



# The Prognostic Value of Lymphovascular Invasion in Truncal and Extremity Soft Tissue Sarcomas: An Analysis from the National Cancer Database

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## ABSTRACT

**Objective.** The aim of this study was to determine the association between lymphovascular invasion (LVI) and overall survival (OS) in truncal/extremity soft tissue sarcomas (STS).

**Methods.** The National Cancer Database (NCDB) was queried for all patients, ages 18–85 years, who underwent resection of primary, truncal/extremity STS between 2010 and 2012, and had LVI data. The primary endpoint was OS.

**Results.** Among 6169 patients identified, the most common histology groups were (1) liposarcoma (LPS, 24%), (2) undifferentiated pleiomorphic sarcoma (UPS, 19%), and (3) leiomyosarcoma (LMS, 15%); 449 patients (7%) were LVI-positive. There were no differences in demographics or comorbidities between the LVI groups. Compared with LVI-negative patients, LVI-positive patients were more likely to have larger (> 5 cm: 80% vs. 66%), deep (80% vs. 68%), and high-grade tumors (82% vs. 57%). They were also more likely to have positive margins (27% vs. 17%), nodal (16% vs. 2%) and metastatic disease (21% vs. 4%), and receive chemotherapy (37% vs. 18%; all  $p < 0.001$ ). LVI was associated with worse

median OS (39 months vs. MNR;  $p < 0.001$ ), which persisted on stratum-specific analyses for all tumor grades, size categories, and stages I–III, but not stage IV. On multivariable Cox regression, LVI was associated with worse OS (hazard ratio [HR] 1.84, 95% confidence interval [CI] 1.39–2.44), while accounting for other significant prognostic factors. Among non-metastatic, curative-intent resections ( $n = 5696$ ), LVI was still associated with worse OS (HR 1.79, 95% CI 1.28–2.49).

**Conclusions.** LVI appears to be an important adverse pathologic factor in truncal and extremity STS. Even when taking into account other established prognostic factors, LVI was predictive of worse OS. Knowledge of LVI status may help to better risk-stratify patients and guide management strategies, and should be considered in future prognostic classification schemes and nomograms.

Soft tissue sarcomas (STS) constitute a rare group of solid tumors of mesenchymal origin, and account for 1% of all adult malignancies.<sup>1</sup> Because they can arise from either lipomatous tissue, muscle, nerves/nerve sheaths, blood vessels, or other connective tissues, STS may be found anywhere in the body. Collectively, the trunk and extremities are the most common primary site of origin, representing over 50% of all STS.<sup>2</sup>

Surgery is the only potentially curative treatment option for truncal/extremity STS, yet survival following surgery is highly variable and is dependent on several factors. Two of the strongest, validated predictors of outcomes are histologic subtype and tumor grade. Other commonly cited factors include tumor size, depth, necrosis, and patient age, although the significance of each of these is subject to

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debate.<sup>2–5</sup> Lymphovascular invasion (LVI) is a histologic finding characterized by tumor cells invading either lymphatic or vascular structures. It has been implicated as a poor prognostic factor in several solid malignancies, including biliary tract cancers, gastric cancer, melanoma, and adrenocortical carcinoma, as well as in uterine sarcomas.<sup>6–11</sup> Although some data have demonstrated the importance of microscopic vascular invasion only in truncal/extremity STS in the Scandinavian population, the prognostic value of LVI in patients from the US is still unclear as it has been inconsistently reported in the literature, despite being routinely evaluated on pathologic examination in this country.<sup>4,5</sup>

Despite extensive work reviewing the histologic predictors of recurrence and survival in patients with STS, there remains marked variability in outcomes.<sup>12</sup> Additional information can be used to inform clinicians and patients about risk, which may aid in decision making regarding therapeutic choices and surveillance protocols. Given the paucity of data around LVI and its association with outcomes in other malignancies, the potential impact of this finding on histologic analysis may be significant. The aim of the current study was to utilize a large, nationwide, US cancer database to assess the influence of LVI on survival in patients with primary, truncal, and extremity STS.

