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**Original Article**

# A Prospective Study of Adjuvant Radiotherapy Concomitant with Cisplatin Followed by Paclitaxel-Carboplatin in High Risk Early Stage Endometrial Cancer

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**Background:** The management of high risk early stage endometrial carcinoma (EC) remains controversial with ongoing efforts to improve the treatment outcome of this group of patients.
**Aim:** To study the efficacy and toxicity of adjuvant radiotherapy (RTH) concomitant with cisplatin followed by paclitaxel, carboplatin in high risk early stage EC.
**Methods:** High-risk EC was defined as having any of the following: myometrial invasion >50%, grade 3 histology, lymphovascular invasion, stage II/IIIA and clear cell or papillary serous histology. After surgery, patients were enrolled to receive adjuvant pelvic external beam RTH (46.8- 50.4 Gy) concomitant with cisplatin (50 mg/m$^2$) every 21 days followed by 4 cycles of paclitaxel (175 mg/m$^2$) and carboplatin (AUC5) every 21 days. The primary end point was disease-free survival (DFS) and the secondary end points were tolerability and toxicity.
**Results:** From June-2013 to March-2016, 21 patients were treated. The median follow up time was 21 months (range: 9- 33). Nineteen patients (90.4%) completed RTH and 4 cycles of adjuvant chemotherapy. Severe hematological toxicity (Grade 3 /4) was seen in 5 (23.8%) patients and was mainly neutropenia. Grade 3- 4 non-hematological toxicity was seen in 3 (14.3%) patients. Disease recurrence was recorded in 3 (14%) patients. The 1 and 2-year DFS were 93.8% and 73.8%, respectively. There were no treatment-related deaths.
**Conclusion:** The results suggest that adjuvant sequential RTH concomitant with cisplatin followed by paclitaxel, carboplatin is a well-tolerated and feasible regimen in patients with higher risk EC. A phase III trial is warranted.

**Key words:** Endometrial cancer, High risk, Concomitant radiotherapy-chemotherapy

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## INTRODUCTION

Endometrial carcinoma (EC) is the most common malignancy of the female genital tract in the United States. In 2015, the estimated number of new uterine cancer cases is 54, 870 with 10, 170 deaths resulting from the disease[1].

In approximately 70% of patients with EC the invasive neoplasm is confined to the uterus at diagnosis[2]. This is because vaginal bleeding, especially in postmenopausal women, lead patients to seek medical advice when the disease is localized[3].

However, the increase in mortality due to EC is more rapid than its incidence[4].

This increased mortality may be related to an increased rate of advanced stage cancers, high risk histologies (e.g. serous carcinomas) and older age. Analysis of Surveillance, Epidemiology, and End results (SEER) data suggests that survival has increased in younger patients in early stage5. Beside grade and depth of myometrial invasion, other risk factors associate with poor prognosis e.g., age, tumor size, lymphovascular space invasion (LVSI) and tumor involvement of the lower uterine segment[6, 7]. To further improve outcome for patients with the disease, physicians need to identify high risk patients and to tailor treatment appropriately to provide the best long term survival.

In this prospective study we aimed to determine the efficacy and toxicity of adjuvant radiotherapy (RTH) concomitant with cisplatin, followed by 4 cycles of paclitaxel-carboplatin in patients with early stages high risk EC and to study the impact of this regimen on the rate and sites of recurrence.

## METHODS

### *Selection of patients*

This prospective study included 21 patients treated at the Clinical Oncology Department, Ain Shams University, from June 2013 till March 2016.

Inclusion criteria are followed:

I. Histologically-confirmed EC, with one of the following postoperative FIGO (International Federation of Gynecology and Obstetrics) stages[8]:

1- Endometrioid EC stage IA: G3 or with LVSI
2- Endometrioid EC stage IB
3- Endometrioid EC stage II/IIIA
4- Clear-cell and papillary serous EC stage I/II/IIIA

II. Other inclusion criteria included: Eastern Cooperative Oncology Group performance 0- 2, adequate bone marrow function, creatinine ≤ 1.25 upper normal limit (UNL), glomerular filtration rate ≥ 60 by Cockcroft formula, aspartate transaminase and alanine transaminase ≤ 3 × UNL, total bilirubin ≤ 1.5 mg/mm$^3$ and written informed consent.

