Undifferentiated Pleomorphic Sarcoma of the Extremity and Trunk: A Retrospective Cohort Study of 166 Cases in a Large Institution

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Abstract

Background: An imperative need for better management strategies to improve the survival in patients with Undifferentiated Pleomorphic Sarcoma (UPS).

Methods: The retrospective analysis of clinicopathological data of 166 UPS patients, who have undergone surgical treatment in our hospital, was carried out from January 2005 to January 2018. Cox regression model and Kaplan-Meier method were employed to identify the relevant factors affecting the rate of local recurrence (LR), distant metastasis (DM), and overall survival (OS) via univariate and multivariate analysis. The *P*-values > 0.05 were found to be statistically considerable.

Results: At the end of follow-up, the rate of LR, DM and OS in 166 UPS patients was 22.9% (38/166), 32.5% (54/166) and 75.3% (125/166) with a median follow-up time of 55 months. The existing study reveals that the UPS in trunk and R1/R2 resection margin are the prognostic markers of poor survival rate. Women are more susceptible to LR, and R1/R2 resection margin is significantly correlated with a high rate of LR. Old Patients (> 60 years), the UPS in trunk and R1/R2 resection margin are susceptible to DM.

Conclusion: R0 resection margin was an only independent favorable prognostic factor, which was correlated with LRFS, DMFS, and OS.

Introduction

Soft tissue sarcoma (STS) is a type of malignant tumor that develops from mesenchymal tissue, which is estimated to be 1–2% of all malignant tumors, and contains more than 50 histological subtypes[1, 2]. Undifferentiated Pleomorphic Sarcoma (UPS) is one of the most common subtypes of STS, previously known as Malignant Fibrous Histiocytoma (MFH)[1, 3, 4]. In 1964, Stout and O'Brien extensively studied the features of MFH and for the first time, it was considered a new type of sarcoma[5]. In 1978, Weiss and Enzinger et al.[6] revealed that the underlined malignancy had variable morphologic characteristics and often revealed transitions from an area of extremely arranged storiform pattern to a less differentiated area with a pleomorphic appearance. In 2002, the World Health Organization (WHO) reconsidered the definition of MFH, and pointed out that it should be a diagnosis of exclusion. In this view, the term ‘malignant fibrous histiocytoma’ was exchanged by the undifferentiated pleomorphic sarcoma[7]. UPS should be labeled as such after the exclusion of particular lines of differentiation[8–10], along with the key element which is composed of several types of pleomorphic sarcoma cells with heterogeneity[7]. The mixed growth mode normally consists of tissue cells while fibroblasts are the leading histological characteristic of UPS, which mainly manifests the function of fibroblasts, however, its important source is tissue cells[7]. As the most common histological subtype in STS[11], once a clear direction of differentiation can be ruled out, the diagnosis must be considered first in the STSs.

The deep-seated, aggressive and enlarged progressively without pain, always represents the clinical manifestations of UPS, and 60–70% occurs in the extremity[3]. Related reports suggest that the recurrence rate of UPS is greater than 31%[12]. Compared with other STSs, the 5-year survival rate is

lower in UPS, around 50–70%[9, 13–15], and some studies revealed that the 5-years OS rate could reach 72%[16]. Surgical treatment is largely followed in the UPS[15, 17], which can achieve significantly local control for primary UPS. 40% of patients with these tumors develop pulmonary metastases[14], which was with 8–12 months of median survival[18].

The current mainstay of treatment for STS is wide resection, and the effectiveness of adjuvant radiotherapy and adjuvant chemotherapy is unclear[17, 19–21]. This research work mainly focuses on the analysis of clinical and pathological features of UPS to confirm the prognostic factors correlated with the overall survival, metastatic survival and local survival. We aimed to provide a more effective surgical approach by statistically evaluating the prognosis in 166 UPS patients in trunk and extremity.

Materials And Methods

Basic information

166 UPS patients (stage II and III in trunk and extremity) were included in the existing study, who underwent surgical treatment at the Cancer Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College from January 2005 to January 2018. Detailed clinical features were carefully collected and classified, and the main clinical features include epidemiological statistics of UPS (gender and age of onset), tumor-associated data (site of the tumor, local recurrence at diagnosis, tumor size, AJCC stage, and resection quality, etc.) and treatment methods (surgery, adjuvant chemotherapy, and adjuvant radiotherapy).

