Primary Excision Margins and Sentinel Lymph Node Biopsy in Clinically Node-negative Melanoma of the Trunk or Extremities

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Received 25 March 2011; accepted 28 March 2011

The systematic review of Wright and colleagues [1] addresses two important issues for patients with primary cutaneous melanoma of the trunk and extremities: the width of primary excision margins and the use of sentinel lymph node biopsy (SLNB).

Standard systematic review methodology was used and recommendations regarding the width of excision margins are generally reasonable: melanomas in situ should be excised where possible with 5 mm margins, melanomas <1 mm in thickness with 1 cm margins, melanomas 1–4 mm in thickness with 1–2 cm margins and melanomas >4 mm in thickness with 2 cm margins. The authors added the caveat that caution is recommended in melanomas 2–4 mm thick, as evidence addressing optimal margins is unclear and suggested that 2 cm margins may be desirable where feasible. We would go further than this and suggest that a 2 cm margin is the default position for this group. However, we agree that clinical judgement should be used with respect to anatomical location and multidisciplinary surgical input sought where necessary. Only one randomised study has been conducted that included melanomas thicker than 4 mm [2]. In this trial, 1 cm margins were compared with 3 cm margins and a significant increase in locoregional recurrence was seen with 1 cm margins. Given that there are no data to suggest that margins less than 3 cm are effective in this group, we would recommend 3 cm margins where feasible. We would also add that there remains some uncertainty regarding optimal excision margins in general and that further research is desirable, although whether further large clinical trials will be carried out is another matter. We would argue that research in melanoma is entering a new phase and that one of the major priorities is to identify and integrate molecular prognostic information with traditional clinicopathological descriptions. There is already preliminary evidence, for example, that the presence of somatic mutations in the BRAF serine threonine protein kinase in tumour cells may be relevant in this regard [3].

Excision margins for melanoma have rarely been a major subject of heated debate in recent years, but the same cannot be said for SLNB. In order to understand the debate, an appreciation of the facts is needed. It is only necessary to be familiar with one clinical trial: the MSLT (Multicenter Selective Lymphadenectomy Trial)-1 trial [4], which was published over 4 years ago and still remains the subject of debate. Patients with melanomas >1 mm in thickness were randomised to wide local excision of the primary melanoma and completion lymph node dissection (CLND) in the event of the development of palpable nodal disease (standard of care arm) versus wide excision plus SLNB with immediate CLND for patients with positive sentinel nodes (experimental arm). After the third of five planned analyses, only a subset of participants was included in the resulting publication, namely those with tumours of intermediate thickness. The primary outcome measure of the trial in this group (melanoma-specific survival) was similar in both arms (87.1% versus 86.6%, hazard ratio 0.92; 95% confidence interval 0.67–1.25, \( P = 0.58 \)). Five-year disease-free survival was higher in the SLNB arm (78.3% versus 73.1%, hazard ratio 0.74, 95% confidence interval 0.59–0.93, \( P = 0.009 \)), perhaps because those in the SLNB arm were less likely to relapse locally as occult melanoma had already been removed from local lymph nodes at the outset. We conclude from these data that this difference in timing of the removal of local lymph nodes involved with melanoma in the two arms had no effect on survival from melanoma.

Wright and colleagues [1] comment that ‘In a planned post-randomisation subgroup analysis, patients who underwent immediate lymphadenectomy after positive SLNB had significantly higher 5-year survival than patients who underwent delayed lymphadenectomy for clinically apparent nodal metastases (observation arm)’ but that ‘the validity of
these results has been challenged’. These statements could be construed as implying that survival in the SLNB arm of the trial was better than the observation arm and must be viewed critically. This analysis was a subgroup analysis and did not compare the two arms of the trial from the point of randomisation, from which 5-year survival was similar. Benefit or otherwise from an intervention in a randomised trial can only be judged by analysing all patients from the point of randomisation. This subgroup analysis compared patients in the observation arm who developed clinically apparent nodal disease with those in the SLNB arm who had microscopic nodal disease at the start of the trial. These are biologically different groups of patients and to compare them is to assume that all microscopic nodal deposits of melanoma inevitably progress to clinically overt disease. This assumption is unproven. We disagree with Wright and colleagues; in our view there is no question about the validity of these results, the real question is their interpretation.

