Posted on Authorea 23 Jun 2021 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.162441361.15835696/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Trends of lymph node sampling and metastasis in pediatric patients with clear cell, epithelioid, and synovial sarcomas

Jennine Weller[1], Carly Westermann[2], Palak Patel[2], Ross Beckman[2], Christine Pratilas[3], Carol Morris[4], and Daniel Rhee[1]

[1]Johns Hopkins School of Medicine
[2]Johns Hopkins University School of Medicine
[3]John Hopkins
[4]The Johns Hopkins University

June 23, 2021

Abstract

Background: Clear cell sarcoma (CCS), epithelioid sarcoma, and synovial sarcoma are rare tumors historically identified as high risk for lymph node metastasis. Nodal metastasis in adults with these subtypes has been described. This study investigates incident nodal metastasis and associated survival in children with these subtypes. Procedure: Using the National Cancer Database (2004-2015), we created a retrospective cohort of 1303 patients (aged [?]25 years) who underwent local control therapy for CCS, epithelioid sarcoma, and synovial sarcoma. Kaplan-Meier curves estimated overall survival (OS) by subtype. Stratifying on subtype, Cox regressions assessed OS by lymph node sampling status and nodal metastasis. Results: There were 103 (7.9%) patients with CCS, 221 (17.0%) with epithelioid sarcoma, and 979 (75.1%) with synovial sarcoma. Lymph node sampling was more frequent in patients with CCS (56.3%) and epithelioid sarcoma (52.5%) versus synovial sarcoma (20.5%, p<0.001). Synovial sarcoma metastasized to lymph nodes less frequently than CCS or epithelioid sarcoma (2.2% vs. 14.6% and 15.0%, p<0.001). Across all subtypes, lymph node metastasis was associated with inferior OS (HR 2.10, CI 1.44-3.07, p<0.001). Lymph node sampling was associated with improved OS in CCS (HR 0.35, CI 0.15-0.78, p=0.010), inferior OS in synovial sarcoma (HR 1.60, CI 1.13- 2.25, p=0.007), and no statistical association with OS in epithelioid sarcoma. Conclusions: Lymph node metastasis is rare in children with synovial sarcoma. Lymph node sampling procedures were not consistently performed for patients with CCS or epithelioid sarcoma, but improved OS supports routine lymph node sampling in children with CCS.

Introduction

Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) are rare childhood malignancies that account for 3-7% of pediatric cancers annually.[1,2] Comprising over 50 histological subtypes, NRSTS have a wide variety of clinical presentations and treatment pathways. Across all histological subtypes, overall survival (OS) is associated with tumor grade, tumor size, evidence of metastasis, and extent of surgical resection.[3] Studying outcomes for individual subtypes is challenging due to low incidence. As a result, pediatric providers rely on results from adult literature as well as pediatric studies that aggregate subtypes by similar clinical or genetic features.[3-5]

One common grouping of NRSTS is by propensity for early lymph node metastasis. Most NRSTS rarely metastasize to lymph nodes[4,6], but higher risk NRSTS subtypes historically included clear cell sarcoma of soft tissue (CCS), epithelioid sarcoma, and synovial sarcoma.[7] Over the past two decades, large database studies in adults and single-center studies in children have corroborated lymph node metastases are prevalent in up to 30% of patients with CCS and epithelioid sarcoma.[4,6,8-10]Conversely, synovial sarcoma in adults is

Posted on Authorea 23 Jun 2021 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.162441361.15835696/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

now understood to have an incidence of lymph node metastasis as low as 4.2%[6,9], but this association has not been well-studied in children.

Understanding the incidence of lymph node involvement in children with NRSTS tumors is important, as both the adult and pediatric literature support an association between lymph node metastasis and inferior OS across all NRSTS subtypes.[3,6,9,11] Additionally, patients identified with lymph node metastasis can receive targeted radiation or completion lymphadenectomy to reduce tumor recurrence.[12] However, physicians must weigh suspicion for lymphatic involvement against the risks associated with sampling procedures, including wound infection and lymphedema.[13] Current recommendations include routine lymph node pathologic evaluation in children with CCS and epithelioid sarcoma. However, further data are needed to understand the impact of lymph node sampling on survival in pediatric patients.

