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Controversies in Dermatology

Sentinel node biopsy has no benefit for patients whose primary cutaneous melanoma has metastasized to a lymph node and therefore should be abandoned now

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Background

Rationale for sentinel node biopsy

In 1992, Morton *et al.*[1] published the results of their study, the first ever undertaken, about the utility of sentinel node biopsy (SNB) for patients with primary cutaneous melanoma (PCM) whose regional lymph nodes were not palpable clinically. The collaborators defined the sentinel node (SN) as 'the lymph node nearest the site of the primary melanoma, on the direct drainage pathway'. They averred that metastasis from a PCM nearly always is found in the SN. Conversely, they opined that if the SN did not harbour a metastasis of melanoma, then nodes other than the sentinel one almost always were negative for metastases.

The purpose of SNB, as it was expressed then by Morton *et al.*, was as follows: '… this technique [SNB] identifies with a high degree of accuracy, patients with early stage melanoma who have nodal metastases and are likely to benefit from radical lymphadenectomy'. The authors declared that SNB followed by dissection of regional nodes would benefit patients by curing them of melanoma. Does it really? Let readers decide by critical analysis of the 'points' and anticipated 'counterpoints' that follow.

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Point 1. Elective node dissection and sentinel node biopsy followed by dissection of regional nodes are one and the same procedure fundamentally, and, therefore, results of studies that pertain to elective node dissection are applicable equally to sentinel node biopsy

In 2003, McMasters and Swetter[2] stated that elective node dissection (END) and regional node dissection (RND) performed because of a positive SN are two different procedures and, that being the case, advised that any comparison between them would be fraught with inaccuracy. They reasoned that because 80% of patients who undergo END did not have metastases of melanoma, only 20%, at most, of patients could benefit from it and, moreover, statistical analysis was unlikely to detect that benefit. The supposition of McMasters and Swetter is wrong: the function of statistical analysis is to determine any possible benefit to survival, and there is no such benefit.

In the same paragraph of the same article, having pronounced that studies of END are not applicable to SNB, McMasters and Swetter drew, inexplicably, on findings in a study by Balch *et al.*[3,4] in order to lend support to the notion that SNB with subsequent RND may benefit certain sets of patients with metastases of melanoma, the rationale for that being that END appears to benefit those patients. But it is both illogical and disingenuous to introduce studies of END that are biased with regard to selectivity and the results of which are contradictory.

In brief, it must be comprehended fully that SNB followed by RND is simply an END that has been preceded by a SNB. The objective and rationale of both procedures is to remove all regional nodes that contain metastases of melanoma as a preventive measure to nodes that harbour metastases from becoming palpable clinically and from disseminating, thereby allowing patients, in theory, to live longer. If END is bereft of benefit, so, too, it must be for SNB followed by RND.

Point 2. Elective node dissection provides no benefit to patients with metastases of melanoma

In 1978 and again in 1986, Sim *et al.*[5,6] in a randomized study carried out prospectively, came to a conclusion about the merits of END that, in time, other investigators also would reach. This is how they set forth their opinion: '… immediate lymphadenectomy [END] seems to be of no significant benefit to the patient'.

In 1980 and again in 1982, Veronesi and collaborators,[7,8] on the basis of a study performed by them prospectively in which 553 patients were randomized either to be followed with observation only or to be subjected to END, came to this conclusion: '… delayed node dissection is as effective as the immediate dissection [END] in stage I melanoma of the extremities…', that is, survival of patients with metastases of melanoma was the same overall irrespective of whether or not they had had a 'delayed node dissection', to wit, either extirpation of regional nodes at the time that metastases became manifest clinically or END.

In 1996 and in 2000, Balch *et al.*[3,4] published results of studies that concerned survival of 740 patients with PCM. Of those, 379 patients underwent END dissection, whereas the remainder (361), after wide local excision of the PCM, simply were observed. They learned, just as had Veronesi *et al.* and Sim *et al.*, that patients who had had an END benefited not a whit from the procedure. In 2000, Balch and coauthors said this tersely about the matter: '… melanoma patients as a group did not benefit from ELND [END]'.