Noteworthy; each prognostic factor was considered separately. If a patient had one of the risk factor, she was enrolled in our study and considered at higher risk.

Patients were excluded in case of having either uterine sarcoma (including carcinosarcoma), or residual macroscopic tumor after surgery, or previous malignancy, or previous pelvic RTH, or uncontrolled medical disease or baseline peripheral neuropathy grade ≥ 2.

***Treatment***

Patients were enrolled post total abdominal hysterectomy and bilateral salpingo-oophorectomy ± lymphadenectomy. Patients received adjuvant external beam two-dimensional radiotherapy (RTH) with a dose ranging from 46.8 to 50.4 Gy, 5 fractions/ week, 180cGy or 200cGy /fraction with high energy linear accelator either 6 MeV or 10 MeV according to the separation of the patients. Concomitant cisplatin (50 mg/m$^2$) was administered every 21 days. This was followed by 4 cycles of paclitaxel (175 mg/m$^2$) and carboplatin (AUC5) every 21 days.

The primary end point was the disease-free survival (DFS) and the secondary end points were tolerability and toxicity.

Acute toxicities were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI-CTCAE v4) [9].

Late radiation toxicities (occurring > 90 days after RTH) were assessed by the Late Effects Normal Tissue Task Force subjective, objective, management and analytic (LENT-SOMA) scale[10].

***Statistical analysis***

Data of 21 patients were calculated using EPI Info 2002 for a DFS of 88.6%+/-13% at confidence interval 95%. Descriptive statistics were used to summarize patients' characteristics and treatment profile. DFS was defined as the time from the date of the primary treatment which is the date of surgery at our study, to the date of disease progression or death from any cause. DFS was analyzed using the Kaplan-Meier method.

## RESULTS

Patients' characteristics are illustrated in Table 1.

All patients had at least a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Twelve (57.1%) patients underwent pelvic lymphadenectomy with a median of 11 dissected lymph nodes (range: 2 -31).

Based on the new ESMO-ESGO-ESTRO consensus[11], 13 (62%) patients were high risk (stage IB G3, stage II/III with no residual, or non-endometrioid histology), 1 (4.8%) was intermediate high risk (stage IA G3), and 7 (33%) were intermediate risk (stage IB G1&2 without LVSI).

The median time from surgery to the beginning of RTH was 40 days (range: 21 - 90 days). Only 7 patients (33.3%) received their RTH within the 6 weeks postoperative period. Fourteen (66.6%) patients received their RTH > 6 weeks postoperative. Four patients (19%) were very late (> 8 weeks post-surgery). They all had completed external beam RTH to the pelvis to a total dose of 46.8 - 50.4 Gy.

Acute toxicities with radiation are detailed in Table 2. Grade 3 or 4 radiation toxicities were seen in 2 (9.5%) patients.

In regards to late radiation toxicities, two (9.5%) patients had grade 2 large bowel toxicity in the form of increased bowel movements. Two (9.5%) patients had grade 2 urinary symptoms in the form of mild dysuria and frequency. Moderate hyperpigmentation grade 2 was seen in 2 (9.5%) patients. As a consequential late effect evolving out of a persistent severe early effect, severe rectal pain accompanied with proctitis seen in one patient (4.8%). Vaginal dryness symptoms were mild, vaginal atrophy or narrowing could not be assessed properly. Grade 3 or 4 late gastrointestinal or genitourinary toxicities were not observed.

The time to chemotherapy (CTH) after finishing RTH was less variable, ranged between 21 to 55 days with a mean of 28.3 days. Of the 21 patients, 2 didn't complete the 4 cycles of paclitaxel-carboplatin. The first one was high risk stage II who decided to be withdrawn from the study after experiencing febrile neutropenia and then she lost to follow up. The second received 2 cycles and experienced grade 4 febrile neutropenia and it was the decision of gynecological committee not to continue for 4 cycles.

There were no episodes of sepsis or CTH related deaths. Myelotoxicity especially neutropenia was the leading adverse event. Overall grade 3/ 4 hematological toxicity was seen in 23.8% (5 / 21) of the patients, it was mainly neutropenia. Three patients experienced febrile neutropenia necessitating hospitalization, intravenous antibiotics, granulocyte colony stimulating factor and supportive treatment. Anemia was seen in 19% (4 / 21) patients and it was maximum grade 2. Only one patient experienced thrombocytopenia and it was grade 2. Overall hematological toxicities were manageable and without clinical sequelae (Table 3).

