Accurate Nodal Staging of Malignant Melanoma

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The incidence of malignant melanoma is increasing at a faster pace than that of any other cancer in the United States. It is estimated that people born in the year 2000 will have a 1:75 risk of developing melanoma sometime during his or her lifetime. Stimulated by novel lymphatic mapping techniques, the surgical care of the melanoma patient is evolving toward more conservative resections that can provide the same staging information but without the added morbidity of more radical surgeries. This approach promises to yield positive results in the age of health care reform, outcome measurements, and cost:benefit considerations.

Introduction

The most significant prognostic factor for survival in most patients with cancer is the presence or absence of lymph node metastasis. Lymph node involvement decreases the five-year survival of malignant melanoma patients by 40% compared with patients with no metastases. While much time, effort, and expense are placed on identifying prognostic factors based on the primary tumor, not enough emphasis is given to identifying those patients who have signs of micrometastatic disease in their nodal basins. At least 27 prognostic variables for melanoma have been identified, based on the primary melanoma (Table 1). Factors such as Clark level, tumor thickness, and ulceration can be effective in predicting survival of the node-negative population, but once nodal disease develops, nodal status dwarfs the other variables in importance.

Table 1. Prognostic Factors for Melanoma Based on the Primary Tumor

<table>
<thead>
<tr>
<th>Tumor thickness</th>
<th>S phase</th>
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<tbody>
<tr>
<td>Ulceration</td>
<td>MDR-1 expression</td>
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<tr>
<td>Clark level</td>
<td>DNA index</td>
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<td>Histologic type</td>
<td>Heat shock protein expression</td>
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<td>p53 mutation</td>
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<td>Mitosis</td>
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<td>Lymphocytic infiltration</td>
<td>Migration-associated molecule</td>
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<tr>
<td>Vertical maturation grade</td>
<td>expression</td>
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<tr>
<td>Blood vessel invasion</td>
<td>Angiogenesis-related factors</td>
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<tr>
<td>Lymphatic space invasion</td>
<td>Glycosphingolipid expression</td>
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<tr>
<td>Evidence of a previous nevus</td>
<td>Estrogen receptor expression</td>
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<tr>
<td>Ploidy</td>
<td>Cytokine, growth factor expression</td>
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Newer molecular biologic assays are orders of magnitude greater in sensitivity for detecting tumor cells than routine histology. These techniques have shown promise in detecting the presence or absence of cancer in lymph node preparations and may help to explain why some histologically node-negative patients recur and die of melanoma. In addition, they may more accurately identify the high-risk population for adjuvant therapy trials by determining only the node-positive patients as those who need adjuvant therapy and thus sparing the toxicities of adjuvant therapy to the node-negative group. This selective approach to adjuvant therapy, which individualizes treatment by tailoring therapy to the specific needs of the patient, may be more sound than the unified therapy proposal of treating all node-negative patients with adjuvant therapy. Economically, a selective approach makes sense in this era of cost containment and health care reform.

Preoperative Lymphoscintigraphy

At our center and at the University of South Florida College of Medicine, preoperative lymphoscintigraphy has been studied as a means to identify lymphatic basins at risk for metastatic disease.[1] To locate the first draining node from the primary site (sentinel lymph node [SLN]) in relation to the rest of the lymphatic basin,[2] to identify the presence of in-transit nodal areas (nodal collections between the primary site and the regional basin),[3] and to estimate the number of SLNs[4] in order to direct the surgical therapy.

In an initial study,[1] preoperative lymphoscintigraphy was performed on 82 patients who had intermediate-thickness melanomas and who were undergoing elective lymph node dissection. Cutaneous drainage patterns identified by lymphoscintigraphy were compared with those predicted by clinical experience or historic, anatomic guidelines and were found to be discordant in 63% of patients with head and neck melanoma and in 32% of those with primary lesions located on the trunk. As a result of these findings, operative intervention was changed in 47% of the patients, with 19% undergoing dissection of nonclassical basins. An additional 28% did not have a node dissection because of lack of documentation by a scintigram of a predominant drainage basin or the demonstration of multiple drainage sites. After a mean follow-up of four years - the period in which 80% of recurring melanomas will appear - no recurrences have developed in basins that were not positive by lymphoscintigraphy, which attests to the accuracy of the test in identifying all basins at risk for disease. This study concluded that if elective lymph node dissection (ELND) is based on clinical experience or classic anatomic
patterns, the procedure may be misdirected in over 50% of cases.

