Analysis of melanoma recurrence following a negative sentinel lymph node biopsy

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Practice points

Background

- In 2008 the global burden of melanoma accounted for the loss of over 2 million disability-adjusted life years (DALYs) including approximately 1.9 million years of healthy life lost.
- In 2012, 69,109 new cases of melanoma were diagnosed and 10,224 deaths were attributed to melanoma in the USA.

Current role of sentinel lymph node biopsy

- Since its introduction, sentinel lymph node biopsy (SLNBx) has been integrated into diagnostic algorithms for the evaluation of cutaneous melanoma.
- Current guidelines recommend wide local excision with SLNBx for stage Ib and stage II melanomas that are >0.1 mm in thickness and without clinical evidence of nodal disease.
- SLNBx determines the final staging and recommendations for systemic and surgical treatment options.
- The probability of developing distant or local disease recurrence following a negative sentinel lymph node (SLN) can range from 4 to 29%.
- Little is reported regarding outcomes of patients with a 'false-negative' (FN) result.

Recurrence after negative SLNBx

- Median time to any melanoma recurrence after negative SLNBx was 9.3–35.4 months.
- Melanoma of the head and neck was observed to recur within the shortest time interval.
- Risk factors associated with recurrence included increased depth of the primary lesion, the presence of ulceration, advanced age at diagnosis and location of the primary lesion on the head and neck.
- Distant disease was the most common site of recurrence, representing 31.3–70.0% of all patients who developed recurrent disease following a negative SLNBx.

Definition of FN rate

- A FN SLNBx is defined as recurrence of melanoma in the previously biopsied lymph node basin.
- The false omission rate or FN predictive value is defined as:
 - $(FN / \text{initially negative SLNBx})$.
- The FN rate (FNR) is defined as: $(FN / [\text{true positive} + FN])$.
- False omission rate ranged from 0.9 to 8.9%.

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Practice points (cont.)

Definition of FN rate (cont.)

- FNR ranged from 2.8 to 32.1%.
- The highest FNR has been observed in patients undergoing SLNBx for head and neck melanoma.
- Five-year overall survival (OS) for patients following a positive SLNBx ranged from 32 to 69.7%, and 5-year OS for patients who develop distant, local or regional disease after FN SLNBx ranged from 48.4 to 60%.
- The majority of patients who develop disease recurrence after a negative SLNBx, do so following a true-negative SLNBx; however, no studies were found which evaluate outcomes or risk factors for recurrence in this population.
- The lack of data regarding survival of patients who develop local, regional or distant melanoma recurrence after true-negative SLNBx call for more in-depth evaluation of this patient population.

Etiology of FN SLNBx

- Possible etiologies of FN SLNBx include:
 - Poor radiographic localization of the SLN;
 - Failed pathologic evaluation of the sampled lymph node;
 - Failure of surgical technique to identify the SLN.

Melanoma biology & recurrence

- Melanoma which recurs after negative SLNBx may exhibit a different tumor biology.
- The development of distant metastases despite negative SLNBx may be due to:
 - Local regression of primary melanoma lesions;
 - Immunologic clearance of the melanoma in the regional lymph node basin;
 - Direct hematogenous spread of the disease;
 - The presence of melanoma leading to obstruction of lymphatic drainage.

Follow-up of patients after negative SLNBx

- Goal of improved risk stratification of melanoma patients at risk for recurrence based on individual patient's inherent biologic activity associated with a specific melanoma.
- The decreased OS of patients who develop recurrent melanoma following a negative SLNBx calls for increased efforts to:
 - Minimize FN SLNBx;
 - Identify risk factors for recurrence;
 - Define the roles of supplementary imaging (such as ultrasound) to aid the localizing of the true SLN;
 - Improve understanding of individual melanoma tumor biology.

