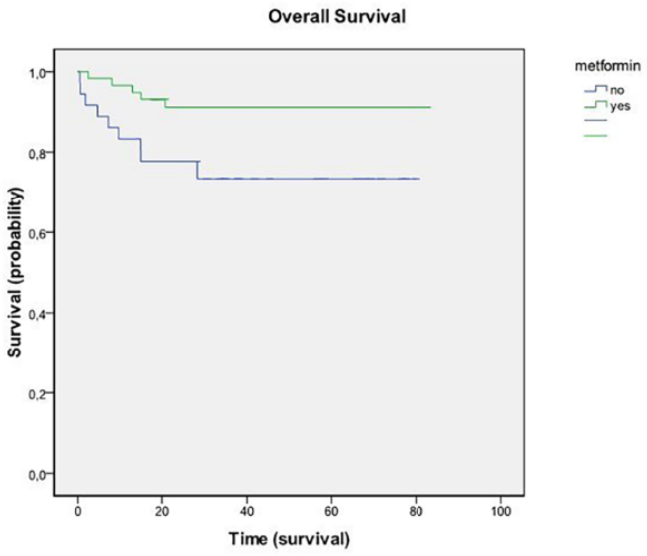

Figure 3. Kaplan-Meier estimates of overall survival, according to Metformin use among diabetic patients

DM also had HT and 35% of those with HT also had DM), presence of HT or DM was jointly included in multivariate analysis as a single variable, which subsequently showed that presence of either disease (or both) was independently associated with lower rate of 5 years survival (HR 8.24, 95% CI 1.09-62.56, p=0.041). Other independent predictors of survival in multivariate analysis were age (p=0.001) and disease stage (p=0.014) (Table 2).

Relapse-free survival

Five-year RFS was 89%. Five-year RFS was 96% for stage 1, 83% for stage 2, 46% for stages 3 and 4 patients. In multivariate analysis, significant independent predictors of RFS were age (p=0.011), disease stage (p=0.024 for stage II vs. stage I and p=0.002 for stage III-IV vs stage I) and presence of lymphovascular invasion. (p=0.042). When adjusted for disease stage and grade, neither adjuvant chemotherapy nor radiotherapy/brachytherapy was associated with RFS or OS.

Metformin

Of the patients 58 (14%) were on metformin (all were diabetic patients) and 352 patients were not on metformin. Five-year RFS of metformin group was %89 whereas RFS of non-metformin group was 85% (p=0,361). Five-year OS was %88 in metformin group however it was 91% in non-metformin group (p=0,81).

Totally there were 94 diabetic patients and 62% (n=58) of them were on metformin. Among patients with diabetes, metformin use was associated with improved 5-year overall survival (91% in metformin users vs 73% in non-users, p=0.024) but not with RFS (85% in metformin users vs 93% in non-users, p=0.47) (Figure 3). According to this results, metformin use was not associated with RFS or OS in whole patient population but OS was significant in diabetic group only.

DISCUSSION

In this study, we found that presence of DM and HT was associated with worse OS, but not RFS in patients with EC. The use of metformin was not associated with OS and RFS, but in the subgroup of patients with DM, it was associated with better OS but not with RFS.

Classical prognostic factors for endometrial cancer are disease stage, tumor histology, vascular space invasion, nuclear grade and age. Various other factors including hormone receptor status, tumor size and DNA ploidy were also found to be associated with prognosis. Being a disease of the elderly, comorbidities are also important in treatment planning and survival of these patients. Older age and comorbidities may preclude ability to receive definitive treatment, other issues including increased toxicity as well as increased frequency of noncancerous deaths are of concern. Biology of the disease also tends to be more aggressive in the elderly (20).

Previous studies have shown that the risk of various cancers including breast cancer, colorectal cancer, pancreatic cancer, ovarian cancer as well as endometrial cancer is increased in diabetic patients (21-24). Metabolic syndrome also confers high risk of endometrial cancer with obesity having the highest hazard ratio (25). It is suggested that abnormal metabolic, immunologic, and hormonal characteristics of DM may promote cancer development. Growth and proliferation of tumor cells, which usually contain insulin and IGF receptors, are stimulated by insulin and insulin-like growth factors or adipocytokines by activating mitogenic and antiapoptotic pathways (26).

