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RESEARCH ARTICLE

PATTERNS OF ADJUVANT TREATMENT FOR ENDOMETRIAL CANCER : THE EXPERIENCE OF A SINGLE INSTITUTION IN MOROCCO

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Abstract

Endometrial cancer is the fourth most common malignant tumor in women in developed countries, and in Morocco it represents the third most common gynecological cancer. It primarily affects postmenopausal women. Our study is a retrospective descriptive study conducted from 01/01/2014 to 01/01/2018 at the radiation therapy department of the National Institute of Oncology in Rabat. Data were collected from medical records and included epidemiological, clinical, therapeutic and prognostic aspects of this cancer. The median age at diagnosis was 61 years. The median delay to consultation was 6 months. The histological diagnosis was made by endometrial biopsy in 52.3% of cases. Pathological examination revealed endometrioid adenocarcinoma in 91% of cases. 32 patients received adjuvant treatment consisting of external radiotherapy at a dose of 46 Gy in 23 fractions, followed by vaginal brachytherapy (37%), of which 6 of these patients also received sequential chemotherapy (7.1%). 21 patients were treated with brachytherapy alone (25%), 11 patients with external radiotherapy alone (13%), and 21 patients with concurrent radiochemotherapy (25%). The treatment interval between diagnosis and surgery was 42 days. In our series, the overall 5-year survival rate was 93.6% for all stages combined.

Introduction:-

Endometrial cancer, also known as uterine cancer, represents the fourth most common cancer in women in developped countries (1), and in Morocco it represents the third most common gynecological cancer(2). It typically occurs in women who have reached menopause. Hyperoestrogenism is the main risk factor. The first exam for endometrial cancer typically includes a pelvic exam and a pelvic ultrasound to check for any abnormal growths or thickening of the endometrial lining. Additional tests such as CT or MRI scan and blood test (CA-125) are recommended to further evaluate the extent of the disease.

Surgery is a the main treatment for endometrial cancer, and the type of surgery performed will depend on the stage and grade of the cancer.
After surgery, the patient may receive additional treatment such as radiation therapy or chemotherapy to kill any remaining cancer cell.

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The aim of this study was to evaluate the use of adjuvant therapy and treatment outcomes in patients with endometrial cancer (EMC).

Materials And Methods:-

A list of patients with EMC treated in the institution between January 2014 and January 2018 was searched. The inclusion criteria for the study were patients who underwent surgery as their primary treatment, had a histopathological diagnosis of endometrial carcinoma or sarcoma and received adjuvant treatment: external radiotherapy and/or vaginal brachytherapy. Patients who received preoperative radiation therapy or chemotherapy or lacked complete medical records were excluded from the study.

An analysis of medical records was conducted to gather information on sociodemographic, clinical, therapeutic and evolutionary aspects of endometrial cancer (EMC).

The tumors were categorized according to the FIGO classification system. To assess the tumor's spread, an abdominal and pelvic magnetic resonance imaging (MRI) was performed, while the distant spread of the cancer was determined based on the presence of any symptoms.

The primary surgical treatment for endometrial cancer is a total hysterectomy, which involves the removal of the uterus and the cervix.

Depending on the stage and grade of the cancer, additional procedures may also be performed during surgery such as lymphadenectomy, annexectomy or radical hysterectomy; removal of the uterus, cervix, ovaries, fallopian tubes, and surrounding tissues.

The surgery allowed for the determination of the cancer stage and the selection of an appropriate adjuvant treatment plan, which could include external radiation therapy, endocavitary therapy, and/or chemotherapy.

Results:-

During the study period, 85 cases of endometrial cancer that were treated surgically were collected. The ages of the patients at the time of diagnosis ranged from 33 to 94 years, with a median age of 61 years. The median delay between the onset of symptoms and the first consultation was 6 months. The attached table provides an overview of the epidemiological and clinical characteristics of the patients.

