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Review

Tamoxifen in breast cancer *ipse dixit* in uterine malignant mixed Müllerian tumor and sarcoma—A report of 8 cases and review of the literature

Ana Luisa Cardoso Vasconcelos[a,*], *Beatriz Nunes*[a], *Catarina Duarte*[a], *Vera Mendonça*[a], *Joana Ribeiro*[b], *Marília Jorge*[a], *Isabel Monteiro Grillo*[a,b,c]

[a] *Serviço de Radioterapia Hospital Santa Maria, CHLN, Serviço de Radioterapia do Hospital Santa Maria, Av. Prof. Egas Moniz, 1649-035 Lisboa, Portugal*

[b] *Serviço de Oncologia Hospital Santa Maria, CHLN, Serviço de Radioterapia do Hospital Santa Maria, Av. Prof. Egas Moniz, 1649-035 Lisboa, Portugal*

[c] *Instituto de Medicina Molecular, FMUL, Serviço de Radioterapia do Hospital Santa Maria, Av. Prof. Egas Moniz, 1649-035 Lisboa, Portugal*

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ABSTRACT

Aim: Report the outcome of 8 patients (pts) with breast cancer (BC) treated with Tamoxifen (TAM) that developed malignant mixed Müllerian tumor (MMMT) and rare uterine sarcoma (RUS).

Patients and methods: Retrospective study based on data collected from the department medical records between April 1999 and September 2010 among 583 pts with endometrial cancer, 36 pts with MMMT and RUS histopathology. Among them, 8 pts underwent TAM between 4 and 10 years due to a previous diagnosis of BC; all pts were post-menopausal with regular gynecological surveillance; 6 pts (75%) with abnormal uterine bleeding. The diagnosis of 6 pts (MMMT) and 2 pts (RUS) occurred at median interval of 8 years (range 4–12) after initial BC treatment. Pts underwent surgical treatment and were staged as stage I (3pts), IIIA (3pts) and IIIC (2 pts) (FIGO 1988); followed by whole pelvis irradiation (50 Gy) and intracavitary HDR brachytherapy boost (24 Gy). Two pts underwent chemotherapy (CT). Overall and disease free survival was calculated by Kaplan Meier method.

Results: With a median follow-up of 47 months (range 17–130), 3 pts remain alive recurrence-free of BC and RUS. Four pts died with distant metastasis within the first follow-up year, without BC. One pt died from non-related cancer cause. No evidence of local recurrence was found in the whole group of pts. At two years, DFS and OS were 40% and 80%, respectively.

Conclusion: As reported in the literature, TAM administration and causal effect on MMMT and RUS in BC pts is still unknown. No reports about outcome from these specific pts were found.

* *Corresponding author*. Tel.: +351 917839583; fax: +351 217805610.
E-mail address: analuvasconcelos@hotmail.com (A.L.C. Vasconcelos).

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1. Background

Breast cancer is the most common cancer in women worldwide, comprising 22% of all female cancers (WHO).[1] Approximately 75% of all cases are diagnosed in post-menopausal women. About one half of breast cancers have favorable biological characteristics (hormone receptor positive disease (ER)), being the rational to the use of TAM. It has been used since the 1980s and is proven to be an effective drug in the adjuvant and metastatic settings.[2–4]

Uterine MMMT was considered as a rare uterine cancer (1.5%),[5] and has been associated to TAM use, as have been rare uterine sarcomas such as stromal sarcoma[6,7] and leiomyosarcomas (LMS).[8–11] These uterine malignancies are highly aggressive neoplasia with a tendency to high stage at diagnosis and a poor prognosis. In addition, TAM increases the incidence of endometrial carcinoma from 1 to 2 cases per 1000 women per year[12–14] and of uterine sarcoma from 0.04 to 0.17 cases per 1000 women per year.[15]

The authors report clinical findings in eight cases of uterine MMMT and RUS following TAM adjuvant treatment for BC and a review of the literature is presented.

2. Patients and methods

The clinical cases which form the basis of the study were retrieved from the archive of the Radiation Oncology Department, at Hospital Santa Maria – CHLN. This retrospective analysis includes 8 patients who underwent treatment for breast and uterine cancer, the latter diagnosed between April 1999 and September 2010.

