Published in final edited form as:

J Surg Res. 2019 December ; 244: 34–41. doi:10.1016/j.jss.2019.05.016.

Retroperitoneal Sarcomas: Does Laterality Matter?

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Abstract

Background: Sarcomas are malignant tumors of connective tissue that can vary widely in etiology. Parameters such as grade, extent of resection, and tumor integrity have been shown to affect prognosis. Our principle aim was to examine associations between the laterality of retroperitoneal sarcomas and tumor characteristics, treatment and patient outcomes.

Materials & Methods: We performed a retrospective study of patients treated at our tertiary referral center with a diagnosis of primary retroperitoneal sarcoma who underwent tumor resection. Categorical variables were compared using the Chi-square test while continuous variables were compared using one-way ANOVA. Cox regression was used to estimate risk of death.

Results: Data from 106 patients was analyzed. A greater proportion of bilateral or midline tumors were leiomyosarcomas ($p=0.02$), while right-sided tumors were more likely to be liposarcoma ($p=0.02$). There was no significant relationship between laterality and tumor grade or stage. Two-thirds of patients had at least one contiguous organ resected ($n=68$, 65.4%). Patients with nephrectomy during sarcoma resection were more likely to have right-sided disease ($p=0.02$). Splenectomy and pancreatectomy were associated with left-sided disease ($p < 0.01$; $p < 0.01$), and

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Dr. Farma contributed to the study design and conception. Ms. Lou contributed to data collection and the writing of the manuscript. Dr. Moten contributed to the data analysis and editing of the manuscript. All authors contributed to interpretation of data, manuscript drafting, and critical revision of the manuscript.

Disclosures

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

pancreaticoduodenectomies with bilateral or midline disease ($p < 0.001$). Adjusting for age, sex, race, grade, stage, histology and treatment, there was no increased risk of death or recurrence based on laterality.

Conclusions: While laterality did not seem to have a measurable relationship with patient outcomes or survival, there was a significant association between laterality, tumor histology, and resection of contiguous organs. These preliminary findings warrant further investigation.

Keywords

retroperitoneal sarcoma; soft tissue sarcoma; surgery

Introduction

Soft tissue sarcomas are rare malignant tumors of connective tissue that account for less than 1% of all adult solid malignancies.¹ There are more than 70 different subtypes of sarcomas, classified by either etiology or location. Retroperitoneal sarcomas comprise a subtype that is relatively rare, making up approximately 12–16% of all soft tissue sarcomas.^{2,3} Part of the difficulty in addressing these tumors is their location in the retroperitoneal compartment, which provides ample space for the tumor to grow while remaining undetected. Often, diagnosis is made when found incidentally on imaging. Once symptomatic, these tumors can be exceedingly large, with 94% of tumors greater than 5 cm in diameter on initial presentation.⁴ While most retroperitoneal sarcomas are not metastatic, they carry a poor prognosis. Nearly half of all primary tumors return within the first five years of treatment, and the 5-year overall survival rate ranges from 33% to 39%.^{2,3,5}

Parameters such as extent of resection, grade, histology, tumor dimensions, and multifocality are all regarded as useful prognostic factors.^{5,6} Chemotherapy and radiation therapy have been limited in their success, making complete surgical resection a cornerstone of retroperitoneal sarcoma treatment.^{3,4,6} Given the asymmetry of the visceral organs in the retroperitoneum, we hypothesize that the side on which a primary retroperitoneal sarcoma presents may provide valuable information for prognosis, surgical parameters, or patient management. The principle aim of this investigation was to examine associations between the laterality of soft tissue sarcomas of the retroperitoneum and tumor characteristics, treatment and patient outcomes.