A fourth study about these issues was carried out by Cascinelli *et al.* who, by 1998, also came to believe that END profited patients not at all.[9] They commented about the matter thus: 'Our results from this randomized trial confirm the inefficacy of elective regional node dissection as routine treatment in all melanoma patients with a primary melanoma of the trunk thicker than 1·5 mm ($P = 0{\cdot}09$)'.

In sum and in short, four prospective randomized studies were performed for the purpose, specifically, of determining the worth of END and all four found it wanting; the results were the same in each investigation, namely, that END provides no benefit to patients whose melanoma has metastasized to nodes.

Point 3: 'Evidence' in favour of benefit of elective node dissection is bogus

Numerous studies undertaken in retrospect have generated results that were interpreted as being proof that END benefits patients with metastases of melanoma. However, it is well established that studies conducted retrospectively are flawed fatally. and that is precisely the reason that advocates of END no longer trumpet the value of those studies.

Only one uncompelling bit of evidence can be marshalled on behalf of the thesis that END may confer benefit on patients, and that is derived from the study conducted by Balch *et al.*[3,4] presented first in 1996 as a work in progress and then in 2000 as a work completed. On the basis of their analysis, Balch *et al.* concluded that some sets of patients with metastases of melanoma may be helped by END, specifically those patients whose PCM was not ulcerated, measured between 1·0 and 2·0 mm in thickness, or was situated on an extremity. But the benefit that accrued to those patients was not substantial, the *P*-values ranging from 0·03 to 0·05. It is established beyond doubt that incorrect inferences may be drawn from analysis of sets, a fact that even was acknowledged by Balch *et al.* in 1996 when they made this telling statement: '… subgroup analysis can yield false-positive conclusions'.

The results of the 'completed' study by Balch *et al.* published in 2000[4] are in synchrony with those of the three other prospective randomized studies on END cited previously, that is, END confers no benefit whatsoever on patients with metastases of melanoma. Rationality demands that that conclusion prevail.

Point 4. The studies conducted on elective node dissection are solid and the results convincing, irrespective of whether or not lymphoscintigraphy was utilized to map nodal basins

In 2001, Reintgen and associates,[10] in what seems to be an attempt deliberately to negate the results of the prospective randomized studies performed by Sim *et al.* and Veronesi *et al.* on one hand and to bolster the

position of Balch *et al.* with regard to END on the other, proclaimed the following in these words: 'The old trials of elective lymph node dissection (ELND) (WHO trials, #1, 13, Mayo Clinic Trial) are un-interpretable in light of what we know about the adequate power of trials and the importance of defining the cutaneous anatomy with the use of lymphatic mapping principles. None of these old trials involved preoperative lymphoscintigraphy to define basins at risk for metastases, and thus the wrong surgery was performed in up to 32% of the patients. The only trial that incorporated the lymphatic mapping principles in the design of the trial was the Balch Intergroup study….'.

Those comments of Reintgen *et al.* do not reflect accurately the situation with regard to analysis of sets, the reason being that Balch *et al.* had performed lymphoscintigraphy prior to END on only 152 patients, the PCM in all of whom was positioned on the trunk. Those patients received no advantage from END. In that particular study by Balch *et al.*[3,4] only 40% of patients who underwent END had a nodal basin defined by lymphoscintigraphy. If the number '32%' given by Reintgen *et al.* in their statement regarding selection of a nodal basin for END is correct, then 73 patients, that is, 19% of patients in the study by Balch *et al.*, may have had a dissection of the wrong nodal basin, which is devastating to an analysis intended to be scientific.

