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Impact of Sentinel Node Biopsy on Outcome in Melanoma

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1. Introduction

The worldwide incidence of malignant melanoma is increasing at an alarming rate. The importance of diagnosing nodal metastatic disease has impacted significantly on the accurate staging and stratification of melanoma patients. As a minimally invasive procedure with low morbidity, sentinel lymph node mapping allows for a detailed histopathologic evaluation involving multiple sections, H&E staining in combination with immunohistochemical staining of the node with the highest chance of containing metastatic foci. Controversy exists regarding the appropriate selection of patients for sentinel lymph node biopsy, particularly among patients with thin melanomas (< 1 mm Breslow thickness), thick melanomas (> 4 mm Breslow thickness), locally recurrent melanoma, nodular melanomas and those affecting the head and neck region. Furthermore, debate continues with regard to false-negative rates, managing in-transit disease, therapeutic benefit and alternatives, such as ultrasound guided biopsy.

In malignant melanoma, no standard systemic adjuvant therapy with confirmed impact on overall survival has been identified thus far for clinically node negative stage I-II patients after excision of the primary, or for clinically node positive stage III patients after lymph node dissection for metastatic regional node involvement. Thus some argue about the initial merits of performing the sentinel node procedure at all.

The aims of this book chapter are

1. to examine the impact of sentinel node biopsy on outcome in melanoma,
2. determine the effect, if any, of stage migration in melanoma
3. to clarify the impact of the different clinical sites on outcome,
4. to ascertain the reasons behind a lack of universal adoption of sentinel node biopsy in melanoma and
5. to critically assess other emerging strategies in the management of melanoma including frozen section analysis of the sentinel node, imprint cytology of the sentinel node, targeted assessment of the regional lymph node basin, the use of risk stratification algorithms of histological factors of the primary tumour and microRNAs.

2. Impact of sentinel node biopsy on outcome in melanoma

The key to survival for patients with melanoma is early detection and treatment of metastatic disease as this may improve disease-free and overall survival rates (Pacifico,

Grover, and Sanders 2004). The status of the regional lymph node basin has been widely shown to be the most important prognostic indicator for patients diagnosed with cutaneous melanoma (Balch et al. 2001). The disease-free survival and overall survival is dependent on the initial disease burden, thus melanomas less than 1mm rarely metastasise while at least 25% of melanomas between 1.5 and 4.0mm and greater than 60% of melanomas greater than 4.0mm thick will have lymph node metastases at presentation (Balch et al. 2001). The disease also depends heavily on the stage at presentation. Patients with early stage disease (i.e. < 1mm thick) achieve long-term survival in more than 90% of cases. However, patients with melanomas greater than 1.0mm thickness have survival rates ranging from 50%-90% (Balch et al. 2001).

The introduction of the sentinel lymph node biopsy (SLNB) technique for the evaluation of patients with truncal and extremity melanoma by Morton et al in 1992 showed that the status of the SLN accurately represented the status of the entire nodal basin from which it was obtained. This study highlighted a novel technique of identifying patients with occult nodal metastasis who warranted possible further therapeutic lymphadenectomy and adjuvant therapy, whilst also sparing the remaining 80% of patients without regional disease the morbidity associated with a formal lymphadenectomy procedure (Morton et al. 1992).

The benefits to performing SLNB versus elective lymphadenectomy are well supported (Pawlik, Ross, and Gershenwald 2004). SLNB is associated with less morbidity and is cheaper to perform (Wrightson et al. 2003). Historically two studies showed a survival benefit in patients who had SLNB performed (Dessureault et al. 2001; Kretschmer et al. 2004). Furthermore a positive sentinel node, Breslow thickness, age and male gender were all independent predictors of overall survival on multivariate analysis (Kretschmer et al. 2004).

The proven benefits for performing SLNB at the time of oncological wide local excision of a primary melanoma in any patient, include both prognostic and staging information, the potential therapeutic impact of a completion lymph node dissection in those with a positive SLN and also has implications of SLN status for adjuvant therapy decisions or entry into pertinent clinical trials. Because the status of the regional lymph nodes is the most single important prognostic factor for patients with melanoma, obtaining this information is essential (Shaw et al. 1985).

