Pathol. Oncol. Res. (2016) 22:501–504
DOI 10.1007/s12253-015-0030-9

ORIGINAL ARTICLE

Serum Sialyl-Tn (STN) as a Tumor Marker in Patients with Endometrial Cancer

Yasunori Hashiguchi[1] · **Mari Kasai**[1] · **Takeshi Fukuda**[1] · **Tomoyuki Ichimura**[1] · **Tomoyo Yasui**[1] · **Toshiyuki Sumi**[1]

Received: 31 July 2015 / Accepted: 14 December 2015 / Published online: 17 December 2015

Abstract There are no potential tumor markers validated for prognosis of endometrial cancer. However, sialyl Tn (STN) is a carbohydrate antigen that is associated with the production of mucin, which reportedly plays important roles in carcinogenesis. Although STN expression in endometrial cancer has been investigated, its prognostic value remains controversial and no studies have investigated serum STN levels in large case series. In this study, we investigated diagnostic and prognostic applications of serum STN for endometrial cancer. Between January 2006 and December 2012, serum STN levels were examined prospectively in patients with endometrial cancer. A total of 146 patients (stage I, 98; stage II, 15; stage III, 17; stage IV, 16) were treated for endometrial cancer. The median age was 60 years (28–83). Subsequently 29 patients (19.9%) relapsed at the time of the last follow-up and the median follow-up time was 44 months (1–83). Elevated serum STN levels were identified in 36 patients (24.7%) and were associated with histological grade ($p = 0.02$) and lymph node metastasis ($p = 0.006$). Elevated serum STN levels were not related to histological types, clinical stages, myometrial invasions, distant metastases, age, menopausal status, body mass index, or relapse. Among the 36 patients with elevated serum STN levels, 33 (91.7%) achieved remission and serum STN levels returned to the normal range. Seven patients (21.2%) with elevated serum STN levels at baseline relapsed and their serum STN levels were again elevated. Serum STN levels are a potential prognostic indicator for endometrial cancer.

✉ Yasunori Hashiguchi
cbl37090yh@nifty.com

[1] Department of Obstetrics and Gynecology, Osaka City University, Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan

Keywords Serum sialyl Tn level · Endometrial cancer · Tumor marker

Introduction

Endometrial cancer is the most common cancer of the female genital tract, and its incidence is increasing globally. Although several biomarkers have been associated with clinical characteristics and prognosis in endometrial cancer [1–5], none have been implemented in clinical practice. Therefore, novel biomarkers for endometrial cancer are required.

Sialyl Tn (STN) is a carbohydrate antigen that is associated with the production of mucins, which play important roles in the carcinogenesis of various malignancies [6]. Overexpression of STN follows premature sialylation of core carbohydrate structures, which blocks further elongation of oligosaccharide chains [7]. Overexpression of STN has been reported in colorectal, pancreatic, gastric, breast, and ovarian cancers [7–11], and its presence in serum has been identified as an independent indicator of poor prognosis for patients with gastric, colorectal, and ovarian cancers [9].

Although STN expression has been investigated in endometrial cancer, controversy continues to revolve around its associations with this malignancy. Semczuk A et al. reported that STN was expressed in most endometrial cancers and is suppressed in normal and hyperplastic human endometrium [12]. In addition, Ohno S et al. correlated overexpression of STN with poor prognoses [6]. However, Numa F et al. reported no STN expression in endometrial carcinomas [13]. Furthermore, serum STN levels have been investigated in only a few small studies of patients with endometrial cancer [14], and no large studies of endometrial cancer report STN levels.

In this study, we investigated the diagnostic and prognostic value of serum STN levels in patients with endometrial cancer.

Materials and methods

This prospective study was approved by the Osaka City University, Graduate School of Medicine Institutional Review Board. Available electronic medical records from January 2006 to December 2012 were reviewed, and serum STN levels and clinicopathological features were analyzed in patients with endometrial cancer. Patients with co-existing malignant disease were excluded from analyses.