## METHODS

Maintained by the American Cancer Society and the American College of Surgeons, the National Cancer Database (NCDB) is an oncology registry comprised of retrospective data using over 30 million patient records from more than 1500 participating facilities across the US. After approval from Emory University's Institutional Review Board, the NCDB Participant Use File was queried for all patients, ages 18–85 years, diagnosed with a primary truncal and extremity STS from 2010 to 2012, who underwent resection and had available LVI data. Patients who had missing, unknown, and not applicable LVI data were excluded ( $n = 12,112$ , 49%). There were no clinically significant differences between patients with and without available LVI data. Similarly, patients who had missing survival data were excluded.

LVI was based on final pathology reports from each participating institution. Tumor, nodal, metastatic, and overall staging were based on the 7th edition American Joint Committee on Cancer (AJCC) staging system.<sup>13</sup> Tumor grade was assigned based on both tumor differentiation and grade, as described in the final pathology reports from each participating institution.

Histologies were identified based on the International Classification of Diseases for Oncology, Third Revision (ICD-O-3) histology codes, and were grouped into six main categories: Liposarcoma (LPS; 8850–8855, 8858); Fibroblastic/myofibroblastic (8810, 8811, 8815, 8821, 8825, 9150); Malignant fibrous histiocytoma/undifferentiated pleiomorphic sarcoma (MFH/UPS; 8802, 8805, 8830, 9251); Leiomyosarcoma (LMS; 8890, 8891, 8896); Synovial, clear cell, angiosarcoma, rhabdomyosarcoma, and epithelioid (SCARE; 9040–9043, 8804, 8900, 8901, 8910, 8912, 8920, 9044, 9120); and Other (8711, 8713, 8800, 8801, 8803, 8806, 8832, 8840, 8842, 8963, 8990, 9130, 9133, 9260, 9364, 9581, 9540). All other histologies were excluded.

Descriptive analyses were performed for all variables. Patients identified as having LVI-positive tumors were compared with those with LVI-negative tumors using Chi-square analyses and Student's *t*-test. The primary outcome was overall survival (OS), calculated from the time of surgery to the time of death. Kaplan–Meier methods and Cox proportional hazards models were used to assess the association of LVI with OS, as well as to identify other independent predictors of survival. Factors included in multivariable analyses were chosen based on clinical importance and statistical significance on univariable analyses. Stratum-specific survival analyses were performed to assess the association of LVI with OS in the context of grade, tumor size, and overall stage group. Additional survival analyses were performed on a subset of patients with localized, non-metastatic disease who underwent curative-intent resections. Patients with metastatic disease (clinical or pathologic M1, or stage IV) and those who underwent R2 resections were excluded from this subset. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA), and SAS macros developed by the Biostatistics and Bioinformatics Shared Resource at the Winship Cancer Institute. Statistical significance was set at 0.05.

## RESULTS

From 2010 to 2012, a total of 6169 patients underwent resection of primary truncal/extremity STS and met the inclusion criteria for analysis. Mean age at the time of diagnosis was 56 years and 55% of patients were male. The most common location was the extremity (65%), and the most common histology groups were LPS (24%), MFH/UPS (19%), and LMS (15%). There was an equal distribution of patients across the included years.

LVI-positive tumors were identified in 449 patients (7%), while LVI-negative tumors were identified in 5720 patients (93%). Comparative analyses of patients with LVI-

positive and LVI-negative tumors are displayed in Table 1. There were no differences between groups in baseline demographics or comorbidities. Patients with LVI-positive tumors were more likely to have SCARE histologies

(synovial, clear cell, angiosarcoma, rhabdomyosarcoma, and epithelioid sarcoma; 23% vs. 10%;  $p < 0.001$ ), high-grade tumors (82% vs. 57%;  $p < 0.001$ ), tumors  $> 5$  cm in size (80% vs. 66%;  $p < 0.001$ ), deep tumors (80% vs. 68%;

