Second Primary Malignancies in Patients with Well-differentiated/Dedifferentiated Liposarcoma

ERIC JUNG¹, MARCO FIORE², ALESSANDRO GRONCHI², VALERIE GRIGNOL³, RAPHAEL E. POLLOCK³, SUSAN S. CHONG¹, SHEFALI CHOPRA⁴, ANN S. HAMILTON⁵ and WILLIAM W. TSENG¹

Departments of ¹Surgery, and ⁵Preventive Medicine, University of Southern California, Keck School of Medicine, Los Angeles, CA, U.S.A.;

²Department of Surgery, IRCCS Foundation National Tumor Institute, Milan, Italy;

³Department of Surgery, The James Comprehensive Cancer Center, Ohio State University, Columbus, OH, U.S.A.;

⁴Discovery Research Program, Department of Pathology and Laboratory Medicine, University of Southern California, Los Angeles, CA, U.S.A.

Abstract. *Background:* Well-differentiated/dedifferentiated (WD/DD) liposarcoma is a rare malignancy of putative adipocyte origin. To our knowledge, there have only been isolated case reports describing second primary cancer in patients with this disease. We report on a combined case series of such patients and explore the frequency of this occurrence using a national cancer database. *Materials and Methods:* Demographics and clinicopathological data were collected from patients with WD/DD liposarcoma who were found to have a concurrent or subsequent second primary cancer, at one of three sarcoma referral centers from 2014-2016. The Surveillance, Epidemiology and End Results (SEER) database was also queried to identify adult patients diagnosed with WD/DD liposarcoma between 1973-2012. Observed/expected (O/E) ratios of second primary malignancies among these cases were calculated by comparison to the age-adjusted cancer incidence in the general population using SEER*stat software. *Results:* In total, 26 out of 312 consecutive patients (8.3%) with WD/DD liposarcoma at our centers had a second primary cancer identified within 2 years of liposarcoma diagnosis. In the SEER database, among 1,845 patients with WD/DD liposarcoma, 75 (4.1%) had a second cancer within 2 years after liposarcoma diagnosis (O/E ratio=1.81, 99% confidence interval(CI)=1.33-

2.40). Patients less than 50 years old at the time of liposarcoma diagnosis had a higher O/E ratio for second primary malignancy compared to older patients. A total of 269 patients (14.6%) developed a second cancer (O/E=1.33, 99% CI=1.15-1.54). Conclusion: In some patients with WD/DD liposarcoma, there appears to be an increased risk of having a second primary cancer. Further validation and investigation is needed, as this finding may have implications (e.g. closer screening) for patients with this disease.

Well-differentiated/dedifferentiated (WD/DD) liposarcoma is a rare malignancy of putative adipocyte origin (1). WD/DD liposarcoma represents a disease spectrum ranging from WD tumors that are low grade and indolent to DD tumors that are high grade and can be aggressive. Both WD and DD liposarcoma exhibit a common amplification of chromosome 12q13-15, which includes genes MDM2 proto-oncogene (an inhibitor of the tumor suppressor gene p53) and cyclin-dependent kinase 4 (CKD4) (a critical regulator of cell cycling) (2). This is characteristic and diagnostic of the disease. There are no known risk factors (e.g. no association with any lifestyle, environmental, or socioeconomic factors) and to date, a genetic predisposition has not been reported.

Clinical management of WD/DD liposarcoma can be very challenging. These tumors tend to occur in deep-tissue spaces such as the retroperitoneum, where they can reach massive size, typically 20-30 cm. Surgery is the mainstay of treatment; however, complete resection is difficult due to tumor size, location, and potential involvement of nearby vital organs and critical structures. WD/DD liposarcoma has a high risk of locoregional recurrence even after apparent complete resection; tumors with evidence of DD also have the potential for distant metastasis (3). To date, radiation therapy and chemotherapy have not been shown to be effective. After treatment (e.g. surgery), close surveillance

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Correspondence to: William W Tseng, MD, Assistant Professor of Surgery, Department of Surgery, Section of Surgical Oncology, University of Southern California, Keck School of Medicine, 1510 San Pablo Street, HCC-I Suite 514, Los Angeles, CA 90033, U.S.A. Tel: +1 3238651535, Fax: +1 3238650164, e-mail: william.tseng@med.usc.edu

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with cross-sectional imaging is critical. Guidelines for surveillance exist for sarcoma in general, however, there are none specific for WD/DD liposarcoma.