In melanoma, the absence of metastatic disease in the SLN correlates with freedom from metastases in the other nodes in the basin. We have experienced no incidence of skip metastases in melanoma,[4] and investigators elsewhere have observed less than a 2% incidence.[5]

Other watershed areas of the body include primary sites near the midline or near a line that runs between the umbilicus and L2 in back, called Sappey's line. Cutaneous lymphatic flow is unpredictable in the entire head and neck area and in regions within 10 cm of either the midline or Sappey's line. Preoperative lymphoscintigraphy is recommended for melanomas located in the head and neck area or truncal lesions within these watershed areas. If this study is not obtained prior to the wide local excision (WLE) and ELND or SLN biopsy, the removal of all basins at risk for metastatic disease may be incomplete, or an unnecessary ELND may be performed on basins that are not at risk for metastatic spread. Expanded watershed areas of ambiguous lymphatic flow are noted when compared with classic anatomic descriptions based on cadaver dissections. In addition, technical failures (eg, no cutaneous lymphatic flow demonstrated) or inaccurate mapping may occur if the lymphoscintigraphy is performed after a WLE, since the true location of the primary melanoma can only be estimated and cutaneous lymphatics may be disrupted by the WLE. Studies performed after a WLE may be unclear as to whether the cutaneous lymphatic flow depicted on the lymphoscintigram accurately depicts the flow from the primary melanoma. It is presumptuous to assume that the lymphatic drainage is the same before and after a WLE. The ideal time to perform either the preoperative or intraoperative lymphatic mapping is after the biopsy and prior to any WLE.

Intraoperative Lymphatic Mapping and Sentinel Node Biopsy

An orderly progression of melanoma nodal metastases has been demonstrated by the emerging technologies of intraoperative lymphatic mapping and SLN biopsy.[4] The SLN has been defined by Morton et al[5,6] as the first node in the lymphatic basin that drains the primary tumor. They postulate that if the SLN is negative, then the rest of the nodes in the basin also should be negative. The SLN histology reflects the histology of the rest of the nodal basin.[4,7] An SLN can be mapped regardless of the location of the primary melanoma. Even in the event of bidirectional flow, SLNs in either basin should be identified. In addition, melanomas at different primary sites that drain to the same lymphatic basin may have different SLNs. Morton et al[5,6] outlined this procedure in which a vital dye, isosulfan blue, is injected around the primary melanoma. After 10 minutes, a small incision, directed by a subcutaneous tattoo from the preoperative lymphoscintigraphy, is made to overlay the primary lymphatic basin.

The strategy of selective lymphadenectomy or SLN biopsy should satisfy both the opponents and advocates of ELND for melanoma. The strongest criticisms of routine ELND are that the procedure is performed unnecessarily in approximately 80% of stage I and stage II melanoma patients[9] and that prospective randomized trials have not demonstrated a survival difference in favor of ELND.[10,11] However, routine harvesting of SLNs would identify those patients with defined evidence of macro- or
micrometastatic disease in the SLNs, and thus most of the melanoma population would be spared the morbidity and expense of a complete dissection. This technique also satisfies the proponents of ELND, since patients would undergo complete pathologic staging of their lymphatic basins with an outpatient procedure that has minimal morbidity. In addition, the strategy allows entrance to adjuvant trials for patients early in their clinical course rather than after grossly palpable disease develops, and it also removes a possible source of metastatic disease, if in fact microscopic disease is present in their basin.

