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Evaluation of adjuvant treatment strategy in stage-I endometrioid adenocarcinoma of uterus: A single centre experience

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Abstract
Background: The role of adjuvant radiotherapy in Stage-1 endometrioid adenocarcinoma is still controversial. This study is an analysis of outcome and patterns of failure associated with adjuvant treatment strategy followed at our centre and the implications for radiotherapy.
Material and Methods: The demographic, surgical, pathological and adjuvant treatment details of 140 patients operated between 2008 and 2013 having FIGO Stage-1 endometrioid adenocarcinoma was analyzed. The risk- stratification was done according to ESMO guidelines.
Results: Ninetytwo (66%) of the patients were categorized as low risk, 39(28%) as intermediate risk and 9(6%) as high risk group. 57(41%) underwent pelvic lymphnode dissection. In the low risk group 68(74%) patients received no adjuvant treatment .In the IR group 20(51%) received Pelvic EBRT, 16(41%) received both pelvic EBRT & VBT. Among the high risk group, out of nine patients 4(44%) received Pelvic EBRT, another 4(44%) received both (EBRT & VBT). There were 9(6.4%) recurrences. The 5 year-DFS(95%) was similar among the LR and the IR group .The Grade1 & Grade2 late bladder toxicity was seen in 6(10%) and 3(5%)patients .Grade1 and Grade2 late GI toxicity developed in 9(15%) and 4(6%) respectively. The Grade2 and Grade3 vaginal stenosis occurred in 4(6%) and 2(3%) patients respectively.
Conclusion: The most consistent factor associated with relapse appears to be advanced age and postmenopausal status. Adjuvant radiotherapy prevented local recurrences and since surgical expertise is limited in India it should strongly be considered in the IR group. Individualized risk models are necessary to increase the predictive ability of current staging system.

Keywords: Adjuvant strategy, radiotherapy, early endometrial carcinoma

Introduction
The incidence of endometrial cancer in India is estimated at 4.3 per 100000 [1], which is comparatively less than the developed world which is around 26 per 100,000 women per year in the U.S [2]. The most common histopathological type of endometrial adenocarcinoma is the endometrioid type, which accounts for 70-80% of cases [3-6]. These tumors are generally low-grade, present in early stage, and are relatively indolent [7]. The initial management in these patients is upfront total abdominal hysterectomy plus bilateral salpingo-oophorectomy and extended surgical staging, which yields a good cure rate. The role of adjuvant treatment with radiotherapy in early stage uterine adenocarcinoma is still a matter of debate. The risk of local recurrence and micro-metastases outside the uterus after surgery determines the need of adjuvant therapy. In order to design an appropriate adjuvant policy for these patients, different studies have risk-categorized them into mainly three groups: low, intermediate and high risk group based on the presence of certain risk factors [8, 9]. Based on aforementioned studies, it has been generally accepted that the low risk patients do not require any form of adjuvant radiotherapy while the high risk group patients require radiotherapy with or without chemotherapy in order to prevent relapse [8, 9, 10]. But the most appropriate adjuvant treatment strategy for intermediate risk group is still not well defined. Moreover, the type of radiation modality to be used i.e. Pelvic external beam radiotherapy (EBRT) or Vault brachytherapy (VBT), or both is also controversial.
The majority of data has been reported from the western world. There is a paucity of reported data from the developing world [11]. Here we report an audit of the outcomes of adjuvant treatment strategy for stage I endometrial adenocarcinoma patients treated at our centre.

Material and Methods

This was a retrospective study carried out at our centre. The case records of all endometrial cancer patients registered between 2008 to 2013 were accessed and those with FIGO Stage-I [12] disease & endometrioid adenocarcinoma histology were selected for analysis. Both premenopausal and post-menopausal women of any age who underwent TAH &BSO were included. The patients registered in 2008-09 were restaged according to FIGO (2009) staging [12]. Those patients who had received prior chemotherapy or pelvic radiotherapy were excluded from the study. The total number of patients eligible for analysis in the current study was 140. The last follow-up date and the patient's disease status at that point were recorded. The primary endpoint was the disease free- survival recorded till the end of 2016. The patients had been on regular follow up and those on irregular follow up were contacted telephonically and enquired about their health status and any alarming symptoms. A detailed clinical examination with gynecological check-up was done at each visit. Further investigations and imaging were done if some abnormality was revealed or suspected on clinical examination. The local and pelvic recurrences were proven either by biopsy or fine needle aspiration cytology (FNAC). For analyses, the patients were divided into three risk groups according to latest ESMO guidelines [13] into low, intermediate and high as shown in the Table 1. These patients were further subdivided into four groups depending on the adjuvant strategy *viz.* 1). Observation 2). Pelvic EBRT 3).Vault Brachytherapy (VBT) and 4).Both pelvic EBRT & VBT (Table-2)

