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Stage I grade 3 endometrioid adenocarcinoma of the endometrium: An analysis of clinical outcomes and patterns of recurrence

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Objectives: The optimal adjuvant treatment modality and patterns of recurrence for patients with stage I, grade 3 endometrial cancer (EC) are unclear. Therefore, we studied the patterns of recurrence and survival outcomes in patients with surgical stage I, grade 3 endometrioid adenocarcinoma of the endometrium (EA) treated with various treatment modalities.

Methods: A retrospective multi-institutional study of patients with stage I, grade 3 EA who underwent comprehensive surgical staging between the years 1988 and 2006 was performed. Data regarding preoperative, surgical and pathologic characteristics, adjuvant therapy and outcomes were collected. After surgery, patients were treated with either observation (OBS) or radiotherapy (RT: vaginal brachytherapy, whole pelvis or both). Data were analyzed using ANOVA and χ^2 tests.

Results: Data were collected for a total of 137 patients with a median age of 66 years. Fifteen (11%) were stage IA, 78 (57%) IB, and 44 (32%) IC. Forty-eight patients (35%) were noted to have lymphvascular space invasion (LVSI), the median tumor size was 3.9 cm and a mean of 18 lymph nodes (LNs) were removed per patient. Forty-four patients (32%) were observed and 93 (68%) were treated with RT. The majority of adjuvantly treated patients ($n=48$, 52%) received vaginal RT, 29 (31%) received pelvic RT, and 16 (17%) received vaginal + pelvic RT. There were no significant differences in age, number of lymph nodes or tumor size by adjuvant modality. LVSI and substage were noted to be significantly different by adjuvant modality, with greater LVSI noted in the RT group (16% in the OBS, 31% in the vaginal RT, 48% in the pelvic RT and 75% in the vaginal+pelvic RT groups, $P=0.001$) and a higher percentage of stage IC patients receiving pelvic or vaginal+pelvic RT (22% of the OBS, 23% of the vaginal RT, 48% of the pelvic RT and 75% of the vaginal+pelvic RT groups, $P=0.02$). Furthermore, LVSI was not present in any of the stage IA patients, whereas 28% of the stage IB and 59% of the stage IC patients had LVSI. After a median follow-up of 58 months (7-187), 18 recurrences (13%) were observed (Table 1). Ninety four percent of all recurrences were in patients with stage IB/IC disease. The mean time to recurrence was 22.5 months (5-74) and 82% of patients with recurrences had extrapelvic recurrences. There was no statistically significant difference in recurrence based on treatment modality or LVSI. Of the patients who did have extrapelvic recurrences, the majority were not salvagable, as 77% (10/13) died of their disease with a median time to death of 47 months. Progression-free survival and overall survival was 44 and 73 months in the OBS group versus 51.2 and 66 months in the RT group.

Conclusions: Patients with stage IB/IC, grade 3 endometrioid adenocarcinoma of the endometrium have a significant risk for extrapelvic recurrence with or without LVSI. In this setting, most patients will not be salvaged and will succumb to their disease. This study suggests that systemic therapy may be needed in the treatment of these patients.

Table 1

	Observation		Vaginal RT		Pelvic RT		Vaginal + pelvic RT		Total recurrences
	N	Recurrence	*N*	Recurrence	*N*	Recurrence	*N*	Recurrence	
Stage IA ($n=15$)	8	0	6	0	1	1 (100%)	0	0	1/15 (7%)
Stage IB ($n=78$)	27	4 (15%)	30	4 (13%)	14	2 (14.3%)	7	0	10/78 (13%)
Stage IC ($n=44$)	10	2 (20%)	11	1 (9%)	14	3 (21%)	9	1 (11%)	7/44 (16%)
All stages	44	Total: 6 (14%) Vaginal: 2 Pelvic: 0 Distant: 4	48	Total: 5 (10.4%) Vaginal: 0 Pelvic: 0 Vaginal+ distant: 3 Distant: 2	29	Total: 6 (21%) Vaginal: 0 Pelvic: 0 Vaginal + pelvic: 1 Vaginal+ distant:1 Distant: 4	16	Total: 1 (6.25%) Vaginal: 0 Pelvic: 0 Distant: 1	18/137 (13%)

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A multicenter evaluation of sequential multimodality therapy and clinical outcome for the treatment of advanced endometrial cancer

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Objectives: The appropriate sequencing of chemotherapy and radiation for the treatment of advanced endometrial cancer has not yet been determined. We sought to evaluate the outcome and adverse effects in patients with advanced-stage endometrial cancer treated with postoperative chemotherapy and radiation to determine whether there was an advantage to a particular sequencing modality.

Methods: A multicenter retrospective analysis of patients with surgical stage III and IV endometrial cancer from 1993 to 2007 was conducted. Inclusion criteria were comprehensive staging procedure including hysterectomy, bilateral salpingo-oophorectomy with or without selective pelvic/aortic lymphadenectomy, surgical debulking and treatment with adjuvant chemotherapy and radiation. Differences in frequencies of adverse events were tested with Pearson's χ^2 test for comparing proportions. Overall survival (OS) and progression-free survival (PFS) rates were calculated using Kaplan-Meier estimates. Estimated hazard ratios (HRs) were from multivariate Cox proportional hazard models.

