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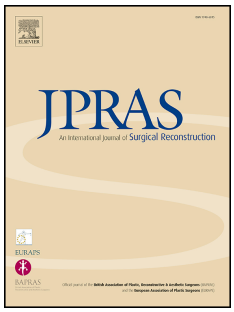

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Is Sentinel Lymph Node Biopsy Warranted for Desmoplastic Melanoma? A Systematic Review

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ABSTRACT

Background

Desmoplastic melanoma (DM) is an uncommon malignancy, associated with a high local recurrence rate. The aim of this systematic review was to determine the positivity rate of sentinel lymph node biopsy (SLNB) in patients with DM. The secondary outcome was to establish if SLNB is warranted for both pure desmoplastic melanoma (PDM) and mixed desmoplastic melanoma (MDM).

Methods

A full systematic literature review of sentinel lymph node biopsy (SLNB) in DM was performed by two authors in January 2016. Ovid MEDLINE, Ovid EMBASE and the Cochrane Central Register of Controlled Trials were searched.

Results

Sixteen studies involving 1519 patients having SLNB for DM were included, of which 99 patients had positive SLNB (6.5%). Two articles reported a significantly reduced disease-free survival (DFS) with positive SLNB, and three published a reduced melanoma-specific survival (MSS). Six studies compared SLNB in MDM and PDM. Of 275 patients, 38 (13.8%) had a positive SLNB in MDM compared to 17 of 313 patients (5.4%) with PDM.

Conclusions

Rates of positive SLNB in DM are reduced compared to other variants of melanoma, however nodal status may still predict DFS and MSS. MDM is associated with a higher rate of micro-metastases to regional lymph nodes than PDM, and DFS and MSS may be reduced compared to PDM. We would recommend consideration of SLNB in MDM. However, with such low rates of positive SLNB for PDM, and in the absence of high risk features to stratify patients, we would not recommend SLNB in PDM.

Keywords: sentinel node; desmoplastic; melanoma

Introduction

Desmoplastic melanoma (DM) is an uncommon malignancy representing 1-3% of all cutaneous malignant melanomas, lacking typical features of commoner variants of melanoma.[1,2] It is characterised histologically by spindle-shaped melanocytes within a fibrocollagenous (desmoplastic) stroma, and has a predilection for the head and neck in older, male patients.[3] It presents as a thicker tumour than non-desmoplastic melanomas and is associated with a high local recurrence rate.[2-5]

Despite patients presenting with thicker tumours, regional metastases are suggested to be lower than other melanomas, and DM may be associated with an improved overall survival. [2-4,6] Estimates of rates of positive sentinel lymph node biopsy (SLNB) have been reported as 0 -18%.[7-10]

In 2004, Busam distinguished pure DM (PDM), with desmoplasia present throughout ≥90% of the tumour, from combined DM, with <90% desmoplasia present.[11] The combined variant was renamed 'mixed' in 2005,[12] and early data suggested PDM metastasised less frequently to regional nodes than mixed DM (MDM), with a longer disease-free survival.[10,12-14] However, recent studies argue the incidence of micro-metastases to regional lymph nodes in PDM is higher than previously reported, and SLNB is warranted for all cases of DM.[7,9,15] It has led to the publishing of conflicting national SLNB guidance in the United States.[16,17]

The aim of this systematic review was to determine the positivity rate of SLNB in patients with DM. The secondary outcome was to establish if SLNB is warranted for both PDM and MDM.

Methods and Materials

Search Strategy

Two authors (JAD and JCRW) independently carried out a full systematic literature review of all studies in Ovid MEDLINE, Ovid EMBASE and the Cochrane Central Register of Controlled Trials. Both 'free-text term' and 'MeSH term' searches were performed, using variations of the keyword 'desmoplas*'. Keywords were combined using Boolean operators. Articles in the English language were considered. Each author's search results were merged and duplicate citations were discarded. Titles and abstracts were screened and studies unrelated to the research objective were discarded. The full text of the relevant papers were retrieved and examined by each author independently for consideration for inclusion/exclusion. The final list of the included studies was compared and discussed between two authors (JAD and JCRW). The reference lists of all identified articles were reviewed for relevant studies. Finally, archives of pertinent journals were hand-searched for relevant

articles (Journal of Plastic, Reconstructive and Aesthetic Surgery, Plastic and Reconstructive Surgery, Annals of Surgical Oncology, and European Journal of Surgical Oncology). The authors of all included studies were contacted to identify potential further or ongoing research. The search was last undertaken in January 2016. Data were extracted by two authors independently (JA and JCRW) using a standardised form. The data were then cross-checked between the two authors to confirm accuracy of extraction.

