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Treatment patterns and outcomes for primary uterine leiomyosarcoma with synchronous isolated lung metastases: A National Cancer Database study of primary resection and metastasectomy

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ABSTRACT

Background: One third of patients with uterine leiomyosarcomas (uLMS) present with distant metastases. Current guidelines do not include recommendations around surgery for metastatic uLMS. Patients with distant metastases commonly receive primary tumor resection for symptoms and so oncologic outcomes after surgery warrant exploration. We describe treatment patterns and outcomes for uLMS patients with synchronous isolated lung metastases (SILM).

Methods: This retrospective analysis of the National Cancer Database identified patients with uLMS and SILM. Patients with non-pulmonary metastases were excluded. We collected demographic, disease, and treatment characteristics and assessed clinicopathologic factors associated with the receipt of surgery on multivariate regression. Median, 1-year, and 5-year overall survival (OS) across treatment approaches were compared using Kaplan-Meier curves and log-rank tests. Multivariate Cox proportional hazard regressions identified independent predictors of survival.

Results: We identified 905 patients with uLMS and SILM between 2004 and 2017. 600 patients had primary tumor resection; 63 also had curative intent surgery with metastasectomy. Patients who did not receive chemotherapy were older ($p<0.01$) with a higher comorbidity index ($p<0.05$). Women with private health insurance were more likely to receive chemotherapy ($p<0.01$) and primary tumor resection ($p<0.01$). Patients who underwent curative intent surgery had 1-year OS of 71.2% and 5-year survival of 18% compared to 1-year survival of 35.6 % and 5-year survival of 5.16 % for patients who had no surgery. Black women had poorer survival on multivariate regression.

Conclusions: Primary tumor resection and curative intent surgery are associated with improved OS in uLMS with SILM and may be a reasonable treatment option in appropriately selected patients.

1. Introduction

In contrast to uterine leiomyomas, which have a lifetime incidence of 70–80 %, uterine leiomyosarcomas (uLMS) are rare uterine tumors that account for only 1–5 % of uterine malignancies (Giuntoli et al., 2003; Tropé et al., 2012; Zivanovic et al., 2009) yet represent up to 45–69 % of uterine sarcomas in large histopathologic series. (Cantú de León et al., 2013; Abeler et al., 2009; Nordal and Thoresen, 1997) Compared to other histologies, LMS has a propensity for distant metastasis; at least 30 % of uLMS patients present with metastatic disease (Seagle et al., 2017; Lusby et al., 2013; Hosh et al., 2016) compared to reported rates of 21 % for endometrial stromal sarcomas. Approximately 74–86 % of patients with distant disease have pulmonary metastases (Bartosch et al., 2017; Tirumani et al., 2014) and some studies suggest that, for one third of

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these patients, metastases are limited to the lungs. (Lusby et al., 2013).

International societies and working groups have developed consensus guidelines for other uterine cancers (ESMO), (Colombo et al., 2016) but a lack of high level evidence has left uLMS – the most common uterine sarcoma – conspicuously absent from consensus statements. Systemic cytotoxic chemotherapy with or without palliative radiation is the standard of care for patients presenting with distant metastases. (Colombo et al., 2016) Evidence for the use of hormone therapy based on receptor status in metastatic uterine LMS is mixed and variably recommended by different consensus guidelines (National Comprehensive Cancer Network (NCCN), Society of Gynecologic Oncology (SGO)). (Sinno et al., 2020; National Comprehensive Cancer Network) From a surgical perspective, while current guidelines recommend assessing for resectability in the setting of isolated metastatic disease, the benefit of primary tumor resection or metastasectomy in uLMS is not well established.

The Memorial Sloan Kettering Cancer Center (MSKCC) uLMS nomogram, a tool validated for patients of any stage who have had resection of their primary tumor, suggests that patients with distant disease and otherwise few negative prognostic features may still have meaningful 5-year survival. (Zivanovic et al., 2012; Iasonos et al., 2013) One retrospective study from MD Anderson evaluated 192 patients with metastatic uLMS where 50 % underwent metastatectomy. They demonstrated that curative intent surgery with metastasectomy may improve overall survival for uLMS. (Lusby et al., 2013) This was corroborated by another series of 130 patients, which demonstrated a survival benefit with metastasectomy. It also demonstrated improved survival for patients with pulmonary metastases compared to metastases of other sites, and for patients with single-site metastases. (Bartosch et al., 2017) Most uLMS patients present with abnormal vaginal bleeding, (Giuntoli et al., 2003; Cantú de León et al., 2013; D'Angelo and Prat, 2010; Mbatani et al., 2018) and are more likely to receive resection of their primary tumor for symptom control in the metastatic setting. Therefore, the oncologic benefit of primary tumor resection and possible added benefit of metastasectomy in appropriate patients warrants further study. This descriptive study aims to explore survival outcomes in patients with primary uLMS and synchronous isolated lung metastases (SILM), including those who had resection of their primary tumor only or primary resection and pulmonary metastasectomy.

