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Clinicopathologic Study in Uterine Cancer

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Abstract

Patients with primary advanced or recurrent endometrial cancer are relatively uncommon and deserve better treatment options. Current treatment options are surgery, radiotherapy, and systemic therapy. Since the outcome is still poor, there is a need to improve our knowledge on molecular markers in order to personalize treatment. In addition, we need to continue the search for new treatment strategies with a better balance between efficacy and toxicity.
In this doctoral thesis, we documented that among molecular and histological markers, blood vessel space involvement and chemotherapy induced regressive changes are new prognostic markers in endometrial cancer. We demonstrated that the tumour biology changes during tumour evolution. The optimal moment to decide on tumour biology is therefore the recurrent setting. A biopsy of the recurrent tumour is the best guarantee to characterize the tumour correctly. Furthermore, this study showed that neoadjuvant chemotherapy followed by interval debulking is a valuable treatment option for endometrial cancer with transperitoneal spread since optimal cytoreduction was achieved in 78% with a low morbidity.
Future studies should look into new biomarkers that predict antitumoral activity and should search for mutations in endometrial cancer and analyse which mutation is sensitive for therapy.

Key words: Endometrial cancer, tumour biology, prognostic markers, new treatment strategies.

Introduction

In the western world, endometrial cancer is the most frequent malignancy of the female genital tract, and the fourth most common site after breast, lung, and colorectal cancers. The incidence is rising as life expectancy increases (Parkin *et al*., 1999). Approximately 43.470 new cases of uterine cancer are estimated for 2010 worldwide, witch 7950 estimated deaths from this disease (Jemal *et al*., 2010).

According to the WHO, there are several histological types in endometrial cancer. From clinicopathologic view, endometrial cancer can be divided into two main groups. Type I (low-grade) endometrial cancer, existing of endometrioid type endometrial cancer (EEC), is the most common subtype, occurring in 80%. They are associated with long-duration unopposed estrogenic stimulation. These tumours have a favourable prognosis, featuring a 15-20% recurrence rate (Bokhman, 1983). About 10% of endometrial cancers are type II (high-grade) lesions. Women with such tumours are at high risk of relapse (> 50%) and metastatic disease (Amant *et al*., 2005).

The development of cancer in general occurs due to the alteration in 3 types of genes: oncogenes, tumour-suppressor genes and stability genes. These genetic alterations lead to self-sufficiency in growth signals, insensitivity to growth inhibition, evasion of apoptosis, angiogenesis, invasion and metastasis, described as the hallmarks of cancer (Hanahan and Weinberg, 2000; Vogelstein and Kinzler, 2004).

The most common genetic alterations in endometrial carcinoma are *K-ras* mutations, *HER-2/neu* gene amplification, *PI3K* mutations, decreased

PTEN activity, *p53* mutations and microsatellite instability (Engelsen *et al*., 2009).

The cornerstone in the treatment of endometrial cancer is surgery. Patients with recurrence at the vaginal vault or pelvis, who did not have adjuvant radiotherapy are treated with external pelvis radiation and/or brachytherapy. Patients with advanced or distant recurrent disease are relatively uncommon and most receive systemic therapy (including chemotherapy and hormonal therapy). Effective chemotherapies are limited to paclitaxel/carboplatin and doxorubicin. Despite treatment, the median time to treatment failure is on average 3 to 7 months and overall survival is less than 13 months. Therefore, there is a need for better treatment options.

Preclinical and clinical research on cancer therapies is more focused on more common solid tumours including breast, colon, lung and ovarian cancer. The low incidence of stage IV endometrial cancer (5-10%) makes this cancer type less interesting for pharmaceutical industries.

We conducted this doctoral thesis to analyse the tumour biology and look into new treatment strategies in endometrial cancer.

I. Assessment of tumour biology

In part I of this doctoral thesis, we assessed the endometrial cancer biology. Improving our knowledge of molecular markers can give us the ability to personalize treatment and consequently improve the response with less side effects.

I.1. *The use of lymph vessel markers to predict endometrial cancer outcome*

Vandenput et al. Int J Gynecol Cancer. 2010;20:363-7.

Lymph node metastasis is known to be the most important prognostic factor in endometrial cancer, however, whether all patients require full nodal staging is still controversial [4]. Little is known about the prognostic value of the processes preceding nodal involvement, including lymph vessel density (LVD) and lymph vessel space involvement (LVSI).

The genesis of lymph vessels and lymphovascular space involvement (LVSI), and the role in promoting the metastatic spread of tumour cells remains poorly understood. A relationship between patient survival and lymphatic vessel density (LVD) in different tumour types has been observed (Van der Auwera *et al*., 2006). LVSI has previously been investigated in endometrial cancer (Briët *et al*., 2005; Watari *et al*., 2005; Gal *et al*., 1991; Alexander-Sefre *et al*., 2004). However, in the absence of specific markers for lymph vessel endothelium, distinguishing lymphatic from blood vessels can be challenging.

Podoplanin, an approximately 38 kDa membrane mucoprotein originally detected on the surface of rat podocytes, is a specific marker for lymphatic endothelium. Based on a consensus report on immunohistochemical assessment of lymphangiogenesis in solid human tumours, podoplanin has become the most reliable marker for detecting lymph vessels, for assessing LVD, and for identifying LVSI (Van der Auwera *et al*., 2006).

We evaluated LVD and LVSI in 62 patients, using podoplanin and blood vessel density (BVD) and blood vessel space involvement (BVSI), using CD31. We correlated our findings with node involvement and clinical outcome.

For all patients, the median podoplanin positive lymph vessel density (LVD) PT was 2577 mm^2 (0-10153) and IT was 5.5 mm^2 (range 0-5527).

The median CD31 positive blood vessel density (BVD) was 210.0 microvessels/mm^2 (range 0-537) peri-tumoral (PT), and 65.8 microvessels/ mm^2 (range 0-272) intra-tumoral (IT).

LVSI (Fig. 1) and BVSI were noted in 32 (52%) and 41 patients (66%) respectively. Twenty-four patients (39%) had LVSI and BVSI. No correlation was found between LVD and LNI: the area under the ROC curve as a measure of overlap of the LVD distributions for patients with and without node involvement equaled 0.50 (95% CI 0.36-0.64) for LVD-PT and 0.56 (95% CI 0.41-0.70) for LVD-IT. Similarly, there was no relation between LVSI and lymph node involvement: 13/32 patients with positive LVSI have node involvement compared to 10/20 patients with negative LVSI (40.6% vs 50.0%, relative risk = 0.81 with 95% CI 0.45-1.54).