Table 1: Risk group stratification (ESMO [13] based

Low risk	Intermediate risk	High risk
Stage IA Grade1 Stage IA Grade2	Stage IA Grade3 Stage IB Grade1 Stage IB Grade 2	Stage IB Grade3

*ESMO (European Society for Medical Oncology) Clinical Practice Guidelines for diagnosis, treatment and follow-up" Annals of Oncology 2013; 24 (Suppl 6): vi33-vi38.Ref:13

Table 2: Patient stratification according to adjuvant strategy Original table

1) Observation	No adjuvant treatment
2) Pelvic EBRT*	46Gy-50Gy by 3DCRT†
3) Vault Brachytherapy	HDR‡ (5Gy X 5 fractions)
4) Both pelvic EBRT* & VBT§	EBRT* 46-50Gy/ 2 Gy per fraction followed by VBT§ 8.5Gy x 2 fractions(HDR‡,one week apart)

* External Beam Radiotherapy, † 3 Dimensional Conformal Radiotherapy‡ High Dose Rate -brachytherapy, §Vault Brachytherapy

Statistical analysis

The statistical analysis was carried out using SPSS version20 software. Descriptive statistical methods were used for calculating mean, median & frequency. Kaplan-Meier survival analysis was used for calculating the survival curves.

Results

Patient characteristics

The data from 140 patients with stage -I disease and endometrioid histology was analyzed. Table-3 describes the risk-group wise patient and treatment characteristics in terms of age, stage, grade, lymphnode dissection, risk stratification and the adjuvant treatment group. 92(66%) of the patients were categorized as low risk, 39(28%) as intermediate risk and nine (6%) as high risk group according to the recent ESMO guidelines. [13] The median age of presentation in low risk, intermediate risk and high risk group was 55, 60 and 59 years respectively. All the 92(100%) patients in low risk group had stage-IA disease, while 34(87%) in intermediate risk group had stage IB disease and rest five (13%) had stage IA grade 3 disease. All the nine (100%) patients in high risk group had stage IB disease. In the low risk group 58(63%) and 34(37%) had grade 1 and grade 2 histopathological grade respectively. In the intermediate group 25(64%) had grade 2 disease while nine (23%) and five(13%) had grade 1 and grade 3 disease respectively. All the 9(100%) patients in high risk group had grade3 disease.

Treatment characteristics

Out of 140 women who underwent TAH with BSO, 57(41%) underwent pelvic lymphnode dissection (PLND). The mean number of pelvic lymph nodes dissected was seven. In the low risk group 68(74%) of 92 patients were not given any adjuvant treatment while nine, eight and seven patients received Pelvic EBRT, VBT and both (EBRT &VBT) respectively. These patients were treated in 2008-09 and received adjuvant radiation despite of being in low risk group. In the intermediate risk group 20(51%) were given Pelvic EBRT, while 16(41%) received both pelvic EBRT & VBT. Among the high risk group patients four(44%) received Pelvic EBRT and another four(44%) received both (EBRT & VBT). One patient in high risk group had been planned for EBRT but did not opt for radiation, so was kept on follow up only. Those who underwent pelvic EBRT had received radiation by 3DCRT technique ranging from 46Gy-50Gy, while vault brachytherapy (VBT) was given as two 1-week apart sessions of HDR @ 8.5Gy as shown in the Table 2. The patients receiving VBT alone as adjuvant treatment were administered 5Gy X 5 sessions. The treatment characteristics according to risk categorization are shown in Table 3.

Table 3: Patient demographics and Risk Groupwise treatment (Original table)

	Low risk	Intermediate risk	High risk
Total (N)	92(66%)	39(28%)	9(6%)
Age:	55yrs	60 yrs.	59 yrs.
Median(years)	(30-80yrs)	(38-70yrs)	(43-67yrs)
Stage			
IA	92(100%)	5(13%)	-
IB	-	34(87%)	9(100%)
Grade			
1	58(63%)	9(23%)	-
2	34(37%)	25(64%)	-
3	-	5(13%)	9(100%)

Lymphnode dissection			
Pelvic	34(37%)	16(41%)	7(78%)
Para aortic	7(8%)	0(0%)	1(11%)
Treatment Group			
Observation	68(74%)	2(5%)	1*
Pelvic EBRT†	9(10%)	20(51%)	4(44.4%)
Vault brachytherapy(VBT)	8(8.6%)	1(2.5%)	0
Both Pelvic EBRT† & VBT	7(7.6%)	16(41%)	4(44.4%)

*didn't opt for radiation, † external beam radiotherapy

Clinical outcome & Patterns of recurrence

The total number of recurrences was 9(6.4%). The mean interval from primary treatment to relapse was 37.7 months. Three patients developed locoregional recurrence in the low risk group, as shown in the Table 4. One patient had local recurrence over vault while the other two recurred in the pelvis. None of them had received any adjuvant treatment. None of the patients who received radiotherapy failed.