During this period, 583 pts with endometrial cancer were referred to the Department including 36 carcinosarcomas and uterine sarcomas, all having undergone RT adjuvant treatment.

These 8 pts underwent a total abdominal hysterectomy with bilateral oophorectomy and salpingectomy and in two cases pelvic lymph node dissection was performed. The uterine histopathology was classified as: malignant mixed Müllerian tumor (5 carcinosarcomas homologous and 1 heterologous malignant cartilage) and high grade LMS in 2 pts. According to the International Federation of Gynecology and Obstetric (FIGO 1988) classification, the pts were staged as follows: 3 pts stage I; 3 pts stage IIIA and 2 pts stage IIIC (Table 1).

Patients received adjuvant external whole pelvic radiation therapy 3D conformal Radiation therapy (3DCRT) with doses of 50 Gy (2.0 Gy per fraction) with a pelvic TC based planning (TPS XIO®), irradiation technique with 4 fields (box technique) with 10–15 MV photon beam energy, followed by brachytherapy intracavitary boost with vaginal applicators with a prescript dose of 24 Gy (6 Gy in 4 fractions/weekly), throughout Ir^{192} HDR brachytherapy PLATO® orthogonal radiographs 2D planning restraining by bladder and rectum dose (OAR) for ICRU 38 reference points. Total doses to the pelvis OAR $EQD_{2\alpha/\beta}$ 3 = 43.2 Gy (BT HDR). Total treatment time was within 7–10 weeks.

Systemic treatment was adjuvant to surgery with 6 cycles (every 28 days) of combination CT [Carboplatin (AUC 5–7, intravenously (IV) D1) followed by Paclitaxel (175 mg/m^2 IV 3 h D1)] in case 6. CT scheme in case 7 was gemcitabine 675 mg/m^2 on D1 and D8 IV over 90 min, followed by docetaxel 75 mg/m^2 on D8 IV over 1 h and subcutaneous granulocyte-colony-stimulating factor (GCSF) – 150 μm/m^2 given on D9 through D15.

3. Statistical methods

Overall survival (OS) was defined from date of uterine MMMT/sarcoma diagnosis to date of death or last follow-up. Disease free survival (DFS) was defined from date ending uterine MMMT/sarcoma treatment until LR or DM. The Kaplan Meier method was used to estimate survival curve distributions. Statistical analysis was performed using SPSS software (version 15.0).

4. Results

Patients had BC diagnosis at a median age of 61 years (range 47–74 years). All underwent radiation therapy to BC and two pts received CMF (3 weeks – alkylator cyclophosphamide 600 (d1); 5-fluorouracil 600 (d1); methotrexate 40 (d1) scheme of chemotherapy). TAM in a dose of 20 mg/day was administered between 4 and 10 years.

None of the pts had prior pelvic irradiation with castration purpose.

All pts had regular gynecological surveillance. Seventy five percent of the pts had abnormal uterine bleeding and 2 pts had endometrial polyp on routine ultrasound. Uterine malignant mixed Müllerian tumor (MMMT) and sarcoma occurred at an

Table 1 – Patients and uterine neoplasia characteristics.

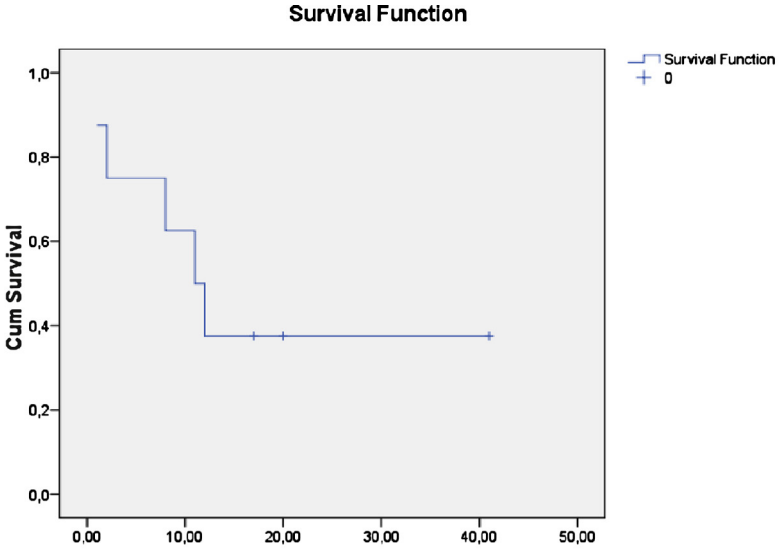
Case	Age diagnosis BC/RUR	Duration tamoxifen therapy (years)	Histologies RUS	FIGO staging
1	49/61	5	High grade leiomyosarcoma	IB
2	63/70	6	MMMT (carcinosarcoma homologous)	IIA
3	58/66	5	MMMT (carcinosarcoma) homologous	IIIC
4	75/79	10	MMMT (carcinosarcoma homologous)	IB
5	63/71	5	MMMT (heterologous – malignant cartilage)	IA
6	47/51	5	MMMT (carcinosarcomahomologous)	IIIC
7	59/71	5	High grade leiomyosarcoma	IIIA
8	70/81	6	MMMT (carcinosarcoma homologous)	IIIA