For overall survival (OS), only thirteen events were recorded such that no strong conclusions can be drawn from the analysis. For OS, univariate analysis showed that BVSI is related to worse prognosis as the hazard of the event is 6.59 times higher if BVSI is positive (HR = 6.59, 95% CI 1.30-120, p = 0.019). In the multivariate model, BVSI still has an independent affect on OS (HR = 7.52, 95% CI 1.32-144, p = 0.019).

For progression free survival, we adopted the same strategy and a priori selected LVD-PT, LVSI, BVSI and lymph node involvement for further investigation. No effects were found in both univariate and multivariate analyses.

Mannelqvist *et al*. (2009) also used podoplanin in their analysis of 176 cases. BVSI was found in 22% and LVSI in only 9% of the cases. LVSI and BVSI (with or without LVSI) were independent prognostic markers for survival and recurrence. Comparing

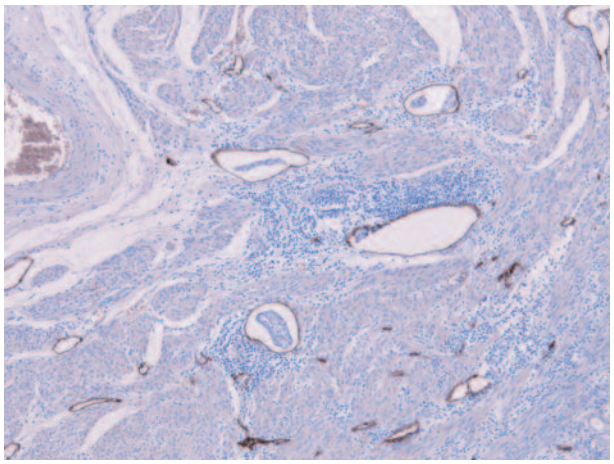

Fig. 1. — Podoplanin positive lymph vessels with tumor invasion (original magnification × 10).

these results with our data, we found a higher percentage of BVSI and LVSI. This difference could be explained by the study population. Our study population existed of 52% type II endometrial cancer compared to only 10% in Mannelqvist's series. In our study, 34% had stage IIIc (node involvement), while only 19% had stage III/IV in Mannelqvist's series.

In contrast, Kawamura *et al*. (2010) recently found an association between high intra-tumoral LVD and more localized disease and better outcome.

These contradictory results regarding the prognostic value of LVD and LVSI indicate the need of future studies with larger series.

From these pooled series including our data we can conclude that BVSI should be acknowledged as a prognostic marker and that future studies should assess whether chemotherapy is beneficial for these patients.

I.2. *Personalizing endometrial cancer treatment based on ERCC1, class III β-tubulin and p53: results from an immunohistochemical study*

Vandenput et al. Int J Gynecol Cancer. 2011;21:1071-7.

Platinum-based chemotherapy is widely used for endometrial cancer with response rates (RR) of 47-62%. Despite the good RR, hematologic toxicity, neuropathy and alopecia are still considerable and the prognosis poor, with a median time to treatment failure of 3 to 7 months and an overall survival of less than 12 months (Tropé *et al*., 2005) The failure of chemotherapy is mainly attributed to the occurrence of drug resistance in tumour cells. Therefore it is critical to identify biological markers of resistance to chemotherapeutic drugs that can guide treatment selection to avoid exposure of patients to toxic agents from which they are unlikely to benefit.

DNA repair mechanisms are important in the resistance to chemotherapy, including platinum-based chemotherapeutic agents, such as cisplatin and carboplatin. The destruction of cells by these agents requires the binding of the drug to DNA and the creation of platinum–DNA adducts. Some of these adducts establish covalent cross-linking between DNA strands, thereby inhibiting DNA replication. Nucleotide excision repair seems to play a key role in mediating resistance or sensitivity to platinum-based chemotherapy. More in particular, nucleotide excision repair repairs DNA lesions which alter the helical structure of the DNA molecule and interfere with DNA replication and transcription (Reed, 1998). The excision repair cross-complementation group 1 (ERCC1) enzyme plays a rate-limiting role in the nucleotide excision repair pathway that recognizes and removes platinum-induced DNA adducts (Sancar, 1994). The relation between the expression of *ERCC1* mRNA and resistance to platinum compounds has been mainly investigated in patients with advanced non–small-cell lung cancer (Olaussen *et al*., 2006; Azuma *et al*., 2007; Ikeda *et al*., 2009; Azuma *et al*., 2009; Azuma *et al*., 2009; Okuda *et al*., 2008). Also, p53 overexpression seems to be correlated with resistance to platinum-based chemotherapy (Manic *et al*., 2003).

Furthermore, tubulin-binding chemotherapeutic agents, including taxanes, can induce chemoresistance. Taxanes exert their growth-inhibitory effects through the inhibition of microtubule dynamics, resulting in the growth arrest of tumour cells at the G2-M phase. One of the major components of microtubules that is targeted by taxanes is class III β-tubulin. The overexpression of class III β-tubulin was associated with taxane resistance in non-small-cell lung cancer, breast cancer and gastric cancer (Sève and Dumontet, 2008).

In the absence of valuable data in endometrial cancer, we investigated the protein expression of ERCC1, class III β-tubulin and p53 in endometrial cancer patients treated with platinum-based chemotherapy with or without paclitaxel and correlated the findings with clinical outcome.

We analysed the expression of ERCC1 and p53 and class III β-tubulin in 2 groups: group A (n = 33) consisted of patients with early stage type II (serous, clear cell and carcinosarcomas) endometrial cancer, who were all surgically staged and treated with adjuvant chemotherapy. Group B (n = 116) existed of primary advanced or recurrent cases. The response of the first line chemotherapy was used in the analysis.

Table 1. — Overview of clinical outcome according to immunohistochemical expression of ERCC1, class III β-tubulin and p53 for group A (early stage endometrial cancer) and group B (primary advanced stage and recurrent endometrial cancer) (n (%)).

	n	Response Rate	Recurrence	DOD
Group A	**33**			
ERCC1positive	11		2 (18)	2 (18)
negative	22		6 (27)	5 (23)
p53 positive	19		4 (21)	4 (21)
negative	14		4 (29)	3 (21)
β-tubulin positive	7		2 (29)	2 (29)
negative	2		1 (50)	1 (50)
Group B	**116**			
ERCC1positive	25	12 (48)	12 (48)	13 (52)
negative	91	35 (38)	52 (57)	54 (59)
p53 positive	61	27 (44)	31 (51)	38 (62)
negative	55 20	(36)	33 (60)	29 (53)
β-tubulin positive	52	25 (48)	26 (50)	25 (48)
negative	18	10 (56)	10 (56)	10 (56)

n: number of patients; Response Rate: complete remission + partial remission; DOD: dead of disease.