In the SLNB arm, 5-year survival was significantly lower for those with positive sentinel lymph nodes than for those without (72.3% versus 90.2%, hazard ratio 2.48, 95% confidence interval 1.54–3.98, \( P < 0.001 \)). This is a dramatic difference and there is no question that the presence of positive sentinel lymph nodes is a powerful prognostic indicator and this is reflected in the 2009 AJCC staging for melanoma [5]. It is worth stressing that it is fact, not opinion, that the results of MSLT-1 show that the procedure of SLNB has no effect on survival.

For clinicians treating melanoma there is really only one relevant question: should patients with intermediate thickness melanoma undergo SLNB? Wright and colleagues [1] recommend that ‘Patients with a melanoma greater than 1.0 mm in thickness should be given the opportunity to recommend that’ the results of MSLT-1 show that the procedure of SLNB is increasingly used in conjunction with adjuvant therapy clinical trials’. We have significant misgivings about carrying out an invasive procedure as part of routine clinical care in order to determine suitability or otherwise for a clinical trial. It is difficult to think of other examples where a potentially morbid procedure is carried out for the sole purpose of trial entry, particularly when the major trials of adjuvant therapy in Europe include observation-only arms.

In our view, it is reasonable to discuss SLNB with patients with intermediate thickness melanoma. We do not believe that SLNB is ever ‘indicated’ or that any patient with melanoma ‘should’ undergo this procedure. Patients should be advised of the possible benefit (knowledge of further prognostic information) and the possible risks: seroma and haematoma, lymphoedema, wound infection, neurapraxia and allergic reactions to dye. Patients should be advised that the prognostic information is not absolute, i.e. it represents a proportional change (e.g. 10% versus 30%) in the risk of relapse. Furthermore, patients should be counselled that adverse prognostic features will not result in the administration of systemic adjuvant therapy, but a discussion of the possible risks and benefits of that adjuvant therapy. A discussion of adjuvant therapy may therefore have to be part of the process of gaining informed consent for SLNB.

Our experience in counselling patients is that risks of survival at distant time points are not necessarily easy to understand. There is a lack of easy to use resources to enable patients and clinicians to understand the change in risk of relapse that a positive SLNB confers in addition to the prognostic information derived from the primary lesion. As a consequence of this and the fact that such resources do exist for other types of cancer, we have developed a web resource...
based on the 2009 AJCC staging system that we hope is easy for patients with melanoma to use in conjunction with their clinicians (www.melanomaprognosis.co.uk).

SLNB is practised widely in many parts of the world, but in the UK there is variation in practice, similar in principle to the ‘postcode lottery’ for access to high cost drugs to treat cancer [9]. As oncologists we are depressingly familiar with this. It is unjust that the availability of any healthcare intervention that is paid for from central taxation should vary depending on geography and this should not be the case for SLNB any more than it is for drugs. For high cost drugs used to treat cancer, NICE conducts an appraisal process in which their cost effectiveness is evaluated. In general, gains in survival and quality of life are analysed in conjunction with costs in order to derive measures of value for money, such as quality-adjusted life years. Currently, a positive opinion from NICE allows clinicians to prescribe drugs to National Health Service patients as they are viewed as an effective use of resources.

Wright and colleagues [1] state that SLNB confers a possible disease-free survival benefit. Although we disagree with this contention, we think that NICE should carry out a review of SLNB in melanoma. This would have a number of potential advantages, such as a dispassionate and independent review of both the evidence and the cost of the procedure in relation to outcomes. This would determine whether or not SLNB in melanoma represents a good use of National Health Service resources.

References