Graph 1 :

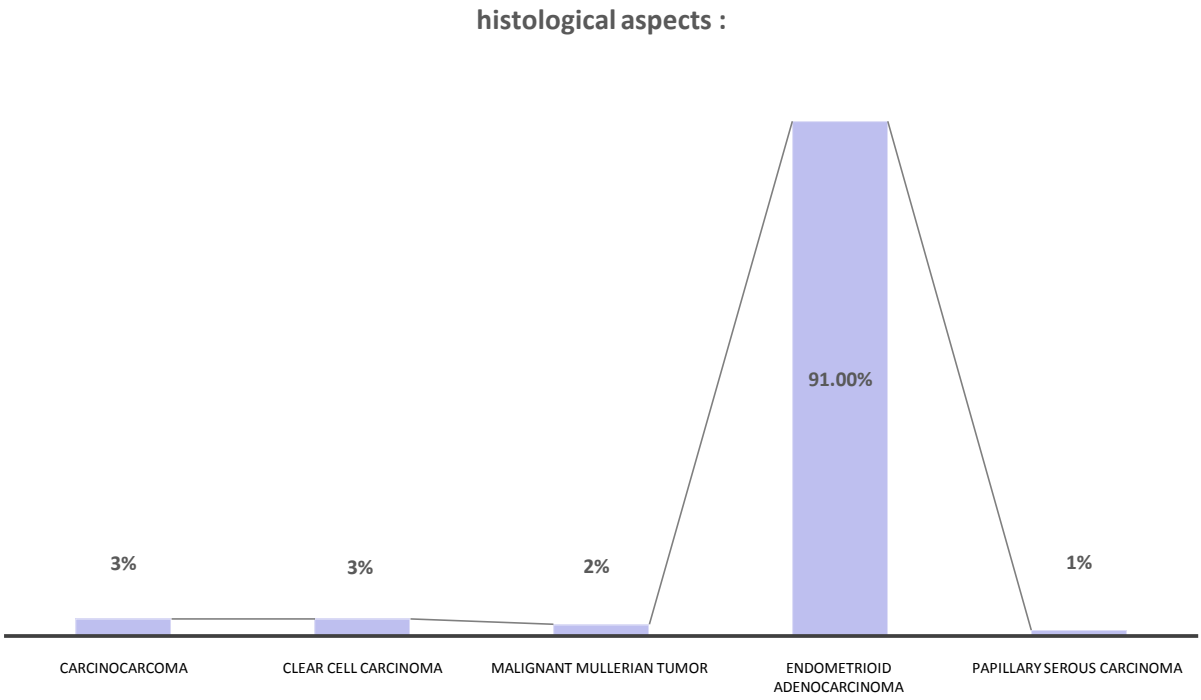
Graph 1:- Patient Characteristics: Number of patients (%).

Age	• Median age : 61 years • range : 33 - 94 years
Hormonal statut	• Menopausal : 77 (91%) • Premonausal : 8 (8%)
Parity	• nulliparous : 53 (63%) • Multiparous 32 (37%)
ATCD	• Without prior history : 22 (25%) • Diabete : 19 (23%) • Hypertension : 38 (45%) • Hypertension + Diabete : 11 (13%)

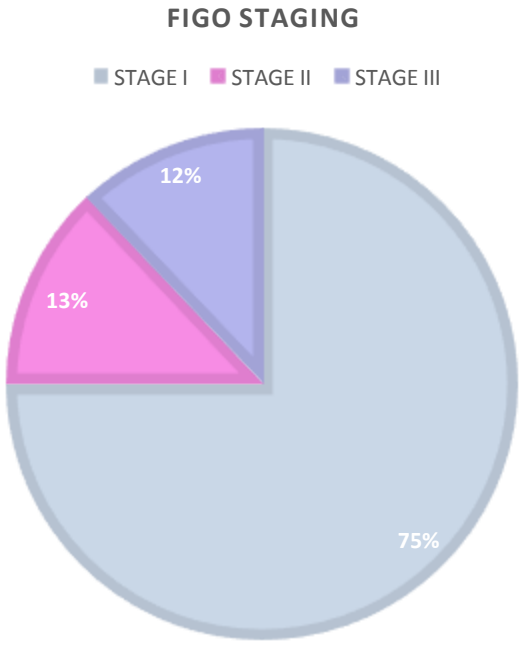
The main symptom was postmenopausal bleeding (90.5%). The histological diagnosis was made from an endometrial biopsy in 52.3% of cases. The pathological examination revealed an endometrioid adenocarcinoma in 91% of cases, of which 48% were grade 2, 33% were grade 1, and 19% were grade 3, a carcinosarcoma in 3% of cases, a clear cell carcinoma in 3% of cases, a mixed malignant Mullerian tumor in 2% of cases, and a papillary serous carcinoma in 1% of cases.