Selection Criteria

The inclusion and exclusion criteria were decided during the protocol stage of the review. All papers reporting on outcomes of patients with DM as a primary outcome were included for review, to optimise population homogeneity. Data were extracted for studies reporting the incidence of positive lymph nodes in SNLB for DM. Studies not reporting SLNB outcomes were excluded. Where a study included SLNB with other lymph node examinations (microscopic and macroscopic disease), and the positivity rate for SLNB could not be determined, it was excluded.[14] Case reports, review articles and duplicate patient populations were excluded. Where two studies used the same database or patient population and the time period was over-lapping there is a risk of duplication bias, so the most extensive data collection was used, with the shorter study excluded. Where two studies had similar time periods from the same database, however one restricted participants by anatomical site, both were included.

The study selection process was performed in accordance with the PRISMA statement and is reported in Figure 1. The search strategy identified 232 papers, which were screened for retrieval, and 191 were deemed irrelevant based on their title or abstract. Forty-one studies were retrieved for detailed review, of which 19 did not meet the inclusion criteria. Six further studies were excluded, as they did not report SLNB outcomes. The remaining 16 papers were included in the review. The principal summary measure was the rate of positive SLNB for patients with DM, expressed as a percentage and the secondary measure was the incidence of positive SLNB comparing PDM and MDM.

Results

Sixteen studies were included in the review, and all were observational in design and conducted in three countries (Table 1).[1,3,7-10,13,15,18-25] Ten of the 16 studies included less than 50 patients and average Breslow thickness was 2.0mm or greater in all articles. Two included only patients with head and neck DM, while the remainder included DM of all sites.[20,21] Almost all studies were retrospective case series (level IV evidence), bar one case-control study (level 3 evidence).[1] There was

considerable variability between the study periods of the included articles, ranging from 5-25 years. The follow-up periods were also heterogenous (range 0.9-9.9 years). However, patient demographics were comparable between groups.

In total, 1519 patients were identified from all studies and 99 SLNB (6.5%) were positive (Table 2). Five of the sixteen studies did not identify a positive SLNB in any patient. Two articles reported a significantly reduced disease-free survival (DFS) with a positive SLNB, and three published a reduced melanoma-specific survival (MSS). Egger et al reported a reduced overall survival (OS) with an ulcerated primary DM and a positive SLNB.

Two studies compared positive SLNB in DM with non-DM. Livestro et al reported a case-control study matched for age, sex, tumour thickness and year of diagnosis, and demonstrated a positive SLNB rate of 8% in DM compared to 34% for non-DM. Pawlik et al performed a similar comparison albeit without matching, and reported a positive SLNB rate of 17.5% in non-DM compared to 6.2% in DM. However, when DM was divided into mixed and PDM, positive SLNB rates were 15.8% and 2.2% respectively, with PDM significantly lower than MDM and non-DM ($P < 0.01$).

Six studies compared SLNB in mixed and PDM. Of a total of 275 patients in these studies, 38 (13.8%) had a positive SLNB in MDM compared to 17 of 313 patients (5.4%) with PDM. Of these, Mohebati et al did not identify a positive SLNB in either cohort. Two studies reported MDM was associated with a reduced DFS. Pawlik et al reported 2.2% and 15.8% of patients with pure and MDM had positive SLNB respectively. All patients in this study had SLNB, and PDM was associated with a significantly improved 3 year DFS compared to the mixed subtype. 100% of their 46 patients with PDM were free of disease at 3 years, compared to 15 patients of a total of 19 (79.1%) in the MDM cohort (P=0.004).

Han et al reported a high rate of melanoma-related deaths in those with a positive SLNB in PDM (2 of 6 patients; 33.3%) compared to 4 of 61 (6.6%) who had a negative SLNB. For patients with MDM, 3 of 15 patients (20%) with a positive SLNB had a melanoma-related death compared to 12 of 46 patients (26.1%) who had a negative SLNB.

Three studies reported a definition of DM that differed from the criteria published by Busam et al, and were more likely to select tumours with PDM.[11] The remaining studies reported DM as defined by Busam or it was not stated. Two studies comparing pure and MDM, defined PDM as 80-90% desmoplasia or greater, compared to ≥90% in the remaining four studies.

Discussion

Data from this systematic review provides further evidence that the prevalence of micro-metastases in DM is lower than other variants of melanoma. A positive SLNB in DM may be associated with a reduced DFS and MSS. In addition, positivity rates differ for the two histological subtypes, with PDM exhibiting lower rates of positive SLNB compared to MDM.

