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ORIGINAL ARTICLE

Risk factors for recurrence and survival in patients with primary retroperitoneal tumors

Bing Li[1], Cheng-Hua Luo[1], Wei Zheng[2]

[1]*Department of Surgical Oncology, Ward 3ST (Colorectal Surgery), Affiliated Beijing Shijitan Hospital of Capital Medical University, Beijing;* [2]*Department of General Surgery, General Hospital of PLA, Beijing, China*

Summary

Purpose: *Postoperative recurrence remains the major cause of death in patients with primary retroperitoneal tumors (PRT). This study aimed at investigating the potential biological and surgical factors associated with postoperative recurrence and survival in PRT patients.*

Methods: *Retrospective data were collected from 231 PRT patients from January 1980 and December 2005 from the General Hospital of PLA and Beijing Shijitan Hospital. Recurrence-free survival (RFS) was determined with the Kaplan-Meier method and Cox model. Clinicopathologocal and surgical variables were analyzed to determine their impact on the outcome of PRT.*

Results: *The median follow-up period was 35 months (range 1-221). The most common histological subtype was liposarcoma (N=93, 40.3%), followed by malignant fibrous histiocytoma (MFH; N=46, 19.9%). Eighty-eight patients had local recurrence (71%) and 36 (29%) developed distant metastasis. On multivariate analysis, the surgical margin status and histological type were associated with postoperative recurrence. Patients with liposarcoma and MFH had significantly increased postoperative recurrence rate (p=0.008 and p=0.002, respectively). The overall survival in PRT patients was comparable between the incomplete resection group and the complete resection group (p=0.060), but significantly associated with the surgical resection (p=0.045).*

Conclusions: *Our results demonstrate that high tumor grade, histological subtype, incomplete resection and positive residual margins are strongly associated with PRT recurrence. Resection should be considered in patients with PRT for improving overall survival while prolonging RFS after resection.*

Key words: *postoperative recurrence, primary retroperitoneal tumors, recurrence-free survival, risk factors*

Introduction

PRT are uncommon malignancies, comprising approximately 15% of all soft tissue tumors [1,2] and accounting for 0.07-0.20% of all tumors and <0.5% of malignant tumors [3]. Although PRT can be found in patients at any age, the incidence of PRT peaks in those aged 50~60 years and the incidence in males is slightly higher than in females [3].

Previous studies have confirmed that complete surgical resection, histological grade, and metastasis were the key prognostic factors for recurrence and overall survival [4-6]. Currently, the American Joint Committee on Cancer (AJCC) staging system proposes that these factors have led to unique therapeutic considerations for the management of PRT [7]. Due to these characteristics (complete surgical resection and histological grade), the tendency for locally advanced disease at presentation, difficulty to assure clear surgical margins, and tendency for postoperative local recurrences contribute to the complexity of their clinical management [8].

Furthermore, positive margins and early recurrence may make complete resection with negative margins difficult to achieve. Several studies have proposed that resectable PRT account for 25-95% of the cases, but microscopic and macroscopic residual disease is often present [9,10]. It is noteworthy that local recurrence is a common problem after complete resection, significantly affecting overall survival.

In the present study, PRT patients from two

Correspondence to: Dr. Cheng-Hua Luo. Department of Surgical Oncology, Ward 3ST (Colorectal Surgery), Affiliated Beijing Shijitan Hospital of Capital Medical University No 10, Tieyi Road, Yangfangdian Street, Haidian District, Beijing, China.
Tel/Fax: +86 10 63936525, E-mail: luoch301@gmail.com
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institutes were retrospectively reviewed. The initial presentation and primary treatment and subsequent recurrence of PRT were analyzed to gain insight into the nature of PRT recurrence and survival in these patients. This study aimed at exploring the potential impact of prognostic factors associated with recurrence and overall survival in PRT patients undergoing surgical resection.