Previous unpublished data from one of the authors (WWT) of our group suggested a higher frequency of second primary malignancies in patients with WD/DD liposarcoma. In order to assess this finding in a systematic manner, we used two datasets. Firstly, we explored the frequency of second cancer among case series of patients with WD/DD liposarcoma at three sarcoma referral centers, two in the United States (US) and one in Europe, and report the frequency of second cancer in our combined case series. Secondly, we assessed the observed *versus* expected occurrence of second cancer among WD/DD liposarcoma cases included in a population-based US national cancer registry database. We hypothesized that this occurrence would be more than would be expected by chance.

Materials and Methods

Consecutive cases of primary incident WD/DD liposarcoma diagnosed between 2014-2016 were combined from three sarcoma referral centers: University of Southern California, including affiliated hospitals under the Sarcoma Program in Los Angeles, CA, USA; The James Comprehensive Cancer Center of Ohio State University in Columbus, OH, USA; and the IRCCS Foundation National Tumor Institute in Milan, Italy.

Demographic and clinicopathological data were collected for patients with WD/DD liposarcoma who were found to have a second primary cancer either concurrently or within 2 years of liposarcoma diagnosis. Each center also provided the total number of consecutive patients with WD/DD liposarcoma seen during the same time period.

The United States National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database was also utilized. The SEER program is a comprehensive source of population-based cancer registry data that includes patient demographics, primary tumor site and histology, and other information provided by cancer registries across the country. All adult patients were selected from nine combined SEER registries who were diagnosed with WD/DD liposarcoma [International Classification of Diseases for Oncology, 3rd edition (4) (ICD-O-3) histology codes 8851.3 for WD and 8858.3 for DD] between 1973-2012. Myxoid liposarcoma (ICD-O-3 code 8852.3) was not included in our study. Patients diagnosed with liposarcoma not otherwise specified (ICD-O-3 code 8850.3) were also excluded to prevent other forms of liposarcoma (*e.g.* pleomorphic) and benign lipomas from being inadvertently included in our analysis. Using this set of nine combined registries covered approximately 9.4% of the total US population based on the 2010 census, and included the largest number of total cases of WD/DD liposarcoma in the SEER database at the time of our study, based on total years of diagnosis (5).

For the SEER database, observed/expected (O/E) ratios of concurrent or subsequent primary malignancies were calculated by comparing the number observed to the number that would have been expected based on the age-adjusted cancer incidence in the general population using the multiple primary standardized incidence ratio (MIP-SIR) session of SEER*stat software. MP-SIR is a method used to perform multiple primary analyses and to test hypotheses that

explore theoretical links in the etiology of two cancers. A defined cohort of persons previously diagnosed with cancer is followed through time to compare their incidence of second primary malignancies (based on SEER coding rules) to the expected incidence of second primary malignancies in the general population. A 99% confidence interval for the O/E ratio was calculated ($p < 0.01$), where a statistically significant confidence interval was one that excluded an O/E ratio of 1. Of note, the O/E ratio measures the number of tumors, not patients. A single patient may have contributed more than one subsequent primary tumor; this distinction was noted in the results. Cases where the diagnosis of WD/DD liposarcoma was made only by death certificate or autopsy were excluded.

Results

Case series. From 2014 to 2016, from three sarcoma referral centers, there was a total of 26 out of 312 (8.3%) consecutive patients with a second primary cancer either concurrent or within 2 years after WD/DD liposarcoma diagnosis. An example of one case is shown in Figure 1. The combined data including second cancer diagnoses are listed in Table I. The frequency of second cancer was 3.1% (three out of 96) at Ohio State University, 8.9% (16 out of 178) at the Milan National Tumor Institute and 18% (seven out of 38) at the University of Southern California.

