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RESEARCH ARTICLE

EPIDEMIOLOGICAL, CLINICAL, THERAPEUTIC AND EVOLUTIONARY ASPECTS OF ENDOMETRIAL CANCER: EXPERIENCE OF THE NATIONAL INSTITUTE OF ONCOLOGY OF RABAT (ABOUT 158 CASES)

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Abstract

Introduction and purpose of the study: Endometrial cancer is the third most common gynaecological cancer in Morocco. Its managementis multidisciplinary.

Materials and Methods:Our retrospective study concerned patients admitted to the National Institute of Oncology between January 1st 2014 and January 1st 2018. The data were collected using a data collection form where the epidemiological, clinical, therapeutic and evolutionary data were specified.

Results and Statistical Analysis: During this period, we collected 158 cases of endometrial cancer. The age of the patients at the time of diagnosis varied between 33 and 94 years, with a median age of 61 years. Our study shows that 83.5% of the patients were postmenopausal, 19% diabetic and 26.6% hypertensive. 84.8% of the patients consulted for postmenopausal metrorrhagia, 3.8% for menometrorrhagia and 1.9% for pelvic pain within an average of 7 months.Patients underwent Endometrial Biopsy orCurettage in 14.6% and 50.6% of cases, respectively; 42.4% hadan endometrioid adenocarcinoma. 39.2% of the patients underwent pelvicMagnetic Resonance Imaging(MRI) and 32.3% pelvic CT. Therapeutically, the main treatment received after a multidisciplinary consultation meeting was surgery alone in 38% of cases, external radiotherapy followed by brachytherapy of the vaginal fundus in 22.8%. Acute toxicity was observed in 32.5% of cases, dominated by renal and haematological toxicities. The analysis of the surgical specimen allowed us to classify our patients into four FIGO(International Federation of Gynaecology and Obstetrics(stages, predominantly stage IB found in 32.9% of cases followed by stage IA in 27.8% of cases; Lymph-vascular space invasion (LVSI)were positive in 14.6% of cases. 10.8% progression and 7% recurrence were observed during the follow-up.Overall survival (OS) at 1year was estimated at 88.3%; 86.8% at 2 years and 86.1% at 5 years.

Conclusion: According to our study, the patients treated during this period in our institute are mostly postmenopausal, diagnosed at an early stage, essentially by surgery alone with an excellent survival rate. These results are consistent with the literature.

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Introduction:-

Endometrial cancer is the third most common gynaecological cancer in Morocco [1]. It occurs mainly in postmenopausal women. Estrogen exposure is a major risk factor [2]. Patients are often diagnosed at early stages. It is classified according to epidemiological and histomolecular criteria into two types (Type I and Type II) [3].

The mainstay of treatment for uterine endometrial cancer is surgery ; its also used to confirm or affirm the diagnosis, to classify the tumour according to the FIGO classification and to guide adjuvant management [3-9]. It has a favourable prognosis with a relatively low mortality rate mainly in the early stages. The aim of our study is to report the epidemiological, clinical, therapeutic and evolutionary characteristics of patients treated for endometrial cancer at the radiation therapy department of the National Institute of Oncology.

Methods:-

Our retrospective study concerned patients admitted to the National Institute of Oncology between January 1, 2014 and January 1, 2018. The data were entered, coded and analysed on an Excel file.

The positive diagnosis of endometrial cancer was made on the basis of clinical and para-clinical data (imaging and histology), confirmed by pathological analysis of the surgical specimen and classified according to the FIGO classification.

Surgery was the primary treatment and provided guidance for adjuvant management. It was either a total hysterectomy, a total colpo-hysterectomy with or without bilateral oophorectomy; with or without lymph node dissection.

The endovaginal brachytherapy was high dose rate (HDR), the total dose delivered varied depending on whether it was exclusive brachytherapy or combined with external radiotherapy. The fractions used were 21 Gy in 3 fractions and 10 Gy in 2 fractions.

Adjuvant external radiotherapy was at a dose of 46Gy normofractionated (23 sessions of 2Gy/session) to the Pelvis with high energy X-ray photons (18-25 MV) using four beams.

Results:-

During this period, we collected 158 cases of endometrial cancer. The age of the patients at the time of diagnosis varied between 33 and 94 years, with a median age of 61 years. Our study shows that 83.5% of the patients were postmenopausal, 19% diabetic and 26.6% hypertensive. 84.8% of the patients consulted for postmenopausal metrorrhagia, 3.8% for menometrorrhagia and 1.9% for pelvic pain within an average of 6 months. These epidemiological and clinical data are summarised in Figures 1 and 2.