We sought to clarify trends of lymph node metastasis in pediatric patients with CCS, epithelioid, and synovial sarcoma from a nationwide database. We also explored lymph node sampling practices for these NRSTS subtypes over the past decade. Finally, we examined the association between lymph node sampling, lymph node metastasis, and overall survival in this population.

Methods

This was a retrospective cohort study of 1303 children and young adults who underwent local control for CCS, epithelioid sarcoma, and synovial sarcoma.

Data Source

We utilized data from the 2004-2015 National Cancer Database (NCDB), a deidentified dataset of adult and pediatric cancers in the United States.[14] Comprising data from over 1500 hospitals, the NCDB captures demographics, tumor characteristics, diagnostic information, treatment modalities, and survival data for approximately 70% of incident cancer cases annually.[14] The data that support the findings of this study are available from the National Cancer Database at https://www.facs.org/quality-programs/cancer/ncdb. These data were derived from the following resources available in the public domain: https://www.facs.org/quality-programs/cancer/ncdb/publicaccess. This study was deemed exempt from review by the Johns Hopkins Hospital Institutional Review Board.

Study Cohort

We identified patients aged [?] 25 years with CCS, epithelioid, and synovial sarcomas as classified by ICD-O-3 codes. Patients were included only if they underwent primary surgical resection or primary site radiation for local control of their tumor. Lymph node metastasis (present vs. absent) was defined using pathologic N-stage and NAACCR Item 820 for regional lymph nodes positive. We excluded patients with documented late entries (n=20), multiple primary tumors (n=48), and unknown lymph node sampling status (n=19), which we defined as a binary variable based on documentation of regional nodal examination or surgery (NAACCR Items 830, 1292).[15] We used multiple imputation by predictive means matching to resolve residual missing values in the dataset.

Outcomes

The primary outcome was OS in months after a patient completed local control. Secondary outcomes were frequency of lymph node sampling and lymph node metastasis.

Statistical Analysis

We compared patient demographics between histologic subtypes using frequencies and central tendency measures. Chi-squared tests determined differences in proportions between histologic subtypes for lymph node sampling and lymph node metastases. We calculated unadjusted survival estimates for OS by histologic subtype using Kaplan-Meier (KM) curves with log-rank statistics and Gehan-Breslow-Wilcoxon tests when hazards crossed. Multivariate Cox proportional hazard models estimated the hazard of death by lymph node sampling and lymph node metastasis statuses. Models adjusted for known prognostic indicators of OS in

Posted on Authorea 23 Jun 2021 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.162441361.15835696/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

pediatric NRSTS patients, including tumor size and grade, neoadjuvant chemotherapy, and surgical margins. Histologic subtype significantly modified the relationship between lymph node sampling and OS, thus we stratified this regression model by histology. For all regression models, we confirmed proportional hazards by testing global goodness of fit for the correlation between Schoenfeld residuals and time. A Bonferroni corrected p-value <0.0125 was applied for multiple comparisons amongst stratified histological subtypes; otherwise p<0.05 was considered significant. All statistical analyses were performed using R v3.6.1 (R Core Team 2017).[16]

Results

Our query identified 1303 children and young adults who met inclusion criteria, consisting of 103 (7.9%) patients with CCS, 221 (17.0%) with epithelioid sarcoma, and 979 (75.1%) with synovial sarcoma. Within the entire cohort, 683 (52.4%) patients were male and 890 (68.3%) were white. The median age at diagnosis was 18 years (range 0-25 years). The most common tumor location was in the extremities and trunk, found in 980 (75.2%) patients. There were 1256 (96.4%) patients who underwent primary surgical resection for local control. Of these patients, 183 (14.6%) received neoadjuvant local radiation, 357 (28.4%) received adjuvant local radiation, 11 (0.9%) received intraoperative local radiation, and 34 (2.7%) received both neoadjuvant and adjuvant local radiation. Radiation was the sole treatment for local control in 47 (3.6%) patients.

Patient demographics and tumor characteristics are compared by histologic subtype in Table 1. Larger tumors were seen in 510 (52.1%) patients with synovial sarcoma as compared to 34 (33.0%) patients with CCS and 71 (32.1%) patients with epithelioid sarcoma. Conversely, 72 (7.4%) patients with synovial sarcoma had distant metastasis, compared to 15 (14.6%) patients with CCS and 26 (11.8%) patients with epithelioid sarcoma. Primary surgical resection with local radiation was the most common method of local control for synovial sarcoma, in 499 (51.0%) patients, while surgery alone was more common for CCS (72 patients, 69.9%) and epithelioid sarcoma (157 patients, 71.0%).