Graph 2 :-

Graph 2:- Shows the different histological aspects.



The analysis of the hysterectomy specimens revealed that 22 patients (26%) had stage IA endometrial cancer (FIGO), 41 patients (49%) had stage IB cancer, 12 patients (13%) had stage II cancer, and 10 patients (12%) had stage III cancer. (Graph 3)



Graph 3:- Tumor stages.

The pathological analysis allowed for the determination of surgical prognostic factors. (table 1)

Table 1:-Surgical prognostic factors.

Tumor Characteristics	Number of patients N(%)
Histological Type :	
Adenocarcinoma	77 (91%)
Type II	8 (9%)
Excision Margins	
healthy	84 (99%)
Tumor-involved	1 (1%)
Myometrial Infiltration	
≤ 50%	26 (31%)
≥ 50%	59 (69%)
Vascular Emboli	
Present	17 (20%)
Absent	57 (67%)
Not specified	11 (13%)
Lymph Node Involvement	
Positive	4 (4%)
Negative	36 (43%)
Not perfomed	41 (48%)
Not specified	4 (5%)

32 patients received adjuvant treatment that included external radiotherapy at a dose of 46 Gy in 23 fractions, followed by vaginal brachytherapy (37%), 6 of whom also received sequential chemotherapy (7%). 21 patients received brachytherapy alone (25%), 11 patients received external radiotherapy alone (13%), and 21 patients received concurrent radiochemotherapy (25%).(table 2)

Table 2:-

Adjuvant treatment	Number of patients N(%)
External Radiation Therapy + Adjuvant Vaginal Brachytherapy	32 (37%)
External Radiation Therapyalone	11 (13%)
Adjuvant Vaginal Brachytherapy	21 (25%)
Concurrent Radiochemotherapy	21 (25%)

A univariate analysis was conducted on the aforementioned characteristics and we found that only the surgical procedure and myometrial invasion were related to the occurrence of tumor recurrence and were statistically significant.

The time interval between diagnosis and surgery was 42 days. In terms of outcome, 73% of patients had no evidence of disease, 11% had locoregional recurrence, 9% had distant metastasis, and 6 deaths were recorded. The overall survival rate at 3 years for all stages combined was 97.4% and 93.6% at 5 years.

Discussion:-

Endometrial cancer is one of the most common gynecological tumors worldwide. Over 75% of patients are postmenopausal at the time of diagnosis and only 3% are under 40 years old (3).

In Morocco, according to GLOBOCAN (2020), endometrial cancer is the fourth most common gynecological cancer in women, after breast, cervical and ovarian cancer, with an incidence of 3.6/100,000 inhabitants. The main risk factors for endometrial cancer are obesity, diabetes, hypertension and tamoxifen treatment (3,4). Hereditary forms represent 2-5% of endometrial cancers, mainly observed in Lynch syndrome,(5) but no hereditary cases were found in our study. The most common reason for consultation and main symptom is postmenopausal bleeding. In our series, it represented over 90% of cases, usually spontaneous, of moderate abundance and painless. Other symptoms such as leukorrhea, pelvic pain and urinary problems were found in a limited number of patients.

The clinical examination for endometrial cancer is generally poor and uninformative, which was the case in our series for most of the patients, except for those with locally advanced stage with cervical extension of the tumor, involvement of the parametria or extension to neighboring organs.

Examination of other sites is systematically performed in all patients, this examination includes palpation of the lymph nodes, palpation of the liver, search for ascites and breast examination for any nodule or breast lesion(4).