The patient's age was recorded at the moment when the initial diagnosis was carried out in our hospital. The tumor size was the largest diameter of the tumor, and the data comes from pathological results or imaging data. Resection quality were classified into R0 and R1/R2. R0, referred to microscopic tumor-negative surgical margins; R1, referred to microscopic tumor-positive surgical margins; and R2, referred to macroscopic tumor-positive surgical margins.

Among them, male patients and female patients were 54.2% (90/166) and 45.8% (76/166), respectively and their ages were 24 to 83 years with median and the average age of 57 and 55.5 years, respectively. The UPS in the trunk, upper extremity and lower extremity accounted for 30.1% (50/166), 15.7% (26/166), and 54.2% (90/166), respectively. Patients with no recurrence tumors and recurrent tumors accounted for 62.7% (104/166) and 37.3% (62/166), respectively. The tumor size ranged from 1 to 22 cm, with an average size of 5.52 cm. The diameter of tumors was 5 cm or less in 57.8% (96/166), while in 42.2% (70/166) the diameter of the tumor was more than 5 cm. According to the American Joint Committee on Cancer (AJCC) staging criteria, stage II and stage III accounted for 57.8% (96/166) and 42.2% (70/166), accordingly, as presented in Table 1.

Table 1
Tumor status and prognosis of 166 UPS patients

Variables	Quantity	percentage
Demographic characteristics		
Age		
≤ 60 years	101	60.8%
⩾60 years	65	39.2%
Gender		
Male	90	54.2%
Female	76	45.8%
Tumor features		
Tumor site		
Trunk	50	30.1%
Upper extremity	26	15.7%
Lower extremity	90	54.2%
Local recurrence at diagnosis		
No recurrence	104	62.7%
Recurrence	62	37.3%
Tumor size(cm)		
≤ 5cm	96	57.8%
⩾5cm	70	42.2%
Tumor grades		
AJCC grades		
II	96	57.8%
III	70	42.2%
Pathological features		
Resection quality		
R0	150	90.4%
R1/R2	16	9.6%
Adjuvant treatment		

Variables	Quantity	percentage
Radiotherapy	84	50.6%
Chemotherapy	56	33.7%
Combined	42	25.3%
Nil	62	37.3%
Prognosis		
Post-treatment local recurrence	38	22.9%
Post-treatment metastases	54	32.5%
Death	41	24.7%

All histopathological specimens of 166 patients were confirmed by two pathologists. UPS usually appears as isolated, leaf-like, or fish-like masses, and the cut surface is commonly white or gray. Under HE staining, it mostly appears as a mixed growth pattern of matted areas and polymorphic areas with a large number of polymorphic areas. The chromatin and irregular nuclei were present in multinucleated giant cells, as depicted in Fig. 1.

Treatment and follow-up data

The resection quality of all patients was conducted at our hospital, and those cases who just received chemotherapy and/or radiotherapy were excluded. Postoperative pathological indications were as follows; 90.4% (150/166) and 9.6% (16/166) patients were R0 and R1/R2 resection, respectively. 50.6% (84/166) patients underwent adjuvant radiation therapy in the period of the disease, with an average radiotherapy dose of 50Gy (15-76Gy) and a median radiation dose of 60Gy. 33.7% (56/166) patients received adjuvant chemotherapy. Ifosfamide and doxorubicin were mainly used as chemotherapeutic drugs. The regular checkups including regular chest CT and local MRI scans were carried out post operation in our hospital. Follow-up data were collected by phone calls and medical records. The follow-up time of 166 patients was 6-168 months, with a mean follow-up time of 62 months and a median follow-up of 55 months.

Statistical Analysis

The statistical analysis was carried out by SPSS 22.0 and GraphPad Prism 6. While the Kaplan-Meier method and Cox regression model were employed for univariate and multivariate analysis. *P*-value less than 0.05 was regarded as statistically considerable.

