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The Application and Indications for Sentinel Lymph Node Biopsy in Pediatric Solid Tumors: Current Status and Future Directions

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Abstract

Oncologic staging of many solid organ malignancies involves an understanding of how cancers spread via the lymphatic system, and ultimately may involve evaluation of the primary nodal drainage basin by performing a sentinel lymph node biopsy. In the adult population, there are well established indications for sentinel lymph node biopsy in diseases like melanoma and breast cancer. However, its use and relevance in the pediatric population is less defined. This review details the history and development of sentinel lymph node biopsy technique, advanced lymph node mapping techniques currently under investigation, and the applications of sentinel node biopsy towards childhood cancers.

Keywords

1. Introduction

The concept of the sentinel lymph node (SLN) as the initial site of lymphatic tumor spread, and therefore a predictor of metastases within the remainder of the nodal basin, was first introduced more than 50 years ago [1] [2]. The use of sentinel lymph node biopsy (SLNB) is widely accepted and considered standard of care for many

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adult malignancies, including melanoma [3]-[5], breast [6], colon [7] and vulvar cancer [8]. Its use in pediatric patients is limited but studies show the technique is pivotal in staging children with malignant melanoma [9]-[12]. Additionally, the application of SLNB can be useful in children who present with pigmented lesions such as atypical Spitz tumors and spitzoid melanomas which are not easy to classify as benign or malignant [13]. Another potential use for lymphatic mapping with SLNB in children is with soft tissue sarcomas and breast cancer. Several institutional experiences using SLNB in pediatric sarcomas have recently been published and demonstrated that SLNB is practical and may be useful in directing treatment of rhabdomyosarcoma (RMS). However, SLNB appears to be less useful in non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) of the extremity, with only one study reporting positive SLNBs in patients with NRSTS [14]-[17]. As the data available on its application in children become more robust, the central role SLNB has helped surgeons avoid radical lymphadenectomies in node negative patients who would previously have undergone a more morbid operation with little benefit. In this article, we present the history and technique of SLNB, discuss the most relevant literature on clinical indications and results of its use in childhood cancer and lastly, provide a contemporary perspective on new technologies for identifying and analyzing the SLN.

2. History

Lymphatic spread of metastatic carcinoma was defined by the work of Gilchrist [18] and Zeidman [19] *et al.* in the mid-twentieth century. Their studies involved injecting various dyes, carbonaceous particles and cancer cells into the lymphatics of animal models. Systematic and reproducible dissemination of disease through the lymphatic system was shown and lymph nodes were found to be a barrier to distant metastases. Gould reported the first SLNB in a case series published in 1960 [2]. He described a total parotidectomy in 1951 where a normal appearing node sent for frozen section was found to contain metastatic tumor. Disease in the lymph node prompted Gould to perform a radical neck dissection in a case where he otherwise would not. Identifying this node, located at the confluence of the anterior and posterior facial vein, and frozen section histopathologic evaluation assisted in the surgical approach in terms of whether the patient required parotidectomy alone or the addition of an extensive neck dissection. Cabanas introduced lymphatic mapping with SLNB in the treatment of penile cancer [20]. However, the technique did not gain widespread use in oncologic resections until it was described by Morton *et al.* in malignant melanoma excisions [3]. SLNB was later adopted and modified for use in the management of a variety of other malignancies including uterine, thyroid, and breast cancers [21]-[23].

Initially, intraoperative SLN imaging was done using blue dye injected peritumorally. In the early 1990s, protocols using radio-isotopes and handheld gamma probes were developed for breast cancer [24] [25]. Radio-isotopes were found to be very effective in assisting in the identification of SLNs. Dual mapping, the use of both blue dye and radio-isotopes, was first described in breast cancer by Albertini *et al.* [26]. Each technique was compared to dual-agent injection by McMasters *et al.* who found dual-agent injection had more successful localization and a lower false-negative rate than either modality alone [27].

In adults, melanoma and breast cancer are the two most common diseases for which lymphatic mapping and SLNB are performed. They are the basis for our discussion of SLNB rationale and technique. The sentinel node is the first node in the lymphatic drainage pathway from the primary tumor to its regional nodal basin. Defining the pathologic status of the sentinel node leads to more accurate staging. If the sentinel node is without disease this may spare patients unnecessary regional lymph node dissections and their associated morbidities [28].

