UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA

Dissertation Thesis Abstract

DIAGNOSIS AND THERAPEUTIC PROBLEMS IN ENDOMETRIAL CANCER

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Introduction

While the early twentieth century uterus tumor pathology was dominated by cervical cancer, endometrial cancer, with an increasing incidence in the last decades, has become the most common cancer of the female genital tract, at least for the socioeconomically developed countries; the causes which led to these changes are the average lifespan increase in the female population (the high incidence of endometrial cancer belongs to the 61-70 year-age group), and the existence of some risk factors such as unopposed estrogen replacement therapy for menopausal women, increased incidence of obesity, which is becoming "epidemic", diabetes and associated hypertension, and the improvement of the investigative possibilities. In Romania, endometrial cancer has been the second most common cancer, after cervical cancer. Although it is the third most common cause of death among the female genital cancers, after ovarian and cervical cancer, the endometrial cancer benefits from a complex treatment, with a survival rate of 50%, even for the FIGO IIIB stage tumors, if the diagnosis is established as early as possible and the treatment is immediately set up.

Material and method

62 endometrial cancer (30% of all uterine cancers with the mean incidence of 12.4 cases/year), hospitalized between 2007 and 2012 in the Obstetrics and Gynecology Clinics of Hospital No. 2 Craiova, were analyzed. The age of the patients (a mean of 62.24 years within the range of 45-80 years) showed us that most patients (53.22%) belonged to the age groups 61-70 years or over 70 years (21 and 11 cases), and that a significant part (28=45.16%) represented relatively young women (51-60 years), many of them in pre- or perimenopausal status; in 2 cases (3.23%) the disease occurred even in women younger than 50 years.

The diagnosis was established on the basis of an algorithm including clinical exam, imaging test, curettage biopsy and pathological examination of operative specimen. The clinical diagnosis was a presumptive one, abnormal uterine bleeding representing the first and most constant sign, present in all cases as postmenopausal metrorrhagia (51 cases = 82.25%), quantitative and/or menstrual flow rate changes in perimenopausal period (7 cases = 11.29%) and as breakthrough bleeding or abnormal

menstrual flow outside menopause in young women working in reproductive period (4 cases = 6.66%) [Table no. 1].

Clinical signs	Cases	%
Metrorrhagia	62	100
- Intermenstrum bleeding	4	6.66
- Perimenopauzal flux rate changing	7	11.29
- Postmenopauzal metrorrhagia	51	82.25
Leucorrhea	7	11.29
Pelvic pain	22	35.48
Dyspareunia	18	29.03
Urinary signs	8	12.90

Table Nr. 1 The endometrial cancer – clinical signs

The delay between the onset of the uterine bleeding and diagnosis establishment varied between a few days and 14 months; so, only 24 (38.70%) from 54 postmenopausal patients have seen the doctor at the first metrorrhagia, the others being diagnosed as follows: 14 cases in the first 3 months (24.50%), 10 cases between 3 and 6 months (19.20%) and 6 cases in more than 6 months (9.80%). In patients with pre- or perimenopausal status, the diagnosis was established during the first 3 months in 1 case, within the first 6 months in 2 cases and over 6 months in 5 cases. Besides abnormal uterine bleeding, the clinical picture was completed by the presence of leucorrhea (7 cases = 11.29%), pelvic pain (22 cases = 35.48%), dispareunia (18 cases = 29.03%) and urinary signs (8 cases = 12.90%), especially in more advanced stages of the disease, usually suggesting spread to cervical invasion or neighboring structures (parameters, annexes, bladder, etc.).

The obesity was the most strongly objective sign, present in 32 cases (51.61%), android type in 21 cases (65.62%) and ginoid type in 11 cases (34.28%). Acne, oily skin (8 cases = 12.90%), skin pigmentation (6 cases = 9.67%) and hirsutism (4 cases = 6.41%) as an expression of hyperoestrogenia and anxiety, insomnia and irritability were found in 7 cases (11.29%), more prominent in the patients with polycystic ovarian syndrome (4 cases). Gynecological examination revealed blood in the vagina and/or red blood leaking through the cervix in 51 cases (82.25%); the cervix was unchanged in 42 cases (67.74%), weakness in 18 cases (29.03%), lesional in 2 cases (3.22%) and

tumoral in one case (1.61%). The volume of the uterus, assessed by vaginal touch (39 cases = 62.90%) ranged from a few centimeters up to that of a 13 week-pregnancy; the consistency of the uterus was of a hard fibroid type in 13 cases (20.96%) and uneven, rough areas, alternating with other soft ones in 12 cases (19.5%).