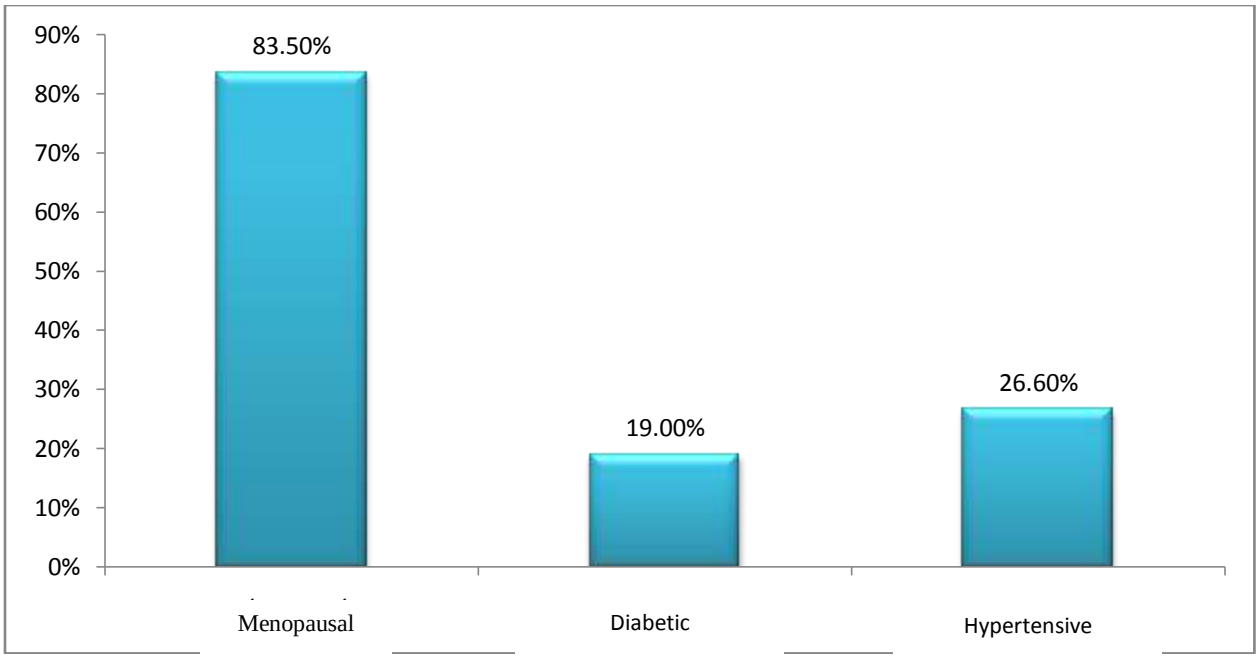

Figure 1:- Epidemiological characteristics of patients.

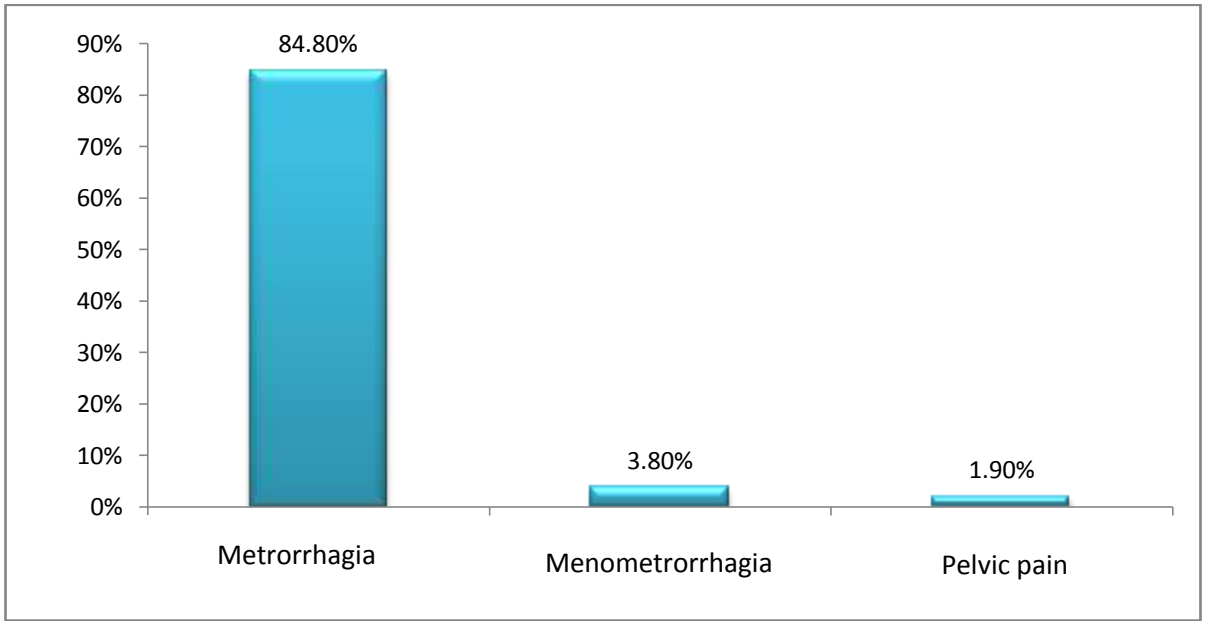

Figure 2:- Clinical characteristics of patients.