2. Materials and Methods

2.1. Study design

We performed a retrospective analysis of the American College of Surgeons (ACS) National Cancer Database (NCDB), an oncologic database composed of aggregate data from over 1500 Commission on Cancer accredited institutions in the United States. (American College of Surgeons) This study was approved by the Johns Hopkins Hospital Institutional Review Board.

Adult patients (>18 years) with a pathologically-confirmed diagnosis of uterine leiomyosarcoma and synchronous isolated lung metastases were included. Leiomyosarcoma cases were defined using histologic codes from the ICD-O-3 limited to those with a malignant designation. (Fritz et al., 2018) Benign leiomyomatous lesions were excluded. Codes for inclusion are listed in Appendix A.

Our patients were limited to those with a primary uterine cancer based on the American Joint Commission on Cancer (AJCC) Collaborative Stage Data Collection System tumor site codes. Site of metastases were similarly defined. Patients were excluded if they had reported metastases to non-pulmonary sites, missing data with respect to the site of metastatic spread, or other data points suggesting evidence of distant metastasis even if not explicitly reported (e.g. radiation therapy to non-uterine or non-pulmonary sites). Patient with non-uterine LMS or those who did not have pulmonary metastases at the time of diagnosis were excluded.

2.2. Data Collection

Demographic data collected included age at diagnosis, sex, race and ethnicity, Charlson comorbidity score (CCS), treatment facility, and insurance status. Cancer characteristics including grade, AJCC T-stage and primary tumor size were recorded. Treatment data collected included surgical procedures for either the primary tumor or lung metastases, receipt, dose, and modality of radiotherapy, and administration of frontline systemic therapy consisting of chemotherapy, hormone therapy, or immunotherapy.

2.3. Outcomes

Outcomes for this descriptive study include rates of resection for primary uterine leiomyosarcomas and rates of metastasectomy for lung metastases. Metastasectomy in conjunction with primary tumor resection was recorded as 'curative intent surgery'. For those undergoing surgery, 30-day postoperative readmission, 30-day post-operative mortality, and 90-day post-operative mortality data were collected. Factors associated with the receipt of primary surgery and chemotherapy were evaluated with univariate and multivariate regression analyses. Median overall survival (OS) in months was calculated from the date of diagnosis to the date of death or last follow-up. Median OS and 1-year and 5-year OS were determined for our entire study population with *a priori* subgroup analyses planned for patients with different treatment approaches.

2.4. Statistical analysis

We reported categorical variables as frequencies and continuous variables using measures of central tendency with standard deviations or interquartile ranges as appropriate based on population distribution.

OS was assessed using Kaplan-Meier curves and log-rank test. One-year and five-year mortality was determined using life tables. Cox proportional hazard regression was used to determine univariate associations between patients and clinical characteristics and overall survival. Multivariate Cox proportional hazard regression analysis included variables with statistical significance on univariate analysis ($\alpha = 0.05$) and variables known to be clinically relevant to the outcome. Hazard ratios with corresponding 95 % CI were reported. Data was analyzed using Stata statistical software, StataCorp 2015. (StataCorp, 2015).

3. Results

3.1. Demographic characteristics

Between the years of 2004 and 2017, we identified 905 patients presenting with a primary uterine leiomyosarcoma (LMS) and synchronous isolated lung metastases (SILM). Population characteristics are denoted in Table 1. Due to NCDB participant user files (PUF) data-reporting restrictions, all included study patients were recorded as female. This shortcoming is revisited in our limitations section. In the setting of metastatic disease, all patients were FIGO stage IV. AJCC T-stage distribution is described in Table 1. 95 % of patients were insured.

3.2. Treatment patterns and outcomes

Among patients with uLMS and SILM, 71.6 % were treated with cytotoxic chemotherapy. Of those for whom chemotherapy data was recorded, 88.9 % (63.7 % of the total population) had multi-agent chemotherapy and 11.1 % (7.9 % of the total population) had single-agent chemotherapy. 40 patients refused chemotherapy. Other systemic therapy provided included hormone therapy for 46 patients (5.1 %), of whom 27 (3.0 %) were treated with hormone therapy alone. Patients treated with hormone therapy alone were significantly older than those treated with chemotherapy (66.1 v. 55.6 years, $p < 0.01$), but

Table 1
Population characteristics for patients with primary uterine LMS with synchronous isolated lung metastases.