Generally, non-hematological toxicities were mild. Grade 1 and 2 adverse events were mainly related to bony

aches and myalgia it occurred in 15 of the 21 patients (71.42%). Peripheral neuropathy was also a common adverse event seen in 12 patients (47.6%), 10 of them (33.33%) the toxicity was mild grade 12- and only 2 patients (9.5%) experienced more severe symptoms limiting their self-care, grade 3 neuropathy. Only one patient experienced grade 3 diarrhea, more than 7 times daily accompanied with abdominal pain while on the paclitaxel-carboplatin CTH regimen.

So, the overall grade 3 non-hematological toxicity was seen in 3 patients (14.28%). No one had experienced grade 4 toxicity. None of the patients experienced allergic reaction or other unexpected toxicities.

The median follow up time was 21 months (range 9- 33 months) and only one patient lost to follow up. Three (14.28%) of the 21 patients experienced a recurrence and they were in the high risk group. The details of these 3 patients are shown in Table 4.

None of the patients developed distant metastases other than the para-aortic lymph nodes, and none of the patients died due to any cause.

DFS at 1 year was 93.8% at 2 years was 73.8%. The median DFS was not reached. The mean DFS was 36.2 months (95% CI: 30.4 – 41.9). Figure 1 shows Kaplan-Meier survival curve of DFS.

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**Table 1:** Patients' characteristics

| | No. | % |
|---|---|---|
| **Age** (years) | | |
| < 60 | 13 | 61.9 |
| ≥ 60 | 8 | 38.1 |
| Mean (± SD) | 56.4 (± 9.31) | |
| Median (range) | 56 (40-72) | |
| **Histology** | | |
| Endometrioid | 20 | 95.2 |
| Papillary serous | 1 | 4.8 |
| **Grade** | | |
| 2 | 16 | 76.2 |
| 3 | 5 | 23.8 |
| **Stage** | | |
| IA | 1 | 4.8 |
| IB | 9 | 42.9 |
| II | 8 | 38.1 |
| IIIA | 3 | 14.3 |
| **Lymphovascular involvement** | | |
| Absent | 15 | 71.4 |
| Present | 6 | 28.6 |
| **Lymphadenectomy** | | |
| Done | | |
| ≥ 12 lymph nodes | 6 | 28.6 |
| 2 to 11 lymph nodes | 6 | 28.6 |
| Not done | 9 | 42.9 |

**Table 2:** Frequency of acute radiation toxicity

| Toxicity | Grade 2 | | Grade 3 | | Grade 4 | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| **Genitourinary** | | | | | | |
| Cystitis | 2 | 9.5 | 0 | 0 | 0 | 0 |
| **Gastrointestinal** | | | | | | |
| Diarrhea | 3 | 14.3 | 1 | 4.8 | 0 | 0 |
| Proctitis | 1 | 4.8 | 1 | 4.8 | 0 | 0 |

**Table 3:** Hematological toxicity

| Hematological toxicity | G1 | | G2 | | G3 | | G4 | |
|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % |
| Neutropenia | 0 | 0 | 2 | 9.5 | 3 | 14.3 | 2 | 9.5 |
| Anemia | 1 | 4.8 | 3 | 14.3 | 0 | 0 | 0 | 0 |
| Throbmocytopenia | 0 | 0 | 1 | 4.8 | 0 | 0 | 0 | 0 |
| Febrile neutropenia | 0 | 0 | 0 | 0 | 1 | 4.8 | 1 | 4.8 |

**Table 4:** Details of three patients with disease recurrence

| Patient | Pathology | LN dissection | Recurrence site | Time to recurrence | Time from surgery to RTH | Time from RTH to CTH | No of CTH cycles |
|---|---|---|---|---|---|---|---|
| **1** | Stage II G2 endometrioid | Not done | Para-aortic LN | 24 months | 50 days | 28 days | 2 cycles |
| **2** | Stage II G2 endometrioid | Not done | Para-aortic LN | 20 months | 47 days | 23 days | 4 cycles |
| **3** | Stage Ib G3, +ve LVSI | Yes, 14 LN | Vaginal stump | 12 months | 47 days | 24 days | 4 cycles |