MMMT – malignant mixed Müllerian tumor.

Table 2 – Patients and treatment characteristics.

Case	Treatment	WPRT + BT HDR	CT	Recurrence/months after RT	Outcome
1	TAH/BSO	50Gy + 24Gy		Lung and brain/12	Died of tumor at 25 months
2	TAH/BSO	50Gy + 24Gy		Peritoneal serosa/11	Died of tumor at 33 months
3	TAH/BSO and LND	50Gy + 24Gy		Peritoneal serosa/8	Died of tumor at 19 months
4	TAH/BSO	50Gy + 24Gy		Lung/1	Died of tumor at 21 months
5	TAH/BSO	50Gy + 24Gy			Alive at 100 months
6	TAH/BSO and LND	50Gy + 24Gy	6× [Carboplatin (AUC 5–7, IV D1) + PTX (175 mg/m^2 IV 3 h D1)]		Alive at 126 months
7	TAH/BSO	50Gy + 24Gy	Gemcitabine (675 mg/m^2 IV D1 + D8-90 min) + DTX (75 mg/m^2 IV D8-1 h)	PA lymph nodes/2	Died at 25 months non cancer-related
8	TAH/BSO	50Gy + 24Gy			Alive at 17 months

TAH – total abdominal hysterectomy; BSO – bilateral oophorectomy and salpingectomy; LND – pelvic lymph node dissection; WPRT – whole pelvic radiation therapy; BT HDR – brachytherapy high dose rate; CT – chemotherapy; RT – radiation therapy; AUC – area under the curve; IV – intravenously; D – day; PTX – paclitaxel; DTX – docetaxel.



Survival Table

	Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
			Estimate	Std. Error		
1	1,000	event	,875	,117	1	7
2	2,000	event	,750	,153	2	6
3	8,000	event	,625	,171	3	5
4	11,000	event	,500	,177	4	4
5	12,000	event	,375	,171	5	3
6	17,000	no event	.	.	5	2
7	20,000	no event	.	.	5	1
8	41,000	no event	.	.	5	0

Means and Medians for Survival Time

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
19,625	5,989	7,886	31,364	11,000	2,828	5,456	16,544

a. Estimation is limited to the largest survival time if it is censored.

Graph 1 – Disease-free survival (Kaplan Meier curves on this group of patients with uterine sarcomas after BC).

average of 8 years (range 4–12 years) after BC initial treatment. At the time of uterine MMMT and RUS diagnosis, all pts were postmenopausal with a median age of 69 years (range 51–81 years).