With regard to melanoma, for example, node status is the most significant predictor of recurrence and survival with one-fifth of all patients presenting with nodal metastases. Node-positive patients have a five-year survival approximately 40% lower than patients without nodal involvement [29]. Ninety percent of melanoma patients present with no clinical evidence of nodal metastases and were previously referred to as clinical stage I (CS-I). Prior to the development of sentinel node techniques, CS-I patients often underwent elective lymph node dissections (ELND) as it was not possible to assess node status without removal of the entire regional node basin [3]. As the above numbers show, 80% of the patients subjected to an ELND received no therapeutic benefit but were subject to all the possible morbidity of the procedure.

3. Sentinel Lymph Node Biopsy Technique

Successful identification and subsequent assessment of a sentinel node for metastatic disease requires a multidisciplinary team. There is a significant learning curve to performing these procedures with consistent, repro-

ducible, and accurate results [23]. Preoperative injection of radiolabeled tracer and lymphoscintigraphy are performed by the nuclear medicine physician. The surgeon must then identify any and all SLNs. Finally, the pathologist needs to correctly assess for the presence of metastatic disease in nodes identified [30]. Mistakes in any portion of the process can lead to inappropriate staging and subsequent failures in treatment.

Lymphoscintigraphy is helpful in assessing anomalous drainage patterns or lesions that may drain to more than one node basin [31]. Aberrant or unexpected drainage patterns usually involve lesions in the truncal midline, near Sappey's lines or in previously operated/irradiated fields [30]. These instances make preoperative imaging and assessment of the patient critical. Patients may require repositioning in the operating room to gain access to regional node basins of interest after addressing the primary lesion [28]. Patients undergo preoperative lymphoscintigraphy following injection with a radiolabeled tracer. Technetium-99m (^{99m}Tc)-labeled sulfur colloid or ^{99m}Tc-labeled trisulfide colloid are generally used with 0.5 mCi or less and a volume less than 1 cm^3 when imaging for melanoma [28]. Injections for cutaneous disease are usually intradermal and serial imaging is begun about 10 minutes after injection. All regional nodal basins at risk should be marked as well as in-transit nodes. Should imaging fail to show migration of radio-tracer after one hour, a second injection can be performed [30].

In-transit nodes, lymph nodes en route to major nodal basins proximal to the lesion are occasionally identified in melanoma cases. This emphasizes the importance of preoperative lymphoscintigraphy even in cases of primary malignancies in extremities. For cutaneous malignancies, surgical procedures should be completed within 6 to 8 hours of radiotracer injection as sentinel node activity will peak within 2 to 6 hours. Preoperative gamma probe evaluation allows the surgeon to assess the primary tumor site and look for in-transit nodes in the path to regional nodal basins prior to placing the patient under anesthesia or positioning in the operating room [28].

Vital blue dye in combination with radio-labeled tracer is often used in identifying sentinel nodes. Dye is injected into the dermis immediately adjacent to cutaneous malignancies like melanoma. For primary sites located in extremities, injections are made proximal to the lesion. Truncal lesions are injected circumferentially to assess all possible regional node beds it may drain into. Time needed to allow dye to disperse prior to sentinel node retrieval will vary based on the distance of regional node basin from the primary lesion and patient physiology [32]. This generally takes 5 to 10 minutes.

Incisions for SLNB should be made over hot spots found using a handheld gamma probe and made in line with possible incisions required for completion lymphadenectomies should the sentinel node return positive for metastatic disease [28]. Sentinel nodes are defined as any node with an *ex vivo* count to background ratio greater than 10:1; a blue node or blue-stained lymphatic channels leading up to a node; or nodes that are firm and palpable. Nodes are removed with as little trauma as possible and careful attention is used to ligate afferent and efferent lymphatic channels to prevent postoperative seroma formation [28]. *Ex vivo* counts should be recorded on all nodes removed. Any lymph node with a count more than 10% of the hottest node should also be removed and included as part of the sentinel node specimen [33]. The sentinel node bed should be probed once again for a final count to document all significant radiolabeled nodes were removed. Visual and manual inspections are then completed to remove all blue nodes, those with blue lymphatic channels leading up to them, and any grossly palpable nodes. After removal, it is up to the pathologist to assess nodes for signs of metastatic disease. In general, nodes are halved and then serially sectioned at no more than 2 mm slices [34]. Sections are initially evaluated by hematoxylin-eosin (H & E) staining. Depending on the disease process being evaluated, immunohistochemical staining may also be done if H & E staining fails to show metastatic disease [35].