Patients underwent preoperative assessment(histology and imaging)with biopsies or curettage of the endometrium in 14.6% and 50.6% of cases, respectively; 42.4% were found to have endometrioid adenocarcinoma. 39.2% of patients had pelvic Magnetic Resonance Imaging (MRI) and 32.3% had pelviccomputed tomography(CT). These data are presented in Figure 3.

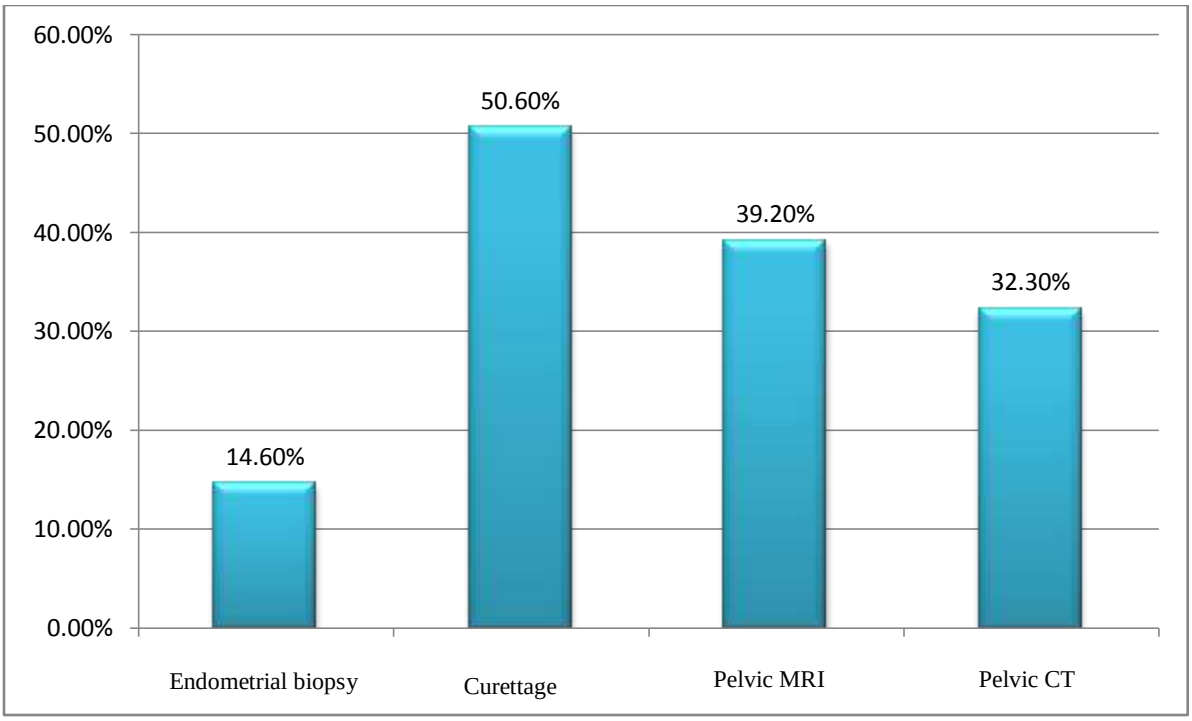

Figure 3:- Preoperative radiological and pathological work-up.

In terms of treatment, the main treatment received after the multidisciplinary consultation meeting was surgery alone in 38% of cases, and external radiotherapy followed by brachytherapy of the vaginal fundus in 22.8% (Figure 4).

