EJGO European Journal of Gynaecological Oncology

Concomitant chemoradiation treatment in selected Stage I endometrioid endometrial cancers

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Summary

Purpose of investigation: To evaluate chemotherapy with concomitant radiotherapy (RT) in "high risk" endometrial cancer (EC) patients. Furthermore to develop a new algorithm for management and treatment. *Materials and Methods:* The study included 182 Stage I endometrioid EC patients who underwent definitive surgery after a first treatment. Stage, grade, ploidy DNA index, lymphovascular space involvement (LVSI), tumor diameter (TD), and p53 were considered to identify "high-risk" patients. Twenty-seven women received adjuvant concomitant chemoradiation (CR). Toxicity related to the CR treatment, disease free interval (DFI), and status of the patients were considered. *Results:* Twenty-seven patients according to the present algorithm treatment were considered at "high risk". Median follow up was 43 months (range 16-68). Twenty-five (92%) patients completed CR treatment. Overall, grade 3/4 hematological toxicity was 18% while gastrointestinal toxicity was 15%. Four patients relapsed with a five-year rate of 14% of recurrences. *Conclusions:* Adjuvant concomitant CR is well tolerated and is a feasible regimen in "high risk" patients. The authors' new algorithm treatment could be used for management and further clinical studies.

Key words: Endometrial cancer; Radiotherapy; Adjuvant chemotherapy; Toxicity.

Introduction

Endometrial cancer (EC) is the most common gynecological cancer [1]. Management of Stage I endometrioid endometrial cancer (EEC) is different among institutions and actually there is no consensus on evidence-based postoperative treatment [2]. Although this cancer is not generally considered aggressive, it is a heterogeneous disease with a five-year survival rate ranging from 42% to over 90% for women at clinical Stage I disease [3]. Traditionally, clinical variables are utilized to stratify patients with Stage I EC into "risk-categories". These variables include age, tumor grade, tumor diameter (TD), DNA ploidy, p53, and lymphovascular space involvement (LVSI) [4]. Consequently, this information is used to plan, when required, postoperative adjuvant treatments (ATs).

Standard treatment for Stage I includes total hysterectomy and bilateral salpingo-oophorectomy. There is no consensus on pelvic/para-aortic lymph node dissection [5]. Radiotherapy (RT) is used in selected "high-risk" but survival had not improve substantially over the last decades [6].

Studies with single chemotherapy (CT) agent or combinations had demonstrated encouraging response rates in patients with recurrent and advanced unresected disease. There are only few trials designed to study the feasibility and/or efficacy of systemic CT combined with RT in "high-risk" patients [7-11].

The present group, in collaboration with the University of Milan, observed good tolerance of concomitant CR in Stage I EEC. The results, even though with limited samples, were encouraging also in terms of reduction of local and distant relapses [12-14]. The authors analyzed their retrospective data to determine toxicity, compliance, and disease free interval (DFI) in first stage EEC treated with concomitant chemoradiation (CR).

Materials and Methods

Two hundred fifty patients underwent total hysterectomy and bilateral salpingo-oophorectomy for Stage I EC during the period between 2001-2012 in a single institution. Twenty-one patients with no endometrioid histology and 47 without pelvic lymphadenectomy were excluded by the study. Ultimately, 182 patients met the eligibility criteria. DNA ploidy was determined from paraffin-embedded tissue. Aneuploidy was defined as a DNA index N1.2 [15]. Para-aortic lymphadenectomy was performed in 21 (11%) patients. According to the Gynecologic Oncology Group study, patients with EEC Grade 1/2 and myometrium invasion (MI) < 50% and TD ≤ two cm or MI 0% any Grade, or Grade 1/2 and MI < 50% with TD > two cm were considered at "low or low-intermediate risk" [16]. These patients did not receive any AT.

Patients with endometrioid tumor, Grade 1/2 with 50% < MI ≤ 66% or Grade 3 with MI < 50% where considered as "high-intermediate and high risk" patients. Adjuvant CR was administered in the 27 (15%) "high-intermediate or high risk" patients

Revised manuscript accepted for publication May 28, 2015

Table 1. — *Clinical variables of patients with Stage I endometrial cancer.*

		Number	%
Stage	IA	138	75.5
	IB	45	25.5
Grading	G1	51	28
	G2	82	45
	G3	49	27
LVSI	Positive	19	10.5
	Negative	163	89.5
Tumor diameter	> 2 cm	113	62
	≤ 2 cm	69	38
Ploidy	Aneuploid	25	14
	Diploid	157	86
p53	> 33%	16	9
	≤ 33%	166	91
VBT	Yes	19	10
	No	163	90
Concomitant CR	Yes	27	17
	No	155	83

LVSI: lymphovascular space involvement, VBT: vaginal brachytherapy, CR: chemoradiation.