***LN:*** *lymph nodes*, ***LVSI:*** *Lympho-vascular space invasion,* ***CTH:*** *chemotherapy, RTH: radiotherapy*

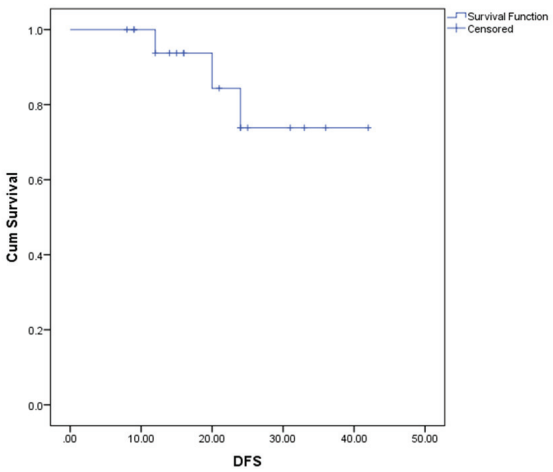


**Figure 1:** Kaplan-Meier survival curve of disease-free survival

## DISCUSSION

The management of high risk early stage EC remains controversial. Although the addition of adjuvant pelvic RTH had reduced the local recurrence, a higher rate of local recurrence and distant metastases remains in patients with higher risk that prompted evaluation of adjuvant CTH.

It is evident that even when pelvic lymph nodes are uninvolved, high risk uterine factors as higher grade, deep myometrial invasion, lymphovascular invasion and cervical involvement predict for a risk of recurrence in the absence of adjuvant therapy.

In the GOG 99 trial, which included 392 patients, stage IB, II endometrioid EC, other histology were excluded and pelvic and para-aortic lymph node dissection were mandatory in that trial, the addition of RTH for this group of patients reduced recurrence compared to no adjuvant therapy. Patients who received adjuvant RTH had a lower recurrence risk 13% but more than half of the recurrences were distant. This relatively high rate of distant metastases prompted evaluating the addition of adjuvant CTH to RTH for this group of patients at relatively higher risk[12]. These findings concur with those of another population-based study in which the prognosis of EC patients with 2 or 3 risk factors and –ve lymph nodes was worse than those with none or one risk factor and +ve lymph nodes[13].

In PORTEC 1 trial, multicenter randomized phase III trial which included 715 patients stage I EC, a total of 104 patients with deep myometrial invasion and grade 3 were not eligible for randomization due to their high risk and they received the adjuvant RTH. In the contrary of GOG 99 trial, they did not undergo pelvic and para-aortic lymph-adenectomy. Noteworthy, the majority of recurrences were distant in this subgroup of patients with 31% distant recurrence and 14% locoregional[14].

The afore mentioned showed poorer outcomes for high risk early stage and the higher rate of recurrence provide the rationale for testing the addition of adjuvant systemic CTH.

In the current work, we enrolled, 21 patients with different risk levels according to the new classification of the ESMO-ESGO-ESTRO consensus[11] as we have designed this in 2013 before publish of that consensus.

In our study, lymph node dissection was optional. Three of the included 21 patients experienced a recurrence with 24 months cumulative incidence rate of recurrence (CIR) of 14.28%. The two-year DFS was 73.8%.

North Eastern German Society of Gynecological Oncology (NOGGO) conducted a prospective phase II study of adjuvant sequential chemo-radiation in high risk EC. They enrolled 35 patients from 2004 to 2008 with the same inclusion criteria as our study in addition to inclusion of stage IIIC. Pelvic and para-aortic lymphadenectomy were mandatory. They gave the adjuvant CTH first, 4 cycles of paclitaxel/carboplatin followed by external beam RTH total dose of 45 Gy followed by vaginal vault brachytherapy (3 × 5 Gy d 1, 3, 5) afterloading techniques. Two patients were lost to follow up, so of the 33 patients, 8 experienced recurrence (24.2%). The two-year DFS was 75.8[15]%.

