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RESEARCH ARTICLE

RADIATION THERAPY IN MANAGEMENT OF ENDOMETRIAL CARCINOMA: THE RESULTS OF A SINGLE INSTITUTION

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Abstract

Purpose: We report the results of retrospective analysis of 50 cases of endometrial carcinoma treated by radiation therapy at the National Institute of Oncology of Rabat in Morocco.

Materials and Methods: Between January 2011 and December 2012, all patients who has benefited from radiation therapy were retrieved. All patients were treated by conformational 3D radiotherapy. We analyzed clinical, histological characteristics, and treatment outcomes.

Results: Median age of patients was 58 years. Main symptoms were metrorrhagia in 100% of cases, pelvic pain in 42 % of cases and vaginal discharge in 28%. The FIGO stages were respectively: IA 20 %, IB in 56%, II in 12%, IIIA in 4%, and IIIB in 2% and IIIC in 6 %. Histological grade was 1 in 30%, 2 in 48% and 3 in 22%. All patients underwent surgery. Adjuvant radiation therapy was delivered at a mean dose of 47 Gy (45-50, 4Gy). All patients were treated by conformational 3D radiotherapy. HDR brachytherapy was delivered in 65% of patients at a dose of 10 Gy (2x5Gy). The mean of total treatment duration was 50 days. The overall 5-year survival rate for our study was 90,1 %, and the overall local control rate was 69,6 %.

Conclusions: The results of our study confirm that radiation therapy is a good option for treatment of endometrial carcinoma, and it is associated to good outcomes.

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Introduction:

Endometrial cancer (EC) is the most common female genital cancer in the developing world and primarily affects postmenopausal women, with adenocarcinoma of the endometrium the most common type [1]. However, in developing countries, it is much less common than carcinoma of the cervix. In Morocco, it concerns 2.7% of all cancers diagnosed at the same period [2].

The large majority of patients are diagnosed at early stage of International Federation of Gynecology and Obstetrics [FIGO] with an overall survival of 95 % [3].

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Surgery is the primary treatment for endometrial cancer. The treatment following surgical staging is based on the risk of relapse and persistent disease, which is defined by the cancer stage at diagnosis and presence of prognostic factors.

Adjuvant radiotherapy options include pelvic radiation, vaginal brachytherapy or whole-abdomen radiation. Radiotherapy improves local control, but does not improve cancer specific or overall survival [4]. Radiotherapy alone has also curative potential in medically inoperable patients.

The aim of our retrospective study was to evaluate the results of adjuvant radiotherapy in management of endometrial carcinoma for Moroccan patients, and to retrieve prognostic factors influencing outcomes.

Materials and Methods:

A population-based registry encompasses patient's data from the north and the centre areas of Morocco. Between January 2011 and December 2012, 50 patients newly diagnosed with endometrial carcinoma has benefited from radiation therapy were retrieved. All patients were treated by conformational 3D radiotherapy.

Staging was made according to the 2009 International Federation of Gynecology and Obstetrics [FIGO].

Patients receiving external beam radiotherapy (EBRT) were treated using a four-field box technique (anterior–posterior and two laterals).

For patients receiving high dose rate (HDR) brachytherapy, a Nucletron HDR unit with Iridium-192 as the source was used to prescribe the dose to 0.5 cm depth. A vaginal cylinder was used for most patients.

HDR brachytherapy fractional dose was converted to equivalent 2-Gy fractions assuming an α/β of 10 for tumor and 3 for normal tissue

For each patient, we retrospectively collected information about symptoms, work-up, staging, and finally clinical outcomes (overall survival (OS), local control (LC)).

Toxicities were retrospectively assessed based on the Common Terminology Criteria for Adverse Events v4.0.

All Patients were examined at 3-month intervals for the first 2 years after treatment, then at 6-month intervals for the next 3 years, then yearly afterward

Statistical analysis was performed using SPSS software, version 10.0. Local control and patient's survival distribution was calculated using the Kaplan–Meier method. Time to recurrence was calculated from the completion of radiation treatment to the time of histological or radiographic confirmation of recurrence. The significance of the survival was tested by log-rank test. Multivariate analysis was performed using the Cox proportional hazard regression. A value of p less than 0.05 was considered statistically significant.

