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Original Research Article

Radiotherapy of Localized Endometrial Cancer, Experience of The Radiation Oncology Department of The Oncology-Hematology Center of The CHU Mohammed VI of Marrakesh: About 85 Cases

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Abstract: Endometrial cancer is the most common gynecological cancer in developed countries. It mainly concerns postmenopausal women. The objective of our work is to report the experience of the radiotherapy oncology department of the oncology-hematology hospital (HOH) of the Mohammed IV University Hospital of Marrakesh in the management of endometrial cancer. We retrospectively analyzed 85 cases of endometrial cancer treated by radiotherapy (external radiotherapy and /or brachytherapy) in our institution between 2014 and 2019. The data collected from our patients concerned the epidemiological, clinical, therapeutic and evolutionary aspects of this cancer. The median age of the patients was 58 years [37, 82], 88% were postmenopausal. The average consultation time was 08 months. The master symptom was post-menopauseal bleeding in 85% of the patients. Pathological examination showed endometrioid adenocarcinoma in 83% of cases. After workup, 51% of patients were stage I (IA 17%, IB 35%), 25% stage II, 23% stage III (IIIA 3%, IIIB 9% and IIIC 10%) and 1% stage IVA according to the classification of the International Federation of Obstetric Gynecology (FIGO). After surgery, 77% of patients received external beam radiation therapy. The dose delivered was between 46 and 50 Gray (Gy) over a mean spread of 42 days associated with concomitant chemotherapy in 16% of cases. Intravaginal brachytherapy was delivered to 98% of patients. It represented the only adjuvant treatment in 27% of cases, after external radiotherapy in 73% of cases. Adjuvant chemotherapy was received in 36% of patients. After a mean follow-up of 3 years, 82% of patients were still followed in a situation of good control of their disease, 8% of cases of local recurrence and 10% of distant metastasis.

Keywords: Radiotherapy Localized Endometrial Oncology-Hematology.

INTRODUCTION

Endometrial carcinoma is the most common gynecological cancer in Europe, with a 5-year prevalence of 34.7% and the 4th gynecological cancer in Morocco (GLOBOCAN 2018). The incidence is highest in North America and Europe compared to other parts of the world. The increasing incidence of endometrial cancer in Europe and North America may be linked to a higher prevalence of obesity and metabolic syndromes in these regions, in addition to the aging of the population and the advancing age of first parity. Endometrial cancer is often diagnosed at a stage at which it can be surgically removed because symptoms such as irregular bleeding are seen from an early stage. Surgery for endometrial cancer has been increasingly performed via laparoscopy1,2 and robot assisted surgery as well as by open laparotomy3. After hysterectomy, appropriate adjuvant treatment after the diagnosis of endometrial cancer is considered to lead to a decrease in the rate of recurrence and improvement of prognosis according to the determination of the cancer stage from the surgical and histopathological risk factors4. The aim of this work is to report the experience of the Radiation Oncology Department of Mohammed VI University Hospital of Marrakech in the management of endometrial cancer.

PATIENTS AND METHODS

We conducted a retrospective study through a series of 85 cases of endometrial cancer treated in the radiotherapy department at Radiation Oncology Department of Mohammed VI University Hospital of Marrakech. The data collected from the medical records of our patients, based on an operating sheet, concerned the epidemiological, clinical, therapeutic and evolutionary aspects of this cancer. The diagnosis was

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clinical and histological. The tumors were classified according to the FIGO classification, the radiological assessment of the loco regional extension was an abdomino-pelvic computed tomography (CT), and the distant extension assessment was according to the signs of calling. Treatment was mainly based on surgery to stage the tumor and then indicate adjuvant therapy (external beam radiation therapy (EBRT) and/or vaginal brachytherapy). The surgery consisted of a total hysterectomy or even a total colpo-hysterectomy associated or not with an adnexectomy, associated or not with a pelvic lymphadenectomy. External radiotherapy was delivered by four beams of high energy X photons (18 to 25 MV). The total dose delivered was 46 Gy in 23 fractions, 2 Gy per fraction. The brachytherapy was high dose rate (HDR), the total dose delivered varied depending on whether it was exclusive brachytherapy or combined with EBRT, it was either 7Gy x 3 fractions, 5Gy x 2 fractions or 6Gy x 3 fractions.

