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Original Research

Ovarian conservation without postoperative radiation improved survival outcomes in patients with stage i uterine leiomyosarcoma

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Summary

Introduction: Little observational data exists regarding the efficacy of different treatment modalities on the survival outcome of patients with uterine leiomyosarcoma. *Objective and Design:* This is a retrospective cohort study using the Surveillance, Epidemiology, and End Results database to identify surgery-based treated patients with uterine leiomyosarcoma diagnosed between 1982 to 2015 (N = 4289). The associations between survival outcomes and treatment modalities regarding postoperative radiation and ovarian conservation were assessed. *Results:* A total of 1104 patients were included in the study, 19.02% (210/1104) patients received postoperative radiation, 11.59% (128/110) patients received ovarian conservation. The median follow-up duration was 37.27 ± 34.69 months (95%CI: 35.39-39.38 months). After propensity score matching, there were no variable differences among compared groups. For FIGO stage I-II patients, postoperative radiation did not improve five-year-overall survival (49.1 *vs.* 47.1%, $p = 0.818$) and five-year-cause-specific survival (51.5 *vs.* 49.9%, $p = 0.910$). For International Federation of Gynecology and Obstetrics stage I patients who were younger than 50 years old, five-year-overall survival (75.4 *vs.* 60.3%, $p = 0.053$) and five-year-cause-specific survival (75.4 *vs.* 65.1%, $p = 0.146$) were similar between women underwent ovarian conservation and those who did not. However, after excluding patients who received radiotherapy, patients showed a better survival outcome than control group (five-year-overall survival: 76.3 *vs.* 54.0%, $p = 0.031$; five-year-cause-specific survival: 76.30 *vs.* 55.3%, $p = 0.046$). *Conclusions:* In women with stage I-II uterine leiomyosarcoma, postoperative radiation did not improve five-year-overall-survival and five-year-cause-specific survival. In young women with stage I uterine leiomyosarcoma who didn't receive postoperative radiotherapy, ovarian conservation was associated with increased overall survival and cause-specific survival.

Key words: Uterine leiomyosarcoma; Ovarian conservation; Postoperative radiation; Propensity score matching.

Introduction

Uterine leiomyosarcoma (uLMS) is the most common histologic subtypes that accounts for approximately 63% of uterine sarcoma [1]. Despite the rare occurrence, the proportion of patients suffered from uterine sarcoma increased over the years. In 2017, an estimated 4910 new cases of uterine sarcoma are anticipated [2]. For women with early-stage leiomyosarcoma, hysterectomy with/without bilateral salpingo-oophorectomy (BSO) is the initial treatment of choice [3]. However, treatment modalities regarding postoperative radiation and ovarian conservation remains controversial.

In regards to radiotherapy, a small but growing body of evidence has suggested that postoperative pelvic radiotherapy improves the local pelvic control but couldn't improve overall survival compared with control group [4-8]. As for ovarian conservation, in selected patients with early-stage uterine leiomyosarcoma who wish to retain hormonal function, the ovary/ovaries may be preserved [9]. Moreover, Kapp *et al.* showed that oophorectomy didn't improve five-year-cause-specific survival [10]. However, according to recent national comprehensive cancer network (NCCN) guidelines [3], these studies have limited quality, for the patients treated may had higher-risk factors (eg, larger tumors, deeper myometrial invasion), thus biasing the data against the treatment. Furthermore, these studies used the same previous International Federation of Gynecology and Obstetrics (FIGO) or American Joint Committee on Cancer (AJCC) staging systems of endometrial cancer, which were not appropriate for staging uterine leiomyosarcoma [11]. The new staging system for uterine leiomyosarcoma from FIGO took effect in 2009, accounting for the differences between uterine sarcoma and endometrial cancer [12].

Since the efficacy and safety of postoperative radiation and ovarian conservation in early stage patients remain uncertain in the existing studies, a more complete picture of the real-world clinical outcomes is needed. Therefore, we conducted a retrospective cohort study of 4289 patients to verify the safety of ovarian preservation in stage I patients and the roles of postoperative radiation and ovarian conservation in selected patients.