Results

Local recurrence

At the end of follow-up, 22.9% (38/166) was the local recurrence rate of 166 UPS patients with a median follow-up of 55 months. The 3-year and 5-year local recurrence-free survival (LRFS) rate were 79.2% and 74.4%, respectively (Figs. 2A). Factors influencing LRFS in univariate analyses and multivariate analysis were listed in Tables 2. Univariate analysis revealed that the significant factors correlated with higher local recurrence rate were female, recurrence patients and R1/R2 (Table 2; Figs. 2B,2C,2D). The multivariate analysis revealed that gender (P = 0.008, HR = 6.948) and resection quality (P = 0.001, HR = 10.695) were two independent risk factors for local recurrence in patients with UPS post operation (P-value < 0.05), which was presented in Table 2. The female patients had a 1.92 folds increased risk of developing LR than male' (HR = 2.285; 95%CI,1.213–4.383; P = 0.0111), as depicted in Figs. 2B. With respect to the resection quality, a considerable variation was found between the two groups for LRFS (HR = 3.758; 95%CI, 3.064–33.63; P = 0.0002), as given in Figs. 2D. R1/R2 resection margins had a high LR rate in UPS,[22] which was confirmed again by us. Radiotherapy is an important means to control tumor recurrence after surgery. However, its application value in soft tissue sarcoma has been controversial. In this article, it is not found that radiotherapy is meaningful for the control of postoperative recurrence of UPS.

Table 2
Univariate and multivariate analysis of factors influencing post-treatment local recurrence-free survival in 166 patients

Variables	Univariate analysis			Multivariate analysis	
	3-year LRFS rate	5-year LRFS rate	P-value	HR	P-value
Gender			0.011	6.948	0.008
Male	85.5	81.9			
Female	71.5	65.3			
Age			0.113		
≤ 60	82.8	79.5			
60	73.6	66.3			
Local recurrence at diagnosis			0.022	3.139	0.076
No recurrence	83.3	81.6			
Recurrence	72.2	61.2			
Tumor sites			0.696		
Trunk	83.7	76.7			
Extremity	77.5	73.4			
Tumor size(cm)			0.183		
≤ 5cm	81.7	78.8			
5cm	75.7	67.5			
AJCC grade			0.183		
II	81.7	78.8			
III	75.7	67.5			
Resection quality			0.000	10.695	0.001
R0	82.7	78.5			
R1/R2	41.3	27.6			
Adjuvant radiotherapy			0.329		
Yes	81.1	78.9			
No	77.3	70.1			

Variables	Univariate analysis		Multivariate analysis
Adjuvant chemotherapy			0.221
Yes	74.4	68.3	
No	81.8	77.5	

Distant metastasis

In 166 UPS patients, the rate of distant metastasis (DM) was 32.5% (54/166). The 3-year and 5-year distant metastasis-free survival (DMFS) rates were 74.5% and 67.6%, respectively (Figs. 2A). In the existing study, univariate analysis revealed that prognostic factors *i.e.*, older (> 60 years), local recurrence at diagnosis, trunk and R1/R2 had considerable variations in DMFS (Table 3; Fig. 3E, 3F, 3G, 3H). The significant results of the univariate analysis were incorporated into the cox multivariate analysis, and then we revealed the independent factors *i.e.*, older (> 60 years) ($P = 0.044$, HR = 4.068), trunk ($P = 0.002$, HR = 9.339), R1/R2 ($P = 0.006$, HR = 7.642), and adjuvant chemotherapy (P-value < 0.001, HR = 13.467) had a more possibility of distant metastasis (all P-value < 0.05), as presented in Table 3.

Table 3
Univariate and multivariate analysis of factors influencing post-treatment distant metastasis-free survival in 166 patients

Variables	**Univariate analysis**			**Multivariate analysis**	
	3-year DMFS rate	5-year DMFS rate	P-value	HR	P-value
Gender			0.695		
Male	70.6	65.9			
Female	78.5	69.6			
Age			0.009	4.068	0.044
≤ 60	78.1	76.3			
60	68.9	52.4			
Local recurrence at diagnosis			0.012	2.863	0.091
No recurrence	82.5	77.3			
Recurrence	61.3	56.8			
Tumor site			0.041	9.339	0.002
Trunk	61.4	58.8			
Extremity	80.0	71.5			
Tumor size(cm)			0.070	0.753	0.386
≤ 5cm	80.1	75.4			
5cm	66.7	57.0			
AJCC grade			0.070	0.753	0.386
II	80.1	75.4			
III	66.7	57.0			
Resection quality			0.001	7.642	0.006
R0	78.5	73.0			
R1/R2	37.5	22.5			
Adjuvant radiotherapy			0.863		
Yse	74.7	68.0			
No	74.2	67.4			

