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The clinical behavior of well differentiated liposarcoma can be extremely variable: A retrospective cohort study at a major sarcoma center

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Abstract

Background: The pathogenesis of well differentiated liposarcoma (WDLPS) is poorly understood and pathologic characterization is often challenging. Descriptive terms (such as sclerosing, myxoid, inflammatory, spindle cell) are frequently encountered in pathology reports and are of unknown clinical significance.

Methods: Sixty-two patients with primary retroperitoneal WDLPS resected at our institution were identified (1996–2011). Pathology reports of surgical resection specimens were retrospectively reviewed and descriptive qualifiers to the WDLPS diagnosis were noted.

Results: Descriptive qualifiers were associated with 36 (58%) cases. WDLPS with descriptive qualifiers were more likely to be larger (median size 32 vs 25.5cm, $p=0.01$) and multifocal (36.1 vs 7.7%, $p=0.01$) at diagnosis, require concomitant organ resection at surgery (50 vs 23.1%, $p=0.03$), and have higher incidence of local recurrence (83.3 vs 38.5%, $p<0.01$). WDLPS with pathologic qualifiers showed significantly shorter local recurrence-free survival (LRFS) and trend towards shorter distant recurrence-free survival and overall survival. Use of pathologic qualifiers with a WDLPS diagnosis independently predicted risk of worse LRFS.

Conclusions: Retroperitoneal WDLPS characterized by pathologic descriptive qualifiers appear to behave more aggressively than their more typical counterparts. Further investigation is warranted to more consistently characterize and define the pathologic features commonly seen in WDLPS as these may impact patient outcomes.

Keywords

liposarcoma; well differentiated; dedifferentiated; retroperitoneal sarcoma; surgical resection

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Introduction

Retroperitoneal sarcomas are rare tumors, allowing only a handful of highly select institutions to gain adequate experience in the multidisciplinary management of these malignancies. Among the 50 established sarcoma histologies, liposarcoma is the most common, accounting for nearly half of all retroperitoneal sarcomas.¹ The pathogenesis of liposarcoma is poorly understood and histologic characterization of these tumors remains challenging. Of the 4 recognized histologic subtypes of liposarcoma, well differentiated liposarcoma (WDLPS) and dedifferentiated liposarcoma (DDLPS) are the most common.²

The concept of dedifferentiation was first introduced by Evans in 1979 for “tumors containing distinct areas of well differentiated liposarcoma and cellular non-lipogenic spindle cell or pleomorphic sarcoma.”³ This description provided a pathologic basis to help explain the observed divergent clinical behavior and aggressiveness between WDLPS and DDLPS. Whereas WDLPS typically have a more indolent course, DDLPS are associated with a systemic metastatic rate of 5–20% and worse patient prognosis.^{4–6} However, the pathogenesis of WDLPS and DDLPS is poorly understood. Molecular analysis has shown that WDLPS and DDLPS share the same cytogenetic features and are both characterized by amplification of chromosome 12q13~15, resulting in amplification of the *MDM2* gene in virtually all cases and *CDK4* in up to 90% of cases.^{7–9}

Although typically associated with a more favorable prognosis compared to DDLPS, the WDLPS subtype itself displays a wide range of clinical behavior and likely represents a spectrum of disease. Pathologic interpretation may be difficult when fibrous or myxoid areas with increased cellularity or a slightly increased mitotic rate is present. Evans in 2007 described a series of 61 patients from 1976–1990 whose tumors were composed “wholly or in part of atypical lipomatous tumor.”¹⁰ He classified these into 4 groups based on histologic findings: conventional atypical lipomatous tumor, cellular atypical lipomatous tumor, dedifferentiated liposarcoma, and atypical lipomatous tumor with pleomorphic liposarcoma-like component. Not unexpectedly, patients with tumors located in “central body sites” fared worse compared to those with subcutaneous or intramuscular tumors. Within this subgroup of patients, those with atypical lipomatous tumor with pleomorphic liposarcoma-like component appeared to fare worse compared to those with conventional atypical lipomatous tumor and cellular atypical lipomatous tumor.