Complications related to sentinel node biopsy are relatively uncommon. These include allergic reactions to blue dye, motor nerve injury, wound infections, seroma, and post-biopsy lymphedema. Compared to patients undergoing completion lymph node dissection, sentinel node biopsies had a complication rate of 4.6% versus 23.2% in the landmark Sunbelt Melanoma Trial [36]. Blue dyes injected during sentinel node biopsy are not completely benign. Isosulfan blue (ISB) and methylene blue (MB) are both used in mapping sentinel nodes [37]. MB is significantly cheaper and some experts say it is a safer and equally efficacious alternative to ISB dye [38]. ISB can cause erythema at the injection site, urticaria, hives, oropharyngeal edema, and even anaphylaxis. MB has a more benign profile but can cause skin necrosis with intradermal injection. Methylene blue has been reported to cause a handful of cases of anaphylactic shock one of which was noted in a 6-year-old healthy girl undergoing treatment for a Spitzoid tumor in our institution [39].

With regard to pregnancy, both ISB and MB are category X as neither have been tested for safety during pregnancy and should be avoided. The minimal amount of radiation imparted on the fetus by radio-labeled tracer for sentinel node biopsy was shown to be low and safe in pregnancy [40]. Long-term outcomes confirmed the

benefit of sentinel node biopsy use in staging and treatment of melanoma with the Multicenter Selective Lymphadenectomy Trial (MSLT-1). The trial compared wide local excision (WLE) and sentinel node biopsy to WLE and close observation in intermediate-thickness melanomas. Positive sentinel nodes prompted immediate therapeutic lymph node dissection (TLND) compared to delayed TLND in the observation arm once clinically apparent nodes were identified. Patients with positive sentinel nodes that received immediate TLND had a 5-year and 10-year survival advantage over the observation arm [41].

4. Advanced Mapping Techniques

In addition to vital blue dyes and conventional radio-labeled tracers, technological advances in lymphatic mapping are moving the SLNB landscape forward. Hybrid tracers containing a dual radioactive and fluorescent label have been introduced to improve the accuracy of SLN biopsy. For example, Technetium-99m (^{99m}Tc)-tilmanocept (Lymphoseek) is a macrophage, radiolabeled sugar that binds to mannose receptors in reticuloendothelial cells in sentinel lymph nodes. These novel tracers have shown superiority over blue dyes in Phase III clinical trials in adult breast cancer and melanoma [42]. Other technical developments include non-invasive imaging with near-infrared fluorescence using indocyanine green and agents that directly conjugate to cancer-targeting moieties [43].

5. Application of SLNB Surgery in Pediatric Neoplasms

The application of SLNB towards several types of cancer remains a clinically proven, minimally invasive technique, that may accurately and reliably identify the disease status in regional lymph nodes in adults [44]. For nearly two decades this important prognostic tool has evolved. It has been pivotal in the accurate staging of adult diseases [3], and potentially avoids a morbid, complete lymph node dissection if evidence of metastatic disease is not found [45]. SLNB has been used and evaluated in children primarily for cutaneous melanoma, atypical spitzoid tumors (AST) and spitzoid melanoma, and soft tissue sarcomas. The following sections incorporate a review of the pediatric literature summarizing the progress with regard to the role of SLNB in these specific, aforementioned, childhood cancers.