For group A, the expression of ERCC1, p53 and class III β-tubulin showed no correlation with FIGO stage, histological type, recurrence and death (Table 1). For group B, no correlation was found for ERCC1 and class III β-tubulin, in univariate or multivariate analysis, with FIGO stage, histological type, grade or ERα/PR expression. Moreover, we could not find a statistically significant difference in response rate, RFS and DSS between positive and negative expression for ERCC1, p53 and class III β-tubulin (Table 1). Limiting the analysis to only type II endometrial cancer, no associations were found either.

In contrast, positive expression of p53 correlated with high tumour grade ($p = 0.001$), type II endometrial cancer (serous, clear cell and carcinosarcomas) ($p = 0.049$) and a negative expression of ERα ($p = 0.001$) and PR ($p < 0.05$). Furthermore, expression of p53 inversely correlated only with overall survival ($p = 0.01$), but not with RFS. These correlations could not be confirmed in multivariate analysis.

We can conclude that his study did not reveal any evidence that the expression of ERCC1 and class III β-tubulin predicts response to cytotoxic treatment and patient outcome in endometrial cancer. In contrast to other solid tumours, different mechanisms of chemoresistance might be involved in endometrial cancer. DNA mismatch repair (MMR) is a potential explanation for chemoresistance. It is believed that an intact MMR repairs the DNA-adducts and signals the cellular apoptotic machinery (Brabec and Kasparkova, 2002). Recently, Resnick *et al*. (2010) showed that patients with advanced stage endometrial cancer and defects in mismatch repair may receive less benefit from adjuvant chemotherapy. In addition, overexpression of the inhibitory protein FADD-like interleukin-1β converting enzyme/caspase 8, an inhibitor of Fas-mediated apoptosis, may also be an important determinant of chemoresistance in endometrial cancer (Chaudhry and Asselin, 2009). Jiang *et al*. (2010) found that high levels of Nrf2 (enhancing the detoxification and removal of xenobiotics, toxicants and carcinogens) determined chemoresistance in type II endometrial cancer.

I.3. *Targeted therapy for receptor tyrosine kinases*

The search for targeted therapies has become more important to optimize the management of cancer, especially in the recurrent setting. Therefore, we analysed whether a selection of available drugs could be used in endometrial cancer.

I.3.1. The *KIT* gene as a potential target for endometrial carcinoma treatment: an immunohistochemical and mutational analysis

Vandenput et al. Int J Gynecol Cancer. 2011;21:203-5.

Receptor tyrosine kinases play an important role in the regulation of cellular proliferation and differentiation. Imatinib mesylate (Gleevec®) is the first commercially available tyrosine kinase inhibitor, which targets specific kinases, including ABL, KIT, and platelet-derived growth factor receptors

(PDGFRs). Currently, imatinib mesylate is approved for the treatment of Philadelphia chromosome-positive chronic myelogenous leukemia (CML), which characteristically expresses a constitutively active ABL tyrosine kinase. In addition, imatinib mesylate has been approved for the treatment of gastrointestinal stromal tumours (GIST), which carry a mutated and constitutively activated KIT oncoprotein. Because of the success of imatinib mesylate in the treatment of CML and GIST tumours, (pre-) clinical studies have been performed evaluating imatinib mesylate in other solid tumours, including melanoma, ovarian, and breast carcinomas.

KIT expression in endometrial carcinoma has been explored showing overexpression ranging widely between 15 and 100% (Menczer *et al*., 2005; Arber *et al*., 1998; Elmore *et al*., 2001; Scobie *et al*., 2003; Slomovitz *et al*., 2004).

We analysed KIT expression in primary and recurrent tumours, of type I and type II endometrial cancer, but could not find any expression. Additionally, we could not find mutations in mutational hot spot exons of *KIT* gene. In contrast to findings from other groups, our data suggest that endometrial carcinoma is unlikely to respond to imatinib mesylate.

I.3.2. Analysis of HER-2/Neu in recurrent endometrial cancer: limited clinical benefit from trastuzumab

Vandenput et al. Gynecol Obstet Invest. 2009;67:46-8.

Targeted anti-HER-2 monoclonal antibody therapy with trastuzumab (Herceptin®) has shown significant therapeutic benefit in patients with breast carcinomas showing strong HER-2/neu overexpression (3+) by immunohistochemistry (IHC) or gene amplification by fluorescence in-situ hybridization (FISH). In endometrial cancer, an overexpression of HER-2/neu was described in up to 80% of the cases and gene amplification in 45% (Odicino *et al*., 2008; Slomovitz *et al*., 2004; Santin *et al*., 2005; Santin, 2003).

In our analysis, 18/23 cases (78%) had a negative expression for HER-2/neu in primary and recurrent tumour. One patient had a strong overexpression and gene amplification. She was treated with paclitaxel-trastuzumab, however without response. We additionally treated 3 more patients with paclitaxel-trastuzumab, who all showed progression (Table 2).

Clinical responses to trastuzumab, as a single agent or in combination with chemotherapy, have been reported in case reports (Villella *et al*., 2006; Jewell *et al*., 2006; Fleming *et al*., 2010). Fleming *et al*. (2010) recently demonstrated no activity of trastuzumab, as a single agent, against 33 cases of endometrial carcinomas. It should be noted that only 18/33 cases had documented gene amplification.

In breast cancer, a combination therapy with chemotherapy is generally more effective than single agent trastuzumab. Taking this into account, we treated 4 cases with paclitaxel-trastuzumab. However, no clinical response could be demonstrated (Table 2).

Mechanisms of resistance to trastuzumab in HER-2-amplified cancers of either breast or another origin remain largely speculative. Potential mechanisms include signaling from other members of the HER family, cross talk from the insulin-like growth factor-I receptor to HER-2, Met activation, and increased signaling through the PI3-kinase pathway by a variety of mechanisms, including PTEN or PIK3CA gene mutation (El-Sahwi *et al*., 2010). A broad study of gene expression in HER-2-amplified endometrial cancers might identify strategies for overcoming trastuzumab resistance, such as combining trastuzumab with mTOR inhibitors, cMET inhibitors or pertuzumab (Santin *et al*., 2008).