Veronesi *et al.* studied PCM of the extremities because they believed that the flow of lymph to nodal basins there is relatively easy to predict by virtue of criteria based on findings clinically. Sim *et al.* studied PCM of the trunk and took care to exclude patients whose PCM was located on any site at which the direction of flow of lymph could not be anticipated accurately by employment of criteria clinically. Early in their study, Cascinelli *et al.* like Sim *et al.* used clinical criteria to select which regional nodes were to be dissected, but late in their study they utilized lymphoscintigraphy for that purpose. The issue of lymphoscintigraphy as prerequisite for accurate assessment of nodes most likely to harbour metastatic melanoma is a red herring because all prospective randomized studies of END have reached the very same conclusion, no matter whether lymphoscintigraphy was operative or not, namely, END provides no benefit to a patient.

Point 5. Analysis retrospectively of studies of sentinel node biopsy is an exercise in futility

In 2001, Dessureault *et al.*[11] presented information extracted, retrospectively, from the database for staging melanoma of the American Joint Committee on Cancer (AJCC). Those colleagues found that patients who had a SNB followed by RND survived longer than patients who had END alone, but that those latter patients, in turn, lived longer than did patients who merely were observed. The results were significant statistically, prompting Dessureault *et al.* to remark as follows: '… [SNB and dissection of the regional nodes] may contribute to a survival benefit in populations of patients with melanoma'. The authors of the publication, among whom were Balch and Reintgen, avoided carefully any semblance of being definitive, employing as they did the subjunctive 'may' and being aware as they were from experience from studies pertaining to END, garnered over a period of 30 years, that analysis conducted retrospectively leads, inevitably, to errors in interpretation.

In 1999, Essner *et al.*[12] came to a conclusion different from that of the cohorts of the AJCC and this is how they expressed it: 'These findings suggest that LM/SL/SCLND [lymphatic mapping/sentinel node lymphadenectomy, to wit, SNB/selective completion lymphadenectomy, that is, dissection of nodal basin involved by metastases of melanoma] is therapeutically equivalent to ELND…'.

In 2003, Morton *et al.*[13] presented data about survival of 287 patients who were deemed to be similar to one another with regard to 'prognostic factors'. Those patients who had a wide excision and a positive SNB followed by a RND survived longer than those who had had only wide excision of the PCM, followed by a RND at the time the nodes became palpable clinically ($P \leq 0{\cdot}001$). This study of Morton *et al.* was not prospective, randomized and controlled and, in fact, patients actually had the opportunity to choose the treatment they received. The authors claim that the results of their study indicate that regional lymphadenectomy after a SNB may cure patients of metastatic melanoma, a statement that is in synchrony with their claim that regional lymphadenectomy may cure patients whose nodes are palpable clinically. Scrupulous examination of the results of this study was not undertaken by Morton *et al.*, which is tacit acknowledgement that the results would not withstand the scrutiny of critical analysis.

It is incontrovertible that results of studies concerning therapeutic advantage of SNB are in conflict and therefore are not illuminating with regard to the worth of that procedure. When, at long last, results are published of a study conducted with precision prospectively and in randomized fashion, the *coup de grace* will be delivered for the ill-conceived and ill-advised notion of SNB.

Point 6. Inferential 'evidence' of benefit from sentinel node biopsy is not evidence at all

In the study brought to colleagues in 1998 by Cascinelli *et al.*[9] the fellow workers made reference to a 'secondary outcome of the study', that being an analysis performed retrospectively on patients who had developed metastasis by the time the study had been completed. Thirty-six patients of those who did not undergo END developed manifestations of metastasis clinically during the course of the period of observation. Those patients were found to have an outcome worse than that of the 27 patients who underwent END that yielded nodes containing melanoma. The data were used by Cascinelli *et al.* to advance the idea that SNB could be utilized to diagnose patients with metastasis of melanoma and who thereby could benefit from dissection of regional nodes.

At the culmination of their study, Balch *et al.* had the data and the means to do an analysis similar to the one done by Cascinelli *et al.* The only ostensible reason for Balch *et al.* not to have performed such an analysis is that it would be lacking entirely of validity scientifically, just as was the analysis by Cascinelli *et al.* undertaken retrospectively unworthy scientifically. In short, analysis that produced coincidentally a 'secondary outcome' does not meet standards which are acceptable scientifically and, therefore, citing such information on behalf of the merit of SNB is sophistry at best.