Variables	Univariate analysis			Multivariate analysis	
Adjuvant chemotherapy			0.001	13.467	0.001
Yes	79.8	75.8			
No	64.2	52.5			

Overall survival

The overall survival (OS) rate of 166 UPS patients was 75.3% (125/166) until the end of follow-up, while the 3- and 5-year OS rates were 81.7% and 76.4%, respectively. In our study, univariate analysis reveals that prognostic factors *i.e.*, older (> 60 years), local recurrence at diagnosis, tumor size (> 5cm), AJCC stage (III) and R1/R2 were considerably associated with the poor OS rate (*P*-value < 0.05) (Table 4; Fig. 3I,3J,3K, 3L). The effective results of the univariate analysis were incorporated into the cox multivariate analysis which confirms the two independent factors *i.e.*, trunk (*P* = 0.026, HR = 4.964) and R1/R2 (*P* = 0.001, HR = 10.182) which correlated with a poorer OS, as presented in Table 4.

Table 4
Univariate and multivariate analysis of factors influencing overall survival in 166 patients

Variables	Univariate analysis			Multivariate analysis	
	3-year OS rate	5-year OS rate	P-value	HR	P-value
Gender			0.758		
Male	84.2	77.3			
Female	81.5	75.0			
Age			0.004	3.089	0.079
≤ 60	86.1	83.8			
> 60	78.2	65.5			
Local recurrence at diagnosis			0.031	1.958	0.162
No recurrence	86.4	83.5			
Recurrence	74.1	65.0			
Tumor site			0.128	4.964	0.026
Trunk	75.3	72.4			
Extremity	84.3	80.9			
Tumor size(cm)			0.012	3.116	0.078
≤ 5cm	85.2	83.4			
> 5cm	76.9	66.7			
AJCC grade			0.012	3.116	0.078
II	85.2	83.4			
III	76.9	66.7			
Resection quality			0.001	10.182	0.001
R0	84.5	81.3			
R1/R2	56.3	35.2			
Adjuvant radiotherapy			0.843		
Yes	82.1	77.0			
No	81.2	75.9			
Adjuvant chemotherapy			0.226		
Yes	84.4	79.0			

Variables	Univariate analysis		Multivariate analysis
No	76.6	71.5	

In the analysis of prognostic factors affecting the overall survival of soft tissue sarcoma, chemotherapy has always been the focus of controversy. In this study, in 54 patients with metastases, whether chemotherapy or not was significantly related to overall prognosis.

Discussion

UPS, called malignant fibrous histiocytoma (MFH) previously, which was recognized as the most common STS in adults, accounting for 50% of diagnoses. However, the pathological diagnosis of UPS shown no evidence of true histiocytic differentiation, meaning it encompasses the morphologic manifestations of a variety of poorly differentiated tumors rather than being a single entity.[14] So the diagnosis and treatment of UPS are still highly challenging because of the confused pathological classification. MRI is commonly used as a non-invasive effective diagnostic tool for STS. Characteristics of UPS in the MRI are mostly presented as the irregular, lobular, or oval-shaped tumors with a large scale, sometimes necrosis and liquefaction can be found in the center of mass.

R1/R2 resection margins identified as predictors of poor outcomes. Herein, the R0 resection margin was an only independent favorable prognostic factor that was correlated with LRFS, DMFS, and OS. The resection margin was found to be the prognostic factor that was effectively correlated with the duration of survival. Peiper et al.[12] proposed that positive microscopic margins were correlated with an elevated local recurrence rate (RR = 4.8, *P*-value < 0.01). Özkurt et al.[23] studied 14 cases of confirmed bone UPS and it was found that the 5-year survival rate of patients with wide resection and border resection were 81.9% and 33.3% (*P*-value < 0.05), which reveals that surgical excision with wide margins and adjuvant chemotherapy provided adequate control of the disease and longer survival. Just like some article says that surgery striving for negative margins, with radiotherapy, is the treatment of choice.[10, 14, 22]

With respect to tumor size, winchester et al.[24] evaluated the prognostic factors of 319 UPS patients and revealed that tumor size (greater than 5 cm) and deep subcutaneous fat infiltration were significant factors that affect the local recurrence rate. In the existing study, compared with those with tumor sizes ≤ 5cm and > 5cm, the 5-year LR, DM and OS rates decreased by 11.3%, 18.4% and 16.7%, respectively. (Table 2) The extensive analysis of the data of more cases may contribute to better resolve the underlined problem.