The preliminary findings of the MSLT-1 trial (Multicentre Selective Lymphadenectomy Trial) represent the first randomised prospective clinical study to show a potential survival advantage to performing sentinel lymph node biopsy in patients with melanoma (Morton et al. 2006). The study included 1269 patients with intermediate thickness (1.2-3.5mm) primary melanomas randomised to either a wide local excision and observation of regional lymph nodes with lymph node dissection if nodal relapse occurred (n=500) or to a wide local excision and SLNB with immediate regional lymphadenectomy if nodal micrometastases were found (n=769).

There was no difference in overall 5-year melanoma-specific survival rate; 87.1% for the SLNB and 86.6% in the control arm. However, the study did show improved disease-free survival in those patients who underwent the SLNB compared to those in the nodal observation arm group; the 5-year survival rate for node positive melanoma was 72.3 ± 4.6% and 90.2 ± 1.3% in the node negative group (hazard ratio for death, 2.48; 95% confidence interval, 1.54 to 3.98; $P < 0.001$).

The incidence of sentinel-node micrometastases was 16.0% and the rate of nodal relapse in the observation group was 15.6%. The corresponding mean number of tumour-involved

nodes was 1.4 in the biopsy group and 3.3 in the observation group (P<0.001), indicating disease progression during observation. Among patients with nodal metastases, the 5-year survival rate was higher among those who underwent immediate lymphadenectomy than among those in whom lymphadenectomy was delayed (72.3+/-4.6% vs. 52.4+/-5.9%; hazard ratio for death, 0.51; 95% confidence interval, 0.32 to 0.81; P=0.004) (Morton et al. 2006). The study authors concluded that the staging of intermediate-thickness (1.2 to 3.5 mm) primary melanomas according to the results of SLNB provided important prognostic information. However, the study did not show a clear survival advantage associated with SLNB.

Further subset analysis from MSLT-1 comparing patients with a positive SLNB + immediate lymphadenectomy versus those in the nodal observation group showed that there was significant progression to more advanced nodal disease in the nodal observation group and more importantly that there was a significant survival advantage in those undergoing immediate lymphadenectomy.

In order to appreciate the full potential applicability of the results from MSLT-1, it is important to consider the results from the WHO Truncal Melanoma international multicentre randomised trial which examined the use of early elective lymph node dissection (ELND) at the time of WLE of truncal melanomas > 1.5mm versus delayed lymphadenectomy until appearance of regional-node metastases (Balch et al. 2000). Firstly, this trial in addition to one carried out in Europe and published 2 years before (Cascinelli et al. 1998) under the title of WHO Melanoma Programme, did show a trend for improved survival in those patients who had ELND at the time of WLE, however this was not significant. But they did show improved 5-year survival rates in patients with occult regional node metastases 48% versus 27% in patients in whom the regional node dissection was delayed until the time of appearance of regional node metastases, which indeed was significant. The patients with regional nodes that became clinically and histologically positive during follow-up had the poorest prognosis. They concluded that SLNB may become a tool to identify patients with occult node metastases, who could then undergo node dissection (Balch et al. 2000).

These same authors showed that nodal micrometastatic deposits detected by the SLNB will become clinically relevant disease eventually therefore the logic of removing these involved lymph node deposits early may improve patient prognosis (Morton, Cochran, and Thompson 2007). Numerous reasons are cited in an article by Ross et al detailing exactly why the microscopic metastases in sentinel lymph nodes would most likely progress to palpable disease if left intact (Ross and Gershenwald 2008).

Most recently, an international panel comprising a cross section of expert melanoma surgeons who have contributed data and leadership to further investigate the role of SLNB in melanoma recently produced a consensus statement, outlining their overall interpretation of current evidence, as a guide to clinical treatment of patients with clinically localized melanoma. They agreed that SLNB is standard of care in current practice because it is incorporated in staging guidelines from the AJCC, incorporated in the treatment guidelines from the National Comprehensive Cancer Network, and practiced by most specialty surgeons who treat melanoma in the United States, Australia and Western Europe (Balch et al. 2009).