In the intermediate risk group, out of the five (13%) patients who had recurrence only one patient had not undergone pelvic LND. The three patients (including the one without pelvic LND) who had received adjuvant radiation developed distant failure. The two patients who had not received adjuvant radiotherapy developed locoregional failure (Pelvis=1, Vault=1). The pattern of recurrence in intermediate risk group is shown in the Table5.

Only one patient in the high risk group who opted out of the adjuvant treatment developed vault recurrence as shown in the Table 6.

Table 4: Pattern of recurrence by treatment group in low risk category (Original table)

	Local (Vault)	Local (Lower vagina)	(Pelvic)	(Distant)
Observation(68)	1	-	2	-
Pelvic EBRT* (9)	-	-	-	-
VBT† (8)	-	-	-	-
Both EBRT*&VBT† (7)	-	-	-	-

* External Beam Radiotherapy, †Vault brachytherapy

Table 5: Pattern of recurrence by treatment group in intermediate risk (original table)

	Local (Vault)	Local (Lower vagina)	Pelvic	Distant
Observation(2)	1	-	1	-
Pelvic EBRT* (20)	-	-	-	1
VBT† (1)	-	-	-	1
Both EBRT*&VBT† (16)	-	-	-	1

* External Beam Radiotherapy, †Vault brachytherapy

Table 6: Pattern of recurrence by treatment group in high risk category (original table)

	Local (Vault)	Local (Lower vagina)	Pelvic	Distant
Observation(1)	1	-	-	-
Pelvic EBRT* (4)	-	-	-	-
VBT† (0)	-	-	-	-
Both EBRT*&VBT† (4)	-	-	-	-

* External Beam Radiotherapy, †Vault brachytherapy

Survivals analysis

At a median follow up time of 48 months the 5 -year overall survival was 98% for the entire study population (Fig.1). The 5 year DFS (95%) was not significantly different among the low risk and the intermediate risk group (log rank=0.1)(Fig.2).

Radiation toxicity

RTOG/EORTC criteria [14] were followed for recording all the radiation toxicities unless otherwise specified. A total of 60 patients received Pelvic EBRT. 46(77%) developed acute Grade 1 skin toxicity, 16(26%) and three (6%) had Grade2 and Grade 3 toxicities respectively. 23(38%) of 60 patients developed acute lower gastrointestinal toxicity among whom 15(25%) and six (10%) developed Grade 1 and Grade 2 toxicities respectively. Acute Grade 3 lower gastrointestinal toxicity was seen in two (3%) patients. The Grade 1 & Grade 2 late bladder toxicity with pelvic radiation was seen in six (10%) and three(5%) at a median FU of 48 months, while no grade 3 or 4 bladder toxicity was noted. Nine (15%) of 60 patients developed late Grade 1 GI toxicity. Only four (6 %) patients developed late Grade 2 lower GI toxicity in the form of Radiation induced hemorrhagic proctitis (RIHP). The Grade 2 and Grade 3 vaginal stenosis (CTCAEv 3) [15] was seen in four (6%) and two (3%) patients respectively.

Discussion

Endometrial cancer commonly affects the postmenopausal women. Since the abnormal vaginal bleeding is one of its most common initial alarming symptoms, [16] most cases are diagnosed at early stages when the disease is still confined to the uterus. [17] Depending on tumor biology, clinical characteristics, and the prognosis two different types of endometrial carcinoma, designated as type I (Endometrioid Endometrial Carcinoma) and type II (Non endometrioid Endometrial Carcinoma) were first proposed by Bokhman. [18] The standard treatment for stage I uterine endometrioid adenocarcinoma remains surgery i.e. TAH & BSO with or without lymphnode dissection. The use of radiotherapy as

adjuvant treatment in these patients has long been controversial. Since the recurrences after the standard treatment occur at a relatively low rate (7%), [19] the use of adjuvant treatment needs to be properly justified considering the involved risks and benefits to the patient. The two currently used methods (PORTEC and GOG) [8, 9] for risk categorization of the patients into low, intermediate and high risk are overlapping with each other. The GOG has further subcategorized intermediate group into high and low subcategories [9]. On the other hand the PORTEC [8] stratification has used similar criteria but has omitted the lymphovascular space invasion (LVSI). The patient population in our study has been stratified into three risk groups according to ESMO guidelines [13]. The 5-year risk of recurrence for patients in the low-risk category is estimated to be between 2% and 10% [10]. The risk of finding positive pelvic lymphnodes in high risk group has been reported to be 28% in a study by Chi *et al.* [20] Hence the low risk group patients do not derive any benefit from adjuvant radiation whereas the high risk group patients have a clear benefit. An equivalent 5 year overall survival rate in untreated low risk group and the treated high risk group patients noted in a study further supports this finding [21]. In our study none of the treated high risk group patients had relapse while three (4%) of 68 patients in the untreated low risk group had loco regional relapse.