Comparing the incidence of lymph node sampling procedures between histologic subtypes in Table 2, there were significantly fewer patients with synovial sarcoma who underwent lymph node sampling (p<0.001). Additionally, only 21 (2.2%) patients with synovial sarcoma had recorded lymph node metastasis, and this number was significantly fewer than the incidence of lymph node metastasis observed in 15 (14.6%) and 33 (15.0%) patients with CCS and epithelioid sarcoma, respectively (p<0.001, p<0.001). Relative rates of lymph node sampling for each histologic subtype remained the same across the 12-year study period.

Unadjusted overall survival differed by histological subtype (Fig. 1). Patients with clear cell sarcoma had a 5-year OS of 56.1%, and this outcome was significantly inferior compared to survival of patients with synovial or epithelioid sarcoma (p<0.001, p=0.001, respectively). There was no significant difference between the 79.5% 5-year OS for patients with synovial sarcoma and the 73.9% 5-year OS for patients with epithelioid sarcoma. When comparing KM estimates of 2-year OS by lymph node status for each histologic subtype (Fig. 2), patients with positive lymph nodes had significantly inferior survival, regardless of the subtype (p<0.001).

Table 3 shows the adjusted hazard ratios for each histological subtype based on lymph node sampling status. Lymph node sampling was associated with a 65% reduction in the risk of death for patients with CCS (p=0.010). In contrast, patients with synovial sarcoma who underwent a lymph node sampling procedure had an associated 60% increase in the risk of death as compared to those who did not have lymph nodes sampled (p=0.007). There was no significant difference in overall survival by lymph node sampling status in children and young adults with epithelioid sarcoma.

For all patients, regardless of histologic subtype, there was a two-fold increase in the risk of death for those with lymph node metastasis (p<0.001) after adjusting for confounding factors, as shown in Table 4. Histologic subtype did not significantly modify this association.

Discussion

Lymph node metastases in pediatric patients with NRSTS are associated with a poor prognosis.[3,6,9,11] Adult

Posted on Authorea 23 Jun 2021 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.162441361.15835696/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

studies suggest that CCS and epithelioid sarcoma have a higher risk of lymph node metastasis as compared to synovial sarcoma[6,9], however this association remains unconfirmed in children. Clarifying the incidence and impact of nodal metastasis for these histologic subtypes is important as locoregional control measures for nodal disease can reduce tumor recurrence.[9,11,12] We therefore sought to examine trends in incident lymph node metastasis and lymph node sampling in a pediatric and young adult cohort.

We conducted a retrospective survival analysis of 1303 pediatric patients with CCS, epithelioid, and synovial sarcoma in the National Cancer Database. Our results confirm that children and young adults with synovial sarcoma have infrequent lymph node metastasis (2.2%), while nodal involvement is more common in patients with CCS (14.6%) and epithelioid sarcoma (15.0%). These frequencies are comparable to those reported in the adult literature[6,9] and support that synovial sarcoma does not have a strong proclivity for lymphatic spread in children.

By utilizing a national database, our study was able to examine the associations between lymph node sampling and overall survival for individual NRSTS histologic subtypes of CCS, epithelioid, and synovial sarcoma. Previous research on lymph node sampling in pediatric NRSTS has relied on single center studies[8,17,18], cohorts of adults and children[6,19,20], or analyses that group histologic subtypes.[3,5] Given the known heterogeneity in treatment and outcomes of NRSTS subtypes[7,9] as well as the differences in survival between older adults and pediatric patients with NRSTS[20], our study results add clarity to the significance of lymph node metastasis in pediatric patients with CCS, epithelioid, and synovial sarcoma subtypes.

This study supports lymph node metastasis as an independent risk factor for OS in pediatric patients with CCS, epithelioid, and synovial sarcoma, but we found tumor histology did not significantly modify this relationship. This finding contrasts with results from a NCDB study of adults with NRSTS, which showed the associated impact of lymph node metastasis on OS was worse in histologic subtypes with good overall prognoses, such as epithelioid sarcoma[11]. With the rarity of lymph node metastasis seen for each histological subtype in our cohort, it is possible that our study was underpowered to detect this difference.