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Table 1. — *Clinicopathologic and Treatment Characteristics of Study Patients.*

Values	n = 1104 (%)	OS-HR	95% CI	*p*-value	CSS-HR	95% CI	*p*-value
Age at diagnosis (y)							
Younger than 35	24 (2.17)	1	-		1	-	
35-50	330 (29.89)	1.621	0.839-3.131	0.151	1.494	0.774-2.886	0.232
50–65	541 (49.00)	2.357	1.225-4.535	0.01	2.142	1.117-4.11	0.022
65 +	209 (18.93)	2.689	1.374-5.262	0.004	2.175	1.108-4.27	0.024
Ethnicity							
White	790 (71.56)	1	-		1	-	
Black	208 (18.84)	1.349	1.101-1.652	0.004	1.317	1.063-1.631	0.012
other	106 (9.60)	1.29	0.980-1.698	0.069	1.223	0.916-1.632	0.172
	Marital status						
Single	245 (22.19)	1	-	-	1	-	
Married	618 (55.98)	0.782	0.637-0.961	0.019	0.758	0.613-0.937	0.01
Separated,widowed,or divorced	241 (21.83)	0.977	0.763-1.249	0.85	0.93	0.718-1.204	0.582
Year at diagnosis							
2001-2010	547 (49.55)	1	-		1	-	
2011–2015	557 (50.45)	0.775	0.632-0.949	0.014	0.739	0.598-0.915	0.005
FIGO stage							
I	663 (60.05)	1	-	-	1		
II	163 (14.76)	2.007	1.597-2.522	< 0.001	1.998	1.574-2.536	< 0.001
III	127 (11.50)	2.893	2.182-3.836	< 0.001	2.65	2.028-3.462	< 0.001
IV	151 (13.68)	3.581	2.688-4.771	< 0.001	3.519	2.616-4.733	< 0.001
Grade							
Well differentiated	60 (5.43)	1	-	-	1	-	-
Moderately differentiated	157 (14.22)	0.847	0.499-1.440	0.541	0.93	0.518-1.668	0.807
Poorly differentiated	345 (31.25)	2.341	1.469-3.731	< 0.001	2.694	1.608-4.514	< 0.001
Undifferentiated	542 (49.09)	2.128	1.341-3.377	< 0.001	2.396	1.435-4.001	0.001
Tumor size (cm)							
5.0 or less	109 (9.87)	1	-	-	1	-	-
5.0-10.0	440 (39.86)	1.118	0.803-1.556	0.509	1.224	0.856-1.749	0.269
10.0-15.0	336 (30.43)	1.459	1044-2.038	0.027	1.597	1.113-2.291	0.011
15.0 or more	219 (19.84)	1.499	1.051-2.136	0.025	1.636	1.117-2.396	0.012
Surgery modality							
Hysterectomy and ovarian conservation	128 (11.59)	1	-	-	1	-	-
Hysterectomy and oophorectomy	842 (76.27)	1.362	0.998-1.857	0.051	1.298	0.947-1.779	0.105
Hysterectomy NOS	22 (2.00)	1.168	0.498-2.744	0.721	1.186	0.504-2.789	0.696
Radical hysterectomy or extension surgery	112 (10.14)	1.314	0.892-1.935	0.167	1.226	0.823-1.828	0.317
Radiation							
No radiation	894 (80.98)	1	-	-	1	-	-
Beam radiation	178 (16.12)	0.857	0.693-1.059	0.153	0.886	0.711-1.104	0.28
Beam radiation and implants	32 (2.90)	0.756	0.455-1.256	0.28	0.774	0.459-1.307	0.338
Lymphadectomy							
No	698 (4.80)	1	-	-	1	-	
Regional lymphadectomy	408 (95.20)	0.859	0.722-1.022	0.087	0.817	0.684-0.977	0.027
Lymph biopsy	1 (0.091)	0.001	2.52E-72-4.19E + 65	0.932	0.001	1.18E-74-8.218E + 67	0.934
Pariaortic lymphadectomy	2 (0.18)	2.507	0.346-18.170	0.363	2.589	0.357-18.793	0.347
Chemotherapy							
No	561 (50.82)	1	-	-	1	-	
Yes	543 (49.18)	1.121	0.938-1.340	0.21	1.166	0.967-1.405	0.107

Table 2. — *Baseline Characteristics of PSM Cohorts for Postoperative Radiation in Stage I-II Patients.*