It is apparent that advocates of SNB invoke data selectively and illogically in order to advance an agenda that may benefit them, but surely does not patients. For example, it is illogical to assert that SNB with dissection of a nodal basin will confer advantage to a patient in terms of survival when END itself adds no benefit in that respect. The procedure of SNB followed by RND is nothing more than a modified END, and END has been proven, beyond doubt, to be worthless for a patient with metastases of melanoma.

Point 7. The premise that metastases of melanoma sojourn for varying periods of time, even years, in a nodal basin, without any dissemination of neoplastic cells beyond it, is fiction because it is fallacious

In 1953, Meyer and Gumport[14] addressed the matter of the future of melanoma cells once they arrived in nodes by way of metastasis and conceived it thus: '… this metastatic melanoma may be a focus and source from which malignant cells may spread to other nodes, or may enter the blood stream and cause distant metastases. These metastases, of course, will seal the fate of the patient'.

Balch *et al.*[3] in 1996 voiced an opinion similar to that of Meyer and Gumport about the behaviour of PCM in regard to metastases as follows: 'Our hypotheses was that melanomas metastasize first to regional lymph nodes and then to distant sites…'. Four years later, Balch and coworkers reinforced that hypothesis in these lines: 'The window of time for which early surgical intervention halts the further dissemination of melanoma metastases from regional to distant sites is estimated at 16 months, which is the average relapse time for patients who had wide excision only, and whose original nodal metastases subsequently evolved into clinical detectable disease'.[4] That estimate, namely, approximately 16 months from the time a metastasis of melanoma reaches a node to the time that that node is replete sufficiently with cells of melanoma that it becomes overtly palpable clinically, is not substantiated in the least by anything that appears in the article by Balch *et al.* And neither did Pack *et al.*[15] in 1945 provide any evidence on behalf of their contention concerning the same matter when they made this assertion: '… we have shown that an average time of 15 months elapses from the time the primary melanoma is recognized before metastasis in inguinal nodes are apparent'. Pack *et al.* claimed that that figure of 15 months derived from a series of patients with metastatic melanoma who were followed at Memorial Hospital in New York City, but they failed to cite data in a single study as the basis for that number. Balch *et al.* may well have taken the estimate of '15 months' from Pack *et al.* and pure speculation it was for both sets of authors who wrote about the same subject 50 years apart. Once again, Balch *et al.* not only were incorrect about what they published, but they engaged yet again in supposition, producing not a jot of compelling data in support of it.

In the judgement of Balch *et al.* once melanoma cells are released into lymphatics, they are carried forthwith to regional nodes where first they are retained, then they proliferate over time, and, only later, are released into the systemic circulation, whence they are disseminated widely. Nearly half a century earlier, Meyer and Gumport had suggested that nodes that harbour melanoma cells are the source of distant metastases. They believed that removal of melanoma-containing nodes in a timely fashion would cure a patient of metastases of melanoma. The hypothesis of Meyer and Gumport and of Balch *et al.*

is predicated on the assumption that cells released from a PCM are carried along with lymph in a stepwise manner, initially to the first node in the path of a particular lymphatic, that node being the SN in which neoplastic cells begin to proliferate, then, in time, to secondary nodes, and, still later, from secondary nodes to be despatched far and wide. That idea has been expressed recently as 'The Incubator Hypothesis',[13] which holds that products released by neoplastic cells of PCM cause the SN, mainly, to become immunosuppressed, thereby facilitating implantation of metastasis in that node. In turn, the neoplastic melanocytes in the node proliferate and produce factors that cause secondary nodes to become immunosuppressed, thus providing a haven for metastases from metastases in the SN. Even were that purported phenomenon to prove to be correct, that, in itself, would not be evidence on behalf of dissemination of melanoma proceeding in a stepwise, predictable fashion; it would merely confirm the obvious, to wit, once melanoma cells enter lymphatics, prognosis is grim.