Current Children's Oncology Group (COG) and European Society for Medical Oncology (ESMO) practice guidelines recommend routine lymph node sampling for pediatric patients with CCS and epithelioid sarcoma, but not synovial sarcoma.[21,22] We found lymph node sampling occurred in only half of patients with CCS and epithelioid sarcoma, and this trend was stable across the 12-year study period. We speculate that the inconsistent practice of lymph node sampling may be due to variation in practice patterns. For example, center-specific variation in routine use of FDG-PET scans or other patient-specific factors which limit the ability to obtain FDG-PET scans may differentially drive staging procedures. Improved adherence to lymph node sampling recommendations may be an important goal for future quality improvement studies.

Our results show an associated survival benefit to lymph node sampling in pediatric patients with CCS. We speculate that sampling procedures more accurately identified lymph node metastases in patients with CSS, leading to augmented treatment plans and ultimately improved patient survival. Unfortunately, database constraints prevented us from detecting if augmented treatment plans were in fact implemented for these patients. However, in support of this theory, we found that children with CCS who did not undergo lymph node sampling had inferior survival rates, which were similar to the 2-year OS seen in those with lymph node metastasis. Given the higher incidence of lymph node metastasis in CCS as seen in this study, our findings support the recommendation for routine lymph node sampling in this histologic subtype.

Our findings also support the recommendation to avoid routine lymph node sampling in patients with synovial sarcoma without clinical or radiographic concern for nodal involvement. As previously mentioned, our study found that lymph node metastasis was rare in children and young adults with synovial sarcoma. Additionally, children with synovial sarcoma who underwent lymph node sampling had an associated decreased survival, likely because those for whom sampling procedures were recommended were at higher risk for advanced disease. Conversely, patients with synovial sarcoma who had negative lymph nodes had similar 2-year OS to those who did not undergo a lymph node sampling procedure.

The benefits of lymph node sampling for epithelioid sarcoma in children remains unclear. Our results showed

Posted on Authorea 23 Jun 2021 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.162441361.15835696/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

that confirming lymph node involvement by sampling was not significantly associated with improved OS, and 2-year OS for patients with epithelioid sarcoma were similar between those who had negative nodes and those who did not undergo a sampling procedure. However, our study corroborates that epithelioid sarcoma does have a high propensity for lymph node involvement. Locoregional staging may remain important for treatment planning for patients with epithelioid sarcoma, as previous literature suggests that imaging underestimates nodal involvement in soft tissue sarcomas.[23]

We acknowledge there were several limitations to our study. First, we utilized a retrospective database with limited granularity. For example, we could not accurately analyze disease-free survival or distinguish timing or technique for lymph node sampling. Second, our inclusion criteria restricted the study cohort to patients who underwent primary surgical resection or primary site radiation. Therefore, our study results may not extrapolate to patients with unresectable or advanced metastatic disease. Finally, there may exist differential sampling bias in our results: in patients with no clinical suspicion for nodal involvement, it is probable that physicians were more likely to sample lymph nodes in those with CCS or epithelioid sarcoma as compared to synovial sarcoma because of current COG and ESMO practice guidelines.

Despite these limitations, our results suggest that pediatric patients with CCS and epithelioid sarcoma, but not synovial sarcoma, are at substantial risk of lymph node metastasis. Lymph node sampling was associated with improved survival in patients with CCS, yet it was inconsistently performed in patients with this subtype. Additionally, the impact of lymph node sampling in patients with epithelioid sarcoma remains unclear. Future research could focus on determining the significance of lymph node sampling in pediatric patients with epithelioid sarcoma, as lymph node metastasis is common in this subtype.

Conflict of Interest Statement: The authors have no potential conflicts of interest.

Acknowledgments: None

References

1. Loeb DM, Thornton K, Shokek O. Pediatric Soft Tissue Sarcomas. Surg Clin North Am. 2008 Jun; 88(3):615-27, vii.

2. Behranwala KA, A'Hern R, Omar AM, Thomas JM. Prognosis of lymph node metastasis in soft tissue sarcoma. Ann Surg Oncol. 2004 Jul;11(7):714–9.