when DNA aneuploidy was present or at least two among LVSI, p53 ≥ 33% or TD > two cm (Figure 1). These patients received paclitaxel 60 mg/m^2 once a week during the five weeks of RT. RT was given in five fractions per week of 1.8 Gy daily doses. The irradiation field encompassed the entire pelvis. At the end of RT, three additional consolidation courses of paclitaxel (80 mg/m^2) were performed once a week in one-hour infusions. Patients were monitored during therapy with a weekly history and physical examination, complete blood count, and documentation of adverse effects. Follow-up after the completion of treatment included a history and physical examination every three months in the first two years, then every six months for the subsequent three years. All recurrences were biopsy-proven.

Results

One hundred eighty-two patients were included in the present study. Median age was 64 years (range, 45-85). Baseline variables of cancer are shown in Table 1. Twenty-seven (15%) patients were in "intermediate-high or high risk" group and received adjuvant CR according to the authors' algorithm treatment (Figure 1).

Two cases (7%) did not complete the five cycles of CT. Five (18%) patients had a delay of at least one cycle of chemotherapy for hematological G3/4 toxicity according to the World Health Organization guidelines. In four (15%) cases the authors observed severe gastrointestinal symptoms. During the three cycles after RT, treatment was stopped in one (3.7%) case and delayed in three (11%) cases. There was no life-threatening toxicity. A total of four (15%) cases had diarrhea (grade 3 in 2 patients), three (11%) cystitis, and two (7%) grade 3 neurological toxicity. Median follow up was 43 months (range, 16-68). The authors observed 4/155 (2.6%) relapses (two vagina, one lung, and one liver) in the groups without AT while they observed 4/27 (15%) relapses in the CR group (one vagina, one lung, one bone, and one peritoneal). The characteristics of cancer relapses are shown in Table 2. The five patients with distant relapses died of disease. Twenty patients died of intercurrent causes.

Discussion

In the present series 27 "intermediate-high/high" risk EEC patients with additional negative prognostic factors (LVSI, aneuploidy, p53, and TD > two cm) were treated with paclitaxel and concomitant RT with a five-year recurrence rate of 15%.

In the PORTEC analysis, IC G3 patients reduced their loco-regional relapse rate of 14% with the use of RT [17].

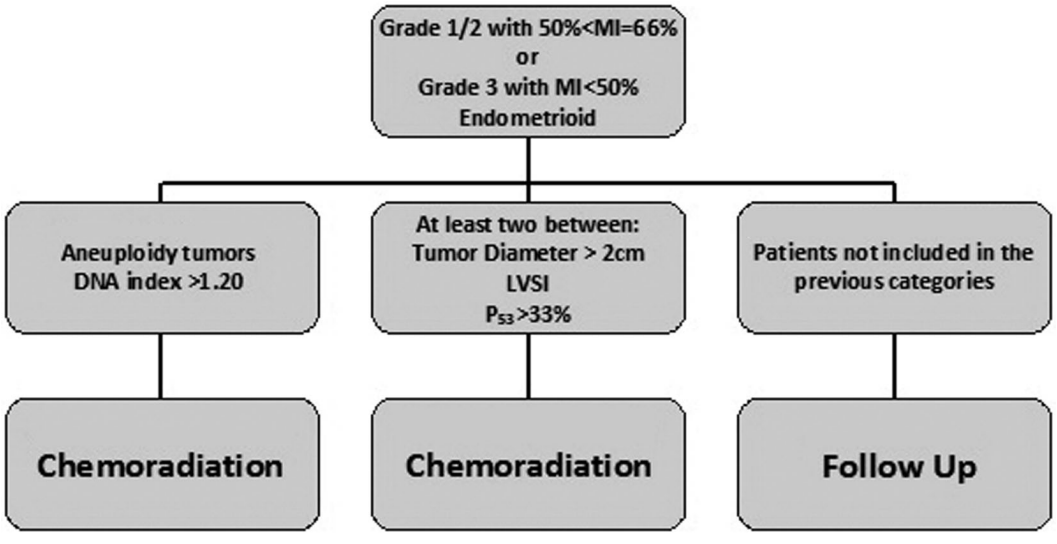

Figure 1. — Algorithm of management and treatment with chemoradiation of patients with Stage I endometrioid endometrial cancer. (MI: myometrial invasion; LVSI: lymphovascular space involvement).