Results: One hundred nine patients with advanced-stage endometrial cancer were identified who received postoperative adjuvant therapies: 41% ($n=45$) chemotherapy followed by radiation and then chemotherapy (CRC), 17% ($n=18$) radiation followed by chemotherapy (RC), and 42% ($n=46$) chemotherapy followed by radiation (CR). The median age was 62 years (range: 35-83); 48% had endometrioid tumors; and 90% were optimally debulked. There was no difference in the frequency of adverse effects due to either chemotherapy ($P=0.35$) or radiotherapy ($p=0.14$), or dose modifications ($P=0.055$) or delays ($P=0.80$), between the various sequencing modalities. There was a significant difference between the adjuvant treatment groups in both OS (log rank $P=0.011$) and PFS (log rank $P=0.025$), with those receiving CRC having a superior three-year OS (88%) and PFS (69%) compared with those receiving RC (54 and 47%) or CR (57 and 52%). After adjustment for stage, age, grade, race, therapy, histology and debulking status, the OS HR for therapy was 5.53 (95% CI=1.86-16.43) for RC and 2.64 (95% CI=1.02-6.87) for CR, compared with CRC ($P=0.0025$). When the analysis was restricted to optimally debulked patients, the adjusted HR for patients who were treated with either RC or CR indicated a significantly higher risk for disease progression (HR=3.67, 95% CI=1.32-10.23, and HR=2.28, 95% CI=0.99-5.29, respectively) and death (HR=6.98, 95% CI=2.12-22.97, and HR=2.73, 95% CI=0.96-7.75, respectively) ($P=0.0011$), compared with patients who received sequential CRC.

Conclusions: Compared with the other sequencing modalities with a similar adverse effect profile and dose alterations, sequential CRC was associated with improved survival in women with advanced-stage disease. Future clinical trials are needed to prospectively evaluate appropriate sequencing and types of adjuvant chemotherapy and radiotherapy for the treatment of advance-stage endometrial cancer.

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Treatment of high-risk endometrial carcinoma following hysterectomy using concurrent chemoradiotherapy with intensity-modulated radiotherapy delivered with helical tomotherapy, a prospective phase I/II trial: The best of modern therapy

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Objectives: On the basis of recent cooperative group clinical trials, patients with endometrial cancer at high risk for recurrence (stage III) are typically treated with adjuvant sequential chemotherapy and radiation. Intensity-modulated radiation therapy (IMRT) is an advanced method of delivering external-beam radiation that minimizes the volume of normal tissue irradiated (especially bone marrow) and thus, should decrease the toxicity of chemotherapy. Helical tomotherapy is a novel device with sophisticated imaging and treatment delivery features that are optimally suited for IMRT. The objective of this prospective trial was to investigate the acute and chronic toxicity of concurrent chemotherapy and IMRT using helical tomotherapy and to evaluate the effect on overall treatment time and patient outcomes.

Methods: Patients with stage III endometrial carcinoma (IIIA cytology only excluded)were treated with carboplatin (AUC 5 or 6) plus paclitaxel (175 mg/m^2) every three weeks initiated two to three weeks postsurgery. IMRT began approximately six to eight weeks following surgery and was given concurrently with chemotherapy. Patients were monitored for acute and chronic toxicity using CTC 3.0 and EORTC/RTOG Late Radiation Morbidity Scoring Schema. Survival data are from date of surgery to last follow-up or death.

Results: Twenty-six of a planned 30 patients were enrolled from April, 2006 to present, and 20 patients have completed therapy and have significant follow-up (>6 months) to be included in this report. Median age of the cohort was 64.5 (53-87), with a median follow-up for the live patients of 17 months. Pathologic assessment included tumor grade (1=20%, 2=30%, 3=50%), stage (IIIA [noncytology only]=20%, IIIC=80%), and histology (endometrioid=50%, mixed=30%, serous=15%, clear cell=5%); all patients had lymphvascular space invasion. Median treatment time for IMRT+brachytherapy was 55 days (47-67), with no patients requiring a treatment break. IMRT doses delivered to the pelvis (median: 51.2 Gy, range: 48-51.2)) and paraaortic region ($n=5$, median=51.2 Gy, range=48-51.2) were well tolerated with minimal gastrointestinal or genitourinary grade 3 ($n=5$) and no grade 4 toxicity. Chemotherapy was generally well tolerated, with 55% receiving optional prophylactic growth factor support allowing for minimal dose delays (all grade 3/4 acute toxicity was hematologic). Grade 3/4 chronic toxicity consisted of one patient with both grade 3 neuropathy and thromboembolism. Median total treatment time from surgery to completion of the combined therapy was 20 weeks (12-33). Six patients recurred or developed progressive disease; these consisted mostly of patients with serous histology with an average of eight positive lymph nodes.

Conclusions: IMRT helical tomotherapy appears to spare bone marrow, allowing for full-dose chemotherapy to be delivered concurrently with minimal toxicity. Overall treatment time is considerably shorter than with sequential regimens and thus, justifies further evaluation in future trials.