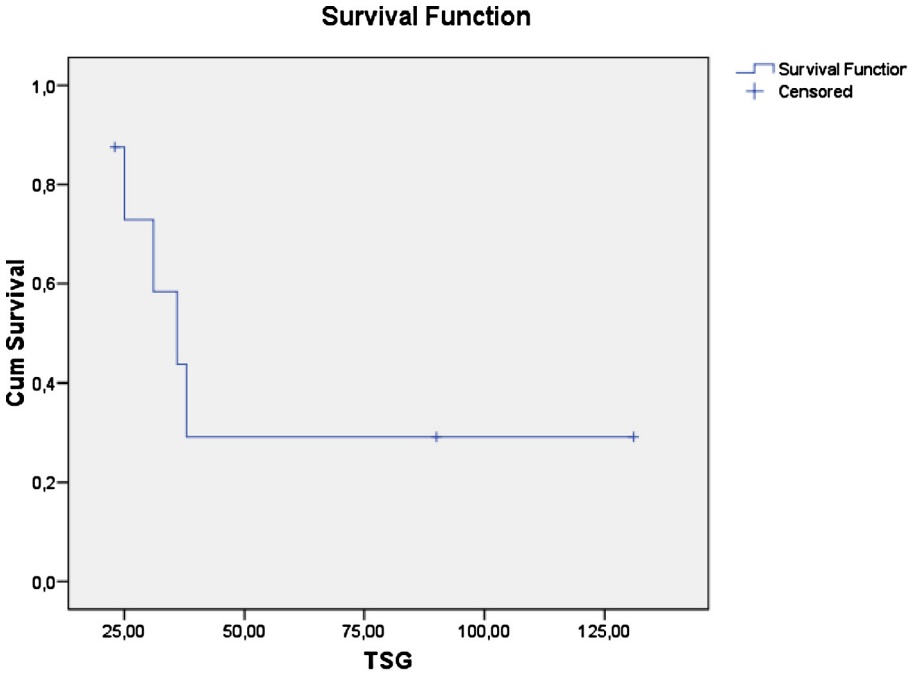
With a median follow-up of 47 months (range 17–130), four pts developed distant metastasis in the first year of follow-up. M1 disease was localized in the lung (1 month), another pt had lung and rare brain metastasis (12 months) 2 pts had peritoneal serosa metastasis (8 and 11 months) and para-aortic lymph nodes (2 months) (Table 2).

One pt died at 25 months of follow-up from non-related cancer cause. The median overall survival was 36 months (95% CI 23–49) for this group of pts; 3 pts were alive, without evidence of BC nor uterine disease after a median follow-up of 81 months (range 17–126).

Two-year local control (LC), disease-free survival (DFS) and overall survival (OS) were 100%, 40% and 80%, respectively (Graphs 1 and 2).

5. Discussion

BC is the most common cancer in women, usually with an excellent prognosis. Long-term survivors are at an increased risk of treatment related events, belonging to a special group of pts in clinical practice.



Survival Table

	Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
			Estimate	Std. Error		
1	23,000	event	,875	,117	1	7
2	23,000	no event	.	.	1	6
3	25,000	event	,729	,165	2	5
4	31,000	event	,583	,186	3	4
5	36,000	event	,438	,188	4	3
6	38,000	event	,292	,173	5	2
7	90,000	no event	.	.	5	1
8	131,000	no event	.	.	5	0

Means and Medians for Survival Time

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
60,042	17,372	25,993	94,090	36,000	6,443	23,371	48,629

a. Estimation is limited to the largest survival time if it is censored.

Graph 2 – Overall survival (Kaplan Meier curves on this group of patients with uterine sarcomas after BC).

Table 3 – Selected NSABP tamoxifen trials.

Protocol	Patient population	Treatment comparison	No. of randomized women	Median follow-up (years)
B-14	Node-negative ER-positive BC (Tx)	Tamoxifen v Placebo	2892	14.9
B-21	Node-negative ≤ 1 cm BC (Tx)	RT v Tamoxifen ± RT	1009	8.0
B-24	Ductal carcinoma-in situ (Tx)	Tamoxifen v placebo	1804	8.1
P-1	High risk (prevention)	Tamoxifen v placebo	8306[a]	6.9

[a] Pts with intact uterus at randomization.

Estrogen exposure is an important risk factor for endometrial cancer.[16,17] Association with lifetime exposure to endogenous estrogen[17] and long-term unopposed estrogen therapy is described as underlying endometrial hyperplasia and cancer in postmenopausal women.[16]

Over the past 3 decades, TAM has been widely used in the prevention[18] and treatment of hormone responsive BC pts, demonstrated in several clinical trials to be successful in either early and advanced BC disease.

According to literature reported by the National Surgical Adjuvant Breast and Bowel Project (NSABP), TAM decreases the incidence of ER-positive BC by 30–60% over a period of 5 and more years at high risk for the disease[3] (Table 3). Nevertheless, an aspect in NSABP trials has been an increased risk of developing endometrial cancer in women who underwent TAM[3,13–16,19] (Table 3). In a more recent update of all BC NSABP trials, the rate of endometrial cancer was 1.26 per 1000 patient years in women treated with TAM versus 0.58 per 1000 patient years in the placebo group.[20]

The following tables illustrate the NSABP studies (excluding pts with CT treatment) with TAM in treatment and prevention (NSABP – 14; 21; 24) of BC and the incidence of sarcoma in (NSABP P-1) (Table 4).