Materials and methods

After obtaining Institutional Review Board (IRB) approval, patients with a diagnosis of primary retroperitoneal sarcoma were identified using the tumor registry at our institution. Patients who underwent surgical resection for their sarcoma at Fox Chase Cancer Center between 2000 and 2015 were included in the study. Waiver of informed consent was requested from and approved by the IRB. Patients were excluded if the location of their tumor was unspecified or unknown ($n = 28$), or if they had recurrent disease after undergoing initial resection at another institution ($n = 13$). This left a sample size of 106 patients for analysis. Clinical and pathologic data were collected retrospectively from patient

medical records. Tumor staging was classified according to the American Joint Committee on Cancer Staging System 7th edition.⁷

The study sample was stratified based on our primary variable, which was the laterality of the tumor within the retroperitoneum. Tumors were categorized as left-sided, right-sided or bilateral/midline according to their location as described in the operative note of the sarcoma resection. To define laterality, we generally used the anatomic zones of the retroperitoneum typically employed for management of traumatic retroperitoneal hematomas. Midline tumors were those primarily located in Zone 1 near the great vessels. Bilateral tumors extended to Zone 2 on both the left and right side. Left or right tumors were unilaterally located in Zone 2. Associations between tumor laterality and patient characteristics were determined. Associations with categorical variables were assessed using Chi-square tests. Associations with continuous variables such as patient age were assessed using one-way ANOVA.

Cox regression was used to estimate the risk of tumor recurrence and the risk of cancer-specific death. The adjusted regression models included the covariates age, sex, race, grade, stage, tumor histology and treatment types in order to account for the impact of these variables on recurrence and survival.

A p-value of < 0.05 was used to determine statistical significance for all tests. All analyses were performed using Stata version 12.1 (StataCorp LP, College Station, TX, USA).

Results

Analysis of the 106 patients in our study found that the mean age at diagnosis was 58.7 years and 41.6% of patients were male (n=44). Caucasians made up 91.5% (n=97) of patients and 81.9% had no prior diagnosis of cancer (n=86). There were 52 right-sided (49.1%), 47 left-sided (44.3%), and 7 bilateral or mid-line sarcomas (6.6%). (Table 1) Overall median survival was 47.5 months.

The majority of patients presented with tumors greater than 5 cm (n = 96, 90.6%). Nearly half our patients were found to have high grade tumors (n = 45, 42.9%). Low grade tumors were seen in 35 patients (33.3%), with intermediate grade seen in 12 patients (11.4%). Although not statistically significant, a greater proportion of right-sided tumors presented as high grade (n = 27, 51.9%), while most left-sided (n = 19, 41.3%) and bilateral or mid-line tumors (n = 4, 57.1%) were low grade (p = 0.19). Only 5 patients had tumors smaller than 5 cm (n = 5, 4.7%, p = 0.90). Most patients had Stage III disease (n = 37, 34.9%), followed by Stage I (n = 32, 30.2%), Stage IV (n = 12, 11.3%), and Stage II (n = 8, 7.6%). The majority of patients with right-sided tumors presented with Stage III disease (n = 21, 40.4%), while Stage I disease was the most commonly seen with left-sided (n = 17, 36.2%) and bilateral or mid-line tumors (n = 4, 57.1%, p = 0.27). The only patients who presented with nodal invasion were those with right-sided tumors (n = 2, 1.9%, p = 0.10), one of which was found to be liposarcoma on histology and the other leiomyosarcoma. Metastatic disease was seen more in patients with left-sided tumors, though without statistical significance (left 14.9% vs right 9.6% vs mid-line 0%, p=0.07). More than half the tumors were found to be

liposarcomas on histology (n = 65, 62.5%). The rest were comprised of leiomyosarcoma (n = 28, 26.9%) or other histological subtypes (n = 11, 10.6%). Right and left-sided tumors were more likely to be liposarcoma (right n = 35, 68.6% vs left n = 29, 63%), while bilateral or mid-line tumors were more likely to be leiomyosarcoma (n = 3, 42.9%, p = 0.02). (Table 2)

There were 19 patients (17.9%) who received neoadjuvant radiation, 17 patients (16%) who received neoadjuvant chemotherapy, and 10 patients who received both. Although not statistically significant, a larger proportion of patients with bilateral or midline tumors received neoadjuvant chemotherapy (midline 42.9% vs left 19.2% vs right 0.6%, p = 0.06). All patients underwent surgical resection, with a median of 1.4 months between their initial visit and their surgery. Negative margins were attained in 47 patients (44.8%), with positive margins in 24 patients (22.9%) and unknown margins in 34 patients (32.4%). No patients underwent re-excision. Approximately half of patients had no major post-operative complications (n = 55, 51.9%), and most did not receive post-operative radiation (n = 89, 84%) or post-operative chemotherapy (n = 97, 91.5%). The most common complications were infections (n=8), pleural effusion (n=5), and post-operative ileus (n=4). Patients with unknown complication did not have “no complications” explicitly stated in their discharge summary or first post-operative office visit note. There were 50 patients found to have a local recurrence, with a range of 1 to 74 months, with no significant difference in laterality (47.2%, p=0.32). (Table 3)

