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Current Perspective

Expert opinion in melanoma: The sentinel node; EORTC Melanoma Group recommendations on practical methodology of the measurement of the microanatomic location of metastases and metastatic tumour burden

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ABSTRACT

The sentinel node (SN) status has been recognised to be the most important prognostic factor in melanoma. Many studies have investigated additional factors to further predict survival/lymph node involvement. The EORTC Melanoma Group (MG) has formulated the following question: How should we report the microanatomic location and SN tumour burden?

The EORTC MG recommends the following: the EORTC MG SN pathology protocol or a similarly extensive protocol, which has also been proven to be accurate, should be used. Only measure what you can see not what you presume. Cumulative measurements decrease the accuracy and reproducibility of measuring. The most reproducible measure is a single measurement of the maximum diameter of the largest lesion in any direction (1-D). If there is any infiltration into the parenchyma, this lesion can no longer be considered solely subcapsular. Reporting of the microanatomic location of metastases should be an assessment of the entire sentinel node, not only of the largest lesion. Multifocality reflects a scattered metastatic pattern, not to be confused with multiple cohesive foci, which fall under the regular location system. A subcapsular metastasis should have a smooth usually curved outline, not ragged or irregular.

We recommend all pathologists to report the following items per positive SN for melanoma patients: the microanatomic location of the metastases according to Dewar et al. for the entire node, the SN Tumour Burden according to the Rotterdam Criteria for the maximum diameter of the largest metastasis expressed as an absolute number, and the SN Tumour Burden stratified per category; <0.1 mm or 0.1–1.0 mm or >1.0 mm.

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1. Introduction

The sentinel node (SN) biopsy has become a routine staging procedure for primary melanoma patients without any clinical evidence of regional or distant metastases. Depending on the extent of the pathology protocol used and the Breslow thickness of the population, SN positivity rates range from 15% to 33%.[1–6] It has been demonstrated that SN positive patients (approximately 50–70% survival at 5 years) have a significantly worse prognosis compared to SN negative patients (approximately 90% survival at 5 years).[3,4,6,7]

Since its introduction in the 1990s increasingly more centres worldwide have been performing, and more patients have been undergoing, SN procedures for melanoma, each year. Together with this increase in the number of performed procedures, came an increase in scientific projects to research and evaluate the efficacy and results of the SN procedure to a deeper extent. Although these studies have answered some questions, they have perhaps raised more new questions at the same time.

One of these issues is the importance of SN tumour burden and possible clinical implications. Many studies have assessed this issue, but agreement has not been achieved.[8–22] One conclusion can be drawn: the prognosis of patients decreases with increasing SN tumour burden, no matter how you measure this, even if only by approximate measurements.[8–22]

Since all these studies have used different methods and most often have not elaborated on how they practically measured SN tumour burden or established the microanatomic location of a metastasis, the following questions present themselves in the everyday clinical practice of pathologists in the reporting of SN tumour burden:

How should we report the microanatomic location of metastases within the SN and how should we measure the amount of tumour burden within the SN?

The following comments are based on the experience of the authors following reporting of several thousands of sentinel node biopsies. They are practical responses to frequently arising questions. They are still subject to further evaluation and may be shown to be suboptimal in the light of further studies, but seem the most appropriate in the current state of understanding of sentinel lymph nodes and melanoma.

2. Literature overview

From the early 2000s onwards, a number of studies have identified certain factors, which predicted survival and/or additional non-SN positivity in the Completion Lymph Node Dissection (CLND) specimen. Table 1 summarises the main results from these studies.

