available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

β-Catenin expression in uterine sarcomas and its relation to clinicopathological parameters

Wanja Kildal[a,b], *Manohar Pradhan*[c], *Vera M. Abeler*[c], *Gunnar B. Kristensen*[a,d], *Håvard E. Danielsen*[a,b,e,*]

[a]*Institute for Medical Informatics, Radiumhospitalet, Oslo University Hospital, Montebello, 0310 Oslo, Norway*
[b]*Centre for Cancer Biomedicine, University of Oslo, Norway*
[c]*Pathology Clinic, Radiumhospitalet, Oslo University Hospital, Montebello, 0310 Oslo, Norway*
[d]*Department of Gynecological Oncology, Radiumhospitalet, Oslo University Hospital, Montebello, 0310 Oslo, Norway*
[e]*Department of Informatics, University of Oslo, P.O. Box 1080, Blindern, 0316 Oslo, Norway*

ARTICLE INFO

Article history:
Received 7 April 2009
Received in revised form 15 June 2009
Accepted 16 June 2009
Available online 20 July 2009

Keywords:
Uterine sarcomas
Wnt pathway
β-Catenin
Leiomyosarcomas
Endometrial stromal sarcomas
Adenosarcomas
Undifferentiated uterine sarcomas
Survival

ABSTRACT

Aberrations in the Wnt/β-catenin signalling pathway are suggested as mediators of chromosomal instability and carcinogenesis. β-catenin acts both as a component of the membranous adhesion system, and as a transcription activator in the nucleus.

β-Catenin immunoreactivity was evaluated in 353 uterine sarcomas (US) including 231 leiomyosarcomas (LMS), 82 endometrial stromal sarcomas (ESS), 22 adenosarcomas (AS) and 18 undifferentiated uterine sarcomas (UUS). Up-regulated membranous β-catenin was observed in 25% of the LMS ($p = 0.039$), 21% of the ESS ($p = 0.072$) and 39% of the UUS ($p = 0.025$). Cytoplasmic β-catenin was up-regulated in 36% of the LMS ($p = 0.008$) and 33% of the UUS ($p = 0.028$). Nuclear β-catenin expression was observed in 23% of the LMS ($p = 0.051$), 61% of ESS ($p = 0.628$) and in the sarcoma component of 68% of the AS. In patients with LMS, membranous β-catenin was associated with poor crude survival in univariate ($p = 0.045$), but not in multivariate analyses. In patients with ESS, nuclear β-catenin expression was related to spread of tumour ($p = 0.033$), but not to survival.

The observation of up-regulated β-catenin expression in US might suggest a so far undocumented role for the Wnt/β-catenin pathway in these malignancies.

1. Introduction

Alterations in cell motility and adhesion through deregulation of signalling pathways are common features in cancer. Aberrations in the Wnt signalling pathway have been implicated in human carcinogenesis and suggested as possible mediators of chromosomal instability.[1,2] The key component of the pathway, β-catenin, is particularly interesting because it acts both as a component of the membranous cadherin–catenin adhesion system and as a transcription activator in the nucleus. Both the cell adhesion and transcriptional activating role of β-catenin have been found to be deregulated in human malignancies. Mutations in several of the components of the Wnt signalling pathway (e.g. APC, Axin, CTNNB1) lead to accumulation of β-catenin in the cytoplasm and eventually translocation to the nucleus causing transcription of downstream targets and stimulation of cell proliferation.[1]

* *Corresponding author:* Address: Institute for Medical Informatics, Radiumhospitalet, Oslo University Hospital, Montebello, 0310 Oslo, Norway. Tel.: +47 22 93 56 17; fax: +47 22 93 56 27.
E-mail address: hdaniels@medisin.uio.no (H.E. Danielsen).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.06.017

Uterine sarcomas (US) are rare tumours, of which the majority are of the histological types leiomyosarcomas (LMS) and endometrial stromal sarcomas (ESS) followed by the less common adenosarcomas (AS) and undifferentiated uterine sarcomas (UUS). LMS are usually associated with prominent nuclear atypia, high mitotic activity, a high frequency of recurrence and a 5-year survival below 50%,[3,4] whereas ESS are associated with minimal atypia, low mitotic activity and a 5-year survival of 67–100%.[4–7] The most important prognostic factor for all US tumour types is the stage of disease.[4] In the patients with disease confined to the uterus, the significant prognostic factors were: for LMS, size of tumour and mitotic index; and for patients with ESS, mitotic index and tumour cell necrosis.[4] Due to the rarity of AS, little information on prognostic factors in these tumours exists, but for the patients included in this study, we recently showed that DNA ploidy was a predictor of survival of the disease.[8]

As it has been shown that β-catenin plays a role in the carcinogenesis of several tumour types, and since the information on Wnt signalling and β-catenin in sarcomas is limited,[9–13] we wanted to determine the expression profile of β-catenin in the US from the total population in Norway.[4] We examined the relation between β-catenin expression and clinicopathological parameters, including crude survival.