Our results are in contrast with the literature concerning the expression of KIT and HER-2 in endometrial cancer.

Table 2. — Overview of cases treated with paclitaxel-trastuzumab: *HER-2* gene amplification in primary and recurrent tumor and response to paclitaxel-trastuzumab.

Cases	***HER-2* gene amplification (FISH)**		**Response to trastuzumab**
	Primary tumor	Recurrent tumor	
1 (*)	+	+	Progressive disease
2	+	+	Progressive disease
3	+	+	Progressive disease
4	+	- (**)	Progressive disease

(*) Case report (chapter 5)
(**) Result was obtained after treatment with trastuzumab.

We could not confirm the reported high immunohistochemical expression of KIT (up to 100%) and HER-2 (up to 80%). We did not find any expression of KIT and only 22% of the cases showed HER-2 overexpression. To find an explanation for this remarkable difference in results, we looked into the method of the studies. Since the staining technique and scoring were equal, the only possible reason we could find is a subjective overinterpretation of the staining in the other studies, resulting in a higher rate of positive expression.

There are several known limitations of immunohistochemical assays. 1) Most immunohistochemical stains are three-step enzyme-catalysed reactions wherein an optically dense substrate is deposited on the cells expressing the antigen. Thus there are multiple steps in this method at which antigen expression may be misrepresented; 2) there is a wide variety of approaches used to 'quantify' immunohistochemical stains; 3) very few papers report interobserver variances in assessing stains. This leads to a high level of interobserver and interlaboratory variability in assessing stains (True and Feng, 2005).

Since the undetectable expression of KIT protein does not exclude the possible presence of mutation in the tumour cells, and given the known difficulties with immunological staining and interpretation, we performed KIT hot spot regions mutational analysis in the subset of cases to verify the genomic wild type status of the gene. Also KIT mutations were absent.

I.4. *Evolution in endometrial cancer: evidence from an immunohistochemical study*

Vandenput et al. Int J Gynecol Cancer. 2011;21:316-321.

Over the last several decades, insight in the molecular events involved in human cancer has increased substantially. Through our understanding of signaling pathways regulating cellular growth, cell cycle, and programmed cellular death, numerous targets for anticancer agents have emerged. Although traditional chemotherapy continues to play a major role in the treatment of cancer, targeted therapies are now an important component of management of many types of cancer, especially in the recurrent setting (Pakkiri *et al*., 2009).

In the current clinical setting, decisions on targeted treatment for recurrent disease are based on primary tumour biology. However, recurrent and metastatic disease is modeled by a dynamic cellular process. Mutations, up – and down regulations of driving genes encompass this malignant process. It is possible that this evolution comprises changes in expression profiles of targets for directed treatment. This has not been investigated for endometrial cancers.

In a collaborative retrospective study we analysed changes in expression of potential molecular targets between the primary tumour and its recurrence in endometrial cancer.

Paired biopsies from primary and recurrent endometrial cancer (n = 85) were stained immunohistochemically for following proteins: oestrogen receptor (ER), progesterone receptor (PR), stathmin (correlating with PI3K activity), HER-2/neu, WT1 (Wilms tumor gene 1), phosphorolated mammalian target of rapamycin (p-mTOR) and p53. We found a change in protein expression between primary and recurrent tumour of 7 to 31% (Table 3, Fig. 2). Furthermore, a negative expression for ER ($p < 0.05$), positive expression for p53 ($p = 0.011$) and p-mTOR cytoplasm ($p = 0.001$) in the recurrent tumour correlated with poor survival, but not with RFS. There was no correlation between time of recurrence (according to the mean RFS of 25 months or the cut-off of 6 months) and change in expression of markers. A change in expression of one marker was independent of the change in expression of other markers.

Benefits of taking a biopsy of metastatic disease include confirmation of recurrence and enables selection of patients for targeted therapy. These benefits clearly outweigh the disadvantages when endometrial cancer recurs at the vaginal vault. Improvements in interventional radiological techniques render most other tissues accessible by minimally invasive methods. Disadvantages however include anxiety, pain, and cost of interventional radiology and pathology evaluation. These factors should be evaluated before invasive procedures for tissue analysis are planned (Amir and Clemons, 2009).

To conclude, this observation shows that endometrial cancer tumour biology changes over time. These findings underscore the importance of taking a new biopsy of the recurrent tumour when targeted treatment is aimed for. It appears that information derived from recurrent endometrial cancer biopsy is clinically important. The effort to take a new biopsy should be balanced against the disadvantages of a biopsy and the risk that ineffective treatment is prescribed. Furthermore, results of studies exploring response rates of new targeted treatments might be masked by the unknown change in target status.

II. Exploring new treatment strategies

In part II of this doctoral thesis, we assessed new treatment strategies in early stage and primary advanced or recurrent endometrial cancer.

Table 3. — Expression of tested markers in primary and recurrent endometrial cancer (n = 85).

Expression	ER n (%)	PR n (%)	Stathmin n (%)	p53 n (%)	HER-2/neu n (%)	WT1 n (%)	p-mTOR nucleus n (%)	p-mTOR cytoplasma n (%)
Discordant	**15 (18)**	**19 (23)**	**26 (31)**	**8 (10)**	**6 (7)**	**6 (7)**	**23 (28)**	**15 (18)**
Gain	6 (7)	4 (5)	12 (14)	6 (7)	4 (5)	2 (2)	20 (24)	9 (11)
Loss	9 (11)	15 (18)	14 (17)	2 (3)	2 (2)	4 (5)	3 (4)	6 (7)
Concordant	70 (82)	66 (78)	58 (68)	67 (79)	79 (93)	72 (85)	51 (60)	61 (72)
Positive	23 (27)	22 (26)	48 (57)	17 (20)	3 (4)	0	12 (14)	15 (18)
Negative	47 (55)	44 (52)	10 (12)	50 (59)	76 (89)	72 (85)	39 (46)	46 (54)
Missing	0	0	1 (1)	10 (12)	0	7 (8)	11 (13)	9 (11)

n: number of cases; gain : ≥ 2 step change from low to high expression; loss : ≥ 2 step change from high to low expression.