As can be observed in Table 1, a number of different characteristics and combinations of these characteristics have been tested with similar and/or different cut-off values. These characteristics include most often the maximum diameter of the metastases,[8–10,15–17,19–22] but also the tumour infiltration from the capsule inwards and the microanatomic location.[11–13,16,22,23] Other factors have also been investigated, such as Breslow thickness, ulceration of the primary, extracapsular extension (ECE) or capsule invasion, the square area of the metastases and the number of positive sentinel nodes.[10,13,14,18,21,24]

Although, sometimes very elaborate, very detailed and time consuming and, sometimes very rough measurements, have been predictive of survival and/or CLND positivity, none of these studies has been able to answer the following crucial question:

Since only approximately 20% of all SN positive patients are CLND positive and the CLND has the risk of considerable morbidity; can we identify a group of SN positive patients, whom we can safely (with regard to regional control and survival) spare a CLND?

Supporters of this idea have argued that these tiny lesions within the SN are clinically non-relevant and should therefore be considered prognostically false positive.[25,26] Patients with minimal SN tumour burden have excellent survival rates, which are identical to SN negative patients.[16,22,27,28] Moreover, these patients have similar primary tumour characteristics to SN negative patients and they rarely, if ever have additional lymph node metastases in their CLND specimen.[16,22,27,28] Finally, the Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1) did not demonstrate any survival benefit for patients undergoing a SN procedure followed by a CLND when positive, compared to patients who only received wide local excision (WLE) followed by a Delayed Lymph Node Dissection (DLND) when metastases became clinically apparent.[4]

Opposition to this idea has argued that all these retrospective studies could only be performed on excised sentinel nodes and that the excision of the SN might have already been beneficial for these patients.[29–31] Similarly, CLND has been performed in all these patients with minimal SN tumour burden and although metastases were rarely seen in the CLND specimen, the CLND specimen was usually analysed only by bivalving and H&E staining.[29–31] Micrometastases could therefore easily have been missed. Moreover, the MSLT-1 subgroup analysis suggested a survival benefit for SN positive patients compared with WLE node positive patients.[4]

Two prospective studies, the MSLT-2 and the EORTC Melanoma Group MINITUB trial, currently both being conducted with different viewpoints, are addressing the issue of performing or omitting a CLND in all SN positive patients or in minimal SN tumour burden patients only, respectively.

3. Measuring questions

Tumors are three-dimensional (3-D), not one-dimensional (1-D), would a 3-D calculation of the metastasis be the most accurate measure?

This would seem logical, but unfortunately this does not seem to work, for a number of reasons: we only have access to a two-dimensional (2-D) slice of the SN, therefore any addition of a third dimension would be, through either a complicated computer calculation, or a rough estimate of

Table 1 – Overview of SN tumour burden studies in the literature.