Early data suggested a poorer prognosis associated with DM compared to other types of melanoma, however more recent studies have reported comparable or improved survival, in particular when matched for tumour thickness.[1,3,4,26] DM tumours are typically thicker on presentation, however the relationship between survival and Breslow thickness is less clear compared to other melanomas, with conflicting reports as to prediction of recurrence and survival. [1,2,3,12] As such, variation in the biology of DM has been proposed, evidenced by differences from other melanomas on microarray profiling, absence of activating BRAF mutations, high local recurrence rates of up to 40%, and reduced rates of nodal metastasis.[1,3,27-31]

Suggested differences in the behaviour and rates of nodal metastasis in DM has led to varying opinions on the value of SLNB in this cohort, in comparison to other variants of melanoma where it is an important prognostic indicator.[32] The overall rate of positive SLNB in the review was 6.5%, considerably lower than the positivity rate of 20% reported in MSLT-I for all melanomas.[32] However, the positive SLNB rate for MDM was 13.8%, which is closer to the rate for all melanomas.

Criteria for which patients were offered SLNB were poorly reported in studies in this review. Differences in positive SLNB rates published may in part be explained by small sample sizes and varying definitions of DM in studies prior to Busam's criteria, posing a risk of misclassification bias. Jaroszewski et al defined DM as a significant invasive component composed of atypical spindle cells in a fibrotic stroma in a series of 12 patients having SLNB, while Gyorki et al similarly described DM as a prominent stromal fibrosis throughout the entire tumor predominantly composed of fusiform melanocytes constituting >90% of the tumor cell population in a cohort of 24 patients having SLNB.[3,8] It is likely both studies have a high proportion of PDM, and may account for the absence of positive SLNB observed. Although two studies comparing pure and MDM defined PDM as 80-90% desmoplasia throughout the tumour rather than >90% in Busam's criteria, the likelihood of misclassification appears less as both report MDM as desmoplasia in <50% of the tumour, maintaining a distinction between the two.[7,13]

Although cumulative rates of positive SLNB in DM are reduced, nodal status may still predict DFS and MSS.[1,9,15,19,20] Offering SLNB for MDM with a positivity rate of 13.8% appears reasonable, however it is less clear with regards to the rate of 5.4% in PDM. MDM is characterised by a more aggressive

course, and associated with a worse DFS and MSS compared to PDM.[10-12] Hawkins et al reported a 5 year melanoma-specific mortality of 31% and 11% for MDM and PDM respectively.[12] Han et al reported 2 of 6 patients (33%) with positive SLNB for PDM had a melanoma-related death compared to 3 of 15 patients (20%) for MDM,[9] and may suggest PDM is aggressive in a small group of patients where micro-metastases are present.

Offering SLNB on a routine basis should consider the benefits of prognostic information, with the surgical risks of a staging procedure and cost-effectiveness within a specified patient population. The National Institute for Health and Clinical Evidence (NICE) in the United Kingdom has ceased to recommend SLNB for thin melanomas (≤1mm Breslow thickness), where the positive SLNB rate is 8-12%, and the complication rate is 10%.[32-34] DM typically presents as a thick tumour, however studies in this review included some patients with tumours ≤1mm Breslow thickness, although how many had SLNB is unclear. High risk features have not been consistently reported in DM, and further research to establish if all patients with MDM should be offered SLNB, based on stratification using clinic-pathological factors, should be undertaken. Analysing patients with PDM who are at the greatest risk of regional metastases and may warrant SLNB could improve outcomes in this small cohort.

Following a positive SLNB, national guidelines advise consideration of completion lymph node dissection (CLND), with the aim of limiting further metastasis and providing regional control.[33] Two studies reported up to a quarter of patients with DM may have non-sentinel lymph nodes identified on CLND histopathological examination, although impact of CLND on DFS and MSS was not reported.[9,15,33]

Distant metastases may develop in 11 to 40% of cases in DM, with a predilection for the lungs and brain.[2,3,30,35,36] Maurichi et al reported development of distant metastases in 24 patients (20%) with PDM, of which only 2 had SLNB, and 92% had one or more local recurrences prior to developing distant metastases.[13] By contrast, 49 patients (40%) with MDM developed a distant metastasis, 80% as the first event. Patients who had a >2mm Breslow thickness melanoma excised with a 2cm margin, had distant spread in 3% of cases of PDM and 40% of those with MDM (P<0.001). Aggressive early surgical management may reduce the risk of distant metastases, however presence of recurrence may signal a high-risk group.