Results:

Median age of patients was 58 years (54, 5–56, 5) (Table 1). More than half of patients were post-menopausal (78%). Nineteen patients had risk factors such as arterial hypertension and diabetes and only one patient had history of taking tamoxifen for breast cancer.

The median duration of symptoms before diagnosis was five months (2–10). Main symptoms were metrorrhagia (100%), pelvic pain in 42 % (21 cases) and vaginal discharge in 28% (14 cases). The histological type was respectively: endometrioid adenocarcinoma in 72% (36 cases), clear cell carcinoma in 4 % (2 cases), and sarcoma in 24 % (12 cases).

The mean size was 2,9 cm (1,3–6,7cm).

Table 1: Clinical and para-clinical epidemiological characteristics of the studied patients.

	N	%
Total	50	100%
Age of diagnosis (years)		
≤ 39	2	4%
40–49	6	12%
50–59	17	34%
60–69	16	32%
≥70	9	18%
Menopausalstatus		
Postmenopausal	39	78%
Premenopausal	11	22%
Parity		
0	9	18%
1-3	20	40%
≥ 4	21	42%
Riskfactors		
Diabetesmellitus	9	18%
Hypertension	10	20%
THS	0	0%
Tamoxifene	1	2%
Duration of symptoms (months)	5	
Presenting complaints		
Abnormal vaginal bleeding	50	100%
Pelvic pain	21	42%
Vaginal discharge	14	28%
Change in bowel or bladder function	0	0%
Para clinicalreview		
Transvaginalultrasonography	42	84%
Abdominal and pelvic CT	39	78%
Pelvic MRI	11	22%
Tumor size		
≤ 2 cm	38	76%
≥ 2 cm	12	24%
Histologicsubtype		
Type 1	36	72 %
Type 2	14	28 %
Histological grade		
Grade 1	15	30 %
Grade 2	24	48 %
Grade 3	11	22%
Lymph-vascularspace invasion	16	32%

Seventy-eight percent of the patients had an abdomino-pelvic CT scan to evaluate the loco regional extent and 22 % of them had a pelvic magnetic resonance imaging (MRI) along with abdominal CT. All of our patients had a chest X-ray for evaluation of thoracic metastases.

The FIGO stages were respectively: IA 20 % (10 cases), IB in 56% (28 cases), II in 12% (6cases), IIIA in 4% (2 cases), and IIIB in 2% (1 case) and IIIC in 6% (3 cases). Histological grade was 1 in 32.4% (17 cases), 2 in 47.9% (24 cases) and 3 in 21, 6% (8 cases) (Figure 1). The lymph-vascular space invasion was present in 31.1 % of cases (14 patients). Tumors stage I were subdivides into: high risk in 38 % of cases (19 patients), intermediate in 34 % of cases (17 patients), low risk in 4% (2cases).

