Published in final edited form as:

J Am Acad Dermatol. 2011 December ; 65(6): 1087–1092. doi:10.1016/j.jaad.2011.06.045.

Spitz nevi and other Spitzoid lesions: Part II. Natural History and Management

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Abstract

(In Part II of this CME, we will maintain the terminology defined in Part I for purposes of continuity. Again, “Spitz tumor” is used as the umbrella term for the entire, category of lesions; common Spitz Nevi (CSN) refers to only the most typical lesions seen in pediatric cases; and atypical Spitz tumors (ASTs) encompasses the “all other” category which continues to cause debate.)

For dermatologists, evidence-based management guidelines for Spitz tumors have not been established. Despite the lack of a standardized approach, most dermatologists recommend excision of Spitz tumors occurring in adults, and adopt more conservative measures towards pediatric cases. The histopathological attributes and the clinical scenario are factored into management in each case. While the metastatic behavior of certain Spitz tumors is well-known, the malignant potential of these lesions remains unclear as they only rarely result in negative outcomes. The risks and benefits of adjunctive measures, such as sentinel lymph node biopsy and interferon use, remain untested, and subjects of ongoing controversy.

NATURAL HISTORY

Key points

- Rare instance of metastasis and death have been observed with Spitz tumors
- Atypical Spitz tumors greater than 1 cm, ulcerated with subcutaneous involvement and mitotic figures are more likely to demonstrate micrometastasis on sentinel lymph node biopsy

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The authors have no conflicts of interest to declare.

- Sentinel lymph node biopsy may dictate further management in a subset of atypical Spitz tumors

Risk stratification

A grading scheme was proposed over a decade ago in order to correlate features with metastatic outcome (Table 1).¹ It is important to note that there are no robust models that predict death from atypical Spitz tumors (ASTs) given the low rate of events. Spatz and colleagues utilized data from 30 AST cases in order to stratify lesions into three escalating risk categories.¹ The following parameters were found to be significantly associated with increased risk metastases: >10 years of age at diagnosis, >10 mm diameter, presence of ulceration, involvement of subcutaneous fat (Clark level V), and mitotic figures $\geq 6/\text{mm}^2$. One point each was assigned to the presence of the first two parameters, two points each to presence of the remaining three, while the last parameter received a 5-point assignment if mitotic figures exceeded $8/\text{mm}^2$ (Table 1). The total score, 0-2, 3-4, and 5-11 reflected the low, intermediate, and high-risk categories, respectively. Grading and stratifying risk for lesions within this study expectedly demonstrated the correlation of increasing grade with more frequent metastatic change. Independent validation of this grading system, however, requires a larger study.

ASTs and nodal metastases

One of the recent advances in the clinical aspects of Spitz tumors is a richer understanding of metastatic behavior (eg. nodal spread) vs malignant behavior (ie. death) with utilization of sentinel lymph node biopsies (SLNB) for uncertain lesions. In an early study of 12 children with 'atypical Spitz-like melanocytic tumors', Barnhill and colleagues described three cases of lymph node metastases; two of which exhibited no evidence of disease on long-term follow-up, while one case resulted in death of the patient.² Over the ensuing decade, more generous use of sentinel lymph node biopsies for uncertain ASTs has created a more refined rate of nodal metastases. As summarized in Table 2, there are now many case series examining rates of SLN involvement for Spitz tumors; the overall positivity rate is about 38%.³⁻¹³ The relatively high rate of lymph node metastases in these studies mirrors the rates observed in conventional melanomas of comparable depth¹³ though the outstanding prognosis for patients, even those with sentinel node involvement, is quite different than melanoma.

The full biological and prognostic significance of a positive sentinel lymph node discovered with ASTs is unclear.¹⁴ Nearly all of the sentinel node positive cases yielded negative nodes upon completion lymphadenectomy. Furthermore, few, if any, led to death in the subsequent 1-3 year follow-up period.^{4, 5, 10, 13} Thus, is nodal metastasis proof of malignancy and therefore diagnostic of melanoma? Some experts contend that these lesions should be classified as Spitzoid melanomas^{6, 13, 15} while others warn against using SLN positivity to define malignancy in histologically ambiguous primaries.¹⁶ It is important to note that completely benign nevus cell aggregates may occur in the capsule, trabeculae, and rarely even the parenchyma of lymph nodes. These nodal nevi are to be distinguished from metastatic melanoma or carcinoma.¹⁷ One should consider the possibility that, in certain cases, Spitzoid nests within lymph nodes represent a similar phenomenon.