Data on the effect of diabetes on EC mortality is conflicting. A number of studies have shown increased mortality in patients with diabetes while the others have not. All studies were based on self-reported diabetes diagnosis, which was previously shown to reflect physician diagnosis. Effect of DM on disease recurrence was not assessed in most of the studies. Zanders et al found lower overall survival but not EC specific survival in diabetic patients with EC (9). Folsom et al found increase in both overall and EC specific mortality in diabetic women compared with non-diabetic ones. Longer duration of diabetes increased the risk further (18). Another study also found that DM adversely affected OS but disease specific survival was not assessed in this study (4). A number of other previous studies also verified these findings showing association with DM and higher overall mortality (19, 27, 28) Population attributable risk estimates imply that 9% of the mortality after endometrial cancer might be diabetes related (18). Disease specific mortality was only assessed in few studies. A recent meta-analysis reviewed 21 studies and found no increased mortality from EC in patients with DM. However, as the authors stated, many potential confounding factors were not assessed including metformin use, age and BMI and great heterogeneity existed for population demographics, study design, duration of follow-up, and adjustment

for confounders (11). Disease specific mortality is difficult to assess if active follow up is not performed and may result in inconsistencies between studies. Our study also showed that diabetes was associated with mortality but not disease recurrence. These findings suggest that diabetic patients might have an increased mortality rate from noncancerous causes, however the effect of DM on disease outcome and disease specific mortality is less marked. Patients with DM may receive suboptimal treatment because of hyperglycemia, renal dysfunction or other diabetic complications. Furthermore, aforementioned hormonal and metabolic factors may imply a more aggressive disease course besides increased incidence of EC. But our data showed that these factors do not have significant influence on disease outcome, which might be elucidated in appropriately designed prospective trials.

We found metformin use was associated with improved overall survival among patients with diabetes. However no association with RFS in whole population or diabetic patients was found. Metformin decreases insulin resistance and hyperinsulinemia, suppresses signaling through the mTOR pathway and may increase sensitivity to some chemotherapeutics (16). Preclinical studies showed inhibition of EC cell lines with metformin but clinical data is lacking (13). A recent metaanalysis showed that metformin was associated with improved OS and cancer-specific survival in patients with cancer and concurrent type 2 DM (29). The benefit was mostly pronounced in breast and colorectal cancer. Only one study reported improved OS with metformin use in patients with EC and DM but these data were obtained from social security death registry and disease recurrence rates and cancer-specific mortality were not reported. Our study is unique in that it evaluates RFS as well as OS in a homogenous patient population. Therefore improvement in OS without any change in RFS suggests that the benefit observed in metformin users may be due to lower risk of death secondary to noncancerous causes in patients with EC rather than anticancer effects of metformin. Metformin is actually associated with improved OS in diabetic patients without cancer. In a recent substudy from the Sibutramine Cardiovascular Outcomes trial which included 8192 overweight patients with type 2 diabetes, metformin monotherapy was associated with lower mortality as well as lower risk of nonfatal myocardial infarction, nonfatal stroke and resuscitation after cardiac arrest when compared with insulin (31). Similarly, The UK Prospective Study Group also showed that all-cause mortality was reduced by 36% in patients using metformin compared with patients treated with insulin or sulfonylurea (30). Therefore prospective studies are needed to delineate whether metformin truly has clinical anti-cancer activity in patients with EC.

Data on the influence of HT on EC survival is scarce. Hypertension is a component of metabolic syndrome, which is known to be associated with higher risk of EC and increased EC mortality (18, 13). Nicholas et al found HT to be independently associated with poorer OS (4). Folsom et al suggested that HT, DM and large waist circumference together predicted increased mortality while HT alone did not (18). Kauppila et al found higher mortality in patients with diabetes and hypertension (19). In our analysis, HT was associated with OS but not with RFS when adjusted for age, stage and grade. As patients with DM and HT largely overlapped, we used the presence of DM and/or HT as a combined variable in multivariate analysis and showed that it significantly predicted OS. As patients with DM and HT largely overlapped, common mechanisms may account for the increased mortality.

The strengths of our study are inclusion of relatively high number of patients treated within a recent and short period of time (410 pts between 2007 and 2012) and with a sufficient follow-up period of 39 months. All patients were operated by the same surgical team and 97% were comprehensively staged. Presence of hypertension, obesity and metformin use were assessed together, along with disease stage, grade, age and histology as potential predictors of mortality. Limitations are the retrospective design, and heterogenous treatment protocols in patients within the same stage. However neither chemotherapy nor radiotherapy had significant prognostic value in multivariate analysis, rendering these differences to account for the differences in mortality unlikely.

CONCLUSION

In conclusion, our study confirms the findings of previous studies that showed DM and HT to be associated with increased mortality in patients with EC but no link was shown between DM/HT and disease recurrence. Metformin might be the treatment of choice in patients with DM and EC, like in those without EC, but beneficial effects are probably through metabolic effects rather than anticancer efficacy. Prospective studies are needed to elucidate the efficacy of metformin in EC patients with or without DM.

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