

Is there a role for sentinel lymph node biopsy in the management of sarcoma?

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Abstract

Is there a role for sentinel lymph node (SLN) biopsy in the management of sarcoma? Sentinel node biopsy has dramatically changed the management of melanoma and breast cancer, helping surgeons avoid radical lymphadenectomies in node negative patients who would previously have undergone a more morbid operation with little benefit, or remained pathologically unstaged. Many investigators have explored the use of lymphatic mapping for malignancies other than breast cancer or melanoma. Lymphatic mapping and sentinel node biopsy has not been investigated in the management of sarcomas, which is not surprising given that the majority of sarcomas spread by local extension or hematogenously. Regional lymph node metastases are rare; developing in about 3–10% of patients with localized disease. However, among certain subtypes of high-grade sarcomas there is a propensity for regional lymph node metastases. These include rhabdomyosarcoma, epithelioid sarcoma, clear cell sarcoma, synovial sarcoma, and vascular sarcomas. It is in these particular subtypes that there may be a benefit to SLN biopsy.

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1. Introduction

The use of sentinel lymph node (SLN) biopsy to assess the regional lymphatic basin for the presence of metastatic disease is quickly becoming the standard of care in the management of melanoma and breast cancer. The concept of lymphatic mapping and SLN biopsy was first described by Cabanas in 1977 in regards to penile cancer [1]. The concept was further developed by Morton, who reported its use for melanoma in 1992 [2]. The core concept behind the sentinel node is that the primary tumor reliably drains to one or a few lymph nodes in the regional lymphatic basin, and therefore histopathologic analysis of these “sentinel” nodes reflects the disease status of the entire lymphatic field. Several studies have supported this hypothesis in both melanoma [3–5] and breast cancer [6–8]. In utilizing SLN biopsy to stage the regional lymphatic basin, surgeons hope to avoid radical lymphadenectomies node negative patients who would previously have undergone

a more morbid operation with little benefit, or remained pathologically unstaged.

Given the potential advantages of SLN biopsy, many investigators have explored the use of lymphatic mapping for malignancies other than breast cancer or melanoma. These include lung cancer [9], colon cancer [10,11], squamous cell carcinoma of the head and neck [12,13], gynecologic cancers [14–16], thyroid cancer [17,18], Merkel cell carcinoma [19–21], upper gastrointestinal cancers [22,23] and non-small cell lung cancer [24]. Though its role has yet to be defined, surgeons are hoping this minimally invasive technique may serve as a means to improve staging, better predict prognosis and utilize adjuvant therapies and decrease morbidity by avoiding unnecessary major lymphadenectomies.

One malignancy for which SLN biopsy has not been investigated is sarcoma. That the technique of SLN biopsy has not been investigated in the management of sarcomas is not particularly surprising given that the majority of sarcomas spread by local extension or hematogenously. Regional lymph node metastases are rare; developing in about 3–10% of patients with localized disease [25]. Recurrence in the regional nodal basin is also rare, representing 4–10% of recurrences,

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often with distant metastases as well [26,27]. Classic teaching in sarcoma stresses radical excision of the primary without need for lymph node evaluation or lymphadenectomy. Though the overall incidence of regional lymph node metastases in sarcoma is low, there do appear to be certain histologic subtypes in which there is an increased incidence. Skinner and Eilber reviewed a number of different studies demonstrating the increased incidence of regional lymph node metastases in certain types of sarcomas [25]. They concluded that lymph node metastases occurred almost exclusively in high-grade lesions. Among high-grade sarcomas, only certain subtypes such as rhabdomyosarcoma, epithelioid sarcoma, clear cell sarcoma, synovial sarcoma, and vascular sarcomas appeared to have a propensity for regional lymph node metastatic spread. It is in these particular subtypes that benefits of SLN biopsy might be realized. In this mini-review for *Surgical Oncology*, we present an argument for the selective use of SLN biopsy in the management of sarcoma.

2. Rhabdomyosarcoma

Rhabdomyosarcoma, sarcomas with demonstrated skeletal muscle differentiation, are common in children and rare in adults. Rhabdomyosarcoma demonstrated regional lymph node metastasis in 11–36% of cases [25,28–30]. As such, it is clearly one of the histologic types of sarcoma with a higher than average likelihood of regional nodal involvement. It is also the only histologic type of sarcoma for which regional nodal treatment is commonly considered as part of initial therapy.