Though the application of SLNB was initially intended to clarify diagnosis, it may have inadvertently generated more surgeries (ie. completion lymphadenectomies) and greater interferon use. With the patient in mind, management of an AST is perhaps more complex given the full range of melanoma directives.

MANAGEMENT

Key points

- Excision is usually recommended for adults with Spitz nevi
- Common Spitz nevi in children may be managed non-surgically
- Atypical Spitz tumors may employ sentinel node biopsy to guide management

The uncertainty surrounding the biologic potential of ASTs has resulted in a lack of consensus regarding their management. Furthermore, with a low rate of negative events (ie. death), it is difficult to design trials to measure effective outcomes (ie. survival). Some general recommendations are provided despite the absence of any high level evidence from randomized controlled trials. The definition for the strength of each level of evidence follows:

- Level IA: Evidence from meta-analysis of randomized controlled trials
- Level IB: Evidence from at least one randomized controlled trial
- Level IIA: Evidence from at least one controlled study without randomization
- Level IIB: Evidence from at least one other type of experimental study
- Level III: Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
- Level IV: Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

Surgical management

While the vast majority of dermatologists will recommend biopsy of Spitz tumors, especially those with clinically concerning features, there is wide range of sampling techniques.¹⁸ Retrospective review shows that most approaches have been associated with high incidence of incomplete removal especially when margins were narrow and uncontrolled (1-3mm) (Level III).¹⁹ Like other atypical pigmented lesions, many experts advise that Spitz tumors be completely excised when possible (Level IV).^{14, 18, 20} Some supportive evidence comes from expert accounts and case reports of recurrence after inadequate resection with a few of these relapses resulting in fatal metastatic events (Level III).^{14, 21} In addition, these recurrent lesions often feature greater atypia than their primaries, and may resemble a desmoplastic Spitz nevus²² or even simulate melanoma.^{23, 24} Excision of the entire lesion also allows for more thorough histological evaluation.¹⁹ Given the risk of a recurrent nevus phenomenon, it is probably most prudent to re-excite a Spitz tumor if the margins are involved.^{18, 20}

ASTs have more melanoma-like features and should thus be treated more aggressively than common Spitz nevi (CSN). For such lesions, some experts recommend a wide resection following melanoma margin guidelines with the minimum margin being 1 cm (Level IV).^{14, 19} It is important to note that there have been no surgical trials involving Spitz tumors and therefore margins >1cm remain unproven.¹⁹ Since many of these lesions occur in children, there may be anatomic constraints that prevent a full 1cm margin; thus, clinical clearance of the lesion should be based on the overall judgment of the surgeon.

Management of the pediatric cases

Many adult and pediatric dermatologists recommend removal of all suspected Spitz tumors, regardless of age.¹⁸ However, since younger age is associated with a lower predictive

probability for true melanoma,²⁵ some experts would perform only a partial biopsy in the pediatric age group for lesions appearing to be CSN (Level IV),¹⁸ while others will monitor clinically and avoid sampling or intervention altogether (Level IV).²⁶ Regular dermatoscopic examination has been proposed as a method to rigorously monitor CSN in children under 12 years of age, with excision reserved for clinically or dermoscopically atypical lesions in children over 12 (Level IV).²⁷

