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Tumors of low malignant potential a single institution experience

Ichraf Jbir[a,b], Montassar Ghalleb[a,b,*], Amira Triki[a,b], Ines Zemni[a,b], Monia Hechiche[a,b], Jamel Ben Hassouna[a,b], Khaled Rahal[a,b]

[a] Surgical Oncology Department, Institute Salah Azaiez de cancer, Tunis, Tunisia
[b] Faculté de medicine, Tunis El Manar, Tunisia

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ABSTRACT

BACKGROUND: The tumors of low malignant potential are an independent group of the ovarian epithelial tumors. They represents 10–20% of all ovarian epithelial tumors.

Our aim through this study to determine how to treat this disease in the most suitable way.

METHODS: A retrospective study involving 73 patients diagnosed with TLMP and treated at our Institute between September 1975 and June 2010.

RESULTS: The median age was 49 years. In 33% of the cases, the patients were younger than 40 years. Our study included 38 mucinous tumors, 30 serous and 5 mixed. The tumors were stage I in 69% of the cases, stage II in 11% and stage III in 20%.

All patients had surgery as a primary treatment. The surgery was radical in 77% of the cases. Five patients had an adjuvant chemotherapy. After a mean follow up of 10 years, we reported 7 cases of local relapses. The prognostic factors for a disease free survival were: the stage of the tumor and the presence of invasive implants. The overall survival at 5 and 10 years was respectively of 96.9% and 92.8%. The prognostic factors for overall survival were: the age, the stage, the existence of a residual tumor, the presence of pseudomyxoma or peritoneal implants. After having a conservative surgery two patients achieved full term pregnancies.

CONCLUSION: Randomized studies are required to back-up our findings and give a higher grade of recommendation to the actual standard of care.

1. Introduction

The tumors of low malignant potential (TLMP) also known as borderline tumors were classified since the 1970s as an independent group of ovarian epithelial tumors (OET) [1]. They represents 10–20% of all OET [2].

The TLMP can be defined as in-between tumors. They have some but not all the features to be classified as benign and they also have some features but not all to be classified as malignant. They differ from the malignant tumors by the absence of a stromal invasion [1]. Their diagnoses is considered a real challenge for the pathologist.

They also clinically differ from the carcinoma by occurring at a younger age by being diagnosed at an early stage and by having better prognoses [3]. Therefore, fertility preservation is critical. Although radical surgery remains the gold standard in the treatment of this disease, the fertility sparing surgery (FSS) can be offered to young patients with the desire of conceiving.

Our aim through this study is to determine the clinical, epidemiologic and histological features of the TLMP, and try to determine how to deal with this disease in the most suitable ways.

2. Methods

2.1. Study design

It is a retrospective study involving 73 patients diagnosed with TLMP and treated at our institute between September 1975 and June 2010.

Patients were managed in the national anti-cancer center. It's an academic institution specialized in treating cancer.

Patients with tumors responding to the following criterias were included:

* Corresponding author at: Surgical Oncology Department, Salah Azaiez Institute, Boulevard 9 Avril 1938, Tunis, 1006, Tunisia.
E-mail addresses: ichraf.jbir@gmail.com (I. Jbir), montaghalleb@gmail.com (M. Ghalleb), amiratriki@gmail.com (A. Triki), ines.zemni@yahoo.fr (I. Zemni), monia.hechiche@rns.tn (M. Hechiche), jamelbhassouna@yahoo.fr (J. Ben Hassouna), Khaled.rahal@planet.tn (K. Rahal).

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- An unusual degree of proliferation of the epithelial cells
- A cellular stratification including architectural atypia and the formation of papillary protuberances.
- The absence of obvious stromal invasion.
- Tumors with a stromal micro invasion of less than 3 mm of maximal dimension or across an area not exceeding 10 mm^2 were also included.

All the therapeutic decisions were made in a multidisciplinary meeting.