3. Stage migration effect

Oncologically, the prognosis for malignant disease is largely determined by the metastatic potential of the primary tumour. Some authors argue that we cannot alter prognosis by

early detection and surgical intervention of involved regional nodes, highlighting the balance between nihilistic pre-determinism and active management. As an oncological community, we have a greater understanding of the mechanisms of action for haematological spread versus lymphatic spread. For many malignancies we know that regional lymphadenectomy improves survival. As to just how far this lymph node dissection is directly therapeutic remains a persistent source of controversy in melanoma.

Many believe that stage-adjusted survival benefit is due in part to the phenomenon of stage migration (*Will Rodgers phenomenon*). In medical stage migration, improved detection of illness (eg when newer technology allows for more sensitive detection of tumour spread) leads to the movement of people from the set of healthy people to the set of unhealthy people. Because these people are not healthy, removing them from the set of healthy people increases the average lifespan of the healthy group. Likewise, the migrated people are healthier than the people already in the unhealthy set, so adding them raises the average lifespan of that group as well. Both lifespan are statistically lengthened, even if early detection of a cancer does not lead to better treatment - because it is detected earlier, more time is lived in the "unhealthy" set of people. It was originally described in 1985 (Feinstein, Sosin, and Wells 1985). Rodgers' original quote -"When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states" - illustrates the theme. It has been shown that stage migration is responsible at least in part for an apparent improvement in survival for patients with stage III and IV non–small cell lung cancer in the era of PET scanning (Chee et al. 2008). It has also been demonstrated in urological, prostate and laryngeal malignancies (Albertsen et al. 2005; Champion and Piccirillo 2004; Gofrit et al. 2008). A large population-based study assessing the surgical treatment trends for 18449 patients with melanoma in the era of sentinel node biopsy using a SEER database concluded that stage migration is evident with increasing use of SLN biopsy (Cormier et al. 2005).

Furthermore, the theme underlying this phenomenon may no longer be confined to interpreting oncology trials as its' use has been cited in other paramedical arenas including healthcare economics. Young et al studied the measured differences in health care utilisation across an indemnity and managed care plan, finding that apparent increases in utilisation in both plans disappeared when viewed together, reflecting the migration of sicker patients from indemnity to managed care plans (Young et al. 1999).

4. Impact of histological site on outcome

While SLNB has a defined role in cutaneous melanomas of the trunk and extremities, several questions remain unanswered with respect to its application in the head and neck region. These account for up 21% of all melanomas diagnosed annually (Gillgren et al. 2000; Golger et al. 2007; Lachiewicz et al. 2008), have worse outcomes relative to melanomas of the trunk and extremities (Gillgren et al. 2000; Lachiewicz et al. 2008), clinically manifest as thicker lesions at their initial diagnosis and thus present at an advanced stage (Gillgren et al. 2000; Hoersch, Leiter, and Garbe 2006). SLNB for melanomas of the head and neck regions is limited by technical difficulties with specific concern surrounding damage to vital structures such as the facial nerve (Eicher et al. 2002). There is growing concern surrounding the reliability of the SLN to accurately predict the disease status of the entire nodal basin. In the head and neck region, the complexity and variability of the interlacing network of cervical lymphatics was highlight by O'Brien et al who showed a 34% discordance rate between the clinical prediction of lymphatic drainage and lymphoscintigraphy findings in 97 cases of

cutaneous melanoma of the head and neck (O'Brien et al. 1995). A recent study from the John Wayne Cancer Institute reported a 'false negative' rate of 8.9%, identifying increasing tumour thickness, the presence of ulceration and head/neck primary tumours as risk factors for the development of recurrence in the presence of a negative node (Gershenwald et al. 1998). A recent study from the Sydney Melanoma Unit showed that up to 30% of patients with lymph node metastases from neck melanomas bypass the nearest node and involve nodes at more distant sites (Pathak et al. 2001), so called "skip metastases".

Numerous studies have evaluated the survival differences between head and neck melanoma versus those of the trunk and extremities and have found that those with melanoma of the head and neck have relatively poorer outcome (Gillgren et al. 2000; Lachiewicz et al. 2008; Thorn et al. 1989).