The metastasis predominantly occurs in the lungs[10, 25] relative to regional lymph nodes[26]. Winchester et al.[13] suggested that the main factors that affect the distant metastasis of UPS were the tumor site, tumor size larger than 2cm, invasion beyond subcutaneous fat, and lymphovascular invasion. In the existing study, cox multivariate survival analysis found that > 60 years were at a higher risk of metastasis than the younger patients, and the chances of metastasis were lower in the R0 resection margin, as presented in Table 3. Furthermore, in multivariate analysis, the tumor site was an independent

predictor correlated with DMFS, as depicted in Fig. 3F. Our findings of increased metastatic disease for the UPS in trunk is likely due to trunk tumors being more possibility and visible to hematogenous metastasis in the early stages of disease.

In the analysis of OS, the Cox multivariate survival analysis revealed that tumor site ($P = 0.026$), tumor size ($P = 0.048$), AJCC stage ($P = 0.048$), and resection quality ($P = 0.001$) were independent factors that affect postsurgical survival in UPS patients (all P-value < 0.05), as represented in Table 4. According to our cohort, for the patients having tumors of the trunk, the tumor size ≥ 5 cm and R1/R2, a more significant and effective approach should be adopted. Winchester et al.[24] found that age, immunosuppression, tumor size larger than 2 cm, and lymphovascular invasion were independent risk factors affecting overall prognosis. Simultaneously, the existing study revealed that patients with severe subcutaneous fatty infiltration of tumors had a bad prognosis rate. In the AJCC staging system, tumor size and tumor depth were significantly associated with the prognosis.

In the AJCC staging guidelines, tumor size is an important criteria for the judgment of soft tissue staging. Univariate analysis revealed that the size of the tumor was not considerably associated with LRFS and DMFS, but was closely associated with OS ($P = 0.012$), as shown in Fig. 2K. In multivariate analysis, tumor size (≥ 5cm) was not an independent prognostic factor affecting LRFS, DMFS, and OS (all $P >$ 0.05). Furthermore, in 2009, Lehnhardt et al.[16] also shown that tumor size ≥ 5 cm was considerably associated with the OS, which was in line with Chen and Al-Agha[25, 27]. Peiper et al.[12] found that tumor size (RR = 6.0, P 0.01) was a significant factor that affects the DFS of UPS patients. Larger tumors suggest a higher ability to divide and proliferate, a wider range of invasion, a higher degree of malignancy, and more complicated surgical methods, so the first visit to the professional sarcoma center is critical.

In the existing study, Univariate K-M analysis revealed that the local recurrence at diagnosis was a significant factor that affects the local recurrence rate, distant metastasis rate, and OS rate (P-value < 0.05). But in multivariate analysis, the presentation of tumor was not an independent prognostic factor affecting local recurrence rate, distant metastasis rate, and OS rate, with P values of 0.076, 0.091, and 0.162, respectively. Lehnhardt et al.[16] shown that a considerable variation was found between the group presenting with primary tumors (5-year survival: 84%, P-value < 0.05) and recurrent tumors (5-year survival: 62%, P-value < 0.05), which is correlated with our existing research work. The prognosis for patients with UPS of the extremities depends predominantly on adequate wide resection of the primary tumor, which is same to the idea that complete surgical resection was the most important UPS treatment strategy for UPS[17]. In short, the local recurrence at diagnosis and then R0 resection in the first therapy may play a crucial role in patient prognosis.

The value of adjuvant radiotherapy and chemotherapy in the diagnosis and treatment of soft tissue sarcoma has been mixed. Radiotherapy is mostly considered to be an effective mean to control local tumor recurrence, but in this study, it was not found that radiotherapy has any significance in the control of UPS. Trials from Gronchi suggested an overall survival benefit with five cycles of adjuvant full-dose

epirubicin plus ifosfamide in localised high-risk soft-tissue sarcoma of the extremities or trunk wall[28, 29]. Adjuvant chemotherapy was associated with improved LRFS only in patients >/= 30 years[30]. Pazopanib and immune checkpoint inhibitors are a new attempt in UPS treatment[31–33]. Undifferentiated pleomorphic sarcoma is an immunologically active subtype of soft tissue sarcoma, which is particularly amenable to immune checkpoint inhibitors[33]. Immunohistochemical biomarkers significantly contribute to predicting the rate of recurrence, metastasis, and OS rate. A significant predictive index for evaluating the effect of VEGFR receptor inhibitors in the treatment of advanced soft tissue sarcoma, TP53 plays a significant role in the diagnosis and treatment of UPS[34].

