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ORIGINAL ARTICLE

The effect of multifocal and multicentric tumours on local recurrence and survival outcomes in breast cancer

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Summary

Purpose: *The purpose of this study was to compare the multifocal (MF)/multicentric (MC) breast cancers with unifocal (UF) breast cancers in terms of tumour characteristics, treatment methods, loco-regional recurrence and survival rates.*

Methods: *Patients who were treated with a diagnosis of early-stage breast cancer (stage I,II) and had regular follow-up were included in the study. MF tumours were defined as having more than one tumour focus in the same quadrant, whereas MC tumours refered to the presence of more than one tumour focus in different quadrants.*

Results: *In total, 1865 patients with invasive breast cancer were evaluated, 1493 (80.1%) of whom had UF cancer, 330 (17.7%) had MF cancer, and 42 (2.3%) had MC cancer. After comparing the groups with each other, it was seen that MF and MC breast cancers occurred more often at early ages and that lymph node invasion (LNI) was greater. No differences were seen between the 3 groups in terms of local recurrence-free survival (RFS) and overall survival (OS) rates . In multivariate analysis, it was found that MF and MC tumours had no impact on local recurrence and OS. In multivariate analysis, it was understood that HER2 positivity and triple-negative breast cancer (TNBC) had an impact on local recurrence, and age, lymphovascular invasion (LVI), T3 tumour, lymph node positivity and TNBC subtype had an impact on OS.*

Conclusion: *Although MC and MF tumours show aggressive features such as high lymph node positivity and LVI, they have similar loco-regional recurrence and survival rates to UF tumours.*

Key words: *multifocal breast cancer, multicentric breast cancer, local recurrence, survival*

Introduction

Especially in women who are young, nulliparous, do not have breast feeding and have intense breast density are needed additional imaging methods to examine breast parenchyma and to avoid false negativity. Due to increasingly use of more developed imaging methods such as tomosynthesis, magnetic resonance imaging (MRI) in these patients, we face more MF/MC breast cancer cases [1-3].

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It is seen that MF/MC breast cancer incidence ranges from 6% to 75% in different series [4-6]. One of the most important causes of this situation is that there is no standard definition. Although MF/MC breast cancer is commonly seen in clinical practice, the tumour characteristics and biology and the relation between different tumour focuses are not well understood, and treatment types remain controversial. Breast-conserving surgery (BCS) and radiotherapy have been adopted as the main treatment methods for early breast cancer. However, there are some studies stating that BCS carries risks for local recurrence in patients with MF/MC breast cancer [7-10].

In a similar manner, there are also some studies indicating that MF/MC breast cancer affects survival unfavourably. In our study, we aimed to compare MF/MC breast cancers with unifocal (UF) disease in terms of tumour characteristics, treatment methods, local recurrence and survival.