3. Waxweiler TV, Rusthoven CG, Proper MS, et al. Non-Rhabdomyosarcoma Soft Tissue Sarcomas in Children: A Surveillance, Epidemiology, and End Results Analysis Validating COG Risk Stratifications. Int J Radiat Oncol Biol Phys. 2015 Jun 1;92(2):339-48.

4. Hayes-Jordan A. Recent advances in non-rhabdomyosarcoma soft-tissue sarcomas. Semin Pediatr Surg. 2012 Feb;21(1):61-7.

5. Brady AC, Picado O, Tashiro J, Sola JE, Perez EA. Lymph Node Sampling and Survival in Child and Adolescent Extremity Soft-Tissue Sarcoma. J Surg Res. 2019 Sep;241:205-14.

6. Miccio JA, Jairam V, Gao S, et al. Predictors of Lymph Node Involvement by Soft Tissue Sarcoma of the Trunk and Extremity: An Analysis of the National Cancer Database. Cureus. 2019 Oct; 11(10): e6038.

7. Fong Y, Coit DG, Woodruff JM, Brennan MF. Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg. 1993 Jan;217(1):72-7.

8 Kayton ML, Delgado R, Busam K, et al. Experience with 31 sentinel lymph node biopsies for sarcomas and carcinomas in pediatric patients. Cancer. 2008 May 1;112(9):2052-9.

9. Jacobs AJ, Morris CD, Levin AS. Synovial Sarcoma Is Not Associated With a Higher Risk of Lymph Node Metastasis Compared With Other Soft Tissue Sarcomas. Clin Orthop Relat Res. 2018 Mar;476(3):589-98.

10. Sherman KL, Kinnier CV, Farina DA, et al. Examination of national lymph node evaluation practices for adult extremity soft tissue sarcoma. J Surg Oncol. 2014 Nov;110(6):682-8.

Posted on Authorea 23 Jun 2021 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.162441361.15835696/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

11. Keung EZ, Chiang YJ, Voss RK, et al. Defining the incidence and clinical significance of lymph node metastasis in soft tissue sarcoma. Eur J Surg Oncol. 2018 Jan;44(1):170-177.

12. Wagner LM, Kremer N, Gefland MJ, et al. Detection of lymph node metastases in pediatric and adolescent/young adult sarcoma: Sentinel lymph node biopsy versus fludeoxyglucose positron emission tomography imaging—A prospective trial. Cancer. 2017 Jan 1;123(1):155-60.

13. de Vries M, Vonkeman WG, van Ginkel RJ, Hoekstra HJ. Morbidity after inguinal sentinel lymph node biopsy and completion lymph node dissection in patients with cutaneous melanoma. Eur J Surg Oncol. 2006 Sep;32(7):785–9.

14. National Cancer Data Base. American College of Surgeons. https://www.facs.org/quality-programs/cancer/ncdb. Cited 2021 Jun 9.

15. Goldberg DW, Kohler B, Kosary C. The Texas A&M, NAACCR, NCI Geocoding Service. http://geo.naaccr.org. Cited 2021 Jun 9.

16. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2017. https://www.R-project.org/.

17. Spunt SJ, Hill DA, Motosue AM, et al. Clinical features and outcome of initially unresected non-metastatic pediatric nonrhabdomyosarcoma soft tissue sarcoma. J Clin Oncol. 2002 Aug 1;20(15):3225-35.

18. Tinkle CL, Fernandez-Pineda I, Sykes A, et al. Non-Rhabdomyosarcoma Soft Tissue Sarcoma (NRSTS) in Pediatric and Young Adult Patients: Results From a Prospective Study Using Limited-Margin Radiotherapy. Cancer. 2017 Nov 15; 123(22): 4419-29.

19. Maduekwe UN, Hornicek FJ, Springfield DS, et al. Role of sentinel lymph node biopsy in the staging of synovial, epithelioid, and clear cell sarcomas. Ann Surg Oncol. 2009 May;16(5):1356-63.

20. Ferrari A, Sultan I, Huang TT, et al. Soft tissue sarcoma across the age spectrum: a population-based study from the Surveillance Epidemiology and End Results database. Pediatr Blood Cancer. 2011 Dec 1;57(6):943-9.