The fact that patients with a negative SN as determined by conventional microscopy almost always have negative secondary nodes has been cited by Reintgen *et al.*[16] and others, as evidence that when melanoma metastasizes, the process is orderly, sequential, and, more or less predictable.

That the ideas of the proponents of SNB just cited are plain wrong is evidenced by the observation that extirpation of regional nodes in the process of END does not cure patients with metastases of melanoma because, in every instance, the metastases have trespassed far beyond the nodes, never, ever, being localized just to them and them alone.

What, then, is the actual route of a metastasis of melanoma? Cameron, in 1968, writing about the spread of melanoma and the mode whereby metastasis occurs, observed that (1) 'spread within the lymphatics is by embolism and also by permeation' and (2) 'melanoma may gain access to the veins and at an early stage travel by the blood stream, causing widespread dissemination.'[17] In actuality, nodes are not traps or dams, as has been alleged dutifully by generations of pedagogues of general pathology and of general surgery, but are filters that have been shown to allow passage of fluid, air, erythrocytes, lymphocytes, bacteria and viable neoplastic cells into the efferent lymphatics and into the rest of the vascular system.[1,18–23]

Experience with mapping of lymphatics and with SNB has confirmed the porous nature of nodes and revealed that vital dyes and radioactive tracers pass through them readily and disseminate widely. Vital dye injected into the dermis reaches, and passes through, the regional nodes in just 20 min and radioactive tracers traverse the SN and arrive at secondary nodes within 4 h, disseminating sometimes from secondary nodes in as little as 24–48 h. In some instances, when both vital dye and radiographic material are used to identify the SN, only radioactive material becomes concentrated in that node, whereas the dye seems to disappear, perhaps because it may not have gained access to lymphatics or it may have taken a course different by virtue of lymphatics that anastomose, from that predicted for it.

Slingluff *et al.* in 1994[24] made this comment about the significance of metastases of melanoma in nodes: 'It is likely that, as in breast cancer and other malignancies, the appearance of tumour in the regional nodes may be a marker of aggressive disease [rather] than a cause of subsequent systemic dissemination of disease'.

Evidence that metastases are not retained in nodes for any significant period of time comes from research conducted on SNs. Metastases of melanoma beyond a SN may manifest themselves in a patient whose SN did not harbour any melanoma cells or in a patient whose SN, but not secondary nodes, contained melanoma cells, no matter how rigorous was the examination of sections of tissue stained by haematoxylin and eosin and by immunohistochemical methods. A metastasis may make itself known (i) in the same basin from which the SN was harvested, (ii) near the site of the primary melanoma, i.e. a 'satellite', (iii) en route to regional nodes, i.e. 'in transit', or (iv) beyond the regional nodes, i.e. 'distant'.[25–27] Molecular techniques, using attributes particular to cells of melanoma and demonstrating thereby the presence of neoplastic cells of melanoma in nodes, including sentinel ones, in peripheral blood, and in bone marrow, confirm the randomness of the process of metastasis. That these findings are important is made manifest in the finding of metastases in some patients in whom no melanoma cells were detected in a SN.[28–31] A SN that does not seem to house melanoma cells on examination by conventional microscopy conveys no information about the matter of metastases possibly lodged elsewhere. However, one day molecular biological techniques should prove to be sensitive enough to do that.

Patients with a positive SN and negative secondary nodes, and those with a positive SN and positive secondary nodes, have metastases of melanoma beyond those nodes, disseminated neoplastic cells that, in time, will become apparent clinically, irrespective of whether

patients have undergone RND or have received any adjuvant therapy available currently. A SN that contains melanoma cells is a sure sign of metastases widely, even if secondary nodes are negative for melanoma. No advantage accrues from attempting to predict the 'extent of the melanoma' within a patient by determination of the number of nodes involved or the number of cells of melanoma in a node. They are mere exercises that confer no additional benefit to patients. Assessment histopathologically of SNs and secondary nodes for the purpose of determining whether or not they house melanoma cells serves only as a springboard for speculation about when metastases beyond nodes in an individual patient will make themselves known clinically; it may be days or decades, but, if the patient does not die of another cause, those metastases are likely in the extreme to become apparent clinically in time; uncertainty exists only with regard to when. None of those speculations is proper for pathologists, whose task should be diagnosis and not prognosis (which is the domain of diviners), and none of those guesses is of value to patients.