Variable	Uterine LMS (N = 905)
Age, mean ± SD	57.49 ± 10.77
Race, N (%)	
White – non Hispanic	521 (57.77)
Black – non Hispanic	236 (26.08)
Hispanic	86 (9.50)
Native American	3 (0.33
Asian	33 (3.65)
Other	26 (2.87)
CCS, N (%)	
0	707 (78.12)
1	151 (16.69)
2+	47 (5.19)
Treatment site, N (%)	
Academic	545 (62.36)
Community	329 (37.64)
Insurance status, N (%)	
Uninsured	45 (4.97)
Private	510 (56.35)
Government	334 (36.91)
Unknown	16 (1.77)
T-stage, N (%)*	
0	11 (2.44)
I	195 (43.24)
a	11
b	134
II	102 (22.62)
a	23
b	56
III	108 (23.95)
a	26
b	32
IV	35 (7.76)
Primary tumor size (cm), N (%)	
<=5	33 (6.56)
>5	470 (93.44)

LMS – leiomyosarcoma, SD – standard deviation, CCS – Charlson Comorbidity Score.

* N for 'a' and 'b' designations may not add to total N for numeric stage due to missing data for 'a' and 'b' designations. Distinction between T1a and T1b can be determined based on reported primary tumor size.

did not differ with respect to their comorbidity score (p = 0.77). Immunotherapy was administered to 24 patients (2.7 %) (Fig. 1**a**), all of whom also received chemotherapy.

Two hundred and seventy patients had no surgery. Ten patients had surgery other than primary tumor resection or metastasectomy: one had ablative therapy with no pathologic specimen and nine patients had an excisional biopsy or limited excision. Six hundred and eighteen patients underwent a major resection: 600 patients had complete resection of their primary tumor with either simple hysterectomy or radical hysterectomy +/- bilateral salpingo-oophorectomy (N = 595) or a pelvic exenteration (N = 5). Bilateral salpingo-oophorectomy was performed at the time of primary resection for 549 patients. Of the 600 patients with resection of their primary tumor, 537 (89.5 %) had resection of their primary tumor alone and 63 (10.5 %) had both primary tumor resection and pulmonary metastasectomy (Fig. 1**b**). Eighteen patients had pulmonary metastasectomy alone. Patients undergoing resection of primary tumor +/- metastasectomy had a median length of stay of 4 days (IQR 2–6) with 30-day readmission rate of 8.5 %. Post-operative mortality rates were 1.8 % at 30 days and 8.3 % at 90 days.

Thirty-seven patients (4.1 %) had radiation to their primary site and 15 (1.6 %) had radiation to their lung metastases. Radiation modality, dose, and fractionation are summarized in Table 2**.**

3.3. Factors associated with resection of primary tumor

There was no correlation between undergoing primary resection and year of diagnosis. On univariate analysis, patients who received resection of their primary tumor were significantly younger (56.2 versus 60.1 years, p < 0.01), were more likely to have private insurance (62.8 % versus 42.6 %, p < 0.01), were less likely to be Hispanic (8.2 % versus 12.5 %, p = 0.04), and were more likely to have received chemotherapy (77.2 % versus 62 %, p < 0.001). There were no significant differences in treatment center type, comorbidity score, or tumor size between groups.

On multivariate analysis, age, race, Hispanic ethnicity, Charlson comorbidity index, insurance status, tumor size, or treatment center type were not associated with increased odds of primary tumor resection. Receipt of chemotherapy (OR 1.70, 95 % CI 1.02–2.83; p = 0.04) and pulmonary metastasectomy (OR 6.04, 95 % CI 1.8–20.3; p < 0.01) were positively associated with primary tumor resection.

3.4. Factors associated with receipt of systemic therapy

A relatively low proportion of patients in our study cohort received chemotherapy (71.6 %) and so a multivariate logistic regression was conducted to identify factors associated with receipt (or non-receipt) of chemotherapy. Patients who did not receive chemotherapy tended to be older (61.5 versus 55.6 years, p < 0.001), had higher CCS (7 % versus 4 % CCS = 2+, p = 0.04), had tumors > 5 cm (97.7 % versus 92.1 %, p = 0.03), were less likely to have private insurance (43.2 % versus 62.7 %, p < 0.01), more likely to receive hormone therapy (11.3 % versus 3 %, p < 0.01), and less likely to undergo primary tumor resection (55 % versus 71.6 %, p < 0.001).

On multivariate regression analysis, increased age was associated with slightly decreased odds of receiving chemotherapy (OR 0.95, 95 % CI 0.93 – 0.98; p < 0.001). Both private (OR 7.3, 95 % CI 2.76 – 19.14, p < 0.001) and government insurance (OR 5.8, 95 % CI 2.09 – 16.00, p < 0.001) increased the odds of receiving chemotherapy over uninsured patients. Tumor size > 5 cm was associated with reduced odds of receiving chemotherapy (OR 0.2, 95 % CI 0.05 – 0.69, p = 0.012). Receipt of hormone therapy was negatively correlated with receipt of chemotherapy (OR 0.2, 95 % CI 0.07 – 0.46, p < 0.001) while resection of primary tumor was associated with increased odds of receiving chemotherapy (OR 1.95, 95 % CI 1.19 – 3.20, p < 0.01).