Author	# of pos SNs	Characteristics	Groups	Survival	CLND positive
Ranieri et al.[8]	90	Maximum diameter	⩽3 mm	86% (3 years)	
			>3 mm	27% (3 years)	
Carlson et al.[9]	104	Maximum diameter	Isolated or cluster of melanoma cells	86% (3 years)	
			⩽2 mm	90% (3 years)	
			>2 mm	57% (3 years)	
Reeves et al.[10]	98	Maximum diameter (⩽2 mm or >2 mm) and ulceration status of the primary	0		0%
			1		16%
			2		31%
Starz et al.[11]	70	Infiltration from the capsule	⩽0.3 mm	±80% (5 years)	
			>0.3 ⩽1.0 mm	±90% (5 years)	
			>1 mm	±60% (5 years)	
Dewar et al.[12]	146	Microanatomic location	Subcapsular		0%
			Combined		11%
			Parenchymal		19%
			Multifocal		37%
			Extensive		42%
Vuylsteke et al.[13]	80	Maximum diameter (<0.3 mm and ⩾0.3 mm), Breslow thickness (<2.5 mm and ⩾2.5 mm) and non-SN status	0	94% (5 years)	
			1	56% (5 years)	
			2	30% (5 years)	
Sabel et al.[14]	232	Extracapsular extension (ECE) and ⩾3 positive SNs	ECE		OR 3.2
			⩾3 positive SNs		OR 65.8
Pearlman et al.[15]	90	Maximum diameter	⩽2 mm	85% (5 years)	6%
			>2 mm	47% (5 years)	45%
van Akkooi et al.[16]	74	Maximum diameter	<0.1 mm	100% (5 years)	0%
			0.1–1.0 mm	63% (5 years)	19%
			>1.0 mm	35% (5 years)	
Govindarajan et al.[17]	127	Maximum diameter	⩽0.2 mm		0%
			0.2–2.0 mm		10.5%
			>2.0 mm		26.1%
Satzger et al.[18]	101	Capsule invasion, tumour infiltrative depth (<2 mm or ⩾2 mm) and size of largest tumour deposit (<30 cells or ⩾30 cells)	0	±100% (5 years)	
			1	±90% (5 years)	
			2	±55% (5 years)	
			3	±20% (5 years)	
Debarbieux et al.[19]	98	Maximum diameter	⩽2 mm	±80% (5 years)	
			>2 mm	±35% (5 years)	
Scheri et al.[20]	214	Maximum diameter	⩽0.2 mm	87% (5 years)	12%
Gershenwald et al.[21]	309	Maximum diameter and tumour square area	⩽0.5 mm		5.3%
			⩽0.1 mm^2		3.7%
EORTC Melanoma Group by van Akkooi et al.[22]	388	Maximum diameter and microanatomic location	<0.1 mm	91% (5 years)	3%
			0.1–1.0 mm	61% (5 years)	21%
			>1.0 mm	51% (5 years)	32%
			Subcapsular		8%
			Combined		32%
			Parenchymal		19%
			Multifocal		15%
			Extensive		40%

the researcher, which has a considerable inter-observer spread.

Moreover, metastases do not take place in nice square or cubic forms, but most often take place along the curve of the capsule or trabeculae, which is difficult to measure in 2-D or 3-D and thus leads to a tremendous spread in reporting and therefore to inaccuracy. At the same time, this also shows us why 2-D calculations (tumour square area) are also less accurate.

Most often there is not one single lesion within the SN, there are a number of lesions visible, would measuring all and adding these to a total be the most accurate measure?

This does seem logical, but unfortunately this would require a considerable amount of work for a pathologist to report per sentinel node, which is practically not feasible. Moreover, if one measurement has inter-observer spread, multiple measurements are certainly increasingly inaccurate: Cumulative measurements are time consuming, decrease the

accuracy and reproducibility of measurements and are therefore not recommended.

Through the use of an adequate SN protocol (such as the recommended EORTC Melanoma Group protocol,[1,5]) two lesions may be visible on one slide, but perhaps these would become one if, deeper sections were available; how can this be assessed?

The most important credo for this issue is: only measure what you can see. This means that if two lesions are interrupted by lymphocytes (or other cells or structures), these are to be considered as two separate lesions. Although it is plausible that these two lesions could be one connective lesion on a deeper level, if this cannot be observed, these lesions should still be considered as two separate lesions, unless or until evidence has been presented that this assumption is untrue.

It is sometimes difficult to measure the 1-D maximum diameter of a metastasis, when it spreads along the curve of the capsule (and thus is not a straight lesion), especially when the metastasis is large, how should this be measured?

Although 1-D measurements of the maximum diameter of metastases seem quite simple, it can be difficult certainly in cases where there are multiple metastases, metastases are large and/or metastases have a curve shape along the capsule or trabeculae. The answer to this is very simple and pragmatic: Do not waste time on very accurately measuring the very large metastases, because they already belong to the group of tumour burden with a bad prognosis (i.e. >1, >2 or >3 mm, depending on your classification system). You can 'eyeball' this, recognise this without measurement, since it is not important to differentiate between say 7.8 mm and 8.3 mm in maximum diameter, as both would have a bad prognosis. More time should be given to measuring smaller lesions and lesions close to a threshold. Thresholds are currently only for the prognosis of patients, but certainly if and when they have clinical management implications, it would be very important to thoroughly measure metastases close to a threshold.