**TABLE 1** Comparative analysis of patients with LVI-positive and LVI-negative tumors

| Variable                | LVI-positive<br>[ <i>n</i> = 449 (7%)] | LVI-negative<br>[ <i>n</i> = 5720 (93%)] | <i>p</i> value |
|-------------------------|--|--|----------------|
| Mean age (years)        | 56                                     | 56                                       | 0.57           |
| Male sex                | 250 (56)                               | 3119 (54)                                | 0.64           |
| Caucasian race          | 361 (82)                               | 4636 (82)                                | 0.31           |
| Charlson–Deyo score     |  |  | 0.20           |
| 0                       | 353 (79)                               | 4682 (82)                                |                |
| 1                       | 79 (18)                                | 829 (14)                                 |                |
| 2                       | 17 (4)                                 | 209 (4)                                  |                |
| Histology group         |  |  | < 0.001        |
| Liposarcoma             | 43 (10)                                | 1405 (25)                                |                |
| Fibro/myofibroblastic   | 31 (7)                                 | 650 (11)                                 |                |
| Fibrohistiocytic        | 85 (19)                                | 1059 (19)                                |                |
| Leiomyosarcoma          | 92 (20)                                | 844 (15)                                 |                |
| SCARE                   | 102 (23)                               | 590 (10)                                 |                |
| Other                   | 96 (21)                                | 1172 (20)                                |                |
| Grade                   |  |  | < 0.001        |
| Low (G1)                | 16 (5)                                 | 1012 (24)                                |                |
| Intermediate (G2)       | 46 (14)                                | 825 (19)                                 |                |
| High (G3)               | 276 (82)                               | 2434 (57)                                |                |
| Mean tumor size (cm)    | 11.6                                   | 10.1                                     | 0.002          |
| Tumor size              |  |  | < 0.001        |
| $\leq 5$ cm             | 87 (20)                                | 1835 (34)                                |                |
| $> 5$ cm, $\leq 10$ cm  | 147 (34)                               | 1639 (30)                                |                |
| $> 10$ cm, $\leq 15$ cm | 100 (23)                               | 939 (17)                                 |                |
| $> 15$ cm               | 95 (22)                                | 978 (18)                                 |                |
| Tumor depth             |  |  | < 0.001        |
| Superficial             | 73 (20)                                | 1373 (32)                                |                |
| Deep                    | 300 (80)                               | 2979 (68)                                |                |
| Lymph node-positive     | 33 (16)                                | 63 (2)                                   | < 0.001        |
| Metastatic disease      | 100 (23)                               | 265 (5)                                  | < 0.001        |
| AJCC stage              |  |  | < 0.001        |
| I                       | 64 (15)                                | 2086 (39)                                |                |
| II                      | 94 (23)                                | 1605 (30)                                |                |
| III                     | 176 (42)                               | 1427 (27)                                |                |
| IV                      | 81 (20)                                | 220 (4)                                  |                |
| Final margin status     |  |  | < 0.001        |
| R0                      | 305 (73)                               | 4508 (82)                                |                |
| R1                      | 103 (24)                               | 932 (17)                                 |                |
| R2                      | 12 (3)                                 | 39 (1)                                   |                |
| Radiation               | 191 (43)                               | 2699 (48)                                | 0.06           |
| Chemotherapy            | 159 (37)                               | 1004 (18)                                | < 0.001        |

Data are expressed as *n* (%) unless otherwise specified

LVI lymphovascular invasion, SCARE synovial sarcoma, clear cell sarcoma, angiosarcoma, rhabdomyosarcoma, epithelioid sarcoma, AJCC American Joint Committee on Cancer

$p < 0.001$ ), and lymph node-positive disease (16% vs. 5%;  $p < 0.001$ ). Patients with LVI-positive tumors were also more likely to have metastatic disease (23% vs. 5%;  $p < 0.001$ ), undergo an R1 resection (24% vs. 17% R0;  $p < 0.001$ ), and receive chemotherapy (37% vs. 18%;  $p < 0.001$ ) (Table 1).