SLN Biopsy

No outcomes data exist with either Spitz tumor or melanoma documenting a survival benefit with sentinel lymph node biopsy. Furthermore, none of the surgical trials involving SLNB specifically enrolled patients with ASTs. Therefore, early application of SLNB in ASTs, especially those thicker than 1mm²⁸ was met with enthusiasm since it provided a possible diagnostic measure, ie. nodal involvement meant metastatic melanoma. However, it soon became clear that up to 40% of AST cases were associated with regional metastasis despite a very low rate of mortality (Table 2). In the largest and most complete long-term follow-up series of ASTs, 27 of the 57 cases that underwent SLN biopsy yielded positive nodal status. Despite the high incidence of positivity (47%), only a single case demonstrated recurrence and eventual death from metastatic disease.¹² Besides a younger average age for SLN positive cases, there were no other significant differences. While this represents observational data from which only extremely limited conclusions may be drawn, it does serve to challenge the significance of nodal involvement, as well as the true case fatality rate of ASTs. Thus, selective lymphadenectomy does not have the same prognostic utility for ASTs as it does for adult type melanoma. In the absence of documented benefit, it is difficult to recommend SLNB for Spitz tumors; likewise, in the absence of major morbidity, it is also difficult to firmly recommend against SLNB in pathologically challenging cases though completion lymphadenectomy in young individuals is not without potential complications. It is best to discuss the utility of SLNB case-by-case in the following contexts.

1. ASTs are clinically and genetically distinct from the common adult forms of melanoma.
2. Evidence to date suggests that nodal metastases from ASTs are not uncommon and yet death from widespread disease is quite rare. Precise death rates are not available, but, from the reported cases series, it is not unreasonable to presume a mortality rate that is less than 5%. Thus, SLNB positivity is poorly predictive of patient negative outcome.
3. Major trials of SLNB to date have not documented a survival benefit even for adult type melanomas. Moreover, these trials were not designed to study ASTs.
4. If one decides **not to** undergo SLNB, the patient should still be instructed on nodal examination, as in melanomas, and the physician should monitor for regional relapse during routine follow up examinations.
5. If one decides **to** pursue SLNB, the morbidity from the procedure itself is generally minor (eg. infection, lymphedema) though not negligible. However, the probability of finding metastatic disease is probably around 25-40%. If nodal deposits are in fact identified in the sentinel node, there is a high likelihood that the surgical oncologist will perform a completion lymphadenectomy. This second more extensive dissection is associated with greater risks especially in the head/neck of young patients.
6. More likely than not, if regional disease is identified, the patient will also be referred to a medical oncologist for discussion of interferon use. There have been

no interferon trials to date that have enrolled individuals with ASTs and therefore all putative benefits represent extrapolations from adult type melanomas. Those with AST cells in the sentinel node will often be treated like Stage III melanoma patients. Even so, the benefits of interferon in microscopic Stage III melanoma are not clear. Moreover, the side effects of interferon can be severe and should be fully discussed by the medical oncologist.

7. There are extraordinary cases of death from Spitz tumors. No clinical, pathological or molecular feature known to date allows one to predict these events with any element of certainty. It is also unclear that additional measures, such as SLNB or interferon use, would have aborted these events. It is thus valuable to continue surveillance on a regular basis (ie. at least annually) and assess for evidence of relapse on a review of systems and full physical examination.

Conclusion

Given its complex behavior and the lack of rigorous outcomes data, the logical underpinnings of Spitz tumor management are not straightforward. Despite a proliferation of more intricate appellations, our understanding of Spitz tumors has been enhanced by the recognition that ASTs frequently metastasize to lymph nodes despite a very low rate of mortality. Within biological contexts, the notion of “benign metastasis” is highly provocative and therefore ASTs represent a unique opportunity in cancer research.

Acknowledgments

This work was made possible by support from the American Cancer Society, the National Institutes of Health K24 CA149202 (both to H.T.), the Seed Grant from the American Medical Association (to S.L.), and the generous donors to the Millennium Melanoma Fund at the MGH.

This scholarly activity has been made possible in part by a grant from the American Medical Association (to S.L.), the National Institutes of Health (K24 CA149202-01 and P50 CA-93683 both to H.T.), the American Cancer Society (RSG MGO-112970 to H.T.) and the generous donors to the MGH Millennium Melanoma Fund.