2. Patients and methods

All patients with LMS (245), ESS (83), AS (23) and UUS (20) from the total population in Norway from 1970 to 2000 were included in our study, comprising a total of 371 patients (Table 1). The only cases excluded from the total population were 19 patients with rare uterine sarcomas and 29 that were not submitted to surgery. All cases were reviewed by one pathologist without knowledge of patient outcome.[4] Of the LMS, 223 were ordinary LMS, while 18 were LMS with myxoid differentiation and 4 were LMS with epithelioid differentiation. According to the Norwegian law, all cancer cases must be reported to the Cancer Registry and all Norwegians have a unique identity number. This provides an efficient follow-up system. The survival dates were provided by The Cancer Registry of Norway on 31st October 2007 for all patients. In addition, tissues from 13 cases of normal uterus, where each slide contained normal endometrial epithelium, endometrial stroma and myometrium, were included as controls. The study has been approved by the Regional Ethics Committee.

For immunohistochemistry, 4 μm sections cut from formalin-fixed paraffin-embedded tissue were put onto silane-coated slides. Preparation of slides, staining with primary antibody specific for β-catenin (Clone 14, Mouse IgG1, Transduction Laboratories) by the peroxidase-labelled avidin–biotin method and inclusion of controls were performed as described previously by Kildal and colleagues.[14] The β-catenin expression in all tumour and control slides was evaluated by one pathologist, and for kappa analysis, 97 cases by another pathologist, both without knowledge of the clinical outcome. Slides were not available for evaluation in 18 cases (14 LMS, 1 ESS, 1 AS and 2 UUS). The percentage of cells positive for membranous, cytoplasmic and nuclear β-catenin expressions were evaluated in each case by examining the whole slide. The expression was scored according to the following scale: 0% = no expression, 1–5%, 6–25%, 26–50% and >50% positive tumour cells.

Table 1 – Clinicopatological data of the 371 patients diagnosed with uterine sarcoma included in the study.

Age, *years* (median (range))	*n*[a] = 371	55.0 (20–90)
Histological diagnosis, *n* (%)	*n* = 371	
LMS		245 (66.0)
ESS		83 (22.4)
AS		23 (6.2)
UUS		20 (5.4)
Tumour size *cm* (median (range))	*n* = 350	7.9 (0–50)
Mitotic index[b] (median (range))	*n* = 367	8.0 (0–60)
Tumour extent, *n* (%)	*n* = 371	
Confined to the uterus		280 (75.5)
Spread outside the uterus		91 (24.5)
Tumour necrosis, *n* (%)	*n* = 368	
Absent		92 (25.0)
Present		276 (75.0)
Vascular invasion, *n* (%)	*n* = 351	
Absent		197 (56.1)
Present		154 (43.9)
Hyaline necrosis, *n* (%)	*n* = 359	
Absent		186 (51.8)
Present		173 (48.2)
Tumour margins, *n* (%)	*n* = 356	
Pushing		80 (22.5)
Infiltrating		276 (77.6)
Cellular atypia, *n* (%)	*n* = 366	
Mild		111 (30.3)
Moderate/severe		255 (69.7)

a *n*, number; LMS, leiomyosarcoma; ESS, endometrial stromal sarcoma; AS, adenosarcoma; UUS, undifferentiated uterine sarcoma.
b Number of mitoses per 10 high power fields.

Based on the results of the control samples, we grouped the cases into: negative versus positive β-catenin immunostaining for membranous and nuclear expressions in the statistical analyses. For cytoplasmic β-catenin expression, 25% was used as a cut-off value. The interobserver variation in the 97 cases was calculated by the use of Cohen's κ-values.