Table 1. Comparison of unifocal, multifocal and multicentric tumours

	Unifocal *n (%)*	*Multifocal* *n (%)*	*Multicentric* *n (%)*	*p*	*Unifocal* *n (%)*	*MF + MC* *n (%)*	*p*
	1493 (80.1)	*330 (17.7)*	*42 (2.3)*		*1493 (80.1)*	*372 (19.9)*	
Age, years				<0.001*			<0.001*
≤50	755 (50.6)[a]	203 (61.5)[b]	31 (73.8)[b]		755 (50.6)	234 (62.9)	
>50	738 (49.4)[a]	127 (38.5)[b]	11 (26.2)[b]		738 (49.4)	138 (37.1)	
Tumour diameter (mm)	20 (1-170)	20 (1-100)	22.5 (1-60)	0.817**	20 (1-170)	20 (1-100)	0.68***
Pathologic T stage							
T1	761 (51)	172 (52.1)	18 (42.9)		761 (51)	190 (51.1)	
T2	655 (43.9)	135 (40.9)	20 (47.6)		655 (43.9)	155 (41.7)	
T3	77 (5.2)	23 (7)	4 (9.5)		77 (5.2)	27 (7.3)	
Pathologic N stage				0.38*			0.26*
N0	875 (58,8)[a]	160 (48,6)[b]	17 (41.5)[a,b]		875 (58.8)[a]	177 (47.8)[b]	
N1	343 (23.1)[a]	69 (21)[a]	9 (22)[a]		343 (23.1)[a]	78 (21.1)[a]	
N2	141 (9.5)[a]	58 (17.6)[b]	9 (22)[b]	<0.001*	141 (9.5)[a]	67 (18.1)[b]	<0.001*
N3	128 (8.6)[a]	42 (12.8)[a]	6 (14.6)[a]		128 (8.6)[a]	48 (13)[b]	
Lymph node positivity							
(+)	612 (41.2)[a]	169 (51.4)[b]	24 (58.5)[a,b]	<0.001*	612 (41.2)	193(52.2)	<0.001*
(-)	875 (58.8)[a]	160 (48.6)[b]	17 (41.5)[a,b]		875 (58.8)	177(47.8)	
Histologic grade							
I	126 (8.8)[a]	27 (8.4)[a]	0 (0)[a]	0.036*	126 (8.8)	27 (7.4)	0.06*
II	623 (43.4)[a]	157 (48.8)	26 (61.9)[b]		623 (43.4)	183 (50.3)	
III	687 (47.8)	138 (42.9)	16 (38.1)		687 (47.8)	154 (42.3)	
Lympho-vascular invasion				0.001*			<0.001*
(+)	716 (49.4)[a]	194 (60.1)[b]	27 (64.3)		716 (49.4)	221 (60.5)	
(-)	732 (50.6)	129 (39.9)	15 (35.7)		732 (50.6)	144 (39.5)	
Molecular subtype				0.96*			0.78*
Lum A	511 (34.8)	118 (36)	16 (38.1)		511 (34.8)	134 (36.2)	
Lum B	670 (45.6)	151 (46)	20 (47.6)		670 (45.6)	171 (46.2)	
Her 2 +	106 (7.2)	24 (7.3)	2 (4.8)		106 (7.2)	26 (7)	
TNBC	182 (12.4)	35 (10.7)	4 (9.5)		182 (12.4)	39 (10.5)	
Surgery type				<0.001*			<0.001*
Mastectomy	322 (21.6)[a]	130 (39.6)[b]	34 (81.0)[c]		322 (21.6)	164 (44.3)	
BCS	1169 (78.4)[a]	198 (60.4)[b]	8 (19.0)[c]		1169 (78.4)	206 (55.7)	
Histologic subtypes				0.03*			0.013*
IDC	1210 (81.0)[a]	243 (73.6)[b]	33 (78.6)[a,b]		1210 (81)[a]	276 (74.2)[b]	
ILC	106 (7.1)[a]	31 (9.4)[b]	5 (11.9)[a]		106 (7.1)[a]	36 (9.7)[a]	
Others	177 (11.9)[a]	56 (17.0)[b]	4 (9.5)[a,b]		177 (11.9)[a]	60 (16.1)[b]	

*Chi-square, **Kruskal-Wallis, *** Mann-Whitney U.

Table 2. Univariate survival analysis of patients (overall survival)

	Total number of patients	*Total number of events*	*5-year OS %*	*10-year OS %*	*p value*
Age, years					<0.001*
≤50	970	72	94±0.01	87±0.02	
>50	868	114	91.1±0.01	79±0.02	
UF	1469	148	92.7±0.008	82.5±0.016	0.390*
MF	327	35	91.8±0.02	82.2±0.034	
MC	42	3	91.6±0.06	91.6±0.06	
UF	1469	148	92.7±0.008	82.5±0.016	0.47*
MF+MC	369	38	91.8±0.018	83.6±0.03	
Tumour diameter					<0.001*
T1[a]	942	63	97.1±0.006	89±0.017	
T2[b]	795	98	89±0.014	79.1±0.02	
T3[c]	101	25	78.6±0.05	47.5±0.09	
N stage					<0.001*
pN0[a]	1044	69	96.4±0.007	88±0.017	
pN1[b]	407	44	92.1±0.015	83.4±0.03	
pN2[b]	203	27	89.7±0.026	76.3±0.05	
pN3[c]	176	44	75.5±0.038	56.6±0.061	
Stage					<0.001*
1[a]	685	39	97.9±0.007	89.9±0.02	
2[b]	757	75	92.9±0.01	83.7±0.022	
3[c]	389	70	83.4±0.022	67.5±0.039	
Histologic type					0.96*
IDC	1462	147	92±0.008	82.9±0.016	
ILC	141	16	92.3±0.028	75.6±0.059	
Others	235	23	93.5±0.018	85.9±0.033	
Histologic grade					0.014*
1[a]	152	6	97.6±0.014	95.7±0.023	
2[a,b]	796	75	94.2±0.010	82.2±0.023	
3[b]	826	95	90.1±0.012	80.8±0.022	
Lymphovascular invasion					<0.001
Non-existent	865	42	96.7±0.008	89.4±0.021	
Existent	922	133	89.2±0.012	78.1±0.020	
Molecular subtypes					0.003*
Lum A[a]	643	53	95.8±0.009	84.4±0.024	
Lum B[a]	825	73	92.7±0.011	84.9±0.020	
Her2+[a,b]	130	14	89.3±0.033	82.3±0.050	
TNBC[b]	218	38	85±0.027	74.9±0.044	
Surgery					<0.001*
Mastectomy	472	85	87.3±0.018	76.4±0.026	
BCS	1362	101	94.6±0.007	85.1±0.017	
Intraductal component					0.01*
Non-existent	534	71	91.2±0.015	78.3±0.029	
Existent	1241	101	93±0.009	84.9±0.017	