Abdominal ultrasound was performed in all cases (52=83.87% cases received vaginal ultrasound examination), the data (table 2) being used both for positive diagnosis and for pre-therapeutic staging.

Abdominal/vaginal ultrasound	Cases	%
Tumor (3-12 cm)	52	100
Inner half myometrial invasion	11	21,15
Complete or more then inner half myometrial invasion	8	15,38
Extension to the cervix	10	19,23
Liver metastasis	3	5,76
Ascites	4	7,62

Table Nr. 2. Endometrial cancer – ultrasound date

Sectional imaging tests (CT, MRI) was performed in 46 (74.19%) patients (MRI 35 and CT 11 cases), the obtained data (Table no. 3) representing the main criteria in the pre-therapeutic stage evaluation of the primary tumor.

Imaging test		Imaging signs	Cases	Stage
IRM	CT			
7		- Endometrial focal weakness - Endometrial hypersignal in T2 weighted sequences - Focal enhancement with contrast media	3 5 7	T1a
8	2	- Endometrial focal weakness extended to myometrium - Endometrial hypersignal in T2 weighted sequences with miometrial extension ≤ ½ - Focal enhancement with contrast media - Hypodense endometrial nodular mass extended to myometrium, and heterogenous hypodense endometro-myometrial	8 9 8 2	T1b

		postcontrast media aspect (T2b over staging)		
6	2	- Endometrial focal weakness extended to the myometrium - Endometrial hypersignal in T2 weighted sequences with miometrial extension ≤ ½ - Focal enhancement with contrast media - Hypodense endometrial nodular mass extended to myometrium, and heterogenous hypodense endometro-myometrial postcontrast media aspect < ½ - T2b in staging	5 6 6 2	T1c
1	3	- Cervical invasion with focal enhancement with contrast media - T2b over staging	4	T2a
9		- Cervical invasion with cervical signal abnormalities and focal enhancement with contrast media	9	T2b
3	3	- Serosal extension with ascites - Lymph nodes invasion with normal size of nodes - Abdominal-pelvic lymph nodes hypertrofia	6 1 1	T3a
2	1	- Abdominal-pelvic structures invasion	3	T4

Table Nr. 3 Endometrial cancer – sectional imaging tests (CT< MRI) – the primary tumor staging

An accurate diagnosis of endometrial cancer belonged to pathological examination, which included two sequences, curettage biopsy and pathological examination of operative specimen, each with well-defined objectives.

The curettage biopsy preceded any therapeutic gesture in all cases; the histological examination confirmed the diagnosis and identified the primary tumor type (endometrioid carcinoma in 51 cases = 82.25% and nonendometrioid carcinoma in 11 cases = 17.75%) and the tumoral grading (G1 33 cases = 53.22%, G2 19 cases = 30.64% and G3 10 cases=19.14%) while the immunohistochemical examination was performed to establish the precise location of the tumor (endometrial or endocervical),

the differential diagnosis between the two tumor locations being particularly important, as the treatment is different for each of these topographical forms.

The exam of the hysterectomy specimen, performed in all 59 operated patients, was also a histopathology and immunohistochemistry one, the obtained data being used both for post-therapeutic staging (pTNM) and for establishing the adjuvant therapy indications. Histopathology established tumor type (48 = 81.3% endometrioid carcinomas and 11 nonendometrioid carcinomas = 18.7%), grading, myometrial, lymphatic and distant invasion. Most endometrioid carcinomas were well or moderately differentiated (G1 28 cases, G2 14 cases, G3 6 cases), while all nonendometrioid carcinomas were poorly differentiated (Table 4).