SPSS software (SPSS 16, SPSS, Chicago) was used for statistical analyses. The differences in distribution of β-catenin expression related to clinicopathological variables were analysed by Fisher's exact test. Mann Whitney *U* analyses were used for comparison of membranous, cytoplasmic and nuclear β-catenin expressions in LMS, ESS and UUS to the respective control samples. Crude survival was calculated from the date of diagnosis to death or end of follow-up using the method of Kaplan and Meier. The median observation time for patients still alive was 163 months (ranging from 82 to 430 months). The log rank test was used for univariate analyses of crude survival and a Cox proportional hazards regression model was used for multivariate evaluation of crude survival. p-Values < 0.05 were considered as statistically significant.

3. Results

3.1. β-Catenin expression

3.1.1. Normal controls

No membranous β-catenin expression was observed in the normal endometrial stromal cells or in the myometrial cells. In contrast, there were more than 50% positive cells in the endometrial epithelium on the same sections (Table 2).

Cytoplasmic β-catenin expression was seen in more than 50% of the normal epithelial cells in most of the cases, whereas the majority of cases had expression between 1% and 50% in the endometrial stromal cells. In the myometrium, there was cytoplasmic expression in less than 25% of the cells in all controls (Table 2). Since the control samples showed all 5 levels of cytoplasmic β-catenin expressions, we chose not to include cytoplasmic expression in the survival analyses.

No nuclear β-catenin expression was observed in the normal myometrial cells. In the endometrial stromal cells, the majority were either nuclear negative or had more than 50% expression. The normal epithelium was nuclear β-catenin positive in all controls, with more than 50% positive cells in the majority of the cases (Table 2).

3.1.2. Uterine sarcomas

Membranous β-catenin expression was observed in 24% of US, whereas most cases were cytoplasmic β-catenin positive (90%) and 36% of the cases were nuclear β-catenin positive (Fig. 1). The percentage of membranous, cytoplasmic and nuclear β-catenin expressions in the different histological subgroups of US is summarised in Table 2. In the 231 evaluable cases of LMS, both the membranous and the cytoplasmic β-catenin expressions were significantly up-regulated in 58 (25%, $p = 0.039$) and 83 (36%, $p = 0.008$) of the cases as compared to normal myometrium, while 53 (23%, $p = 0.051$) cases had nuclear β-catenin expression. The up-regulation of membranous β-catenin was nearly exclusively restricted to ordinary LMS, as 3 of 4 epithelioid LMS and all the 17 analysed myxoid LMS were membranous β-catenin negative. In the 82 cases of ESS, we observed an up-regulation of membranous β-catenin in 17 (21%, $p = 0.072$) of the cases as compared to normal endometrial stroma, and we also observed a high level of cytoplasmic ($n = 54$, 66%, $p = 0.060$) and nuclear ($n = 50$, 61%, $p = 0.628$) β-catenin expressions compared to controls. In the 18 evaluable cases of UUS, the membranous β-catenin expression was significantly up-regulated in 7 (39%, $p = 0.025$) of the cases compared to endometrial stroma, whereas both the membranous and the cytoplasmic β-catenin expressions were significantly up-regulated in 7 (39%, $p = 0.025$) and 6 (33%, $p = 0.028$) of the cases compared to normal myometrium. In the 22 cases of AS, the epithelial component had membranous expression, while the sarcoma component had nuclear β-catenin expression (Fig. 1). Nuclear β-catenin expression was observed in 15 (68%) of the AS.

The interobserver variation, as determined by Cohens κ-value, was 0.405 for positive versus negative membranous expression, 0.579 for cytoplasmic expression above or below 25% of cells and 0.708 for positive versus negative nuclear β-catenin expression.

Table 2 – β-Catenin expression in normal controls, leiomyosarcomas, endometrial stromal sarcomas, adenosarcomas and undifferentiated uterine sarcomas