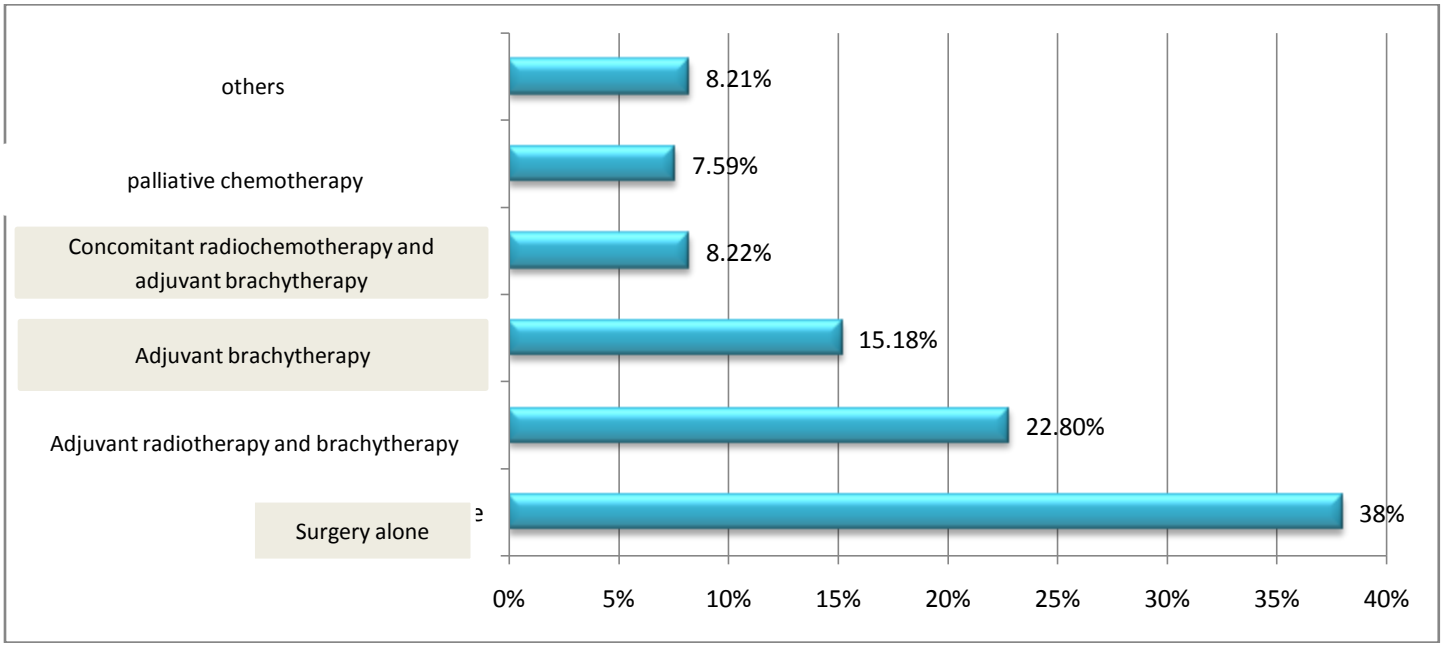

Figure 4:- Preoperative radiological and pathological work-up.

The analysis of the surgical specimen allowed us to classify our patients into four FIGO stages, predominantly stage IB found in 32.9% of cases followed by stage IA in 27.8% of cases; LVSI were positive in 14.6% (Graph 5).