Smaller curved lesions, i.e. lesions up to 1 mm in maximum diameter, even if showing a slight curve, can be measured sufficiently accurately by a straight line between the furthest points. Larger lesions have already been assigned bad prognosis and thus will not complicate matters with difficult curve measurements. Therefore, it is appropriate to measure in a straight line, in any direction; the maximum diameter and it will be sufficiently accurate (within 0.1 mm difference) between different observers.

There are a number of metastases, how do I know which one has the largest maximum diameter?

You may not know initially, but you can usually differentiate most by simply screening these lesions. Often there is one lesion, which is clearly largest, which saves you the time of measuring many smaller lesions. Sometimes, especially when lesions are small, they might be in the same order of size. In such cases measurement of all these to differentiate which one is the largest would be necessary to accurately reflect the maximum diameter of the largest deposit.

Sometimes the metastasis is mostly in the subcapsular space, but some cells, such as a few loose cells or a small cluster, seem dissociated from the main metastasis and no longer solely confined to the subcapsular space. What type of microanatomic involvement is this?

Subcapsular involvement is only observed, when there is a well-defined and cohesive lesion, solely confined to the subcapsular space or paratrabecular. When there is any lesion inside the parenchyma, either connective to the main lesion as infiltrative satellite or tentacle, or as a separate cluster within the parenchyma, interrupted by lymphocytes between the two, the metastases can no longer be solely regarded as subcapsular and this lesion should be considered as combined involvement (subcapsular and parenchymal).

Quite often there are multiple metastases. The majority of the metastases are confined to the subcapsular space, including the largest lesion. However, there is another smaller lesion with parenchymal infiltration. Should we report the microanatomic location of the largest lesion or of the entire node?

Microanatomic location is a reflection of the biologic behaviour of the metastases within the entire SN, not just of a single lesion. Although the size of the largest lesion gives good prognostic information, the microanatomic information of this single lesion does not reflect the biology of the disease in the entire node. Therefore, any parenchymal involvement, anywhere within the SN should be judged as such. Only when all metastases, in case of multiple lesions, are confined to the subcapsular space, can the metastases be considered as solely subcapsular.

The histopathological examination of a SN often reveals multiple deposits of tumour. Is this considered multifocality within the microanatomic location classification or should there be a minimum number of foci to be considered as such?

Literally multifocality means more than one focus. However, in the microanatomic classification system, this reflects the pattern of, several to many, usually tiny lesions, but most importantly these groups are scattered throughout the greater part of the node.

There is also another, a very different pattern of multiple metastases, which can be numerous metastases, but entails a pattern of clearly cohesive lesions and certainly not the one of widely scattered loose cells (this is a combined pattern). Therefore, a cut-off threshold for the number of lesions to be considered for either of these patterns cannot be specified, but the decision is based on the overall morphological distribution of the lesions.

EORTC Melanoma Group recommendations:

- The EORTC Melanoma Group SN pathology protocol or a similarly extensive protocol, which has also been proven to be accurate, should be used.
- Only measure what you can see, not what you presume.
- Cumulative measurements decrease the accuracy and reproducibility of measuring. This includes tumour square area (2-D) and 3-D reconstructions.
- The most reproducible measure is a single measurement of the maximum diameter of the largest lesion in any direction (1-D).
- If there is any infiltration into the parenchyma, this lesion can no longer be considered solely subcapsular.
- Reporting of the microanatomic location of metastases should be an assessment of the entire sentinel node, not only of the largest lesion.

- Multifocality reflects a scattered metastatic pattern, not to be confused with multiple cohesive foci, which fall under the regular location system (subcapsular, combined, parenchymal or extensive).
- A subcapsular metastasis should have a smooth usually curved outline, not ragged or irregular.
- We recommend all pathologists to report the following items per positive SN for melanoma patients:
  (1) The Microanatomic Location of the metastases according to Dewar et al. for the entire node.
  (2) The SN Tumour Burden according to the Rotterdam Criteria for the maximum diameter of the largest metastasis expressed as an absolute number (e.g. 0.6 mm).
  (3) The SN Tumour Burden stratified per category; <0.1 mm or 0.1–1.0 mm or >1.0 mm.