RESULTS

During the study period, 85 patients with localized endometrial were admitted to our department for adjuvant radiotherapy. Median age was 58 years and 75 patients were postmenopausal. Average time to consultation was eight months [2-12 months], The master symptom was post-menopausal bleeding in 85% of the patients followed by leucorrhoea in 12% and pelvis pain in 3% of patients. Pathological examination showed an Endometrioid adenocarcinoma in 83% of cases, Serous carcinoma (5, 8%), Mucinous carcinoma (3, 5%), Mixed carcinoma (3,5%) and uterin leiomyosarcoma was present in 4,8% of cases. The analysis of histopronostic factors was performed on hysterectomy specimen with lymph node dissection in all patients; the results are shown in Table 1:

Table-1: Histopronostic factors of patient after surgical treatment

Histopronostic factor	Variants	Number of patients	%
Stage (FIGO)	I A	14	17%
	I B	30	35%
	II	21	25%
	III A	03	3%
	III B	08	9%
	III C1	07	8%
	III C2	02	2%
	VI A	01	1%
Grade of differentiation	1	15	18%
	2	50	59%
	3	20	23%
Tumor size	<2 cm	16	18%
	2-5 cm	22	26%
	>5 cm	47	56%
Myometrial infiltration	< 50%	30	35%
	> 50%	55	65%
Margins	R0	78	92%
	R1	7	8%
Lymphovascular invasion (LVI)	Absent	26	30%
	Present	45	53%
	Not specified	14	17%
Nodes (pN)	N0	70	82%
	N+	11	13%
	Not specified	4	5%

External radiotherapy was performed in 77% of patients using a three-dimensional conformal radiotherapy technique, the delivered dose was 46-50 Gy on the tumor bed and pelvic lymph nodes delivered by 4-field box technique with a conventional fractionation of 1.8 Gy-2 Gy per fraction over an average duration of 42 days. Concomitant chemotherapy was performed in 16% of cases using weekly cisplatin at a dose of 40mg/m². Intravaginal brachytherapy was delivered to 98% of patients. It represented the only adjuvant treatment in 27% of cases, 73% after external radiotherapy. The patterns used were 7Gy in 3fractions in case of exclusive brachytherapy, 5Gy in 2 fractions or 5,5Gy in 2 fractions when it was associated with external radiotherapy. This radiotherapy was complicated by acute complications in 30% of cases and delayed complications in 5% (Table 2). After a mean follow-up of 3 years, 82% of patients were still followed in a situation of good control of their disease, 8% of cases of local recurrence and 10% of distant metastasis.

Table-2: Acute and late complications after radiotherapy/brachyterapy

Complications		Incidence
Acute 30%	Radiodermatitis	7%
	Acute rectitis	16%
	Vulvovaginitis	2,3%
	Acute cystitis	4,7%
Delayed 5%	Chronic rectitis	2,3%
	Lymphedema of the lower limbs	1,2%
	Chronic cystitis	1,5%

DISCUSSION

Worldwide, endometrial cancer is the 7th most common malignant disorder, but incidence varies among regions [5]. In less developed countries, risk factors are less common and endometrial cancer is rare, although specific mortality is higher [6, 7]. The incidence is ten times higher in North America and Europe than in less developed countries in these regions, this cancer is the commonest of the female genital tract and the fourth commonest site after breast, lung, and colorectal cancers [5, 8]. The incidence is rising as life expectancy increases [9]. Age-adjusted incidence is increasing even when corrected for hysterectomy [10]. The rise has been associated with an epidemic of obesity and physical inactivity [9, 11]. For example, in the year 2000 in Belgium, with a female population of just over 3 million, 743 women were diagnosed as having endometrial cancer. In Flanders, this cancer is the 3rd commonest in the female population, after breast and colon cancers. The incidence of 24, 7 per 100 000 women in this region is much the same as that in other western European countries. The incidences per 100 000 women in the same region for cervical, ovarian, and breast cancers were 13·6, 20·8, and 161·9. The cumulative risk of endometrial cancer up to age 75 years has been estimated as 1·7% [12].

Endometrial cancer commonly has been classified into three types

- Type I commonly is estrogen-related and occurs in younger, obese, or perimenopausal women. These tumors are usually low-grade and arise in a background of hyperplasia. It represents the majority of endometrial cancers. Endometrioid is the most common histology. These tumors may show microsatellite instability and mutations in PTEN, PIK3CA, K-ras, and CTNNBI [13].
- Type II disease generally has high-grade tumors, is of serous or clear cell histology, occurs in an older cohort of women than type I, and is more common in black women. These tumors may exhibit p-53 mutations in approximately 10–30% of cases. Type II disease represents up to 10% of cases. The epidemiologic profile of women with type II disease is not certain [14].

Definition of risk recurrence

Classification of the risk of recurrence varies depending on the country and region. Risk classifications as newly defined by ESMO (European Society for Medical Oncology)-ESGO (European Society of Gynecological Oncology)-ESTRO (European Society for Radiotherapy and Oncology) consensus have been published [15] (Table 3). The classifications of low-intermediate risk and high-intermediate risk were recognized during the GOG 99 trial [16].