As a retrospective study, although this study has given us a crucial hint, there are some shortcomings in the existing study. Firstly, the statistics on chemotherapy and radiotherapy are not sufficient due to the low incidence rate of the underlined disease, limited samples, and a large time span and the significant evaluation of the adjuvant therapy is also very difficult. Nevertheless, the accumulation and analysis of more comprehensive medical data for UPS can objectively reflect the characteristics and outcome of the disease that needs to be improved.

Conclusion

The existing study determines that the UPS in trunk and R1/R2 resection margin are prognostic markers of poor over survival. R1/R2 resection margin significantly correlated with high local recurrence rate and women are more susceptible to LR. The UPS in trunk and R1/R2 resection margin are significantly correlated with distant metastasis and old patients (> 60 years) are more susceptible to distant metastasis. Therefore, an extensive study on the molecular mechanism is needed to explore the targeted therapy and feasibility of immune checkpoint inhibitors.[17, 35–37]

Abbreviations

Soft tissue sarcoma (STS)

Undifferentiated Pleomorphic Sarcoma (UPS)

Malignant Fibrous Histiocytoma (MFH)

World Health Organization (WHO)

American Joint Committee on Cancer (AJCC)

Declarations

Ethics approval and consent to participate:

The study was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of National Cancer Center/ National Clinical Research Center for Cancer/ Cancer Hospital. Written informed consent was obtained from individual or guardian participants.

Consent for publication:

Not applicable.

Availability of data and material:

All data generated or analysed during this study are included in this published article.

Competing interests:

The authors declare that they have no competing interests.

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All authors were involved in the preparation of this manuscript. Conception and designSGZ and SJY Analysis and interpretation: SGZ and SJYData collection: SGZ, CYJ and HMLWriting the article: SGZ Critical revision of the article: ZGZ, LBX, SFX, XXZ,TL and SGY. All authors read and approved the final manuscript.

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Figures

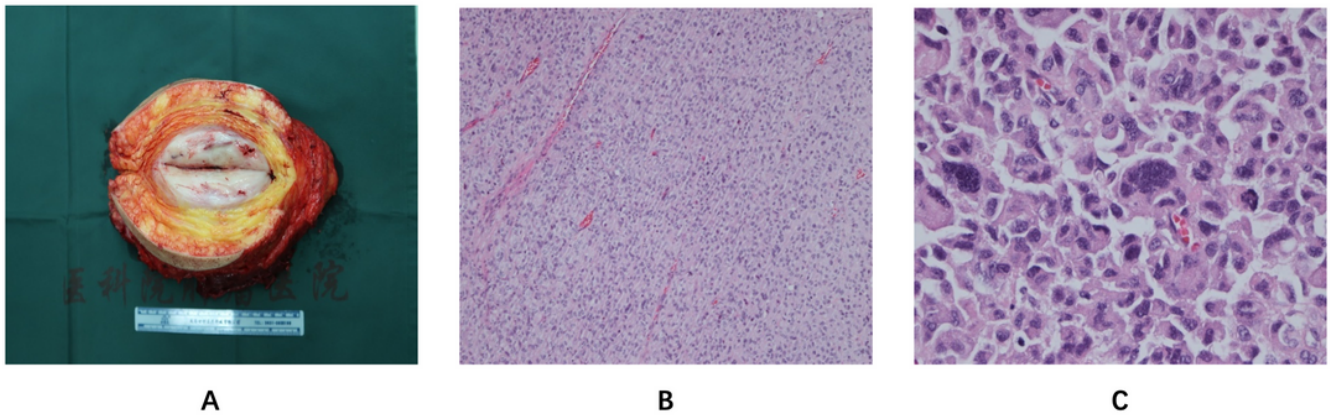

Figure 1

Macroscopic and HE staining pictures of tumor samples from UPS patients. A Isolated, leaf-like or fish-like masses, and the cut surface is mostly gray or white. B and C HE staining, it appears as a mixed growth pattern of matted areas and polymorphic areas with a large number of polymorphic areas appearance. Multinucleated giant cells with chromatin and irregular nucle.