Teaching examples

Fig. 1 shows a completely subcapsular metastasis, which has a smooth outline, not irregular or ragged (as shown in Fig. 3). Due to the curve shape, it might be somewhat challenging to measure, but our recommendation is to measure in a straight line from one end to the other end of the largest cohesive cluster (as shown in Fig. 1).

Fig. 2: although this metastasis is for the largest part confined to the subcapsular space, beginning infiltration into the parenchyma is visible. Therefore this metastasis is to be considered a combined (subcapsular and parenchymal) lesion.

Fig. 3: this metastasis is located for the most in the subcapsular space, however, compared to that shown in Fig. 1, this metastasis does not clearly have a smooth outline, but is very irregular and ragged. Therefore this lesion is to be considered a combined (subcapsular and parenchymal) involvement.

Fig. 4: this slide shows us three clear separate lesions: one located solely in the subcapsular space, which is smooth and regularly shaped. But there are also two others, which are located solely in the parenchyma. Although there are multiple foci, these lesions are very cohesive and not at all scattered. Therefore this is not to be considered a multifocal involvement, but it is also a combined (subcapsular and parenchymal) type of involvement.

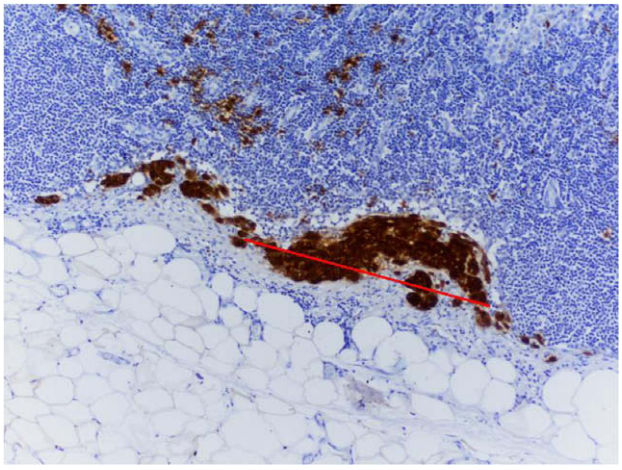

Fig. 1 – Subcapsular metastasis.

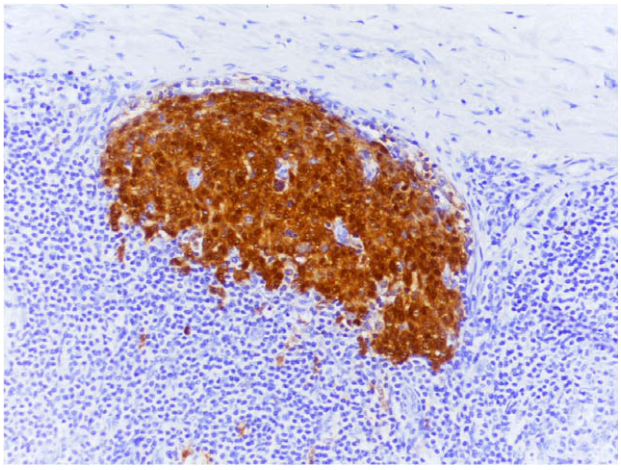

Fig. 2 – Combined metastasis.