Nearly 2/3 of patients had at least one contiguous organ resected at the time of sarcoma resection (n=68, 65.4%). The overall most frequent organ resected was the kidney (n=51, 48.1%), followed by adrenals (n=30, 28.3%), colon (n=18, 17%), pancreas (n=12, 11.3%), spleen (n=11, 10.4%), small bowel (n=9, 8.5%), gallbladder (n=8, 7.6%), and stomach (n=2, 1.89%). Resection of the stomach, gallbladder, adrenals, small bowel, and colon did not differ between right-sided, left-sided, and bilateral or midline tumors (respectively, p=0.69, p=0.06, p=0.17, p=0.12, p=0.38). Resection of right-sided tumors was more likely to involve additional resection of the kidney (right 57.5% vs left 44.7% vs midline 0%, p=0.02). (Figure 1) Resection of left-sided tumors was more likely to involve additional resection of the pancreas (right 1.9% vs left 17.0% vs midline 42.9%, p < 0.01) and spleen (right 0% vs left 21.3% vs midline 14.3%, p < 0.01). Patients with bilateral and midline tumors were more likely to undergo a pancreaticoduodenectomy (right 1.9% vs left 0% vs midline 28.6%, p=<0.0001). (Table 4) There was no significant difference in whether multiple organs were resected during surgery between patients with right-sided (40.4%), left-sided (36.2%), and bilateral or midline (42.9%) tumors (p = 0.89).

The risk of recurrence did not change when looking at the laterality of the tumor, even when adjusted for age, sex, race, grade, stage, histology and treatment. (Table 5) Similarly, there was no difference in risk of disease-specific death based on tumor laterality. (Table 6)

Discussion

Surgical resection is a cornerstone of retroperitoneal sarcoma treatment. Multiple groups have found a relationship between negative surgical margins and improved overall survival.

3–6, 8,9 While several groups have addressed multifocality with patient prognosis, no studies to date have directly considered the relationship of laterality of retroperitoneal sarcomas with tumor characteristics or patient outcomes.^{9–10}

Laterality does not seem to have a direct measurable relationship with patient outcomes or survival. However, we found an association between laterality and tumor histology. A greater proportion of bilateral or midline tumors were leiomyosarcomas, and both right and left-sided tumors were more likely to be liposarcomas. Previous studies by Liles et al and Lewis et al found liposarcomas more associated with local recurrence than distant metastatic disease.^{3–4} As such, we would expect patients with exclusively right or left-sided lesions to have more local recurrence. When controlled for histology, we found no increased risk of recurrence in these patients compared to those with bilateral or midline tumors. This suggests that laterality plays a minimal role when considering the potential for recurrent disease in patients.

Compared to liposarcomas, leiomyosarcomas are more aggressive and have a worse prognosis. They are more often associated with involvement of retroperitoneal vasculature, such as the inferior vena cava and renal veins.⁹ Hassan et al found leiomyosarcomas to have a higher probability of developing distant metastasis (44% vs 14% overall).¹¹ The reported 5-year survival ranges from 0–30%, compared to an overall survival of 30–39%.³ However, our investigation did not find patients with bilateral or midline tumors to have any increased risk of death compared to patients with right or left-sided tumors. While not significant, there may be an association between patients with bilateral or midline tumors and neoadjuvant chemotherapy. Chemotherapy, in general, is not a standard treatment for initial management of retroperitoneal sarcomas; however, with the increasingly personalized approach to the management of retroperitoneal sarcomas, there is a role for systemic therapy especially with certain histologies.^{12–13} Given that patients with bilateral and midline tumors were more likely to have leiomyosarcomas, there may be a role for neoadjuvant chemotherapy in these patients presenting with aggressive tumor histologies.