3.5. Survival analysis

3.5.1. Systemic therapy

Patients receiving chemotherapy (either single- or multi-agent) had a median OS of 16.9 months (95 % CI 15.34 – 19.15) compared to 6.7 months (95 % CI 4.90 – 8.48) for patients not receiving chemotherapy (p < 0.001) (Fig. 2, Fig. 3**a**). Median survival was greater in patients receiving both chemotherapy and hormone therapy (median OS 19.2 months, 95 % CI 12.45 – 30.12), but this increase was not significant over chemotherapy alone. Patients receiving chemotherapy had better OS at 1-year (65.1 % versus 35.5 %) but this trend was not observed at 5 years (Fig. 2). On a multivariate Cox proportional hazards model, receipt of chemotherapy was independently associated with improved OS (Table 3).

Patients receiving hormone therapy, of whom 58.7 % received hormone therapy alone, had a median OS of 23.6 months (95 % CI 14.75 – 48.20) compared to 14.2 months (95 % CI 12.70 – 15.34) in patients not receiving hormone therapy (p < 0.01) (Fig. 3**b**). Patients receiving hormone therapy had 1-year OS of 76 % and 5-year OS of 36 % versus 55.4 % at 1 year and 10 % at 5 years for patients not receiving hormone therapy. On Cox regression, hormone therapy was independently associated with improved OS (Table 3).

In the study population, 24 (2.65 %) patients received immunotherapy, all of whom also received chemotherapy. Median survival for patients receiving immune therapy was 16.7 months (95 % CI 15.34 – 19.12). There were too few events to determine whether there was improved survival in patients receiving immunotherapy and chemotherapy compared to chemotherapy alone.

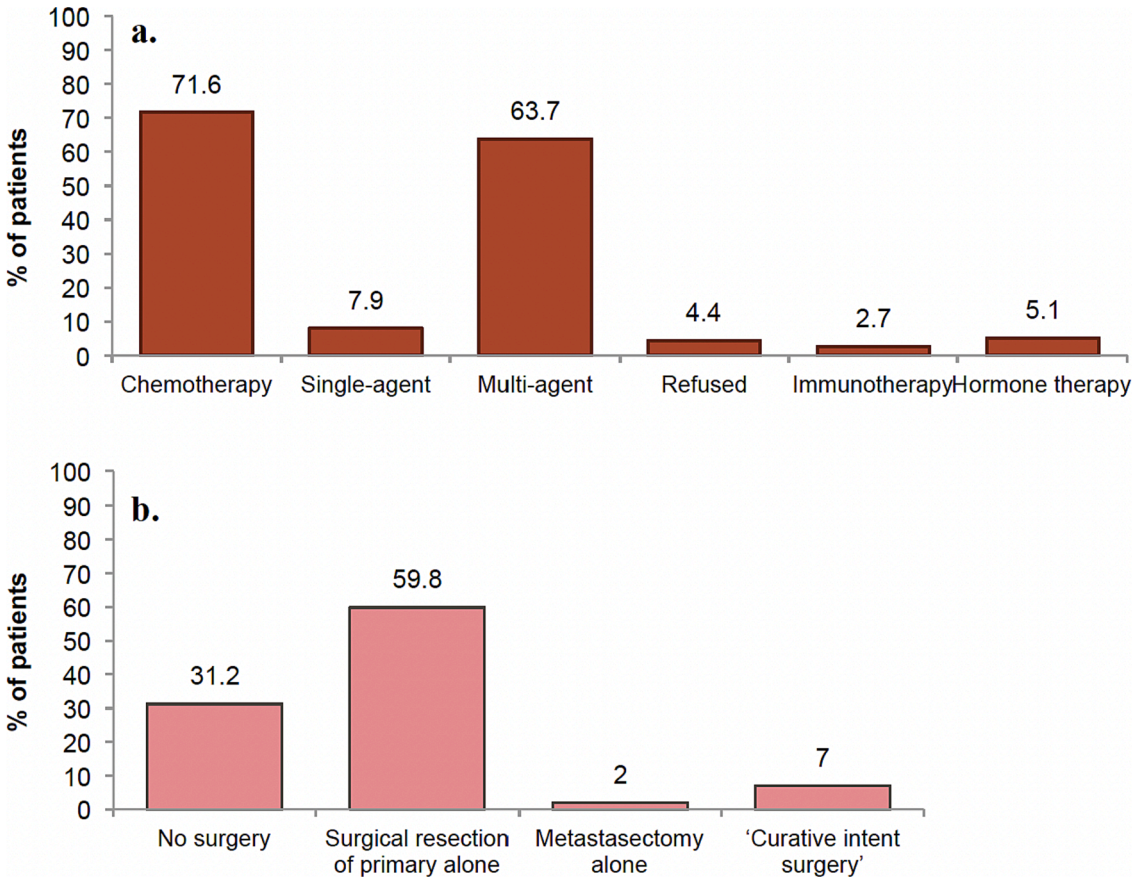

Fig. 1. Patterns of management in uLMS with SILM for **a.** systemic therapy and **b.** surgical therapy.