Clinical management of endometrial cancer in our institution was performed by gynecologic oncologists and diagnoses were established by curettage. All patients were clinically and/or surgically classified according to the International Federation of Gynecology and Obstetrics (FIGO) surgical staging system (2008) [15]. Histological diagnoses were confirmed using microscopic examinations of hematoxylin- and eosin-stained sections according to the World Health Organization criteria. In operable cases, patients received total abdominal or radical hysterectomy plus bilateral salpingo-oophorectomy. Peritoneal fluid samples were obtained for cytological testing, and systemic pelvic lymphadenectomy was performed in most cases. Para-aortic lymph node sampling was performed in patients with intermediate or high risk disease. In patients without lymph node adenectomy, lymph nodes of >1cm were detected using computed tomography (CT) and/or resonance imaging (MRI) and were considered positive lymph nodes. After surgery, adjuvant chemotherapy was provided for patients with intermediate or high risk disease. No hormonal therapies or targeted treatments such as monoclonal antibodies or tyrosine kinase inhibitors were administered. Patient treatments were followed with gynecologic examinations including trans-vaginal and/or abdominal ultrasonography and cytological testing of vaginal cut edges, and laboratory examinations including assessments of tumor marker expression. Further CT and/or MRI examinations were performed for patients with clinically suspicious symptoms and/or elevated tumor marker levels. Recurrent disease was diagnosed using biopsy or imaging methods.

Serum STN levels were measured before therapy during pre-treatment examinations. A lower level of 45 U/ml was used as the cut-off for normal values of serum STN levels. In patients with elevated baseline serum STN levels, these were measured again during treatment and at scheduled follow-up examinations.

Statistical analysis

Relationships between clinical groups were analyzed using Fisher's exact probability test. In the analyses of disease relapse, survival distributions were calculated using the Kaplan–Meier method, and relapse-free patients included those with no evidence of disease recurrence and those who died due to unrelated causes. Univariate and multivariate Cox regression analyses were used to identify variables associated with relapse-free survival and associations were considered significant when $p < 0.05$.

Results

Clinical characteristics of patients with endometrial cancer

During the study period, a total of 146 patients (stage I, 98; stage II, 15; stage III, 17; stage IV, 16) were treated for endometrial cancer. The median age was 60 years (28–83) and histology types included 132 endometrioid adenocarcinomas, four serous cancers, three carcinosarcomas, three mucinous cancers, two adenosquamous carcinomas, one clear cell carcinoma, and one small cell carcinoma). Histological grades were defined as grades 1, 2, and 3 in 48, 56, and 42 cases, respectively. Surgery was performed as primary therapy in 143 cases (97.9%) and chemotherapy was performed in three inoperable cases (2.1%). Surgery included total abdominal or radical hysterectomy plus bilateral salpingo-oophorectomy in 141 patients (96.6%) and additional lymphadenectomy was performed in 120 patients (82.2%). Para-aortic lymph node biopsies were performed in 16 patients (11.2%) and tumor biopsies were taken from two patients (1.4%) with advanced disease. After surgery, adjuvant chemotherapy was provided for 99 patients (67.8%) with intermediate or high risk disease, and included paclitaxel and carboplatin therapy (TC) in 84 patients, docetaxel and carboplatin therapy (DC) in 10 patients, and docetaxel and cisplatin therapy (DP) in five patients. TC therapy was provided for three inoperable cases, and 29 patients (19.9%) experienced disease relapse at the time of the last follow-up. The median follow-up time for all patients was 44 months (1–83).

Serum STN level in patients with endometrial cancer

Serum STN levels and clinical characteristics are shown in Table 1. Elevated serum STN levels were detected in 36 patients (24.7%), and were significantly more elevated in patients with histological grade 3 (38.1%) disease than in those with grades 1 and 2 (19.2%) disease ($p = 0.02$). Serum STN levels were also significantly more elevated in patients with lymph node metastasis (50.0%) than in patients without lymph node metastasis (20.2%; $p = 0.006$). Elevated serum STN levels were not associated with histological types, clinical stages, myometrial invasions, distant metastases, age, menopausal status, body mass index (BMI), or disease relapse.