Values	Before Matching		p	After Matching		p
	Postoperative Radiation (n = 172)	No Postoperative Radiation (n = 652)		Postoperative Radiation (n = 172)	No Postoperative Radiation (n = 167)	
Age at diagnosis (y)			Z = 1.728, $p = 0.084$			Z = 0.328, $p = 0.743$
Younger than 35	5	12		5	3	
35-50	59	206		59	59	
50–65	81	305		81	75	
65 +	27	129		27	30	
Ethnicity			Z = 1.508, $p = 0.132$			Z = 0.572, $p = 0.568$
White	128	479		128	121	
Black	29	107		29	25	
Other	15	66		15	21	
Marital Status			Z = 0.120, $p = 0.904$			Z = 0.675, $p = 0.500$
Single	31	140		31	39	
Married	106	362		106	93	
Separated, Widowed, Divorced	35	150		35	35	
Year at diagnosis			Z = 0.808, $p = 0.419$			Z = 0.428, $p = 0.668$
2000–2010	121	348		121	121	
2011–2015	51	304		51	46	
FIGO stage			Z = 0.637, $p = 0.524$			Z = 0.280, $p = 0.779$
IA	24	81		24	21	
IB	102	454		102	111	
IIA	7	15		7	2	
IIB	24	44		24	20	
II, NOS	15	58		15	13	
Grade			Z = 0.324, $p = 0.746$			Z = 0.508, $p = 0.611$
Well Differentiated	11	44		11	12	
Moderately Differentiated	24	109		24	26	
Poorly Differentiated	54	195		54	52	
Undifferentiated	83	304		83	77	
Tumor Size (cm)			Z = 1.658, $p = 0.092$			Z = 0.836, $p = 0.403$
5.0 or less	28	89		28	24	
5.0-10.0	78	261		78	72	
10.0-15.0	44	205		44	46	
15.0 or more	22	97		22	25	
Surgery Modality			Z = 1.267, $p = 0.205$			Z = 0.026, $p = 0.980$
Hysterectomy and Ovarian Conservation	17	89		17	20	
Hysterectomy and Oophorectomy	139	491		139	128	
Hysterectomy NOS	3	18		3	1	
Radical Hysterectomy or Extension Surgery	13	54		13	18	
Lymphadectomy			Z = 4.800, $p < 0.001$			Z = 0.289, $p = 0.773$
Yes	82	221		82	77	
No	90	431		90	90	
Chemotherapy			Z = 3.332, $p < 0.001$			Z = 1.009, $p = 0.313$
Yes	73	270		73	80	
No	99	382		99	87	

Table 3. — *Baseline Characteristics of PSM Cohorts for Ovarian Conservation in Stage I Patients.*

Values	Before Matching		*p*	After Matching		*p*
	Ovarian conservation (n = 68)	No Ovarian Conservation (n = 146)		Ovarian Conservation (n = 68)	No Ovarian Conservation (n = 59)	
Age at daignosis (y)			Z = 0.123, $p = 0.902$			Z = 0.294, $p = 0.769$
Younger than 35	3	7		3	2	
35-50	65	139		65	57	
Ethnicity			Z = 0.355, $p = 0.723$			Z = 0.321, $p = 0.748$
White	49	102		49	44	
Black	10	22		10	8	
Other	9	22		9	7	
Marital Status			Z = 0.029, $p = 0.977$			Z = 0.370, $p = 0.711$
Single	17	36		17	11	
Married	43	93		43	43	
Separated, Widowed, Divorced	8	17		8	5	
Year at diagnosis			Z = 0.381, $p = 0.704$			Z = 0.111, $p = 0.912$
2000–2010	41	84		41	35	
2011–2015	27	62		27	24	
FIGO stage			Z = 2.316, $p = 0.021$			Z = 1.643, $p = 0.100$
IA	20	23		20	10	
IB	48	123		48	49	
Grade			Z = 1.799, $p = 0.072$			Z = 0.844, $p = 0.398$
Well Differentiated	6	10		6	3	
Moderately Differentiated	24	27		24	15	
Poorly Differentiated	11	41		11	18	
Undifferentiated	27	68		27	23	
Tumor size (cm)			Z = 1.276, $p = 0.202$			Z = 1.029, $p = 0.304$
5.0 or less	20	24		20	11	
5.0-10.0	26	71		26	22	
10.0-15.0	16	39		16	21	
15.0 or more	6	12		6	5	
radiation			Z = 1.102, $p = 0.270$			Z = 0.705, $p = 0.481$
Observation	58	116		58	53	
Beam Radiation	9	22		9	4	
Beam Radiation and Implants	1	8		1	2	
Lymphadectomy			Z = 2.304, $p = 0.021$			Z = 0.145, $p = 0.885$
Yes	12	48		12	11	
No	56	98		56	48	
Chemotherapy			Z = 0.163, $p = 0.871$			Z = 0.731, $p = 0.465$
Yes	29	64		29	29	
No	39	82		39	30	

Table 4. — *Baseline Characteristics of PSM cohorts or Ovarian Conservation without Radiation in Stage I Patients.*

