PLASTIC SURGERY

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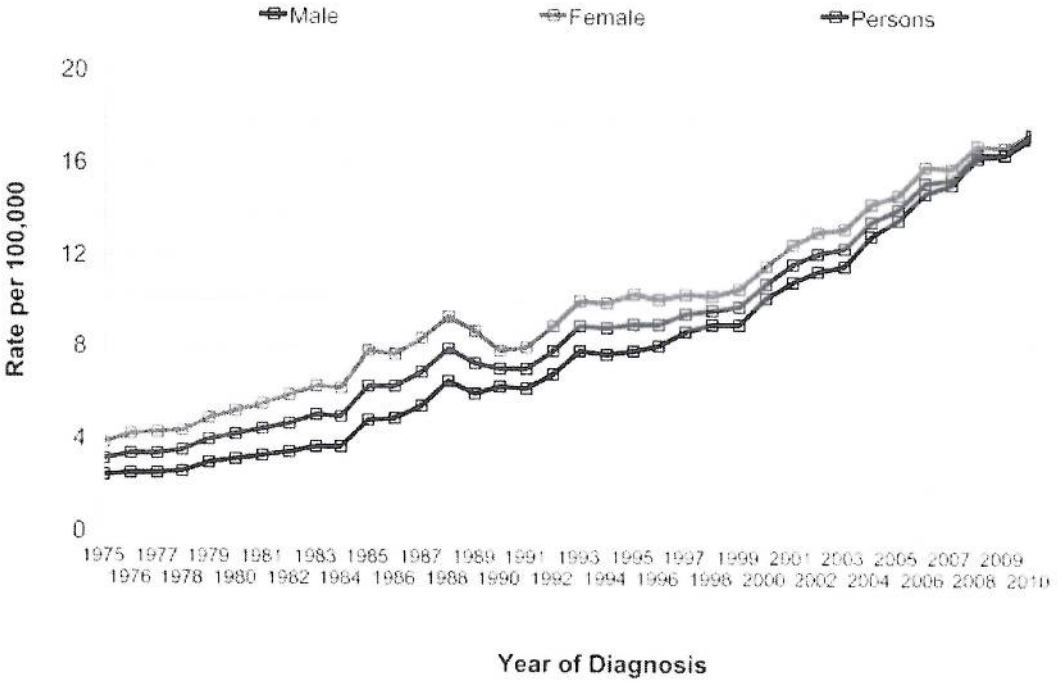
Melanoma and the current role of sentinel node biopsy

Malignant melanoma (MM) is a tumour of the melanocytes, found predominantly in the skin but also in the bowel and eye. Melanoma is the 5th most common cancer in the UK, accounting for 4% of all cancers. In 2010, there were 12,818 new cases of MM with a male:female ratio of around 10:11, in the same year 2,203 deaths were attributed to melanoma.

Over the last 30 years the incidence of melanoma has dramatically increased, rates are now seven times higher in men, and four times higher in women than in 1975.



Malignant Melanoma (C43): 1975-2010; European Age-Standardised Incidence Rates per 100,000 Population, by Sex, Great Britain.

Prepared by Cancer Research UK

After a MM is diagnosed, the disease is staged according to the 2009 American Joint Committee on Cancer (AJCC) staging system. Patients in stage IA have a primary tumour of

less than 1mm Breslow thickness with no ulceration and mitoses of $<1mm^{-2}$. These patients have a 95% 5 year survival rate. The 5 year survival rate falls as the tumour thickness increases in stage I and II disease, with significantly worse outcomes in stage III when lymph node metastasis are present (5 year survival 57-79%), or in stage IV when other sites or organs are involved (5 year survival 5-22%).

Accurate staging is considered important and is widely accepted as the basis for counselling, therapeutic decision making, and prognostication in melanoma. Prognostic information is often invaluable and helps the vast majority of patients in an informed decision-making process. Patients with a MM of Breslow thickness 1.2–3.5 mm and a positive sentinel node have a 75% 5-year survival compared with 90% if the sentinel node is negative.

In the early 1990s the sentinel node hypothesis was introduced as a minimally invasive procedure to stage the entire nodal basin and, thus, identify those with stage III disease who could potentially benefit from a complete lymphadenectomy and spare those with a negative sentinel node biopsy the morbidity associated with a lymphadenectomy.

The sentinel lymph node (SLN) is the first lymph node to which cancer cells are thought to metastasize from the site of the primary tumour. Accordingly, a tumour-negative sentinel node should predict with high confidence the absence of metastatic disease in the rest of the nodal basin.

Complications commonly associated with the sentinel node biopsy are reported to include wound separation, seroma, and infection, and approximately 10% of pateints undergoing a sentinel node biopsy experience one of these complications.

False-negative findings have challenged the validity of the sentinel node procedure. A false negative sentinel node biopsy is a node found to have no disease on pathological assessment, but clinical or histological evidence of disease in the nodal basin is later found. The causes for false-negative results are thought to be due to three main causes:

- technical failure,
- pathologic failure, and
- biological failure.

A technical failure is a failure of the surgical procedure. This can be caused by inexperience, as evidence suggests a surgeon must be well practiced in the sentinel node procedure before the correct node can be reliably identified and sampled. However, even experienced surgeons have false-negative results; in about 5% of cases it is not possible to identify the sentinel node either on lymphoscintigraphy, at surgery, or both.

A pathologic failure may be caused by lack of sensitivity of current histopathology methods to identify nodal metastases that are in fact present. In the UK The Royal College of Pathologists has produced a set of standards which should be adhered to by pathologists. Amongst their recommendations include double reporting of specimens and immunohistochemical staining (S100 and Melan A). However, less than 2% of sentinel node

specimen volume is actually sectioned and only 6 to 20 sections are examined for occult metastases. It is possible, therefore, that tumour can be missed.