Grading	Cases	%
G1	28	47,45
G2	14	23,72
G3	17	28,83
Total	59	100

Table Nr. 4 Endometroid carcinoma – grading

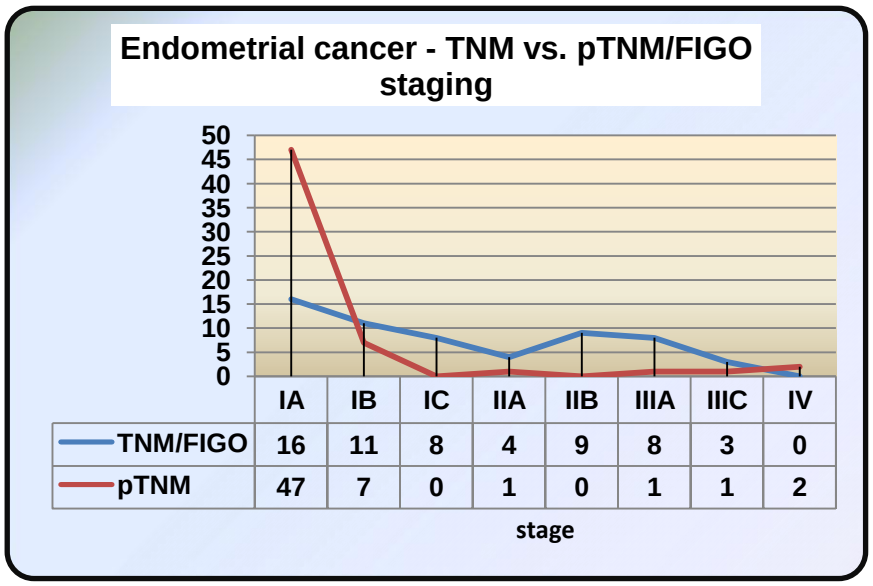
Myometrial invasion (Table 5) involved its inner half in 75.8% of the cases and the external half in 24.2% of them, the latter belonging to nonendometrioid or endometrioid G3 carcinomas. In 54 (91.52%) cases the tumor invasion was limited to the myometrium, while in the remaining 5 (8.48%) cases the extension of malignancies in neighboring or remote structures was noticed (cervix1 case, cervix and annexes 1 case and cervix, annexes, lymph nodes and liver 3 cases). The immunohistochemical study established the hormonal profile of tumor, by watching the ER and PR hormone receptor expression, and also evaluated the expression of some markers (p53 and HER2 oncoprotein and proliferation factor Ki67), necessary for determining the various types of endometrial carcinoma aggressiveness.

Miometrial invasion	cases	%
Inner half	47	79,6
External half	12	20,4
Total	59	100

Table Nr. 5 Endometrial cancer – miometrial invasion

There are two distinct moments for the tumor staging which is the main criterion in establishing the therapeutic algorithm: the pre-therapeutic staging (TNM) based on clinical examination data, imaging tests and curettage biopsy, useful to choose a surgical procedure and to determine a neoadjuvant therapy, and the postoperative surgical and anatomic staging (FIGO/pTNM) based on intraoperative exploration and histopathology and immunohistochemical exam of the hysterectomy specimen, useful to determine the indications and to choose the sequence of the adjuvant therapeutic means. The comparative analysis of the pre-therapeutic (TNM) and postsurgical staging (pTNM/FIGO) showed us the following (Chart 1):

- 59 cases, preoperatively staged, were classified in stage I 35 cases (59.32%), stage II 13 cases (22.03%) and stage III 11 cases (18.64%), the two basic morphological types of endometrial cancer (squamous endometrioid and non-endometrioid carcinoma), being distributed in all stages
- The operated cases (59=95,16%) and postoperatively staged ones (pTNM/FIGO) were classified in stage IA, all of them being endometrioid carcinomas;
- All cases assigned after surgery (pTNM / FIGO) in advanced stages (III and IV) were non-endometrioid carcinomas.



Graphic Nr. 1 Endometrial cancer: TNM vs. pTNM/FIGO

The treatment of endometrial cancer is a complex one, the following therapeutic means being available: surgery, radiotherapy, and chemotherapy and hormone therapy.