From a patient management standpoint, the sentinel node biopsy technique promises to change melanoma surgical care. With four reports in the literature from major cancer centers (University of Texas M.D. Anderson Cancer Center,[7] John Wayne Cancer Institute,[8] Sydney Melanoma Unit in Australia,[9] and Moffitt Cancer Center & Research Institute[4]) supporting the concept that the histology of the SLN is reflective of the remainder of the basin, there is no justification for continuing to expose the melanoma patient population to the morbidity of elective node dissection to obtain nodal staging information. From a tumor biology point of view, the technique is promising since a nonrandom nodal metastatic pattern is described with lymphatic mapping and SLN biopsy. Most solid tumors were thought to demonstrate a random nodal metastatic pattern. The best example with data available is with breast cancer, in which the incidence of skip metastasis has been reported to be as high as 15%.[13,14] precluding the use of level 1 axillary sampling procedures to obtain an accurate staging of the patient. However, the previously noted skip metastases may be explained by the inability of previous investigators to map lymphatic flow. In this regard, using similar intraoperative mapping techniques for breast cancer as in melanoma, direct drainage to level 2 and level 3 axillary lymph node has been demonstrated from the primary tumor in the upper outer quadrant.[15] This data suggest that the random distribution of metastases implied by the incidence of skip metastasis was the result of an inability to accurately map lymphatic flow from the primary tumor. The incidence of skip nodal metastases precluded the use of sampling procedures of first station nodal basins to achieve adequate pathologic staging. Malignant melanoma may be different from other malignancies in that the cutaneous lymphatic flow is better defined and can be accurately mapped. Investigators from Duke Comprehensive Cancer Center, M.D. Anderson Cancer Center, and our institute performed preoperative and intraoperative mapping of the cutaneous lymphatics from the primary melanoma in an attempt to identify the SLN in the regional basin by using the technique of Morton et al.[5,6] In the initial study, all patients had primary melanomas with tumors more than 0.76 mm in thickness, and all were considered candidates for ELND. The SLN was harvested and submitted separately to pathology, and a complete node dissection followed. The null hypothesis that nodal metastases from malignant melanoma occurred in equal proportions among SLNs and non-SLNs was tested.

Based on prognostic factors of their primary melanoma, 42 patients met the criteria of the protocol. Negative SLNs were present in 34 of these patients, and the remainder of the nodes in the basin also were negative. Thus, no skip metastases were documented. Positive SLNs were present in eight patients, and the SLN was the only site of disease in seven of them. In these seven patients, the frequency of sentinel nodal metastases was 92%, while none of the higher nodes had documented metastatic disease. A comparison of nodal involvement between the sentinel and non-sentinel nodal groups was based on the binomial distribution. Under the null hypothesis of equality in distribution of nodal metastases, the probability that all seven unpaired observations would demonstrate involvement of the SLN was highly significant (P=0.006).[4] The data demonstrate that nodal metastases from cutaneous melanoma are not random events. The SLNs in the lymphatic basins can be mapped and individually identified and have been shown to contain the first evidence of melanoma metastases.

An initial report by Morton et al[6] and a confirming study[4] from a melanoma consortium changed the "standard of practice" used at these institutions to stage the melanoma patient in favor of performing an SLN biopsy instead of a complete ELND. A second study from the consortium included 132 patients in whom only the SL sol was harvested, and the lymphatic basins were followed for signs of recurrence. In this study, only those patients with a positive SLN would be exposed to the morbidity and expense of a complete node dissection. In addition, skip metastases were defined as occurring in patients who recurred in a lymphatic basin after a negative SLN biopsy. The results of this study show that 109 (83%) of the 132 patients had histologically negative SLNs, while SLN metastases were present in 23 patients (17%). Subsequently, these 23 patients with SLN metastases underwent complete node dissections, and the SLN was the only site of disease in 78%.[16] With a mean follow-up of two years, two patients recurred in an SLN-negative basin (skip metastases = 1.5%). The pathology block from the SLNs in these two patients was serially sectioned and stained with immunohistochemical stains specific for melanoma, including S-100 and HMB-45. No metastatic cells could be identified with this intensive review. However, part of the SLNs was submitted for reverse transcriptase-polymerase chain reaction (RT-PCR) for tyrosinase gene products.[17] The SLN preparations were RT-PCR-positive in the two patients who recurred in the basin and whose SLNs were histologically negative, which suggests that the abnormal cells were missed by routine histology and immunohistochemical staining.