	β-Catenin expression														
	Membranous (%)					Cytoplasmic (%)					Nuclear (%)				
Percentage of positive cells	0	1–5	6–25	26–50	>50	0	1–5	6–25	26–50	>50	0	1–5	6–25	26–50	>50
Controls															
Myometrium ($n = 13$)[a]	13 (100)	0	0	0	0	5 (38)	4 (31)	4 (31)	0	0	13 (100)	0	0	0	0
Endometrial stroma ($n = 13$)	13 (100)	0	0	0	0	0	7 (54)	1 (8)	3 (23)	2 (15)	6 (46)	0	2 (15)	1 (8)	4 (31)
Endometrial epithelium ($n = 13$)	0	0	0	0	13 (100)	0	0	0	1 (8)	12 (92)	0	3 (23)	1 (8)	1 (8)	8 (62)
US															
LMS ($n = 231$)	173 (75)	19 (8)	17 (7)	6 (3)	16 (7)	30 (13)	43 (19)	74 (32)	36 (16)	47 (20)	177 (77)	39 (17)	7 (3)	2 (1)	5 (2)
ESS ($n = 82$)	65 (79)	5 (6)	5 (6)	4 (5)	3 (4)	2 (2)	8 (10)	18 (22)	23 (28)	31 (38)	32 (39)	14 (17)	12 (15)	6 (7)	18 (22)
AS ($n = 22$)	18 (82)	2 (9)	2 (9)	0	0	1 (5)	3 (14)	5 (23)	5 (23)	8 (36)	7 (32)	5 (23)	1 (5)	5 (23)	4 (18)
UUS ($n = 18$)	11 (61)	4 (22)	2 (11)	0	1 (6)	1 (6)	4 (22)	7 (39)		6 (33)	14 (78)	4 (22)	0	0	0

a n, number; US, uterus sarcoma; LMS, leiomyosarcoma; ESS, endometrial stromal sarcoma; AS, adenosarcoma; UUS, undifferentiated uterine sarcoma.

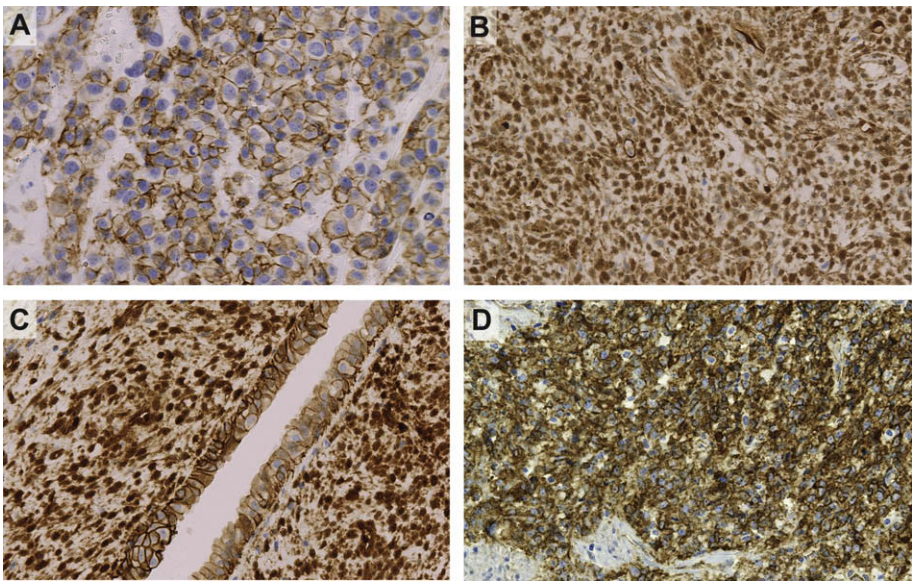

Fig. 1 – β-catenin expression in uterine sarcomas (400×). Panel A shows a leiomyosarcoma with membranous β-catenin expression. Panel B shows an endometrial stromal sarcoma with nuclear β-catenin expression. Panel C shows an adenosarcoma, where the sarcoma component has nuclear β-catenin expression while the epithelial component has membranous β-catenin expression and panel D shows an undifferentiated uterine sarcoma with membranous β-catenin expression.

3.2. *Differences in distribution of β-catenin expression as related to clinicopathological parameters for patients with LMS and ESS*

For patients with LMS or ESS, there were no significant differences in distribution of membranous and nuclear β-catenin expressions related to mitotic index (>10⩽), tumour size (⩾10 cm<), cellular atypia, vascular invasion, tumour margins, hyaline necrosis and tumour necrosis (the data were grouped as in Table 1).

In patients with ESS, expression of nuclear β-catenin was significantly more frequent in tumours extending outside the uterus at time of diagnosis ($p = 0.033$). However, this was not the case for LMS.