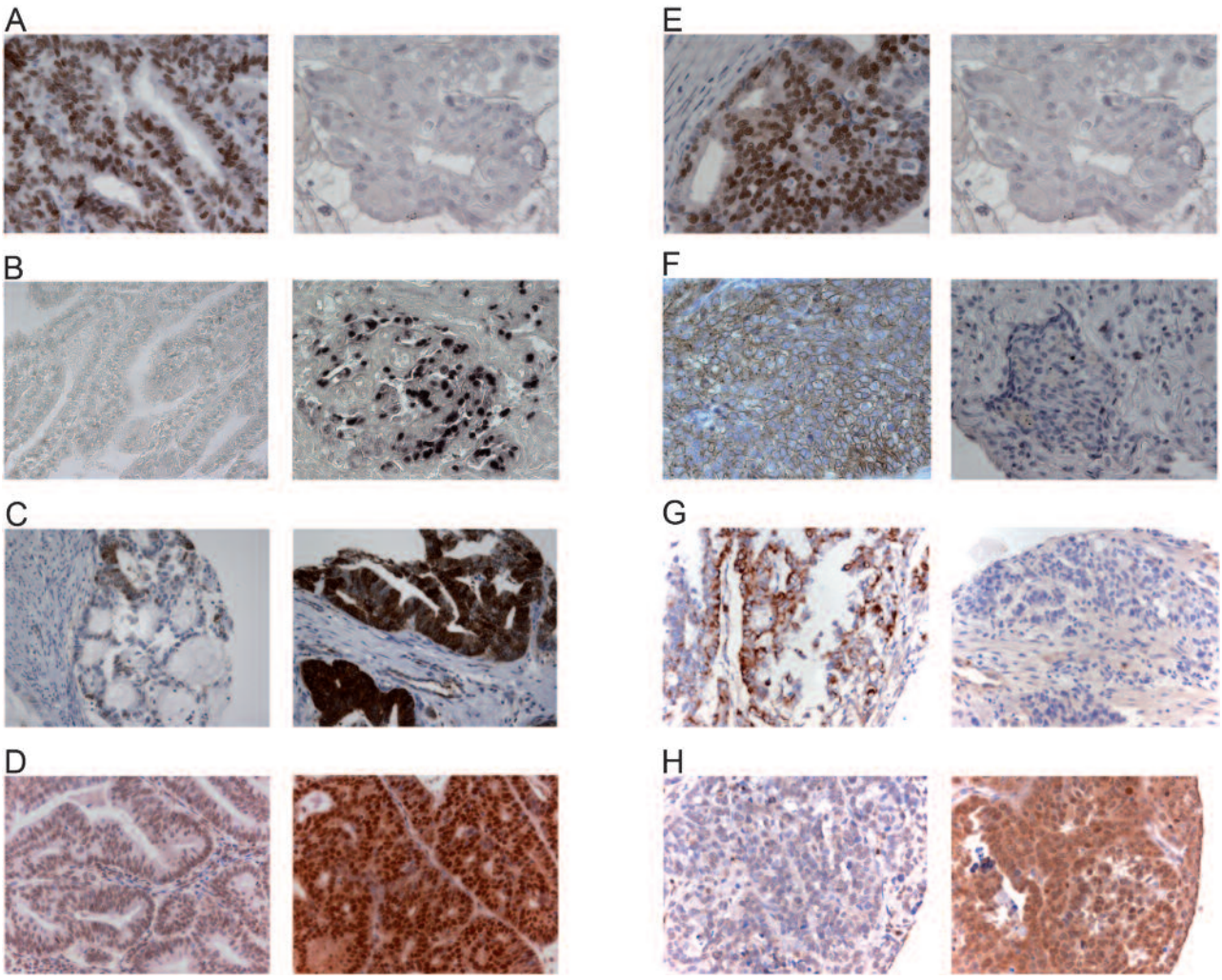

Fig. 2. — Examples of changes in expression of different molecular markers between primary (left) and recurrent (right) tumor

II.1. *Ineffective attempt to preserve fertility with a levonorgestrel-releasing intrauterine device in a young woman with endometrioid endoemtrial carcinoma: a case report and review of the literature*

Vandenput et al. Eur J Gynaecol Oncol. 2009;30:313-316.

In 4.5% of the cases, endometrial cancer occurs in women less than 40 years. These women often wish to preserve their fertility. This poses the dilemma whether or not to perform a definitive hysterectomy since conservative treatment remains a challenge. We treated a case with a levonorgestrel intrauterine contraceptive device (LNG IUCD) for 10 months. Unfortunately, recurrence was noted 9 months after removal. Reviewing the literature, we concluded that the use of oral progestins or LNG IUCD showed little clinical benefit but that hysteroscopic resection looked promising in 3 cases (Mazzon *et al*., 2005; Sparac *et al*., 2006; Vilos *et al*., 2007). Therefore, we treated a second case with hysteroscopic resection followed by progestin therapy. Recurrence was noted after 3 months. These cases underscore the difficulty in finding an effective conservative therapy, even in the presence of favourable prognostic markers.

Recently, Perri *et al*. (2011) found a complete remission in 24/27 (89%) cases treated with oral progestins with our without LNG IUCD. However, 15 cases (63%) recurred. In contrast, Laurelli *et al*. (2011) reported only 1/14 (7%) recurrence after hysteroscopic resection followed by oral progestins or LNG IUCD. The data from these larger studies suggest that hysteroscopic resection followed by progestin therapy may have a role in safe and effective conservative management.

II.2. *The Role of Adjuvant Chemotherapy in Surgical Stages I-II Serous and Clear Cell Carcinomas and Carcinosarcoma of the Endometrium: A Collaborative Study*

Vandenput et al. Int J Gynecol Cancer. 2011;21:332-6.

Type II endometrial cancer (serous (S) and clear cell (CC) account for 10% of cases (Amant *et al*., 2005). The behaviour of uterine carcinosarcomas (CS) parallels more closely that of type II endometrial carcinomas than sarcomas, judging from the pattern of spread and the histological appearance of the tumour in vascular channels and in metastatic sites (Bitterman *et al*., 1990; Silverberg *et al*., 1990; Sreenan and Hart, 1995). Type II endometrial cancer and CS are characterized by lymphatic and transperitoneal spread. Optimal surgical exploration should assess these sites of spread.