Values	Before Matching		*p*	After Matching		*p*
	Ovarian conservation (n = 58)	No Ovarian Conservation (n = 116)		Match-Ovarian conservation (n = 58)	No Ovarian Conservation (n = 50)	
Age at diagnosis (y)			Z = 0.255, $p = 0.799$			Z = 1.623, $p = 0.105$
Younger than 35	3	5		3	0	
35-50	55	111		55	50	
Ethnicity			Z = 1.016, $p = 0.309$			Z = 0.605, $p = 0.545$
White	43	77		43	34	
Black	8	21		8	10	
other	7	18		7	6	
Marital status			Z = 0.190, $p = 0.849$			Z = 0.018, $p = 0.986$
Single	15	28		15	13	
Married	36	74		36	31	
Separated, Widowed, Divorced	7	14		7	6	
Year at diagnosis			Z = 0.429, $p = 0.688$			Z = 0.536, $p = 0.592$
2000–2010	33	62		33	31	
2011–2015	25	54		25	19	
FIGO stage			Z = 1.956, $p = 0.051$			Z = 1.807, $p = 0.071$
IA	15	16		15	6	
IB	43	100		43	44	
Grade			Z = 1.322, $p = 0.186$			Z = 0.249, $p = 0.804$
Well Differentiated	6	8		6	6	
Moderately Differentiated	20	25		20	11	
Poorly Differentiated	9	33		9	15	
Undifferentiated	23	50		23	18	
Tumor size (cm)			Z = 0.990, $p = 0.322$			Z = 1.782, $p = 0.075$
5.0 or less	15	17		15	6	
5.0-10.0	23	55		23	20	
10.0-15.0	14	35		14	17	
15.0 or more	6	9		6	7	
Lymphadectomy			Z = 1.741, $p = 0.082$			Z = 0.620, $p = 0.535$
Yes	10	33		10	11	
No	48	83		48	39	
Chemotherapy			Z = 0.431, $p = 0.666$			Z = 0.893, $p = 0.372$
Yes	24	52		24	25	
No	34	64		34	25	

Table 5. — *Survival Outcomes of Different Local Modalities in Patients of Uterine Leiomyosarcoma.*

Values	5-y, OS (%)	95% CI (%)	p-value, Log-rank test	5-y, CSS (%)	95% CI (%)	p-value, Log-rank test
Postoperative radiation						
No	47.1	47.06, 47.12	$p = 0.818$	49.9	49.86, 49.94	$p = 0.910$
Yes	49.1	49.06, 49.14		51.5	51.47, 51.53	
Ovary conservation						
Yes	75.4	75.29, 75.51	$p = 0.053$	75.4	75.29, 75.51	$p = 0.146$
No	60.3	60.16, 60.44		65.1	64.96,65.24	
Ovary conservation without postoperative radiation						
Yes	76.3	76.18, 76.42	$p = 0.031$	76.3	76.18, 76.42	$p = 0.046$
No	54	53.84, 54.16		55.3	55.14, 55.46	

Materials and Methods

This study was a retrospective study involving data from patients with leiomyosarcoma registered in the Surveillance, Epidemiology, and End Results (SEER) registry (Third Edition, SEER 18 registry database November 2017 submission) [13] from 1982 to 2015. The SEER 18 database contains data from the SEER 9 registries (Atlanta, Georgia; Connecticut; Detroit, Michigan; Hawaii; Iowa; New Mexico; San Francisco-Oakland, California; Seattle-Puget Sound, Washington; and Utah), the SEER 13 registries (SEER 9 plus Los Angeles, California; San Jose Monterey, California; rural Georgia; and the Alaska Native Tumor Registry), and registries of greater California, Kentucky, Louisiana, New Jersey, and greater Georgia. This database covers approximately 27.8% of the U.S. population and is publicly available and de-identified. The data reported in this study represent the most recent follow-up (Dec 31, 2015) available in the SEER database.

Patients who were diagnosed between Jan 1, 1982 and Dec 31, 2015, had primary uterine leiomyosarcoma and treated with surgery were eligible for participation. Patients who didn't undergo surgeries for any reasons were excluded. Patients were also excluded when it's difficult to decide whether they matched inclusion criteria because of missing data (eg, surgery information or tumor size).