Little attention has been paid to the characteristics and outcomes of patients who experience distant, local or regional recurrence of melanoma following a negative sentinel lymph node biopsy. This article aims to review the published literature on the topic and presents some general summaries regarding this patient population. Patients who experience a disease recurrence following a negative sentinel lymph node biopsy have a worse overall survival compared with patients with a positive sentinel lymph node biopsy. The implications and possible explanations for these findings are discussed in order to both underscore the need for in-depth investigation of local, regional or distant melanoma recurrence among patients following a true negative sentinel lymph node biopsy, as well as increased efforts to minimize the rate of false negative sentinel lymph node biopsies.

In 2008 the global burden of melanoma was estimated to account for the loss of over 2 million disability adjusted life years including approximately 1.9 million years of healthy life lost [1]. In 2012, 69,109 new cases of melanoma were diagnosed and 10,224 deaths were attributed to melanoma in the USA [2]. While the incidence of newly diagnosed melanoma has continued to increase, the mortality rate has been stable [3,4]. These trends likely reflect early detection coupled with preventative measures by public health organizations providing education to reduce ultraviolet light exposure via skin protection and avoidance of tanning beds [4].

Current role of sentinel lymph node biopsy

Sentinel lymph node biopsy (SLNBx) was first proposed in 1992 as a method of identifying high-risk patients who would most benefit from early, aggressive surgical and systemic therapies, as well as identifying the patients who could forego regional lymph node dissection, and thereby avoid the associated morbidity of a regional lymph node dissection [5]. Sentinel lymph node biopsy has since been hypothesized to prevent progression of regional disease [6,7]. Since its introduction, SLNBx has been rapidly integrated into diagnostic algorithms for the evaluation of cutaneous melanoma. Current National Comprehensive Cancer Network guidelines recommend wide local excision with SLNBx for stage Ib and stage II melanomas that are >0.1 mm in thickness and without clinical evidence of nodal disease. This determines the final staging and appropriateness for additional systemic and surgical treatment options [8].

The sentinel lymph node (SLN) is defined as the first lymph node in the regional lymph node basin to receive drainage from the affected skin. During a SLNBx, the SLN is localized using two dyes which are both injected intra-dermally at the site of the primary lesion. The blue dye allows for intraoperative visualization of the SLN and results in an 80–85% identification rate. The radioactive dye's migration to the SLN is traced with imaging (lymphoscintigraphy) and detected with an intraoperative gamma probe; this technique results in a 95% identification rate, whereas the technique combining use of both dyes demonstrates a 99% localization rate. The probability of developing distant or local disease recurrence following a negative SLN is largely dependent of the

tumor depth and biology and can range from 4 to 29% [9,10].

While the overall outcomes of patients following positive and negative SLNBx have been well described in the literature, little is reported regarding patients with a 'false negative' (FN) result. Furthermore, the current literature lacks a clear definition for both a 'FN result' and for this patient population, which contributes to the challenge in reporting associated outcomes. Here, we review the current literature focusing upon this population and discuss future directions for investigation.

For this article, we performed a broad review of medical literature over the past 15 years using PubMed, Google Scholar, EBSCO Host with the following MeSH terms and keywords: 'melanoma', 'recurrence', 'sentinel lymph node biopsy', 'false negative' and 'outcome.' We included all studies that discussed local, regional or distant recurrence of melanoma after negative sentinel lymph node biopsy. When aggregating data, values and rates were most often averaged by weighting the study values by the inverse of the sample size of the source population. Survival data were aggregated using standard, random effects meta-analysis techniques [11], the results of which can be found in [Figures 1 & 2](#); however performance of this test was severely limited by the small number of studies which provided measures of data distribution (standard error or standard deviation), with which to perform the meta-analysis. Time to recurrence was most often presented as a median value, for which we were unable to perform a meta-analysis.

Recurrence after negative SLNBx

In the reviewed studies, the median time to any melanoma recurrence after negative SLNBx was 9.3 to 35.4 months following SLNBx; the average, median time to first recurrence is 21.8 months ([Table 1](#)). Melanoma of the head and neck was observed to recur within the shortest time interval (9.5–19 months following SLNBx) [10,12]. Risk factors associated with recurrence of melanoma following a negative SLNBx included increased depth of the primary lesion, the presence of ulceration, advanced age at diagnosis and location of the primary lesion on the head and neck [13,14]. Distant disease was the most common site of recurrence, representing 31.3–70.0% of all patients who developed recurrent disease following a negative SLNBx (mean: 46.2%) ([Table 2](#)).