One- and 3-year OS for all patients was 90.8% and 76.4%. Median follow-up was 29 months. Patients with LVI-positive tumors had a lower 1- and 3-year survival (72.1% and 51.4%, respectively) compared with those with LVI-negative tumors (92.2% and 78.4%, respectively;  $p < 0.001$ ) (Fig. 1). Stratum-specific survival analyses are shown in Table 2. LVI positivity was still associated with worse OS when stratified by grade, size, and AJCC stages I–III. There was no difference in OS between the LVI-positive and LVI-negative groups among patients with stage IV disease (Table 2). On multivariable analysis for all patients, LVI positivity was associated with worse survival (hazard ratio [HR] 1.84, 95% confidence interval [CI] 1.39–2.43;  $p < 0.001$ ), along with increasing age, higher Charlson–Deyo score, ‘Other’ histologic subtype, intermediate- and high-grade, increasing tumor size, tumor depth, and metastatic disease (Table 3). Lymph node-positive disease, resection status, and receipt of chemotherapy were not associated with survival on multivariable analysis.

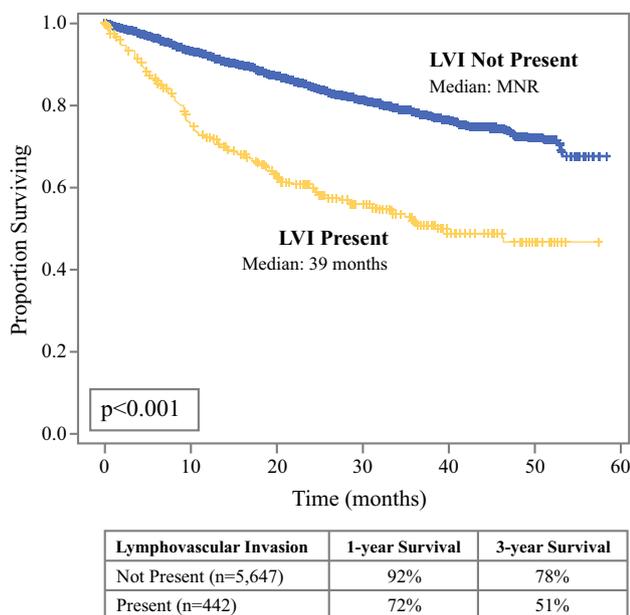
Of the total 6169 patients, 5773 (94%) had localized, non-metastatic disease and underwent curative-intent resection. One- and 3-year survival was 93.1% and 79.6%, respectively, among this patient cohort. Three hundred and forty-two patients (6%) had LVI-positive tumors and 5431 (94%) had LVI-negative tumors. Among patients with

localized, non-metastatic disease who underwent curative-intent resection, patients with LVI-positive tumors had lower 1-year (81.3% vs. 93.8%) and 3-year survival (59.2% vs. 80.9%;  $p < 0.001$ ) (Fig. 2) compared with those with LVI-negative tumors. On multivariable analysis, LVI positivity was associated with worse survival (HR 1.86, 95% CI 1.34–2.59;  $p < 0.001$ ), along with increasing age, a Charlson–Deyo score of 1, SCARE and ‘Other’ histologic subtypes, intermediate and high grade, larger tumor size, tumor depth, lymph node-positive disease, and an R1 resection. Receipt of chemotherapy was not associated with OS (Table 3).

## DISCUSSION

STS are rare solid neoplasms of mesenchymal origin that can arise from nearly anywhere in the body.<sup>1,2</sup> There are more than 80 different histologic subtypes of STS, each of which display their own anatomic predilection, clinicopathologic characteristics, and biologic behavior, underscoring both the heterogeneity of this disease and the associated challenges with diagnosis, treatment, and prognostication.<sup>14</sup> Identifying independent factors that unify this diverse group of rare tumors, help predict patient outcomes, and guide management strategies is of critical importance. The purpose of this study was to utilize the NCDB, a nationwide dataset representing over 1500 US cancer programs, to assess the influence of LVI on OS following curative-intent resection for truncal and extremity STS.