We hypothesize that there is a spectrum of clinical behavior and tumor aggressiveness among what is currently classified as the WDLPS entity and that being able to better identify the risk associated with a given WDLPS tumor may in the future impact treatment and surveillance decisions. The aim of this study was to identify and characterize primary, surgically resected WDLPS that are associated with pathologic descriptive qualifiers in the surgical pathology report and compare their clinical behavior and patient outcomes with those of patients with more pathologically homogeneous (“typical”) WDLPS tumors.

Materials and Methods

Patient Selection and Clinicopathologic Variables

After obtaining institutional review board approval, all adult patients (age ≥ 18 years at WDLPS diagnosis) with primary retroperitoneal WDLPS who underwent surgical resection of their sarcoma between May 1996 and December 2011 at The University of Texas MD Anderson Cancer Center were identified from the Department of Pathology database.

Patient and tumor-related variables recorded included age at diagnosis, gender, race, tumor size, and tumor multifocality. Continuous variables (age, tumor size) were dichotomized using the median value. Final pathologic diagnosis as well as any applied pathologic descriptive qualifiers in the surgical pathology reports were abstracted and tabulated. “Typical” WDLPS were adipocytic tumors that were diagnosed as either atypical lipomatous tumor or WDLPS with no other features noted on pathologic review. Pathologic descriptive qualifiers in this study were grouped into 1) those concerning for but not meeting criteria for dedifferentiated liposarcoma, 2) cytologic atypia, 3) background changes (including “myxoid features,” “myxoid background,” “myxoid areas,” “inflammation”, and “sclerotic pattern”) and 4) other. Treatment variables obtained included surgical procedure(s) performed, number of organs resected, and extent of resection (R0/R1 vs macroscopically incomplete [R2]). Data regarding disease recurrence, last follow-up visit, and death were also recorded.

Statistical Analyses

Categorical patient characteristics were compared using Fisher’s exact tests and continuous patient characteristics were compared using Wilcoxon rank-sum tests. $P < 0.05$ was considered statistically significant. For patients alive and without evidence of disease recurrence or progression, follow-up was censored at the date of last disease assessment. Local recurrence-free survival (LRFS) was determined for patients who had a R0/R1 resection and was defined as the interval from date of tissue diagnosis to date of first local recurrence or censored at date of last follow-up or death if there was no evidence of recurrence. All patients who experienced a distant disease recurrence had an earlier local disease recurrence. Distant recurrence-free survival (DRFS) was defined as the interval from date of tissue diagnosis to date of first distant recurrence or censored at date of last follow-up or death. Overall survival (OS) was defined as the interval from date of tissue diagnosis to death or censored at last known date of survival. Survival curves were obtained using the Kaplan-Meier method. Univariate and multivariate Cox proportional hazards regression models were used to assess the associations between patient characteristics and LRFS, DRFS, and OS. Patient characteristics that were significant in the univariate models at the 0.20 level were included in the primary model. Backward elimination was implemented until all remaining predictors had a p value less than 0.1. Since pathologic descriptive qualifier was the main focus of this study, it was locked in the model.^{11,12} Statistical analyses were performed using SPSS version 24 (IBM) and Stata software version 14.1 (StataCorp, College Station, Texas).

Results

Patient Characteristics and Treatment

We identified 62 patients with primary RP WDLPS who underwent surgical resection at The University of Texas MD Anderson Cancer Center. Patient demographics and tumor characteristics are summarized in Table 1. Median age at diagnosis was 56.5 years (range 32 to 80 years) with a slight male gender predominance (56.5 vs 43.5%). Median tumor size was 30 cm (range 8.5 to 100 cm). Complete gross resection (R0/R1) was achieved in 91.9% of patients and R2 resections in 8.1% of patients. The majority of patients had unifocal disease (75.8%) and did not require organ resection at the time of WDLPS resection (61.3%).

Of the cohort, the pathologic diagnosis of WDLPS in 36 patients (58%) was associated with pathologic descriptive qualifiers (Table 2). The most common pathologic qualifiers applied in the description of the RP WDLPS tumors in this cohort included “focal areas of increased cellularity,” “necrosis,” “myxoid background,” “hyalinization, fibrosis, sclerotic pattern,” and “focal area of dedifferentiation/incipient dedifferentiation.” There was no difference between patients with WDLPS associated with pathologic descriptive qualifiers compared to those with typical WDLPS with respect to age at diagnosis, sex or ethnicity (Table 1). However, primary WDLPS tumors associated with pathologic descriptive qualifiers were more likely to be larger (median size 32 vs 25.5cm, $p=0.01$) and multifocal (36.1 vs 7.7%, $p=0.01$) at diagnosis. Patients with primary WDLPS associated with pathologic descriptive qualifiers were additionally more likely to undergo organ resection at the time of surgery (50 vs 23.1%, $p=0.03$).