SEER data. From the SEER database, 1,845 patients (61.0% male) were identified with the diagnosis of WD/DD LPS between 1973 and 2012. A total of 1,345 patients (60.0% male) were diagnosed with WD LPS, while 500 patients (63.0% male) were diagnosed with DD LPS. Among them, 75 (4.1%) had 80 concurrent or subsequent additional primary malignancies within 2 years (23 months) of liposarcoma diagnosis (1.47 mean person-years at risk). This represents a statistically significant O/E ratio of 1.81 (99% CI=1.33-2.40, $p < 0.01$). For patients under the age of 50 years at initial diagnosis, a higher O/E ratio of 4.94 (99% CI=4.83-5.06, $p < 0.01$) was observed compared to patients aged 50 years or more (O/E ratio=1.66, 99% CI=1.65-1.67). Males had a higher O/E ratio of 6.49 for those younger than 50 years (99% CI=6.24-6.75), while females had a higher O/E ratio of 2.02 for those aged 50 years and older (99% CI=2.00-2.04).

A total of 269 (14.6%) patients had 314 concurrent or subsequent additional primary cancer at any point following liposarcoma diagnosis. Mean person-years at risk was 6.52. This was also statistically significant, with an O/E ratio of 1.33 (99% CI=1.15-1.54, $p < 0.01$). The O/E ratio for the occurrence of second primary cancer for patients under the age of 50 years at initial diagnosis was 1.73 (99% CI=1.71-1.75, $p < 0.01$), while that for patients aged 50 years or more was 1.14 (99% CI=1.13-1.14, $p < 0.01$). The most common locations of second cancer and associated O/E ratios are shown in Table II. The highest O/E ratios were associated with second cancer in the retroperitoneum, testis, soft tissues, and kidney diagnosed within 2 years of the LPS diagnosis.

Figure 1. Example of a patient with de-differentiated liposarcoma and concurrent gall bladder adenocarcinoma. Coronal computed tomographic scan showing large liposarcoma (circled) in the right retroperitoneum (a). Histological images confirming the diagnosis of liposarcoma (b) and gallbladder adenocarcinoma (c).

Table I. Combined case series data from three referral centers for patients with liposarcoma (LPS) and a second primary cancer.

Center	Age, years	Gender	LPS subtype	LPS location	Second primary cancer diagnosis	Time interval between LPS and second cancer
USC	59	M	WD	RP/pelvis	T-Cell lymphoma	Concurrent
USC	74	M	WD	RP/pelvis	Prostate cancer	Concurrent
USC	67	M	DD	Ant. abdomen	Papillary thyroid carcinoma	Concurrent
USC	68	M	DD	RP/pelvis	Gallbladder carcinoma	Concurrent
USC	47	M	DD	RP/pelvis	Renal cell carcinoma	24 Months
USC	63	M	DD	SBM	Sigmoid colon carcinoma	Concurrent
USC	58	M	WD	RP/pelvis	Renal angiomyolipoma, GIST	Concurrent
Milan	35	M	WD	RP	Pheochromocytoma	Concurrent
Milan	68	F	DD	RP	Breast cancer	Concurrent
Milan	80	M	DD	RP	Neuroendocrine tumor	Concurrent
Milan	60	F	WD	RP	Lung cancer	
Milan	40	F	DD	RP	GIST	Concurrent
Milan	77	M	DD	RP	Multiple myeloma	Concurrent
Milan	59	F	DD	RP	Granular cell tumor of the ovary	Concurrent
Milan	75	M	DD	RP	Head and neck cancer (pharynx)	1 Month
Milan	67	F	DD	RP	Lung cancer (bronchioloalveolar carcinoma)	4 Months
Milan	68	M	WD	Upper leg	Prostate cancer	Concurrent
Milan	71	M	WD	RP	Renal cancer	Concurrent
Milan	63	F	DD	RP	PIN	Concurrent
Milan	68	F	WD	RP	PIN and renal cancer	Concurrent
Milan	71	M	WD	Spermatic cord	Renal cell carcinoma	2 Months
Milan	82	F	DD	RP	Chronic lymphocytic leukemia	Concurrent
Milan	54	F	DD	RP	Mesenteric non-Hodgkin lymphoma	
Ohio	71	F	WD	RP/pelvis	Follicular lymphoma	11 Months
Ohio	69	M	DD	RP/pelvis	RP leiomyosarcoma, small bowel endocrine tumor, ascending colon cancer	22 Months, 28 months
Ohio	64	M	WD	Ant. abdomen	hepatocellular cancer	Concurrent