KEYWORDS

- false-negative rate
- melanoma • outcomes
- recurrence • sentinel lymph node • survival

Figure 1. Results of meta-analysis evaluating 5-year disease free survival (%) for patients following a positive sentinel lymph node biopsy.

Definition of FN rate

When considering recurrence of disease following a negative SLNBx, two populations of patients are often described: patients who develop recurrent disease after a true negative (TN) SLNBx, and patients who develop recurrent disease after a FN SLNBx. We define a FN SLNBx as recurrence of melanoma in the previously biopsied lymph node basin [13,15]. While the FN rate of SLNBx for cutaneous melanoma has been reported to broadly range from 1 to 32%, attention should be paid to the manner of calculation of this value [16]. The FN rate (FNR) for a SLNBx has been previously calculated as the number of patients who develop disease recurrence in the locally draining lymph node basin (FN) divided by the number of patients with an initially negative SLNBx, or as the number of patients who recur in the locally draining lymph node basin divided by the total number of patients with a positive SLNBx (true positive + FN) [17]. While, the former definition (FN/initially negative SLNBx) provides an estimate of the false omission rate (FOR or FN predictive value) of a SLNBx for cutaneous melanoma [12], the more accurate method of calculating the FNR is represented by the latter definition (FN/true positive+FN). This latter definition more appropriately estimates the proportion of patients who are initially incorrectly categorized as being free of disease in their sentinel lymph node following a negative SLNBx. When defined in this way, the FOR ranges from 0.9 to 8.9% (mean FOR 3.8%, calculated using simple weighting by the inverse sample size of source study), while the FNR ranges from 2.8 to 32.1% (mean FNR 14.0%, calculated using simple weighting by the inverse sample size of source

study), as seen in Table 1. The highest FNRs have generally been observed in patients undergoing SLNBx for head and neck melanoma, with this association being attributed to the complex lymphatic drainage of the head and neck leading to increased technical failures due to difficulty identifying the SLN [18].

Patients who develop distant, local or regional disease following a negative SLNBx may have been incorrectly categorized by a FN SLNBx [13]. Direct comparison of the outcomes of patients who develop recurrent disease following negative SLNBx with patients whose SLNBx was positive reveals that reported 5-year overall survival (OS) for patients following a positive SLNBx ranged from 32 to 69.7%, and 5-year OS for patients who develop distant, local or regional disease after FN SLNBx ranged from 48.4 to 60% (mean 52%, 95% CI: 40.8–63.2%). (Table 3 & Figure 2). The mean 5-year OS for patients who develop distant, local or regional disease following FN SLNBx (calculated using simple weighting by the inverse of the source sample size) was 53.2% (52% when calculated using meta-analysis techniques), compared with 61.8% for patients following a positive SLNBx. This expected decrease in 5-year OS could be the result of either more aggressive tumor pathology among patients with a TN or FN SLNBx, the presence of a therapeutic benefit afforded by SLNBx that patients with a FN SLNBx fail to receive (surgical technique alteration), or a delay in diagnosis resulting in lead time bias.

When the FN SLN is clearly defined, the majority of patients who develop disease after a negative SLNBx, do so following a TN SLNBx, meaning their disease develops outside of the

regional lymphatic basin. However, none of the studies reviewed here specifically evaluate outcomes or risk factors for recurrence in this population. When focusing on the subset of patients who develop distant, local or regional recurrence after FN SLNBx, these patients also have both an expectedly poorer 5-year OS when compared with the total population of patients who undergo negative SLNBx. The 5-year OS of patients who develop distant, local or regional recurrence after FN SLNBx ranged from 48.4 to 60%, compared with 70–92.7% [19] in the total population with negative SLNBx. While this discrepancy in survival is expected, the lack of data regarding survival of patients who develop local, regional or distant melanoma recurrence after TN SLNBx call for more in-depth evaluation of this patient population to identify specific risk factors and formulate guidelines for monitoring and evaluation of these patients following wide local excision and SLNBx.