The initial work up consisted of a full body examination, a chest X-ray, an abdominal and transvaginal sonography.

Not all the patients had a thoraco-abdominal-pelvic computed tomography or a Magnetic resonance imaging (MRI), due to the unavailability and to the high cost of this type of imaging.

The mostly used tumor marker was the CA 125. It was considered positive when superior to 35 U/ml. The decision to add other tumor markers was decided in a multidisciplinary meeting depending of the clinical presentation and the availability of those markers.

Our patients had either radical surgery or FSS:

- FSS consisted on removing the disease leaving at least a part of one of the adnexa and the uterus.
- Radical surgery consisted on a total hysterectomy with a bilateral salpingoophorectomy.
- Those two types of surgery were associated to a peritoneal staging (Peritoneal washing, peritoneal biopsy, omentectomy and appendectomy)
- Para aortic and/or pelvic lymphadectomy were performed in old cases, if another gynecologic malignancy was associated, or following the result of a false positive frozen section.

Those procedures were performed by a team composed of a professor with at least 7 years of experience, a senior doctor with at least more than 2 years of experience and a trainee in surgical oncology.

The FIGO 2009 ovarian cancer staging classification was used while writing this manuscript. The pathological diagnosis was made according to the international histologic classifications provided by the World Health Organization (WHO).

The follow up was initially conducted every 3 months, including physical examinations and tumor markers. Two years post-treatment, follow-ups were conducted every 6 months for the next 3 years. Then the patients received annual follow-ups. An abdominopelvic sonography was also conducted annually.

2.2. Statistical analysis

All statistical analysis were performed with SPSS ver. 18(SPSS, Inc., Chicago, Illinois). We first ran descriptive statistics of all potential risk factors. We then performed a bivariate analysis with a Pearson's chi-square or a Fisher's exact test. Significant variables were then included in a multivariable Cox's regression model.

Significance was set at p value inferior or equal to .05, and both univariate and bivariate tests were two-tailed.

This the research work has been reported in line with the PROCESS criteria [4].

3. Results

During the period of recruitment 1200 patients were referred to our institution with ovarian malignancies. From those, 73 achieved our inclusion criteria, representing 6%.

The median age of our patients, was 49 years old (16–83 years).

Table 1
Correlation between histologic type and age.

	Age < 40 years	Age ≥ 40	Total
Mucinous	9 24%	29 76%	38
Serous	13 43%	17 57%	30
Mixed	2 40%	3 60%	5

Table 2
Patients medical history.

Patient's characteristics	valuable numbers
Menarche	13 years (9–19 years) 43% puberty before 12 years
Marital status	63 (86%) married
Parity	19 (26%) nulliparous
Age of first pregnancy	22 years
Menopause	36 (49,3%)
Hormone therapy	10 (13,6%)
Personal history of cancer	3 (4,1%) 2 breast cancer 1 rectal cancer
Familial history of cancer	2 direct relative with breast cancer

Table 3
Chief complaints.

Chief complaints	Number	Percentage
Abdominal pain	37	51%
Increased abdominal volume	24	33%
Palapted Mass	12	16%
Aménorrhea	1	1%
Metrorrhagia	5	7%
Post menopausic bleedind	8	11%
General status detorioration	8	11%
Adnexal torsion	3	4%
Sonography for other reasons	10	14%

Two frequency peaks were found between the age of 25 and 34 (14 patients) and between 45 and 54 years (17 patients). The median age for patients varied according to the histologic subtype. It was respectively 55 years and 41 years for the Mucinous TLMP and serous TLMP (Table 1).

The other relevant data from the medical history of our patients have been summed up in Table 2.

The mean time to consult was 6 months (0–36 months). Fifty nine percent consulted before 3 months. The chief complaint was abdominal pain found in 37 patients (51%) (Table 3).

We also found that women with mucinous TLMP were statistically more symptomatic than women with serous TLMP (92% vs 86,5%) (p = 0,006).