And finally, a biologic failure may occur when lymphatic's are obstructed by melanoma cells or if an inadequate initial excision is performed, leaving cells at or near the primary site that acquire the capability to disseminate secondarily through lymphatic channels into nodes other than the original sentinel node.

A question fundamental to the sentinel node procedure is whether or not biopsy followed by immediate lymphadenectomy improves regional disease control and/or survival. Uncontrolled regional disease is recognized as a significant source of melanoma-related morbidity and can have a major negative impact on quality of life. There is currently no direct evidence that the sentinel node biopsy followed by immediate complete lymphadenectomy results in better regional control than delayed nodal clearance. The prospective, randomized multinational Multicenter Selective Lymphadenectomy Trial (MSLT-I) trial may help provide evidence to answer this question. The design of this study is outlined below:

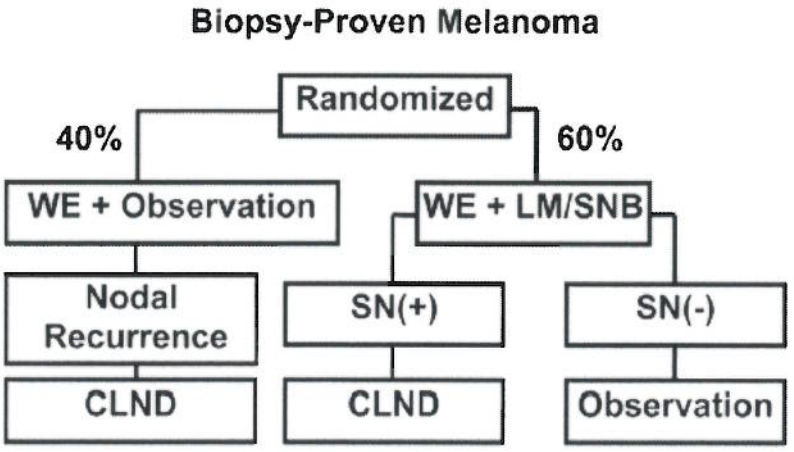


FIGURE 1. MSLT-I study design. Patients with primary cutaneous melanoma ≥1 mm or Clark level IV are assigned in a 60:40 distribution to wide excision (WE) plus lymphatic mapping and sentinel node biopsy, with immediate complete lymphadenectomy (CLND) for occult nodal metastases, or to WE plus observation, with delayed CLND or other treatment of palpable nodal metastases. All patients are followed up for disease-free and melanoma-specific survival.

The sentinel node arm of this trial simulates the practice currently recommended by the British Association of Dermatologists who recommend that patients with stage IB or higher primary melanoma should be offered a sentinel lymph node biopsy if available followed by completion lymphadenectomy if positive. The process is described as a staging procedure of no proven therapeutic value.

Thus far the MSLT-I has shown that a sentinel node biopsy can accurately identify occult nodal metastases that will lead to more advanced disease if left in situ. The authors therefore recommend that a sentinel node biopsy remains part of the AJCC staging system for prognostication and to identify candidates to whom immediate therapeutic completion lymphadenectomy may be recommend.

However, the trial has also demonstrated that only 10% to 20% of patients with tumour-positive sentinel nodes have tumour in other nodes which has led the authors to suggest that potentially the morbidity of complete nodal clearance could be avoided for most patients with early, clinically occult nodal involvement. This theory will be tested in MSLT-II which aims to determine if immediate nodal clearance provides a therapeutic advantage over care based on postoperative ultrasonographic monitoring of the nodal basin.

The MSLT-I is the only current prospective randomized trial designed to address the survival benefit of the sentinel node biopsy and its full outcome is awaited although provisional results have shown no overall 5-year survival benefit following sentinel node biopsy and completion lymphadenectomy.

Conclusion

The current evidence supports the use sentinel node biopsy in MM as it is an independent factor useful to predict survival and has the highest sensitivity and specificity of any nodal staging test available today.

The value of the procedure with respect to survival benefit is currently uncertain and in the UK is described as a staging procedure only with no therapeutic benefit. This issue will be clarified by the MSLT-I trial.

Rather than surgery the most significant advances in melanoma treatment of recent years have been with biological agents such as the BRAF kinase inhibitor, Vemurafenib, for the

treatment of unresectable locally advanced or metastatic BRAF V600 mutation positive malignant melanoma. This drug has produced improved rates of overall and progression-free survival in patients with previously untreated melanoma with the BRAF V600E mutation.

An immunomodulation agent Ipilimumab which potentiates an antitumor T-cell response has also been shown to improve overall survival in patients with previously treated metastatic melanoma.

Other ongoing clinical trials include:

- A trial looking at bevacizumab after surgery for melanoma skin cancer (AVAST-M)
    - The monoclonal antibody Bevacizumab targets vascular endothelial growth factor (VEGF) to inhibit angiogenesis and therefore tumour growth.
- Screening and Surveillance Ultrasound of Nodes in Melanoma (SUNMEL Trial)
    - A study of ultrasound surveillance of regional lymph nodes after resection of primary cutaneous melanoma as an alternative to sentinel node biopsy.
- Nilotinib to Treat Acral and Mucosal Melanoma Skin Cancer That Has Spread (NICAM) clinical trial
    - In 20% of these melanomas there is a mutation in the cell signalling molecule c-KIT. Nilotinib is a novel drug given to blocks c-KIT.

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