Patient Outcomes

Median follow-up was 72.8 months (range 9.5 to 248.5 months) (Table 1) with a median survival of 10.9 years (95% CI: 93.1 – not estimable) and 5-year OS of 84.6% (95% CI 71.6–92%). Forty-five patients (72.6%) developed local disease recurrence (LR) or progression while 5 (8.1%) developed distant disease recurrence (DR). Twenty (32.3%) patients expired during the study period.

Compared to patients diagnosed with typical WDLPS, those with WDLPS with pathologic descriptive qualifiers had higher cumulative incidence of local recurrence (LR 83.3 vs 38.5%, $p<0.01$) and did worse with respect to LRFS (Figure 1a). Median and 5-year LRFS were 2 years and 14.3%, respectively, for patients with WDLPS with pathologic descriptive qualifiers but 9.9 years and 79% for patients with typical WDLPS ($p<0.001$). Patients with WDLPS with pathologic descriptive qualifiers also demonstrated a trend toward higher cumulative incidence of distant recurrence (DR 13.9 vs 0%, $p=0.05$) and worse DRFS and OS (Figure 1b–c). Median and 10-year DRFS were 19.2 years and 79.2%, respectively, for patients diagnosed with WDLPS with pathologic descriptive qualifiers while for those with typical WDLPS, median DRFS was not reached and 10-year DRFS was 100% ($p=0.05$). There was a trend towards worse OS for WDLPS with pathologic descriptive qualifiers compared to typical WDLPS (median OS 8.2 vs 13.7 years, $p=0.20$; 5-year OS 76.7 vs 92.3%).

We next performed univariable and multivariable analyses to identify factors associated with patient outcomes among patients who underwent complete (R0/R1) surgical resection of their primary WDLPS (Table 3). On univariable analysis, the presence of pathologic descriptive qualifiers (HR 3.5, 95% CI 1.8–7.0, $p<0.001$) and presence of multifocal disease (HR 2.3, 95% CI 1.1–4.9, $p=0.028$) were associated with worse LRFS. On multivariable analysis, we found that younger age (<55 years, HR 0.48, 95% CI 0.25–0.89, $p=0.021$) and the presence of pathologic descriptive qualifiers with the diagnosis of WDLPS (HR 4.0, 95% CI 2.0–8.1, $p<0.001$) were independent predictors of worse LRFS. Although the presence of pathologic descriptive qualifiers with the diagnosis of WDLPS was independently associated with worse LRFS, in our models it was not independently predictive of DRFS or OS.

Discussion

The aim of this study was to identify primary, surgically resected WDLPS associated with pathologic descriptive qualifiers and compare their clinical behavior and patient outcomes with those of typical WDLPS tumors. Primary WDLPS with pathologic descriptive qualifiers tended to be larger tumors and more frequently multifocal at initial presentation and require concomitant organ resection at the time of surgery compared to typical WDLPS. Compared to patients with typical WDLPS, those with primary WDLPS with pathologic descriptive qualifiers had worse outcomes with respect to both local and distant recurrence without differences in achievement of complete surgical (R0/R1) resection at time of resection, suggesting that these tumors may behave more aggressively than typical WDLPS. Additionally, we found that use of one or more pathologic descriptive qualifiers with the diagnosis of WDLPS was an independent predictor of worse LRFS (Table 1).

These data support the concept that the well differentiated subtype of liposarcoma represents a spectrum of disease and are a heterogeneous group of tumors. Although previous authors have sub-classified WDLPS into morphologic subtypes (adipocytic [lipoma-like], sclerosing, inflammatory, and spindle cell),^{7,13,14} this is the first study to evaluate the potential clinical implication of histologic differences within WDLPS on patient outcome. A previous study from the MD Anderson Cancer Center described some of the variable pathologic characteristics seen in lipomatous tumors; however, this study included patients with lipomatous tumors occurring in the extremity and trunk, as well as tumors in the retroperitoneum.¹⁰ As we have subsequently learned, the behavior of these tumors is very much location-specific and, therefore, limiting the scope of the patient population to the retroperitoneum will potentially provide a more accurate analysis and results. Patients in this study with primary WDLPS with pathologic descriptive qualifiers have better LRFS, DRFS, and OS outcomes than those historically reported for patients withDDLPS;^{6,10} however, they fare worse than patients with typical WDLPS.