In the abdominal examination, a mass was palpated in 42 patients (57,5%). It was mobile in 89% of the cases. The ascites were clinically found in 20 patients (27%). In the combined pelvic touches a latero-uterine mass was found in 26 patients (41%). A mass in the Douglas pouch was found in 18 cases (28%).

Abdomino –pelvic Sonography was done for 67 patients (93%). We found that mucinous TLMP were more likely to present as a multiloculated cyst 56% versus 23% for serous TLMP. In the other case we found that 50% of serous TLMP were seen as a simple cyst versus 16% for the mucinous TLMP. Those differences were statistically significant (p = 0.02).

The CA-125 was measured in 55 cases (75,3%). The CA-125 levels were in adequacy with the disease stage (Table 4). It was also in adequacy with the size of the tumor. The higher the size the higher percentage of pathologic CA-125 levels. It was pathologic for 40%

Table 4
Variation of the CA-125 levels and the stage of the disease.

Stage	Normal	Pathologic	Total
I	19 (49%)	20 (51%)	39
II	2 (33%)	4 (67%)	6
III	3 (30%)	7 (70%)	10

of tumors with a size lesser than 10 cm and pathologic in 68% of the cases of a tumor bigger than 20 cm. No correlation between the histologic subtype and CA125 levels were found (Table 4).

All our patients had surgery. FSS was done in 17 cases (23%). It consisted on a unilateral salpingo-oophorectomy in four cases and in the remaining 13 cases it was associated with a peritoneal staging.

Eight patients had a wedge a biopsy in a macroscopically healthy ovarian tissue. It was positive in only one case (12,5%).

Lymphadenectomy was performed in 11 patients. All the removed lymph nodes were negative. A residual disease was left in 11 cases.

A Frozen section was done in 65 cases (89%). The sensitivity of the frozen section was 87%.

The peritoneal washing was positive in 14 patients. We found that a strong statistical relation between the presence of an exocystic vegetation and the positivity of the peritoneal washing ($p = 0.009$).

Sixty nine % of the cases were FIGO stage I and 20% were stage III.

We found that 32% of the mucinous TLMP were stage III vs 11% for the serous TLMP. However, this difference wasn't statically significant.

Five patients had an adjuvant Chemotherapy. One patient had six courses of endoxan-cisplatinulm for the presence of infiltrative implants. The second patient treated in 1980 had a stage IIIC disease and no sign of invasion in the implants; she received eight courses of 5FU-endoxan-methotrexate.

The remaining patients had a pseudo-myxoma perotoneii. The first one who achieved complete surgery had 9 courses of 5-FU. The two others had residual tumors and received 6 courses of Endoxan-Platinum.

After a mean follow up of 10 years, seven patients had a local relapse (Table 5).

The disease free survival (DFS), at three, five and 10 years was respectively of 96.7%, 92.9% and 90.4%.

Stages higher than stage I (0,011) and the presence of peritoneal implants ($p = 0,01$) were found to be negative prognostic factors for DFS. The age, the histologic subtype, the type of surgery and the presence of micro-invasion did not show a statistical significance.

However, we noted that patients with micro-invasion tended to relapse earlier than the other patients (20 VS 13 years).

The DFS after a conservative treatment was 87,4% versus 95% for a radical surgery with $p = 0,85$.

The Overall survival at five and 10 years was respectively of 96.9% and 92.8%.

We found that patients over 60 years old ($p = 0,03$), stages higher than stage I($p = 0,001$), the presence of residual disease ($p = 0,001$), pseudomyxoma perotenii ($p < 0,001$), peritoneal implants ($p = 0,003$) and tumor rupture ($p = 0,01$) were all negative prognostic factors for DFS.

For the histologic subtype, we found that the serous TLMP had a 100% survival at ten years versus 85.1% for the mucious TLMP. However it did not reach the statistical significance with a $p = 0,052$.