Radiolymphoscintigraphy for Selective Lymphadenectomy

Technical difficulties associated with using only the vital blue dye method have occurred in up to 20% of the dissections, thereby resulting in unsuccessful explorations for the SLN. Intraoperative radiolymphoscintigraphy for lymphatic mapping recently has been added to the surgeon's armamentarium.[18,19] An average of 450 mCi of technetium-labeled sulfur colloid is injected around the primary site of the cutaneous melanoma. The nuclear probe (Neoprobe, Neoprobe Corporation, Columbus, Ohio) is then used to trace lymphatic channels from the primary site to lymph nodes in the regional lymphatic basin. The SLN in the basin is identified by intense radioactivity, and when the node is excised, the high levels of residual activity in the node and the low background activity in the rest of the basin confirm that the SLN has been removed. The hot spot can be located through the skin to help the surgeon direct the incision. In an initial study[19] from our center involving 14 patients with melanomas greater than 0.76 mm in thickness, radiolymphoscintigraphy was used and correlated with the vital blue dye mapping technique. Twenty-five SLNs and 10 neighboring non-SLNs were harvested from the 14 patients. The results indicated that ratio of in vivo preoperative SLN:background activity was 2.46:1, while the ratio after making the skin incision and exposing the lymphatic basin was 3.79:1. In addition, in seven patients who had non-SLNs harvested, the mean ratio of ex vivo SLN activity to non-SLN activity was 22.1:1. When correlated with the vital blue dye mapping, 20 (80%) of 25 SLNs were identified with both techniques; however, five (20%) additional SLNs were identified with the radioisotope alone.

The use of radiolymphoscintigraphy can improve the accuracy of identification of all SLNs during selective lymphadenectomy. The discovery of an additional 20% of SLNs with just the probe may offer an explanation for the previously reported low incidence of skip metastases in melanoma patients whose lymphatics were mapped with only the vital blue dye.

A recent update[18] of this series included both the vital blue dye and the radiocolloid used to map lymphatic flow from the primary tumor. The series consisted of 106 consecutive patients who presented with cutaneous melanomas greater than 0.76 mm in thickness in all primary sites. Based on the preoperative lymphoscintigraphy, more than one lymphatic basin was sampled in 22 patients. Two hundred SLNs and 142 non-SLNs were harvested from 129 basins in 106 patients (1.6 SLNs per patient). After making the skin incision, the mean ratio of hot spot to background activity was 8.5:1. The mean ratio of ex vivo SLN activity to non-SLN activity was 135.6:1 in 72 patients who had a non-SLN harvested. When correlated with the vital blue dye mapping, 139 (69.5%) of 200 SLNs demonstrated blue-dye staining, while 167 (83.5%) were defined as being "hot" by radioisotope localization. With the use of both intraoperative mapping techniques, identification of the SLN was possible in 124 (96%) of 129 basins sampled. Hot, non-blue-stained SLNs contained metastatic tumor in two of 16 patients with metastases, suggesting that the SLNs found with the Neoprobe are clinically important.[18] Furthermore, use of the gamma-detecting probe to localize SLNs enabled more focused and more conservative dissections, while simplifying the detection of the blue-stained lymph nodes. Both mapping methods provide not only the assurance of a visual identification (blue dye), but also a quantifiable method (radiocolloid) to ensure that all
Investigators at our center are studying the dynamics of lymphatic flow from the primary melanoma site by using the Neoprobe. Sulfur colloid appears to be the colloid of choice for performing the mapping, since in direct comparison between this compound and human serum albumin, filtered sulfur colloid provided improved localization ratios. A comparison also was made of gamma count ratios obtained when the radiocolloid was injected immediately prior to the skin incision in 90 patients or approximately four hours prior to the surgery in 16 patients. The ratio of skin to background was essentially identical in the two groups; however, the ratios of SLN to background in vivo and SLN to non-SLN ex vivo were significantly increased in the delayed group (P<0.001), which enables better localization ratios and easier explorations.

The data were subsequently used to define criteria for SLN identification. All criteria were based on activity ratios of hot spot to background or SLN to non-SLN to remove the influences of amount of colloid injected, the location of dissection to the primary injection site ("shine through"), and the timing of the injection. In this context and combined with the blue-dye mapping parameters, an SLN is defined as a node with blue-staining afferent lymphatics draining into a blue-staining node. In addition, the minimal acceptable criterion for SLN identification is a ratio of in vivo hot spot to background activity of at least 3:1 or an ex vivo SLN to non-SLN ratio of at least 10:1. Locating additional SLNs should be attempted if the ratio of hot spot to background remains elevated above 150% after removal of an initial SLN.