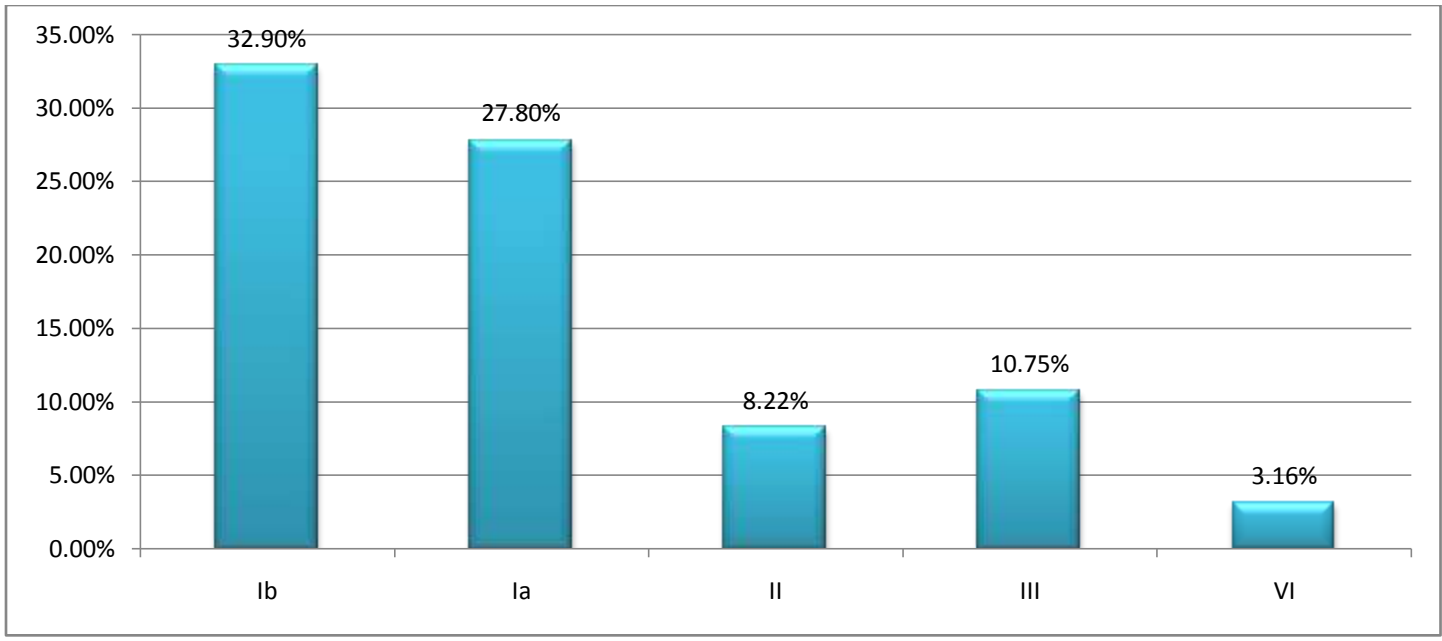

Figure 5:- FIGO classification of the surgical specimen.

During adjuvant treatment; acute toxicity was observed in 32.5% of cases dominated by renal and haematological toxicities. During post-treatment follow-up, a progression rate of 10.8% and a recurrence rate of 7% were observed; overall survivalat one year was estimated at 88.3%; at two years 86.8% and at five years 86.1% (Graph and 7).

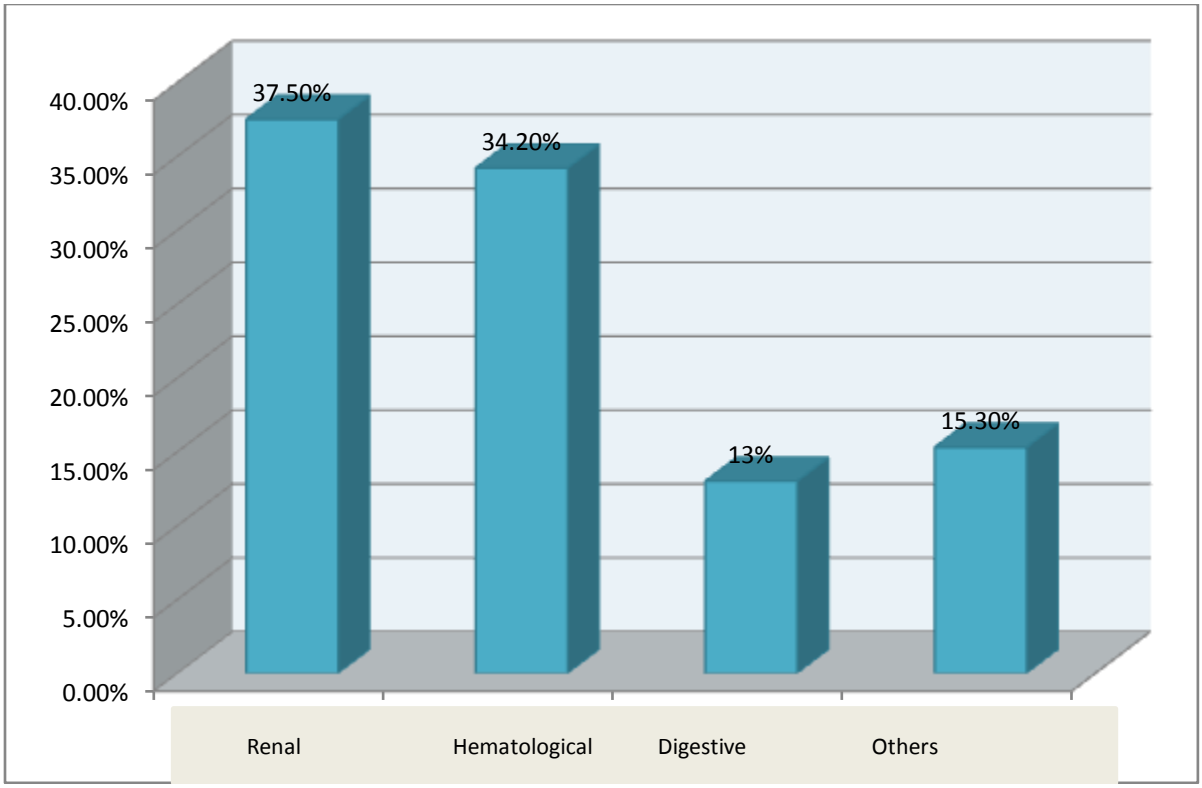

Figure 6:- Toxicities observed during adjuvant treatment.