*Log rank.

Methods

The demographic, clinical, pathologic and survival data of patients who presented to the breast disease centre of Istanbul Florence Nightingale Breast Center between 2004 and 2017 were prospectively re-evaluated. MF breast cancer has been defined as having two or more invasive tumour focuses in the same quadrant, where MC breast cancer has been defined as having two or more invasive tumour focuses in different quadrants.

Tumours with greatest diameter were considered as the primary lesion. Carcinomas *in situ*, inflammatory breast cancers, and patients receiving neoadjuvant treatment were not taken under review. Diameters of focality (unifocal, multifocal, multicentric), the primary tumour, and other tumour focuses were evaluated according to the pathology report. Synchronous bilateral breast cancer was assessed as two different cases. The patients were assessed in terms of age, tumour characteristics, lymph node status, molecular subtypes, tumour diameters, number of focuses, histologic type, grade, and hormone status. The patients were divided into three groups as UF, MF, and MC. The groups were compared with each other in terms of patient and tumour characteristics, age, tumour diameter, tumour type, lymph node positivity, LVI, histologic type and grade, hormone receptor positivity, and HER 2 positivity.

Statistics

Statistical analyses were performed using the SPSS software version 20. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to determine whether they were normally distributed. Descriptive analyses are presented using means and standard deviations for normally distributed variables. Parametric variables were analysed using one-way analysis of variance (ANOVA) test, and non-parametric variables were investigated using the Mann-Whitney U-test. Where appropriate, either a x^2 test or a Fisher's exact test (when x^2 test assumptions did not hold due to low expected cell counts) was used to assess proportions of nominal/ordinal variables in different groups. The 5-year OS rate was calculated from the date of diagnosis to the date of the last follow-up or death of any cause using Kaplan-Meier analysis. The univariate difference between the curves was assessed by using the log-rank test. The possible factors identified with univariate analyses were further subjected to multivariate analyses, with backward selection, to determine independent predictors of survival. Among correlated factors with similar effects on survival, only those with clinical significance were included. A p value <0.05 was accepted as statistically significant.

Results

In total, 1865 invasive breast cancer cases were assessed; 1493 patients were UF, 330 MF, and 42 MC. MC and MF tumours occurred more often at early ages (age <50 years, UF: 50.6%, MF: 61.5%, MC: 73.8%, p<0.001). No difference was seen between the 3 groups in terms of primary tumour diameters and pathologic T stages. Axilla positivity of MC + MF tumours was more frequent compared with UF tumours (MC+MF: 52.2%, UF: 41.2%, p<0.001). It was also seen that LVI was more in MF and MC tumours (MF+MC: 60.5%, UF: 49.4%, p<0.001). When the groups were evaluated in terms of molecular subtypes, no statistical difference was found. When the patients were evaluated regarding the type of surgery performed, we found that mastectomy was applied more in the MC+MF patient group; the difference was statistically significant (MC+MF: 44.3%, UF: 21.6%, p=0.001) (Table 1).