Articles[25,32] that tell of patients with metastases of melanoma proven by SNB and in whom RND was performed often mislead readers because they indicate that patients do well following those surgeries when, in fact, the period of time of follow-up is not sufficient to permit any accurate assessment to be made about the actual effectiveness of those procedures. A prospective, randomized study carried out internationally, namely, the Multicentre Selective Lymphadenectomy Trial, in which Morton was the principal investigator and the John Wayne Cancer Institute, with which he is affiliated, the centre for organization of it, is being conducted currently. The results are certain to indicate that those operations, to wit, SNB with dissection subsequently of the entire basin (if the SN has been found to contain a metastasis of melanoma), have no efficacy whatsoever because once cells of a PCM enter the lymphatics, they are likely to be swept to, and through, nodes or bypass them completely, either by way of lymphatic channels that anastomose or by entry of lymph directly into the blood vascular system. For that reason, terms meant to convey a sense of progressively worse prognosis for metastases of melanoma, that is, 'satellite', 'in transit', 'regional' and 'distant', are deceptive and wholly without merit. A metastasis is a metastasis, with all that that implies with regard to prognosis, i.e. grim. In actuality, a 'satellite' metastasis is a sure indicator of 'distant' metastases.

That nodes do not halt malignant cells in their tracks has been demonstrated unequivocally by studies performed recently on carcinoma of the breast,[33] cells of the carcinoma being noted by conventional microscopy to be present in bone marrow even when regional nodes were negative for carcinoma. This fact, together with molecular studies carried out on tissue of patients with melanoma in whom no metastases were discernible by conventional techniques, indicates that once cells of a malignant neoplasm are released into the circulation, either lymphatic or blood vascular, or both, they disseminate rapidly and widely, and do not advance in stepwise fashion from node to node and, only then, beyond nodes. When and where, exactly, metastases will manifest themselves clinically cannot be gauged now with any degree of confidence, and probably never will be.

Point 8. No systemic therapy available currently is effective for metastases of melanoma, which gives the lie to sentinel node biopsy being a method for identifying patients with melanoma who would benefit from such therapy

Morton and collaborators advocated SNB as a vehicle for identifying patients with metastases of melanoma to nodes at a time when those metastases were not yet detectable clinically, the purpose being to enable such patients to benefit from lymphadenectomy. Because no evidence could be mustered on behalf of benefit derived from SNB, other justifications had to be generated in order to give the appearance of legitimacy of SNB. The principal justification that emerged was that SNB identifies patients who are candidates for adjuvant systemic therapy, specifically, interferon alfa-2B.

With regard to adjuvant therapy for metastatic melanoma, although many systemic agents have been tried medically, none has been shown to be effective except, it is claimed, interferon in high doses. For that reason advocates of SNB aver that that procedure can be utilized to identify patients with a positive SN who may be aided by interferon.

Soon after it was first touted as a wonder drug for metastatic melanoma, interferon was administered in low doses. In the early stages of some clinical trials, interferon in low doses seemed to be of value to patients. However, the final results of published studies showed that patients who received interferon in low doses did not live longer than patients who were not treated with it. Because interferon was demonstrated to

be without value in low doses, attempts were undertaken to improve and prove its effectiveness by giving it in high doses.

Creagan *et al.* in 1995[34] tested interferon in patients with melanomas thicker than 1·69 mm and in patients with melanomas of any thickness when nodes were found to harbour metastases of melanoma. Those metastases were discovered easily because those nodes were enlarged clinically. Creagan *et al.* observed that if patients received interferon in high doses, it took longer for them to manifest metastases of melanoma clinically than would be expected had they not taken the drug. No matter; patients on interferon had the same overall survival as patients who were not.