M: Male, F: female, LPS: liposarcoma, WD: well-differentiated, DD: de-differentiated, RP: retroperitoneum, Ant.: anterior, SBM: small bowel mesentery, GIST: gastrointestinal stromal tumor, PIN: Pancreatic intraepithelial neoplasia; USC: University of Southern California.

Table II. Risk of subsequent primary cancer after well-differentiated (WD)/de-differentiated, (DD) liposarcoma, SEER 1973-2012.

	Months after WD/DD liposarcoma diagnosis								
	0-23		24-59		60+		Total		
Persons starting interval	1,845		1,396		1,004		1,845		
Person-years in interval at risk	3,175		3,535		8,022		14,732		
Subsequent primary cancer	O	O/E	O	O/E	O	O/E	O	O/E	EAR
All sites	80	1.81	61	1.17	173	1.24	314	1.33	53.1
All sites excluding non-melanoma skin	79	1.80	61	1.18	172	1.24	312	1.33	52.36
All solid tumors	72	1.83	52	1.12	154	1.24	278	1.32	46.29
Oral cavity and pharynx	0	0	1	0.79	3	0.96	4	0.72	-1.03
Digestive system	17	1.92	14	1.33	39	1.35	70	1.45	14.68
Esophagus	1	1.84	0	0	5	2.89	6	2.06	2.09
Stomach	3	3.44	4	3.83	3	1.03	10	2.07	3.51
Small intestine	2	11.35	0	0	1	1.7	3	3.09	1.38
Colon, rectum and anus	3	0.59	5	0.82	10	0.61	18	0.65	-6.44
Liver, gallbladder, intrahepatic bile duct and other biliary	1	1.12	0	0	2	0.69	3	0.62	-1.24
Liver	0	0	0	0	1	0.59	1	0.35	-1.27
Gallbladder	0	0	0	0	0	0	0	0	-0.42
Intra/extrahepatic bile ducts, and other biliary	1	4.15	0	0	1	1.22	2	1.48	0.44
Other biliary	1	5.97	0	0	0	0	1	1.07	0.04
Pancreas	3	2.51	1	0.7	4	0.98	8	1.2	0.89
Retroperitoneum	3	88.00	4	103.30	13	131.70	20	116.60	13.46
Peritoneum, omentum and mesentery	1	29.52	0	0	1	8.87	2	10.69	1.23
Other digestive organs	0	0	0	0	0	0	0	0	-0.2
Respiratory system	8	1.12	9	1.06	26	1.13	43	1.11	2.91
Nose, nasal cavity and middle ear	0	0	0	0	0	0	0	0	-0.22
Larynx	1	2.25	0	0	1	0.77	2	0.89	-0.18
Pleura	0	0	0	0	0	0	0	0	-0.01
Lung, bronchus, trachea, mediastinum and other respiratory organs	7	1.05	9	1.14	25	1.16	41	1.14	3.32
Lung and bronchus	7	1.05	8	1.02	25	1.16	40	1.11	2.69
Trachea	0	0	0	0	0	0	0	0	-0.02
Mediastinum and other respiratory organs	0	0	1	152.46	0	0	1	34.29	0.66
Bones and joints	1	24.36	1	21.53	2	17.39	4	19.75	2.58
Soft tissue including heart	3	14.02	1	4.01	14	20.85	18	15.86	11.45
Skin excluding basal and squamous	5	2.89	0	0	11	2.1	16	1.79	4.78
Melanoma of the skin	4	2.55	0	0	10	2.13	14	1.74	4.04
Other non-epithelial skin	1	6.22	0	0	1	1.8	2	2.2	0.74
Breast	3	0.75	4	0.85	10	0.83	17	0.82	-2.51
Female breast	3	0.76	4	0.87	9	0.76	16	0.79	-2.96
Male breast	0	0	0	0	1	4.81	1	2.88	0.44
Female genital system	1	0.62	1	0.53	4	0.85	6	0.73	-1.49
Cervix uteri	0	0	0	0	0	0	0	0	-0.55
Corpus and uterus, NOS	1	1.15	1	0.99	2	0.8	4	0.91	-0.26
Corpus uteri	1	1.17	1	1.01	2	0.82	4	0.94	-0.19
Uterus, NOS	0	0	0	0	0	0	0	0	-0.07
Ovary	0	0	0	0	2	1.51	2	0.88	-0.19
Vagina	0	0	0	0	0	0	0	0	-0.09
Vulva	0	0	0	0	0	0	0	0	-0.3
Other female genital organs	0	0	0	0	0	0	0	0	-0.1
Male genital system	20	2.06	12	1.04	25	0.81	57	1.1	3.42
Prostate	17	1.77	11	0.97	23	0.76	51	0.99	-0.26
Testis	2	32.01	0	0	0	0	2	8.5	1.2
Penis	0	0	0	0	0	0	0	0	-0.17
Other male genital organs	1	58.73	1	49.9	2	36.93	4	43.85	2.65
Urinary system	12	3.08	8	1.74	16	1.27	36	1.71	10.13
Urinary bladder	5	1.95	5	1.65	8	0.96	18	1.29	2.74
Kidney and renal pelvis	7	5.68	2	1.4	8	2.08	17	2.61	7.12