The average length of follow-up for the patients was 58.5 months (range, 1-380). When the groups were evaluated in terms of OS no statistical difference between MF, MC, and UF patients for 5-year and 10-year survival was found (p=0.39). OS was 282.42 months in the UF group, 198.03 in the MF group, and 183.91 months in the MC group (p=0.39). In the univariate analysis, age over 50 years, tumour stage and grade, tumour diameter, pathologic N stage, LVI, molecular subtype, surgery type, and intraductal component were risk factors that affected survival. In the multivariate analysis, age, lymphovascular invasion, LVI, tumour diameter and TNBC molecular subtype were risk factors affecting survival. We found that MF and MC tumour occurrence had no effect on survival (Table 2 and 3).

The patients were evaluated in terms of local recurrence, which was seen in 77 (5.3%) patients in the UF group, in 8 (2.4%) patients in the MF group, and in 3 (7.1%) patients in the MC group; no statistical difference was found. No difference was seen

Table 3. Multivariate survival analysis of patients (overall survival)

Variables	*HR*	*95% CI*	*p*
MF vs. UF	1.12	0.75-1.68	0.48
MC vs. UF	0.48	0.11-1.99	0.061
Mastectomy vs. BCS	0.72	0.51-1.01	0.001
LVI	1.97	1.31-2.97	
IDC			0.42
No vs. Yes	0.70	0.50-0.98	
Age, years			<0.001
>50 vs. ≤50	2.02	1.46-2.79	
T3 vs. T1	2.54	1.44-4.50	0.001
T2 vs. T1	1.41	0.98-2.03	0.06
LN positivity vs.negativity	1.6	1.1-2.3	0.011
Molecular subtype			0.001
Others vs. TNBC	1.98	1.33-2.96	

Table 4. Univariate analysis of local recurrence-free survival

	Total number of patient (*n*)	*Event number* (*n*)	*5-year loco-regional control* (%)	*10-year loco-regional control* (%)	*p*
Age, years					0.27*
≤50	967	50	95.7	89.9	
>50	867	38	96.8	93.3	
UF	1465	77	95.7	91	0.17*
MF	327	8	98.7	98.7	
MC	42	3	97	82.4	
UF	1465	77	95.7	91	0.15*
MF/MC	369	11	98.6	94.2	
Tumour diameter					0.13*
T1	939	37	96.8	93.5	
T2	794	47	95.5	89.1	
T3	101	4	96.5	94.1	
Pathologic N stage					0.75*
N0	1040	46	96.8	91.4	
N1	407	23	95.2	90.6	
N2	203	9	96	96	
N3	176	7	96	93.3	
Lymph node positivity					0.41*
Existent	786	39	95.6	92.5	
Non-existent	1040	46	96.8	91.4	
Stage					0.76*
1	682	28	96.9	93.1	
2	755	40	96	89.5	
3	389	17	95.7	94.5	
Histologic type					0.22*
Ductal	1459	76	95.9	91.2	
Lobular	141	4	100	95.7	
Others	234	8	96.2	91.6	
Grade					0.025*
1	151	3	100	96	
2	795	31	97.8	93.9	
3	824	48	94.4	88.5	
Lymphovascular invasion					0.27*
Existent	919	49	96.1	90.5	
Non-existent	864	32	96.7	93.8	
Molecular subtypes					<0.001*
Luminal A	641	15	98.9	97.4	
Luminal B	824	42	96.5	90.3	
HER 2+	130	10	90.6	82.4	
TNBC	217	19	91.3	85.5	
Surgery type					0.61*
Mastectomy	472	30	95.7	90.4	
BCS	1358	58	96.4	92.1	
Surgical margin					0.24*
≤2 mm	244	14	93.3	89.3	
Negative	1532	69	96.8	91.8	

*Log rank

Table 5. Multivariate analysis of local recurrence-free survival (UF vs. MF/MC)