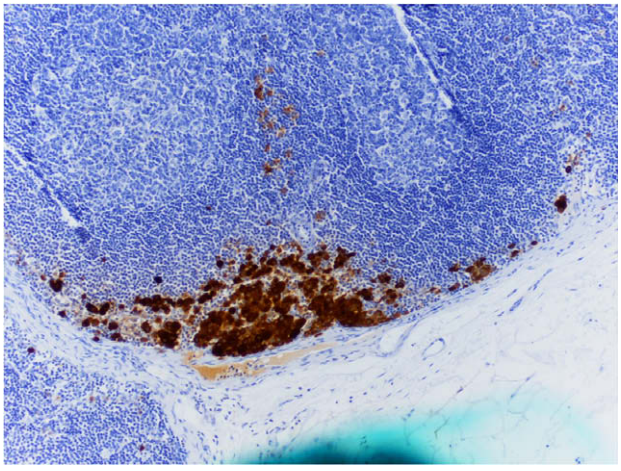

Fig. 3 – Combined metastasis.

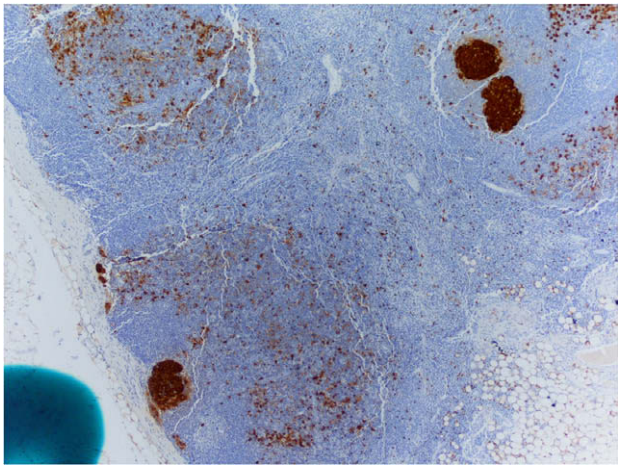

Fig. 4 – Combined metastasis.

Fig. 5: this slide demonstrates a multifocal pattern of metastases. The cells and small clusters of cells are scattered throughout the greater part of this lymph node. It is clearly different from the pattern shown in Fig. 4, where there are three well-defined lesions.

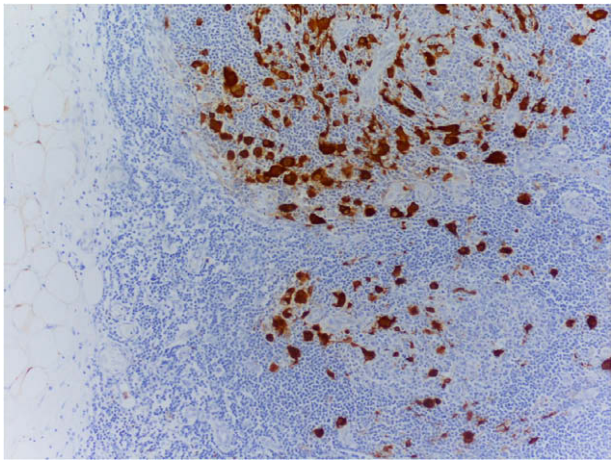

Fig. 5 – Multifocal metastasis

Fig. 6: this lymph node is almost solely taken in with a metastasis. The metastasis is disrupting the normal anatomic structure of the lymph node. This pattern is called the extensive involvement pattern. There is no size limitation (cervical nodes can be small, yet still almost completely displaced by tumour) to this type of involvement.

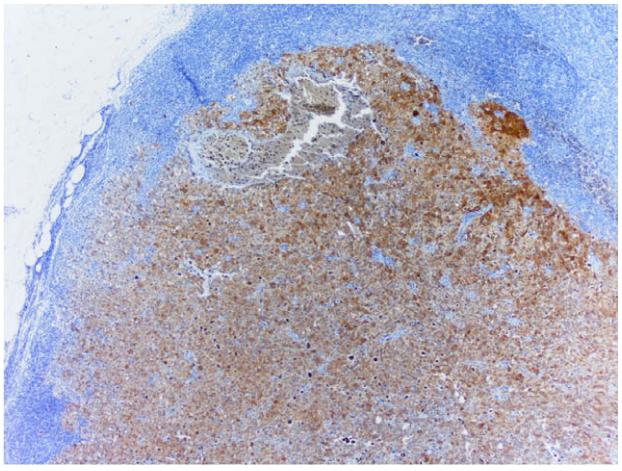

Fig. 6 – Extensive metastasis.