2.1. Pediatric rhabdomyosarcoma

SLN biopsy is likely to ultimately prove to be beneficial in the initial management of pediatric rhabdomyosarcoma. Rhabdomyosarcoma is the most common soft tissue sarcoma in children under 15 years of age and is the sixth most common form of cancer in childhood. Pediatric rhabdomyosarcoma is clearly a responsive tumor, with defined roles for adjuvant therapy with radiation and systemic chemotherapy. There are several sites where these tumors preferentially occur. Rhabdomyosarcomas originating in the extremities and the genitourinary tract appear to be particularly associated with regional lymphatic spread. One review found that the percentage of patients with nodal metastases from extremity lesions was 12% [31]. The presence or absence of regional lymphatic spread in extremity lesions was a significant prognostic factor in 3-year survival rates in these patients. A follow-up study confirmed the necessity of surgically evaluating lymph node basins in extremity rhabdomyosarcoma in order to

more accurately stage patients, with the ultimate hope of using improved staging to develop optimal risk-based therapies [32]. Performing SLN biopsy in these children may assist oncologists in projecting survival for these children while at the same time preventing unnecessary major lymphadenectomies. Those with positive SLNs could undergo completion lymphadenectomy, and be treated systemically as for clinically node-positive disease.

In the case of rhabdomyosarcoma of the genitourinary tract in children, regional lymphatic spread has been reported in up to 24% of children with this type of disease [31]. As with pediatric rhabdomyosarcoma of the extremities, understanding the nodal status in these patients directly impacts therapy. Patients with known nodal disease of the regional lymphatic basin in rhabdomyosarcomas of the bladder, prostate, vagina/uterus, and paratesticular tissues routinely undergo systemic chemotherapy and radiation therapy to the regional lymphatic basin [33].

The evolving management of paratesticular rhabdomyosarcoma over the past 2 decades is especially illustrative of the potential benefit of SLN biopsy in the management of pediatric genitourinary rhabdomyosarcoma. Initially, all patients with paratesticular rhabdomyosarcoma required ipsilateral retroperitoneal lymph node dissection. Subsequently, the Intergroup Rhabdomyosarcoma Study Group recommended clinical evaluation of retroperitoneal lymph nodes using computerized tomography [34]. Only those patients with suspicious lymph node involvement on CT scan underwent surgical evaluation of the lymph node basin. Comparison of these two approaches suggested that reliance on CT scan evaluation of the regional lymph node basin resulted in understaging of lymphatic spread and resulted in underutilization of effective adjuvant therapy [34]. Developing SLN protocols seems a very appealing technology as a means to avoid the morbidity of retroperitoneal lymph node dissection in those patients with clinically localized disease.

Of course, techniques for identifying sentinel nodes from genitourinary tract primaries are far less developed than those for tumors arising on the extremities and trunk. Given the focus of pediatric oncologists on treating rhabdomyosarcoma patients in nationwide clinical trials, prospective evaluation of SLN biopsy in this disease seems feasible and worthwhile, but may require new approaches not routinely used when SLN biopsy is performed for other tumor types.

2.2. Adult rhabdomyosarcoma

In contrast to the pediatric population, the literature describing adult rhabdomyosarcoma is limited, reflecting its rarity and the paucity of prospective trials in adult sarcomas. The prognosis for adults diagnosed with

rhabdomyosarcoma is poor—worse than pediatric sarcomas and worse than other adult soft tissue sarcomas of comparable stage and grade. In one series, the overall 5- and 10-year survival rate for patients diagnosed with rhabdomyosarcoma was 31% and 27%, respectively [35]. Relatively little is known about the frequency and prognostic impact of nodal status in adult patients treated with multimodality therapy. Hence, while SLN biopsy in adult rhabdomyosarcoma appears to merit prospective evaluation, its overall impact on the disease is likely to be small at best.

3. Epithelioid sarcoma

Epithelioid sarcoma is a rare high grade soft tissue sarcoma that presents most commonly in adult males in their 20s and 30s and occurs almost exclusively in the extremities. Because of an innocuous presentation, diagnosis is often delayed. Five- and ten-year overall survival is 70% and 42%, respectively [36]. Epithelioid sarcoma clearly has a propensity for regional lymphatic spread [37]. Regional lymph node metastases in these patients ranges from 17% to 80% [25,28–30]. A more recent report demonstrated regional lymph node metastases during the course of the disease to be 44% [38]. Lymphatic spread has been shown to be an independent prognostic factor in predicting survival rates for these patients [39].

With conservative surgery, nodal failure rate ranges between 19% and 44% [38,40,41]. However, nodal failures are often associated with distant metastases, suggesting that nodal failures represent a component of widespread dissemination rather than a purely locoregional event. Routine treatment of the nodal basin, either by surgery or irradiation, appears unlikely to benefit these patients [38,42]. With such a high incidence of regional spread though, evaluation of the regional lymph node basin by lymphatic mapping and SLN biopsy may be an excellent strategy for selecting those patients who might benefit from lymphadenectomy or early systemic therapy [40].