Selective estrogen receptor modulators (SERM), such as first-generation TAM, a nonestroidal triphenylethyl compound, produce antagonist effect in breast tumor cells with estrogen receptors (ER). The process is the competitive binding of TAM metabolites to ER and inhibition of the growth-promoting activity of endogenous estrogens in breast,[21] yet with agonist tissue-specific effects in bone, cardiovascular system[22] and endometrium including thickness, stromal fibrosis, cystic changes and polypoid formation have been described in pts that underwent TAM.[23,24]

Follow-up of pts in TAM treatment, include an annually disease-specific history, a gynecological evaluation with a Papanicolaou smear and pelvic examinations with endometrial ultrasound assessment. Transvaginal ultrasonography is not recommended for routine screening. Even though, in these high risk pts an endometrial measurement on ultrasonography of more than 8 mm or abnormal bleeding, discharge, abnormal glandular cells on Papanicolaou smear an invasive procedure should be done to evaluate endometrium.[25,26] Abnormal vaginal bleeding is the most common presenting symptom in all types of uterine neoplasia, occurring between 75 and 95% of the pts. In the current series of pts, this symptom occurred in 75%.

In endometrial tissue, TAM has estrogenic effect not only in epithelial proliferation but also in the mesenquimal component. Decensi et al.[27] compared the endometrium of TAM-treated BC pts and controls and observed an antiproliferative effect of TAM on the epithelium and a growth-promoting effect on the stroma, suggesting that the endometrial proliferation is mediated by the stromal component. TAM dose, duration and association with other known risk factors (obesity, arterial hypertension, diabetes mellitus, nulliparous or previous use of hormonal replacement therapy) may increase the risk of uterine malignancies.

The first evidence of the carcinogenicity of TAM was described in the Stockholm trial with doses of 40 mg during 2–5 years, increasing the risk of endometrial cancer RR 6, 4.[28] All pts in this current series received 20 mg of TAM between 4 and 10 years. None of the pts had prior pelvic irradiation with castration purpose since pelvic irradiation has been thought to be a risk factor to uterine sarcomas. Schaepman-Van Geuns[12] reported that previous irradiation was not a determinant etiologic factor in these tumors.

The first available report of Tamoxifen-related MMMT was described by Hardell[29] in 1988, then there were occasional reports in the mid 1980s and 1990s of uterine MMMT and sarcoma occurring in pts treated with TAM. Pharmaceutical database worldwide contains 140 uterine sarcomas and in the NSABP data, 9 of the 12 sarcomas were MMMT histopathology. Studies from 2004 indicated that the tamoxifen-related risk of *uterine corpus* cancer may be especially high for some uncommon cell types, although the magnitude of risk has not been quantified.[30]

According to NCBI online research, until 2006, approximately 65 cases of non-epithelial neoplasia had been reported, including MMMT (carcinosarcoma homologous and heterologous components) and RUS (LMS, stromal sarcomas).[31] Few

Table 4 – Incidence of uterine sarcoma in NSABP treatment trials and BC prevention trial P-1.

Protocol	Sarcoma			
	Tamoxifen		No tamoxifen	
	No.	Rate[a]	No.	Rate
B-14	4	0.10	0	0
B-21	0	0	0	0
B-24	1	0.14	0	0
P-1	4	0.17[b]	0	0[b]

Reference: D. Lawrence Wickerham, Bernard Fisher, Norman Wolmark, John Bryant, Joseph Constantino, Leslie Bernstein, Carolyn D. Runowicz, Association of Tamoxifen and uterine sarcoma, JCO 20 (June (11)) (2002) 2758–2760.

[a] Rate per 1000 women-years.

[b] Rate per 1000 women-years, Pts with intact uterus at randomization.

Table 5 – Patients characteristics in the literature.