SEER*Stat 8.2.3 was used to extract the data and women fulfilling the aforementioned enrollment criteria were offered participation. Detailed demographic, oncological, and survival data were collected. Patients were divided into two groups according to treatment modalities: postoperative radiation (group 1) and ovarian conservation (group 2). Group 1 was defined as patients with FIGO stage I or II leiomyosarcoma underwent pelvic radiation after surgery, including postoperative simple beam radiation and postoperative beam radiation combined with implants. Group 2 contained patients younger than 50 years old with FIGO stage I leiomyosarcoma. They had undergone all kinds of hysterectomy based surgery without oophorectomy. Fifty years old was the mean age of spontaneous menopause in the north American population [14]. Cancer stage was reclassified into FIGO 2009, based on tumor size, tumor extension and lymph node status recorded in the database. Those without a code for oophorectomy or specific ovarian conservation were considered as unknown oophorectomy status, and therefore excluded.

Propensity score matching for each group was computed for each case determined by multivariable logistic regression analysis. Patient demographics, tumor characteristics, and treatment patterns were entered in the propensity score model. One-to-one propensity score matching in group 1 and group 2 seperately, and group 2 was performed through an automated algorithm with the propensity score difference cutoff being 1%.

Survival data, including five-year-cause-specific survival and five-year-overall survival (all-cause mortality), were collected through linkages with state mortality records and the National Death Index [13]. Cause-specific survival was defined as the time interval between the initial diagnosis of uterine leiomyosarcoma and the date of death resulting from this specific disease. Overall survival was defined as the time interval between the initial uterine leiomyosarcoma diagnosis and date of death for any reason. Among women who died, causes of death were examined (uterine leiomyosarcoma and other diseases) and grouped as previously described.

The primary outcome was to examine the 5-year-overall survival among women in the two groups, respectively. The secondary outcome was to examine the 5-year-cause-specific survival in the two groups, respectively.

Rank sum test or χ^2 test were used to exam base-line characteristics: age at diagnosis, ethnicity, marital status at diagnosis, year at diagnosis, FIGO stage, grade, tumor size, surgery modality, postoperative radiation, chemotherapy. Cox regression was used to evaluate proportional hazard regression models, and the magnitude of statistical significance was expressed with hazard ratio (HR) and 95% CI.

Kaplan-Meier analysis was used to construct survival and cumulative risk curves, and statistical significance between the curves was compared with log-rank tests. Survival was also examined using Cox Covariates, entered in the final model were patient demographics, tumor factors, and treatment patterns. Statistical analyses were conducted using SPSS23. All p-values reflected 2-sided tests, and sig-nificance was set at < 0.05.