6. Melanoma

Melanoma in children is uncommon and for this reason the treatment algorithm continues to be extrapolated from the adult literature [46]. The National Cancer Institute [47], and National Comprehensive Cancer Network [48] recommend that lymphatic mapping and SLNB can be considered to assess the presence of occult metastasis in the regional lymph nodes of patients with primary melanomas larger than 1 to 4 mm (intermediate thickness) [49], however, performing SLNB in thin melanomas continues to be controversial [44] [50]. The value of a positive SLNB is based on identifying whether there is histological evidence of micrometastatic disease in the SLN in patients with no other evidence of metastatic disease [29] [41]. In adults, determining the lymph node status currently remains the single most important prognostic factor for intermediate thickness cutaneous melanoma and is the standard of care [51]. To ensure adequate staging and identification of the SLN, lymphatic mapping (lymphoscintigraphy) and removal of the SLN is recommended to precede wide excision of the primary melanoma [47]. Although higher rates of lymph node metastasis have been reported in pediatric melanoma patients, the prognostic value of SLNB has not been extensively studied. During the past decade there has been limited, yet increasing number of reports evaluating the role of SLNB in children and adolescents [11] [12] [14] [15] [52]-[59].

Indications for SLNB in pediatric and adolescent patients include the presence of lesions thicker than 1 mm, or the presence of ulceration, or a Clark's level of invasion of IV or V in patients with lesion less than 1 mm [46] [51] [60]. Over the past decade reports of SLNB positivity in pediatric melanoma has ranged between 25% and 50% [9] [11] [15] [45] [53] [55] [58] [60] [61] [63]. The prognostic value of SLNB for pediatric melanomas is supported based on the fact that patients with a positive SNLB had significantly worse recurrence-free survival, melanoma-specific survival [53] [54], and correlated with overall survival [64]. However, others have been unable to demonstrate a significant association between a positive SLNB and overall survival [65]. Despite higher rates of positive SLNB, children and adolescents have a lower incidence of recurrence and improved disease-free survival when compared to adults [45] [57] [66].

Ferrari *et al*. described a series of 54 patients with cutaneous melanoma collected by the Italian Rare Tumors

in Pediatric Age Project [61]. They routinely adopted the use of SLNB according to the American Joint Committee on Cancer (AJCC) adult guidelines [51], and they found 42.3% (14/33) had a positive SLN [61]. Parida *et al*. retrospectively found a 38% (11/29) positive SLN rate, and an overall 96.5% (28/29) first attempt success rate at identification of the SLN [9]. Gow *et al*. found 50% (2/4) of patients had a positive SLN [15]. Han *et al*. found that 28.8% (17/59) had SLN positivity, were associated with significantly thicker lesions, and children with melanoma had higher rates of SLN metastases than adults with comparable melanomas [53]. Howman-Giles *et al*. demonstrated a SLNB positivity rate of 25.5% (14/55). Patients less than 10 years of age tended to have thicker melanomas, and a higher SLNB positivity rate as compared to those aged greater 10 years (33% vs. 17% respectively) [10]. Livestro *et al*. demonstrated a 43.7% (7/16) SLNB positivity rate and were associated with a median tumor thickness of 2.8 mm [67]. Raval *et al*. evaluated the National Cancer Data Base between 2003 and 2007, and identified 671 patients with cutaneous melanoma. SLNB was performed in 461 patients and 118 had a positive SLN. Patients less than 5 years of age represented the group with the highest likelihood of lymph node metastases [62].

The 2008 Surveillance, Epidemiology and End Results (SEER) database in pediatric and young adults melanoma demonstrated pediatric characteristics that were associated with SLN metastases included increasing thicknesss, ulceration, and nodular histology. It was also found that children who had melanoma thickness between 1.01 mm and 2.00 mm had SLN metastases more often than young adults (age 20 - 24). Children were more likely than young adults to have SLN metastases for all analyzed characteristics (ulceration, histology, thickness, sex, and primary site) [54]. Survival analyses showed that a positive SLNB was a poor prognostic factor in pediatric and young adult melanoma [54]. SLNB has a prognostic role for pediatric melanoma patients since lymph node metastases are seen at a higher rate within this population [53]. Recommendations of the AJCC Melanoma Staging Committee for SLNB in patients with clinically localized melanomas greater than 1 mm thickness, (and selectively with thinner high-risk lesions), should be offered SLNB [51]. SLNB has enhanced accurate staging in pediatric melanoma, resulting in improvements in stage-specific survival [45].