LVI has been shown to be an adverse pathologic finding associated with decreased survival in several solid malignancies, including uterine carcinosarcomas.<sup>6–8,15</sup> For STS, several studies from Scandinavia have been published examining the prognostic value of vascular invasion, specifically, although none review the broader finding of LVI. In 1994, Gustafson published a series of 508 patients with STS and found that vascular invasion was a strong and independent predictor of survival. Combining vascular invasion with tumor size and microscopic tumor necrosis, the authors developed the ‘SIN System’, which was validated a decade later within a similar European cohort.<sup>5,16</sup> More recently, another Scandinavian study evaluated the influence of vascular invasion on metastatic spread in truncal and extremity STS. In this study, Carneiro and colleagues proposed a new prognostic tool, adding growth pattern to the previously mentioned SIN System to create the ‘SING’ model. In addition, the authors found vascular invasion had the greatest association with the development of metastases, and, as a result, modified the system to rely more heavily on vascular invasion. When compared with the AJCC staging system and the widely used nomogram



**FIG. 1** Overall survival among all patients, comparing those with and without LVI. LVI lymphovascular invasion

**TABLE 2** Stratum-specific survival analysis comparing patients with LVI-positive and LVI-negative tumors

|                   | 3-year overall survival |                  | Univariable Cox regression |                             |
|-------------------|-------------------------|------------------|----------------------------|-----------------------------|
|                   | LVI-positive (%)        | LVI-negative (%) | HR (95% CI)                | <i>p</i> value <sup>a</sup> |
| <b>Grade</b>      |                         |                  |                            |                             |
| Low (G1)          | 86.7                    | 96.1             | 4.35 (1.34–14.14)          | 0.008                       |
| Intermediate (G2) | 66.9                    | 84.9             | 3.52 (2.04–6.07)           | < 0.001                     |
| High (G3)         | 44.3                    | 67.6             | 2.13 (1.77–2.57)           | < 0.001                     |
| <b>Tumor size</b> |                         |                  |                            |                             |
| ≤ 5 cm            | 64.9                    | 89.0             | 4.36 (2.86–6.65)           | < 0.001                     |
| > 5 cm, ≤ 10 cm   | 57.3                    | 76.2             | 2.23 (1.67–2.97)           | < 0.001                     |
| > 10 cm, ≤ 15 cm  | 47.2                    | 72.7             | 2.38 (1.73–3.26)           | < 0.001                     |
| > 15 cm           | 27.2                    | 68.2             | 3.03 (2.24–4.09)           | < 0.001                     |
| <b>AJCC stage</b> |                         |                  |                            |                             |
| I                 | 74.6                    | 90.2             | 2.61 (1.49–4.59)           | < 0.001                     |
| II                | 62.4                    | 82.1             | 2.98 (2.06–4.29)           | < 0.001                     |
| III               | 46.2                    | 63.6             | 1.69 (1.32–2.15)           | < 0.001                     |
| IV                | 26.2                    | 29.8             | 1.23 (0.90–1.69)           | 0.20                        |

<sup>a</sup>Log-rank *p* value

AJCC American Joint Committee on Cancer, LVI lymphovascular invasion, HR hazard ratio, CI confidence interval

from Memorial Sloan Kettering Cancer Center (which, notably, do not utilize vascular invasion or LVI to risk-stratify patients), the SING model performed favorably.<sup>3,4,13</sup>

While the results from these studies are promising, evaluation for specific vascular invasion has limitations. LVI is typically defined as the presence of tumor cells within the lumen of either lymph or blood vessels on hematoxylin-eosin (H&E) staining. Because both have endothelial linings and a similar structure, differentiating between lymphatic and vascular channels is notoriously challenging on H&E, and requires specific immunohistochemistry studies that are not routinely performed and can be time-consuming.<sup>17</sup> Thus, LVI is the standard nomenclature used in the US, and has been routinely evaluated in and reported for most cancer specimens for the last decade. Yet, despite having readily available LVI data in addition to the previously mentioned results on specific vascular invasion, LVI has been rarely studied in STS within a US population.