Review limitations included two instances of studies identified in the search strategy which had used the same database or population cohort. This introduced the risk of multiple publication bias, albeit by different authors. Therefore, duplicate patient cohorts had the smaller series excluded where there was overlap in time periods. As such, some patients who were not in the overlapping period

were not included, limiting the patient pool. Where one study reported one anatomical site only over a similar period, both were included. The review should be repeated in two years as an update.

In conclusion, rates of positive SLNB in DM (6.5%) are reduced compared to other variants of melanoma, however nodal status may still predict DFS and MSS.[1,9,15,19,20] MDM is associated with a higher rate of micro-metastases to regional lymph nodes (13.8%) than PDM (5.4%), and DFS and MSS may be reduced compared to PDM. With consideration of the rate of positive SLNB in histological subtypes of DM, procedural complications and cost, we would recommend consideration of SLNB in MDM. However, with such low rates of positive SLNB for PDM, and in the absence of high risk features to stratify patients, we would not recommend SLNB in PDM.

Conflict of interest: Nil

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Figure 1. Study Attrition Chart

Table 1. Demographic Data for Included Studies

Study	Year	Study Design	Country	Study period (years)	N	Median Age (years)	M:F	DM Site	Median follow-up (years)
Jaroszewski	2001	Case series	USA	15	59	62.8	1.7:1	All	3.83*
Gyorki	2003	Case series	USA	5	27	64	2.8:1	All	2.25
Su	2004	Case series	USA	5	33	61	3.1:1	All	1.66
Livestro	2005	Case-control	USA	32	89	63.9	1.7:1	All	4.3
Pawlik	2006	Case series	USA	11	65	61	1.3:1	All	2.9
Posther	2006	Case series	USA	23	129	55.2	1.7:1	All	5.1*
Thelmo	2006	Case series	USA	6	16	57.5*	2.2:1	All	0.9*
Cummins	2007	Case series	USA	5	28	64	1:1	All	1.74
Maurichi	2009	Case series	Italy	25	242	64	1.3:1	All	9.9
Murali	2010	Case series	Australia	14	252	61	1.9:1	All	2.9
Wasif	2011	Case series	USA	18	1735	69	1.8:1	All	5**
Mohebati	2012	Case series	USA	24	47	71	1.4:1	Head and neck	5
Eppsteiner	2012	Case series	USA	5	467	70*	2.3:1	Head and neck	4.9**
Broer	2013	Case series	USA	12	22	64	3:1	All	2.1*
Egger	2013	Case series	USA	11	47	57	2.1:1	All	6.4
Han	2013	Case series	USA	18	205	66	2.2:1	All	6.3

*mean

**longest recorded follow-up

Table 2. SLNB Outcomes for Included Studies

	Study	Median Breslow thickness (mm)	Primary Outcome		Secondary Outcome		Positive SLNB association with DFS, MSS and OS
			SLNB patients (n)	SLNB positive (%)	MDM SLNB positive (n) / total cases (n)	PDM SLNB positive (n) / total cases (n)	
1	Jaroszewski 2001	6.5*	12	0 (0%)	-	-	-
2	Gyorki 2003	2.2	24	0 (0%)	-	-	-
3	Su 2004	2.8	33	4 (12.1%)	-	-	-
4	Livestro 2005	2.6	25	2 (8%)	-	-	Reduced MSS
5	Pawlik 2006	2.9	65	4 (6.2%)	3/19 (15.8%)	1/46 (2.2%)	Reduced DFS for mixed vs pure
6	Posther 2006	4.4*	12	0 (0%)	-	-	-
7	Thelmo 2006	3.9*	16	0 (0%)	-	-	-
8	Cummins 2007	2.3	15	1 (6.7%)	-	-	-
9	Maurichi 2009	1.9 MDM 2.1 PDM	100	9 (9%)	7/51 (13.7%)	2/49 (4.1%)	-
10	Murali 2010	2	252	17 (6.7%)	11/129 (8.5%)	6/123 (4.9%)	Reduced DFS Reduced DFS for mixed vs pure

11	Wasif 2011	3.0*	505	14 (2.8%)	-	-	-
12	Mohebati 2012	6.1*	21	0 (0%)	0/7 (0%)	0/14 (0%)	-
13	Eppsteiner 2012	3.5	165	8	-	-	Reduced MSS
14	Broer 2013	3.9*	22	4 (18.2%)	2/8 (25%)	2/14 (14.3%)	-
15	Egger 2013	2.6	47	8 (17.0%)	-	-	Reduced DFS With ulcerated primary - reduced OS
16	Han 2013	3.7	205	28 (13.7%)	15/61 (24.6%)	6/67 (9.0%)	Reduced MSS
		TOTAL	**1519**	**99 (6.5%)**	**38/275 (13.8%)**	**17/313 (5.4%)**	

*mean