7. Spitz Nevi, Atypical Spitzoid Neoplasm and Spitzoid Melanoma

Spitz nevi (SN) are a type of benign melanocytic tumor that may grossly and histologically mimic melanoma [58]. Another type of skin lesion known as atypical spitzoid neoplasms (ASN) are challenging to distinguish from melanoma [68] [69]. ASNs present a diagnostic dilemma because of a confusing combination of histologic qualities making it difficult to classify as benign (SN) or malignant (spitzoid melanoma) [70] [71]. The extreme variant, known as spitzoid melanoma (SM), has been defined as a rare melanoma subtype which shares many histopathologic features with spitz nevi and is one of the most difficult lesions to diagnose in dermatopathology [69]-[73].

Despite the fact that there is no single set of criteria that can distinguish ASNs from melanoma with total certainty [74], anxiety regarding the malignant potential or mis-diagnosis of ASNs has led to aggressive diagnostic and treatment procedures in children [74]. As a modality to distinguish ASNs from SN, the presence of micro-metastasis in the SLN was initially proposed as a useful adjunct allowing for histologic analysis based on the premise that only melanoma will metastasize to the SLN [58] [75] [76]. However, this may confer a misdiagnosis of melanoma [58] since the use of metastasis as the only diagnostic criteria for malignancy is thought to lead to an overestimation of their biological aggressiveness [73].

SM may develop lymph node metastasis without further progression, or widespread metastasis and fatal outcome [73]. Therefore, the role of SLNB is of significant concern. The premise that the SLNB status may provide useful information and insight that may help better assess the true biologic potential of these tumors and allow for better counseling and subsequent therapy [75] [77] has yielded mixed results. Studies have both supported [78]-[80] and refuted [81] the use of SLNB for prognostic purposes when malignant melanoma cannot be entirely ruled out. Pathologists have cautioned against classifying cutaneous melanocytic tumors based on SLN alone [82] [83]. Spatz *et al*. identified factors predictive of metastasis which included age greater than 10 years, ulceration, extension into the subcutaneous fat, diameter greater than 10mm, and more than 6 mitosis per mm^2 [84]. SLN status in patients with ASNs and SM may not have the same prognostic predictive value as in patients with conventional melanoma [70] [76] [77] [80] [82] [83] [85]-[89].

Paradela *et al*. demonstrated a SLNB positive rate of 56% (14/25) in patients with SM. They observed that SM had poorer prognostic factors such as higher Breslow thickness, mitotic rate, and metastases, but the mortal-

ity rate trend was lower in this group as compared to the non-spitzoid melanoma group (5.9% vs 12%) [73]. Better long-term outcomes in patients with ASNs or SM and positive SLN have been reported as compared to conventional melanomas [70] [76] [77] [90]. Cerrato *et al.* treated 29 patients using excision with clear surgical margins, had favorable outcomes, and demonstrated that SLNB is not warranted in the routine management of pediatric ASNs [74]. Parida *et al* retrospectively found that patients with ASNs and SMs had a 66.7% (2/3) and 33.3% (1/3) positive SLN rate, respectively [9]. Han *et al.* showed that 33.3% (1/3) of patients with SM were SLN positive [53]. Hung *et al.* demonstrated a series of patients with either ASNs and SM that underwent SLNB. The numbers of pediatric and young adult patients with ASN and SM SLNB positivity were 50% (3/6) and 57.1% (4/7), respectively [91]. With all patients combined there was a 26% and 35% SLN positivity rate in ASNs and conventional melanomas. Ludgate *et al.* demonstrated a high rate of SLNB positivity (47%) in patients with ASNs [77]. Additionally, all SLN positive ASN patients were disease free with a median follow up of 43.8 months [77].

AST frequently involves regional lymph nodes in up to 50% of patients [76] [77] [80] [87] [88] [92]. The clinical meaning of intraparenchymal SLN deposits is debated [93], with consideration of these features as unhelpful in determining the true biological potential of malignancy in these lesions [93] [94], and associated patient death is extremely rare [91]. Although SLNB continues to be an option for these patients since these lesions harbor metastatic potential, the result remains unclear as to whether this is a poor prognostic marker as in the case of melanoma. Counseling patients and families regarding the potential risks and benefits of SLNB in ASNs is necessary since they do not appear to behave like conventional melanomas [77]. It is only with long-term prospective studies that the true risk of malignancy will become more clear. Conversely, the recommendations and treatment modality for SM is similar to adult melanoma with regard to excision and timing of SLNB.