The type and sequences of the therapeutic means were established according to NCCN Guidelines, the main criterion being the pre-therapeutic (TNM) and postsurgical staging (pTNM/FIGO).

Surgery was the main therapeutic method, 59 (95%) patients being operated on (Table no. 6); according to the pre-therapeutic staging (TNM) we performed two types of surgery:

- - total hysterectomy with bilateral anexectomy and pelvic lymphadenectomy, performed in 38 (64.4%) cases: 35 stage I and 3 in stage III C
- - lymphadenocolpohysterectomy with bilateral anexectomy, Wertheim type, in 21 (35.6%) cases in stage II and IIIA

TNM stage	Pelvic radiotherapy 75-80 Gy	Vaginal brahitherapy	Chemotherapy	Surgical procedure		Nr Cazuri
				Total hysterectomy with bilateral adnexectomy + pelvic lymphadenectomy	Total lymphadenocolpo-hysterectomy + bilateral adnexectomy (Wertheim type)	
I				35		35
II	13				13	13
IIIA/IIIB	8	8	8		8	8
IIIC				3		3
IV	0	0	0	0		0
Total	21	8	8	38	21	59

Table Nr. 6 Endometrial cancer – treatment

Neoadjuvant therapy (Table no. 6) preceded surgery and consisted of pelvic radiation (75-80Gy dose) for 13 patients classified in stage II and a complex neoadjuvant treatment for 8 patients in stage IIIA (vaginal brachytherapy + external radiotherapy + chemotherapy).

Adjuvant therapy was indicated, according to NCCN Guidelines recommendations and taking into account the pTNM stage, grading and recurrence rate. The most used therapeutic means were vaginal brachytherapy, external beam radiation and chemotherapy with specific indications:

- vaginal brachytherapy – 9 patients with pTNM stages IB and C with G3, II with G3 and III with G1-3
- external radiation – 11 patients with pTNM stages IB and C with G3 and II, III and IV, regardless of G
- chemotherapy (CAP formula: cyclophosphamide + anthracycline + taxane) in 4 patients with stages III and IV
- hormone therapy (progestins, progestogens - megestrol 1tb/day for 2 years) indicated in patients with positive expression of progesterone receptor (PR +), with local or systemic advanced cancer or recurrence.

Results

48 (81.4%) operated patients had a fair evolution; we registered 11 postoperative complications (postoperative morbidity rate of 18.6%): local complications in 6 cases (4 wound abscesses and 2 prolonged dynamic ileus) and general complications in 5 cases (pulmonary infection 2 cases and deep vein thrombosis in 3 cases), all of them managed by conservative methods.

We did not register any postoperative death (postoperative mortality rate: 0)

Regarding the late survival rate, we have to mention that, at the end of our studied period, only 14 (22.58%) patients had more than 5 years from the diagnosis establishment and the beginning of the treatment, so that the 5 year-survival rate could not be evaluated for all patients. So, for 44 patients who remained in evidence at the end of our study, we noticed the following survival rate: 82.78% for the patients in stage I, 69.83% for the patients in stage II, and 54.54% for those in stage III.

pTNM stage	Grading		
	G1	G2	G3
IA	**Clinical follow up**		
IB	**Clinical follow up**		**Vaginal brahitherapy ± External radiotherapy**
IC	**Clinical follow up ± Vaginal brahitherapy**		**Vaginal brahitherapy ± External radiotherapy**
II	**Vaginal brahitherapy ± External radiotherapy**		**Vaginal brahitherapy ± External radiotherapy**
III	**Chemotherapy + external radiotherapy ± vaginal brahitherapy**		
IV	**Chemotherapy + external radiotherapy**		

Table Nr. 7 Endometrial cancer – the indications of the adjuvant therapy according to NCCN Guidelines

Discussions

Endometrial cancer, with an increasing incidence, tends to be the most common genital tract cancer, at least in advanced countries (second place in Romania after cervical cancer and 30% of all uterine cancers in our statistics).