The FSS did not show a negative impact on OS with 100% survival at ten years.

In our study, 17 patients had FSS. Two women (11.7%), achieved a full term pregnancy.

The first patient had a stage IIb serous TLMP, she refused radical surgery and was treated with an unilateral salpingo-oophorectomy and a cystectomy for a benign lesion in the other ovary. She also had six courses of chemotherapy. She succeeded to achieve two full term natural pregnancies one and two years after the surgery.

The other patient had a stage Ia serous TLMP, she had an unilateral salpingo-oophorectomy and peritoneal staging. She achieved a full term natural pregnancy 16 months after surgery.

4. Discussion

TLMP of the ovary are rare. They represent approximately 10–20% of all malignant epithelial ovarian tumors (MEOT) [5]. They also occur at a younger age than MEOT (45vs 55 years) (2,3). When the diagnoses of TLMP is suspected the gynecologic oncologist will face some questions.

4.1. How to access the abdominal cavity?

In the last decade laparoscopy became the gold standard in the treatment of adnexal benign masses. Offering undeniable advantages, a less postoperative pain, a quicker recovery, a shorter hospital stay and less adhesions [6]. However for TLMP especially with highly suspicious tumors there is some other aspects to take into account. The possibility of tumors rupture, tumor spillage, trocar site metastasis and the risk of underestimating the extent of the disease can worsen the prognoses [6].

That's why the way entry should be chosen case by case, based on how suspicious the lesion is and on the surgeon experience with laparoscopy and with ovarian surgery [5,6].

In our study only one women had laparoscopy and this is maybe due to a bias of selection considering that we are a tertiary center receiving highly suspicious cases.

4.2. Can we be conservative?

Radical surgery with a complete staging includes a midline laparotomy, a complete inspection, and a palpation of the abdominal cavity, cytology, resection of all suspicious tissue, bilateral salpingo-oophorectomy, total hysterectomy, omentectomy, and multiple peritoneal biopsies is the gold standard treatment for TLMP.

Table 5
Relapsing patients' characteristics.

Case	Age	Histologie	Stage	First surgery	Residual tumor	CT	Time of relapse(year)	Second line treatment
Case 1	70	mucinous	Ia	Radical	R0	–	1	Surgery
Case 2	44	Serous	Ib	Radical	R0	–	22	Surgery + chemotherapy + Hormone therapy
Case 3	16	mucinous	Ib	Radical	R0	–	4	Surgery
Case 4	28	Serous	IIb	Conservative	R0	+	4	Surgery
Case 5	30	mucinous	IIc	Conservatrive	R0	–	2	Surgery
Case 6	75	Mucinous	IIIb	Radical	R0	–	7	Biopsy
Case 7	46	Serous	IIIc	Radical	R < 2 cm	–	12	Surgery + chemotherapy

