Clin Transl Oncol (2015) 17:835–839
DOI 10.1007/s12094-015-1309-8

BRIEF RESEARCH ARTICLE

Metabolic syndrome is an independent prognostic factor for endometrial adenocarcinoma

J. Ni[1] · T. Zhu[1] · L. Zhao[1] · F. Che[1] · Y. Chen[1] · H. Shou[1] · A. Yu[1]

Received: 11 April 2015 / Accepted: 23 May 2015 / Published online: 11 August 2015

Abstract
Objective To study the association between metabolic syndrome (MS) and the prognosis of patients with endometrial adenocarcinoma.
Methods A total of 385 patients with endometrial adenocarcinoma in the Department of Gynecologic Oncology, at the Zhejiang Cancer Hospital in China, between January 2001 and December 2008 were chosen. The deadline for the completion of follow-up was December 2013. The overall survival (OS) of the patients with MS was analyzed by the Kaplan–Meier method. Various clinical characteristics (e.g., clinical and surgical stage, vascular invasion, histological grade, tumor size, age at start of the first treatment, and lymphatic metastasis) related to the prognosis of endometrial adenocarcinoma were also evaluated.
Results A univariate analysis demonstrated that the OS rate of the patients with endometrial adenocarcinoma with MS was significantly worse than that of the patients without MS for all 385 patients ($P = 0.001$). Multivariate Cox proportional hazards regression analyses showed that stage ($P = 0.001$), lymphatic metastasis ($P = 0.021$), and MS ($P = 0.049$) were independent prognostic factors for endometrial adenocarcinoma. Furthermore, statistical analyses demonstrated that MS was closely related to stage ($P = 0.021$), grade ($P = 0.022$), vascular invasion ($P = 0.044$), tumor size ($P = 0.035$), and lymphatic metastasis ($P = 0.014$) but not with age at start of the first treatment ($P = 0.188$). Finally, according to the univariate analysis of the OS rate of 129 cases of endometrial adenocarcinoma with MS, stage ($P = 0.001$), vascular invasion ($P = 0.049$), tumor size >2 cm ($P = 0.028$), lymphatic metastasis ($P = 0.002$), and CA19-9 value >37 U/m ($P = 0.002$) all showed significantly low P values for OS.
Conclusion Metabolic syndrome is an independent prognostic factor for endometrial adenocarcinoma.

Keywords Endometrial adenocarcinoma · Metabolic syndrome · Prognosis

Introduction

Endometrial carcinoma (EC) is one of the most common gynecological malignancies. Surprisingly, the incidence rate of EC has continued to increase in both developing and developed countries [1]. The exact pathogenesis is still unclear despite advances in modern medicine, and most scholars believe that EC, especially endometrial adenocarcinoma (type I), is related to a series of endocrine and metabolic disorders [2–4].

Metabolic syndrome (MS), including obesity, hypertension, insulin resistance, diabetes, and dyslipidemia, increases the risk of developing multiple types of cancer, including liver, colorectal, and bladder cancers in men, and endometrial, pancreatic, breast post-menopausal, and colorectal cancers in women [5–7]. However, the role played by each single component of the syndrome on cancer risk is still unclear. For endometrial cancer, obesity and/or high circumference waist explain all the risk associated with the full metabolic syndrome. Observations that link blood

H. Shou and A. Yu have contributed equally to this work.

✉ H. Shou
hfshou@126.com

✉ A. Yu
yaj1993@126.com

[1] Department of Gynecologic Oncology, Zhejiang Cancer Hospital, 38 Guangji Road, Hangzhou 310022, People's Republic of China

pressure, glucose metabolism, and insulin resistance to endometrial cancer have come mostly from retrospective studies. These retrospective studies have provided less conclusive results because of self-reported disease history and anthropometry or an absence of adjustment for body mass. In fact, many metabolic disorders may influence estrogen/progesterone levels and expose women to a permanent hormonal imbalance, which may increase the risk of malignant endometrial changes. However, few reports on the relationship between MS and the prognosis of endometrial adenocarcinoma exist in the literature. This retrospective study compared the prognosis of patients with endometrial adenocarcinoma who also have MS with that of patients who only have EC. At the same time, we assessed the relationship between MS and clinicopathological features of patients with endometrial adenocarcinoma.