Etiology of FN sentinel lymph node biopsy

Possible etiologies of FN SLNBx include poor radiographic localization of the SLN, failed pathologic evaluation of the sampled lymph node and failure of surgical technique to identify the SLN. Poor reproducibility and operator error of cutaneous lymphoscintigraphy have been suggested as one etiology of FN SLNBx [16,20]. The presence of multiple sentinel lymph node basins has the potential to contribute to an increased risk of recurrence after negative SLNBx due to the complexity of the draining nodal systems; notably, the evaluation by Vidal *et al.* demonstrated the presence of multiple sentinel lymph node basins in up to 28% of patients [21]. In regions of the body where lymphatic drainage is known to be complex (head, neck), single-photon emission computerized

tomography/computed tomography (SPECT/CT) has been proposed as a method for better identifying lymph nodes with possible metastatic disease, with the use of SPECT/CT associated with a statistically significant disease-free survival benefit at 4 years (93.9% survival in the SPECT/CT cohort vs 79.2% survival in the SLNBx cohort) [22]. Another source of possible FN SLNBx is surgical failure, wherein the operative surgeon fails to identify the SLN or samples non-sentinel lymph nodes in the targeted basin [7,23–24]. Furthermore, pathologic misclassification has been described as a potential source of FN SLNBx, with re-examination of sentinel lymph nodes demonstrated that 27 to 80% of patients who developed clinical progression of disease secondary to a FN SLNBx had histologic evidence of metastatic disease at the time of initial SLNBx [7,16,25].

Melanoma biology & recurrence

While every effort should be made to minimize the radiographic, histologic or surgical errors that lead to a FN SLNBx, it is also possible that melanoma which recurs after negative SLNBx exhibits a different tumor biology that is responsible for either the negative SLNBx, or the increased risk of recurrent disease. Current studies have identified phenotypic factors such as increased tumor thickness [7,13–14,18,26–30], presence of ulceration [7,13–14,26–27,29–32], increased number of mitoses [26,29,31] and increased patient age [13–14,18,27] as risk factors for tumor recurrence. Attempts to further identify high-risk melanoma patients using molecular studies for melanoma markers such as *in situ* PCR and RT-PCR for MART1, MAGE-3, GalNAc-T and PAX3 mRNA have had some success, but suffer from the challenges of both broadly deploying complex technology as well

Figure 2. Results of meta-analysis evaluating 5-year overall survival (%) for patients following a false-negative sentinel lymph node biopsy.

Table 1. Recurrence of melanoma following negative sentinel lymph node biopsy.