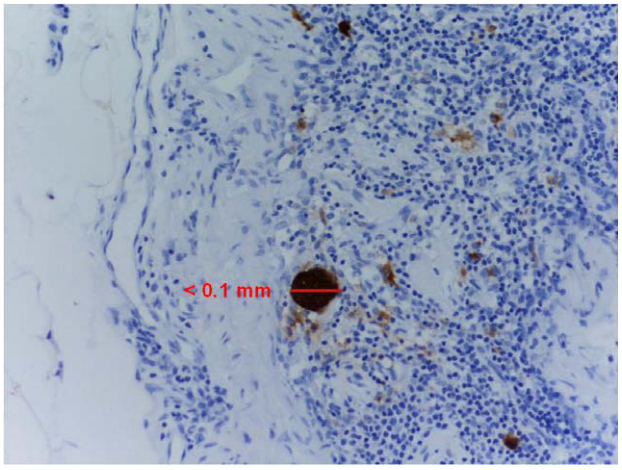

Fig. 7 – Subcapsular <0.1 mm sub-micrometastasis.

Fig. 7: this metastasis is the largest within the SN of this patient. It is confined to the subcapsular space (smooth and regularly shaped) and the size is <0.1 mm in maximum diameter.

REFERENCES

1. Cook MG, Green MA, Anderson B, et al. The development of optimal pathological assessment of sentinel lymph nodes for melanoma. *J Pathol* 2003;**200**:314–9.
2. Doubrovsky A, De Wilt JH, Scolyer RA, et al. Sentinel node biopsy provides more accurate staging than elective lymph node dissection in patients with cutaneous melanoma. *Ann Surg Oncol* 2004;**11**:829–36.
3. Gershenwald JE, Thompson W, Mansfield PF, et al. Multi-institutional melanoma lymphatic mapping experience. the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol* 1999;**17**:976–83.
4. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. *New Engl J Med* 2006;**355**:1307–17.
5. Ruiter DJ, Spatz A, van den Oord JJ, et al. Pathologic staging of melanoma. *Semin Oncol* 2002;**29**:370–81.
6. van Akkooi AC, de Wilt JH, Verhoef C, et al. High positive sentinel node identification rate by EORTC melanoma group protocol. Prognostic indicators of metastatic patterns after sentinel node biopsy in melanoma. *Eur J Cancer* 2006;**42**:372–80.
7. Kretschmer L, Beckmann I, Thoms KM, et al. Sentinel lymphonodectomy does not increase the risk of loco-regional cutaneous metastases of malignant melanomas. *Eur J Cancer* 2005;**41**:531–8.
8. Ranieri JM, Wagner JD, Azuaje R, et al. Prognostic importance of lymph node tumor burden in melanoma patients staged by sentinel node biopsy. *Ann Surg Oncol* 2002;**9**:975–81.
9. Carlson GW, Murray DR, Lyles RH, et al. The amount of metastatic melanoma in a sentinel lymph node: does it have prognostic significance? *Ann Surg Oncol* 2003;**10**:575–81.
10. Reeves ME, Delgado R, Busam KJ, et al. Prediction of nonsentinel lymph node status in melanoma. *Ann Surg Oncol* 2003;**10**:27–31.
11. Starz H, Siedlecki K, Balda BR. Sentinel lymphonodectomy and s-classification: a successful strategy for better prediction and improvement of outcome of melanoma. *Ann Surg Oncol* 2004;**11**:162S–8S.
12. Dewar DJ, Newell B, Green MA, et al. The microanatomic location of metastatic melanoma in sentinel lymph nodes predicts nonsentinel lymph node involvement. *J Clin Oncol* 2004;**22**:3345–9.
13. Vuylsteke RJ, Borgstein PJ, van Leeuwen PA, et al. Sentinel lymph node tumor load: an independent predictor of additional lymph node involvement and survival in melanoma. *Ann Surg Oncol* 2005;**12**:440–8.
14. Sabel MS, Griffith K, Sondak VK, et al. Predictors of nonsentinel lymph node positivity in patients with a positive sentinel node for melanoma. *J Am Coll Surg* 2005;**201**:37–47.
15. Pearlman NW, McCarter MD, Frank M, et al. Size of sentinel node metastases predicts other nodal disease and survival in malignant melanoma. *Am J Surg* 2006;**192**:878–81.
16. van Akkooi AC, de Wilt JH, Verhoef C, et al. Clinical relevance of melanoma micrometastases (<0.1 mm) in sentinel nodes: are these nodes to be considered negative? *Ann Oncol* 2006;**17**:1578–85.