3.3. *Survival analyses*

The 5-year crude survival for all the 371 patients included in the present study was 53.4%. For patients with LMS, the 5-year crude survival was 44.9%. For this patient group, membranous β-catenin expression was a significant predictor of crude survival in univariate analysis as patients with expression had a 5-year survival of 48.0% compared to 32.8% for patients without expression ($p = 0.045$, Fig. 2). When analysing the 210 ordinary LMS, the difference between the groups was even more distinct ($p = 0.021$). For LMS patients with nuclear β-catenin expression, the 5-year crude survival was 37.7% compared to 46.1% for patients without expression ($p = 0.074$).

For patients with ESS, the 5-year crude survival was 74.7%. For this patient group, neither membranous nor nuclear β-catenin expression was of statistical significance in univariate analyses. The 5-year crude survival was 76.5% for patients whose tumours had membranous β-catenin expression compared to 75.4% for patients without expression ($p = 0.253$). For patients whose tumours had nuclear β-catenin expression, the 5-year crude survival was 72.0% compared to 81.2% for patients without expression ($p = 0.734$). In Cox regression survival analyses, neither membranous nor nuclear β-catenin expression was a significant predictor of survival for patients with LMS or ESS.

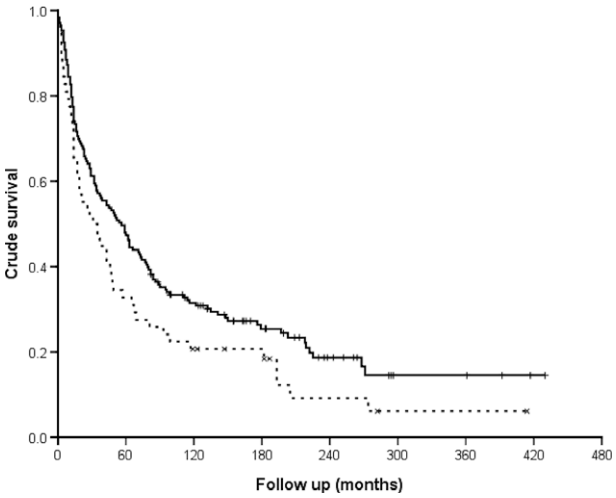

Fig. 2 – Crude survival as related to membranous β-catenin expression in 231 cases of leiomyosarcomas. Solid line – membranous β-catenin negative ($n = 173$). Dotted line – membranous β-catenin positive ($n = 58$), $p = 0.045$.

4. Discussion

In the cell membrane, β-catenin forms a complex with type I cadherins and functions as an adhesion molecule. Membranous β-catenin expression is frequently found in both normal and malignant epithelial tissues such as ovarian[14] and endometrial carcinomas.[15,16] The few studies presenting β-catenin expression in sarcomas[9–13] found no or a low level of membranous β-catenin expression. We found that the membranous β-catenin expression was up-regulated in LMS, and UUS, as compared to respective normal controls. To our knowledge, membranous β-catenin expression in US has not been reported previously.

An association between reduced expression of membranous β-catenin and worse outcome is reported in carcinomas such as ovarian,[17] non-small cell lung cancer,[18] cervix,[19] breast,[20] bladder,[21] pancreatic[22] and nasopharyngeal[23] cancers. Down-regulation of membranous β-catenin and thereby loss of adhesion is one of the mechanisms for the mesenchymal transition of epithelial cells, and this phenomenon might be linked to the invasiveness of carcinomas.[24–26] In contrast to these findings, we observed up-regulated membranous β-catenin expression in LMS which is a tumour type characterised by a poor survival, mostly due to distant metastases.[4] Further, in our study, up-regulated membranous β-catenin expression was related to poor crude survival in univariate although not in multivariate analyses. Crude survival was chosen as an end-point because this is a more robust end-point than disease-related survival. Given a median age of 55 years and a median 5-year survival of only 53%, relatively few patients have died of intercurrent disease during the first 5 years. Our survival analyses were repeated limited to the first 5 years giving essentially the same results (data not shown). Our results indicate that the mechanisms for membranous β-catenin expression might be opposite in mesenchymal and epithelial tissues. Interestingly, none of the 17 myxoid LMS had membranous β-catenin, which might suggest a distinction in the role for the Wnt signalling pathway in LMS with and without a myxoid growth pattern. However, the number of myxoid LMS is limited and conclusions must therefore be drawn with caution.

We found nuclear β-catenin in 53 (23%) of the LMS analysed, this is not in agreement with other studies that did not observe nuclear β-catenin expression in LMS.[11,12] However, the cited reports were on a limited number of cases ($n = 10$ and $n = 16$).