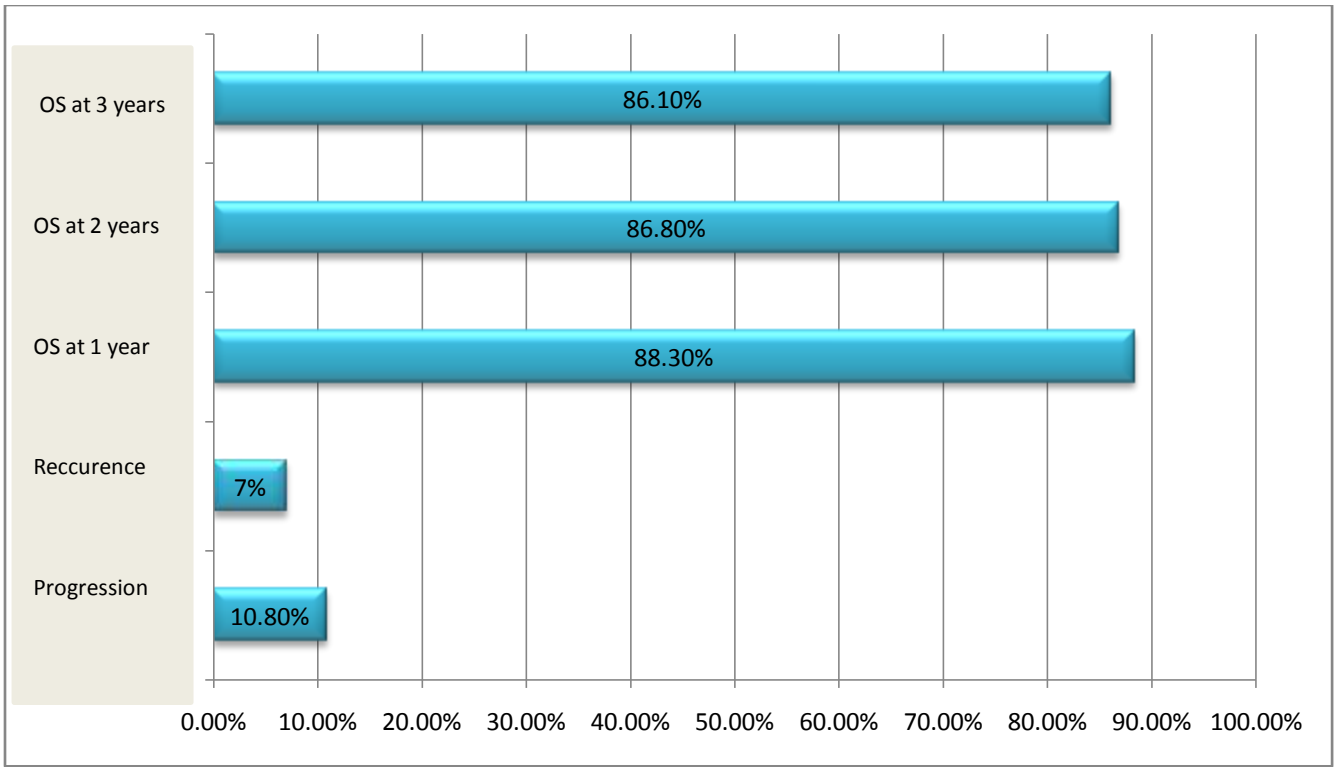

Figure 7:- Results of post-treatment follow-up of patients.

Discussion:-

Endometrial cancer is the fourth most common cancer in women in industrialised countries [1], the third most common gynaecological cancer in Morocco [1] and accounts for 3.1% of all cancers in women, with a crude incidence of 4.7/100,000 in Rabat and a standardised incidence of 3.5/100,000 in the world population [5]. In our study, the age of the patients at the time of diagnosis ranged from 33 to 94 years, with a median age of 61 years; the median time to consultation was 6 months; and 83.5% of the patients were postmenopausal (Figure 1).

Several risk factors have been described; they are physiological (Age, Multiparity, Early menarche and Late menopause); pathological (Obesity, Diabetes, Hypertension, Polycystic ovary syndrome); iatrogenic (Hormone replacement therapy, Tamoxifen; Pelvic irradiation); genetic [3] (HNPCC increases the risk of endometrial cancer by 27% to 71%).There are also Protective Factors (Progestin, Exercise; Smoking) [1, 2, 3,6,7].

In our series our patients had the following risk factors: menopause; hypertension and diabetes (Graph 1).

The usual clinical symptomatology is spontaneous, painless, irregular postmenopausal metrorrhagia (~90%); other symptoms (abdominal-pelvic pain, abdominal distension, rectal bleeding and constipation) may be symptoms of advanced disease [8].

In our patients 84.8% of the patients consulted for postmenopausal metrorrhagia, 3.8% for menometrorrhagia and 1.9% for pelvic pain (Graph 2).