An NCI-sponsored trial[20] is underway to investigate the possible therapeutic benefits of the selective lymphadenectomy approach to melanoma surgical care. Patients are randomized between WLE of the primary site and observation of the nodal basin vs WLE of the primary site and selective lymphadenectomy of the regional nodes. Patients with a positive SLN will then undergo a complete node dissection. The applicability of the technique across institutions will be investigated, as well as the five-year disease-free survival and the actuarial survival of the two groups.[20] The timely staging information leading to the use of adjuvant therapies when tumor burdens are small and the possible therapeutic benefits of selective lymphadenectomy that are being investigated in the NCI trial are factors that outweigh the more conservative "wait and see" approach to the regional node in the melanoma patient.

Polymerase Chain Reaction to Determine Occult Metastases

Since lymphangiography can accurately predict all basins at risk for metastatic disease and intraoperative lymphatic mapping can identify nodes in the basin that are most likely to harbor metastatic disease, an assay was needed to accurately identify the presence or absence of metastatic disease in the node. For most solid tumors, the presence or absence of lymph node metastases is the most critical prognostic factor for predicting survival. If regional nodal metastases are found, the five-year survival for the patients with melanoma decreases by approximately 40%. If the presence or absence of regional nodal metastases dictates if patients either receive formal dissections or enter adjuvant trials, then a technique is needed to accurately screen lymph node samples for occult disease.

Routine histopathologic examinations commonly underestimate the number of patients with metastases. Serial sectioning of the lymph node[21] and immunohistochemical staining,[22,23] which can double the number of positive dissections, have been available for 10 years, but due to the time and expense involved,[24] these techniques have not been incorporated into routine histologic examinations. By using an initial cell culture method in which the nodes from the regional dissection are divided (with half being used for routine histologic examination and the other half being teased into a single-cell suspension and placed in cell culture), 21% of the node-negative stage I and stage II patients could be upstaged to stage III with the growing out of melanoma cells from their lymph node culture.[25] In addition, clinical correlation was demonstrated.[26] The disease-free survival was shorter for histologically node-negative patients with node-positive cell cultures compared with that for patients who were node-negative by both methods. However, the cell-culture technique was criticized because the results were unavailable for three to four weeks, and the widespread applicability was questioned because many hospitals did not have tissue-culture facilities. A more efficient and economical technique was needed.

Investigators at our institution initiated a study[17] to develop a highly sensitive method of detecting micrometastases by examining lymph nodes for the presence of tyrosinase messenger RNA (mRNA). It was hypothesized that the presence of mRNA for tyrosinase in the lymph node preparation indicates that metastatic melanoma cells are present.

The assay was accomplished by combining reverse transcription and double-round RT-PCR. The amplified samples were examined on a 2% agarose gel, and tyrosinase cDNA was seen as a 207-kilo base-pair fragment. Lymph nodes from 29 patients with intermediate-thickness melanoma were analyzed by standard pathologic staining and RT-PCR. Eleven (38%) of the 29 lymph node samples were pathologically positive, and 19 (66%) of the 29 samples were RT-PCR-positive and included all of the pathologically positive samples (Fig 4). While the sensitivity of routine histology is reported to be the identification of one abnormal cell in a background of 10 to the fourth normal cells, we detected one SK-MEL-28 melanoma cell in 10 to the sixth normal lymphocytes in a spiking experiment, thus indicating the increased sensitivity of this method. In addition, analysis by restriction enzyme mapping showed that the amplified 207-kilo base-pair PCR product was part of the tyrosinase gene sequence. Four patients were node-negative stage I and stage II melanoma were analyzed by standard pathologic staining and RT-PCR.