ABBREVIATIONS

CSN	common Spitz nevi
AST	Atypical Spitz tumor
SLNB	sentinel lymph node biopsy

REFERENCES

1. Spatz A, Calonje E, Handfield-Jones S, Barnhill RL. Spitz tumors in children: a grading system for risk stratification. *Arch Dermatol*. 1999; 135:282–5. [PubMed: 10086449]
2. Barnhill RL, Flotte TJ, Fleischli M, Perez-Atayde A. Cutaneous melanoma and atypical Spitz tumors in childhood. *Cancer*. 1995; 76:1833–45. [PubMed: 8625056]
3. Gow KW, Rapkin LB, Olson TA, Durham MM, Wyly B, Shehata BM. Sentinel lymph node biopsy in the pediatric population. *J Pediatr Surg*. 2008; 43:2193–8. [PubMed: 19040933]
4. Roaten JB, Partrick DA, Pearlman N, Gonzalez RJ, Gonzalez R, McCarter MD. Sentinel lymph node biopsy for melanoma and other melanocytic tumors in adolescents. *J Pediatr Surg*. 2005; 40:232–5. [PubMed: 15868590]
5. Gamblin TC, Edington H, Kirkwood JM, Rao UN. Sentinel lymph node biopsy for atypical melanocytic lesions with spitzoid features. *Ann Surg Oncol*. 2006; 13:1664–70. [PubMed: 17024556]

6. Lohmann CM, Coit DG, Brady MS, Berwick M, Busam KJ. Sentinel lymph node biopsy in patients with diagnostically controversial spitzoid melanocytic tumors. *Am J Surg Pathol*. 2002; 26:47–55. [PubMed: 11756768]
7. Urso C, Borgognoni L, Saieva C, Ferrara G, Tinacci G, Begliomini B, et al. Sentinel lymph node biopsy in patients with “atypical Spitz tumors.” A report on 12 cases. *Hum Pathol*. 2006; 37:816–23. [PubMed: 16784980]
8. Magro CM, Crowson AN, Mihm MC Jr. Gupta K, Walker MJ, Solomon G. The dermal-based borderline melanocytic tumor: a categorical approach. *J Am Acad Dermatol*. 2010; 62:469–79. [PubMed: 20159313]
9. Cochran AJ, Binder S, Morton DL. The role of lymphatic mapping and sentinel node biopsy in the management of atypical and anomalous melanocytic lesions. *J Cutan Pathol*. 2010; 37(Suppl 1):54–9. [PubMed: 20482676]
10. Murali R, Sharma RN, Thompson JF, Stretch JR, Lee CS, McCarthy SW, et al. Sentinel lymph node biopsy in histologically ambiguous melanocytic tumors with spitzoid features (so-called atypical spitzoid tumors). *Ann Surg Oncol*. 2008; 15:302–9. [PubMed: 18000712]
11. Ghazi B, Carlson GW, Murray DR, Gow KW, Page A, Durham M, et al. Utility of lymph node assessment for atypical spitzoid melanocytic neoplasms. *Ann Surg Oncol*. 2010; 17:2471–5. [PubMed: 20224858]
12. Ludgate MW, Fullen DR, Lee J, Lowe L, Bradford C, Geiger J, et al. The atypical Spitz tumor of uncertain biologic potential: a series of 67 patients from a single institution. *Cancer*. 2009; 115:631–41. [PubMed: 19123453]
13. Su LD, Fullen DR, Sondak VK, Johnson TM, Lowe L. Sentinel lymph node biopsy for patients with problematic spitzoid melanocytic lesions: a report on 18 patients. *Cancer*. 2003; 97:499–507. [PubMed: 12518375]
14. Barnhill RL. The Spitzoid lesion: rethinking Spitz tumors, atypical variants, ‘Spitzoid melanoma’ and risk assessment. *Mod Pathol*. 2006; 19(Suppl 2):S21–33. [PubMed: 16446713]
15. Zuckerman R, Maier JP, Guiney WB Jr. Huntsman WT, Mooney EK. Pediatric melanoma: confirming the diagnosis with sentinel node biopsy. *Ann Plast Surg*. 2001; 46:394–9. [PubMed: 11324881]
16. Elder DE, Xu X. The approach to the patient with a difficult melanocytic lesion. *Pathology*. 2004; 36:428–34. [PubMed: 15370112]
17. Biddle DA, Evans HL, Kemp BL, El-Naggar AK, Harvell JD, White WL, et al. Intraparenchymal nevus cell aggregates in lymph nodes: a possible diagnostic pitfall with malignant melanoma and carcinoma. *Am J Surg Pathol*. 2003; 27:673–81. [PubMed: 12717252]
18. Gelbard SN, Tripp JM, Marghoob AA, Kopf AW, Koenig KL, Kim JY, et al. Management of Spitz nevi: a survey of dermatologists in the United States. *J Am Acad Dermatol*. 2002; 47:224–30. [PubMed: 12140468]
19. Murphy ME, Boyer JD, Stashower ME, Zitelli JA. The surgical management of Spitz nevi. *Dermatol Surg*. 2002; 28:1065–9. discussion 9. [PubMed: 12460304]
20. Casso EM, Grin-Jorgensen CM, Grant-Kels JM. Spitz nevi. *J Am Acad Dermatol*. 1992; 27:901–13. [PubMed: 1479095]
21. Barnhill RL, Argenyi ZB, From L, Glass LF, Maize JC, Mihm MC Jr. et al. Atypical Spitz nevi/ tumors: lack of consensus for diagnosis, discrimination from melanoma, and prediction of outcome. *Hum Pathol*. 1999; 30:513–20. [PubMed: 10333219]
22. Stern JB. Recurrent Spitz's nevi. A clinicopathologic investigation. *Am J Dermatopathol*. 1985; 7(Suppl):49–50. [PubMed: 3940090]
23. Harvell JD, Bastian BC, LeBoit PE. Persistent (recurrent) Spitz nevi: a histopathologic, immunohistochemical, and molecular pathologic study of 22 cases. *Am J Surg Pathol*. 2002; 26:654–61. [PubMed: 11979096]
24. Omura EF, Kheir SM. Recurrent Spitz's nevus. *Am J Dermatopathol*. 1984; 6(Suppl):207–12. [PubMed: 6528921]
25. Vollmer RT. Patient age in Spitz nevus and malignant melanoma: implication of Bayes rule for differential diagnosis. *Am J Clin Pathol*. 2004; 121:872–7. [PubMed: 15198360]