Materials and methods

A total of 385 patients with histologically confirmed endometrial adenocarcinoma (type I) were selected from January 2001 to December 2008 at the Department of Gynecologic Oncology, Zhejiang Cancer Hospital, in China. The study protocol was approved by the Ethics Committee of Zhejiang Cancer Hospital, and informed consent was obtained from each patient enrolled in the study. The median age at the start of the first treatment was 55.0 years (range 40–72 years). Patients were divided into two groups based on the presence of comorbidities (Group 1: EC and MS, Group 2: EC alone). We selected all patients with International Federation of Gynecology and Obstetrics (FIGO) stages I, II, III, and IV according to the 2009 version of the FIGO staging system. Overall survival (OS) was defined as the time from the date of surgery to the date of the last follow-up examination or death. The follow-up deadline was December 2013. The range of the follow-up period was 2–144 months. None of the patients had any other malignant tumors and none used oral contraceptives (OC) or hormone replacement therapy (HRT) for at least a year before admission. They had all undergone laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, or retroperitoneal lymphadenectomy therapy. Adjuvant treatment was recommended after surgery depending on surgical findings and disease stage. Self-reported information on height and weight at different ages was collected. Waist circumference (2 cm above the umbilicus) was also measured. A history of medical conditions, including type 2 diabetes, clinical obesity, drug-treated hypertension, and drug-treated or clinical diagnosis of hyperlipidemia, was self-reported and included age at first diagnosis. Patients with diseases with an onset <1 year before hospital admission were not considered for this study. Body mass index (BMI) was calculated according to Quetelet's index (weight/height^2, kg/m^2). The values of CA19-9 and CA125 were pre-surgery values.

MS was defined as a combination of the presence of the following: (1) type 2 diabetes (2) history of drug-treated hypertension (as an alternative indicator of elevated blood pressure), (3) history of a clinical diagnosis of or drug-treated hyperlipidemia [as a proxy indicator of increased low-density lipoprotein/reduced high-density lipoprotein (HDL) cholesterol levels], and (4) (abdominal) obesity. Using different proposed definitions of MS, (abdominal) obesity was defined as a waist circumference $\geq$80 cm or BMI $\geq$28 kg/m^2 for women who did not provide their waist circumference. A summary indicator of MS was also defined according to the International Diabetes Federation criteria, and was adapted to our data, as the simultaneous presence of (abdominal) obesity plus at least two other components of MS [8].

Results

We first analyzed the correlation between MS and OS in endometrial carcinoma using the Kaplan–Meier method and compared the survival curves using the log-rank test. Of the 385 patients, 129 patients with endometrial adenocarcinoma also had MS, while 256 patients had endometrial adenocarcinoma but did not have MS. The OS rate among patients with MS was 74.42 % (96/129), and the OS rate among patients without MS was 87.89 % (225/256). A univariate analysis demonstrated that the OS rate among the patients with endometrial adenocarcinoma and MS was significantly worse than that among the patients without MS for all 385 samples ($P = 0.001$) (Fig. 1). Furthermore, multivariate Cox proportional hazards regression analyses showed that stage ($P = 0.001$), lymphatic metastasis ($P = 0.021$), and MS ($P = 0.049$) were independent prognostic factors for endometrial adenocarcinoma (Table 1). These results suggest that MS is a prognostic factor for endometrial adenocarcinoma patients.

To investigate the significance of MS in endometrial adenocarcinoma, we next compared the relationship between MS and clinicopathological features. Statistical analyses demonstrated that MS was closely related to the FIGO stage ($P = 0.021$), grade ($P = 0.022$), vascular invasion ($P = 0.044$), tumor size ($P = 0.035$), and lymphatic metastasis ($P = 0.014$) but not with age at the start of the first treatment (Table 2). These results suggest that MS may be associated with multiple clinicopathological features in endometrial adenocarcinoma.

Finally, in the univariate analysis of the OS rate among the 129 patients with endometrial adenocarcinoma and MS, higher stage ($P = 0.001$), vascular invasion ($P = 0.049$),