17. Govindarajan A, Ghazarian DM, McCready DR, et al. Histological features of melanoma sentinel lymph node metastases associated with status of the completion lymphadenectomy and rate of subsequent relapse. *Ann Surg Oncol* 2007;**14**:906–12.
18. Satzger I, Volker B, Al Ghazal M, et al. Prognostic significance of histopathological parameters in sentinel nodes of melanoma patients. *Histopathology* 2007;**50**:764–72.
19. Debarbieux S, Duru G, Dalle S, et al. Sentinel lymph node biopsy in melanoma: a micromorphometric study relating to prognosis and completion lymph node dissection. *Br J Dermatol* 2007;**157**:58–67.
20. Scheri RP, Essner R, Turner RR, et al. Isolated tumor cells in the sentinel node affect long-term prognosis of patients with melanoma. *Ann Surg Oncol* 2007;**14**:2861–6.
21. Gershenwald JE, Andtbacka RH, Prieto VG, et al. Microscopic tumor burden in sentinel lymph nodes predicts synchronous nonsentinel lymph node involvement in patients with melanoma. *J Clin Oncol* 2008;**26**:4296–303.
22. van Akkooi ACJ, Nowecki Z, Voit C, et al. Minimal sentinel node (SN) tumor burden according to the Rotterdam criteria is the most important prognostic factor for survival in melanoma patients. A multicenter study in 388 SN positive patients. *Ann Surg* 2008:248.
23. Starz H, Balda BR, Kramer KU, et al. *Cancer* 2001;**91**:2110–21.
24. Cochran AJ, Wen DR, Huang RR, et al. Prediction of metastatic melanoma in nonsentinel nodes and clinical outcome based on the primary melanoma and the sentinel node. *Mod Pathol* 2004;**17**:747–55.
25. Thomas JM. Sentinel-node biopsy in melanoma. *New Engl J Med* 2007;**356**:418 [author reply 419–21].
26. Thomas JM. Prognostic false-positivity of the sentinel node in melanoma. *Nat Clin Pract Oncol* 2008;**5**:18–23.
27. van Akkooi AC, de Wilt JH, Voit C, et al. Sentinel lymph-node false positivity in melanoma. *Nat Clin Pract Oncol* 2008;**5**:E2.
28. de Wilt JH, van Akkooi AC, Verhoef C, et al. Detection of melanoma micrometastases in sentinel nodes – the cons. Surg Oncol 2008.
29. Morton DL, Cochran AJ, Thompson JF. The rationale for sentinel-node biopsy in primary melanoma. *Nat Clin Pract Oncol* 2008;**5**:510–1.
30. Scolyer RA, Murali R, Gershenwald JE, et al. Clinical relevance of melanoma micrometastases in sentinel nodes: too early to tell. *Ann Oncol* 2007;**18**:806–8.
31. Scolyer RA, Murali R, Satzger I, et al. The detection and significance of melanoma micrometastases in sentinel nodes. *Surg Oncol* 2008;**17**:165–74.