Though our analysis did not show a relationship between laterality and risk of death, Hassan et al found that patients with leiomyosarcomas were twice as likely to die of their tumor compared to patients with liposarcomas.¹¹ Gronchi et al noted that with the adoption of extended resection, local recurrence of leiomyosarcoma has significantly improved. However, this approach does not impact the potential for distant spread, which contributes to the shorter overall survival of patients with this histological subtype.^{11,16,17} Patients presenting with metastatic disease trended towards having left-sided tumors, although this was not significant. Given the strength of histology as a prognostic factor and significant difference found between laterality and histological subtype, laterality may not play a significant prognostic role.

Our investigation showed that about 67% of patients had at least one organ resected with their tumor, with several significant associations between laterality and specific organs. The overall proportion of contiguous organ resection may be attributed to studies by Gronchi et al, which demonstrated a relationship between extended surgery, local control and overall survival, thus prompting more aggressive surgical approaches.^{14,15} Patients who underwent

simultaneous nephrectomy were more likely to have right-sided tumors. The location of the liver limits the size of the retroperitoneal space on the right, which may lead to more aggressive surgical resection in order to obtain negative margins. While we saw a relationship with gallbladder resection during tumor resection and right-sided disease, it was not statistically significant. However, we did not take into account any history of prior cholecystectomy, which would contribute to fewer contiguous gallbladder resections during the sarcoma operation. Resection of the spleen was more often seen in patients with left-sided disease. While this might be expected given the laterality of the spleen to the left side, it is not a retroperitoneal organ and only about one-fifth of left-sided tumor resections involved additional spleen resection. There were also a significant number of pancreatectomies in patients with left-sided tumors, which may be explained by the close anatomical association of the pancreatic tail to the spleen. Pancreaticoduodenectomy was significantly associated with midline or bilateral retroperitoneal sarcomas, likely due to the location of the duodenum and pancreas in the retroperitoneal space. While there is literature supporting sarcoma excision en bloc with contiguous organs, there has not been any investigation into specific organs that are resected.^{14,15} Further studies should investigate the extent of en bloc organ resection.

There are some limitations to our study. The patients included in our analysis were limited to those who underwent surgical resection for their retroperitoneal sarcomas. This selects for patients who are operative candidates and excludes patients with either minimal tumor burden or extensive disease. Additionally, our sample size is small, and the majority of patients in our study were Caucasian, potentially decreasing the statistical power of our study and limiting the generalizability of our findings. Given the rarity of retroperitoneal sarcomas, our sample size is comparable with many other single-site institutional studies. Though this study occurred at an NCI-designated cancer center, future investigation would benefit from a larger sample size and collaboration across other institutions.

Conclusion

While laterality does not seem to have a measurable relationship with patient outcomes, disease recurrence, or survival, there is an association between laterality, tumor histology, and resection of the kidney, spleen, or pancreas. Patients with left-sided tumors trend towards having metastatic disease. These preliminary findings warrant further investigation with a larger sample size across different institutions.

Acknowledgements

Dr. J.F. contributed to the study design and conception. All authors contributed to analysis and interpretation of data, manuscript drafting, and critical revision of the manuscript. All authors approved the final version of the manuscript.

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Figure 1.
Laterality vs. tumor histology (p=0.02)

Table 1.

Demographics of the study population

	All, n (%)	Right, n (%)	Left, n (%)	Bilateral/Midline, n (%)	p-value
Total	106 (100)	52 (49.1)	47 (44.3)	7 (6.6)	
Mean Age in Years (SD)	58.7 (12.9)	59.3 (13.1)	58.4 (13.2)	57.0 (10.5)	0.88
Sex					0.97
Male	44 (41.5)	21 (40.4)	20 (42.6)	3 (42.9)	
Female	62 (58.5)	31 (59.6)	27 (57.5)	4 (57.1)	
Race					0.20
White	97 (91.5)	48 (92.3)	44 (93.6)	5 (71.4)	
Black	7 (6.6)	3 (5.8)	2 (4.3)	2 (28.6)	
Other	2 (1.9)	1 (1.9)	1 (2.1)	0	
Cancer History					0.45
No	86 (81.9)	44 (86.3)	36 (76.6)	6 (85.7)	
Yes	19 (18.1)	7 (13.7)	11 (23.4)	1 (14.3)	

Table 2.