26. Nino M, Brunetti B, Delfino S, Panariello L, Russo D. Spitz nevus: follow-up study of 8 cases of childhood starburst type and proposal for management. *Dermatology*. 2009; 218:48–51. [PubMed: 18832809]
27. Brunetti B, Nino M, Sammarco E, Scalvenzi M. Spitz naevus: a proposal for management. *J Eur Acad Dermatol Venereol*. 2005; 19:391–3. [PubMed: 15857482]
28. Kelley SW, Cockerell CJ. Sentinel lymph node biopsy as an adjunct to management of histologically difficult to diagnose melanocytic lesions: a proposal. *J Am Acad Dermatol*. 2000; 42:527–30. [PubMed: 10688734]

Part II. CAPSULE SUMMARY

- Adult Spitz tumors are usually excised despite a lack of a uniform standardized protocol, while pediatric cases are most often non-surgically managed.
- Use of the sentinel lymph node biopsy has been a recently controversial management adjunct for selected questionable Spitz tumors
- While the metastatic potential of Spitz tumors has been clearly demonstrated, their true malignant potential is debatable and an important consideration prior to surgical interventions.

Table 1

Assessing Risk of Metastasis in Atypical Spitz Tumors

Presence of parameter	Score conferred
Age >10 years old:	1
Diameter >10 mm:	1
Subcut. fat involvement:	2
Ulceration:	2
Mitoses: <5/mm ²	0
6-8/mm ²	2
>8/mm ²	5
	Max. total: 11
	↓
Risk categories:	
Low	0-2
Intermediate	3-4
High	5-11

Adapted from Spatz et al. 1999

Table 2

Sentinel Lymph Node (SLN) Status in Atypical Spitz Tumors

Study	# of SLN positive	Total # of SLN	Rate of positivity
Gow et al.	1	3	33%
Roaten et al.	2	3	67%
Gamblin et al.	3	10	30%
Lohmann et al.	5	10	50%
Urso et al.	4	12	33%
Magro et al.	5	14	36%
Cochran et al.	8	18	44%
Murali et al.	6	21	29%
Ghazi et al.	6	27	22%
Ludgate et al. *	27	57	47%
Total:	67	175	38%

* Includes patients from the University of Michigan 2003 series by Su et al.