In 2000, Kirkwood *et al.*[35] came to the same conclusion as had Creagan *et al.* Overall, their patients with metastatic melanoma who received interferon in high doses did not live longer than those who did not receive it.

In 1996 and again in 2001, Kirkwood *et al.*[36,37] noted that patients who were given interferon in high doses went for longer periods of time during which metastases did not become evident clinically, and those patients, overall, also lived longer. A major objection to the results obtained in the study carried out by Kirkwood *et al.* in 2001[37] is the absence of an observation group, an omission that qualifies as a major flaw. The studies performed by Kirkwood as lead investigator and author in 1996 and 2001 yielded results that confuse, rather than enlighten. In those studies, analyses of sets were performed, but the conclusions from the analyses were in conflict. In the study published in 1996, patients with nodes positive for melanoma seemed to benefit from interferon in high doses, yet in the study published in 2001, patients with melanoma thicker than 4 mm and without involvement of nodes benefited from interferon in high doses. Curiously, patients in the observation group in the study brought to publication in 2000 lived longer 'by virtue of being in that study' than patients who were followed in the study of 1996, a benefit that was significant statistically.

Interferon in high doses is associated consistently with side-effects that not only are severe, but may be lethal. For that reason, the dose almost always is reduced prior to completion of a course of it, some patients themselves insisting on terminating the treatment. Injurious effects include toxicity to bone marrow, flu-like illness, fever, chills, lethargy, headache, myalgia, nausea, weight loss and, rarely, death.

Many serious students of the subject of interferon in high doses are not awed by benefit from it. That sense of being underwhelmed is reflected in comments in 2000 by Eggermont[38] who said this: 'IFNα [interferon] has only modest activity in melanoma.… In the adjuvant setting, results are heterogeneous and inconsistent, reflecting its modest activity, which overall translates into an impact on relapse-free survival, which can be seen with various doses of IFNα, but no proof of a significant impact on survival'. Retsas, in 2001,[39] concurred with Eggermont as follows: '… there is currently no standard adjuvant treatment that unequivocally prolongs overall survival'. A systematic review of the matter of interferon as adjuvant therapy for metastatic melanoma was published in 2002 by Lens and Dawes,[40] whose position was that there was: '… no clear benefit of IFNα therapy on OS [overall survival] in melanoma patients'.

In sum, four prospective randomized studies have been carried out for the purpose of assessing the worth of interferon in high doses as adjuvant therapy for patients with metastatic melanoma. The results of those studies do not compel a conclusion that interferon is beneficial to patients. In fact, quite the opposite is true. Because interferon is not effective, provides no benefit to patients, and often is harmful, it cannot be invoked thoughtfully as justification for SNB.

Point 9. Sentinel node biopsy provides no information of importance about the prognosis of a patient with metastases of melanoma

The issue of benefit of SNB with regard to prognosis was raised by Reintgen *et al.*[41] in these words: '… [This issue] arises in discussing the significance of nodal staging and missed micrometastatic [sic] disease…'. Those coworkers then made these observations: 'There is evidence to suggest that it [metastasis discovered by virtue of SNB] is clinically relevant disease.… Nodal staging of melanoma patients with the SLN biopsy procedure will be a significant advanced [sic] for clinical trial work'. Of course, metastases of melanoma are of crucial importance because they are harbingers of likely death, in time, from the effects of them. and it is conceivable even that SNB could have value in clinical trials designed to test new and innovative adjuvant medical therapies for patients with known metastases of melanoma. However, in the setting of routine practice of medicine, SNB does not provide any benefit in itself, in conjunction

with RND, or as a means to determine whether adjuvant therapy should be a component of management of a patient with metastatic melanoma. Until this day, as has been stated repeatedly, no effective treatment of any kind, including interferon, is available for metastases of melanoma. Moreover, it is well recognized that 11–12%[26,27] of patients whose SN seems not to harbour cells of melanoma nonetheless develop signs at a later time of indubitable metastases of melanoma, and patients whose SN harbours cells of melanoma may die within months or they may survive for decades. In short, prognostications with regard to an individual patient with metastases of melanoma are pure conjecture and profit no one, not least a patient. That being the case, physicians should desist from issuing pronouncements that are nothing more than surmise.