Tumor Characteristics

	All, n (%)	Right, n (%)	Left, n (%)	Bilateral/Midline, n (%)	p-value
Grade					0.19
Low	35 (33.3)	12 (23.1)	19 (41.3)	4 (57.1)	
Intermediate	12 (11.4)	8 (15.4)	3 (6.5)	1 (14.3)	
High	45 (42.9)	27 (51.9)	17 (37.0)	1 (14.3)	
Unknown	13 (12.4)	5 (9.6)	7 (15.2)	1 (14.3)	
Stage					0.27
I	32 (30.2)	11 (21.2)	17 (36.2)	4 (57.1)	
II	8 (7.6)	6 (11.5)	2 (4.3)	0	
III	37 (34.9)	21 (40.4)	15 (31.9)	1 (14.3)	
IV	12 (11.3)	5 (9.6)	7 (14.9)	0	
Unknown	17 (16.0)	9 (17.3)	6 (12.8)	2 (28.6)	
T Stage					0.90
T1	5 (4.7)	3 (5.8)	2 (4.3)	0	
T2	96 (90.6)	46 (88.5)	43 (91.5)	7 (100)	
Unknown	5 (4.7)	3 (5.8)	2 (4.3)	0	
N Stage					0.10
N0	60 (56.6)	24 (46.2)	33 (70.2)	3 (42.9)	
N1	2 (1.9)	2 (3.9)	0	0	
Unknown	44 (41.5)	26 (50.0)	14 (29.8)	4 (57.1)	
M Stage					0.07
M0	55 (51.9)	24 (46.2)	29 (61.7)	2 (28.6)	
M1	12 (11.3)	5 (9.6)	7 (14.9)	0	
Unknown	39 (36.8)	23 (44.2)	11 (23.4)	5 (71.4)	
Histology					0.02*
Leiomyosarcoma	28 (26.9)	13 (25.5)	12 (26.1)	3 (42.9)	
Liposarcoma	65 (62.5)	35 (68.6)	29 (63.0)	1 (14.3)	
Other	11 (10.6)	3 (5.9)	5 (10.9)	3 (42.9)	

Treatment characteristics

Table 3.

	All, n (%)	Right, n (%)	Left, n (%)	Bilateral/Midline, n (%)	p-value
Surgery	106 (100)	52 (100)	47 (100)	7 (100)	
Median Time to Surgery in Months (IQR)	1.4 (3.6)	1.2 (2.9)	1.4 (5.8)	3.5 (6.9)	0.15
Neoadjuvant Radiation					0.72
No	87 (82.1)	44 (84.6)	37 (78.7)	6 (85.7)	
Yes	19 (17.9)	8 (15.4)	10 (21.3)	1 (14.3)	
Neoadjuvant Chemotherapy					0.06
No	89 (84.0)	47 (90.4)	38 (80.9)	4 (57.1)	
Yes	17 (16.0)	5 (9.6)	9 (19.2)	3 (42.9)	
Margin Status					0.49
Negative	47 (44.8)	24 (46.2)	19 (41.3)	4 (57.1)	
Positive	24 (22.9)	14 (26.9)	10 (21.7)	0	
Unknown	34 (32.4)	14 (26.9)	17 (37.0)	3 (42.9)	
Re-excision for Positive Margins					
No	106 (100)	52 (100)	47 (100)	7 (100)	0.32
Local Recurrence					
No	56 (52.8)	24 (46.2)	27 (57.5)	5 (71.4)	
Yes	50 (47.2)	28 (53.9)	20 (42.6)	2 (28.6)	0.86
Post-operative Complications					
No	55 (51.9)	26 (50.0)	24 (51.1)	5 (71.4)	
Yes	25 (23.6)	12 (23.1)	12 (25.5)	1 (14.3)	
Unknown	26 (24.5)	14 (26.9)	11 (23.4)	1 (14.3)	0.68
Post-operative Radiation					
No	89 (84.0)	42 (80.8)	41 (87.2)	6 (85.7)	
Yes	17 (16.0)	10 (19.2)	6 (12.8)	1 (14.3)	0.58
Post-operative Chemotherapy					
No	97 (91.5)	49 (94.2)	42 (89.4)	6 (85.7)	
Yes	9 (8.5)	3 (5.8)	5 (10.6)	1 (14.3)	

IQR = interquartile range

Table 4.