Reference	No.	Age (range years)	Dur. TAM (range months)	Latency (range months)	Stage	Histological type
Hardell[29]	1	55	72	?	?	Carcinosarcoma
Bocklage et al.[77]	1	54	13	?	?	Adenosarcoma
Cutili et al.[78]	1	44	96	?	?	MMMT
Beer et al.[6]	1	61	60	?	?	Stromal sarcoma
Barakat et al.[79]	5	66 (mean)	54 (mean)	?	?	MMMT
Clement et al.[80]	6	59 (mean)	6–48	?	?	Adenosarcoma
Silva et al.[10]	1	?	?	?	?	MMMT
Clarke[81]	1	83	108	108	I	MMMT
Altaras et al.[82]	1	82	108	108	?	MMMT heterologous
Magriples et al.[83]	2	70–71	12	12	IVB	MMMT
Seoud et al.[84]	1	86	24	?	IIA	Carcinosarcoma
Fisher et al.[13]	1	54–62	42–66	65	IIB	Carcinosarcoma
Evans et al.[85]	6	43–83	36–144	?	?	MMMT
Ariad et al.[86]	1	65	37	37	?	?
Fornander et al.[87]	1	67	24	42	I	?
Sasco et al.[88]	1	80	72	121	?	Carcinosarcoma
Sasco et al.[89]	1	4	61–76	90–156	?	?
Mccluggage et al.[90]	19	47–91	1–15	?	IA–IVA	MMMT
Treilleux et al.[91]	6	44–77	30–120	?	?	Carcinosarcoma, adenosarcoma, MMMT
Dumortier et al.[92]	1	64	60	120	IB	MMMT
Fotiou et al.[93]	2	67–72	72–84	72–84	III	Carcinosarcoma
Kloos et al.[94]	5	50–84	60–240	84–240	IIA–IVA	Carcinosarcoma
Hubalek et al.[95]	1	40	24	24	?	MMMT
Yildirim et al.[96]	4	61–73	36–132	?	?	MMMT, leiomyosarcoma
Arenas et al.[31]	3	?	36–84	60–84	I	Carcinosarcoma, adenosarcoma
Magnani et al.[97]	1	54	60	?	?	MMMT
Lavie et al.[98]	4	?	24 to >48	?	?	Carcinosarcoma, rabdomyosarcoma, mixed mesodermal tumor
Leung et al.[99]	2	?	?	?	?	Carcinosarcoma
This series	8	51–81	60–120	48–144	IA–IIIC	MMMT, leiomysarcoma
Total	88	40–90	6–240	12–240		

cases have been published; Table 5 summarizes, by author, the characteristics of the pts which have been found in the literature.

The rarity of uterine sarcoma powerless the causal effect among TAM use and the incidence of the disease. In NSABP data, Bergman et al. and Zelmanowicz et al.[32,33] showed an increased rate of endometrial adenocarcinomas and MMMTs, as did some retrospective studies[9,10] considering dose and TAM duration.

In the past, there has been no standardized nomenclature. Potential pitfall in diagnosing sarcomas is the variability of the threshold for distinction between atypical benign tissues and clearly malignant tissues. A histopathology review was done to resolve the doubt.

The new WHO and FIGO classification for uterine sarcomas since 2009 include:

(1) Leiomyosarcoma; endometrial stromal sarcomas and undifferentiated or pure heterologous;
(2) Adenosarcomas;
(3) Carcinosarcoma (malignant mixed Müllerian tumor or malignant mixed mesenquimal tumor – MMMT), the latter staged and treated as endometrial carcinomas.[34] Although according to this new classification, carcinosarcomas of the *uterus* should no longer be identified as *uterine sarcomas*,[35] we joined in our series 6 pts with MMMT and 2 with LMS, all high risk uterine histopathologies in TAM administration.

Uterine sarcoma is a rare tumor and represents 1% of all gynaecologic malignancies and 4–9% of all malignant uterine neoplasms.[36,37] The majority of pts are post-menopausal with a poor prognosis (5 years survival of 50%), diagnosed in advanced stages.

In a large French case–control study, BC pts who developed endometrial cancer and TAM treatment had a more advanced disease and a poorer prognosis than those with endometrial cancer without prior TAM.[38]

Danish BC Cooperative Group (DBCG) during 1977–2001, analyzed BC survivors and reported a group of pts that developed second primary cancers. Cancer incidence rates of the Danish population were used for calculation of standardized incidence ratios (SIRs). The authors concluded that there was an increased risk of cancer of corpus uteri (SIR = 1.83 vs 1.04)[39] for TAM treated pts, compared to non-TAM treated pts.