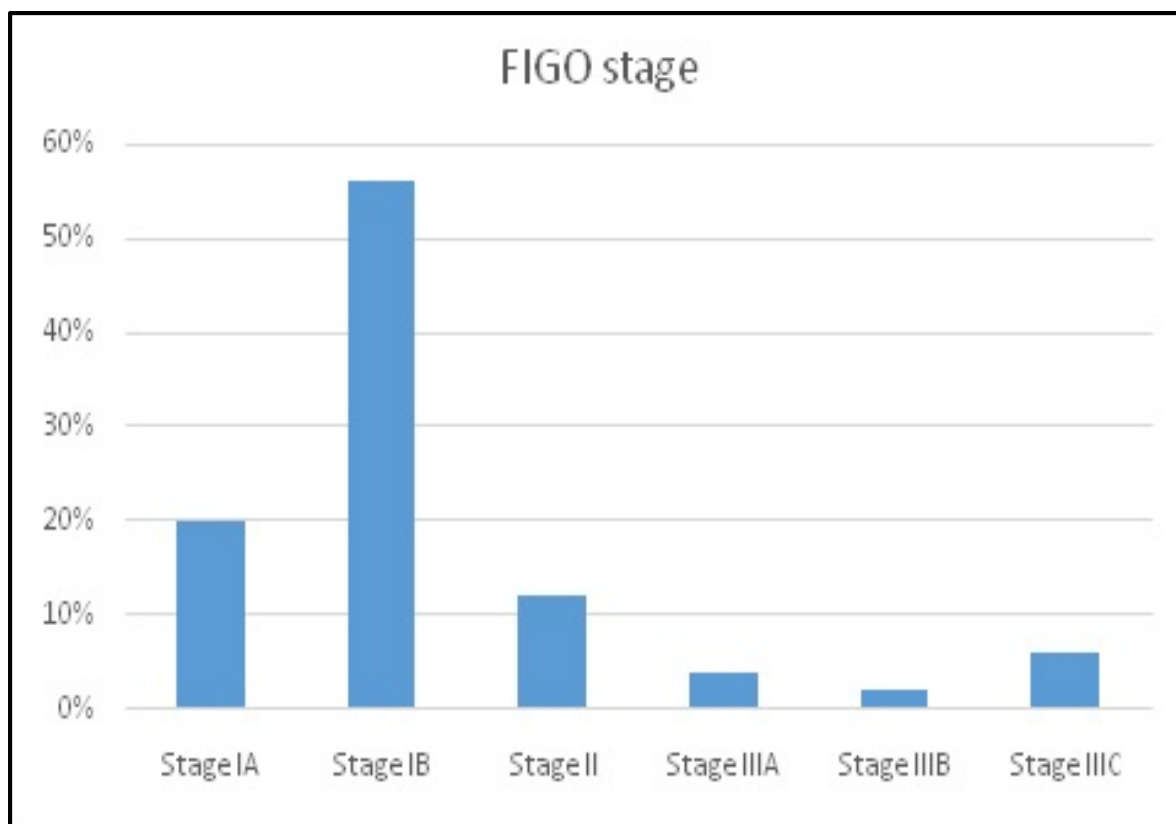


Figure 1: FIGO stage of disease

All patients underwent surgery. The iliac lymphadenectomy was performed in 64 % of cases (32 patients) and Para-aortic lymph node dissection in 4 % of cases (2 patients).

Treatment modalities (Table 2):

For the external beam radiotherapy (EBRT), all patients were treated by conformational 3D radiotherapy using a four-field box technique (anterior-posterior and two laterals).

The clinical target volume (CTV) included the proximal vagina, the parametrial tissues, and the internal, external and distal common iliac lymph node regions up to the upper S1 level. If the external or internal iliac lymph node are involvement, the common iliac lymph node regions are to be included up to the aortic bifurcation with Planning Target Volume consists of the CTV with a 7-10 mm margin a dose range of 45 to 50.4 Gy at 1.8 Gy fractions.

Vaginal cuff brachytherapy was delivered in 65% of patients at a dose of 10 Gy, two fractions of five Gy was be specified at 5 mm from the surface of the cylinder, in the central plane. Proximal one -third of vagina were irradiated.

The mean of total treatment duration was 50 days.

All patients were completed the radiotherapy without any interruptions. Main acute toxicity was diarrhea (66% of patients: 40% were grade 1 and 26% were grade 2.) and radio cystitis (28% of patients: 12%were grade 1 and 16% were grade 2) and no grade 3 or 4 was noted.

The most common late toxicity was vaginal synechiae (48% of patients) (Table 3).

Table 2: Therapeutic modalities

Modalities	FIGO stage						
	I			II	IIIA	IIIB	IIIC
	LOW	INTERMEDIATE	HIGH-RISK				
Surgery+ EBRT	0 (0)	10 (20)	4 (8)	0 (0)	0 (0)	0 (0)	0 (0)
Surgery + EBRT+vaginalbrachytherapy	0 (0)	3 (6)	15 (30)	6 (12)	2 (4)	1 (2)	3 (6)
Surgery + Vaginal brachytherapyalone	2 (4)	4 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Surgery + Concomitant radio-chemotherapy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Exclusive radiotherapy	0 (0)	0 (0)	0(0)	0 (0)	0 (0)	0 (0)	0 (0)