Table 2
Characteristics of radiation therapy.

RT to lung metastases, N = 15		
Metastasectomy, N (%)	2	13.33C
EBRT, N (%)	15	100
# Fractions, median (IQR)	5	4–12
Boost, N (%)	1	6.67
Total dose (cGy), median (IQR)	3250	2650–5000
RT to primary site, N = 37		
No primary resection, N (%)	18	48.65
Resection of primary tumor, N (%)	19	51.35
Neoadjuvant	2	5.40
Adjuvant	17	45.95
Modality, N (%)		
EBRT	35	94.59
Brachytherapy	2	5.41
# Fractions, median (IQR)	10	7–17
Boost, N (%)	3	8.1
Total dose (cGy), median (IQR)	3000	3000–3500

RT – radiation therapy, EBRT – external beam radiotherapy, IQR – interquartile range, cGy - centigray.

3.5.2. Surgical therapy

Patients who had resection of their primary tumor had improved median OS compared to those who had no surgery (16.9 v. 7.9 months, $p < 0.01$). This effect was sustained at 1 year (65.4 % v. 35.6 % survival) and 5 years (11.4 % v. 5.2 % survival) (Fig. 2). There was no difference in survival between patients who has BSO at the time of their primary tumor resection ($p = 0.41$). Curative intent surgery with primary tumor resection and pulmonary metastasectomy had a median OS of 21.8 months, 1-year OS of 71.2 %, and 5-year OS of 18 % (Fig. 2). It was associated with an increased survival benefit over primary tumor resection alone and over no surgery ($p < 0.01$) (Fig. 3**c**). On multivariate Cox regression, curative intent surgery was significantly associated with reduced hazard of death (HR 0.44, 95 % CI 0.32 – 0.62, $p < 0.001$) (Table 3).

3.5.3. Standard of care population

Cytotoxic chemotherapy is standard of care for stage IV uLMS and our population's survival outcomes with and without systemic therapy are described above. Among patients who received standard of care cytotoxic chemotherapy or hormone therapy (if cytotoxic chemotherapy was not given), surgical interventions impacted oncologic outcomes as follows:

For patients who received cytotoxic chemotherapy and did not undergo surgery, median OS was 10.4 months (12.5 months for patients who received both chemotherapy and hormone therapy, N = 6); 1-year OS was 45.5 % at 5-year OS was 4.5 %. For patients who received chemotherapy *and* had resection of their primary tumor, median OS was 20.2 months (21.4 months with the addition of hormone therapy, N = 6); 1-year OS was 73.1 % at 5-year OS was 11.5. For patients who both received chemotherapy and underwent curative intent surgery with primary tumor resection and pulmonary metastasectomy, median OS was 22.2 months (25.8 months with the addition of hormone therapy, N = 2). Survival was 72.8 % at one year and 10.6 % at five year.

3.5.4. Other factors associated with survival

Demographic factors associated with an increased hazard of death on univariate analysis were age ($p < 0.05$) and Black – non-Hispanic race ($p < 0.05$). On multivariate analysis controlling for both receipt of systemic therapy and surgical interventions, Black – non-Hispanic race persisted as a negative predictor for survival (HR 1.38, 95 % CI