Biologic Significance and the Clinical Correlation of Melanoma Nodal Metastases

Gross Disease

For patients with clinically positive nodal examinations, the diagnosis can be confirmed by fine needle aspiration, followed by complete node dissection. This approach controls local-regional disease, since nodal disease can become uncontrolled and can subject the extremity to a proximal amputation. This also addresses the possibility of ulceration and bleeding of the nodal deposit, as well as the problem of a wound management. In addition, this approach adequately stages the patient. Patients with two to four positive nodes have a worse prognosis than patients with one positive node and have a better prognosis than those with more than four positive nodes. A complete node dissection should be performed on those patients whose diagnosis of metastatic melanoma is established with an excisional biopsy. If the diagnostic biopsy is performed for grossly palpable disease, the risk of further disease in the basin is 50%. If the diagnostic biopsy is an SLN biopsy and microscopic disease is discovered, the risk of more positive nodes in the basin is 22%.4

The five-year survival for patients with clinically positive, resected nodal disease ranges from 15% to 35% in various reports, suggesting that some patients are salvaged with...
complete node dissection despite having grossly involved nodes. A possible mechanism for the extended survival is the removal of a source of possible future systemic metastases (the metastasis of metastases).

**Microscopic Disease**

Theoretically, the removal of microscopic disease in the nodal basin, if in fact there is a period of time in which the disease is confined to only the lymphatic basin (lymph node arrest period), should be associated with an improvement in survival of the resected patients. However, this theory has not been proven in randomized, prospective trials and is controversial in the surgical treatment of malignant melanoma. The five-year survival of patients treated with ELND with disease found on dissection is 50% to 60%, depending on the number of positive nodes. This survival is better than the five-year survival of patients resected with gross nodal disease (15% to 35%), but lead-time bias may account for some or most of the difference. Lead-time bias refers to the fact that metastatic disease may be found earlier but without an effect on long-term survival. While difficult to estimate, lead-time bias must be considered in survival calculations.

**Submicroscopic Lymph Node Metastases**

Routine histology will identify 15% to 20% of the ELNDs containing metastatic melanoma. The standard examination across the country usually involves taking one or two sections from the central cross-section of the node, staining with hematoxylin and eosin, and thus studying less than 1% of the submitted tissue. While routine histology understimates the number of patients with nodal metastases, serial sectioning and immunohistochemical staining may double the yield of positive dissections.[20-22] These techniques have not been incorporated into the routine examination of nodal tissue by pathologists because serial sectioning is expensive and time consuming.[24] Compared to routine examination, immunohistochemical staining has an increased sensitivity with the ability to find one abnormal cell in a background of 10 to the fifth normal cells. However, the rate-limiting step, which is still the number of sections made, stained, and examined, remains for immunohistochemical staining.

**Table 2. Clinical Correlation of Nodal Status With RT-PCR Assay**

<table>
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<tr>
<th>Nodal Status</th>
<th>Number of Patients</th>
<th>Recurrences Local-Regional Systemic</th>
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<tbody>
<tr>
<td>Histology +, PCR +</td>
<td>14</td>
<td>6 (42%)</td>
</tr>
<tr>
<td>Histology - , PCR +</td>
<td>27</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>Histology - , PCR -</td>
<td>33</td>
<td>2 (6.6%)</td>
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* Patients with melanomas >0.76 mm in thickness. RT-PCR = reverse transcriptase polymerase chain reaction

Table 2 illustrates clinical correlation with RT-PCR data. A total of 74 patients with melanomas greater than 0.76 mm in thickness underwent biopsy of either their entire lymph node preparation or their SLNs. Half were submitted for routine histology, and half were processed for RT-PCR. These patients were then followed for two years and recurrences were noted. Of 14 patients with both histologically positive and PCR-positive nodes, six (42%) recurrent within this limited follow-up. Of 33 patients whose nodes were negative with both assays, recurrences appeared in only two patients (6.6%). In a third group that consisted of 27 patients who were histologically negative but PCR-positive, 10 patients (37%) were upstaged with the RT-PCR technique to an intermediate prognosis, with recurrences in six patients (22%). Recurrences were divided between local-regional and systemic areas. The P value for this difference is 0.12, but follow-up was limited as well as the number of recurrences. Since there are more recurrences than deaths due to metastatic melanoma, survival analysis cannot be performed at this time.[28]

Fig 5. As melanoma tumor thickness increases, the frequency of nodal metastases identified with RT-PCR for the tyrosinase gene product also increases. The fact that the PCR data correlate with a prognostic factor that in itself is linearly correlated with melanoma patient survival suggests clinical relevancy of the new PCR assay.

