When is a sentinel node biopsy indicated for patients with primary melanoma? – an update of the Australian Guidelines for the Management of Cutaneous Melanoma

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Abstract

Sentinel lymph node biopsy (SLNB) is a surgical staging procedure performed for patients with primary cutaneous melanoma who are clinically lymph node negative to determine whether there is low volume nodal metastasis in the draining lymph node field. A systematic review was recently performed to update the Australian Clinical Practice guidelines for the Diagnosis and Management of Melanoma, addressing the question "When is a sentinel lymph node biopsy indicated?"

This article discusses the findings of the systematic review and the evidence base for the recommendation that "*Sentinel lymph node biopsy should be considered for all patients with melanoma greater than 1 mm in thickness and for patients with melanoma greater than 0.75 mm with other high risk pathological features, to provide optimal staging and prognostic information and to maximise management options for patients who are node positive."*

Keywords

Melanoma
Sentinel node biopsy
guidelines

Learning points

- Sentinel lymph node biopsy provides the best available prognostic stratification for patients with clinically lymph node negative melanoma >1mm thick (or >0.75mm thick with adverse features)

- The status of the sentinel lymph node has important implications for patient management and follow up
- The latest update of the Australian clinical practice guidelines recommends that patients with clinically lymph node negative melanoma be considered for sentinel lymph node biopsy

Introduction

Sentinel lymph node biopsy (SLNB) is a surgical staging procedure performed for patients with primary cutaneous melanoma who are clinically lymph node negative to determine whether there is low volume nodal metastasis in the draining lymph node field. A sentinel lymph node (SLN) is a lymph node that receives direct lymphatic drainage from the site of the primary tumour. The evidence base for the SLNB procedure continues to accumulate. A systematic review was performed to update the Australian Clinical Practice Guidelines for the Diagnosis and Management of Melanoma. The new guidelines have now been published through an online wiki platform (http://wiki.cancer.org.au/australia/Guidelines:Melanoma) [1]. This manuscript details the findings of the systematic review, and gives details of the new, evidence-based national guidelines relating to SLNB.

Search methodology

The multidisciplinary Melanoma Guidelines Working Party devised the question "When is a sentinel node biopsy indicated?", and a literature search was performed following the protocol for guideline development of the Cancer Council Australia Cancer Guidelines Wiki. The guideline development process involved a thorough literature search using PubMed, EMBASE, Trip and Cochrane Databases using the terms 'melanoma' and 'sentinel node biopsy'. The literature search undertaken by the German Dermatologic Cooperative Oncology Group (DeCOG) to develop the German melanoma management guidelines, published in 2013 [2] was used as a starting point. The extracted evidence was graded according to objective criteria.

Sentinel lymph node biopsy for optimal staging

Sentinel lymph node biopsy for intermediate thickness (T2 and T3) melanoma

The most important publication relating to SLNB in melanoma patients is the final report of the first Multicenter Selective Lymphadenectomy Trial (MSLT-1)[3]. This

was a large international randomised controlled trial comparing wide excision of the primary melanoma and regional node observation with wide excision and SLNB followed by immediate completion lymph node dissection for patients found to have a positive SLN. Patients in the observation arm underwent therapeutic lymph node dissection if they developed clinical lymph node involvement during the course of follow-up. The study included 1661 patients and the main study population were the 1347 patients with melanomas of Breslow thickness 1.2 - 3.5 mm (designated intermediate thickness melanomas for the purpose of the study).

In a multivariate analysis, the MSLT-1 study showed that the status of the SLN (positive or negative) was the most significant predictor of overall survival (OS) (HR for death = 3.09; 95% CI 2.12-4.49; P<0.001). The 10 year melanoma-specific survival (MSS) for SLN-positive patients was 62.1% versus 85.1% for SLN-negative patients (level of evidence – III). Many large retrospective studies have also demonstrated the preeminence of SLNB in risk stratification, with all but one [4] showing the status of the SLN to be the most significant predictor of MSS (HR 1.5-6.9)[5-8].

SLNB for thin (T1) melanoma

Most patients diagnosed with melanoma have a thin primary tumour (T1) and as a result more deaths from melanoma occur in this group of patients than from thick tumours (>4mm), even though the risk of death for individual patients with thicker primary melanomas is greater[10]. Patients with primary melanomas 0.75 – 1mm in thickness and another adverse pathological feature such as ulceration, an elevated mitotic rate (≥1/mm^2), Clark level IV or V invasive or lymphovascular invasion have a risk of SLN involvement of greater than 5% and should therefore be considered for SLNB [11-13]. The presence of SLN involvement in patients with thin primary melanomas is associated with significantly worse MSS[12].