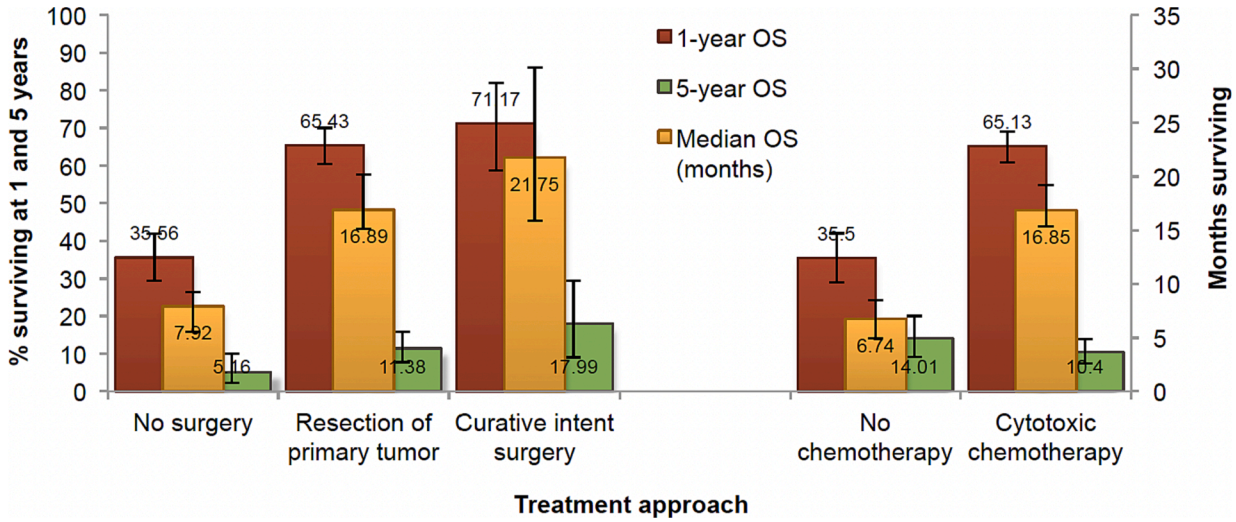

Fig. 2. Median, 1-year, and 5-year OS based on surgical approach and receipt of chemotherapy. Error bars represent positive and negative 95% CI. Value labels represent percentages or months as appropriate.

1.140–1.685, $p < 0.001$) (Table 3). Black patients had 53.8 % 1-year and 7.9 % 5-year OS compared to 57.2 % 1-year and 12.7 % 5-year OS for non-Black patients, and median OS was 2 months less (12.9 v. 14.9 months).

4. Discussion

Although uterine sarcomas are rare, greater attention and collaborative efforts have allowed us to analyze large population databases and institutional datasets and to develop nomograms that have predictive power for all stages of disease. As the largest study of patients with uLMS and synchronous isolated pulmonary metastases, our study adds to the body of existing literature that can inform treatment decisions and prompt prospective studies for uLMS patients with metastatic disease.

At this time, standard of care therapy for metastatic uLMS is cytotoxic chemotherapy. (National Comprehensive Cancer Network; Pautier et al., 2012) A relatively low proportion of our metastatic population received chemotherapy: only 71.6 %. Those who did not receive chemotherapy were more likely to be uninsured (5 % of our population), had higher CCS, larger tumors, and were older. Most patients who did receive chemotherapy (89 %) received multi-agent chemotherapy. This data, collected from 2004 to 2017, preceded the 2017 GEDDIS trial that demonstrated single agent therapy had similar efficacy with lower toxicity, and subsequently became an option for standard of care. (Seddon et al., 2017).

The new paradigm of single agent doxorubicin rather than multi-agent chemotherapy may mitigate some toxicity concerns but, in our relatively young population, chemotherapy toxicity should not have been a prohibitive factor for many patients. With respect to other correlated factors, sequence of therapy or presenting symptoms may have accounted for those who received hormone therapy instead of chemotherapy, and patients with large tumors may have had mass effects that required early surgical intervention; patients may have become ineligible for later chemotherapy due to recovery time, death, or complications. Finally, 4 % of patients refused chemotherapy. Cumulatively, however, this does not account for the entire proportion of our study population that did not receive chemotherapy. Failure to offer chemotherapy could conceivably result from extrapolation of guidelines for patients with stage III disease after complete resection. However, barriers to receipt of standard of care treatment including – but not limited to – insurance status should be more closely explored at an institutional level.

We did not explore timing of chemotherapy administration in depth because symptoms often dictate the sequence of therapy for patients with uterine cancer and the NCDB PUF does not include presenting symptoms. For women with significant bleeding or the inability to tolerate chemotherapy due to mass effects, primary tumor resection will precede administration of systemic therapy. It may even be undertaken for definitive diagnosis. For women with an established diagnosis and without debilitating symptoms, it is widely accepted that chemotherapy should precede any curative intent surgery to test disease biology and ensure disease stability. The authors are not advocating for deviation from those principles; however, consideration of resection of the primary tumor and limited metastases in uLMS is particularly important for three reasons: first, patients with uterine sarcoma are likely to undergo hysterectomy for symptoms irrespective of oncologic impact, as approximately half of patients with uLMS present with vaginal bleeding. (Giuntoli et al., 2003; Tropé et al., 2012; Cantú de León et al., 2013; D'Angelo and Prat, 2010; Mbatani et al., 2018) In our study, 600 women of the 905 studied had a hysterectomy. In a disease where primary tumor resection is so frequently undertaken, the oncologic benefit of such resections should be better defined. Second, the best predictive nomogram we have for uLMS is limited to patients who have had resection of their primary tumor. (Zivanovic et al., 2012; Iasonos et al., 2013) Within that population, it retains good predictive power in the metastatic setting and suggests that patients with metastases and otherwise few poor prognostic characteristics may still have meaningful 5y OS. (Iasonos et al., 2013) Therefore, we should take advantage of this tool to select patients who may benefit from an aggressive curative intent surgical approach. Third, we found significantly improved survival with primary tumor resection, and even better survival with the addition of pulmonary metastasectomy in our study population. With a number of studies showing benefit of pulmonary metastasectomy for LMS (Chudgar et al., 2017) and uLMS in particular (Lusby et al., 2013), the utility of metastasectomy for carefully selected patients with synchronous disease, especially those who have had their primary resected, may provide patients with limited metastatic burden a significant improvement in survival.