Although up to 20% of patients withDDLPS may develop distant metastasis during their disease course, it is exceedingly uncommon for patients with WDLPS to develop distant metastases. One might suspect that the 5 patients in this study who developed distant metastases may, in fact, have hadDDLPS rather than WDLPS at primary diagnosis (Supplemental Table 1). Of these 5 patients, only 1 patient was noted to have a focus of

dedifferentiation not meeting criteria for diagnosis of DDLPS at primary WDLPS diagnosis. This patient developed DDLPS at distant recurrence and had short OS of 13.3 months after initial diagnosis, raising concern that perhaps they indeed may have had primary DDLPS rather than WDLPS. Of the remaining 4 patients, 1 patient had “typical” WDLPS at primary WDLPS presentation and developed DDLPS at distant recurrence while the other 3 patients had WDLPS with pathologic qualifiers (noting focal marked cytologic atypia of adipocytes, extensive inflammation, and focal myxoid areas). Although these remaining 4 patients developed distant disease, median time to DR was 123.2 months, median OS in this group is 127 months, and 3 patients remain alive with disease.

A fundamental limitation in our understanding of the heterogeneity among WDLPS tumors is that there are currently no guidelines to aid the pathologist and no systematic approach towards further characterizing and describing pathologic features in WDLPS tumors. The French Federation of Comprehensive Cancer Centers (FNCLCC) is most commonly used to grade soft tissue sarcomas. Under the FNCLCC system, all WDLPS are by definition low grade while DDLPS can be either intermediate or high grade, most often the former. Other classification systems, such as the College of American Pathologists Protocol for Examination of Specimens for Soft Tissue Sarcoma and the 2013 WHO Classification of Soft Tissue Tumors, both based on the FNCLCC grading system similarly define all WDLPS as low grade without guidelines on further characterization or description of pathologic features among WDLPS tumors.

Over the study period in our institution, multiple sarcoma specialized pathologists have reviewed surgical resection specimens at our institution and there are likely inter-observer differences in the diagnosis of WDLPS and reporting of pathologic qualifiers. Indeed, we found notable variation in degree of detail and histologic findings described within pathology reports of surgical resection specimen (Table 2). Given the potential prognostic impact that various pathologic features found among WDLPS may have on patient outcome, there is a clear need for an improved and systemic approach towards the pathologic characterization of WDLPS that is more consistently and uniformly applied during surgical pathologic reporting. The results of this study support our hypothesis that even at a high volume sarcoma center of excellence, with dedicated sarcoma pathologists, there still exists a subjective component to the pathologic characterization of WDLPS. In addition to documenting the heterogeneous behavior of WDLPS, the results of this study are important to bring attention to the need for an improvement of the pathologic characterization of WDLPS.

This study is not without limitations. First, this study is limited by small cohort size as the cohort of interest were patients with primary retroperitoneal WDLPS who underwent surgical resection at our institution. Although our institution is a quaternary referral center with expertise in the multidisciplinary management of soft tissue sarcoma, retroperitoneal sarcomas are rare tumors and patients are frequently referred to our center at disease recurrence, having often undergone resection of their primary liposarcoma at other hospitals. Additionally, primary retroperitoneal liposarcomas often are characterized by mixed histologies, with both WDLPS and DDLPS components. The patients included in this study included those with only WDLPS. It is possible that our study was underpowered to detect,

for example, the use of one or more pathologic descriptive qualifiers with WDLPS diagnosis as an independent risk factor for DRFS and OS. Interestingly, factors reported in other studies to be predictors of OS such as tumor size and multifocal disease, for instance, failed to predict OS in this study. Retrospective studies including the current study are also limited to potential selection bias as well as potential heterogeneity and changes in WDLPS multidisciplinary management and pathologic diagnosis and reporting over the study period.