4. Clear cell sarcoma

Clear cell sarcoma, often referred to as malignant melanoma of the soft parts, has a distinct behavior from other sarcomas—including a tendency to nodal recurrence and widespread metastasis throughout the body. In its pattern of spread, it more closely resembles melanoma than sarcoma, hence the alternate name melanoma of soft parts. It is a rare tumor constituting 1% of all soft tissue sarcomas, with only about 300 cases having been described in the literature to date [43]. It arises most commonly in the extremities as a bulky,

locally invasive tumor. As such, it is a logical candidate for SLN biopsy.

The incidence of lymph node metastases in clear cell sarcoma range from 25% to 50% [25,43]. Complete surgical excision is the standard of care in the management of clear cell sarcoma. The role of adjuvant chemotherapy and radiation therapy has yet to be determined. At this time, tumor size has been the only feature to predict tumor recurrence, with tumors greater than 5 cm demonstrating a high incidence of metastatic spread. Currently, those patients with tumor size > 5 cm undergo some form of adjuvant therapy, primarily doxorubicin-based chemotherapy [43]. However, because this sarcoma is so rare, it has been difficult to sort out optimal clinical management. With 5-, 10-, and 20-year survival of 67%, 33%, and less than 10%, respectively, there is work to be done to better manage this rare sarcoma [43]. The addition of SLN biopsy to the management of clear cell sarcoma could be a valuable technique to better predict prognosis and to further refine adjuvant therapy. Equally important will be ongoing biologic studies to better define the origin and nature of this rare tumor, in order to determine if it should be treated like a sarcoma or a melanoma [44].

5. Synovial sarcoma

Synovial sarcomas account for 7–8% of all soft tissue sarcomas and are the most common non-rhabdomyosarcoma soft tissue sarcomas in pediatric patients. Overall 5-year survival rates for patients diagnosed with synovial sarcoma ranges from 57% to 88% [45,46]. Review of the literature demonstrates regional lymphatic spread between 2% and 17% of the time [25,28–30]. As such, synovial sarcoma is the most common form of sarcoma for which regional spread is a potential clinical concern. More than 90% of these sarcomas are found in the extremities or trunk. In one recent report on synovial sarcoma, the authors contend that complete resection with clear margins and evaluation of regional lymphatic spread is the treatment of choice for this tumor [47]. The role of radiation and chemotherapy continues to evolve in the management of these sarcomas, but synovial sarcomas also appear to be among the most responsive of adult sarcomas to chemotherapy [48]. The addition of SLN evaluation in the management of synovial sarcoma could possibly refine the role of chemoradiation protocols in the future, particularly if subgroups of synovial sarcoma with higher rates of nodal spread could be identified. Given the variable reports about the true incidence of regional spread in synovial sarcoma, any evaluation of sentinel node biopsy in this disease should clearly be done in the context of a prospective trial.

6. Vascular sarcoma

Vascular sarcomas include both angiosarcoma and lymphangiosarcoma. Malignant vascular sarcomas comprise only approximately 2% of all soft tissue sarcomas in the adult population [49]. These highly malignant sarcomas are rare in the adult population and even rarer in the pediatric population. Lymph node metastases in vascular sarcomas range from 11% to 40% [25,28–30]. A more recent study notes regional lymphatic spread in 25% of patients with angiosarcoma [50]. However, the potential utility of SLN biopsy in the management of these tumors is less likely than with other sarcomas with a propensity to nodal spread.

Vascular sarcomas are notoriously difficult to achieve local control and often present with disseminated disease. In one study, 42 of 67 patients developed recurrent local disease after definitive local excision [49]. Over half of patients with angiosarcoma presented with metastatic disease on first admission, with 5-year survival rates of just over 20% [49,50]. The role of radiation therapy and chemotherapy in the management of these tumors is uncertain and many authors report negligible benefits with either treatment modality. While it is feasible that SLN biopsy may have a role in targeting cases where radiation therapy or chemotherapy might have the most benefit, the inability to achieve local control and the frequency of metastatic disease at presentation make its potential utility difficult to support.

7. Conclusion

Sentinel lymph node (SLN) biopsy has revolutionized the management of melanoma and breast cancer, and is beginning to be applied to other tumors with a propensity for lymphatic spread. Although as a whole sarcomas do not have such a propensity, certain types of sarcomas have rates of nodal metastases comparable to that for an intermediate thickness cutaneous melanoma (10–20%). The sentinel node biopsy procedure has a very low morbidity and a high likelihood of success, particularly for extremity primaries. As with melanoma and breast cancer, questions exist regarding the impact of selective regional lymph node dissection on distant relapse free survival and overall survival. In addition, the prognostic information obtained from nodal involvement of these sarcomas and the benefit of adjuvant systemic therapy in these patients is less clear than for other malignancies. In order to determine how best to use this technology in the rare types of sarcoma for which it may be ultimately useful, prospective multicenter clinical trials should be conducted. For the vast majority of soft tissue sarcomas, however, SLN biopsy

does not have a role to play, and its indiscriminate use should be condemned.

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