

# Adjuvant Carboplatin and Paclitaxel Chemotherapy and Involved Field Radiation in Women with High-Risk Endometrial Cancer: A Sequential Approach

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## ABSTRACT

**Purpose:** To determine the feasibility of adjuvant paclitaxel and carboplatin chemotherapy interposed with involved field radiotherapy for women with advanced endometrial cancer.

**Methods and Materials:** This was a prospective cohort study of women with Stage III and IV endometrial cancer. Adjuvant therapy consisted of four cycles of paclitaxel (175mg/m<sup>2</sup>) and carboplatin (350mg/m<sup>2</sup>) every three weeks, followed sequentially by external beam radiotherapy (RT) to the pelvis (45 Gy), followed by an additional two cycles of chemotherapy. Para-aortic RT and/or HDR vault brachytherapy (BT) were added at the discretion of the treating physician.

**Results:** Thirty-three patients (median age 63 years) received treatment between April 2002 and June 2005. Median follow-up was 21 months. Stage distribution was as follows: IIIA (21%), IIIC (70%), IVB (9%). Combination chemotherapy was successfully administered to 30 (91%) and 25 patients (76%), before and after RT respectively. Nine patients (27%) experienced acute Grade 3 or 4 chemotherapy toxicities. All patients completed pelvic RT; 19 (58%) received standard 4-field RT and 14 (42%) received IMRT. Ten (30%) received extended field radiation. Four patients (12%) experienced acute Grade 3 or 4 RT toxicities. Six patients (18%) developed chronic RT toxicity. There were no treatment-related deaths. Two-year disease-free and overall survival rates were both 55%. There was only one pelvic relapse (3%).

**Conclusions:** Adjuvant treatment with combination chemotherapy interposed with involved field radiation in advanced endometrial cancer was well tolerated. This protocol may be suitable for further evaluation in a clinical trial.

## INTRODUCTION

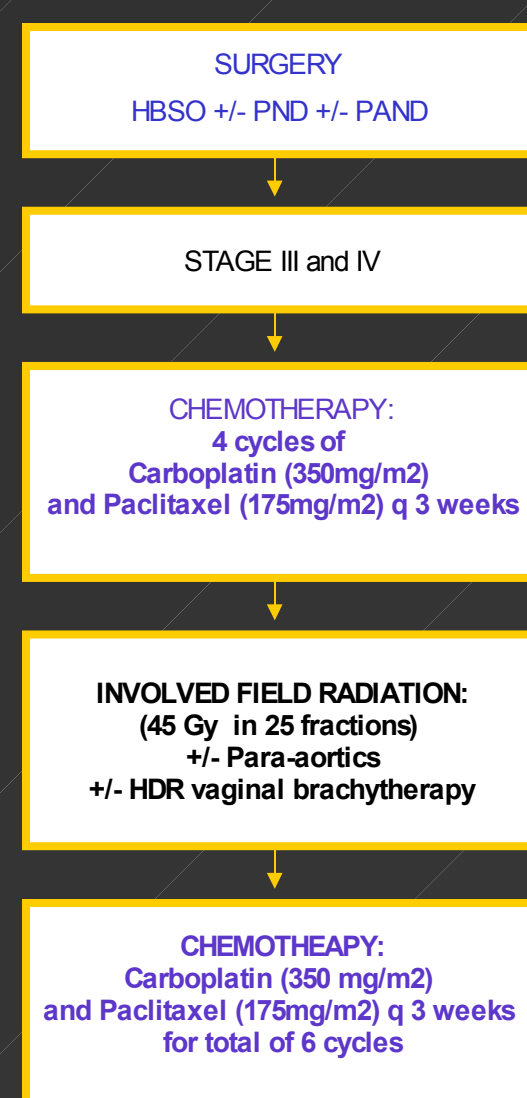
Endometrial Cancer is the fourth most common malignancy in women and the most common gynecologic malignancy in North America. Women with extra-uterine disease (Stage III and IV) are at significant risk of death with 5 year survival rates ranging from 30 – 50%.

Pelvic radiation reduces local relapse in women with high risk tumors (high grade, LVI, deep myometrial invasion) but the risk of systemic relapse remains high, suggesting a role for chemotherapy.

Phase II trials demonstrate good response rates to paclitaxel and carboplatin (60-78%). However, treatment with chemotherapy alone appears to be associated with high rates of pelvic relapse (18 – 46%).

Given the high recurrence rates observed with single modality therapy, we developed a pilot protocol using adjuvant carboplatin and paclitaxel with involved field radiation for women with advanced endometrial cancer. The primary aim of the study was to assess toxicity. Secondary objectives included assessment of disease-free and overall survival.