In summary, this study the first to examine and compare outcomes among patients who underwent surgical resection for primary WDLPS tumors of the retroperitoneum associated with pathologic descriptive qualifiers with those who underwent resection for primary typical WDLPS tumors. We found that primary retroperitoneal WDLPS with pathologic descriptive qualifiers were associated with worse LRFS and appear to behave more aggressively than typical WDLPS. These findings suggest that there is a spectrum of clinical behavior and tumor aggressiveness within the currently defined WDLPS histologic subtype and that achieving a more detailed and reproducible pathologic description will allow for a better understanding of the disease spectrum and diversity of clinical behavior within WDLPS which will enable clinicians to provide more personalized treatment and improve patient outcome. We are currently evaluating new and reproducible pathologic markers that can potentially be used to more objectively identify tumors which are more likely to behave in a clinically aggressive fashion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Synopsis:

Pathologic characterization of WDLPS is often challenging. Descriptive terms are frequently included in the pathologic evaluation of WDLPS. The inclusion of these descriptive terms appears to be associated with a more aggressive phenotype in patients undergoing surgical resection of primary WDLPS.

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A

Primary WDLPS with Pathologic Qualifiers are Associated with Shorter Local Recurrence-Free Survival (LRFS)

Median LRFS: 2.0 vs 9.9 years
5-yr LRFS: 14.3 vs 79.0%

B

Primary WDLPS with Pathologic Qualifiers are Associated with a Trend Towards Shorter Distant Recurrence-Free Survival (DRFS)

Median DRFS: 19.2 years vs NR
10-yr DRFS: 79.2 vs 100%

C

Primary WDLPS with Pathologic Qualifiers are Associated with a Trend Towards Shorter Overall Survival (OS)

Median OS: 8.2 vs 13.7 years
5-yr OS: 76.7 vs 92.3%

Figure 1. Association between pathologic qualifiers to WDLPS diagnosis and patient outcomes. Among patients undergoing surgery for WDLPS, pathologic qualifiers are associated with (A) shorter local recurrence-free survival, (B) a trend towards shorter distant recurrence-free survival, and (C) a trend towards shorter overall survival.

Table 1.

Clinicopathologic characteristics and outcomes of patients with well differentiated liposarcoma at primary presentation

	Total (n=62)	Without pathologic qualifier (n=26)	With pathologic qualifier (n=36)	p value
Median age at diagnosis, yrs (range)	56.5 (32–80)	57 (39–80)	54 (32–76)	0.30
Age 55				0.56
No	29 (46.8%)	11 (42.3%)	18 (50%)	
Yes	33 (53.2%)	15 (57.5%)	18 (50%)	
Gender				0.80
Male	35 (56.5%)	15 (57.7%)	20 (55.6%)	
Female	37 (43.5%)	11 (42.3%)	16 (44.4%)	
Ethnicity				0.69
White	49 (79%)	20 (76.9%)	29 (80.6%)	
Hispanic	9 (14.5%)	4 (15.4%)	5 (13.9%)	
African-American	3 (4.8%)	1 (3.8%)	2 (5.6%)	
Other	1 (1.6%)	1 (3.8%)	0 (0%)	
Median tumor size, cm (range)	30 (8.5–100)	25.5 (9–100)	32 (8.5–78)	0.01
Tumor size >30cm				0.02
No	25 (40.3%)	15 (57.7%)	10 (27.8%)	
Yes	37 (59.7%)	11 (42.3%)	26 (72.2%)	
Surgical resection margins				0.93
R0/R1	57 (91.9%)	24 (92.3%)	33 (91.7%)	
R2	5 (8.1%)	2 (7.7%)	3 (8.3%)	
Organ resection at time of primary tumor resection				0.03
No	38 (61.3%)	20 (76.9%)	18 (50%)	
Yes	24 (38.7%)	6 (23.1%)	18 (50%)	
Multifocal disease				0.01
No	47 (75.8%)	24 (92.3%)	23 (63.9%)	
Yes	15 (24.2%)	2 (7.7%)	13 (36.1%)	
Local recurrence				<0.01
No	17 (27.4%)	15 (57.7%)	2 (5.6%)	
Yes	40 (64.5%)	10 (38.5%)	30 (83.3%)	
Progression (R2 resection)	5 (8.1%)	1 (3.8%)	4 (11.1%)	
Distant recurrence				0.05
No	53 (85.5%)	24 (92.3%)	29 (80.6%)	
Yes	5 (8.1%)	0 (0%)	5 (13.9%)	
Missing	4 (6.5%)	2 (7.7%)	2 (5.6%)	
Histology on first recurrence				0.98
WDLPS	23 (57.5%)	7 (53.8%)	16 (59.2%)	
DDLPS	10 (25%)	3 (23.1%)	7 (25.9%)	