Variables	*HR*	*95% CI*	*p*
MF/MC vs UF	0.56	0.28-1.13	0.11
Age, years	0.74	0.46-1.17	0.20
>50 vs ≤50 years			
Tumour diameter	1.24	0.77-1.99	0.35
T2-3 vs. T1	1.01	0.58-1.75	0.96
Grade 3 vs. 1-2	1.11	0.69-1.80	0.65
Lymph node positivity			
Molecular subtypes	1.9	1-3.5	0.42
Luminal B vs. Luminal A			
HER2 vs. Luminal A	4	1.77-9.03	0.001
TNBC vs. Luminal A	3.09	1.5-6.36	0.002

between the groups in terms of local RFS. In the univariate analysis, it was seen that tumour grade and molecular subtypes were the factors which had impact on local RFS. On the other hand, in the multivariate analysis, molecular subtypes were found as factors affecting local RFS. It was seen that HER 2 positivity and TNBC existence within molecular subtypes increased the local recurrence. We also found that MF and MC had no impact on local RFS (Table 4 and 5).

Discussion

Although there is no exact consensus in the identification of MF and MC tumours, the tumours are classically defined according to the presence of tumour focuses in the same quadrant or invasive tumour focuses in more than one quadrant [11]. Alternatively, some studies may also be based on the distance between two lesions [12-14]. In our study, the classic method was used to define MF/MC tumours. Previous studies showed that MC and MF tumours occurred at earlier ages [15,16]. In the study conducted by Kanumuri et al, 49% of patients with MC were aged less than 50 years. This rate was 35% in patients with MF and 33% in those with UF cancer (MC vs. UF p=0.005) [15]. In another study by Lynch et al, MF and MC tumours were seen more often in early ages and the premenopausal patient group as compared with UF tumours (p<0.001) [16]. In our study, we found that MF and MC cancers occurred more often at early ages as compared with UF cancers (p<0.001).

It is generally considered that MC and MF breast cancers are more aggressive and have a higher potential for metastasis. In recent studies, lymph node positivity was found at higher rates in MF and MC tumours [17-21]. In multivariate analyses, lymph node positivity was shown as a prognostic factor that affected survival. In the study conducted by Kanumuri et al, lymph node positivity was 31% in the UF group, 39% in the MF group, and 62% in the MC group. When MC tumours were compared with UF tumours, lymph node positivity in MC tumours was significantly higher than in UF tumours (p<0.001). Molecular subtypes had no impact on this situation [15]. In the study by Lynch et al, lymph node positivity was 27.3% in the UF group and 43.1% in the MF/MC group (p<0.001) [16]. In another study by Lang et al, lymph node positivity was 33.1% in the UF group and 56.4% in the MC/MF group [22]. In our study, lymph node positivity was 41.2% in the UF group, 51.4% in the MF group and 58.5% in the MC group (UF vs. MC/MF, p<0.001). Similar to previous studies [5,23,24], LVI was seen at higher rates in MF and MC tumours in our study. The existence of LVI in MF tumours was statistically significantly higher as compared with UF tumours (p=0.001).

Local recurrence

Treatment type in MF/MC tumours is controversial. In previous studies, breast-conserving surgery (BCS) was considered as contraindicated because of the poor prognosis and high local recurrence rate in MF/MC cancers. In a study by Kurtz et al, it was emphasized that local recurrence rate was higher in patients with MF/MC tumours to whom BCS applied than in patients with UF tumours [26]. In a study conducted by Oh et al containing 97 patients with MF/MC, no difference was found between 5-year local recurrence rates among patients who received anthracycline-based neoadjuvant chemotherapy+BCS, mastectomy, and mastectomy+radiotherapy after mastectomy (UF: 10%, MF/MC: 7%, p=0.78) [25]. Similarly, in a study by Cabioglu et al that comprised 1322 patients, 147 had MF/MC tumours, and patients receiving neoadjuvant treatment were excluded from the study. Thirty of the patients with MF/MC tumours were subjected to BCS, 117 patients to mastectomy, and 77 patients to radiotherapy after mastectomy. The median follow-up period was 55 months. The local recurrence rate was 5.4% in patients with MF/MC tumours, 3.7% in patients with UF tumours, without statistical difference between these two groups (p=0.36) [18]. In a study by Lynch et al that contained 2816 patients with UF tumours, 673 patients with MF tumours and 233 with MC tumours, the median follow-up period was 52 months. Local recurrence was observed in 49 (1.7%) patients in the UF group, 9 (1.3%) in patients in the MF group, and 6 (2.6%) in patients in the MC group. There