Table II. Continued

Table II. *Continued*

Subsequent primary cancer	O	O/E	O	O/E	O	O/E	O	O/E	EAR
Renal pelvis, ureter and other urinary	0	0	1	3.97	0	0	1	0.86	-0.11
Kidney	7	6.20	2	1.54	8	2.27	17	2.86	7.5
Renal pelvis	0	0	0	0	0	0	0	0	-0.38
Ureter	0	0	1	12.17	0	0	1	2.65	0.42
Other urinary organs	0	0	0	0	0	0	0	0	-0.15
Eye and orbit	0	0	0	0	1	5.35	1	3.06	0.46
Eye and orbit-non-melanoma	0	0	0	0	0	0	0	0	-0.04
Eye and orbit – melanoma	0	0	0	0	1	6.65	1	3.77	0.5
Brain and other nervous system	0	0	1	1.92	1	0.77	2	0.88	-0.19
Brain	0	0	1	2.01	1	0.8	2	0.92	-0.12
Cranial nerves other nervous system	0	0	0	0	0	0	0	0	-0.07
Endocrine system	3	6.21	0	0	3	2.32	6	2.59	2.5
Thyroid	3	6.77	0	0	3	2.55	6	2.84	2.64
Thymus, adrenal gland and other endocrine	0	0	0	0	0	0	0	0	-0.14
All lymphatic and hematopoietic diseases	6	1.64	8	1.86	15	1.27	29	1.47	6.29
Lymphoma	4	2.18	1	0.47	5	0.86	10	1.02	0.15
Hodgkin lymphoma	0	0	0	0	0	0	0	0	-0.37
Non-Hodgkin lymphoma	4	2.32	1	0.49	5	0.91	10	1.08	0.51
Nodal	4	3.41	0	0	2	0.54	6	0.96	-0.18
Extranodal	0	0	1	1.55	3	1.68	4	1.34	0.69
Myeloma	0	0	2	2.77	6	2.88	8	2.34	3.11
Leukemia	2	1.66	5	3.51	4	1.02	11	1.68	3.03
Lymphocytic leukemia	2	3.28	2	2.79	1	0.51	5	1.53	1.17
Acute	0	0	0	0	0	0	0	0	-0.12
Chronic	2	3.76	2	3.2	1	0.58	5	1.73	1.44
Other	0	0	0	0	0	0	0	0	-0.15
Non-lymphocytic leukemia	0	0	3	4.24	3	1.53	6	1.84	1.86
Acute	0	0	2	4.43	2	1.6	4	1.92	1.3
Myeloid and monocytic leukemia	0	0	3	4.9	3	1.78	6	2.13	2.16
Acute myeloid leukemia	0	0	2	5.25	2	1.88	4	2.26	1.52
Acute monocytic leukemia	0	0	0	0	0	0	0	0	-0.07
Chronic myeloid leukemia	0	0	1	5.44	1	1.99	2	2.37	0.79
Mesothelioma	0	0	0	0	0	0	0	0	-0.48
Kaposi sarcoma	0	0	0	0	0	0	0	0	-0.16
Miscellaneous	1	1.05	1	0.86	3	0.94	5	0.94	-0.22