Histologically, endometrial cancers can be distinguished into two main types: Endometrioid and non-endometrioid with other rarer types (squamous cell carcinoma, neuroendocrine carcinoma, mucinous carcinoma, papillary serous carcinoma, clear cell carcinoma, carcinosarcoma, sarcoma, undifferentiated carcinoma and dedifferentiated carcinoma).

Histopronostic grade Used only for endometrioid Adenocarcinoma; corresponds to the Degree of glandular differentiation it is a Factor of aggressiveness of the tumour (Grade 1: < 5%; Grade2: 6 - 50%; Grade3: > 50%).According to the new recommendations; it is referred to as Low grade (grade 1-2) or High grade (grade 3).

There are twoHistomolecular and prognostic Types described: Type I is the most common (80% of cases), characterised by endometrioid, hormone-sensitive, diploid carcinomas with a good prognosis. A number of molecular abnormalities have been described for this type: wild-type, loss of PTEN, mutation of the β- catenin gene [8].

Type II is much rarer (15-20% of cases) and has a higher risk of metastasis, combined with a poor prognosis. Histologically, it corresponds mainly to serous or clear cell carcinoma. Unlike endometrioid carcinomas, where atypical glandular hyperplasia is the first step towards neoplasia, serous or clear cell carcinomas are derived from a malignant transformation of the surface epithelial lining. They most often develop on lesions of intraepithelial carcinoma in a context of atrophic mucosa. At the molecular level, these carcinomas are aneuploid and mutated for p53[8].

In our series, the anatomopathological analysis of the surgical specimen showed endometrioid carcinoma in 84%, carcinosarcoma in 6.5%, serous carcinoma in 2.9%, and LVSI were positive in 14.6%.

The preoperative extension assessment is based essentially on pelvic magnetic resonance imaging (MRI) which evaluates myometrial, cervical and serosal invasion as well as lymph node invasion; In the absence of MRI or in the event of contraindication to MRI, an abdomino-pelvic computed tomography (CT) scan can be performed [4]. This assessment will be completed by a CT or PET scan, which has a higher sensitivity than a CT scan without reducing specificity in the event of suspected metastatic disease.

In our study, our patients underwent preoperative histology and imaging with biopsiesor curettageof the endometrium in 14.6% and 50.6% of the cases, respectively,which objectifiedendometrioid adenocarcinoma in 42.4% of the cases. 39.2% of patients had pelvic MRI and 32.3% had pelvic CT (Figure 3).

Surgery is the primary treatment for endometrial cancer and is used to guide adjuvant management. It consists of total hysterectomy and bilateral salpingo-oophorectomy and additional procedures may be performed depending on clinical stage, histological type and histopronostic grade. This will confirm the diagnosis; classify the tumour according to the FIGO classification and thus guide adjuvant management [3-9].

In our series it was either a total hysterectomy, a total colpohysterectomy with or without bilateral adnexectomy; with or without lymph node dissection depending on the preoperative work-up.

Radiotherapy is the main therapeutic means after surgery, external radiotherapy allows to decrease locoregional recurrences from intermediate risk according to four randomized trials including GOG 99 and PORTEC 1, but seems more favorable in terms of survival for high intermediates. External radiotherapy is performed according to conformal modalities and according to the recommendations of the Radiation Therapy Oncology Group (RTOG), with high energy photons.

Radiation therapy is administered to the pelvis in the absence of common iliac or lumbar adenopathies. On the contrary, the volume of irradiation is extended to the lumbar region in case of common iliac or lumbar adenopathies. The total dose is 45 to 50 Gy, in 5 fractions per week of 1.8 to 2 Gy per fraction. In the case of treatment with exclusive external radiation therapy, the total dose should be increased to at least 60 Gy [10, 11].

Adjuvant external beam radiation therapy was administered in our patients under three-dimensional conformal conditions and according to RTOG (Radiation therapy oncology group) recommendations, using high energy photons. Target volumes were based on the initial work-up.

Brachytherapy allows the delivery of high doses of radiation in contact with the vaginal vault while sparing a maximum of surrounding healthy tissues thanks to a strong adjuvant dose gradient. It is performed at a high dose rate in order to reduce the duration of in-patient treatment and to avoid complications as a result.The total dose administered is 21Gy in 3 sessions of 7Gy or 24Gy delivered in 4 sessions of 5 to 6 Gy. This total dose is calculated at 5mm thickness of the vaginal mucosa.The total dose is reduced to 10Gy in 5Gy per session in case of initial external radiotherapy. [12, 13, 14]. Brachytherapy is appropriate at intermediate risk and according to prognostic factors according to PORTEC2 and ESTRO-ESMO-ESGO 2021.