Among the 36 patients with elevated serum STN levels, 33 (91.7%) achieved remission and serum STN levels fell to

Table 1 Serum STN level and clinicopathological characteristics

Variables	Serum STN level		*p*-value
	Elevated	Normal	
Age (years)			
< 65	26 (26.8%)	71 (73.2%)	0.43
≧65	10 (20.4%)	39 (79.6%)	
Stage			
I + II	24 (21.2%)	89 (78.8%)	0.11
III + IV	12 (36.4%)	21 (63.6%)	
Histological grade			
Grade1 + 2	20 (19.2%)	84 (80.8%)	0.02
Grade3	16 (38.1%)	26 (61.9%)	
Histology			
Endometrioid	32 (24.2%)	100 (75.8%)	0.74
Other	4 (28.6%)	10 (71.4%)	
Lymph node metastasis			
Negative	25 (20.2%)	99 (79.8%)	0.006
Positive	11 (50.0%)	11 (50.0%)	
Distant metastasis			
Negative	30 (22.7%)	102 (77.3%)	0.11
Positive	6 (42.9%)	8 (57.1%)	
Myometrial invasion			
< 1/2	18 (19.6%)	74 (80.4%)	0.07
> 1/2	18 (33.3%)	36 (66.7%)	
Menopause			
Pre	7 (19.4%)	29 (80.6%)	0.51
Post	29 (26.4%)	81 (73.6%)	
Body mass index			
< 25	22 (23.9%)	70 (76.1%)	0.84
> 25	14 (25.9%)	40 (74.1%)	
Relapse of disease			
No	26 (22.2%)	91 (77.8%)	0.20
Yes	10 (34.5%)	19 (65.5%)	

within normal ranges. However, seven of these patients (21.2%) relapsed and had concomitant increases in serum STN levels.

Discussion

Overexpression of STN has been reported in several cancers, including colorectal, pancreatic, gastric, breast, and ovarian cancers [7–11]. Moreover, Semczuk A et al. showed STN expression in most endometrial cancers and comparatively limited expression in normal and hyperplastic human endometrium [12], and Ohno S et al. showed that overexpression of STN was correlated with poor prognosis [6]. In contrast, Numa F et al. controversially reported the absence of STN expression in endometrial carcinomas [13], and few reports show serum STN levels in patients with endometrial cancer. Although elevated serum STN levels were reported in 42 patients with endometrial cancer and 112 healthy volunteers, the authors concluded that serum STN levels lacked prognostic utility in patients with endometrial cancer [14]. Taken together, these reports indicate the requirement for a comprehensive investigation of serum STN levels as a tumor marker for preoperative diagnosis and subsequent management in a large series of endometrial cancer cases. To the best of our knowledge, the present study is the first to address these issues and to clarify the diagnostic and prognostic value of serum STN as a tumor marker for endometrial cancer.

In the present study, elevated serum STN levels were identified in 36 patients (24.7%) with endometrial cancer. In general, 15% to 25% of patients with disease that is clinically confined to the uterus have elevated serum CA125 levels [16–18], whereas approximately 75% of patients with metastatic disease have elevated serum CA125 levels [17]. Thus, elevated STN levels in 21.2% of the present patients with stage I and stage II disease indicates comparable diagnostic value to that of serum CA125 levels in patients with early stage disease.

The present study also shows that significantly elevated serum STN levels were more common (38.1%) among patients with histological grade 3 than in those with grade 1 + 2 disease (19.2%; $p = 0.02$). Moreover, elevated serum STN levels were significantly more prevalent in patients with lymph node metastasis (50.0%) than in those without (20.2%; $p = 0.006$). However, elevated serum STN levels were not associated with histological type, clinical stage, myometrial invasion, distant metastasis, age, menopausal status, body mass index (BMI), or relapse. In agreement, although immunohistochemical studies by YH et al. showed that STN expression is associated with histological grades of endometrial cancers, no correlations with other clinicopathologic features such as age, clinical stage, or myometrial invasion depth were observed [19]. Semczuk A et al. also correlated the expression of STN in endometrial cancer with histological grade [12], and Ohno S et al. correlated overexpression of STN with histological grade and menopausal status in endometrial cancer patients, and demonstrated that strong expression of STN correlated with poor prognosis in these patients [6]. Although these data strongly support the prognostic value of STN expression, 19 of the present patients had myometrial invasion depths of <50% and concomitantly elevated serum STN levels, although two of these patients (10.5%) had lymph node metastases. Hence, after preoperative diagnosis of stage IA endometrial cancer using CT or MRI examinations, lymphadenctomy may be indicated for patients with elevated serum STN levels. However, measurements of STN may not provide further prognostic information after surgical risk stratification.