8. Soft Tissue Sarcomas

Soft tissue sarcomas (STS) are uncommon malignancies [95] and the discovery in children is even more rare [96]. STS may metastasize and most commonly develops in the lung. However, in the natural history of STS, dissemination to regional lymph nodes is not common [97]-[102]. Certain histologic subtypes including synovial sarcoma, epithelioid sarcoma, RMS, angiosarcoma, and clear cell sarcoma (CCS) may have a higher rate of nodal metastasis [98] [102]-[104]. Pediatric sarcomas [9] [14]-[17] [105] [106], and to a much lesser extent, non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) have received attention with regard to lymph node evaluation in the form of SLNB [16] [17] [105].

De Corti *et al.* reported on 17 children with STS of the extremities of which 2 had positive SLNB (alveolar RMS and undifferentiated sarcoma) [16]. They found SLNB to be technically feasible, reliable, and without complications. Kayton *et al.* found SLN positivity in 1/9 RMS, and none of the patients with CCS, epithelioid sarcoma, fibrosarcoma, synovial sarcoma or alveolar soft part sarcoma [17]. Alcorn *et al.* reviewed eight patients that underwent SLNB for STS and found 25% (2/8) of RMS were positive. The remaining patients (2 epithelioid sarcoma, 1 synovial sarcoma, 3 RMS) were SLN negative. They attempted to correlate those with SLNB positivity and computed tomography and/or positron emission tomography imaging. However, they found that imaging may not be sufficient to determine the lymph node status of pediatric patients with STS [96]. Andreou *et al.* evaluated SLNB positivity in patients with synovial sarcoma, CCS, epithelioid sarcoma, and RMS], and concluded that this modality is an important diagnostic tool for patients with CCS, who have a high rate of clinically occult regional lymph node metastasis at diagnosis [97]. Maduekwe *et al.* evaluated 29 patients with STS, and only one patient with synovial sarcoma had a positive SLNB. They found that SLNB in STS was not clinically useful in patients with localized synovial, epithelioid, or clear cell sarcoma [95].

Despite the prognosis for a child or adolescent with RMS being related to the age of the patient, site of origin, tumor size (widest diameter), resectability, presence of metastases, number of metastatic sites or tissues involved, presence or absence of regional lymph node involvement, histopathologic subtype (alveolar vs. embryonal), as well as unique biological characteristics of rhabdomyosarcoma tumor cells [107], data to support the role of SLNB in staging is extremely limited. Since regional lymph node metastases are unusual in NRSTS except in epithelioid and CCS [108], data is also limited to support the use of SLNB.

9. Breast Cancer

Male breast cancer is a rare but increasingly prevalent disease in adults [109]. To our knowledge this has not been reported in male children or adolescents. Flynn *et al.* demonstrated a SLNB positivity rate of 49% (37/76)

and demonstrated that SLNB is successful and accurate in male breast cancer patients [109]. Kayton *et al*. reported 5 patients under the age of 21 who underwent SLN for either invasive ductal carcinoma or juvenile secretory carcinoma. All five were females, two had positive SLNB with a diagnosis of invasive ductal carcinoma [17]. The application of SLNB seems theoretically appropriate towards the application in children with breast cancer, however, its rarity and lack of data do not justify such a recommendation.

10. Conclusion

Although SLNB has been supported as a pivotal part of staging pediatric cancers, and the technical feasibility has been demonstrated [11] [14] [58] [59] [110], the procedure can have dramatic consequences such as wound infection and lymphedema. For pediatric melanoma SLNB complications were seen in 52% of inguinal dissection, 17.1% of axillary dissection, and 0% in cervical dissection [111]. There is abundant literature regarding the safety and feasibility of performing SLNB in adults. Over the past decade this technique has been applied to pediatric melanoma, atypical spitzoid neoplasm, spitzoid melanoma, RMS, NRSTS, and breast cancer. Despite several studies demonstrating that SLNB is a safe technique in children, there clearly is a lack of evidence supporting its universal use in treatment algorithms for these rare pathologies in the pediatric population.

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