Our patients had received high dose rate endovaginal brachytherapy with the following regimens: 21 Gy in 3 fractions for patients treated with adjuvant brachytherapy alone and 10 Gy in 2 fractions for the patient treated with initial adjuvant external beam radiotherapy.

Adjuvant management depends on the results of the pathological examination of the surgical specimen, which looked for poor prognostic factors indicating and guiding adjuvant treatment, namely age, stage of the disease, histological type, endocervical infiltration and the presence of LVSI [15,16].

The low-risk group is defined as endometroid adenocarcinoma classified as IA according to FIGO; of low histopronostic grade; without LVSIor focal and substantial character of LVSI. It is characterised by a low risk of lymph node involvement on curage (0-3%); an estimated 95% recurrence-free survival after surgery; and a risk of local recurrence without adjuvant treatment of <5% [17].

No benefit to external radiotherapy or vaginal brachytherapy has been demonstrated in this subgroup of patients in several retrospective studies [18].

The Intermediate risk group includes: FIGO IA endometroid adenocarcinomas of high Histopronostic grade; without LVSIor of focal and substantial character OF LVSI; FIGO IB endometroid adenocarcinomas of low Histopronostic grade; without without LVSI or of focal and substantial character OF LVSI; or type 2 carcinomas, limited to stage IA.

As shown in the large randomised trials: the PORTEC-2 trial and the Swedish trial: external beam radiation therapy improves pelvic control; with little difference in overall survival or vaginal relapse. In contrast, the addition of adjuvant brachytherapy offers excellent vaginal control with lower morbidity and overall survival rates similar to those after adjuvant radiotherapy in this intermediate risk population [19].

The intermediate-high risk group includes type I Adenocarcinomas with LVSI ; type Icarcinomas of high histopronostic grade IB; FIGO stage II.

In case of absence of adenopathy on surgical specimen analysis (pN0), brachytherapy was performed to decrease the risk of vaginal recurrence. According to the new recommendations of 2021, external radiotherapy is performed in case of substantial vascular emboli also for stage II, in order to reduce the risk of lymph node recurrence. Chemotherapy can be proposed in case of high histopronostic grade and/or substantial vascular emboli. Finally, surveillance after surgery alone remains an option.

In case of absence of clinical lymph node invasion and absence of lymph node curage (cN0/pNx) adjuvant external radiotherapy is indicated in case of presence of vascular emboli of substantial character, with the aim of reducing pelvic recurrences, it is also recommended in case of stage II.Brachytherapy is performed in case of absence of vascular emboli for high histopronostic grade carcinomas and in case of low grade stage II endometrioıdes carcinomas, with the aim of reducing local recurrences.Chemotherapy may be indicated in case of substantial lymphovascular invasion or for high histopronostic grade tumours[20].

The high-risk group for recurrence includes: Stage III-IVA with complete resection or Stage I-IVA, non-endometrioid tumours. Concurrent or sequential radio-chemotherapy is currently indicated to improve locoregional control as well as overall and progression-free survival. Chemotherapy alone is also possible according to the results of the GOG-258 study in stage III-IV.

For advanced endometrial cancer, the combination of chemotherapy and radiotherapy is still indicated after multidisciplinary consultation [20].

Currently, the advent of molecular biology (analysis of the POLE exonuclease domain mutation) and the development of immunohistochemical markers (p53, MLH1, PMS2, MSH6, and MSH2) with prognostic and predictive value have made it possible to establish a molecular classification to assess prognosis and guide the choice of adjuvant therapy. Indeed; POLE mutated tumours have an excellent prognosis and de-escalation of toxic treatment is recommended.for TP53 mutated tumours with a poor prognosis without chemotherapy they present a

benefit to the addition of platinum in adjuvant.MSI/NSMP tumours have an intermediate prognosis and present a less clear benefit of adjuvant chemotherapy [21].

The evolution of endometrial cancer is characterised by a recurrence rate in 15% of cases for stages I and II. 70% of recurrences occur in the first 2-3 years. Surveillance is done clinically every 3-6 months x 2-3 years, then /6 months up to 5 years; then annually and by Imaging: If clinical sign of call; in case of Stage III/IV to CT TAP / 6 months X 3 years then /6 to 12 months X 2 years) [22].

Conclusion:-

Endometrial cancer is characterised by its increasingly clear curability and its excellent survival rate, mainly in the early stages; this requires adequate collaboration between gynaecological radiologists, anatomopathologists, radiotherapists and oncologists; this multidisciplinary management aims to offer a more effective and less toxic treatment; according to our study, the patients treated during this period in our institute are mostly postmenopausal, diagnosed at an early stage, essentially by surgery alone with an excellent survival rate. These results are consistent with the literature.

Currently, the advent of molecular biology is required to improve the efficiency of endometrial cancer management.

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