The progress in evidence based management of type II endometrial cancer and CS over the past decade has been limited. In patients receiving adjuvant chemotherapy, recurrence rates vary from 0-66%, with recurrences outside the pelvis between 0-33% and OS rate between 33-100% (Fader *et al*., 2009; Huh *et al*., 2003; Elit *et al*., 2004; Kelly *et al*., 2005; Dietrich *et al*., 2005; Thomas *et al*., 2007; Alektiar *et al*., 2009). Recurrences in patients without adjuvant chemotherapy were noted in 0-49% of patients of which 0-32% were systemic recurrences; OS in this group varied between 46-100% (Fader *et al*., 2009; Huh *et al*., 2003; Elit *et al*., 2004; Kelly *et al*., 2005; Thomas *et al*., 2007; Slomovitz *et al*., 2003; Grice *et al*., 1998; Bristow *et al*., 2001; Havrilesky *et al*., 2007). Some studies (Huh *et al*., 2003; Kelly *et al*., 2005; Dietrich *et al*., 2005; Thomas *et al*., 2007) advocate the administration of adjuvant chemotherapy, since they demonstrated that patients treated with platinum based chemotherapy have improved outcomes when compared with no adjuvant chemotherapy. On the other hand, Kwon *et al*. (2008) and Grice *et al*. (1998) found a recurrence rate of 0-5% in the observation group. Previous trials have been flawed by the fact that surgical staging is frequently not mandatory, resulting in similar treatment regimens for different stages of disease.

Due to lack of randomized trials for this patient group we decided to retrospectively evaluate the impact of adjuvant chemotherapy on clinical outcome for surgically staged I-II type II endometrial cancer and CS.

Patients were divided into 2 groups: group A (n = 34), patients who received postoperative chemotherapy and group B (n = 35), patients who did not receive adjuvant chemotherapy.

Recurrences occurred irrespective of adjuvant chemotherapy (32% for group A versus 34% for group B). The median RFS was different for both groups, however not significant (p = 0.537): 22 months (range 13-51 months) for group A versus 10 months (range 1-59 months) for group B. Recurrence and RFS according to the histological subtype for each group, is presented in Table 4. It appears that the carcinosarcomas may benefit from chemotherapy since we notice a lower recurrence rate and longer RFS and DSS compared to the carcinosarcomas of group B.

Five patients (15%) of group A and nine (26%) of group B died of disease after a median follow-up of 29 months (range 20-59) and 17 months (range 4-64) respectively (p = 0.168) (Table 4).

We acknowledge that the small numbers hamper statistic interpretation and conclusions. Like other studies in the literature, this study did not give clear answers whether or not chemotherapy should be

Table 4. — Recurrence according to histological subtype and survival data for group A (adjuvant chemotherapy) and group B (no adjuvant chemotherapy).

	Group A n (%)		**Group B** n (%)	
Total number of patients	34		35	
Recurrence	11 (32)		12 (34)	
RFS (months (range))	22 (13-51)		10 (1-59)	
DOD at time of analysis	5 (15)		9 (26)	
DSS (months (range))	29 (20-59)		17 (4-64)	
	Type II	**CS**	**Type II**	**CS**
Total of patients	23	11	28	7
Median time of follow up (months (range))	48 (20-159)	44 (13-64)	32 (4-179)	17 (1-64)
Recurrence according to type	8 (35)	3 (27)	8 (29)	4 (57)
pelvic	1 (4)	0	1 (4)	1 (14)
systemic	7 (30)	3 (27)	7 (25)	3 (43)
RFS (months (range))	23 (17-51)	14 (13-47)	13 (3-44)	7 (1-59)
DOD at time of analysis	3 (13)	2 (18)	5 (18)	4 (57)
DSS (months (range))	29 (25-49)	30	29 (4-56)	16 (8-64)

n: number of patients; Type II: serous and clear cell endometrial cancer; CS: carcinosarcoma; median time of follow up: from diagnosis till death or last follow up; RFS: recurrence free survival; DOD: dead of disease; DSS: disease specific survival.

administered for this group. Only prospective randomized intergroup trials can address the benefit of adjuvant chemotherapy in early stage high risk endometrial cancer. Such a project is now initiated within the European Organization for Research and Treatment of Cancer (EORTC). In this study, surgically stage I and II grade 3 endometrioid and serous endometrial cancer are randomized between no further treatment or 6 cycles paclitaxel-carboplatin.

II.3. *The Leuven dose dense paclitaxel-carboplatin regimen in patients with primary advanced or recurrent endometrial carcinoma*

Vandenput et al. Int J Gynecol Cancer. 2009;19:1147-1151.

The weekly paclitaxel-carboplatin (TC) regimen in patients with primary advanced or recurrent endometrial carcinoma.

Vandenput et al., Submitted

On the basis of the low toxicity, ease of administration and efficacy (RR of 47-61%), the combination of paclitaxel and carboplatin 3-weekly has become standard in the treatment of advanced or recurrent endometrial cancer in many centres (Hoskins *et al.*, 2001; Sovak *et al.*, 2007). Despite these responses, overall survival is only 13 months and better treatment schedules are necessary.

An increase of efficacy could be reached by increasing the dose of the chemotherapy agents or by shortening the treatment interval. We evaluated the response and toxicity of dose dense regimen (6 courses of T (90 mg/m^2) and C (AUC 4) on d1 and d8 q3w) and the weekly regimen (18 weekly cycles of T (60 mg/m^2) and C (AUC 2.7)).

Results are shown in Table 5. For TC dose dense, response rate (RR) was 62% and 21% for chemo-naïve patients and patients with previous chemotherapy, respectively. For TC weekly, RR for chemo-naïve patients was 50% and for patients with previous chemotherapy 39%.

Comparing these data with responses to TC 3-weekly regimen, administered at our hospital, it seems that TC dose dense and TC weekly regimen is less effective with considerable toxicity (Table 5). The absence of randomized trials necessitates us to compare our data with other phase II trials. This indirect comparison between small studies makes it impossible to draw strong conclusion.

We can conclude that the TC dose dense and TC weekly regimen is active in primary advanced or recurrent endometrial cancer. The hematologic toxicity however is considerable. The main benefit is a reduction in alopecia and neurotoxicity. Larger trials are needed to confirm these data.

Table 5. — Overview of efficacy and toxicity in chemo-naïve patients and patients with previous chemotherapy between different regimens of paclitaxel/carboplatin (TC) administered at University Hospitals Leuven.