Other institutional studies have demonstrated similar outcomes in smaller but more granular populations. A study from the MD Anderson Cancer Center retrospectively evaluated 349 uLMS patients, of whom 192 had metastatic disease. (Lusby et al., 2013) Thirty-two had lung-only metastasis and they found that single-organ metastases and oligometastatic disease were positively associated with survival. Furthermore, in a population where more than 50 % of patients were treated with metastasectomy at any site with curative intent, patients with lung

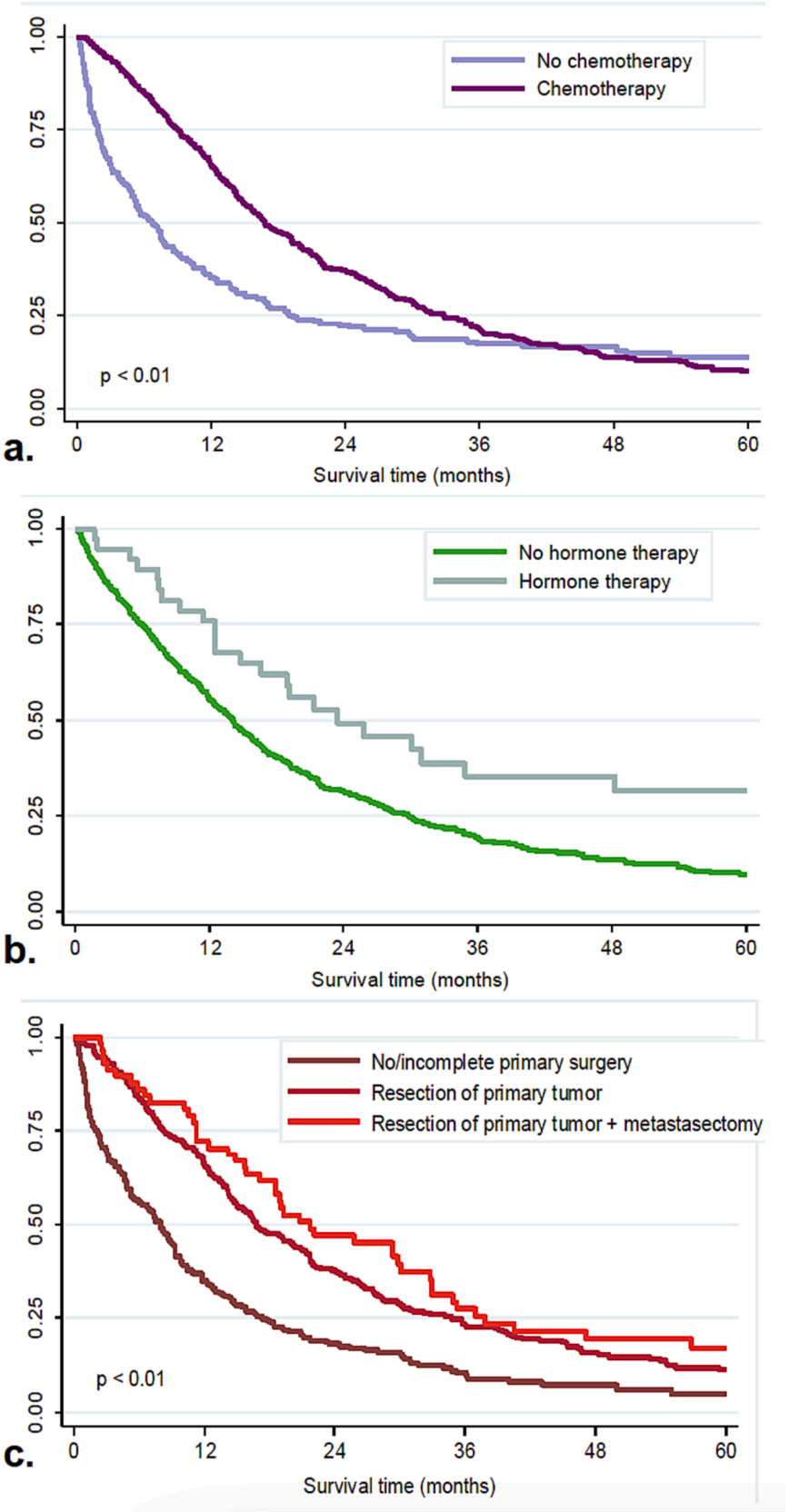

Fig. 3. Kaplan-Meier curves for uLMS patients receiving **a.** chemotherapy, **b.** hormone therapy, or **c.** resection of primary tumor or curative intent surgery.

Table 3
Multivariate Cox proportionate hazards model for patient and treatment factors associated with OS.