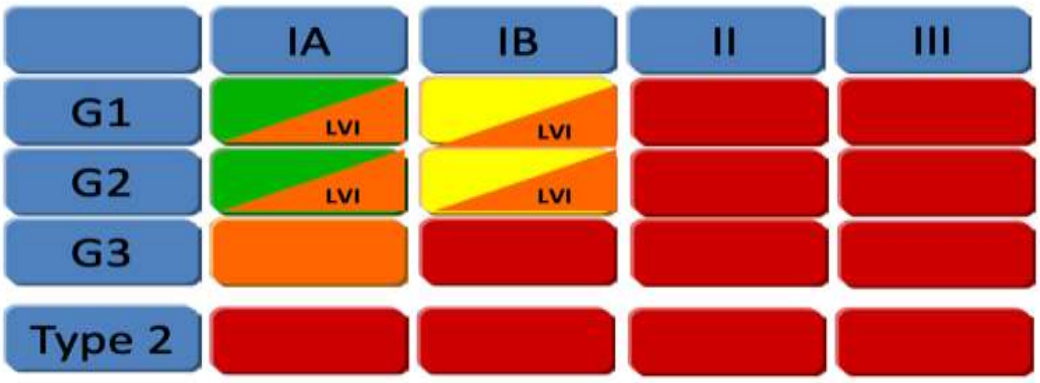
The initial examination for any abnormal uterine bleeding relies on transvaginal ultrasound, the endometrial thickening found will lead to a biopsy, which will later confirm malignancy and will allow to define the histoprognostic grade in case of type 1, However, the final therapeutic management is based on the anatomopathological report of the hysterectomy specimen.

The histological classification of endometrial cancer divides it into two types: type I, which is estrogen-related and accounts for about 80% of cases, and type II, which is non-hormone dependent. Type I is characterized by adenocarcinomas that are slow-growing and have a better prognosis. The European Society for Medical Oncology (ESMO) has defined three histological grades of endometrial adenocarcinoma: grade 1, which has less than 5% solid (non-glandular) areas; grade 2, which has between 6 and 50%; and grade 3, which has more than 50%. The most common type I mutations are PTEN, KRAS, and microsatellite instability. Type II includes serous, mucinous, and clear cell carcinomas, which are known for their aggressive behavior towards surrounding tissues and are considered high-grade histologically. They have a poor prognosis due to a high risk of distant metastasis at diagnosis and often deeply infiltrate the myometrium, up to the serosa. Type II is responsible for 40% of endometrial deaths, despite only representing 10-20% of cases.

The most common mutations are TP53, HER-2, and P16 (6).

The 2015 classification system for endometrial cancer helped us to divide it into four groups, based on factors like the FIGO stage, grade, presence of vascular emboli, histological type, and patient age. This system also helps in determining the need for additional treatment options such as external radiation therapy, brachytherapy or chemotherapy.(Table 3)

Table 3:- Endometrial classification according to histoprognostic factors 2015.



Low risk	2-4 % relapses
Intermediary risk	
Intermediary/high risk	
High risk	21-23 % relapses

The TCGA (2013) and the Trans-PORTEC (2015) have identified 4 molecular groups, namely POLE, MSI, MSS/NSMP, and mutated P53, which have mainly a prognostic value. These different molecular groups have been integrated into the latest classification (ESGO-ESTRO-ESP/2021) in order to adjust the treatment for localized stages and to increase the treatment for more advanced stages (8). The initial staging of cervical cancer is based on the 2009 classification of the International Federation of Gynecology and Obstetrics (FIGO) (Table 4) and it is done by abdominal-pelvic magnetic resonance imaging (MRI) which is considered the best examination for evaluating the locoregional extent of the tumor in terms of myometrial invasion, cervical invasion, involvement of adjacent organs and the assessment of pelvic and lumbar-aortic lymph node status, if not an abdominal-pelvic CT can be performed (9), in our series, all our patients have benefited from an abdominal-pelvic MRI.

Table 4:- FIGO Staging of Uterine Corpus Carcinoma.

Stage I	Confined to the uterine corpus
• IA	Limited to endometrium or involves less than half of the myometrium
• IB	Invasion of half or more of the myometrium
Stage II	Invasion of the cervical stroma but no extension outside the uterus
Stage III	Local and/or regional spread of the tumor‡
• IIIA	Invasion of uterine serosa, adnexa, or both (direct extension or metastasis)
• IIIB	Metastases or direct spread to the vagina and/or spread to the parametria
• IIIC	Metastases to pelvic or para-aortic lymph nodes or to both
• IIIC1	Metastases to pelvic lymph nodes
• IIIC2	Metastases to para-aortic lymph nodes, with or without metastases to pelvic lymph nodes
Stage IV	Involvement of the bladder and/or intestinal mucosa and/or distant metastases
• IVA	Invasion of the bladder, intestinal mucosa, or both
• IVB	Distant metastases, including metastases to the inguinal lymph nodes or intraperitoneal disease

When there is a suspicion of metastatic disease, a CT or PET scan is the best way to confirm the diagnosis. These scans have a higher sensitivity than a scan without reduction in specificity, meaning they are more likely to detect the presence of metastatic disease.