Specifically in a study involving 51,704 patients with melanoma, 5- and 10-year Kaplan-Meier survival probabilities for scalp/neck melanoma were 83.1% and 76.2%, respectively, compared with 92.1% and 88.7%, respectively, for melanoma of the other sites, including extremities, trunk, face, and ears. They found that patients with melanoma of the scalp/neck had an 84% greater chance of melanoma-related death compared with those with melanomas of the extremity (Lachiewicz et al. 2008). Within this head and neck group, another large population-based study involving 27,097 patients to evaluate tumour location as a prognostic factor in patients with head and neck melanoma (using the Surveillance, Epidemiology, and End Results (SEER) database), showed a 10-year overall survival rate of 56% and a disease free survival rate of 85%, respectively with those patients diagnosed with scalp/neck melanoma having poorer survival versus those with facial melanoma (Tseng and Martinez).

5. Lack of universal adaptation of sentinel node procedure

There has been some international criticism leveled directly at the manner in which MSLT-1 was carried out and the conclusions derived from it (Thomas 2006, 2009). Stated evidence that, tiny sentinel nodal deposits of melanoma have no prognostic relevance and will not progress or disseminate further as determined by the hosts' immune system, is now accruing. Associating a poorer prognosis to these deposits is called prognostic false positivity; which can lead to patients being incorrectly upstaged, undergoing unnecessary completion lymphadenectomy and possibly unnecessary adjuvant therapy (Thomas 2008). The results of the fourth interim analysis of MSLT-I support the hypothesis that prognostic false-positivity is the explanation for the large survival advantage claimed for patients having early lymphadenectomy versus delayed lymphadenectomy. Further detailed analysis of the results of MSLT-1 suggested that the incidence of prognostic false positivity is about 24% in patients with intermediate thickness melanoma and 34% for all patients (Thomas 2008). Further credence is given to this stance from studies confirming that patients with these tiny deposits of nodal melanoma (ie detected by immunohistochemistry alone or <0.1mm in size), have similar prognosis to those who are sentinel node negative (Spanknebel et al. 2005; van Akkooi et al. 2006).

Some believe that a positive sentinel node is likely to be associated with disseminated melanoma deposits elsewhere because they believe that melanoma tumour biology is not predictable. Are these cells released into the circulation, either lymphatic or blood vascular, disseminating widely and beyond? The timing of their manifestation is that which is unpredictable. These disseminated deposits (nodal, in-transit or distant disease) may

become clinically apparent at some point in time, in spite of a positive sentinel node (and subsequent regional lymphadenectomy). Thus, assessment histologically of the sentinel node and the extent or number of lymph node deposits does not confer any additional benefit to patients, apart from the fact that they have melanoma deposits outside of their primary site and that in time they are at greater risk of further distant disease.

Some experts argue against the routine use of SLNB as they feel that it is associated with an increased risk of in-transit disease, however this has been readily refuted by evidenced based study who showed that there was no significant difference in the rate of in-transit metastasis between patients who had WLE alone (4.9%) and those who had WLE + SLNB (4.5%) (Pawlik et al. 2005).

Clinicians opposed to the use of the sentinel node will argue that in spite of its' prognostic importance, there is still no clear evidence to support a direct survival advantage from the procedure alone and, that no effective adjuvant therapy (including vaccines, combinations of chemotherapeutic agents, immunostimulants, cytokines and growth factors) has been heretofore discovered and subsequently proven to be of clear benefit (unequivocally prolongs overall survival) in clinical trials to date for these patients (Otley and Zitelli 2000; Thomas and Patocskai 2000; Eggermont and Gore 2007; Sabel and Sondak 2002; Spitler 2002).

Confusion remains whether early completion lymphadenectomy imparts a survival advantage when compared directly to those patients who wait until clinically occult nodal metastatic disease becomes apparent. Some authors site compelling evidence that the assessment of the sentinel node in melanoma is of no benefit whatsoever, does not alter the course of melanoma that has metastasised and should be immediately abandoned from current practice (Medalie and Ackerman 2004). There is growing concern surrounding the reliability of the SLN to accurately predict the disease status of the entire nodal basin. Specific problems have been identified in the head and neck region where the complexity and variability of the interlacing network of cervical lymphatics was highlighted by O'Brien et al who showed a 34% discordance rate between the clinical prediction of lymphatic drainage and lymphoscintigraphy findings in 97 cases of cutaneous melanoma of the head and neck (O'Brien et al. 1995).