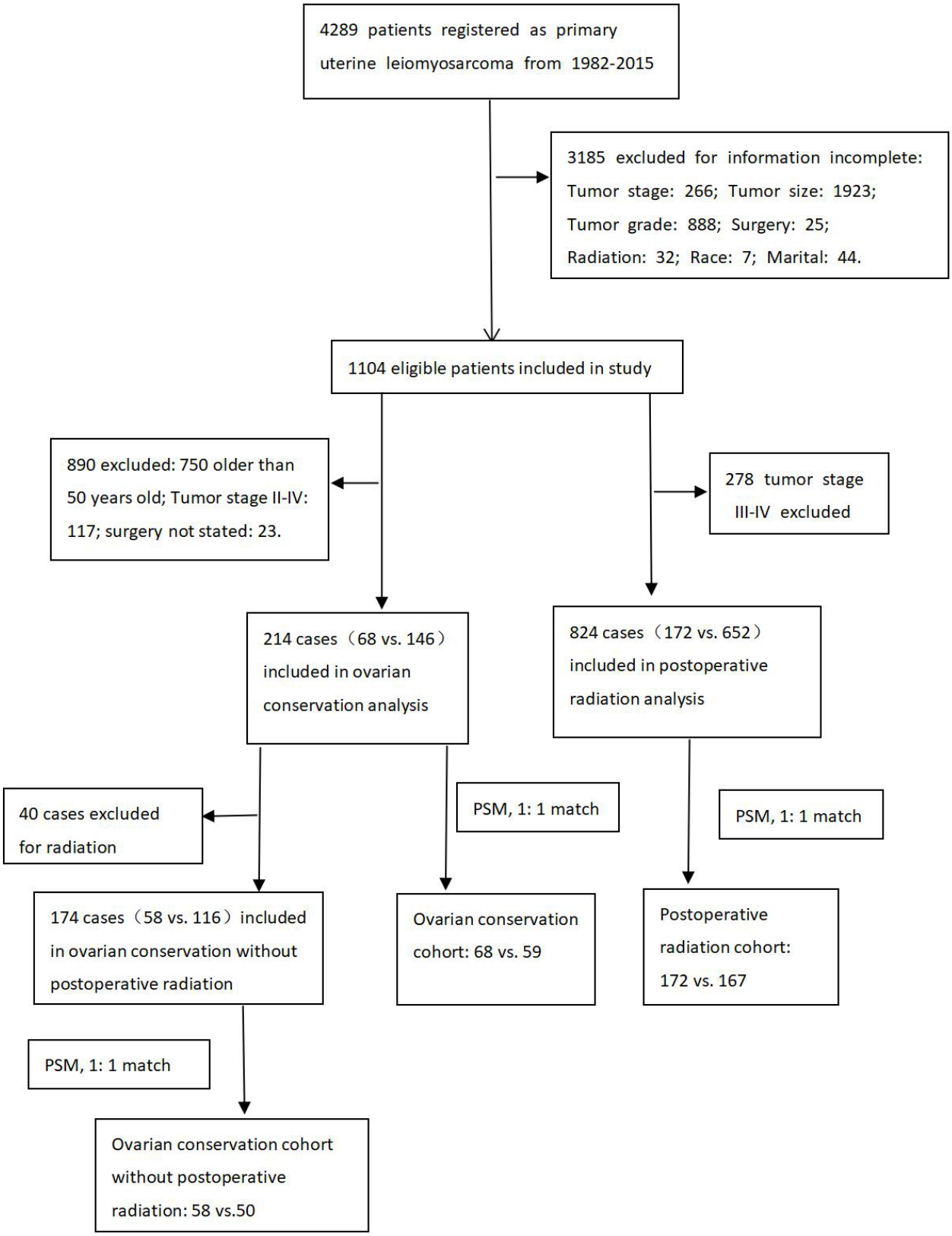

Figure 1. — Flwchart of Retrospecrive Cohort to Assess Survival Outcomes. Three cohorts were extracted from the Surveillance, Epidemiology, and End Results (SEER) database, including postoperative radiation cohort, ovarian conservation cohort, ovarian conservation cohort without postoperative radiation. **PSM:** propensity score matching.