Study, year	n	Relative weight (%)	TP SLNBx (n)	(-) SLNBx (n)	Median follow-up (months)	Any recurrence after (-) SLNBx		FN SLNBx		Time to recurrence (median, months)	FN rate (%)	Rate of any recurrence after TN SLNBx (%)
						n	%	n	% (FOR)			
Yee, 2005	991	8.79	145	846	42.1	83	9.8	27	3.2	24.3	13.9	6.6
Zogakis, 2007	915	8.11		773	36.7	69	8.9	13	1.7	23 [‡]	8.4	7.2
Dalal, 2007	1046	9.28	163	883	36	126	14.3	28	3.2	24	14.7	11.1
Gomez-Rivera, 2008 [†]	113	1.00	23	90	34	21	23.3	5	5.6		17.9	17.8
Mattsson, 2008	361	3.20	73	288	12	39	13.5	12	4.2		14.1	9.4
Chao, 2002	1183	10.49	233	950	16	58	6.1	11	1.2		4.5	4.9
Clary, 2001	332	2.94	56	276	23	39	14.1	11	4.0	16.2	16.4	10.1
Gershenwald, 1998	295	2.62	52	243	35	27	11.1	14	5.8		21.2	5.3
Carlson, 2008	1287	11.41	227	1060	44.3	133	12.5	35	3.3	23.9	13.4	9.2
Saltman, 2010 [†]	218	1.93	28	190	37	55	28.9	12	6.3	19	30.0	22.6
Savoia, 2012	688	6.10		503	48	114	22.7	39	7.8	13.2	17.4	14.9
Rughani, 2010	694	6.15	162	532	46	53	10.0	16	3.0		9.0	7.0
de Vries, 2011	429	3.80	119	310	64.8	69	22.3	17	5.5		12.5	16.8
Miller, 2011 [†]	150	1.33	19	131	28.8	19	14.5	9	6.9		32.1	7.6
Hinz, 2011	121	1.07	5	116	50.9	5	4.3	1	0.9	35.4 [§]	16.7	3.4
van den Broek, 2013	305	2.70	54	251	50	24	9.6	6	2.4		10.0	7.2
Fairbairn, 2012 [§]	66	0.59	22	44	36.8	10	22.7	2	4.5		8.3	18.2
Biver-Dalle, 2012	197	1.75	44	153	39.5	20	13.1	10	6.5	17.4	18.5	6.5
Jones, 2013	619	5.49	104	520	61	83	16.0	21	4.0	23	17.5	11.9
Beger, 2013	201	1.78	33	168		20	11.9	15	8.9	28.5	31.3	3.0
Sanchez, 2013	128	1.14	35	93	34	6	6.5	1	1.1		2.8	5.4
Morton, 2014	765	6.78	122	643				31		21		
Morton, 2014 [§]	173	1.53	57	116				12		9.3		
Sum or range	11277	100	1776	9179	12–64.8	1073	4.3–28.9	348	0.9–8.9	9.3–35.4	2.8–32.1	3–22.6
Average	490		85	400	38.9 [*]	76	12.8	21	3.8	21.8 [#]	14.0	9.2

TP SLNBx were considered the result of a positive initial sentinel lymph node biopsy. Negative SLNBx [(-) SLNBx] were considered the result of a negative initial sentinel lymph node biopsy.

FN SLNBx were defined as the number of patients who developed recurrent melanoma in a nodal basin previously sampled during a negative initial SLNBx.

The FN rate was defined as the number of FN SLNBx divided by the sum of FN SLNBx and TP SLNBx: FN/(TP+FN)*100.

The FOR was calculated as the percent of initially negative SLNBx resulting in FN SLNBx: FN/(-) SLNBx *100.

The rate of recurrence after (-) SLNBx was calculated as the percent of patients with a negative initial SLNBx who develop recurrence of melanoma, regardless of location: recurrence after (-) SLNBx/(-) SLNBx *100.

The rate of recurrence after TN SLNBx was calculated as the percentage of patients with a negative initial SLNBx who develop recurrence of melanoma outside of the previously sampled nodal basin: Rate of recurrence after (-) SLNBx-FOR. Averages of point estimates (X) were obtained by weighting by the sample size (n) of the parent study (x) relative to the summed sample sizes of all studies evaluated (n total); average = Sum(Xx*n x/n total).

Relative weight (%) = n/Sum (n)*100.

[†]Head and neck melanoma only.

[‡]Local and in-transit progression of disease.

[§]Thick melanoma (>3.5 mm in depth).

^{*}Mean value.

[#]Please note, this value is a weighted average of median values.

FN: False negative; FOR: False omission rate; n: number of successful SLNBx; SLNBx: Sentinel lymph node biopsy; TN: True positive; TP: True positive.

as relatively high false-positive results [33]. Similar to local regression of primary melanoma lesions, Yee *et al.* (2005), suggest the possibility that immunologic clearance of the melanoma in the regional lymph node basin prior to SLNBx may be responsible for the

development of distant metastases despite negative SLNBx [26]. Among patients with head and neck melanoma, perhaps 55% of patients with melanoma-specific deaths developed metastatic disease without evidence of nodal involvement, suggesting a more direct hematogenous

spread of the disease [7,12]. Similarly, metastatic melanoma leading to obstruction of lymphatic drainage has been proposed as a possible etiology of metastatic disease following a negative SLNBx, with case studies describing obstruction of lymphatic channels leading to failed lymphoscintigraphy, requiring ultrasound to diagnose the presence of metastatic nodal disease [34,35]. Management of distant or recurrent disease may be altered by clarifying the mechanism of melanoma metastasis.