	Chemo-naïve patients n (%)			Patients with previous chemotherapy n (%)	
Chemo type	***TC weekly***	***TC 3-weekly***	***TC dose dense***	***TC weekly***	***TC dose dense***
Dosage	T (60mg/m²) C (AUC 2.7)	T (175mg/m²) C (AUC 6)	T (90mg/m²) C (AUC 4)	T (60mg/m²) C (AUC 2.7)	T (90mg/m²) C (AUC 4)
EFFICACY					
Total of patients	**16**	**21**	**26**	**13**	**14**
Response Rate (n (%))	8 (50)	18 (86)	16 (62)	5 (39)	3 (21)
Progressive disease (n (%))	7 (44)	0	5 (19)	8 (62)	6 (43)
Recurrence (n (%))	6 (75)	11 (61)	15 (94)	5 (100)	2 (67)
Median time to progression (mths (range))	7 (5-14)	10 (4-27)	12 (6-37)	8 (6-10)	9
Median PFS (mths (range))	9 (5-27)	12 (4-67)	12 (6-47)	8 (6-10)	11 (4-19)
DOD	10 (65)	12 (57)	21 (81)	11 (85)	11 (79)
Median OS (mths (range))	12 (2-27)	15 (5-69)	19 (1-53)	9 (2-18)	7 (1-19)
TOXICITY					
Total of patients	**15**	**19**	**26**	**12**	**14**
Hematologic toxicity					
Grade 3/4 anemia	7 (47)	6 (32)	3 (11)	8 (67)	3 (21)
Grade 3/4 neutropenia	13 (87)	15 (79)	23 (82)	11 (92)	11 (79)
Neutropenic fever	1 (7)	2 (11)	2 (7)	0	1 (7)
Grade 3/4 thrombocytopenia	8 (53)	5 (26)	6 (21)	6 (50)	5 (36)
Treatment reduction	9 (60)	6 (32)	10 (38)	5 (42)	4 (29)
Treatment delay	14 (93)	9 (47)	18 (69)	9 (75)	9 (64)
Switch of therapy	0	2 (11)	4 (15)	1 (8)	4 (29)
No administration	2 (13)	0	4 (15)	0	4 (29)
≥ 1 treatment adjustment	14 (93)	10 (53)	21 (81)	9 (75)	10 (71)
Non-hematologic toxicity					
Neuropathy grade 2	0	12 (63)	1 (4)	2 (17)	3 (21)
Alopecia grade 2	0	21 (100)	UN	0	UN

(n: number of patients; mths: months; PFS: progression free survival; OS: overall survival; UN: unknown).

II.4. *Neoadjuvant chemotherapy followed by interval debulking surgery in patients with serous endometrial cancer with transperitoneal spread (stage IV): a new preferred treatment?*

Vandenput et al. Br J Cancer 2009;101:244-9.

When we started the study, patients with stage IV endometrial cancer based on transperitoneal spread, received either no surgery (systemic treatment only) or primary debulking surgery. The amount of residual disease after surgery for advanced endometrial cancer has an impact on the median survival and PFS (Goff *et al*., 1994; Chi *et al*., 1997; Bristow *et al*., 2001; Memarzadeh *et al*., 2002; Lambrou *et al*., 2004; Thomas *et al*., 2007). These data correspond to the findings in ovarian cancer. Primary debulking is however associated with 36-39% of postoperative complications (Bristow *et al*., 2001; Memarzadeh *et al*., 2002). Taking also the age and co-morbidities of endometrial cancer patients into consideration, there is a need for better treatment options.

In endometrial cancer, the experience of neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) only appears from case reports (Resnik and Taxy, 1996; Price *et al*., 1999; Le *et al*., 1999; Despierre *et al*., 2006).

A strategy of NACT enables to identify chemo sensitive disease that is more likely to benefit from debulking surgery when compared to chemoresistant disease. Furthermore, resection of a reduced tumour burden, permits less aggressive surgery and can improve the patients' quality of life by reduced morbidity and shorter operations, intensive care unit stays and overall hospitalisations.

Cytotoxic therapy leads to morphologic and histopathologic changes within tumour tissue and in involved stromal tissue. Successful treatment results

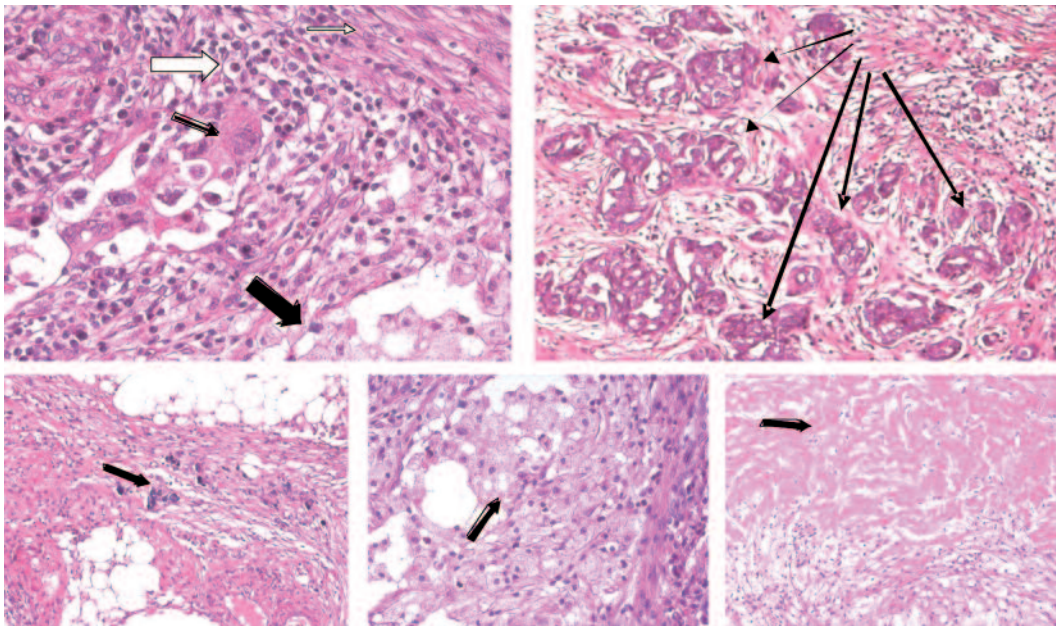

Fig. 3. — Histopathologic response on chemotherapy

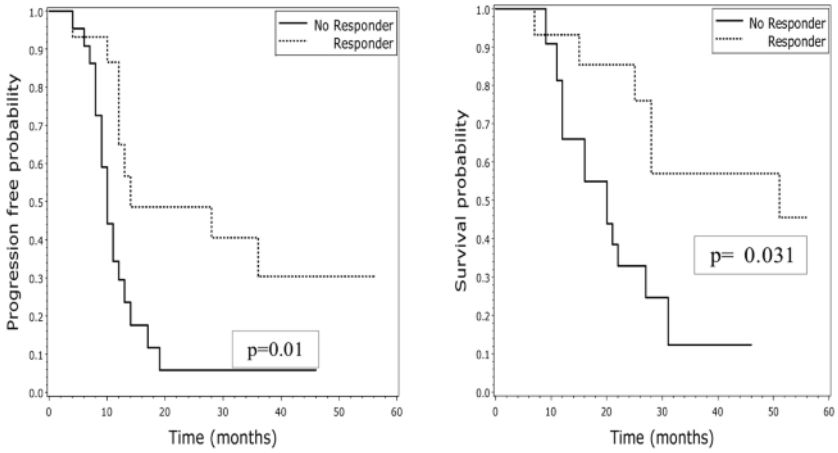

Fig. 4. — Correlation of all histopathologic features with recurrence and overall survival of the update series