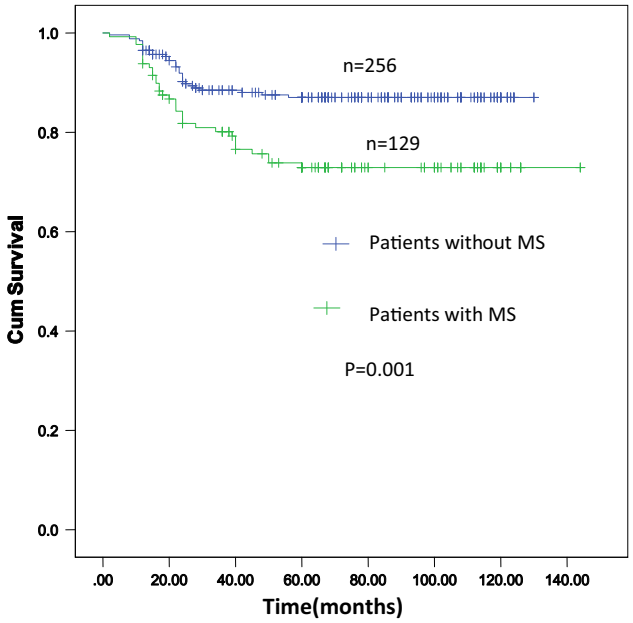

Fig. 1 Univariate analyses of factors that were associated with OS in patients with and without MS according to the Kaplan–Meier method and the log-rank test

Table 1 Multivariate analyses of the factors that were associated with OS in the patients with endometrial adenocarcinoma according to a Cox proportional hazard regression model performed in a stepwise manner (forward: condition, entry $\alpha = 0.05$, stay $\alpha = 0.1$)

Variable	OS hazard ratio (95 % CI)	*P* value
Stage	2.354 (1.399–3.959)	0.001**
Lymphatic metastasis (yes vs no)	1.989 (1.108–3.569)	0.021*
MS (yes vs no)	6.649 (1.925–47.791)	0.049*

* $P < 0.05$; ** $P < 0.01$

tumor size >2 cm ($P = 0.028$), lymphatic metastasis ($P = 0.002$), and CA19-9 >37 U/ml ($P = 0.002$) all showed significantly low *P* values for OS (Table 3). These results suggest that MS in particular may negatively affect the prognosis of human endometrial adenocarcinoma to a greater extent than the stage, vascular invasion status, tumor size, lymph node status, and CA19-9 value.

Discussion

On the basis of differences in histology and clinical outcomes, ECs have long been divided into two types [9–11]. Type I tumors, comprise the large majority of ECs, are mostly endometrial adenocarcinomas, are associated with unopposed estrogen stimulation, and are often preceded by endometrial hyperplasia. Type II tumors, are predominantly

Table 2 Relationship between MS and clinicopathological features of patients with endometrial adenocarcinoma

Variable	MS		χ^2 value	*P* value
	No ($n = 256$)	Yes ($n = 129$)		
Stage			7.768	0.021*
I	174	70		
II	38	23		
III + IV	44	36		
Grade			7.661	0.022*
G1	92	30		
G2	112	61		
G3	52	38		
Vascular invasion			4.05	0.044*
No	211	95		
Yes	45	34		
Tumor size >2 cm			4.446	0.035*
No	171	72		
Yes	85	57		
Age at start of the first treatment			1.735	0.188
Age ≤60 years	103	43		
Age >60 years	153	86		
Lymphatic metastasis			5.988	0.014*
No	212	93		
Yes	44	36		

* $P < 0.05$; ** $P < 0.01$

serous carcinomas, are commonly described as estrogen-independent, arise in atrophic endometrium, and are derived from intraepithelial carcinoma, a precancerous lesion. Many studies have shown that multiple factors characterize the initiation, development, and poor prognosis of endometrial cancers [12]. Thus, it is urgent to find new prognostic factors that are involved in EC to improve the survival of patients.

MS is a cluster of risk factors including obesity, hypertension, insulin resistance, and dyslipidemias for cardiovascular disease and type 2 diabetes and constitutes a growing problem worldwide [13].

Individual components of MS have previously been linked to the development of various types of cancer. Evidence has begun to emerge that links MS with certain types of cancer [14, 15], but data are still sparse [16, 17]. Cust et al. [18] recently reported on MS and the risk of EC in a case–control study nested within the European Prospective Investigation into Cancer and Nutrition. MS was found to be directly associated with endometrial cancer, and the risk increased with the number of MS factors present. A large prospective study also showed direct associations between MS, as well as between individual MS factors (except for cholesterol), and the risk of endometrial carcinoma. This study offers further evidence

Table 3 Univariate analysis of the OS rate among the patients with endometrial adenocarcinoma and MS