Morpho-pathologically, endometrial carcinomas represent a diverse group of malignant epithelial tumors, which are biologically, morphologically and pathogenically

different, having two basic forms, type I (endometrioid type) and type II (non-endometrioid type), including serous carcinomas and other aggressive endometrial carcinomas, with different clinical, pathological, immunohistochemical and molecular biology characters, suggesting the existence of two pathways of endometrial carcinogenesis.

The diagnosis of endometrial cancer is a complex one, established on an algorithm that includes clinical examination, imaging tests, curettage biopsy and pathologic exam of the hysterectomy specimen and has several features to be taken into account.

Endometrial cancer does not benefit from a screening test to detect early disease and early clinical diagnosis is difficult, because of its nonspecific clinical picture and because of the fact that the disease may progress asymptomatically for a long time (several years) before becoming clinically manifested.

Abnormal uterine bleeding pre-, peri- or postmenopausal (82.25%), the first and most constant sign of endometrial cancer, present in all our cases (over 90% in the literature) without marking the onset of the disease, represents a warning sign, which imposes a complex investigation involving clinical exam, imaging tests and pathological exam, thus leading to diagnosis. Leucorrhea (11.29%), pelvic pain (35.48%), dyspareunia (29.03%) and urinary signs (12.90%), suggesting spread to cervix or invasion of neighboring structures (parameters, appendices, bladder, etc..) together with obesity (51.61%) and signs of hyperoestrogenia (acne, oily skin pigmentation and hirsutism) completed the clinical picture, while gynecological examination provided useful data for evaluating the size, structure and mobility of the uterus, invasion of the cervix, parameters and/or neighborhood viscera.

There is no biological test that can confirm the presence of endometrial cancer.

Imaging tests (abdominal and transvaginal ultrasound, CT and/or MRI) are indispensable for the diagnosis of endometrial cancer, the provided data (size and topography of the primary tumor, invasion of myometrium and/or neighborhood structures, lymph node invasion and distant metastasis) can confirm the diagnosis and can also be the main criteria for pre-therapeutic staging and therapeutic algorithm choice. Abdominal and transvaginal ultrasound, a first-line imaging, precedes curettage biopsy and is mandatory in all the patients with abnormal uterine bleeding in postmenopausal, pre- and/or perimenopausal period. The main information provided by ultrasound investigation in the study group was: evidence of heterogeneous endometrial

masses, (3-12 cm in size), imprecise bounded face of myometrium (52 cases), myometrium invasion in 19 cases, extension to cervix in 10 cases, distant metastasis in 3 cases and ascites in 4 cases.

Sectional imaging tests (CT 11 cases, MRI 35 cases), although less currently used for the initial diagnosis, are essential for the initial staging of endometrial carcinoma, since the evaluation of lymphatic extension, abdomino-pelvic and distant metastasis cannot be assessed clinically and, from this point of view, ultrasound is listed with a significantly lower sensitivity and specificity. Preoperative imaging performed for staging addresses to the cases with clinically difficult diagnosis, those with other associated injuries and with aggressive tumor histological subtypes or advanced stages. MRI was superior in revealing loco-regional extension to parameters and lymph node invasion while CT is more commonly used to evaluate extrapelvine extension (better to assess lung parenchyma) and radiotherapy planning.

The certainty of diagnosis belongs to the pathological exam (histopathology and immunohistochemistry) and includes two distinct sequences: examination of the pathological material taken by curettage biopsy and pathological exam of the hysterectomy specimen.

Curettage biopsy, performed in all cases, preceded any therapeutic gesture, and the pathological material collected was subjected to histological examination to confirm the diagnosis of endometrial cancer and to determine the type and grading of the primary tumor and to immunohistochemical examination necessary to establish the very centre of the tumor (endometrial or endocervical), the differential diagnosis between the two tumor locations being particularly important, since the treatment is different.

The pathological exam of the hysterectomy specimen, performed in 59 operated patients, was also a histopathology and immunohistochemical one, the obtained data being used both for post-therapeutic staging (pTNM) and for establishing the indications of the adjuvant therapy.