Qualitative variables presented as number and percentages n (%)

Table 3: acute and late side effects of radiotherapy

Acute toxicity								
	G1	G2	G3	G4	G1	G2	G3	G4
Diarrhea	20	13	0	0	40%	26%	0%	0%
colitis	8	9	0	0	16%	18%	0%	0%
cystitis	6	8	0	0	12%	16%	0%	0%
Rectovaginalfistulas	-				-			
vesicovaginalfistulas	-				-			
Latetoxicity								
	G1	G2	G3	G4	G1	G2	G3	G4
bladdertoxicity	12	9	1	0	24%	18%	2%	0%
gastrointestinaltoxicity	7	11	0	0	14%	22%	0%	0%
vaginal synechiae	24				48%			
Bone fracture	-				-			

Treatment outcomes:

With a median follow-up of 30 months, 71 patients (88.75%) have been regularly followed.

Three patients had local recurrence, one patient developed distant metastases.

The overall 5-year survival rate for our study was 90,1 %, and the overall local control rate was 69,6 % (Figure 2). A univariate and multivariate analysis was achieved to define prognostic factors associated to recurrences (Table 4).

In univariate analysis, old age and lymph-vascular space invasion were significantly associated with local recurrence. The involvement of old age was confirmed in multivariate analysis.

We could not demonstrate the role of FIGO stage, histologic type and tumor grade as prognostic factors involved in relapse because of the small number of events.

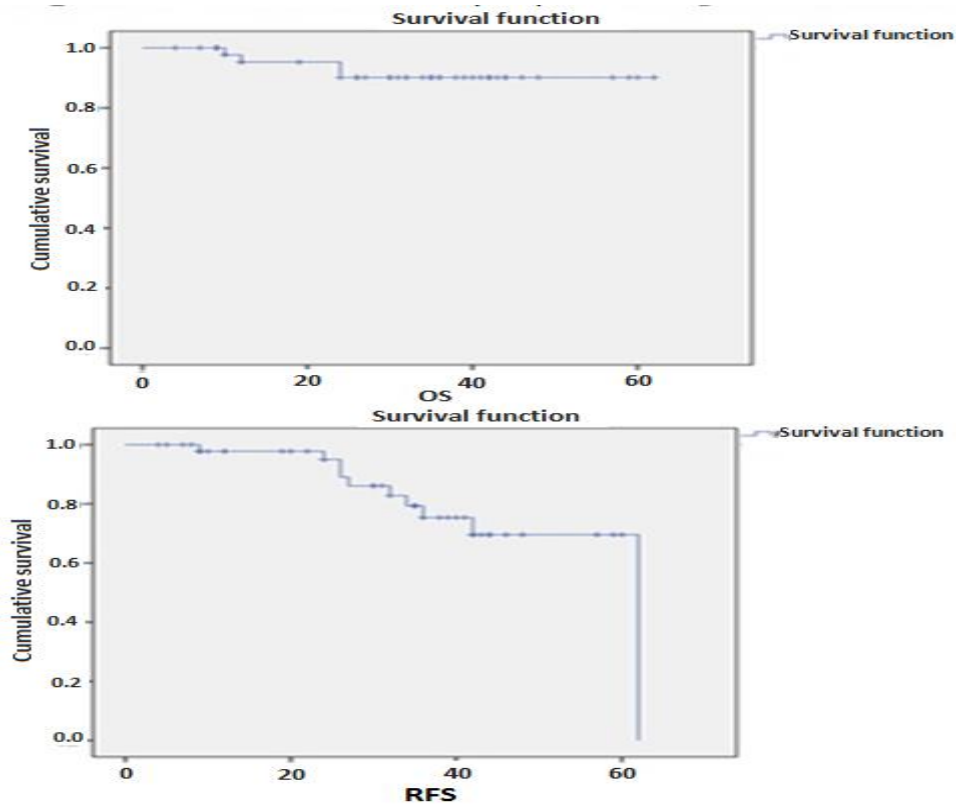


Figure 2: Overall survival (OS) and Relapse free survival (RFS)

Table 4: Univariate analysis for clinical parameters associated with the occurrence of relapse and/or metastasis