SLNB for thick (T4) melanoma

The prognostic stratification provided by SLNB also extends to patients with thick (T4) primary melanomas. A recent meta-analysis of 2104 patients with T4 melanomas demonstrated a consistent pattern across all the included studies, with the status of the SLN representing the most important predictor of outcome and the hazard ratio for overall survival according to SLN status of 2.3 (95% CI, 1.95-2.71)[9].

The role of SLNB in optimally staging patients with clinically lymph node-negative melanoma has been recognized in the recently published American Joint Committee on Cancer (AJCC) Cancer Staging Manual, Eighth Edition [14]. Patients with melanomas >1.0mm (T2-T4) can only be designated N0 if staged by SLNB, while patients with T2-T4 melanoma who do not undergo SLNB are designated Nx.

Effect of sentinel node biopsy on patient survival

The primary endpoint of the MSLT-1 study[3] was MSS. The final report showed a small but not statistically significant difference in MSS for patients with intermediate-thickness melanoma (as defined for the study) between those in the SLNB group (10 year MSS 81.4%) compared with the observation group (10 year MSS 78.3%) (HR for death=0.84; 95% CI 0.64-1.09; P=0.18) (level of evidence – II). However, the rate of SLN-positivity was only 16%, which was lower than the rate that had been used for statistical modelling of the trial, and therefore it is possible that the study was underpowered to demonstrate the primary endpoint.

A post-hoc latent subgroup analysis was performed using a new statistical technique[15] in an attempt to estimate treatment effect for the subgroup of patients who were SLN positive (ie. at baseline in the SLNB arm and those who developed clinically-positive nodes during follow up in the observation arm and who would have been expected to be SLN-positive had SLNB been performed). This analysis showed that patients with intermediate thickness melanomas and nodal metastasis had a 10-year MSS of 62.1% with CLND compared to 41.5% with observation (HR for death=0.56; 95% CI 0.37-0.84; P=0.006). The results of MSLT-I thus suggest that early removal of tumour-bearing lymph nodes substantially improves MSS, although there is some controversy about the validity of comparing these two groups as it is not possible to prove that they represent the same patient populations.

Morbidity of sentinel lymph node biopsy

SLNB is a low morbidity, day surgery procedure. Complications are mainly minor and self-limiting with reported rates varying from 5.9-13.8%[16, 17]; these are much lower than for completion lymph node dissection (after positive SLNB) or therapeutic lymph node dissection for macroscopic nodal disease. Hospitals with a higher procedure volume of SLNB have lower complication rates[17].

Management implications of sentinel lymph node status

Today SLNB forms an important part of the multidisciplinary management of patients with primary melanoma. It is the best currently available test for risk stratification, and therefore plays a key role in optimally staging patients with primary melanoma. As previously discussed, patients with a positive SLN are two to three times more likely to die from their disease and therefore should be considered for adjuvant systemic therapy. In Australia, the only PBS-listed adjuvant systemic therapy currently available is interferon alpha 2B. However, the results of the recently published EORTC 18071 trial comparing post-operative ipilimumab versus placebo for resected stage III melanoma demonstrated a significant OS benefit for adjuvant ipilimumab[18]. This is the first study to show a survival benefit of checkpoint blockade immunotherapy in the adjuvant setting. The trial used a high dose (10mg/kg) of ipilimumab and was associated with significant toxicity and therefore has not been immediately practice changing in the Australian setting. However, it demonstrates the utility of this class of agent in the adjuvant setting. In the near future, results will be available from a number of randomised controlled trials of other adjuvant therapiesfollowing which adjuvant systemic treatment is likely to become standard for patients with SLN-positive melanoma.

Guideline recommendations

The final evidence-based recommendation in the new Australian Guidelines for the Management of Melanoma for the question “When is a sentinel lymph node biopsy indicated?” states:

Sentinel lymph node biopsy should be considered for all patients with melanoma greater than 1mm in thickness and for patients with melanoma greater than 0.75 mm with other high risk pathological features to provide optimal staging and prognostic information and to maximise management options for patients who are node positive.

This recommendation has been assigned a grade B (good) level of evidence, indicating an evidence base with a low risk of bias with substantial clinical impact, generalisability and applicable to the Australian healthcare context.

The previous “Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand”, published in 2008[19] recommended only that patients with a melanoma greater than 1.0mm in thickness “be given the opportunity to discuss sentinel lymph node biopsy”. With the rapid and dramatic progress in the management of patients with advanced melanoma in recent years, patients with an early clinical stage of disease should now be considered for SLNB, a staging

procedure that will optimally determine their prognosis and allow informed planning of management for their melanoma.

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