Compared to our study the cumulative incidence risk of recurrence was higher in the NOGGO trial. This difference may be attributed to the inclusion of stage IIIC in the German trial as they represented 45.7% of the patients. However, the two-year DFS was nearly the same. The benefit of CTH in addition to pelvic RTH for early stage EC has also been demonstrated in two European phase III randomized trials, the NSGO-EORTC (Nordic Society of Gynecological Oncology - European Organization for Research and Treatment of Cancer) and MaNGO (Mario Negri Institute) trials.In the NSGO-EORTC, RTH was applied according to the individual departmental guidelines ± optional brachytherapy. CTH was applied before or after RTH. Initial defined as consisting of doxorubicin and cisplatin, CTH was subsequently changed to that's of physician's choice. Between 1996 and 2007, a total of 383 patients were enrolled, initially they included stage I. Later they included stage II and III. Lymph node dissection was optional. In this study, the recurrence rate was 46 /191 patients (24%) and 28/ 187 patients (15%) in the RTH and the RTH-CTH respectively[16].

The MaNGO trial included 157 patients stage IIB, IIIA (+ve cytology only) and IIIC. Serous and clear cell were excluded and lymphadenectomy was optional. They gave the CTH. First 30 days post-surgery, doxorubicin/cisplatin 3 cycles then RTH. The other arm received RTH only. Progression was seen in 24 /76 (32%) in the RTH arm, compared to 15/ 80 (19%) in the CTH-RTH arm. But this difference was not statistically significant[17].

Chemotherapy sequential to RTH in the NSGO-EORTC trial was associated with decrease of 36% in the risk of relapse/death. Analysis of data pooled from the NSGO-EORTC and MaNGO trials showed that the progression was seen in 76 /267 (28%) in the RTH arm versus 53 /267 (28%) in the RTH arm *versus* 53/ 267 (20%) in the CTH-RTH arm. This result was statistically significant with p-value = 0.009. A five-year DFS was 69% and 78% in RTH *versus* CTH-RTH, respectively[17]. But this trial had the following limitations; first they included patients of different risk levels, second they used different CTH regimens, while the majority was anthracycline and platinum. The objective of these studies was to find out if systemic therapy added to RTH could improve the efficacy of any specific regimen. So, it was thought that it is appropriate to allow different regimens to increase inclusion rate. Finally, lymphadenectomy was optional.

The higher rate of recurrence in the NSGO-EORTC and MaNGO trials compared to ours are likely the results of the inclusion of higher stage (78% stage I and II) and non-endometrioid histology (29%) of patients, as in our study stage I and II represented 85.8% and there was only one case papillary serous histology representing 4.76%.

The outcomes of combined modality adjuvant treatment were also investigated in the RTOG 9708 phase II trial which included 46 patients with high risk EC. After treatment with concurrent RTH and cisplatin, vaginal brachytherapy and 4 cycles of cisplatin (50 mg/$m^2$) and paclitaxel (175 mg/$m^2$) were administered. At 24 months, the locoregional recurrence was 5%, and distant recurrence was 17%, respectively (in total 22%). The two-year DFS was 83% [18].

Compared to our study, one patient (4.76%) experienced loco-regional recurrence, which is the same incidence as with RTOG trial, which may show that external beam RTH without brachytherapy give good local control in EC patients. Two of our patients (9.5%) experienced para-aortic recurrence, which is a lower percentage compared to the 17% of the RTOG trial. Which may be explained by the inclusion of 10 patients (22%) stage IIIC and 17 (39%) stage IIIA in the RTOG.

In 2013, Jutzi and colleagues published a population based retrospective cohort study of patients with high risk early stage EC received adjuvant paclitaxel-carboplatin followed by RTH after primary surgery minimum hysterectomy. They were compared to 17 patients historical cohort who all underwent surgery besides lymphadenectomy followed by RTH. High risk was defined as the presence of two or more high risk uterine factors: grade 3, > 50% myometrial invasion and or cervical stromal involvement.The CTH-RTH arm included 55 women. Four (7.3%) patients developed recurrence, including three with distant recurrence and one with both a pelvic and para-aortic nodal recurrence. The historical cohort 5 patients of 17 recurred (29.4%) at a median of 17 months (6- 17 months), including 3 pelvic and 2 distant (bone, abdomen) recurrences. The five-year progression free survival rates were

88.6% and 97.3% respectively. The reduction in recurrence rate was not significant[19].