## METHODS



### STUDY PROTOCOL:

- Prospective cohort study
- Exclusion criteria: previous CT or RT, KPS < 60, previous malignancy within 5 yrs (except BCC, SCC skin), sarcoma, hepatic or pulmonary metastases

### Chemotherapy:

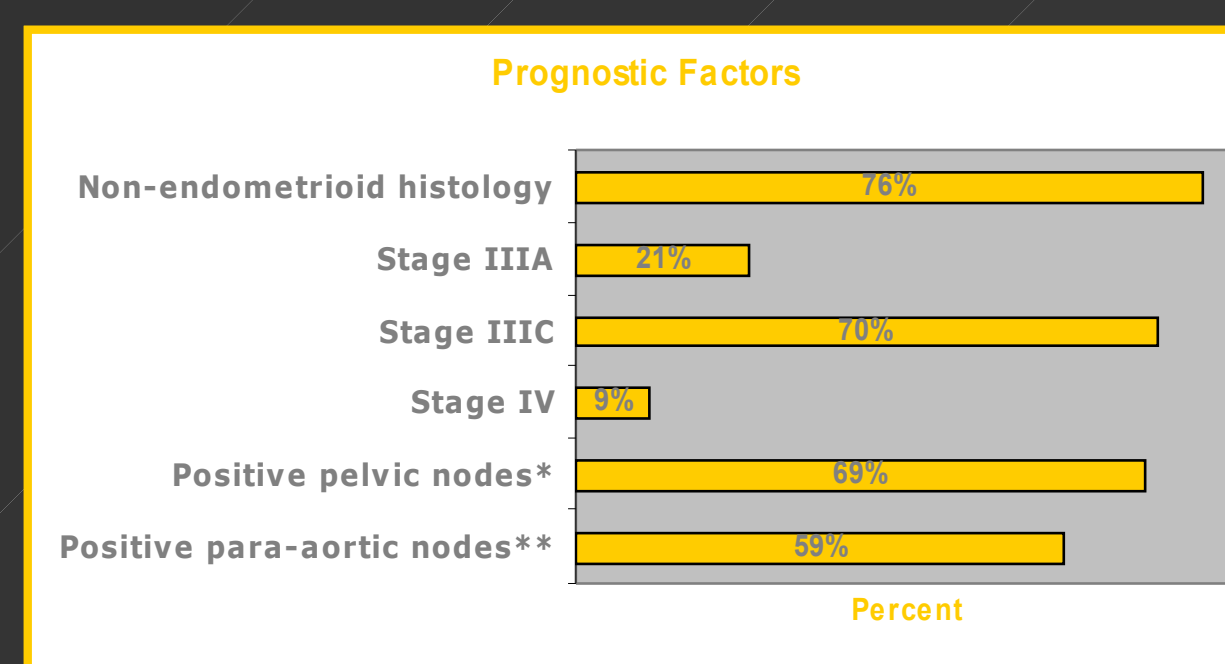
- Delayed 1 week if neutrophils < 1.5, platelets < 100, creatinine > 120
- Carboplatin reduced by 20% if Cr > 120 for more than 1 week
- Paclitaxel reduced by 20% for Gr. 3/4 peripheral neuropathy and discontinued for hypersensitivity reaction

### Radiation:

- External Beam Radiation
  - standard 4-field or IMRT
  - +/- extended fields
  - +/- vault brachytherapy

## RESULTS

### Patient and Tumor Characteristics:



- 33 pts, median age 63 (range 46 - 83)

- 30 (91%) had HBSO + node dissection
  - \* 29 had pelvic node dissection
  - \*\* 17 had para-aortic node dissection

- 6 (18%) had macroscopic residual disease (< 1cm, except 1 pt)

### Chemotherapy:

#### Pre-radiation chemotherapy

- 30 (91%) completed pre-radiation chemotherapy

Event	Total	Reasons
Grade 3 or 4 toxicity	7 (22%) (6 pts)	<ul style="list-style-type: none"> <li>• 3 paclitaxel hypersensitivity*</li> <li>• 1 neuropathy</li> <li>• 1 fatigue</li> <li>• 1 nausea/vomiting</li> <li>• 1 neutropenia</li> </ul>
Dose Reduction	5 (15%)	<ul style="list-style-type: none"> <li>• 4 paclitaxel and carboplatin [Gr. 2/3 neuropathy, old age**]</li> <li>• 1 carboplatin [Gr. 1 ↑ in Cr]</li> </ul>
Delay	1 (4%)	<ul style="list-style-type: none"> <li>• pancytopenia [Gr. 1/2]</li> </ul>
Discontinuation of Therapy	3 (9%)	<ul style="list-style-type: none"> <li>• 1 paclitaxel and carboplatin [refusal***]</li> <li>• 2 paclitaxel hypersensitivity</li> </ul>