The observation of high extent of nuclear β-catenin in ESS is in agreement with the studies by Jung and colleagues[13] reporting β-catenin expression in 92% (11/12) and Ng and colleagues[9] in 40% (4/10) of the ESS examined. Limited numbers of cases and differences in the methods used may explain the difference in the percentage of nuclear β-catenin positive cases observed in these studies. Moreover, it has been reported that Wnt signalling pathway-related proteins are deregulated in ESS.[10] Our study including 82 ESS is an important addition to the existing literature, and it confirms that nuclear β-catenin expression is common in ESS. Jung and colleagues[13] suggested nuclear β-catenin expression as a diagnostic tool in the distinction between normal endometrium and ESS since all the cases with normal endometrium were negative[15] while 11 (92%) of the ESS were positive. Our results do not support their suggestion, as 4 (31%) of our normal endometrial stroma cases were strongly nuclear β-catenin positive, and 32 (39%) of the ESS were nuclear β-catenin negative. We did not observe prognostic value of nuclear β-catenin expression in our series of uterine sarcomas, this observation is in contrast to studies that have showed prognostic value of nuclear and cytoplasmic β-catenin expressions in soft tissue sarcomas.[27,28]

We observed nuclear β-catenin positivity in 68% of the AS. To our knowledge, this has not been reported previously, and even though the number of cases is limited, this might implicate a so far undocumented role for the Wnt signalling pathway in AS. In the evaluation of β-catenin in US, we obtained good interobserver agreement with respect to nuclear expression and moderate agreement in the evaluation of membranous and cytoplasmic expressions, respectively.[29] In addition to interobserver variation, the differences in how the immunohistochemical staining is performed e.g. antibody, antigen retrieval and the interpretation of data, complicates the direct comparison of expression studies further.

In conclusion, we found that nuclear β-catenin expression was associated with the histological subtypes ESS and AS, which might implicate involvement of the Wnt signalling pathway in the carcinogenesis of these histological subtypes. We observed a significant up-regulation of β-catenin in LMS and UUS, suggesting a so far undocumented role for β-catenin and the Wnt signalling pathway in these US. However, further investigation is needed to fully understand the implications of Wnt signalling in the studied mesenchymal malignancies.

Conflict of interest statement

None declared.

Acknowledgements

We greatly acknowledge Ellen Hellesylt and Mette S. Førsund at the Pathology Clinic, Radiumhospitalet, Rikshospitalet HF for performing the immunohistochemical staining of the slides.

REFERENCES

1. Giles RH, van Es JH, Clevers H. Caught up in a Wnt storm: Wnt signaling in cancer. *Biochim Biophys Acta* 2003;**1653**(1):1–24.
2. Aoki K, Aoki M, Sugai M, et al. Chromosomal instability by β-catenin/TCF transcription in APC or β-catenin mutant cells. *Oncogene* 2007;**26**(24):3511–20.
3. Major FJ, Blessing JA, Silverberg SG, et al. Prognostic factors in early-stage uterine sarcoma. A Gynecologic Oncology Group study. *Cancer* 1993;**71**(4 Suppl.):1702–9.
4. Abeler VM, Røyne O, Thoresen S, et al. Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. *Histopathology* 2009;**54**(3):355–64.