The correlation of PCR-positive lymph node preparations with another known prognostic factor for stage I and stage II melanoma was recently studied. Fig 5 shows that as tumor thickness increases, the number of PCR-positive lymph node dissections increases. For those patients with tumors between 0.76 and 1.5 mm in thickness, 33% had positive nodes by the RT-PCR technique. For patients with melanomas greater than 4.0 mm in thickness, 75% had positive dissections with this molecular biology technique. The fact that the RT-PCR data correlate with another prognostic factor (tumor thickness) that shows a linear relationship to survival also suggests some clinical correlation for this new prognostic variable. The true value of RT-PCR nodal data awaits multiple regression analysis of prognostic models that include this new variable with other important prognostic factors for stages I, II, and III melanoma, such as tumor thickness, ulceration, primary site, and sex. However, several regression analyses have confirmed that when nodal status is included in models of outcome with prognostic variables based on the primary tumor, nodal status dwarfs the other variables in importance in predicting survival.

Critics of this new technology argue that RT-PCR may be "too sensitive" and that the finding of RT-PCR-positive lymph nodes may not be an indication of clinically relevant disease.

Multiple studies in the past two years have shown that molecular staging will be an important part of our oncologic clinical care and may supplant routine histologic examination. In a poignant article from the New England Journal of Medicine, a series of retrospective examinations showed that Hubert Humphrey's bladder cancer was diagnosable by molecular biology techniques nine years before it was clinically apparent and 10 years before he received any type of therapy.[29] Hubert Humphrey eventually died of metastatic bladder cancer in 1967 at the age of 67.

Molecular staging also is important in the identification of occult metastases in historically negative patients with colon cancer,[30] hepatocellular cancer,[31] prostate cancer,[32] and melanoma.[33] In each instance, the finding of the occult metastases corresponded with increasing staging of disease. Molecular biology staging has been shown recently to be important in identifying high risk for breast cancer relapse bone marrow transplant patients who are infused histologically negative but PCR-positive bone marrows[34] and for identifying those patients with squamous cell carcinoma of the head and neck who are at an increased risk of local-regional recurrence whose surgical margins or lymph nodes are histologically negative but PCR-positive.[35] Being "node-positive" with the RT-PCR assays implies that the patient is node-positive. Confirming studies will be needed to prove these clinical correlations. With data being reported from many institutions with various tumors, the argument that PCR-positive findings of occult metastasis is clinically relevant disease becomes more persuasive.

**Staging, Adjuvant Treatment, and Health Care Reform**
Cost considerations are important when any new technology is introduced. As a result of two recent reports[36,37] demonstrating that interferon-alfa may be an effective adjuvant for patients with nodal metastases (high risk for recurrence), accurate nodal staging becomes even more important in the treatment of the patient with melanoma. Adjuvant therapy should be administered only to those who will benefit most from the therapy, since toxicity exists with the interferon therapy, and some deaths have been attributed to the drug.[37] A selective approach to adjuvant therapy would be advantageous.

Conclusions

Cutaneous lymphatic mapping promises to alter the surgical care of the melanoma patient. Full lymphatic basin staging information is available with more conservative surgical procedures that reduce the morbidity of the patient while saving costs for the health care system. This surgical strategy should satisfy opponents of ELND, since only those individuals with solid evidence of metastatic disease in their lymphatic basins will be exposed to the expense and morbidity of a complete node dissection. Supporters of ELND also should embrace the concept, since full nodal staging information will be obtained early in the clinical course of the patient. Patients with positive nodes can then be entered into adjuvant trials, and the nodal basin can be completely dissected to remove a possible source of tumor dissemination. The current national multicenter trial[20] sponsored by the National Cancer Institute randomizes patients to either WLE and observation of the nodal basin or WLE and SLN biopsy, with complete dissections being performed only in patients with positive SLNs. The goals of this study are to demonstrate a survival difference and to evaluate whether this strategy can provide staging information, as well as improve the survival of patients with melanoma.

References

20. Multicenter Selective Lymphadenectomy Trial (MSLT). National Cancer Institute Grant No. P01 CA29605.