Staging, using both classification systems (TNM and FIGO), is the most important moment in the therapeutic decision; there are two distinct moments for the tumor staging: the pre-therapeutic staging (TNM) based on clinical examination data, imaging tests and curettage biopsy, useful to choose surgical procedure and determine whether neoadjuvant therapy is necessary and the postoperative surgical and anatomic staging (FIGO/pTNM) based on intraoperative exploration and histopathology and immunohistochemical exam of the hysterectomy specimen, useful to determine the

indications, type and sequence of the adjuvant therapeutic means. Comparative analysis of the case distribution according to pre-therapeutic (TNM/FIGO) and postsurgical staging (pTNM) showed, on the one hand, that all the cases assigned after surgery in advanced stages (III and IV pTNM/FIGO stage) were nonendometrioid carcinomas and, on the other hand, we could notice the limits of the imaging tests (ultrasound, CT, MRI) in assessing tumor invasion, so that the pre-therapeutic staging is usually an overstated one.

Although it is the third most common cause of death in female genital cancers, the endometrial cancer benefits from a complex treatment and has a survival rate of 50% including for IIIB FIGO stage tumors, if the diagnosis is early and treatment is initiated immediately it is established. The treatment of the endometrial cancer is a complex, sequential one with the following fundamental therapeutic means: surgery, radiotherapy, chemotherapy and hormone therapy, the choice of the treatment methods and their sequence being determined by pre- and post-surgical staging (pTNM/FIGO), according to NCCN Guidelines recommendations.

Surgery was the main therapeutic method, 59 (95%) being operated on; according to the pre-therapeutic staging (TNM) we had to choose between two surgical procedures: total hysterectomy with anexectomy and bilateral pelvic lymphadenectomy performed in 38 (64.4 %) patients (35 in stage I and 3 in stage I IIIC) and total lymphadenocolpohysterectomy with bilateral anexectomy, type Wertheim, performed in 21 (35.6%) patients in stage II and IIIA.

Neoadjuvant therapy preceded surgery and consisted in pelvic radiation (75-80Gy dose) as the only neoadjuvant method for the patients classified in stage II (13 cases), while the patients classified in stage IIIA (8 cases) needed a complex neoadjuvant treatment: vaginal brachytherapy + external radiotherapy + chemotherapy.
Adjuvant therapy was indicated, according to NCCN Guidelines recommendations, guided by the pTNM stage, grading and recurrence rate. Therapeutic means were vaginal brachytherapy, external beam radiation and chemotherapy with specific indications: vaginal brachytherapy for the patients classified in pTNM stages I B, C with G3, II with G3, and III with G1-3 (9 cases), external radiation for the patients classified in stages I B, C with G3 and II, III and IV, regardless of G (11 cases) and chemotherapy (CAP formula: cyclophosphamide+anthracycline+taxane) for the patients classified in stage III and IV (4 cases). We also used hormone therapy (progestins,

progestogens - megestrol 1tb/day for 2 years) in patients with positive expression of progesterone receptor (PR +), with local or systemic advanced or recurrence cancer.

Conclusions.

1. Endometrial cancer, with maximum incidence in postmenopausal women belonging to the 61-70 year-age group (53.22%), tends to be the most common genital tract cancer, at least in the advanced countries (second place in Romania after cervical cancer)
2. Abnormal uterine bleeding pre-, peri-or postmenopausal- the first and most constant sign of endometrial cancer - imposes a complex investigation plan, involving clinical exam, imaging tests and pathological exam, leading to diagnosis.
3. Curettage biopsy is mandatory, prior to any therapeutic gesture.
4. Staging (pre-therapeutic and postsurgical), using both classification systems (TNM and FIGO), is the most important moment in the therapeutic decision.
5. Surgery, the main therapeutic method, according to the pre-therapeutic staging (TNM), had to choose between two surgical procedures: total hysterectomy with anexectomy and bilateral pelvic lymphadenectomy, and total lymphadenocolpohysterectomy with bilateral anexectomy, type Wertheim.
6. Adjuvant and neoadjuvant therapy have specific indications, according to NCCN Guidelines recommendations, guided by the tumoral type, grading, stage and recurrence rate
7. Endometrial cancer has a good therapeutic response and a 5-year survival rate of over 50%, even for tumors of stage III B, if the diagnosis is early established and the treatment is immediately initiated.

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