Methods

Patients

Patients with pathologically proven RPT were recruited from the Department of General Surgery of the General Hospital of the People's Liberation Army (PLA), and the Department of Colorectal & Anal Surgery of the Beijing Shijitan Hospital of Capital Medical University from 1980 to 2005. Initial histopathologic findings, operative records and follow-up data were retrospectively reviewed. A total of 469 PRT patients were identified, of which 231 were subjected to primary surgical treatment and resection of recurrence. Patients who didn't receive any treatment from primary surgery to subsequent recurrence in the 2 hospitals as well as those who received neoadjuvant chemoradiotherapy were excluded from study.

Prognostic variables

Potential prognostic variables included age, sex, size of PRT, histological subtype, and grade determined according to the criteria of World Health Organization of Tumors in 2002. Tumor size was measured in the resected specimen, or if not completely resectable, by radiological examination. Initial management variables included multidisciplinary preoperative discussion, biopsy, and experience with this type of surgery according to the number of patients operated on for RPT.

Surgery

Treatment variables analyzed included the type of surgery and microscopic margins. When surgery was grossly complete, it was classified as follows: 1) complete compartmental resection was defined as a systematic resection of uninvolved contiguous organs performed to obtain a rim of normal tissue surrounding the tumor (like muscles in limb sarcomas), thus ensuring wide margins. 2) Simple complete resection was defined as shelling out of the tumor alone. 3) Contiguously involved organ resection was defined as resection of macroscopically involved adjacent organs. 4) Incomplete tumor resection was defined as resecting the most part of tumor. Groups 2 and 3 represent standard procedures.

Patients and disease characteristics

The 231 patients with complete medical records and follow-up data were further analyzed. Overall survival was calculated from the date of surgery to the date of last follow-up or death.

Table 1. Characteristics of 231 patients with primary retroperitoneal tumors

Characteristics	*N*	*%*
Patients	231	100.0
Sex		
Male	117	50.6
Female	114	49.4
Age, years		
Median (range)	45 (2-76)	
<50	141	61.0
≥50	90	39.0
Tumor size (cm)		
Median (range)	16 (3-65)	
<10	106	49.3
≥10	109	50.7
Histological subtype		
Liposarcoma	93	40.3
Neurinoma	41	17.7
MFH	46	19.9
Others	53	22.1
Tumor grade, FNCLCC		
Low	90	39.0
Intermediate	82	35.5
High	59	25.5
Type of surgery		
Incomplete tumor resection	53	22.9
Simple complete resection	36	15.6
Compartmental complete resection	70	30.3
Contiguously involved organ resection	72	31.2
Histologic margins, UICC		
Microscopic negative margins, R0	109	47.2
Microscopic positive margins, R1	69	29.9
Gross residual disease, R2	53	22.9

MFH: malignant fibrous histiocytoma, FNCLCC: French National Federation of Cancer Centres, UICC: Union Internationale Contre le Cancer

Statistics

The cutoff date of the last follow-up was December 31, 2005, for the censored data analysis. The median follow-up period was calculated using the Schemper's method. Survival analysis was performed using Kaplan-Meier method and Cox model. Cox univariate and multivariate survival analyses were conducted to determine the factors related to survival. A p value<0.05 was considered statistically significant. Relative risk was expressed with 95% confidence inter-

Table 2. Non-recurrence and recurrence after surgical resection

Characteristics	*N*	*%*
Recurrence		
Non-recurrence	107	46.3
Recurrence	124	53.7
Once	73	31.6
Twice	29	12.6
Thrice or more	22	9.5
Recurrence pattern		
Local	88	71.0
Distant	36	29.0
Overall survival	173	74.9
Deaths	58	25.1

val (CI) for factors achieving statistical significance in multivariate analysis. Data were expressed as mean ± standard error and median with range. SPSS version 13.0 for Windows was used for statistical analyses.

Results

Patients and biological characteristics of PRT

During the study period, 231 PRT patients meeting the inclusion criteria were recruited. The clinical and pathologic characteristics of these patients are shown in Table 1. The median age was 45 years, and 50.6% of the patients were male. More than half (N=109, 50.7%) of the tumors measured ≥10 cm in diameter. The most common histological subtype was liposarcoma (40.3%), followed by neurinoma (17.7%), MFH (19.9%) and unclassified tumors (22.1%). Low histological grade was found in 39% of the patients; intermediate in 35.5%, and high in 25.5%. Complete resection was achieved in 77.1% of the patients, including simple complete resection (15.6%), compartmental complete resection (30.3%) and contiguously involved organ resection (31.2%). Fifty-eight patients (25.1%) died and 173 were still alive at the time of the last follow-up.