Surgery is the primary treatment for endometrial cancer, usually consisting of a total hysterectomy and removal of the bilateral fallopian tubes and ovaries. Depending on the stage, type, grade, and presence of lymphatic emboli surrounding the tumor, additional procedures such as lymph node removal and/or removal of the omentum may be required. The extent of lymphatic involvement and preoperative staging are also considered, but the final treatment plan is determined based on the results of the surgical pathology examination in a multidisciplinary consultation meeting, to ensure consistency and re-evaluation of imaging.External radiation therapy is performed using conformal methods and according to the recommendations of the Radiation therapy oncology group (RTOG) with very high energy photons. The volume of irradiation depends on the tumor's extension.

It is performed at the pelvic level and, if necessary, at the lumbar-aortic region in case of involvement in this region. The total dose to be delivered is 45 to 50 Gy, with 5 fractions per day of 1.8 to 2 Gy in 25 fractions. This radiation therapy should be initiated less than 9 weeks after surgery; after this time, the risk of relapse is increased (12). In our series, 11 patients received exclusive adjuvant radiation therapy, while 32 patients benefited from radiation therapy combined with brachytherapy.

Brachytherapy allows for high doses of radiation to be delivered in contact with the vaginal vault while sparing as much healthy tissue as possible with a high dose gradient. Once indicated, it is preferably performed at high dose rate. In case of brachytherapy alone, the recommended dose is 21 Gy in three fractions, 20 Gy in four fractions, or 24 Gy in four fractions, while after external radiation therapy, it is recommended to deliver 6.5 or 7 Gy in one session or 10 Gy in two fractions (13)

In our research, 37% of patients experienced positive results from receiving radiation therapy followed by endovaginal brachytherapy at a dose of 21 Gy in 3 fractions, and 25% received 10 Gy in 2 fractions for exclusive brachytherapy.

For high-risk cases, concurrent chemoradiation (CCRT) is recommended. Studies, such as PORTEC 3, have shown that CCRT improves overall survival and relapse-free survival, especially for serous types and stage III.(14)

Additionally, molecular subgroup analysis suggests that p53 mutants may benefit more from concurrent and adjuvant CCRT due to their poor prognosis. However, the GOG 258 randomized study did not find a significant difference in survival between CCRT and radiation therapy alone. In our study, 29 patients received CCRT, but 8 of them were unable to benefit from it due to their advanced age. The field is moving towards more personalized treatment options that integrate molecular classification with histoprognostic factors.

The impact of these molecular risk factors on optimal treatment is still being evaluated with the PORTEC-4 trial. After initial treatment, monitoring includes a clinical examination every 6 months for the first three years and

annually thereafter to check for vaginal relapse. Imaging exams are not systematically recommended, but may be used based on warning signs such as metrorrhagia or pain. Despite a good overall prognosis for endometrial cancer, between 10-15% of patients will relapse (15,16). In our study, 11% of patients experienced locoregional relapse and 9% had distant metastases.

The treatment for metastatic recurrences in our study was the carboplatin-taxanes chemotherapy regimen. A 2012 Cochrane meta-analysis of 14 randomized trials found that more intensive treatment improves progression-free survival and overall survival, but also increases the risk of severe acute toxicity(17).

Overall, the five-year survival rate for all stages of endometrial cancer is 76%(18). For localized stages, the rate increases to 95%. In our series, the overall five-year survival rate was 93.6%, which may be due to the fact that the majority of patients in the study had a localized stage.

Conclusion:-

The management of endometrial cancer includes utilizing all traditional cancer treatment options such as surgery for curative and staging goals, external and endocavitary radiation therapy, and chemotherapy. Generally, this type of cancer has a good prognosis. Through this retrospective study, we have shared our institute's experience in treating this tumor.

Conflicts of interest:
The authors declare no conflict if interest.

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