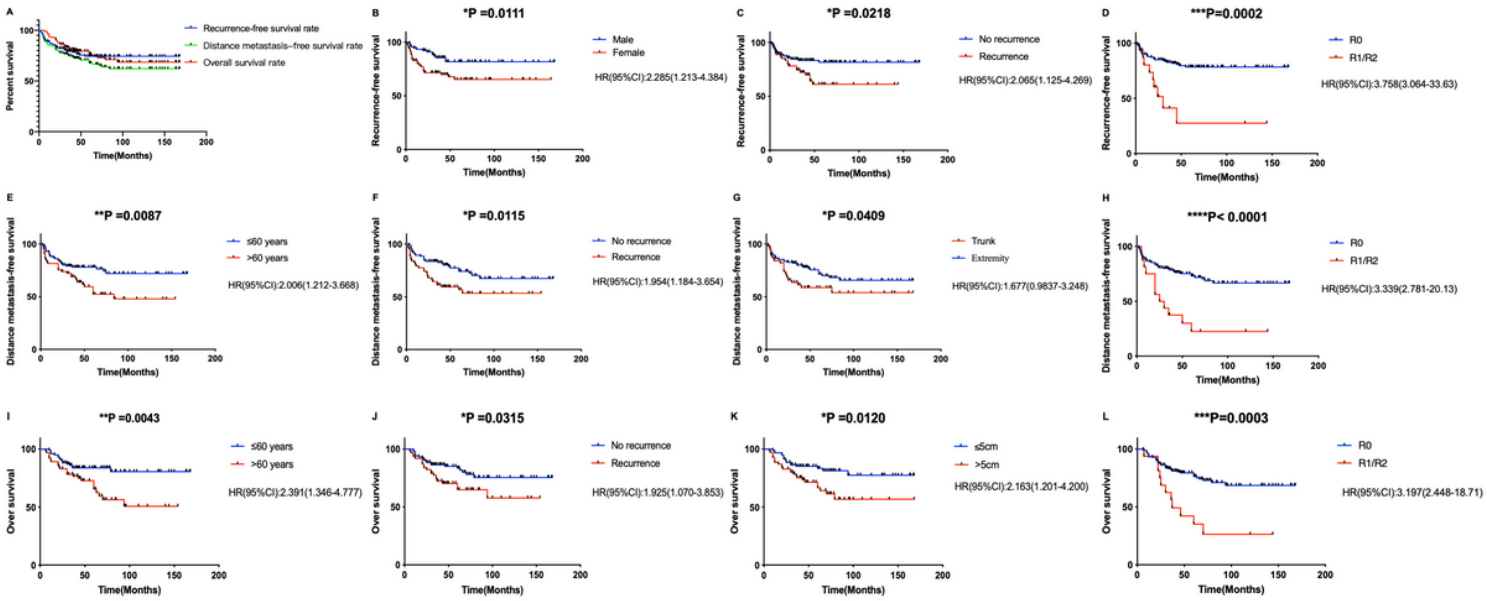

Figure 2

Kaplan-Meier curve for local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS) and overall survival (OS) based on different prognostic variables.（A）Local recurrence-free survival rates， distant metastasis-free survival rates and overall survival rates at 3 and 5 years for 166 patients were 79.2% and 74.4%, 74.5% and 67.6% and 81.7% and 76.4%，respectively.（B,C,D） Kaplan-Meier curve for local recurrence-free survival (LRFS) based on the gender, local recurrence at diagnosis and surgical margin. Patients with female, recurrence patients and R1/R2 have a worse LRFS than patients with male, no recurrence patience and R0 in all tumor groups. (E,F,G,H) Kaplan-Meier curve for distant metastasis-free survival (DMFS) based on the age, local recurrence at diagnosis, tumor location and surgical margin. Patients with age (>60 years), recurrence patients , trunk and R1/R2 have a worse DMFS than patients with age (≤60 years)，no recurrence patients, extremity and R0 in all tumor groups. (I,J,K,L) Kaplan-Meier curve for overall survival (OS) based on the age, local recurrence at diagnosis, tumor size and surgical. Patients with age (>60 years), recurrence patients, tumor size (>5cm) and R1/R2 after metastasis have a worse OS than patients with age (≤60 years), no recurrence patience, tumor size (≤5cm) and R0 in all tumor groups.