Local recurrence and distant metastasis

The median RFS was 41 months (range:1-221) and the median progression-free survival was 32 months (range:3-169). About half of the patients (N=124, 53.7%) developed recurrence (Table 2), in which local recurrence was found in 88 patients (71.0%) and distant metastasis in 36 (29%). Meanwhile, as shown in Table 2, recurrence was found once in 73 patients (31.6%), twice in 29 (12.6%) and more than twice in 22 (9.5%).

On univariate analysis, histological subtype, high tumor grade, incomplete resection and histological margin (positive margin) were associated with increased risk for PRT recurrence, while sex (p=0.644, 95% CI: 0.763-1.550), age (p=0.920, 95% CI: 0.684-1.408) and tumor size (p=0.275, 95% CI: 0.855-1.736) were not. On Cox multivariate analysis, histological subtype and surgical margin (positive margin) were associated with increased risk for PRT recurrence (Table 3).

Survival analysis

Follow-up data were complete for all patients, yielding a mean follow-up period of 44±2.4 months. The median follow-up period was 35 months (range 1-221), and median overall survival was 74.9%, while 25.1% of the patients died of PRT recurrence during the study period.

Patients with PRT who had undergone the best extent of surgery, which included systematic resection of uninvolved contiguous organs to obtain a rim of normal tissues surrounding the tumor, had significantly better overall survival (Mantel-Cox test, p=0.045; Figure 1). However, there was no significant difference (p=0.060; Figure 2) in overall survival between the grossly incomplete resection group and the complete resection group. As depicted in Figures 3-5 statistically significant difference was found between RFS and histological type (p=0.005), histological grade (p=0.037) and subtype of surgical resection (p=0.046).

Sex (p=0.804), age (p=0.482), tumor size (p=0.165), histological grade (p=0.114), histological subtype (p=0.294) and surgical margin (p=0.290) showed no impact on overall survival.

Discussion

Local recurrence is the primary pattern of recurrence and a major cause of ultimate mortality in PRT patients [11,12]. It is generally thought that local recurrence reflects aggressive disease in patients who are at high risk for developing metastatic disease anyway [13]. Consequently, locoregional control has remained a challenge, particularly with the propensity of these tumors to involve adjacent abdominopelvic organs. Our study has demonstrated that histological subtype and complete resection were the risk factors for PRT recurrence which were similar to those in previous reports [11,14].

It has been demonstrated that histological type is an important and independent predictor

Table 3. Cox proportional hazards analysis of clinicopathologic variables and recurrence-free survival in 231 PRT patients

Characteristics		*Univariate*			*Multivariate*		
		Exp (B)	*95%CI*	*p-value*	*Exp(B)*	*95%CI*	*p-value*
Total patients	231						
Sex		1.087	0.763-1.550	0.644			
Age, years		0.982	0.684-1.408	0.920			
Tumor size		1.218	0.855-1.736	0.275			
Histological subtype		0.872	0.746-1.019	0.084			
Liposarcoma	93			0.008			0.008
Neurinoma	41	0.367	0.194-0.696	0.002	0.367	0.194-0.696	0.002
MFH	46	0.894	0.572-1.398	0.624	0.894	0.572-1.398	0.624
Others	53	0.595	0.360-0.985	0.044	0.595	0.360--.985	0.044
Tumor grade, FNCLCC		1.336	1.068-1.672	0.011			
Low	90			0.041			
Intermediate	82	1.408	0.922-2.148	0.113			
High	59	1.783	1.133-2.804	0.012			
Type of surgery		1.022	0.871-1.198	0.793			
Incomplete tumor resection	53			0.060			
Simple complete resection	36	0.398	0.202-0.786	0.008			
Compartmental complete resection	70	0.875	0.555-1.380	0.566			
Involved organ tumor resection	72	0.910	0.570-1.452	0.691			
Histologic margins, UICC		1.346	1.092-1.660	0.005			
Microscopic negative margins, R0	109			0.008			0.013
Microscopic positive margins, R1	69	1.789	1.176-2.722	0.007	1.769	1.162-2.694	0.008
Gross residual disease, R2	53	1.767	1.138-2.742	0.011	1.690	1.089-2.625	0.019