Regional nodal failures in melanoma patients following a negative SLNB are not common. Various reasons have been suggested as to why SLNM fails which include (1) when the primary lesion is overlying the draining lymph node basin, (2) learning curve of the performing surgeon / pathologist / nuclear medicine staff, (3) inappropriately high radioactivity level, (4) movement of the dye into the second or non-sentinel lymph node and (5) incorrect injection technique of the dye. It has been suggested that at least a 30 person learning curve be recommended for a surgeon performing these cases (Morton et al. 1999). Patients undergoing SLNM for cutaneous melanoma should be managed via a multi-disciplinary team and the overall success rate of the procedure may be attributable in some part to this.

It is also well recognised that 11–12% (Gadd et al. 1999; Gershenwald et al. 1998) of patients whose sentinel node apparently doesn't harbour cells of melanoma subsequently develop signs of metastatic melanoma disease and conversely patients whose sentinel node does harbour metastatic cells may succumb to their illness in months or they may survive for decades. This high figure does little to add confidence to the therapeutic benefit of sentinel node biopsy.

6. Other emerging strategies

In an ideal oncological world, intra-operative evaluation of the sentinel node for metastatic disease allows a simultaneous completion lymphadenectomy if a positive deposit is immediately identified, preventing the higher costs and additional morbidity associated with a second operation. There is evidence that the sentinel node biopsy procedure is cost-effective compared to wide excision alone (Morton, Howard, and Thompson 2009). Here we discuss some of the emerging strategies addressing this specific issue.

Frozen section analysis of the lymph node was studied in 368 patients with primary cutaneous melanoma ≥1mm or Clarks level IV. 20% (74/368) of sentinel nodes were identified by traditional H&E and immunohistochemical stains, and further frozen sectioning only identified the metastases in 59% (44/74) of these patients (Stojadinovic et al. 2002). The SLN was the only positive lymph node in 86% (64/74) of patients. Additional positive non-SLNs were identified in 10 of 74 patients (14%). This low sensitivity was confirmed in other subsequent studies (Koopal et al. 2000; Tanis et al. 2001). The authors do suggest the potential use of frozen sectioning of a sentinel node found within the parotid gland or neck, thereby reducing the risk of facial and spinal accessory nerve injury during a second operative procedure. Frozen sectioning is a technically difficult procedure to perform and results in freezing artefact of the lymph node, rendering it unsuitable for further analysis.

Another recent development concerning the sentinel node is imprint cytology, which involves bisecting the node, imprinting it and subsequently staining the relevant sections. One study involving 93 patients showed that imprint cytology had a sensitivity and specificity of 38% and 100% respectively (similar figure to that of frozen section) (Creager et al. 2002). Even though it is easier to perform this procedure and without subsequent damage to the lymph node, the low sensitivity severely limits its use in the routine evaluation of the sentinel node. Other algorithms of histological factors concerning the primary tumour have also been developed (vertical growth phase, tumour infiltrating lymphocytes, mitotic rate and thickness) (Kruper et al. 2006). These are able to stratify patients into high and minimal risk for sentinel node disease based on the analysis of their primary lesion, and upon validation, these models could possibly provide a clinically useful tool for making treatment decisions (remove the use of the sentinel node procedure in those with minimal risk), aid in assessing patient risk, and for planning and analyzing clinical trials (Soong et al.).

Some molecular biology techniques for the staging of regional lymph nodes have yielded promising results (Wang et al. 1994). Wang et al, using real-time PCR to identify tyrosine messenger RNA for the detection of micrometastatic lymph node disease, showed that this was a highly sensitive and clinically applicable method to detect micrometastases (tyrosine messenger RNA is found almost exclusively in melanocytes). Furthermore, studies using reverse transcription and polymerase chain reaction to determine tyrosinase mRNA in peripheral blood, (which indicates the presence of circulating melanoma cells), showed that this may be a promising serum marker for melanoma staging and for predicting recurrence, prognosis and response to immune therapy (Brossart et al. 1993). The same group found that the amount of circulating tumour cells correlates with the tumour burden and that in patients with regression of melanoma metastases after immunotherapy, a decrease of the amount of tumour cells in the peripheral blood was observed (Brossart et al. 1995), associating the rate of positivity with stage of the disease.