Clinicopathological factor	OS		χ^2 value	*P* value
	Yes	No		
Stage			18.393	0.001**
I	60	10		
II	16	7		
III + IV	20	16		
Grade			2.932	0.087
G1 + G2	71	20		
G3	25	13		
Vascular invasion			3.883	0.049*
No	75	20		
Yes	21	13		
Tumor size >2 cm			4.848	0.028*
No	59	13		
Yes	37	20		
Age at start of the first treatment			2.932	0.087
Age ≤60 years	28	15		
Age >60 years	68	18		
Lymphatic metastasis			9.333	0.002**
No	76	17		
Yes	20	16		
CA19-9 value			9.763	0.002**
≤37 U/ml	72	15		
>37 U/m	24	18		
CA125 value			3.588	0.058
≤35 U/ml	72	19		
>35 U/ml	24	14		

* $P < 0.05$; ** $P < 0.01$

that the influence of MS with respect to the risk of EC extends beyond the risk conferred by obesity alone, particularly in women with a high BMI [19]. Our results confirmed that MS may be incorporated into the screening of individuals for endometrial adenocarcinoma [20]. However, the prognostic value of MS in human endometrial adenocarcinoma remains unknown.

It is generally accepted that the factors that affect the prognosis of EC include age, grade, vascular and myometrial invasion, tumor size, and lymph node status. In the current study, we attempted to determine the association between MS and the prognosis of endometrial adenocarcinoma. A univariate analysis demonstrated that MS significantly affected the prognosis of endometrial adenocarcinoma. Furthermore, through an analysis of the correlation between different variables and OS, we found that MS was an independent prognostic factor for endometrial adenocarcinoma. This result was consistent with the findings of Bjorge T., who examined the association between MS and the risk of fatal uterine corpus cancer in a large prospective cohort study. Approximately 290,000 women from Austria, Norway, and Sweden were enrolled during the years 1974–2005. They found an increased risk of fatal uterine corpus cancer in women with MS [relative risk = 1.56, 95 % confidence interval (CI): 1.32, 1.84] [19].

The mechanisms that link MS and endometrial adenocarcinoma are not fully understood. Mechanisms that may contribute to the adverse impact of MS and its components on the risk of endometrial carcinoma include insulin resistance [21–24], a proinflammatory milieu that favors the development of neoplastic transformation [24], and mechanisms related to the metabolism of sex steroids [25].

To explore the manner in which MS affects the prognosis of endometrial carcinoma, we compared the relationship between MS and the clinicopathological features of patients with endometrial adenocarcinoma. We found that the presence of the following factors was significant when they were individually evaluated in patients with endometrial adenocarcinoma and MS: higher stages, low differentiation, vascular invasion, tumor size >2 cm, and lymphatic metastasis. MS may be an important etiologic factor in the development and progression of endometrial adenocarcinoma, as well as in overall cancer mortality. But the causation between MS and these clinicopathological features is open to speculation.

In clinical practice, we sometimes encounter patients with endometrial adenocarcinoma and MS whose prognosis is rather favorable. To determine what factors may predict a favorable outcome, we analyzed 8 clinicopathological prognostic factors in patients with endometrial adenocarcinoma and MS. Most of the factors that were examined in this analysis were shown to have a significant effect on the prognosis of endometrial adenocarcinoma. However, we initially conjectured that MS may be such a critical prognostic factor that none of the other clinicopathological factors would be significant in our case analysis. In fact, according to the univariate analysis of the clinicopathological prognostic factors in endometrial adenocarcinoma cases with MS, higher stage, vascular invasion, tumor size >2 cm, lymphatic metastasis, and CA19-9 values >37 U/ml were the factors that showed significantly low *P* values for OS. Therefore, the absence of these factors suggests a relatively favorable prognosis in patients with endometrial adenocarcinoma and MS.

However, the current study is limited because of its retrospective nature and because of the all Chinese patient population. In addition, further work, such as a prospective study and an investigation of the associated molecular mechanisms, should be performed to clarify issues that were not explored in this study. Moreover, we should treat patients in a different way based on the presence of MS.

In conclusion, we clarified that MS is associated with FIGO stage, grade, vascular invasion, tumor size, and lymphatic metastasis. We also confirmed that MS leads to a poor outcome in patients with endometrial adenocarcinoma. Moreover, MS is an independent prognostic factor in patients with endometrial adenocarcinoma. Thus, MS potentially offers clinical value in the personal treatment of patients with endometrial adenocarcinoma.

Acknowledgments This work was supported by the Medical Science Project of Zhejiang Province (No. 2013KYB045).

Conflict of interest All authors confirm that they have no conflicts of interest.