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Dietary vitamin D exposure reverses the effects of obesity-inducing high-fat diet on premalignant and malignant endometrial changes in Pten+/- mice

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Objectives: A growing body of epidemiologic and environmental evidence suggests that vitamin D may lower the risk of a number of epithelial malignancies, including endometrial adenocarcinoma. In this study, we sought to determine whether vitamin D exposure reverses endometrial carcinogenesis in an animal model and, furthermore, whether it modifies the markedly enhanced risk of endometrial carcinoma associated with obesity.

Methods: Heterozygous Pten+/- mice commonly develop endometrial hyperplasia between four and six months of life, and a proportion subsequently develop endometrial carcinoma. Both four-week-old female Pten+/- and wild-type (WT) mice were divided into four treatment groups ($n = 8$-12 per group) and fed an AIN93G-based diet containing either (1) 18% energy from fat and no added vitamin D, (2) 18% fat and 25,000 units of cholecalciferol/kg diet (~2× RDA for the dietary form of vitamin D), (3) 60% fat to induce obesity and no added vitamin D, and (4) 60% fat and 25,000 units of cholecalciferol/kg diet. Mice were kept on these diets until they were sacrificed at six months of age. The uterine endometrium was examined histologically for evidence of hyperplasia or malignancy, and the uterus for changes in estrogen receptor (ER)-α, ER-β, and progesterone receptor (PR) using reverse transcription polymerase chain reaction.
Results: Exposure to an obesity-inducing high-fat diet doubled body weight in WT mice ($P < 0.001$). Although the increase in body weight was also significant in Pten+/- mice ($P < 0.001$), it was notably smaller (26% increase) than in WT mice. None of the WT mice developed premalignant lesions, whereas 58% of Pten +/- mice did. Feeding Pten+/- mice a high-fat diet increased the premalignant and malignant lesions to 78%, with one mouse exhibiting endometrial adenocarcinoma. Dietary vitamin D exposure significantly decreased the incidence of these endometrial lesions in Pten+/- mice fed the high-fat diet to 25% (χ^2 test: $P < 0.001$). When the mRNA values in WT mice fed the control diet were used as the reference point, no changes in the expression of ER-α, ER-β, or PR were seen between WT and Pten+/- mice. Further, dietary exposures did not modify ER-α levels. ER-β levels were significantly increased by the high-fat diet ($P < 0.003$), and vitamin D exposure reversed the increase in WT mice but not in Pten+/- mice. Expression of PR was significantly elevated in WT mice fed a vitamin D-supplemented, high-fat diet ($P < 0.004$).
Conclusions: Our data confirm the known epidemiologic positive association between increased body weight and endometrial cancer risk. Dietary exposure to vitamin D may reverse the carcinogenic effect of obesity in the endometrium. The highest level of PR mRNA expression was seen in mice fed the vitamin D-supplemented, high-fat diet, and this diet also reversed the high fat diet-induced increase in ER-β mRNA expression. As these effects were seen only in WT mice, the mechanisms by which vitamin D can reverse the incidence of endometrial lesions in Pten+/- mice remain to be determined.

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Sentinel lymph node metastasis in patients with vulvar cancer mandates adjuvant groin treatment, independent of size

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Objectives: The Groningen International Study on Sentinel Nodes in Vulvar Cancer (GROINSS-V) recently indicated that the sentinel node (SN)procedure is a safe treatment option in early-stage vulvar cancer. Ultrastaging of SNs allows detection of so-called "micrometastases." However, the clinical significance of these micrometastases has never been determined. The aim of this study was to determine the prognostic impact of "micrometastases" in early-stage vulvar cancer patients.
Methods: SNs from all patients from GROINSS-V who were treated in the Dutch participating centers were analyzed. Pathological review of the SNs was performed by two pathologists without knowledge of clinical data and original pathological assessment.
Results: In total, 663 SNs from 239 patients were revised (2.8 SNs/patient): 512 originally negative SNs and 151 positive SNs. In 73 groins with a positive SN, a subsequent inguinofemoral lymphadenectomy was performed; in 25% of the groins additional metastases were found. In 22 groins single tumor cells were diagnosed only after pathology review, and therefore, no additional treatment had been given. No groin recurrences were observed in these patients. Overall, chances of additional metastases increased with size of SN metastasis: 5.4% when only single tumor cells were found, 28% when the SN metastasis was ≥1 mm, and 45% when the SN metastasis was ≥5 mm (Table 1).
Conclusions: Chances of additional inguinofemoral metastases in patients with early-stage vulvar cancer with a positive SN increase with the size of the SN metastasis. There is no clear cutoff point for size of SN metastasis below which the chance of additional metastases is negligible. Patients whose groins contain a SN with a metastasis, no matter what the size, require additional therapy.

Table 1
Percentage of additional metastases relative to size of metastasis in the SN

Size of SN metastasis	Number of groins	Additional metastases
1-10 cells	37	2
>10-100 cells	5	0
≤1 mm	12	1
>1-2 mm	10	1
>2-5 mm	13	2
>5-10 mm	13	5
>10 mm	7	4
Total	97	14