E: Expected number of subsequent primary cancers; O/E: ratio of observed to expected cancers; EAR: excess absolute risk per 10,000 person-years= $[(O-E)/\text{person-years at risk}] \times 10,000$.

Discussion

In this study, we found that there was an increased risk of a second primary cancer in patients with WD/DD liposarcoma, especially among males diagnosed under 50 years of age. There are numerous previous case reports of concurrent cancer (Table III) (6-20) in WD/DD liposarcoma which add further evidence to support our observation; however, to our knowledge, the current study is the first to report data from a large case series and provide data from analysis of a national population-based cancer database to assess this occurrence.

This study raises questions regarding the etiology of second primary cancer in patients with WD/DD liposarcoma. The younger group (<50 years old) in the SEER database

had a higher O/E ratio for second cancer, especially for those occurring within 2 years. WD/DD liposarcoma is characterized by 12q13-15 amplification, a hallmark genetic feature in this disease. While there are no known genetic cancer syndromes associated with 12q13-15 amplification, liposarcoma has been infrequently reported in select patients with Li-Fraumeni syndrome and neurofibromatosis (9, 21-23). There are no other defined genetic cancer syndromes associated with a higher risk of liposarcoma to our knowledge. Interestingly, a recent study by Ballinger *et al.* found that in a large combined cohort of 1,162 patients with sarcoma, using targeted exon sequencing, more than half were actually found to have an excess of pathogenic germline monogenic and polygenic variants (24). These variants were associated with earlier age of onset, and

Table III. Case reports in the literature on well-differentiated (WD)/de-differentiated, (DD) liposarcoma (LPS) and second primary malignancies (6-20).

First author (Ref)	Year	Age, years	LPS subtype	LPS location	Second primary cancer diagnosis
Christodoulidou <i>et al.</i> (6)	2015	60	DD	Paratesticular	Paratesticular angiolipoma (contralateral)
Hoshi <i>et al.</i> (7)	2014	34	WD*	Retroperitoneum	Clear cell renal cell carcinoma
Frank and Velasco (8)	2013	74	DD	Retroperitoneum	Papillary cell renal cell carcinoma
Coyle <i>et al.</i> (9)	2013	69	DD	Paratesticular	Prostate adenocarcinoma and unilateral renal cell carcinoma
Saleh <i>et al.</i> (10)	2013	62	WD	Esophageal	Hurthle cell carcinoma of right thyroid
Kast <i>et al.</i> (11)	2012	40	DD/WD	Unspecified	Myxofibrosarcoma of right arm, bilateral breast cancer
Borriello <i>et al.</i> (12)	2012	59	WD/myxoid	Axilla	Breast cancer
Demirci <i>et al.</i> (13)	2010	69	WD	Paratesticular	Prostate adenocarcinoma
Kinebuchi <i>et al.</i> (14)	2009	60	WD	Peri-renal	Clear cell renal cell carcinoma
Jeong <i>et al.</i> (15)	2009	68	WD	Buttock	Amelanotic melanoma
Williamson <i>et al.</i> (16)	2008	79	WD	Retroperitoneum	Papillary cell renal cell carcinoma
Hatano <i>et al.</i> (17)	2007	78	WD	Spermatic cord	Adenocarcinoma of rectum
Hirata <i>et al.</i> (18)	2006	40	WD	Thigh	Urothelial bladder cell cancer, rectal cancer. MSH2 mut. in HNPCC
Galazka <i>et al.</i> (19)	2003	58	DD	Cardiac (by autopsy)	Papillary cell renal cell carcinoma
Lewis <i>et al.</i> (20)	1994	71	WD	Perirenal	Granular cell renal cell carcinoma