Associated organ resection

	All, n (%)	Right, n (%)	Left, n (%)	Bilateral/Midline, n (%)	p-value
Any contiguous organ resected?					0.42
No	36 (34.6)	16 (32.0)	16 (34.0)	4 (57.1)	
Yes	68 (65.4)	34 (68.0)	31 (66.0)	3 (42.9)	
Multiple Organs Resected					0.89
No	65 (61.3)	31 (59.6)	30 (63.8)	4 (57.1)	
Yes	41 (38.7)	21 (40.4)	17 (36.2)	3 (42.9)	
Stomach					0.686
No	102 (96.2)	49 (94.2)	46 (97.9)	7 (100)	
Yes	2 (1.89)	1 (1.9)	1 (2.1)	0 (0)	
Unknown	2 (1.9)	2 (3.9)	0 (0)	0 (0)	
Gallbladder					0.69
No	96 (90.6)	45 (86.5)	46 (97.9)	5 (71.4)	
Yes	8 (7.6)	5 (9.6)	1 (2.1)	2 (28.6)	
Unknown	2 (1.9)	2 (3.9)	0 (0)	0 (0)	
Kidney					0.06
No	53 (50)	20 (38.5)	26 (55.3)	7 (100)	
Yes	51 (48.1)	30 (57.7)	21 (44.7)	0 (0)	
Unknown	2 (1.9)	2 (3.9)	0 (0)	0 (0)	
Adrenal					0.02*
No	74 (69.8)	32 (61.5)	35 (74.5)	7 (100)	
Yes	30 (28.3)	18 (34.6)	12 (25.5)	0 (0)	
Unknown	2 (1.9)	2 (3.9)	0 (0)	0 (0)	
Pancreas					0.17
No	92 (86.8)	49 (94.2)	39 (83.0)	4 (57.1)	
Yes	12 (11.3)	1 (1.9)	8 (17.0)	3 (42.9)	
Unknown	2 (1.9)	2 (3.9)	0 (0)	0 (0)	
Pancreatoduodenectomy					<0.01*
No	101 (95.3)	49 (94.2)	47 (100)	5 (71.4)	

	All, n (%)	Right, n (%)	Left, n (%)	Bilateral/Midline, n (%)	p-value
Yes	3 (2.83)	1 (1.9)	0 (0)	2 (28.6)	< 0.001 *
Unknown	2 (1.9)	2 (3.9)	0 (0)	0 (0)	
Spleen					
No	93 (87.7)	50 (96.2)	37 (78.7)	6 (85.7)	0.122
Yes	11 (10.4)	0 (0)	10 (21.3)	1 (14.3)	
Unknown	2 (1.9)	2 (3.9)	0 (0)	0 (0)	
Small bowel					0.380
No	95 (89.6)	48 (92.3)	42 (89.4)	5 (71.4)	
Yes	9 (8.5)	2 (3.9)	5 (10.6)	2 (28.6)	
Unknown	2 (1.9)	2 (3.9)	0 (0)	0 (0)	0.380
Colon					
No	86 (81.1)	42 (80.8)	37 (78.7)	7 (100)	
Yes	18 (17.0)	8 (15.4)	10 (21.3)	0 (0)	0.380
Unknown	2 (1.9)	2 (3.9)	0 (0)	0 (0)	

Table 5.

Hazard ratios for recurrence.

	Unadjusted Hazard Ratio	95% CI	Adjusted** Hazard Ratio	95% CI
Right	Reference		Reference	
Left	1.000	0.557 – 1.795	1.336	0.626 – 2.853
Bilateral/Midline	0.879	0.205 – 3.773	8.588	0.806 – 91.540

** Adjusted for age, sex, race, grade, stage, histology and treatment

Table 6.

Cancer-specific hazard ratios for death.

	Unadjusted Hazard Ratio	95% CI	Adjusted** Hazard Ratio	95% CI
Right	Reference		Reference	
Left	0.921	0.370 – 2.295	2.019	0.565 – 7.220
Bilateral/Midline	0.672	0.086 – 5.231	0.522	0.028 – 9.904

** Adjusted for age, sex, race, grade, stage, histology and treatment