Table-3: New risk groups to guide adjuvant therapy use[15]

Risk group	Description
Low	Stage I endometrioid, grade 1–2 <50% myometrial invasion, LVSI negative
Intermediate	Stage I endometrioid, grade 1–2 ≥50% myometrial invasion, LVSI negative
High-intermediate	Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status Stage I endometrioid, grade 1–2, LVSI unequivocally positive, regardless of depth of invasion
High	Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status Stage II Stage III endometrioid, no residual disease I Non-endometrioid (serous or clear-cell or undifferentiated carcinoma, or carcinosarcoma)
Advanced	Stage III residual disease and stage IVA
Metastatic	Stage IVB

Treatment options

A- **Surgery**

The most important therapy for endometrial cancer is surgery. The procedures include acquisition of peritoneal fluid or washings for cytology, total hysterectomy including the uterine cervix, and bilateral salpingo-oophorectomy; in selected cases, there is a place for omentectomy and a thorough retroperitoneal lymph-node dissection. Laparoscopy-assisted vaginal hysterectomy is feasible when operating for endometrial cancer; fluid for cytology, peritoneal biopsy samples, lymph nodes, and omentum can be obtained in a single procedure [17]. Standard surgery is total hysterectomy with bilateral salpingo-oophorectomy without vaginal cuff, Ovarian preservation can be considered in patients younger than 45 years old with grade 1 EEC with myometrial invasion <50% and no obvious ovarian or other extra-uterine disease, In cases of ovarian preservation, salpingectomy is recommended, Ovarian preservation is not recommended for patients with cancer family history involving ovarian cancer risk [15].

B- **Adjuvant treatment**

Adjuvant treatment recommendations for endometrial carcinoma depend on the prognostic risk group (table 3):

Radiation can be delivered externally to the pelvis, as vaginal brachytherapy, or both. Treatment can also be directed to the whole abdomen or to an extended field that includes the pelvis and para-aortic region. Exclusive radical radiotherapy with intrauterine brachytherapy is curative but should be applied only in medically inoperable patients [18]. The goal of adjuvant radiotherapy is to treat the pelvic lymph-node regions that might contain microscopic disease, as well as the central pelvic region including the upper vagina:

- For patients with low-risk endometrial carcinoma, no adjuvant treatment is recommended.
- For intermediate risk group, adjuvant brachytherapy can be recommended to decrease vaginal recurrence. Abandonment of adjuvant brachytherapy is considered, especially for patients aged <60 years.
- High-intermediate risk: Adjuvant brachytherapy is recommended to decrease vaginal recurrence, also EBRT can be considered for substantial LVSI and for stage II and abandonment of any adjuvant treatment is an option.
- High risk patients: EBRT with concurrent and adjuvant chemotherapy or alternatively sequential chemotherapy and radiotherapy is recommended. Chemotherapy alone is an alternative option.
- Advanced risk: Primary systemic therapy should be used if upfront surgery is not feasible or acceptable. In cases of a good response to systemic therapy, delayed surgery can be considered. For unresectable tumors, multi-disciplinary team discussion should consider definitive radiotherapy with EBRT and intrauterine brachytherapy, or neoadjuvant chemotherapy prior to surgical resection or definitive radiotherapy, depending on response. Image-guided brachytherapy is recommended to boost intrauterine, parametrial, or vaginal disease. Chemotherapy should be considered after definitive radiotherapy [19].

The combination of surgery and postoperative radiotherapy is not without risk of serious complications. They occur in 1–10% of women, depending on the patient's status, irradiated volume of bowel, bladder, or vagina, radiation dose, fraction size, dose rate (low, pulsed, or high), and especially in combination with lymph-node resection. Modern radiotherapy techniques with belly board and multiple fields or three dimensional conformal radiotherapy are recommended to limit side-effects. Prophylactic brachytherapy should be restricted to the upper third of the vagina, and contact doses should not exceed 60 Gy low-dose-rate equivalent to limit long-term side-effects[20].

Follow-up

The recommended monitoring is clinical, every 6 months for 3 years for 3 years, then annually, adapted to the general condition and the patient's age, without any improvement in survival time [39]. survival has not been demonstrated [21]. It uncovers 70% of pelvic pelvic recurrences, most of which are already symptomatic. In cases of low risk of recurrence, annual surveillance can be performed by the treating physician or the gynecologist. The smear is useless because it is negative in retrospective series in patients with no clinical signs and difficult to interpret after brachytherapy delicate interpretation after brachytherapy, with dystrophic cells that are difficult to characterize, leading to the repetition of useless and/or invasive examinations. Additional examinations should only be considered in case of clinical signs, with signs, with a biopsy being performed [22].

CONCLUSION

Endometrial cancer is increasingly common in our country, the main treatment is surgery, Radiotherapy (EBRT) and brachytherapy represent the main adjuvant treatment while the place of chemotherapy remains in the locally advanced or metastatic stages.

Conflict of interest statement

The authors declare no conflicts of interest.

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