In the current study, we identified 6169 patients who underwent resection of primary truncal/extremity STS and had available LVI data. Because the NCDB captures patients from across the US, the baseline demographics and clinicopathologic findings of our cohort are believed to be representative of the general STS patient population in this country. We found that LVI was associated with worse OS, even in a multivariable model taking into account other prognostic factors, including patient age, Charlson–Deyo score, histopathologic group, tumor grade, size, depth,

margin status, lymph node status, metastatic disease, and receipt of chemotherapy. The association between LVI and survival persisted on stratum-specific analysis among patients with low-, intermediate-, and high-grade tumors; patients with tumors ≤ 5 cm, > 5 cm but ≤ 10 cm, > 10 cm but ≤ 15 cm, and > 15 cm in size; and those with AJCC TNM stage I, II, and III disease. Interestingly, there was no difference between LVI-positive and LVI-negative tumors among patients with stage IV disease, which supports the common idea that once metastases develop, it is the presence of systemic disease rather than primary tumor characteristics that really drives outcomes. To account for the potential bias of patients with metastases, we next evaluated the influence of LVI on survival only among patients with localized, non-metastatic disease. Once again, the presence of LVI maintained its independent association with worse OS in a multivariable model, including patient age, Charlson–Deyo score, histopathologic group, tumor grade, size, depth, margin status, lymph node status, and receipt of chemotherapy.

There are several limitations to this analysis. While the NCDB provides a wealth of information and is a powerful tool to study rare diseases, its retrospective design, lack of granular data, and inability to assess disease recurrence and disease-specific survival limit the conclusions that can be drawn from this study. Information on pathologic findings, including LVI, was obtained from pathology reports at each respective institution, rather than through a centralized pathologic review process. Furthermore, documentation of LVI status during the years of this study

**TABLE 3** Multivariable Cox regression analysis for overall survival

| Variable              | All patients     |                | Non-metastatic, curative-intent <sup>a</sup> |                |
|-----------------------|------------------|----------------|--|----------------|
|                       | HR (95% CI)      | <i>p</i> value | HR (95% CI)                                  | <i>p</i> value |
| LVI                   | 1.84 (1.39–2.44) | < 0.001        | 1.79 (1.28–2.49)                             | < 0.001        |
| Age                   | 1.02 (1.01–1.02) | < 0.001        | 1.02 (1.01–1.03)                             | < 0.001        |
| Charlson–Deyo score   |                  |                |  |                |
| 0                     | Reference        |                | Reference                                    |                |
| 1                     | 1.46 (1.14–1.88) | 0.003          | 1.46 (1.12–1.92)                             | 0.006          |
| 2                     | 1.57 (1.00–2.46) | 0.05           | 1.25 (0.76–2.08)                             | 0.38           |
| Histopathology group  |                  |                |  |                |
| Liposarcoma           | Reference        |                | Reference                                    |                |
| Fibro/myofibroblastic | 1.44 (0.93–2.23) | 0.10           | 1.56 (0.97–2.49)                             | 0.07           |
| Fibrohistiocytic      | 1.41 (0.99–2.01) | 0.06           | 1.63 (1.10–2.40)                             | 0.01           |
| Leiomyosarcoma        | 1.15 (0.78–1.70) | 0.48           | 1.51 (0.99–2.29)                             | 0.06           |
| SCARE                 | 1.85 (1.21–2.28) | 0.004          | 2.04 (1.27–3.28)                             | 0.003          |
| Other                 | 1.67 (1.15–2.42) | 0.007          | 1.95 (1.31–2.92)                             | 0.001          |
| Grade                 |                  |                |  |                |
| Low (G1)              | Reference        |                | Reference                                    |                |
| Intermediate (G2)     | 2.76 (1.60–4.76) | < 0.001        | 2.57 (1.48–4.49)                             | < 0.001        |
| High (G3)             | 4.66 (2.81–7.71) | < 0.001        | 4.28 (2.57–7.15)                             | < 0.001        |
| Tumor size            |                  |                |  |                |
| ≤ 5 cm                | Reference        |                | Reference                                    |                |
| > 5 cm, ≤ 10 cm       | 1.56 (1.11–2.20) | 0.01           | 1.66 (1.14–2.41)                             | < 0.001        |
| > 10 cm, ≤ 15 cm      | 2.74 (1.92–3.92) | < 0.001        | 3.36 (2.28–4.94)                             | < 0.001        |
| > 15 cm               | 3.16 (2.20–4.54) | < 0.001        | 3.66 (2.46–5.45)                             | 0.008          |
| Tumor depth: deep     | 1.40 (1.04–1.89) | 0.03           | 1.34 (0.98–1.83)                             | 0.07           |
| Lymph node-positive   | 1.25 (0.81–1.92) | 0.31           | 1.64 (0.92–2.86)                             | 0.09           |
| Metastatic disease    | 2.70 (1.97–3.71) | < 0.001        | –  |                |
| Final margin status   |                  |                |  |                |
| R0                    | Reference        |                | Reference                                    |                |
| R1                    | 1.23 (0.95–1.58) | 0.12           | 1.33 (1.01–1.76)                             | 0.046          |
| R2                    | 1.93 (0.88–4.23) | 0.10           | –  |                |
| Chemotherapy          | 1.12 (0.87–1.44) | 0.38           | 1.18 (0.90–1.56)                             | 0.24           |