21. Casali PG, Abecassis N, Aro HT, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018 Oct 1;29(Suppl 4):iv51-iv67.

22. Splunt SL, Million L, Chi Y, et al. Prospective Analysis of a Risk-Based Treatment Strategy for Non-Rhabdomyosarcoma Soft Tissue Sarcomas in Patients Under 30 Years of Age: A Report from Children's Oncology Group Study ARST0332. Lancet Oncol. 2020 Jan; 21(1):145-61.

23. Alcorn KM, Deans KJ, Congeni A, et al. Sentinel lymph node biopsy in pediatric soft tissue sarcoma patients: utility and concordance with imaging. J Pediatr Surg. 2013 Sep;48(9):1903-6.

Legends

FIGURE 1 Kaplan-Meier estimates of 5-year overall survival (in months from the end of local control therapy) for children and young adults with clear cell sarcoma (CCS), epithelioid sarcoma, and synovial sarcoma.

FIGURE 2 Kaplan-Meier estimates of 2-year overall survival (in months from the end of local control therapy) by lymph node sampling status for children and young adults with (A) clear cell sarcoma, (B) epithelioid sarcoma, and (C) synovial sarcoma. Statistical significance is set at $p<0.0125$.

Hosted file

2a.TABLE 1_Pediatric Sarcoma Nodal Metastasis.docx available at https://authorea.com/users/328404/articles/527342-trends-of-lymph-node-sampling-and-metastasis-in-pediatric-patients-with-clear-cell-epithelioid-and-synovial-sarcomas

Hosted file

Posted on Authorea 23 Jun 2021 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.162441361.15835696/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

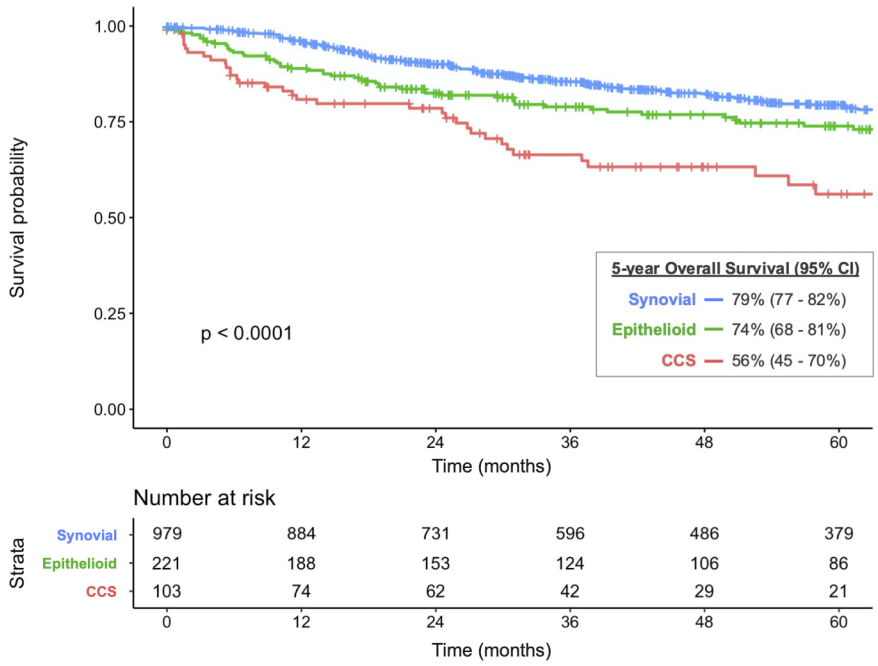
2b.TABLE 2_Pediatric Sarcoma Nodal Metastasis.docx available at https://authorea.com/users/328404/articles/527342-trends-of-lymph-node-sampling-and-metastasis-in-pediatric-patients-with-clear-cell-epithelioid-and-synovial-sarcomas

Hosted file

2c.TABLE 3_Pediatric Sarcoma Nodal Metastasis.docx available at https://authorea.com/users/328404/articles/527342-trends-of-lymph-node-sampling-and-metastasis-in-pediatric-patients-with-clear-cell-epithelioid-and-synovial-sarcomas

Hosted file

2d.TABLE 4_Pediatric Sarcoma Nodal Metastasis.docx available at https://authorea.com/users/328404/articles/527342-trends-of-lymph-node-sampling-and-metastasis-in-pediatric-patients-with-clear-cell-epithelioid-and-synovial-sarcomas



Posted on Authorea 23 Jun 2021 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.162441361.15835696/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.