of both all-cause and disease-specific mortality in PRT patients [15]. Histological type remained a statistically significant predictor of survival even after excluding patients with distant disease, not undergoing resection and controlling for histological grade, reinforcing the conclusion that the effect of histological type on survival was not due to perplexity from these important covariables. These findings support that histological type independently impacts the prognosis of PRT [16,17]. In contrast, further subgroup analysis revealed that the effect of histological type on the PRT recurrence appeared to be most robust for tissue differentiation. As depicted in Kaplan-Meier curve in Figures 2A and 2B, statistically significant difference was found in the recurrence based on histological type while histological grade of tumors was analyzed separately. Although the variable survival differences among histological types when stratified by histological grade may derive from the inherent limitations of subgroup analysis and multiple hypothesis testing, they may also reflect substantial biological or treatment differences based on histological type. Therefore, the reliability of the pathologic analysis and interpretation is a potential limitation of our study, but these findings may reinforce the premise that individual histological types display unique biological behaviors despite otherwise similar clinicopathologic characteristics. Precise determination of histological type and awareness of individual histology biological behavior is important in the multimodality care of PRT patients.

Some authors have shown that complete surgical resection of PRT was the most important factor related to the increased overall survival and significantly decreasing the local recurrence rate and tumor-related mortality [18,19]. It is note-

worthy that histological margins were strongly linked to the type of surgery, with complete compartmental resection yielding a significantly better result. In this study, our results revealed that the histological margin was a significant prognostic factor in univariate and multivariate analyses and associated with the RFS of PRT patients. As previously reported, our findings demonstrated that the recurrence and survival in PRT patients were associated with the type of operation in the Kaplan-Meier analysis. However, of note, PRT is often large and locally advanced at presentation, and usually invades vital viscera and major vascular structures. Complete surgical resection is achievable in only 67% of patients who present with primary disease [19]. Generally, to our knowledge, complete surgical resection is likely to attain the best chance for RFS and incomplete gross resection to increase the risk for recurrence and mortality even if optimal supportive treatment is offered.

Naturally, this study has several limitations. First, several studies had mentioned the association between adjuvant therapy with overall survival, while others hadn't analyzed it, so the role of chemotherapy or radiation therapy is controversial and still needs to be defined [20]. In the present study, recruited were patients without

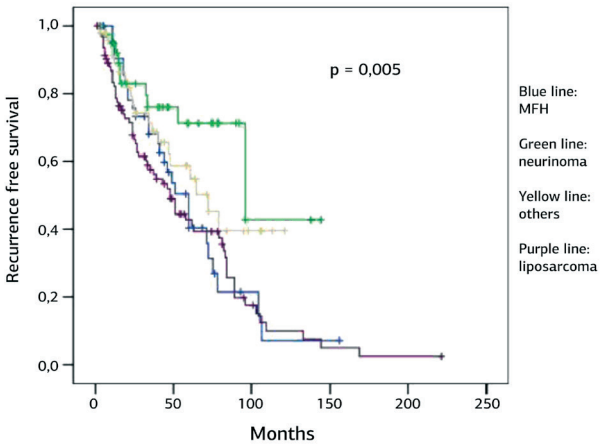

Figure 3. Recurrence free survival showing significant differences among histological types.

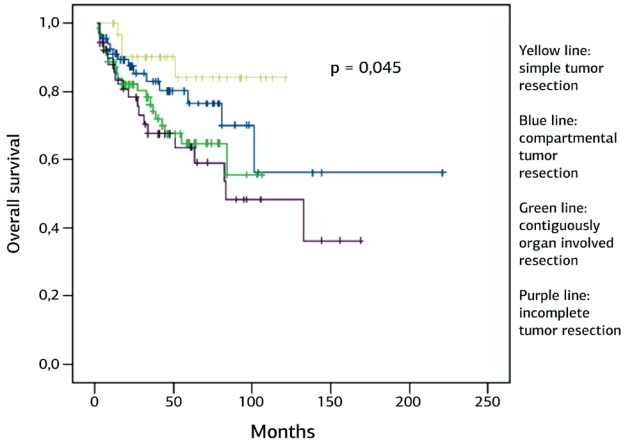

Figure 1. Overall survival showing significant differences among different types of surgery.