in fibrosis and scarring of tumoral stroma and the surrounding tissue. Histopathologic tumour regression has been established as the gold standard for the assessment of treatment response in several types of solid tumours (osteosarcomas, gastric, esophageal, non-small cell lung cancer) (Sassen *et al*., 2007). Histopathologic assessment of tumour regression in ovarian cancer patients showed a correlation between composite pathologic tumour response score and prolonged progression free survival (Sassen *et al*., 2007; Le *et al*., 2006).

Since the experience of NACT followed by IDS in endometrial cancer only appears from case reports, we prospectively investigated the value of NACT followed by IDS for stage IV endometrial cancer and tested the hypothesis that the histopathological assessment of response is predictive for the outcome.

We evaluated the response to NACT on three levels: response according to RECIST criteria, the amount of residual tumour after IDS and thirdly, the extent tumour regression assessing eight histopathological features (Fig. 3) in uterus and omentum (presence of fibrosis, necrosis, inflammatory cell infiltrates, foamy macrophages, isolated psammoma bodies, giant cells of foreign-body type, giant tumour cells and pattern of tumour infiltration).

We found a RR of 74% according to the RECIST. 80% had an optimal cytoreduction (R ≤ 1 cm) of which 92% without residual tumour. Minor complication rate was only 13%. Finally, we observed that the overall extent of tumour regression was related to better PFS (HR = 0.785, 95% CI 0.599-0.964) and better OS (HR = 0.707, 95% CI 0.482-0.943). The features 'fibrosis', 'necrosis' and the grade of 'tumour infiltration' were more often present compared

to other regressive changes and were separately analysed to tentatively investigate which features contributed most to the effect of the overall tumour regression score. It was suggested that less tumour infiltration and more necrosis were related to better PFS (infiltration: HR = 0.721, 95% CI 0.475-1.081; necrosis: HR = 0.341, 95% CI 0.087-0.878) and better OS (infiltration: HR = 0.717, 95% CI 0.445-1.140; necrosis: HR = 0.215, 95% CI 0.036-0.682), in contrast to fibrosis.

These data show that NACT followed by IDS is a valuable option for endometrial cancer with transperitoneal spread. Furthermore, the degree of regressive changes after NACT has been identified as a new prognostic marker.

Additionally, we enlarged the study population with 16 patients and extended the follow up. We found a response of 74% according to RECIST. Of the patients who had IDS, 94% had no residual tumour. Median PFS and OS were 12 and 20 months respectively. The analysis of these 46 patients confirms our previous results and conclusion (Fig. 4).

Although this should be confirmed in a larger study, given the notion that type II endometrial cancer is uncommon, it is unlikely to examine this in a large randomized study.

Conclusion

In conclusion, this clinical study adds to daily practice on two levels. Firstly, when information on molecular markers is needed to start targeted treatment, a biopsy of the recurrent tumour is the best guarantee to characterize the tumour correctly. Secondly, this study suggests that neoadjuvant chemotherapy followed by interval debulking is a valuable option in the treatment for endometrial cancer with transperitoneal spread. The chemotherapy induced regressive changes appear to be a new prognostic marker for women with advanced stage endometrial cancer.

Future studies should look into new biomarkers that predict antitumoral activity. Furthermore, one should search for mutations in endometrial cancer and analyse which mutation is sensitive for therapy.

In addition, novel drugs are currently under evaluation for patients with primary advanced or recurrent endometrial cancer. Ixabepilone, the first of a new class of microtubule-stabilizing drugs known as epothilones, has shown promising second-line activity. A phase III trial is currently comparing ixabepilone activity against standard chemotherapy (paclitaxel or doxorubicin) in the second-line treatment of endometrial carcinoma (NCT00883116 study synopsis, 2009). Moreover, GOG 86D will evaluate the benefit of integrating ixabepilone and targeted therapies into first-line treatment of endometrial carcinoma (3 treatment arms of carboplatin/paclitaxel/bevacizumab, carboplatin/ixabepilone/bevacizumab, and carboplatin/ taxane/ everolimus) (NCT00977574 study synopsis, 2010). In addition, various targeted therapies, including mTOR, EGFR and VEGF inhibitors, appear promising after failure of up to 2 previous chemotherapy regimens.

As results from these and other clinical trials become available in the next few years, it will hopefully be possible to define a better treatment sequence for patients with advanced endometrial carcinoma and improve clinical outcome.

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What is already known?

- Endometrial cancer is the most frequent malignancy of the female genital tract in the western world.
- Endometrial cancer can be divided into two main groups: Type I (endometrioid) endometrial cancer occurring in 80 % and Type II (serous, clear cell) endometrial cancer that occur in only 10% and are highly aggressive.
- The cornerstone in the treatment of endometrial cancer is surgery.
- Patients with advanced or recurrent disease are uncommon and receive systemic therapy (chemotherapy of hormone therapy). Despite treatment, survival is still poor.

What is new from this research?

- This study demonstrated that blood vessel space involvement and chemotherapy induced regressive changes are new prognostic markers.
- Since the tumour biology changes over time, a biopsy of the recurrent tumour characterizes the tumour correctly, especially when information on molecular markers is needed to start targeted treatment.
- Although HER-2 expression has been reported as the Achilles heel in endometrial cancer, 78% of patients in this study had a negative expression. Four patients with gene amplification were treated with paclitaxel-trastuzumab, however without response. These data suggest that trastuzumab does not seem promising in endometrial cancer.
- TC dose dense and TC weekly regimen is active in primary advanced or recurrent endometrial cancer. The hematologic toxicity however is considerable. The main benefit is a reduction in alopecia and neurotoxicity.
- Finally, this study suggests that neoadjuvant chemotherapy followed by interval debulking is a valuable option in the treatment for endometrial cancer with transperitoneal spread.

Which questions will these new questions arise?

- Future studies should look into new biomarkers that predict antitumoral activity.
- Studies should explore mutations in endometrial cancer and analyse which mutation is sensitive for therapy.

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