References

1. Furberg AS, Thune I. Metabolic abnormalities (hypertension, hyperglycemia and overweight), lifestyle (high energy intake and physical inactivity) and endometrial cancer risk in a Norwegian cohort. Int J Cancer. 2003;104(6):669–76.
2. Kim JJ, Chapman-Davis E. Role of progesterone in endometrial cancer. Semin Reprod Med. 2010;28(1):81–90.
3. Bjørge T, Engeland A, Tretli S, Weiderpass E. Body size in relation to cancer of the uterine corpus in 1 million Norwegian women. Int J Cancer. 2007;120(2):378–83.
4. Setiawan VW, Yang HP, Pike MC, McCann SE, Yu H, Xiang YB, et al. Type I and II endometrial cancers: have they different risk factors? J Clin Oncol. 2013;31(20):2607–18.
5. Friedenreich CM, Biel RK, Lau DC, Csizmadi I, Coumeya KS, Magliocco AM, et al. Case–control study of the metabolic syndrome and metabolic risk factors for endometrial cancer. Cancer Epidemiol Biomarkers Prev. 2011;20:2384–95.
6. Rosato V, Zucchetto A, Bosetti C, Dal Maso L, Montella M, Pelucchi C, et al. Metabolic syndrome and endometrial cancer risk. Ann Oncol. 2011;22:884–9.
7. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care. 2012;35(11):2402–11.
8. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A consensus statement from the international diabetes federation. Diabet Med. 2006;23:469–80.
9. Sherman ME. Theories of endometrial carcinogenesis: a multidisciplinary approach. Mod Pathol. 2000;13(3):295–308.
10. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15(1):10–7.
11. Emons G, Fleckenstein G, Hinney B, Huschmand A, Heyl W. Hormonal interactions in endometrial cancer. Endocr Relat Cancer. 2000;7(4):227–42.
12. Hecht JL, Mutter GL. Molecular and pathologic aspects of endometrial carcinogenesis. J Clin Oncol. 2006;24(29):4783–91.
13. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640–5.
14. Zhou JR, Blackburn GL, Walker WA. Symposium introduction: metabolic syndrome and the onset of cancer. Am J Clin Nutr. 2007;86(3):s817–9.
15. Cowey S, Hardy RW. The metabolic syndrome: a high-risk state for cancer? Am J Pathol. 2006;169(5):1505–22.
16. Lund Haheim L, Wisløff TF, Holme I, Nafstad P. Metabolic syndrome predicts prostate cancer in a cohort of middle-aged Norwegian men followed for 27 years. Am J Epidemiol. 2006;164(8):769–74.
17. StürmerT Buring JE, Lee IM, Gaziano JM, Glynn RJ. Metabolic abnormalities and risk for colorectal cancer in the physicians' health study. Cancer Epidemiol Biomarkers Prev. 2006;15(12):2391–7.
18. Cust AE, Kaaks R, Friedenreich C, Bonnet F, Laville M, Tjønneland A, et al. Metabolic syndrome, plasma lipid, lipoprotein and glucose levels, and endometrial cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr Relat Cancer. 2007;14(3):755–67.
19. Bjørge T, Stocks T, Lukanova A, Tretli S, Selmer R, Manjer J, et al. Metabolic syndrome and endometrial carcinoma. Am J Epidemiol. 2010;171(8):892–902.
20. ShouHF Ni J, Zhu T, Chen JH, Zhang X, Xu XX, et al. Association between endometrial cancer and metabolic syndrome. Zhonghua Fu Chan Ke Za Zhi. 2010;45(2):128–31.
21. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Manson JE, Li J, et al. A prospective evaluation of insulin and insulin-like growth factor-I as risk factors for endometrial cancer. Cancer Epidemiol Biomarkers Prev. 2008;17(4):921–9.
22. Cust AE, Allen NE, Rinaldi S, Dossus L, Friedenreich C, Olsen A, et al. Serum levels of C-peptide, IGFBP-1 and IGFBP-2 and endometrial cancer risk; results from the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2007;120(12):2656–64.
23. Lukanova A, Zeleniuch-Jacquotte A, Lundin E, Micheli A, Arslan AA, Rinaldi S, et al. Prediagnostic levels of C-peptide, IGF-I, IGFBP -1, -2 and -3 and risk of endometrial cancer. Int J Cancer. 2004;108(2):262–8.
24. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer. 2004;4(8):579–91.
25. Rapp K, Schroeder J, Klenk J, Ulmer H, Concin H, Diem G, et al. Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. Diabetologia. 2006;49(5):945–52.