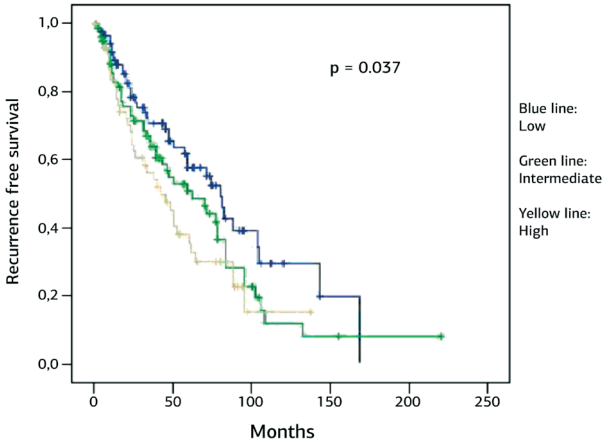

Figure 4. Recurrence free survival showing significant differences among histological grades.

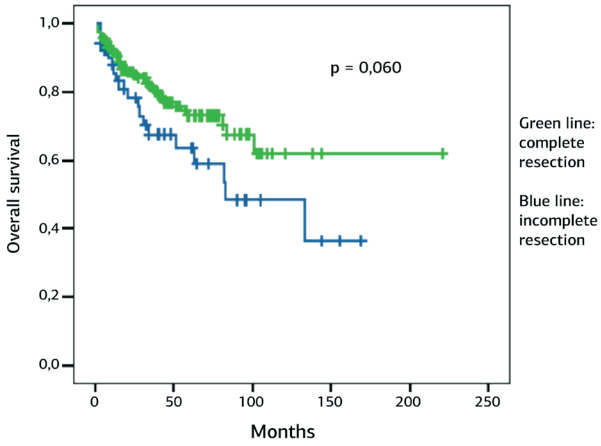

Figure 2. Overall survival showing no significant differences according to the extent of resection (complete or incomplete).

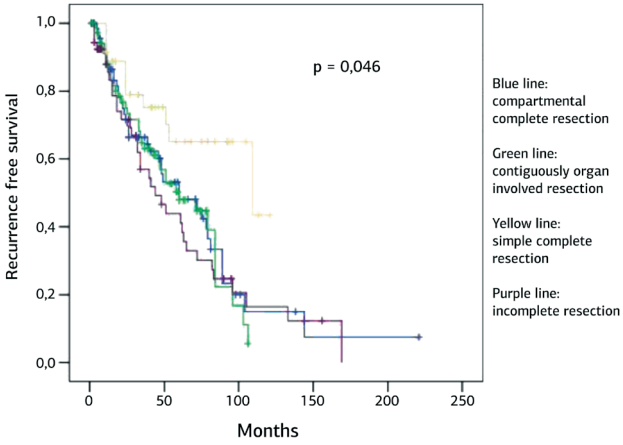

Figure 5. Recurrence free survival showing significant differences among different types of surgical resection.

postoperative adjuvant radiotherapy and chemotherapy. However, as we know, radiotherapy is beneficial for local control. If adjuvant treatments will be considered in future randomized trials, their results would be more reasonable should they be interpreted with caution. Second, with regard to surgical treatment, few studies mention the compartmental resection applied in the treatment of PRT and studies with large sample size are encouraged.

In conclusion, our findings demonstrate histological type and complete surgical resection are the important predictors of recurrence and overall survival in PRT patients. Precise understanding of the biological behaviors of PRT is helpful for the individualized treatment of patients with PRT.

Conclusion

Complete surgical resection and tumor biological features (i.e. histological type and grade) in PRT are the important prognostic factors influencing survival and recurrence of PRT. However, the role of chemotherapy and radiotherapy was not evaluated in this study and the effect of adjuvant therapy should be evaluated in future randomized trials.

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