The type of adjuvant radiation modality and its use in intermediate risk patients still remains a matter of debate. In our country there has been a tendency to give adjuvant treatment in low risk and intermediate risk patients which might be because of the unreliable surgical treatment received in non-institutional settings. In our study, 24(26%) of 92 patients in low risk group had received some form of adjuvant radiation. Most of them had been registered in the year 2008 and 2009. This clearly reflects a gradual shift in the trend of the adjuvant treatment policy over the years. Table-7 shows the modalities used for adjuvant treatment in some of the studies in our country.

Table 7: Type of adjuvant treatment given in various studies from India.

	Number of patients	Adjuvant treatment	Type of adjuvant treatment
Mahantshetty *et al.* [22]	249 StageI= 218(88%) StageII=31(12%)	160(64%)	VBT* only 26(16%) WPRT† 17(10%) WPRT† with VBT* 114(71%)
Dessai *et al.* [23]	34 (StageI)	23(67%)	WPRT† with VBT* 14(61%) VBT* only 9(39%)
Thomas Anitha *et al.* [24]	107(StageI)	54(50%)	VBT* only 19(35%) WPRT† 7(13%) WPRT† with VBT* 28(52%)

*vault brachytherapy, †whole pelvis radiotherapy.

The treatment options investigated in the management of intermediate-risk uterine carcinoma have failed to reflect a benefit in terms of overall survival in the published randomized trials [8, 9, 25-29]. The extent of surgical staging in the form of lymphnode dissection and its effectiveness is yet another important issue in the management of these patients. Except for Stage 1A Grade1 disease simultaneous paraaortic and pelvic lymphnode dissection has been considered indispensable by certain authors [30]. In the ASTEC [29] and Benedetti-Panici *et al.* [31] study in Italy, clear benefit of LND for staging was seen in early disease. However no therapeutic advantage in the form of improved clinical outcome with LND was noted [29, 31]. The PORTEC-2 study supports the use of VBT alone in intermediate risk group irrespective of the lymphnode dissection [25]. But if pelvic lymphnodes have not been evaluated VBT alone seems to be inadequate as adjuvant treatment. In the PORTEC study the Stage I patients who did not undergo lymphnode dissection and the adjuvant radiotherapy had worse 5-year survival than those who had received both modalities.[8] In a retrospective study from TMC Mumbai involving patients with Stage I & Stage II disease only 47.3% patients had undergone complete surgical staging [22]. In our study, 57(41%) patients had undergone pelvic lymph node dissection.

In the intermediate risk group out of the five patients who had recurrence; two had not received adjuvant treatment and developed locoregional failure, rest of the three patients had distant failure. This pattern clearly highlights the role of radiation in the prevention of local relapse. In a referral centre like ours, where substantial number of patients undergo surgery outside, the surgical expertise may often be limited, leading to inadequate surgical staging and hence, may confer a higher risk of relapse. The patient compliance is generally poor in our country. The cancer care facilities required for surveillance and early detection are poorly available and non-existent in rural areas [32].

The late radiotherapy toxicities remain a major concern and can have a significant impact on the quality of life of the patients. The adjuvant treatment was well tolerated in our patient population with 13 (21%) developing late GI toxicity. Only four (6%) patients developed Radiation induced hemorrhagic proctitis (RIHP). The vaginal toxicity was seen in six (10%) patients only. All of our patients were treated with conformal 3 DCRT (Three Dimensional Conformal Radiotherapy). But the lower incidence of vaginal toxicity might be because of poor documentation during follow-up.

Conclusion

In our study the most consistent factor associated with relapse appears to be advanced age and postmenopausal status (although a longer follow up is needed). Adjuvant radiotherapy was effective in preventing local recurrences but some of the patients failed at distant sites. Since, unlike the western world the surgical expertise is limited in India, the patients with intermediate risk category should strongly be considered for adjuvant Pelvic EBRT. The adjuvant treatment was well tolerated in our patient population. Some patients who were put into low risk group and received no adjuvant treatment developed relapse. So individualized risk models are necessary to increase the predictive ability of current staging system.

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