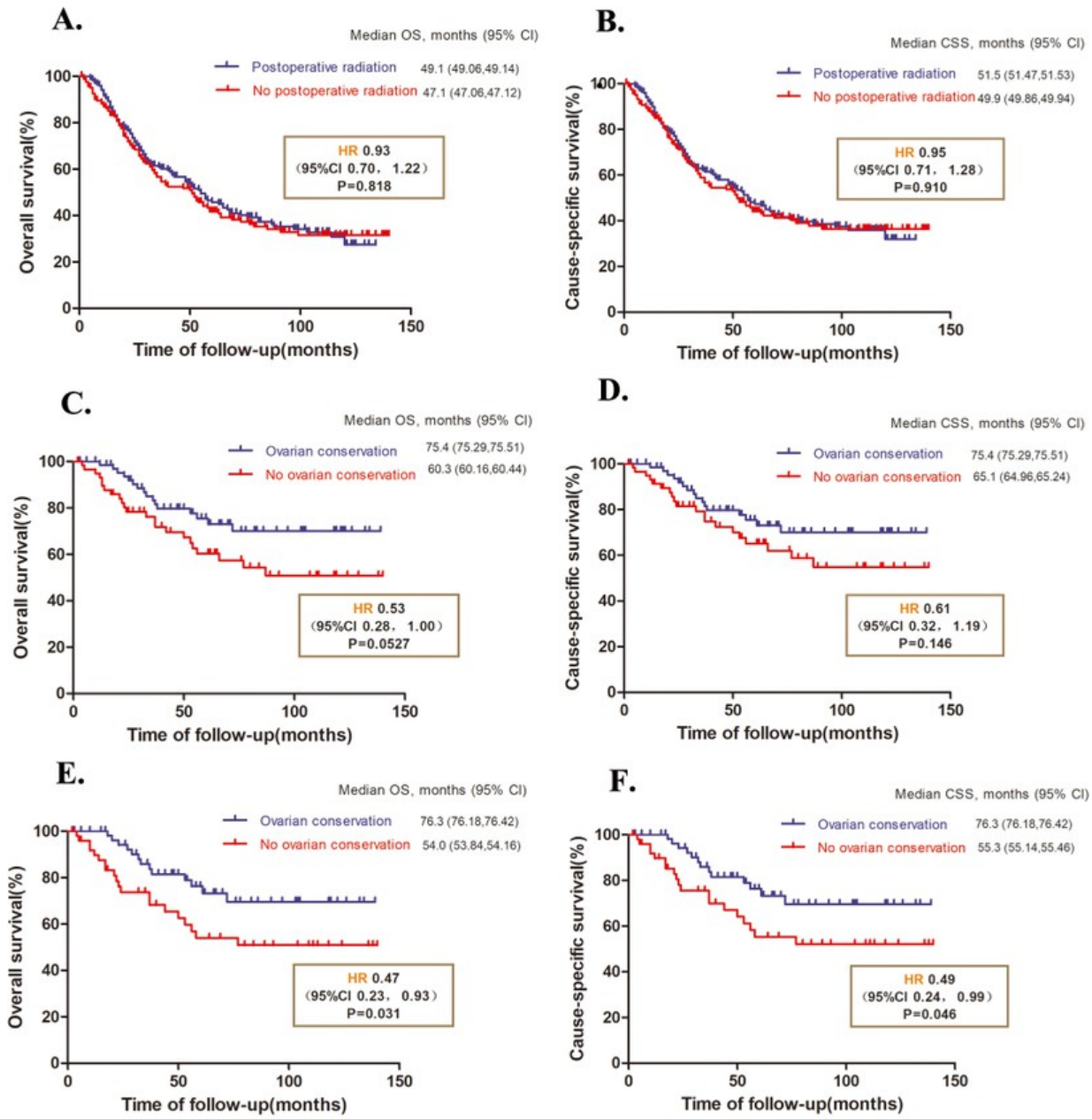

Figure 2. — Overall survival Cause-specific survival of patients with different local treatment modalities in the marched data. A. Overall survival of postoperative radiation group B. Cause-specific survival of postoperative radiation group C. Overall survival of ovarian conservation group D. Cause-specific survival of overian conservation group E. Overall servival of ovarian conservation without radiation group F. Cause specific survival of ovarian conservation without radiation group.

Results

A total of 1104 patients with uterine leiomyosarcoma met the inclusion criteria and were retrospectively analyzed (Figure I). The median follow-up time was 37.27 ± 34.69 months (95% CI: 35.39-39.38months). The demographic, oncological, according to survival data appeared in Table 1. The median onset age was 54.98 years (range: 22–85 years) and 32.6% of patients were aged 50 years old or more. The risk of death is higher in black and other ethnicities compared with white women. Patients who were older than 50 years old, with higher FIGO stage, had larger tumor size, or suffered from poorly or undifferentiated grades had higher hazard ratio for death ($p < 0.05$ in overall survival or cause-specific survival).

A total of 1104 patients were included in the final study. In 19.02% (210/1104) patients received postoperative pelvic radiation, 16.12% (178/1104) patients received simple beam radiation, 2.90% (32/1104) patients received postoperative beam radiation combined with im-

plants. 11.59% (128/1104) patients have their ovarian conserved. Compared with hysterectomy-based ovarian conservation, other hysterectomy-based surgery showed a tendency of higher hazard ratio for death but none of them had statistical differences. Beam radiation with/without implants, lymphadectomy, and chemotherapy had no statistic differences of five-year-survival outcomes in cox regression analysis.

After propensity score matching (PSM), there were no statistical significances among the compared groups (Tables2-4). Table 5 shows the results of Kaplan-Meier analyses of five-year-overall survival and five-year-cause-specific survival associated with different treatment modalities. There were no differences in the survival outcomes (overall survival: 49.1 *vs.* 47.1%, $p = 0.818$; cause specific survival: 51.5 *vs.* 49.9 %, $p = 0.910$) between women who underwent postoperative radiation and those who did not. In ovarian conservation group, the five-year-overall survival was 75.4% *vs.* 60.3% (Log-rank test: $p = 0.053$) and the five-year-cause-specific survival was 75.4 *vs.* 65.1% (Log-rank test: $p = 0.146$). After excluding women who received radiotherapy, the stage I patients with ovarian conservation showed a better survival outcome (five-year-overall survival: 76.3 *vs.* 54.0%, $p = 0.031$; five-year-cause-specific survival: 76.30 *vs.* 55.3%, $p = 0.046$) (Table 5 and Figure 2).