Point 10. Sentinel node biopsy should not be used to determine whether a melanocytic neoplasm primary in the skin is a melanoma or a naevus

In 2000, Kelley and Cockerell[42] proposed a novel use for SNB when they advised that it could be employed in an effort to resolve the problem of what they termed 'melanocytic neoplasms of uncertain behaviour'. The idea of Kelley and Cockerell was this: if the SN was positive, diagnosis of the original melanocytic neoplasm could then be made with certainty, namely, PCM. However, if the SN was negative, it might indicate that the original neoplasm was benign. This proposal with regard to SNB, which, unhappily, is now becoming a fad,[43–45] is as ill-conceived as is the procedure itself. Diagnosis of a melanocytic neoplasm primary in the skin is made on the basis of morphological criteria, gross and microscopic, applicable to that very lesion. It borders on the ludicrous to make a diagnosis of a neoplasm primary in the skin by scrutinizing a lymph node. If that illogic obtains, then it will not be necessary to do biopsies of primary cutaneous melanocytic neoplasms (or primary neoplasms of any kind in any organ); the surgeon need head only for the nodes directly! Of course there are times when even the most competent histopathologist misinterprets a melanoma as a Spitz naevus (and vice versa) and the actual diagnosis of melanoma becomes apparent by virtue of its biological behaviour, to wit, metastasis. But that situation is exceptional. When criteria that now are well known and accepted are employed scrupulously, distinction by conventional microscopy between a melanocytic naevus and a melanoma can be made in the vast majority of instances. Parenthetically, there is no such thing as a 'melanocytic neoplasm of uncertain biologic potential'; that phrase conveys the idea that the neoplasm itself is uncertain about its character biologically when, in actuality, it is the histopathologist who really is uncertain. That being the case, it is in the best interests of a patient for a histopathologist to render a diagnosis of 'naevus', 'melanoma', or 'melanoma in association with a naevus', or to admit, directly and forthrightly, 'I don't know'. In the last circumstance, another opinion may be sought from a respected colleague but, irrespective of the diagnosis of the consultant, recommendation should be made to the referring managing physician that the neoplasm in doubt diagnostically should be excised completely with a narrow margin. A second opinion is not necessarily better than a first one.

Point 11. With regard to the proposition that sentinel node biopsy has no benefit for a patient with primary cutaneous melanoma, the evidence is incontrovertible and, therefore, that procedure should be abandoned now

In summary, the evidence against SNB is damning, conviction of that procedure is just, and a verdict of 'Guilty on all counts as charged' should be pronounced for it. SNB has no value to patients at all. If the SN is negative it means nothing vis-à-vis the possibility of metastasis having occurred already, and if it is positive it means a lot, namely, that melanoma has disseminated far beyond the node with likely fatal consequence in time, no adjuvant therapy for it being effective. Cells of a metastasis of melanoma do not simply germinate in a SN, but pass through it soon, bypass it, and even bypass secondary nodes. The evidence in the literature that pertains to metastases of melanoma, much of it culled from articles devoted to SNB, refutes the notion that metastases of melanoma progress in an orderly, sequential, predictable fashion. On the contrary, the data convey plausibly that once cells of melanoma gain access to lymph vessels or blood vessels, they metastasize widely, proliferate at variable rates, become manifest clinically in time, and eventuate usually in death.

A SNB does nothing to alter the course of melanoma that has metastasized, not by itself, not in conjunction with dissection of a nodal basin, and not in combination with any adjuvant medical therapy available currently, but it may be disadvantageous to a

patient—side-effects from SNB occur and some of them, like chronic lymphoedema of an extremity, may have grave consequences.

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