was no statistical difference between the 5-year local recurrence rates (p=0.44). In the univariate analysis, risk factors for local recurrence were age, tumour diameter, tumour grade, LVI, histologic subtype and adjuvant hormonal therapy. In multivariate analysis, age, tumour grade and LVI were risk factors. Two hundred fifty-six patients in the MF group received BCS, whereas 1757 patients received BCS in the UF group. Local recurrence was seen in 5 (1.95%) patents in the MF group and in 18 (1.02%) patients in the UF group; there was no statistical difference between the two groups [28]. In a study by Weissenbacher et al that contained 288 patients with UF disease and 288 patients with MF/MC disease, the median follow-up period was 70 months. The local recurrence rate was 17.4% in the MF/MC group, and 7.3% in the UF group. The local recurrence in the MF/MC group was statistically significantly different (p<0.001). Some 43.1% of the patients were treated by BCS in the MF/MC group, and this rate was 50.3 % in the UF group [29]. In our study, the median follow-up period was 58.5 months (range, 1-380). One thousand one hundred sixty-nine (78.4%) patients in the UF group, 198 (60.4%) patients in the MF group and 8 (19%) patients in the MC group received BCS; it was determined that statistically significantly more BCS were performed in the UF tumours (p<0.001). Seventy-seven (5.3%) patients in the UF group, 8 (2.4%) patients in the MF group and 3 (7.1%) patients in the MC group had local recurrence. When 5-year and 10-year local recurrence was evaluated, there was no difference between the 3 groups (p=0.17). The fact that the number of patients with recurrence in the groups was low could account for this result. When the factors affecting local recurrence in the univariate analysis were examined, it was found that histologic grade and molecular subtypes had an impact on local recurrence and that surgery type, focality status, and lymph node positivity had no impact. On the other hand, in the multivariate analysis, it has been seen that HER2 positivity and TNBC had an impact on local recurrence rate.

Survival

The impacts on survival of MF and MC tumours are also controversial. In a study by Lynch et al, the median follow-up period was 51 months (range, 1-162). The 5-year RFS was statistically significantly different between UF (95%) and MC (90%) while there was no difference between UF and MF. The 5-year BCS was 97% in the UF group, 95% in the MC group, and 98% in the MF group. The difference between the UF group and MC group was statistically significant (p=0.001). There was no statistically significant difference in 5-year OS. In the multivariate analysis, after equalization of independent risk factors, no impact of MF and MC on OS was seen (RFS, BCS, OS). In the univariate analysis, it was found that African-American race, large tumour diameter, high tumour grade, LVI, and lymph node metastasis negatively affected OS. Multi-focality and multi-centricity were not independent determinants of survival [16]. Again, in a study by Cabioglu et al that contained 147 patients with MC/MF tumours, no significant difference was seen in 5-year DFS and OS compared with the UF group. Five-year DFS (UF 88% vs. MF/MC 82%, p=0.14) and OS rates (UF 92% vs. MF/MC 93%, p=0.43) showed no significant difference between the two groups [18].

In a study conducted by Wolters et al containing 8935 patients with breast cancer (79% UF, 15.6% MF, 5.2% MC), when the group containing patients with MF and MC tumours as combined was compared with the UF group, OS was significantly poorer. When MC and MF tumours were compared separately, it was found that MC tumours were linked with poor OS [28]. In a study by Weissenbacher et al, it was shown in the multivariate analysis that MF and MC affected adversely RFS and BCS [27]. A study by Djordjevic-Jovanovic et al showed no statistical difference in the 5-year LRFS and OS between UF and MF/MC groups [29]. In our study, no statistically significant difference in 5-year and 10-year results was seen between the 3 groups in terms of survival (p=0.39). In the univariate analysis, age over 50 years, diameter of the index tumour, pathologic N stage, tumour stage and grade, LVI, molecular subtype, and intraductal component were found as factors affecting OS. In the multivariate analysis, age, LVI, T3 tumour, lymph node positivity and TNBC existence were found as factors that affected OS (UF 89.9%, MF 89.3%, MC 92.9%).

In conclusion, although MC and MF tumours show aggressive features such as high lymph node positivity, we determined that MC and MF tumours have local recurrence and survival characteristics similar to UF tumours using appropriate surgical and oncologic treatments.

Conflict of interests

The authors declare no conflict of interests.

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