Uterine sarcomas spread by lymphatic and hematogenous paths[40–44] as well as by local extension and peritoneal spread. Several studies have addressed the metastatic pattern of uterine sarcomas. Chen[42] revised nodal metastases in 20 pts with clinical stage I uterine sarcomas: fourteen pts with MMMT, 4

with LMS, and 2 with endometrial stromal sarcoma (ESS). He found nine pts (45%) with lymph node metastases (6 with para-aortic and pelvic node involvement and 3 with pelvic node involvement). Rose et al.[40] reviewed the autopsy findings of 73 pts with uterine sarcoma, including 43 pts with MMMT, 19 with LMS, 9 with ESS and 2 with endolymphatic stromal myosis. The peritoneal cavity and omentum were the most frequently involved sites (59%), followed by the lung (52%), pelvic (41%) and para-aortic (38%) lymph nodes, and liver parenchyma (34%). Of note, the presence of lung metastasis was not associated with pelvic or para-aortic nodal metastasis or intraperitoneal disease.

A non-uniform surgical management in MMMT has been reviewed by Vorgias et al.[44] who described the rationale for lymphadenectomy, which, beyond staging information, offers a measurable survival benefit. However, pelvic lymphadenectomy the histopathology non-MMMT has still no agreement for the majority of the authors.[45]

As adjuvant treatment, all pts in the current series received external whole pelvic 3DRT in conventional fractionation followed by a HDR brachytherapy intracavitary boost. BT dose and technique can also be optimized in these particular cases improving results.[46–48]

Adjuvant radiotherapy in RUS non-metastatic pts is conflict-ridden, as nowadays carcinosarcomas were excluded. A number of reports have documented the pattern of recurrences in pts with stage I or II sarcomas, and showed in those who received *radiation therapy* to the pelvis a statistically significant reduction of recurrences within the *radiation* treatment field.[49] A recent phase III randomized trial in stage I and II uterine sarcomas reported that post-operative pelvic radiotherapy did not improve survival for LMS when compared with observation, but in a 20-year center analysis study published in the literature the authors observed a decreased pelvic failure.[50–54]

Adverse prognostic factors for MMMT were recognized,[55–58] pelvic recurrence rate was 56%, whereas the distant metastasis rate was 45%,[59] demonstrating a meaningfully higher relative risk for pelvic recurrence than that seen in pts with LMS.[57,60–62] Pelvic recurrence rate in MMMT corroborates the use of adjuvant therapy for loco-regional control and also asserts that surgery alone, for disease apparently limited to the uterus, is not enough to achieve a pelvic control of the disease. Studies showed a 53% reduction in the risk of LRF at 5 years,[63] even though survival benefit has not been demonstrated in randomized trials.[34,61,64–70]

Few reports address the second neoplasia treatment outcome in these specific cases.[71]

The published GOG 150, a phase III study of the whole abdominal radiotherapy versus ifosfamide/mesna with cisplatin in pts with optimally debulked stage I–IV MMMT, did not find a statistically significant advantage in the recurrence rate or survival for adjuvant CT over RT in pts with uterine carcinosarcoma.[72]

6. Conclusion

For most women, the benefits of TAM in preventing a recurrence of BC outweigh by far the potential risk of uterine cancer. Furthermore, benefit from the TAM has evident survival. In the adjuvant setting, TAM is recommended for a maximum of 5 years.[73] Nowadays, other inhibitors are used in clinical practice, well-tolerated adjuvant therapy for postmenopausal women with predictable and apparently more preventable and manageable adverse effects than those associated with TAM, yet needing a longer follow-up.[74–76] Gynecological surveillance and long time follow-up is the main key.

This case report as well as other from the literature,[15,76] may empower the relation between TAM treatment and causal effect in uterine MMMT and sarcomas. Reports of second tumors, therapeutic management and outcomes, although the known dismal prognosis show acceptable outcomes in some pts. This ought to prospect future research in areas including surgery, RT, and CT, to increase the probability of disease control.

Conflict of interest

Authors: Radiation oncology physicians – initiated retrospective clinical study.

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