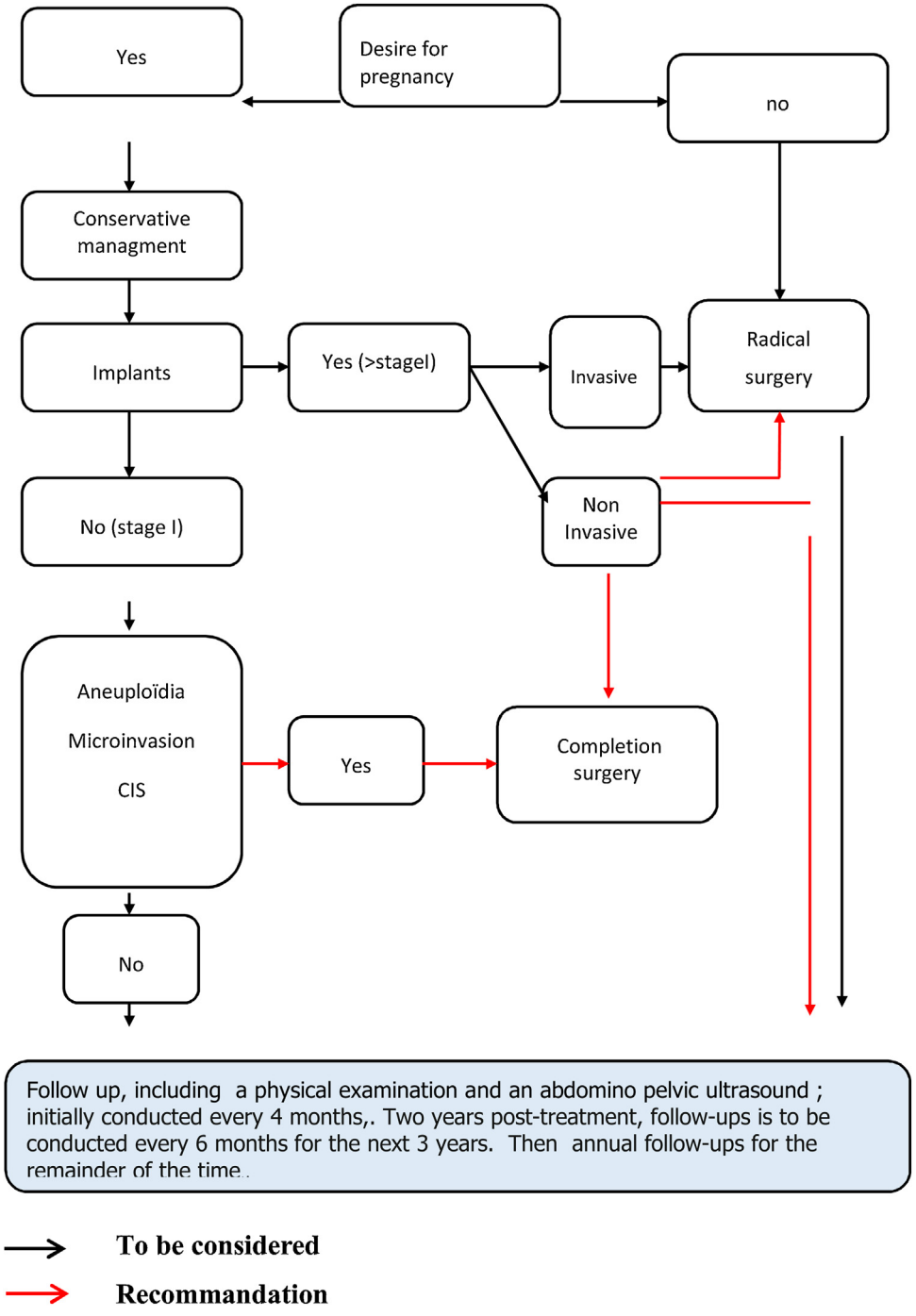

Fig. 1. Decisional Tree for borderline tumors.

One third of the patients with TLMP are under 40 years old [1], therefore fertility preservation is a critical issue. Conservative surgery is defined as complete staging in which the uterus and at least a part of one ovary are preserved. This surgery can help women achieve pregnancy but also preserving the hormonal function of the ovary avoiding the side effects of early menopause [1].

Regarding oncologic safety, the relapse rate is higher with conservative surgery (15% vs 5%) [7]. The ROBOT trial also showed a 71% increased risk for unilateral salpingo-oophorectomy(USO) when compared to bilateral salpingo-oophorectomy (BSO) [8]. However in our study no significant statistical difference in OS or DFS was found.

The risks and benefits of the conservative management should be discussed after a clear explanation of the risks and benefits.

The use of completion surgery after pregnancy, or after the age of 40 years old is still debated, but can be considered in order to reduce the risk of recurrence on the spared ovary [8]. In the presence of peritoneal implant conservative treatment can be an option after fulfilling two conditions [3]:

- ◯ the absence of tumor invasion.
  ◯ the complete removal of the disease.