5. Chang KL, Crabtree GS, Lim-Tan SK, Kempson RL, Hendrickson MR. Primary uterine endometrial stromal neoplasms. A clinicopathologic study of 117 cases. *Am J Surg Pathol* 1990;**14**(5):415–38.
6. Evans HL, Chawla SP, Simpson C, Finn KP. Smooth muscle neoplasms of the uterus other than ordinary leiomyoma. A study of 46 cases, with emphasis on diagnostic criteria and prognostic factors. *Cancer* 1988;**62**(10):2239–47.
7. Nordal RR, Kjørstad KE, Stenwig AE, Tropé CG. Leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS) of the uterus. A survey of patients treated in the Norwegian Radium Hospital 1976–1985. *Int J Gynecol Cancer* 1993;**3**(2):110–5.
8. Kildal W, Abeler VM, Kristensen GB, et al. The prognostic value of DNA ploidy in a total population of uterine sarcomas. *Ann Oncol* 2009;**20**(6):1037–41.
9. Ng TL, Gown AM, Barry TS, et al. Nuclear β-catenin in mesenchymal tumors. *Mod Pathol* 2005;**18**(1):68–74.
10. Hrzenjak A, Tippl M, Kremser ML, et al. Inverse correlation of secreted frizzled-related protein 4 and β-catenin expression in endometrial stromal sarcomas. *J Pathol* 2004;**204**(1):19–27.
11. Carlson JW, Fletcher CD. Immunohistochemistry for β-catenin in the differential diagnosis of spindle cell lesions: analysis of a series and review of the literature. *Histopathology* 2007;**51**(4):509–14.
12. Bhattacharya B, Dilworth HP, Iacobuzio-Donahue C, et al. Nuclear β-catenin expression distinguishes deep fibromatosis from other benign and malignant fibroblastic and myofibroblastic lesions. *Am J Surg Pathol* 2005;**29**(5):653–9.
13. Jung CK, Jung JH, Lee A, et al. Diagnostic use of nuclear β-catenin expression for the assessment of endometrial stromal tumors. *Mod Pathol* 2008;**21**(6):756–63.
14. Kildal W, Risberg B, Abeler VM, et al. β-catenin expression, DNA ploidy and clinicopathological features in ovarian cancer: a study in 253 patients. *Eur J Cancer* 2005;**41**(8):1127–34.
15. Fukuchi T, Sakamoto M, Tsuda H, Maruyama K, Nozawa S, Hirohashi S. β-Catenin mutation in carcinoma of the uterine endometrium. *Cancer Res* 1998;**58**(16):3526–8.
16. Saegusa M, Okayasu I. Frequent nuclear β-catenin accumulation and associated mutations in endometrioid-type endometrial and ovarian carcinomas with squamous differentiation. *J Pathol* 2001;**194**(1):59–67.
17. Faleiro-Rodrigues C, Macedo-Pinto I, Pereira D, Lopes CS. Loss of β-catenin is associated with poor survival in ovarian carcinomas. *Int J Gynecol Pathol* 2004;**23**(4):337–46.
18. Choi YS, Shim YM, Kim SH, et al. Prognostic significance of E-cadherin and β-catenin in resected stage I non-small cell lung cancer. *Eur J Cardiothorac Surg* 2003;**24**(3):441–9.
19. Imura J. β-Catenin expression as a prognostic indicator in cervical adenocarcinoma. *Int J Mol Med* 2001;**8**(4):353–8.
20. Yoshida R, Kimura N, Harada Y, Ohuchi N. The loss of E-cadherin, α- and β-catenin expression is associated with metastasis and poor prognosis in invasive breast cancer. *Int J Oncol* 2001;**18**(3):513–20.
21. Garcia S, Martini F, De MC, et al. Immunoexpression of E-cadherin and β-catenin correlates to survival of patients with hepatocellular carcinomas. *Int J Oncol* 1998;**12**(2):443–7.
22. Chetty R, Serra S, Asa SL. Loss of membrane localization and aberrant nuclear E-cadherin expression correlates with invasion in pancreatic endocrine tumors. *Am J Surg Pathol* 2008;**32**(3):413–9.
23. Zheng Z, Pan J, Chu B, et al. Downregulation and abnormal expression of E-cadherin and β-catenin in nasopharyngeal carcinoma: close association with advanced disease stage and lymph node metastasis. *Hum Pathol* 1999;**30**(4):458–66.
24. Brabletz T, Jung A, Reu S, et al. Variable β-catenin expression in colorectal cancers indicates tumor progression driven by the tumor environment. *Proc Natl Acad Sci USA* 2001;**98**(18):10356–61.
25. Brembeck FH, Rosario M, Birchmeier W. Balancing cell adhesion and Wnt signaling, the key role of β-catenin. *Curr Opin Genet Dev* 2006;**16**(1):51–9.
26. Guarino M, Rubino B, Ballabio G. The role of epithelial-mesenchymal transition in cancer pathology. *Pathology* 2007;**39**(3):305–18.
27. Saito T, Oda Y, Sakamoto A, et al. Prognostic value of the preserved expression of the E-cadherin and catenin families of adhesion molecules and of β-catenin mutations in synovial sarcoma. *J Pathol* 2000;**192**(3):342–50.
28. Engellau J, Bendahl PO, Persson A, et al. Improved prognostication in soft tissue sarcoma: independent information from vascular invasion, necrosis, growth pattern, and immunostaining using whole-tumor sections and tissue microarrays. *Hum Pathol* 2005;**36**(9):994–1002.
29. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;**33**(1):159–74.