There is accumulating evidence to support the use of targeted ultrasound assessment of the regional nodal basin at the time of diagnosis of the primary tumour, thus enhancing routine

clinical palpation. It is possible to identify deposits as small as 3-4mm (Bafounta et al. 2004). This does not take into account those nodal deposits below that diameter ie <3mm. Voit et al showed that specific features on preoperative ultrasound (peripheral perfusion, balloon shape and loss of central echoes) and fine needle aspiration cytology can identify 65% of sentinel node metastases and thus reduce the need for surgical procedures on the sentinel node, allowing those patients identified to proceed directly to completion lymphadenectomy (Voit et al.). However these results must be considered with caution. Ultrasound is heavily user-dependent. Given the fact that some patients will present with micrometastatic deposits in their regional nodes that will not be identifiable on ultrasound lowers its' sensitivity. Therefore, a negative ultrasound is not a reliable substitution for biopsy and subsequent histopathological examination of the sentinel node.

MicroRNAs (miRNAs) are non-coding short ribonucleic acid molecules that are post-transcriptional regulators that bind to complementary sequences in the three prime untranslated regions of mRNAs, leading to gene silencing. MiRNAs are present in human plasma in a very stable form that is protected from endogenous RNase activity (Mitchell et al. 2008). There has been a recent surge in reports demonstrating the use of miRNAs as modulators of gene expression and their potential role as both diagnostic and prognostic markers in many malignancies (Iorio and Croce 2009; Osaki, Takeshita, and Ochiya 2008). This is also true for malignant melanoma, where it has been shown that serum levels of miR-221 were significantly increased in melanoma patients, differentiated between in situ and invasive disease, were useful in evaluating tumour progression and monitoring patients during follow-up and that levels of of miR-221 correlated with tumour thickness (Kanemaru et al.).

7. Conclusion

In spite of a lack of definitive evidence associating a positive SLNB result and increased survival rate, the routine use of this novel approach is justified in patients presenting with primary cutaneous malignant melanoma because it provides valid and reliable staging information about the regional nodes using a minimally invasive technique, allows for regional disease control in the presence of a positive sentinel node and increases the potential for cure in patients with at least intermediate thickness disease. Cumulative evidence from MSLT-1, ELND trials and large retrospective trials mentioned above support the view that survival is better for patients with clinically occult sentinel node deposits.

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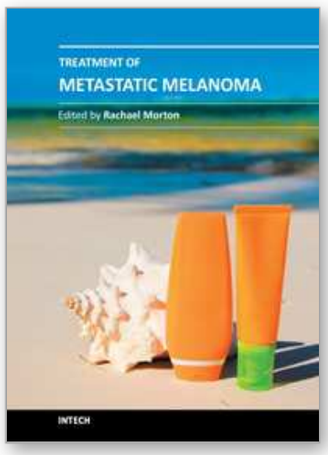

Treatment of Metastatic Melanoma
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Surgery continues to be the mainstay treatment for melanoma localized to the primary tumor and/or lymph nodes. Results from randomized controlled trials indicate that sentinel node biopsy for the treatment of cutaneous melanoma of intermediate thickness has a beneficial effect on recurrence rates, and adjuvant radiotherapy to regional lymph node fields following surgical resection reduces loco-regional recurrence in patients at high risk of relapse. Isolated limb perfusion, electrochemotherapy, and photodynamic therapy continue to be evaluated for treatment of stage IV disease. However, the greatest excitement in new treatment has been with targeted therapies for genetic mutations. In particular, the promising results of partial and complete tumor response in stage IV disease from early phase trials of the B-RAF kinase inhibitors. This book provides a contemporary insight into the therapeutic treatment options for patients with metastatic melanoma and is relevant to clinicians and researchers worldwide. In addition, an update on current clinical trials for melanoma treatment has been included, and two chapters have been reserved to discuss the treatment of oral and uveal melanoma.

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