\* All during first cycle. One pt continued paclitaxel with 12 hour infusion  
 \*\* Chemotherapy dose reduced at the discretion of attending physician  
 \*\*\* 60 y/o pt refused further chemotherapy because of fatigue, myalgias, nausea and vomiting (completed pelvic radiation)

#### Post-radiation chemotherapy

- 25 (76%) completed post-radiation chemotherapy

Event	Total	Reasons
Grade 3 or 4 toxicity	4 (12%) (3 pts)	<ul style="list-style-type: none"> <li>• 1 fatigue</li> <li>• 3 neuropathy</li> </ul>
Dose Reduction	3 *(9%)	<ul style="list-style-type: none"> <li>• 1 carboplatin [prolonged Gr. 4 neutropenia]</li> <li>• 2 paclitaxel [Gr. 2/3 neuropathy]</li> </ul>
Delay	4 (12%)	<ul style="list-style-type: none"> <li>• neutropenia [Gr. 4]</li> <li>• anemia [Gr. 2]</li> <li>• thrombocytopenia [Gr. 3]</li> <li>• neuropathy [Gr. 3]</li> </ul>
Discontinuation of Therapy	5**(15%)	<ul style="list-style-type: none"> <li>• 1 paclitaxel and carboplatin [refusal]</li> <li>• 4 paclitaxel [1prolonged G. 4 neutropenia &amp; 3 G. 3 neuropathy]</li> </ul>

\* In addition to 5 dose reductions maintained from pre-radiation chemotherapy (∴ total dose reductions 8/33 or 24%)  
 \*\* In addition to 3 chemotherapy discontinuations maintained from pre-radiation chemotherapy (∴ total discontinuations 8/33 or 24%)

### Radiation:

- 33 (100%) completed external beam radiation
  - 19 (58%) standard four-field, 14 (42%) IMRT
  - 10 (30%) extended fields
  - 3 delays (1-4 days) due to neutropenia
- 32 (97%) received HDR vault brachytherapy, one refused to finish
  - 23 (72%) had 15 Gy/3, 3 (9%) had 18 Gy/3 and 5 (16%) had 22.5 Gy/3

### Acute Radiation Toxicity:

Toxicity	Standard 4-field (n=19)		IMRT (n=14)	
	Grade 3	Grade 4	Grade 3	Grade 4
Diarrhea	0	0	0	0
Urinary	0	0	0	0
Nausea/emesis	0	0	0	0
Proctitis	1	0	0	0
Neutropenia	0	3	0	0

- 4 (12%) had Gr. 3/4 acute RT toxicity

- 3 delays (1-4 d) due to neutropenia

### Chronic Radiation Toxicity:

Toxicity	Standard 4-field (n=19)		IMRT (n=14)	
	Grade 3	Grade 4	Grade 3	Grade 4
Cystitis	0	0	2	0
Proctitis	1	0	3	0
Small bowel obstruction	1	0	0	0

- 5 (15%) had chronic RT toxicity

- 2 had RT proctitis and cystitis (pelvis only, IMRT)

- 1 treated with extended fields

### Outcomes:

- Median follow up 21 months (range 9 - 43 months)
- 14 (42%) relapsed, 13 died of disease
- 1 (3%) failed in pelvis concurrently with distant relapse
- 2 year disease-free and overall survival rates both 55%

### Sites and Frequency of Initial Relapse:

Site of relapse	N (% of total)
Distant (beyond radiated field)	13 (39%)
• Bone	3
• Lung †	5
• Liver	2
• Perihepatic	1
• Supraclavicular lymph node	1
• Peritoneal carcinomatosis	5
Pelvic	1 (3%)

† relapsed in lung and pelvis

## SUMMARY

- 90% completed pre-radiation chemotherapy, 76% completed post-radiation chemotherapy
- 100% completed external beam radiation
- 39% had acute Grade 3 and 4 toxicities
- 3% pelvic relapse rate
- 2-year disease-free and overall survival rates both 55%

## CONCLUSIONS

Treatment of advanced endometrial cancer with sequential carboplatin/ paclitaxel and involved field radiation has an acceptable toxicity profile and a very low pelvic failure rate (3%). The pelvic failure rate in our study is much lower than observed rates with chemotherapy alone (18 – 46%), suggesting that radiation may significantly reduce the risk of pelvic relapse.

There are too few patients in our study to compare the toxicity profiles of women treated with standard four-field radiation vs. IMRT and longer follow-up is required to assess survival outcomes.

Combined modality treatment is feasible and radiation appears to be more effective in controlling pelvic disease than chemotherapy alone. We feel this protocol should be considered for further investigation against established chemotherapy regimes.

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