MSH2 mut.: Mutation in DNA mismatch repair protein Msh2; HNPCC: hereditary nonpolyposis colorectal cancer. *WD on pathology, myxoid on magnetic resonance imaging.

suggested that a large percentage of sarcomas may in fact have some underlying hereditary and genetic component. These findings were supported by Chan *et al.* in a similar study of an Asian cohort of patients with sarcoma, which found that 13.6% of patients with sporadic sarcomas exhibited at least one pathogenic germline mutation in 10 cancer-associated genes (25).

It is also possible that the occurrence of a second cancer in patients with WD/DD liposarcoma may have another etiology. The amplified locus at 12q13-15 contains several genes overexpression of which may account for the development of some of the secondary cancers. Alternatively, the presence of liposarcoma, especially given its often large tumor size, may induce systemic immune responses (*e.g.* relative immunosuppression) that predisposes the patient to the development of a second cancer. Interestingly, both the current SEER*stat analysis (Table II) and case reports in the literature (Table III) show that these second primary cancers often occur in the genitourinary system. Specifically, concurrent renal cell carcinoma is frequently observed. While this may be a sampling bias as the ipsilateral kidney is often removed along with retroperitoneal liposarcoma during surgery, this could also be due to local immune responses in the kidney being shifted to a pro-tumorigenic bias due to the large, adjacent liposarcoma. These hypotheses deserve further study, and may also be relevant to other, more common cancer types.

The true frequency of a second primary cancer in WD/DD liposarcoma is currently unknown and cannot be definitively derived from this study. In general, it is recognized that all

patients with cancer, regardless of cancer site, have a somewhat increased risk of developing another primary cancer during their lifetime. In reported epidemiological studies, this frequency ranges from 1% for liver cancer up to 16% for bladder cancer (26, 27). One study found a cumulative incidence of second cancer in all cancer survivors (of any cancer type) to be 5.0% at 5 years and up to 13.7% at 25 years. Our analysis of the SEER database suggests that the lifetime risk of developing a second cancer in patients with WD/DD liposarcoma (14.6%) is in concordance with these prior reports and positions these patients at or beyond the higher end of this frequency range. Interestingly, a post-hoc survey of a large online patient support group for liposarcoma ("Liposarcoma Survivors" on Facebook) was performed from Feb-Aug 2017. Among 134 members with WD/DD liposarcoma that responded to the survey, 26 (19%) reported responded "yes" to ever having a history of a second cancer. Ten of these patients (8% total) reported the identification of the second non-liposarcoma cancer concurrently or within 2 years of the liposarcoma diagnosis, similar to the results in this study.

The true timing of a second primary cancer in relation to WD/DD liposarcoma is also unclear. Liposarcomas are usually very large at the time of detection, with a typical size of 20-30 cm. In fact, these are probably the largest tumors in the human body (see Figure 1) (28). The growth rate and progression of liposarcoma prior to detection is poorly defined, and therefore it is possible that these tumors may have been present in a smaller, clinically occult form while the other cancer was detected (and even treated) or *vice versa*.

Overall, the findings reported in the current study are intended to increase awareness of this occurrence and stimulate deeper investigation through research into this rare disease. Clinically, closer screening for the possibility of a second cancer should be incorporated into the management of patients with WD/DD liposarcoma. Ultimately, if our observations are validated, surveillance algorithms may need to be specifically modified to incorporate this risk.

Conclusion

In this study, we observed that there was an increased risk of second malignancy in some patients with WD/DD liposarcoma, especially those diagnosed under 50 years of age. These findings are based on data from a combined case series of patients with sarcoma and supported by analysis of a national population-based cancer database. Further validation is needed and laboratory-based investigation is warranted to provide insight into etiology.

Disclosures

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