Characteristics	Relapse		Univariate Analysis			Multivariate Analysis		
	Yes (n=4)	No (n=45)	OR	95%CI	P value	OR	95%CI	P value
Age (Mean±SD)	66.4±10.1	54.4±7.8	1.23	1.07-1.41	0.004	1.21	1.04-1.42	0.016
FIGO stage								
IA:1	0(0)	10(22.2)	1 (Ref)					
IB:2	2(50)	25(55.6)	13.10 ⁷	0-<0.001	0.999			
II:3	1(25)	5(11.1)	28.10 ⁷	0-<0.001	0.999			
IIIA:4	1(25)	1(2.2)	17.10 ⁸	0-<0.001	0.999			
IIIB:5	0(0)	1(2.2)	2.61	0-<0.001	0.999			
IIIC:6	0(0)	3(6.7)	2.61	0-<0.001	0.999			
Histology type								
ADK	1(25)	30(66.7)	1 (Ref)			1 (Ref)		
Others	3(75)	15(33.3)	5.58	0.44-70.34	0.184	4.17	0.34-51.34	0.265
Grade								
1	0(0)	13(37.1)	1 (Ref)					
2	0(0)	17(48.6)	1	0-<0.001	0.999			
3	2(100)	5(14.3)	64.10 ⁷	0-<0.001	0.999			
EV								
-	6(60)	36(92.3)	1 (Ref)			1 (Ref)		
+	4(40)	3(7.7)	8	1.42-45.06	0.018	1.62	0.09-26.96	0.737

Discussion:

Endometrial carcinoma is the most common gynecologic malignancy in developed countries and the second most common in developing countries [1].

Most cases of endometrial cancer occur between the ages of 60 and 70. A few cases may occur before age 40, which is consistent with our results with a median age of 58 years.

The foremost symptom was, similar to the reports in the literatures reviewed, abnormal perimenopausal or postmenopausal vaginal bleeding [5].

The majority of cases are diagnosed at an early stage[3]. In our series, 70, 4% of cases are diagnosed at FIGO stage I.

Endometrial cancer can be organized broadly into two categories: type I, or endometrioid adenocarcinoma, is the most common histologic type of endometrial cancer which accounts for more than 80% of cases [6], and type II is characterized by clear cell and papillary serous tumor histologies.

Multiple prognostic factors exist for endometrial cancer. These prognostic factors generally are related to surgical pathologic findings. As in all cancers, the stage of the disease is the most important prognostic factor [7], [8].

In addition to stage, other pathologic factors are used to determine risk of recurrent or persistent disease: histopathologic subtypes, the degree of histologic differentiation of endometrial cancer, the degree of myometrial invasion, presence of lymphovascular invasion within the cancer, tumor size, peritoneal cytology, lymph node metastasis, older age, expression of the cell adhesion molecule L1CAM. In our series, stage, age, histological type, grade, depth of myometrial invasion, and presence of lymph-vascular space invasion are prognostic factors significantly associated with local recurrence[9].

In this regard, the European Society for Medical Oncology (ESMO), subdivides stage I into three risk categories : low, intermediate, or high-risk for recurrence [10].

The gold standard management of endometrial cancer is surgery, consisting of a total abdominal hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and paraaortic lymph node dissection [11].

The site of first relapse is usually the upper vagina, or vaginal vault, and this can be reduced by adjuvant postoperative radiotherapy [12].

The risk of relapse after surgery for low-risk and low-intermediate risk disease is very low. Generally, no further treatment is recommended.

For high-intermediate risk endometrial cancer, four randomized trials have established the role of radiotherapy [13], [14], [15], [16]. Adjuvant radiotherapy improves local control, but does not improve cancer specific or overall survival [4], [12].