The previous retrospective cohort study showed better results than ours.

In our study, 57.14% of patients underwent pelvic lymphadenectomy or sampling. None of our patients had para-aortic lymphadenectomy, while in the study by Jutzi et al. 60% underwent pelvic lymphadenectomy and 5.4% underwent para-aortic lymphadenectomy. Moreover, Jutzi et al didn't include stage IIIA but we included with a rate of (14.3%). Finally, in our trial 14 patients (66.6%) started their adjuvant RTH after more than 6 weeks from surgery and 6 of those 14 started even after 8 weeks. In the previous study, all patients started RTH 30 days after CTH with only one patient who was delayed due to hip fracture.

An Egyptian retrospective study from Mansoura reviewed stage I and II EC with one or more of the following risk factors; LVSI, grade 3, aggressive pathology, age >60 years. Arm I included 57 patients who received RTH alone, arm II included 51 patients who received adjuvant RTH and then paclitaxel-carboplatin. After a median follow up of 48 months, the relapse rate was higher in arm I than in arm II (22.7% vs 9.8%). A 5-year PFS was 66.7% in arm I *versus* 84.3% in arm II (p = 0.03) [20]. This study from Mansoura had lower recurrence rate and longer PFS than ours, which may be due to inclusion of only stage I and II (i.e., without stage IIIA).

In a phase II trial from the 70s, treatment with doxorubicin resulted in an encouraging response rate of 37% among patients with advanced/recurrent EC[21]. Later, the addition of cisplatin prolonged progression-free survival [22]. After that, and based on the promising results of paclitaxel as a single agent, the GOG 177 trial compared a three drugs (taxane, anthracycline and platinum [TAP]) regimen to doxorubicin plus cisplatin. The TAP regimen resulted in a significantly better OS. However, the TAP regimen was associated with significant toxicity [23].

Then, GOG 209 trial was launched in 2003. This was a phase III randomized controlled assessing whether carboplatin-paclitaxel is not inferior in survival to TAP. Preliminary results showed that carboplatin-paclitaxel is not inferior in terms of PFS and OS[24]. That is the reason why we have chosen paclitaxel-carboplatin in our study.

In the RTOG 9708 phase II trial, patients received pelvic RTH with cisplatin followed by vaginal brachytherapy and 4 cycles of cisplatin-paclitaxel. The toxicity was grade 1 in 7%, grade 2 in 9%, grade 3 in 21% and grade 4 in 62%. Severe toxicity was primarily hematologic. This study had shown more grade 3 -4 toxicity compared to ours, which supports that paclitaxel-carboplatin is preferred over paclitaxel-cisplatin.

Compared to the German NOGGO trial, where patients had the same regimen as ours, but the CTH was given prior to RTH, the overall grade 3 -4 hematological toxicity was 25.6% *versus* 23.8% in our study.

Grade 3 -4 non hematological toxicity were rare < 3% *versus* 14.28% in our study, our patients experienced more grade 3 neuropathy than the German population but we have no explanation except population variability in grade 3- 4 non hematological toxicity. Similar to our results regarding the hematological toxicity, which showed that CTH before RTH or the opposite did not differ regarding hematological toxicity.

In the MaNGO trial, where patients received cisplatin-doxorubicin, the toxicities observed were grade 3 -4 neutropenia in 30% of patients, grade 2 thrombocytopenia in 9% and grade 2 anemia in 9%. Hematological toxicity was less among our patients. In the MaNGO trial, grade 3- 4 non-hematological toxicity was mainly nausea/vomiting seen in 4/ 74 (5%)patients. While in our study, the main non-hematological toxicity was neuropathy which can be attributed to usage of paclitaxel.

This work provides an insight into the utility of CTH for the high risk subgroup of EC patients. Although DFS and the rate of recurrence seems better than other studies not using the adjuvant CTH, a comparison of outcomes and getting final conclusion is difficult because of the heterogeneity of studied patients and differences in study design.

***Conclusion***

The results of this study suggest that adjuvant RTH concomitant with cisplatin followed by 4 cycles of paclitaxel-carboplatin is a well tolerated and feasible regimen in patients with higher risk EC.

We recommend starting the adjuvant RTH prior to 6 weeks post-surgery.

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