Follow-up of patients after negative sentinel lymph node biopsy

Better risk stratification of melanoma patients at risk for recurrence awaits results from data analysis of genomic and protein sequencing that can assess the individual's inherent biologic activity associated with a specific melanoma. The decreased OS of patients who develop recurrent

melanoma following a negative SLNBx calls for increased efforts to minimize FN SLNBx, identify risk factors for recurrence, define the roles of supplementary imaging (such as ultrasound) to aid the localizing of the true SLN and improve understanding of individual melanoma tumor biology. Follow-up of patients following a negative SLNBx can be challenging. National Comprehensive Cancer Network guidelines provide a range of options, from physical exam to routine imaging, depending on the estimated conditional probability of melanoma recurrence. For example, given that patients with primary melanoma of the head and neck develop recurrence of disease between 9.5 and 19 months after SLNBx, these patients should be monitored closely every 3–6 months after SLNBx. In the setting of a negative SLNBx, other factors that would suggest a greater risk of melanoma recurrence (and need for further

Table 2. Site of first recurrence after negative sentinel lymph node biopsy for cutaneous melanoma.

Study, year	n	Relative weight (%)	(-) SLNBx (n)	Recurrence after (-) SLNBx (n)		Site of first recurrence							
				n	%	Distant		Local		Nodal		In-transit	
						n	%	n	%	n	%	n	%
Yee, 2005	991	10.07	846	83	9.8	45	54.2	6	7.2	22	26.5	10	12.0
Zogakis, 2007	915	9.30	773	69	8.9	37	53.6	9	13.0	13	18.8	14	20.3
Dalal, 2007	1046	10.63	883	126	14.2	63	50.0	8	6.3	28	22.2	26	20.6
Gomez-Rivera, 2008 [†]	113	1.15	90	21	23.3	10	47.6	6	28.6	7	33.3		
Mattsson, 2008	361	3.67	288	39	13.5	14	35.9	11	28.2	12	30.8	2	5.1
Chao, 2002	1183	12.02	950	58	6.1	26	44.8	11	19.0	11	19.0	9	15.5
Clary, 2001	332	3.37	276	39	14.1	14	35.9	7	17.9	11	28.2	7	17.9
Gershenwald, 1998	295	3.0	243	27	11.1	9	33.3	4	14.8	10	37.0	8	29.6
Carlson, 2008 ^{‡§}	1287	13.08	1060	133	12.5	76	57.1	22	16.5	35	26.3		
Savoia 2012 [§]	688	6.99	503	114	22.7	41	36.0	43	37.7	39	34.2		
Rughani, 2010	694	7.05	532	53	10.0	19	35.8	11	20.8	17	32.1	6	11.3
de Vries, 2011	429	4.36	310	69	22.3	34	49.3	9	13.0	17	24.6	9	13.0
Hinz, 2011	121	1.23	116	5	4.3	3	60.0	1	20.0	1	20.0		
van den Broek, 2013 [‡]	305	3.10	251	24	9.6	9	37.5	6	25.0	6	25.0	2	8.3
Fairbairn, 2012 ^{‡§}	66	0.67	44	10	22.7	5	50.0	3	30.0	2	20.0		
Biver-Dalle, 2012 [§]	197	2.00	153	20	13.1	14	70.0	8	40.0	10	50.0		
Jones, 2013	619	6.29	520	83	16.0	26	31.3	19	22.9	21	25.3	12	14.5
Beger 2013 ^{‡§}	201	2.04	168	20	11.9	7	35.0	7	35.0	15	75.0		
Sum or Range	9843	100	8006	993	4.3–22.7	452	31.3–70.0	191	6.3–40.0	277	18.8–75.0	105	5.1–29.6
Average	547		445	55	12.5	37	46.2	13	18.3	20	27.1	8	11.4

[†]Head and neck melanoma only.