Thirty-three of 36 patients (91.7%) with elevated serum STN levels specifically achieved remission, and serum STN

levels fell below the normal range in all cases. Moreover, in seven relapsing patients (21.2%), serum STN levels were again elevated, indicating that STN levels may reflect disease status. Therefore, serum STN levels may facilitate management of endometrial cancer patients with elevated serum STN levels. In conclusion, this study is the first to investigate serum STN levels at follow-up, and strongly indicates the potential of STN as a clinically useful prognostic factor for endometrial cancer.

Acknowledgments This work was supported by no grant.

Compliance with ethical standards

Conflicts of interest The authors have no conflicts of interest to declare.

References

1. Staff AC, Trovik J, Eriksson AGZ et al (2011) Elevated plasma growth differentiation factor-15 correlates with lymph node metastases and poor survival in endometrial cancer. Clin Cancer Res 17(14):4825–4833
2. Kurihara T, Mizunuma H, Obara M et al (1998) Determination of a normal level of serum CA125 in postmenopausal women as a tool for preoperative and postoperative surveillance of endometrial carcinoma. Gynecol Oncol 69:192–196
3. Lo SS, Cheng DK, Ng TY et al (1997) Prognostic significance of tumor markers in endometrial cancer. Tumour Biol 18:241–249
4. Gadducci A, Colsio S, Capri A et al (2004) Serum tumor markers in the management of ovarian, endometrial and cervical cancer. Biomed Pharmacother 1:24–38
5. Kaku T, Kamura T, Hirakawa T et al (1999) Endometrial carcinoma associated with hyperplasia-immunohistochemical study of angiogenesis and p53 expression. Gynecol Oncol 72:51–55
6. Ohno S, Ohno Y, Nakada H et al (2006) Expression of Tn and sialyl-Tn antigen in endometrial cancer: its relationship with tumor-produced cyclooxygenase-2, tumor-infiltrated lymphocytes and patient prognosis. Anticancer Res 26:4047–4053
7. Sewell R, Backstrom M, Dalziel M et al (2006) The ST6GalNAc-I sialyltransferase localizes throughout the Golgi and is responsible for the synthesis of the tumor-associated sialyl-Tn O-glycan in human breast cancer. J Biol Chem 281(6):3586–3594
8. Ogata S, Koganty R, Reddish M et al (1998) Different models of sialyl-Tn expression during malignant transformation of human colonic mucosa. Glycoconj J 15(1):29–35
9. Kim GE, Bae HI, Park HU et al (2002) Aberrant expression of MUC5AC and MUC6 gastric mucins and sialyl Tn antigen in intraepithelial neoplasms of the pancreas. Gastroenterology 123(4):1052–1060
10. Conze T, Carvalho AS, Landegren U et al (2010) MUC2 mucin is a major carrier of the cancer-associated sialyl-Tn antigen in intestinal metaplasia and gastric carcinomas. Glycobiology 20(2):199–206
11. Van Elssen CH, Frings PW, Bot FJ et al (2010) Expression of aberrantly glycosylated Mucin-1 in ovarian cancer. Histopathology 57(4): 597–606
12. Semczuk A, Paszkowska A, Miturski R et al (2002) Sialyl-Tn expression in normal and pathological conditions of human endometrium. An immunohistochemical study. Pathol Res Pract 198(9): 589–595
13. Numa F, Tsunaga N, Michioka T et al (1995) Tissue expression of sialyl Tn antigen in gynecologic tumors. J Obstet Gynaecol 21(4): 385–389
14. Inoue M, Ogawa H, Nakanishi K et al (1990) Clinical value of sialyl Tn antigen in patients with gynecologic tumors. Obstet Gynecol 75(6):1032–1036
15. Pecorelli S (2010) Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 108(2):176
16. Duk JM, Aalders JG, Fleuren GJ et al (1986) CA125: a useful marker in endometrial carcinoma. Am J Obstet Gynecol 155: 1097–1102
17. Patsner B, Mann WJ, Cohen H et al (1998) Predictive value of preoperative serum CA 125 levels in clinically localized and advanced endometrial carcinoma. Am J Obstet Gynecol 158:399–402
18. Bruce P, Yim GW (2013) Predictive value of preoperative serum CA-125 levels in patients with uterine cancer: the Asian experience 2000 to 2012. Obstet Gynecol Sci 56(5):281–288
19. An YH, Zhang HF, Sun M et al (2012) sTn is a novel biomarker for type I endometrial carcinoma. Prog Biochem Biophys 39(6):548–555