Discussion

The study revealed the association between survival outcomes and two treatment modalities: postoperative radiation and ovarian conservation in selected patients. So far, this study is the largest retrospective cohort study using new FIGO leiomyosarcoma stage in diagnosis and using propensity score matching in statistics. Still, to date, the study of adjuvant radiotherapy in non-metastatic uterine leiomyosarcoma is controversial. The National Comprehensive Cancer Network suggests that the routine postoperative radiotherapy is not recommended for stage I patients with uterine leiomyosarcoma. It needs to be individualized and based on careful analysis of surgical pathologic findings if used in more advanced stages [3]. A phase III randomized trial of stages I and II uterine sarcomas reported that postoperative pelvic radiotherapy did not improve overall survival for uterine leiomyosarcoma when compared with observation [4-8]. Also, many retrospective studies have shown adjuvant radiotherapy might control the progression of local pelvic disease but could not increase the overall survival [6-8]. However, these studies either used old FIGO/AJCC staging system or had severe bias, as the patients treated with adjuvant radiotherapy presumably had higher-risk factors (eg, larger tumors, deeper myometrial invasion). In this study, patient demographics, tumor characteristics, and treatment pattern were entered in the propensity score model and were computed for each case determined by multivariable logistic regression analysis. This study showed postoperative radiation was not associated with higher overall survival and cause-specific survival in stage I-II patients. Thus, the present results, together with previous studies, support that postoperative pelvic radiotherapy did not improve overall survival for uterine leiomyosarcoma in patients without extra pelvic metastases. Furthermore, adjuvant radiotherapy needs to be individualized and should be based on careful analysis of surgical pathologic findings.

The safety of ovarian conservation has been evaluated in several retrospective studies, suggesting a very low rate of adnexal involvement, and similar relapse rate and survival compared to women who underwent bilateral salpingo-oophorectomy [7,15-18]. In a retrospective analysis of SEER database conducted in 2007 enrolled 341 patients aged < 50 years with stage I or II uterine leiomyosarcoma, 240 (70.4%) underwent oophorectomy. The result showed that oophorectomy didn't improve five-year-cause-specific survival [10]. In selected patients with early-stage uterine leiomyosarcoma who wish to retain hormone function, the ovaries may be preserved [9]. However, these results were biased by heterogeneity and small sample sizes. This study showed even controling the variables of age, tumor stage and postoperative radiotherapy through propensity score matching, the results were similar to the previous studies, no statistical significances were found between ovarian conservation group and comparison group.

Interestingly, two previous [15,19] studies both showed that ovarian conservation had a decreased risk of death, one of them was also based on SEER database. However, neither of them approached statistical significance ($p > 0.05$). Besides, they didn't control age or tumor stage, and didn't exclude women who had received radiotherapy. After controlling the variables of age, tumor stage and postoperative radiotherapy through propensity score matching, and excluding the women who also received radiotherapy, we found ovarian conservation was associated with an improvement of five-year survival for premenopausal women with leiomyosarcoma limited to the uterus. An obvious explanation for the better survival outcome in patients who had preserved ovaries without radiation would be that radiation suppress ovarian functions, thus have the similar effect of oophorectomy. Another reason for the better survival outcome of patients who had preserved ovaries could be that these patients tend to focus more on life quality, and have more positive life attitude. Therefor they may be more positive in treatment and follow-up. The most conspicuous finding is that postoperative radiation doesn't improve survival outcomes in patients with early stage leiomyosarcoma, but ovarian conservation without radiation can improve survival outcomes in stage I leiomyosarcoma. Therefore, it is recommended that no radiotherapy in stage I leiomyosarcoma, or at least ovarian transposition should be done if radiotherapy is applicated.

This study did not acquire any information on tumor recurrence or exact details, which could have helped to investigate differences in the progression free survival. A

small number of women who were administered hormonal replacement therapy and underwent bilateral/unilateral salpingo-oophorectomy were not excluded. Data from large-scale trials and prospective multiple-centered study are needed because of the rarity of uterine leiomyosarcoma.

In conclusions, postoperative adjuvant radiotherapy neither improves the overall survival nor cause-specific survival,and therefore should be individualized in stage I-II patients with uterine leiomyosarcoma. On the other hand, the ovaries may be preserved in selected stage I patients for the improvement of survival, but postoperative radiotherapy is not recommended.

Author Contributions

Drs. Wu and Wang proposed the concept and designed the study. Dr. Wang contributed to the acquisition of data. Dr. Wu supervised the data collection. Drs. Wang and Meng performed the statistics. Drs. Wang and Meng wrote the manuscript. Dr. Meng assisted data analyses and editorial work. All authors provided inputs for the manuscript. Dr. Wu performed critical revision of the manuscript and addressed the comments from the journal.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.The institutional ethics review committee of Beijing Obstetrics and Gynecology Hospital approved the protocol. We submitted the data agreement form to the SEER administration. Upon acceptance of the agreement, the SEER*Stat software and data files were downloaded directly from the SEER website. The data released by the SEER database do not require informed patient consent because cancer is a reportable disease in every state in the United States.

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Conflict of interest

All the authors have no conflict of interest to be disclosed.

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