[‡]Source publication unclear whether site of first recurrence vs total recurrences.

[§]Local and in-transit disease reported as combined value by source authors, grouped under local recurrence for this analysis.

SLNBx: Sentinel lymph node biopsy.

Table 3. Five-year disease-free survival, overall survival, and melanoma-specific survival following false-negative and true-positive sentinel lymph node biopsy for cutaneous melanoma.

Study, year	n	Relative weight (%)	TP SLNBx (n)	(-) SLNBx (n)	Median follow-up (months)	TP SLNBx (5 year, %)		FN SLNBx (5 year, %)	
						DFS	OS	MSS	OS
Yee, 2005	991	8.14	145	846	42.1	43.5	56.0		
Nowecki, 2006	1207	9.91	285	922	35.8				53.7
Dalal, 2007	1046	8.59	163	883	36.0	72.0			
Caraco, 2007 [†]	801	6.57	151	650	42.8	52.0	66.3		48.4
Gomez-Rivera, 2008 [‡]	113	0.93	23	90	34.0	39.0	62.0		
Carlson, 2008	1287	10.56	227	1060	44.3				60.0
Gajdos, 2009 [§]	227	1.86	107	120	43.0	47.8	47.0		
Testori, 2009	1313	10.78	229	1084	54.2		67.7		49.8
Scoggins, 2010	2451	20.12	486	1965	61.0	69.1	62.3		52.8
Kelly, 2012 [§]	57	0.47	18	39		11.0	32.0		
Van den Broek, 2013	305	2.50	54	251	50.0	41.0			
Parrett, 2012 [‡]	365	3.0	40	325	96.0	42.0	50.6	62.5	
Fairbairn, 2012 [§]	66	0.54	22	44	36.8	35.4	63.7		
Biver-Dalle, 2012	197	1.62	44	153	39.5	58.7	69.7		
Jones, 2013	619	5.08	99	520	61.0		63.0		
Beger, 2013	201	1.65	33	168		34.9			
Morton, 2014 [†]	765	6.27	122	63		69.8		45.2	
Morton, 2014 ^{‡,§}	173	1.42	57	116		60.8		19.4	
Sum or Range	12184	100	2305	9879	34.0–96.0	11–69.8	32–69.7	19.4–62.5	48.4–60.0
Average	677		128	549	48.3	59.0	61.8	46.6	53.2

[†]False-negative cases of melanoma only.

[‡]Head and neck melanoma only.

[§]Thick melanoma (>3.5 mm in depth).

DFS: Disease-free survival; FN: False negative; MSS: Melanoma-specific survival; n: Number of successful SLNBx; OS: Overall survival; SLNBx: Sentinel lymph node biopsy; TP: True positive.

monitoring) include increased depth, the presence of ulceration and increased number of mitoses of the primary melanoma lesion, as well as increased age of the patient at the time of SLNBx.

Conclusion

Of patients undergoing a SLNBx, approximately 13% experience a recurrence at an average of 21 months following the procedure. Risk factors associated with recurrence include increasing depth of the primary melanoma, ulceration of the primary, older age at diagnosis and primary location on the head and neck. A distant site of recurrence was more common than local or regional recurrences. Overall survival at 5 years for patients experiencing a recurrence after a negative SLNBx is approximately 52%.

Future perspective

As research progresses forward, we encourage future efforts to be directed at investigating outcomes associated with recurrence following true-negative SLNBx. Furthermore, we suggest

standardization in the presentation of outcomes data; including the definition of FN sentinel lymph node biopsy, calculation of FNRs and false omission rates, and presentation of data in a format allowing aggregation using meta-analysis techniques (including measures of central tendency and data spread). As time progresses, our hope and expectation is that ongoing basic science research will further define molecular markers able to predict risk of recurrence and enable the development of tailored, individualized chemotherapeutic regimens for our patients.

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