<sup>a</sup>Excludes metastatic disease, R2 resections

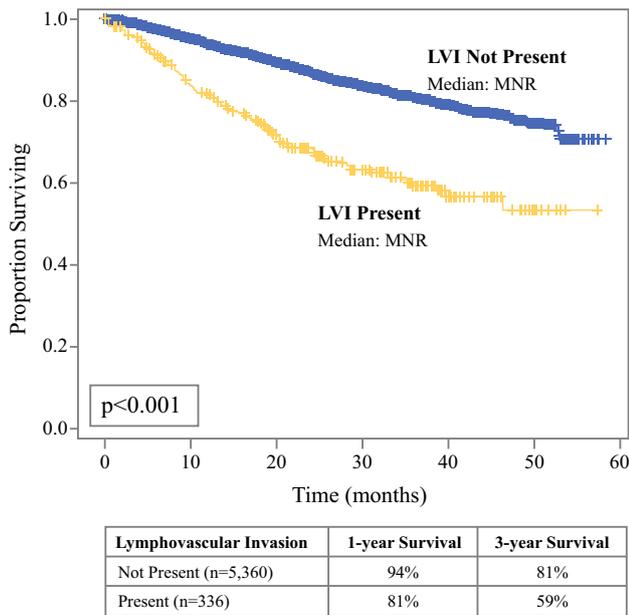
HR hazard ratio, CI confidence interval, LVI lymphovascular invasion, SCARE synovial sarcoma, clear cell sarcoma, angiosarcoma, rhabdomyosarcoma, epithelioid sarcoma

was considered an optional data point for NCDB collection. Thus, approximately half of the cases that otherwise met the inclusion criteria were excluded due to missing LVI status, which may introduce selection bias. The relatively small number of patients with LVI data also limited our ability to appropriately power histology-specific analyses. Yet, to our knowledge, this is the first and largest US-based analysis of the influence of LVI on patients with STS. It is also important to understand that both surgical and non-surgical patients are included in the NCDB, and those without surgical specimens were unlikely to have LVI data. Furthermore, the reliance on institutional and

interpreter-specific pathology data reflects a clinical reality and enhances the applicability of our findings to the general practice in this country.

## CONCLUSIONS

The results of this large, US population-based study demonstrate that LVI is an important pathologic factor that influences survival in truncal and extremity STS. Even when taking into account other previously established prognostic factors, such as age, histology, grade, size, depth, and margin status, the presence of LVI was still predictive of worse OS. Knowledge of LVI status may help



**FIG. 2** Overall survival among only patients with localized, non-metastatic disease who underwent curative-intent resection, comparing those with and without LVI. LVI lymphovascular invasion

to better risk-stratify patients and guide management strategies, and should be considered in future prognostic classification schemes and nomograms.

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**DISCLOSURE** None.

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