Table 2. — *Characteristics of cancer relapses.*

S/G	PLOIDY	P53	LVSI	TD	VBT	CR	Site of relapse	Treatment relapse	DFS	Status
IA-2	D	< 33%	No	> 2 cm	No	No	Vagina	S	7	NED
IA-2	D	< 33%	No	> 2 cm	No	No	Vagina	S	6	NED
IB-2	D	< 33%	No	> 2 cm	Yes	No	Peritoneum	CT	15	DOD
IB-2	D	< 33%	No	> 2 cm	No	No	Lung	CT	12	DOD
IB-3	AN	< 33%	No	≤ 2 cm	Yes	Yes	Bone	CT	18	DOD
IB-3	D	> 33%	No	> 2 cm	Yes	Yes	Lung	CT	16	DOD
IB-3	D	> 33%	No	> 2 cm	Yes	Yes	Vagina	S	11	NED
IB-3	AN	< 33%	Yes	> 2 cm	Yes	Yes	Aortic nodes	S+CT	14	DOD

S/G: FIGO Stage and Grade, D: Diploidy, AN: aneuploidy, LND: lymph node dissection, LVSI: lymphovascular space invasion, DFS: disease free survival, NED: No evidence of disease, AWD: alive with disease, DOD: dead of disease, CR: chemoradiation , CT: Chemotherapy, S: surgery, RT: radiotherapy.

The rate of distant relapses remains high with 25% of cases reported [18].

The combination of RT and CT was observed as a promising feasible approach to reduce local and distant relapses. Different modality of administration, type of chemotherapeutic agents, and doses were reported with different toxicities and outcomes. The inability to complete the combined treatments for toxicity ranged between 0% and 30%. The main chemotherapeutic agents used were doxorubicin, cisplatin, paclitaxel, carboplatin [19-26]. Paclitaxel was associated with high response rate in EC [27]. The combination of paclitaxel with other chemotherapeutic agents is the standard treatment for advanced EC [28].

Lupe *et al.* reported a study about the feasibility of adjuvant carboplatin and paclitaxel interposed with involved-field radiation in advance stages EC [29]. In this paper 9% of the patients did not terminate the CT cycles. Grade 3/4 hematological and neurological toxicities were observed in 39% of the patients. Many reports show the efficacy of paclitaxel as a single agent and its radio-sensitizing properties in EC [30-31]. In order to reduce toxicity De Marzi *et al.* reported results about the feasibility of concomitant RT and CT in "high-risk" EC [14]. In particular, they observed a low rate of neurological toxicity and a favorable findings regarding tolerability using paclitaxel and absence of recurrences within the irradiation field.

In the present study 27 patients at "intermediate-high/high" risk with additional negative prognostic factors (Figure 1) were treated with concomitant CR. In the published literature, patients with combinations of prognostic factors, including older age, LVSI, G3, p53, and TD > two cm, had worse outcomes [32-34]. The possible correlation between a combination of these negative factors and recurrences remain unclear mainly for the inadequate samples size of the studies or their retrospective modality.

Some authors showed ploidy as a strong prognostic parameter. Aneuploidy tumors were clinically aggressive and relapsed mainly outside pelvis similar to serous and clear-cell adenocarcinomas [35, 36]. Mariani *et al.* reported that DNA aneuploidy was a predictor for distant failure, indicating that these patients can be potential candidates for a combined treatment [37]. TD has been reported to be a prognostic factor with implication value in the disease management of various malignancies. TD greater than two cm was associated with increased risk of deep myometrial invasion, poorer grade, risk group, and LVSI [38].

LVSI emerged as the strongest independent variable associated with pelvic lymph node metastasis and a predictor of lymphatic failure [39]. Most recently, in a large series of women with EC with LVSI, Simpkins *et al.* demonstrated a high rate of local and distant disease recurrence, and therefore suggested the possible need for adjuvant systemic therapy for this group of patients [40].

P53 is a tumor-suppressor protein that causes cell cycle arrest in case of DNA damage to allow DNA repair or induction of apoptosis in case of substantial damage. In malignancies, p53 is often overexpressed because of mutations and thereby incapable of performing DNA repair. The p53 overexpression was related to a high stage of disease, grade, and poor prognosis. It appeared to be a strong prognostic marker even when analyzing patients with Stage I disease only [41].

Conclusion

In the present study, based on the data of literature and on our experience, the authors developed an algorithm treatment in order to treat only patients at "high risk" with concomitant adjuvant CR .

In the present results concomitant CR with paclitaxel 60 mg/m^2 was well tolerated in 20 (74%) cases. The authors confirm the published data about feasibility and tolerability of this combined treatment. The present data also confirm the better local and distant control with a rate of 11% and 3.7%, respectively, of relapses.

The limitation of this study included the fact that is was a retrospective study with inherent associated biases. In contrast, the strength of the current study is the introduction of a new algorithm treatment, which could be helpful to identify patients for combined ATs. The authors believe it is essential to provide sufficient statistical power to detect a true difference in recurrence risk, considering the excel-

lent prognosis of Stage I EC and thereby the very low recurrence rate.

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