After surgery for intermediate-risk endometrial carcinoma, the vagina is the most frequent site of recurrence. Recent data suggested that VBT is as effective as EBRT but less toxic and therefore considered as standard of care in patients with a certain risk of local recurrence [17]. The randomized PORTEC 2 trial estimated that 5-year rates of vaginal recurrence were 1.8% (95% CI 0.6-5.9) for VBT and 1.6% (0.5-4.9) for EBRT. 5-year rates of locoregional relapse (vaginal or pelvic recurrence, or both) were 5.1% (2.8-9.6) for V cuff BT and 2.1% (0.8-5.8) for EBRT. Rates of acute grade 1-2 gastrointestinal toxicity were significantly lower in the VBT group than in the EBRT group at completion of radiotherapy (12.6% vs 53.8%).

Sorbe 2011 reported a significant difference in locoregional relapse in favour of the EBRT plus Vaginal brachytherapy group for women with endometrial carcinoma of intermediate-risk but significantly more severe late side effects [18].

For high risk tumors, advanced-stage EC or unfavorable histologic types, pelvic EBRT is still regarded as an essential treatment component [19], [20], [21].

Vaginal cuff Brachytherapy alone may be also sufficient for Stage II disease presenting in the absence of other high-risk features [22].

For stage III disease, chemotherapy was often recommended as a single-modality treatment due to increased risk for relapse with an increasing number of extrauterine sites of disease.

However, multiple studies suggest the benefit of the combination of chemotherapy and external radiotherapy in order to reduce the risk of both local and distant recurrence [23], [24], [25].

A number of trials are currently ongoing which further explore the role of concurrent chemoradiation and/or adjuvant chemotherapy for patients with high-risk EC.

The RTOG have reported a phase II trial of concurrent pelvic radiotherapy (45 Gy in 1.8 Gy fractions and a brachytherapy boost) and cisplatin (2 courses of 50 mg/m² on days 1 and 28), followed by four courses of cisplatin and paclitaxel after RT for high risk or advanced stage endometrial carcinoma [26]. At 4 years pelvic, regional and distant recurrence rates are 2% and 19%, respectively. Overall survival and disease-free survival (DFS) rates at 4 years are 85% and 81%, respectively with excellent treatment completion rate and expected toxicity.

Two ongoing randomized trials comparing concurrent chemoradiation and adjuvant chemotherapy (two cycles of cisplatin during RT, followed by four adjuvant cycles of carboplatin and paclitaxel), with pelvic radiation alone in high risk and advanced stage endometrial carcinoma: PORTEC-3(Phase III trial) and GOG-258(phase II trial).

The American Society for Radiation Oncology (ASTRO) guideline recommend that for women with grade 1 or 2 cancer and less than 50% myometrial invasion or grade 3 cancer and less than 50% myometrial invasion, the vaginal brachytherapy is as effective as pelvic radiation therapy at preventing vaginal recurrence and is preferred. Patients with grade 3 cancer and less than 50% myometrial invasion or cervical stroma invasion may benefit from pelvic radiation to prevent pelvic recurrence. For women with high-risk early-stage disease and advanced disease, chemotherapy is recommended (with or without radiation therapy) [27].

3D- conformal radiotherapy typically employs four photon fields (AP/PA and opposed laterals) [28] inducing irradiation of large volumes of small bowel, rectum, bladder and femoral heads that can increase the risks of acute and late toxicity.

Manydosimetric studies have sought to demonstrate the advantages of intensity-modulated radiotherapy (IMRT). IMRT can reduce gastrointestinal, genitourinary, and hematological toxicities compared with 3D-conformal radiotherapy [29],[30], [31], [32].

In our study, all patients were treated by conformational 3D radiotherapy and it was generally tolerated. The most common late toxicities are represented by gastrointestinal and urinary toxicities [33].

Our results are comparable to data published in international studies, with an overall 5-year survival rate for our study of 90,1 %, and an overall local control rate of 69,6 %. Most relapses were associated with locally advanced disease.

Conclusion:

In Our country, endometrial carcinoma is a common cancer, with mostly diagnosed at early stage. The results of our study confirm that radiation therapy is a good option for treatment of endometrial carcinoma, and it is associated to good outcomes with an overall 5-year survival rate of 90,1 %, and an overall local control rate of 69,6 % with age and lymph-vascular space invasion as prognostic factors of relapse. The IMRT shows great promise in the treatment of endometrial carcinoma to reduce the rate of both acute and late side effects.

Conflict of interest:

“The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.”

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