The biopsy of the remaining ovary was routinely used. However, most of the studies showed that those biopsies were positive in less than 10% of the cases [9] and a negative impact on fertility was demonstrated since 1989 in Chambers review [10]. This led most of the authors to avoid touching a macroscopically healthy ovary [7].

In our study eight patients had a wedge biopsy of the remaining ovary and only one sample was positive for TLMP. None of these women succeeded to achieve pregnancy and three of them had an early menopause.

4.3. Is cystectomy feasible?

The ROBOT trial showed that the cystectomy only with preservation of the primarily affected ovary showed the highest risk of relapse when compared to USO and BSO [8]. In the literature, the rates of relapse for cystectomy varies from 12 to 58% versus 0 to 25% for USO [3].

Vasconcelos et al. [11], found in their review, that the pooled recurrence rate for patients undergoing cystectomy was 25.3%, compared to 12.5% for USO. Following those findings most authors agrees that cystectomy should be left for special cases such as women with one ovary or women with bilateral tumors wishing to preserve fertility [3,12] (Fig. 1).

4.4. Is systematic lymphadenectomy mandatory?

The nodal involvement is not rare, it accounts for 7–27% of the cases. For advanced stages it accounts for 25% [13,14].

The rate of lymph node involvement increases with the presence of invasive implants and enlarged suspicious lymph nodes [15,16].

A meta-analysis including over 4000 patients with ovarian tumors of low malignant potential, reported 98% survival at 6.5 years in women with lymph node metastasis [17]. That's why systematic lymphadenectomy is not considered as a part of the staging procedure [11]. However, removing the enlarged or clinically suspicious lymph node is recommended.

4.5. Is there a need for adjuvant treatment?

Adjuvant chemotherapy is often reserved for patients with invasive implants or bulky unresectable residual tumors [18]. At present, there is no evidence to support the use of adjuvant treatment in patients with invasive implants in the primary treatment setting [19–21]. However, and since TLMP with invasive implants were considered by FIGO as a low-grade serous carcinoma, the larger part of these patients will have chemotherapy.

4.6. The follow up

Regular follow-up including vaginal ultrasound of patients is mandatory for the early detection of BOT recurrence or malignant transformation. Du Bois et al review of the literature showed that 37.1% of the recurrences are diagnosed during the first 2 years, 31.8% of the patients experience a relapse after 5 years, and 10.4% of the patients relapse occur after more than 10 years [22]. Therefore a prolonged follow up is recommended.

4.7. Treatment of relapse

Surgery remains the cornerstone of the treatment in case of relapse and a complete removal of the disease remains an important prognostic factor [1].

Seventy percent of the tumors will relapse as a TLMP, the other 30 percent will relapse as an invasive carcinoma. According to du Bois et al. [8], most of these invasive recurrence are low-grade carcinomas, but up to 36% can relapse as high-grade invasive ovarian cancer, which significantly impacts the prognosis (5-year survival rates 98% vs 50%, $p < 0.0001$).

5. Conclusion

For TLMP surgery remain the cornerstone of the treatment. The balance between recurrence risk, organ preservation and fertility-sparing surgery deserves further studies.

Through our work we tried to report a single institution experience with TLMP and tried to establish with the help of the literature the most accurate standard of care. However, due to the rarity of this disease, more randomized studies are required to back-up our findings and give a higher grade of recommendation to the actual standard of care.

Conflicts of interest

NO financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

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Consent

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Author contribution

IJ; concept or design, data collection, data analyses or interpretation, writing the paper.

MG; concept or design, data collection, data analyses or interpretation, writing the paper.

AT, IZ; concept or design, data collection, data analyses or interpretation, writing the paper.

MA, LN; data collection, data analysis or interpretation, writing the paper.

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