	Total (n=62)	Without pathologic qualifier (n=26)	With pathologic qualifier (n=36)	<i>p</i> value
Missing	7 (17.5%)	3 (23.1%)	4 (14.8%)	
Last known status				0.87
Alive	37 (59.7%)	17 (65.4%)	20 (55.6%)	
Deceased	25 (40.3%)	9 (34.6%)	16 (44.5%)	

DDLPS: dedifferentiated liposarcoma

R0: complete gross resection with negative margins

R1: complete gross resection with positive margins

R2: incomplete gross resection

WDLPS: well differentiated liposarcoma

Table 2.

Pathologic qualifiers associated with the diagnosis of well differentiated liposarcoma at primary presentation

Pathologic qualifier	Number of cases with qualifier on pathologic evaluation (% of cases with any pathologic qualifier)
No pathologic qualifier	26
Any pathologic qualifier [*]	36
Concerning for but not meeting criteria for dedifferentiated liposarcoma	
Focal areas of increased cellularity	12 (33.3%)
Focal area of dedifferentiation, incipient dedifferentiation	4 (11.1%)
Increased mitotic activity (but less than 5 per 10 HPF)	2 (5.5%)
Cytologic atypia	
Marked cytologic atypia of adipocytes	1 (2.7%)
Increased pleomorphism	1 (2.7%)
Bizarre cells	1 (2.7%)
Background changes	
Myxoid background	9 (25%)
Hyalinization, fibrosis, sclerotic pattern	7 (19.4%)
Inflammation	2 (5.5%)
Other	
Necrosis	12 (33.3%)
Spindle cells exhibiting fibro-histiocytic features	1 (2.7%)

^{*} Some cases may have had more than one pathologic qualifier

Factors associated with local recurrence-free survival, distant recurrence-free survival, and overall survival among patients undergoing complete gross (R0/R1) resection of primary well differentiated liposarcoma

Table 3.

Local Recurrence-Free Survival (n=56)					
Description	Univariate model			Multivariate Model	
	HR	95% CI	p value	HR	95% CI p value
Age, 55 vs <55 years	0.59	0.32–1.08	0.087	0.48	0.25–0.89 0.021
Pathologic Qualifier, yes vs no	3.52	1.77–6.97	<0.001	4.02	1.98–8.12 <0.001
Tumor size, >30 cm vs 30 cm	1.27	0.68–2.38	0.447		
Multifocal disease, yes vs no	2.31	1.09–4.87	0.028		(did not remain in the model)
Organ Resection, yes vs no	1.38	0.75–2.55	0.304		
Distant Recurrence-Free Survival (n=56)					
Description	Univariate model			Multivariate Model	
	HR	95% CI	p value	HR	95% CI p value
Age, 55 vs <55 years	0.97	0.42–2.21	0.935		
Pathologic Qualifier, yes vs no	2.06	0.86–4.96	0.105	1.76	0.72–4.33 0.217
Tumor size, >30 cm vs 30 cm	1.87	0.77–4.58	0.169		(did not remain in the model)
Multifocal disease, yes vs no	1.21	0.39–3.72	0.737		
Organ Resection, yes vs no	2.76	1.14–6.65	0.024	2.49	1.01–6.12 0.047
Overall Survival (n=56)					
Description	Univariate model			Multivariate Model	
	HR	95% CI	p value	HR	95% CI p value
Age, 55 vs <55 years	1.02	0.42–2.48	0.965		
Pathologic Qualifier, yes vs no	1.69	0.67–4.21	0.264		
Tumor size, >30 cm vs 30 cm	1.53	0.61–3.87	0.366		
Multifocal disease, yes vs no	1.48	0.47–4.63	0.505		
Organ Resection, yes vs no	2.95	1.17–7.46	0.022		