Variable	HR	95 % CI	*p* value
Patient and tumor characteristics			
Age, mean ± SD	1.01	0.995–1.014	0.198
Black – non Hispanic	1.38	1.140 – 1.685	**0.001**
CCS, N (%)			
0	ref		
1	0.85	0.676 – 1.079	0.185
2+	1.00	0.654 – 1.543	0.983
Treatment characteristics			
Resection of primary tumor	0.54	0.443 – 0.647	**< 0.001**
'Curative intent surgery' – resection of primary tumor + metastasectomy	0.44	0.316 – 0.619	**< 0.001**
Chemotherapy	0.66	0.508 – 0.854	**< 0.001**
Hormone therapy	0.40	0.246 – 0.634	**< 0.001**

CI – confidence interval SD – standard deviation, CCS – Charlson Comorbidity score.

metastases ($p = 0.02$) and those who underwent curative intent metastasectomy ($p < 0.0001$) had significantly improved survival on multivariate analysis. (Lusby et al., 2013) Although they performed correlative analyses between outcomes and biomarkers only in localized cases, they did identify increased expression of Ki-67, VEGF, and p16 in resected metastases compared to primary tumors on pathology. In the setting of moderate evidence favoring metastasectomy, and in a population where primary tumor resection is frequently undertaken, differential expression of biomarkers in uLMS patients SILM may help better delineate which patients will benefit from a curative intent approach with further study.

In this large cohort of women with FIGO IV uLMS, we identified worse survival for Black women after controlling for other demographic, socioeconomic, oncologic, and treatment characteristics. This is a well-established phenomenon in the gynecologic oncology population, with numerous large database studies from 1988 to the present documenting worse survival for Black women with uterine cancers. (Seagle et al., 2017; Hicks et al., 1998; Randall and Armstrong, 2003; Brooks et al., 2004; Clarke et al., 2019; Sherman and Devesa, 2003; Kapp et al., 2008; Baskovic et al., 2018) The disparities are substantial: one study of 7455 women with uLMS demonstrated median survival was reduced by 15 months for Black women compared to White women (Seagle et al., 2017) and a study of 2677 women with uterine sarcomas showed 10 % worse 5-year OS for Black women compared to White women. (Brooks et al., 2004) Several large studies of uterine cancers have demonstrated worse survival for Black women at every stage of disease after controlling for other demographic, tumor, and treatment variables. (Clarke et al., 2019; Sherman and Devesa, 2003; Baskovic et al., 2018) The well-documented persistence of this phenomenon across decades of cancer research is unacceptable. As leaders in cancer care and cancer research, academic hospitals must explore their institution-specific survival disparities so we can confront the racism and disparate care that exists in each of our institutions and prioritize interventions to abolish it.

4.1. Limitations

Because the NCDB does not capture adverse event data, we were unable to explore complication rates associated with primary tumor resection alone or as part of a curative intent surgical approach. Readmission and 30- and 90-day mortality rates are the most appropriate surrogates for these measures in the NCDB, but are insufficient to capture adverse events that may delay or prevent patients from receiving the systemic therapy that would be a standard part of the metastatic treatment paradigm. As a result, uncaptured adverse events may have impacted our reported survival outcomes.

Finally, the NCDB suppresses gender designations for transgender men and women and gender-diverse individuals, as this could be deemed identifiable data based on the relatively few transgender individuals captured across other specific identifiers in the dataset (e.g. geographic region). This represents a significant shortcoming in the NCDB and other large databases. It is essential that we explore patterns of disease management and oncologic outcomes in transgender patients, who are disproportionally underserved and poorly advocated for with respect to cancer screening and interventions. (Weyers et al., 2021; Clarke et al., 2022; Cruz, 2014; Dhillon et al., 2020; Jaffee et al., 2016; Gatos, 2018; Labanca et al., 2020; Patel et al., 2019; Puechl et al., 2019) Accessing population data for uLMS and other uterine, cervical, and ovarian cancers in transgender men will depend on timely and valuable changes in large data reporting.

5. Conclusions

Primary tumor resection, often undertaken for symptoms, as well as curative intent surgery with pulmonary metastasectomy were both associated with improved OS for patients with uLMS and SILM in this study cohort. This may be a reasonable treatment option in appropriately selected patients presenting with advanced stage LMS. Prospective studies are needed to better assess this difference. Our study corroborates the overwhelming evidence in gynecologic oncology literature that Black women with uLMS have worse survival despite controlling for other factors. This disparity needs to be examined, addressed, and intervened upon at the institutional level.

Financial Disclosures.
None.

Synopsis.
This study evaluates the management patterns and outcomes for patients with primary uterine leiomyosarcoma presenting with synchronous isolated lung metastases.

Disclosures.
None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. ICD-10 uterine leiomyosarcoma histology codes

1. 8890
2. 8891
3. 8896.

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