

## Melanoma: Changes Below the Surface

Sometimes deeper changes can be masked by a placid surface. Something of this nature is afoot in melanoma. While many melanoma trials have shown only limited or no benefit, we have every reason for justified optimism; new discoveries in the pathogenesis of melanoma, changes in its surgical treatment, and a new generation of immunotherapeutic agents and signaling inhibitors suggest that we are on the cusp of real progress in changing outcomes.

It is now recognized that exposure to ultraviolet radiation increases the risk of developing melanoma. Risk reduction is being actively explored in clinical trials. Large-scale chemoprevention trials have shown the effectiveness of tamoxifen in breast cancer and that statins can reduce the risk of colorectal cancer. In the first paper in this issue on melanoma, Marie-France Demierre and Vernon K. Sondak discuss a complex interaction between inherited susceptibility and environmental factors that can influence the risk of developing melanoma. They also discuss a planned phase IIB trial for chemoprevention of melanoma that should provide more data to foster further progress.

Melanoma staging has changed appreciably in the past few years. Many of these alterations were initially described by the American Joint Commission on Cancer in 2001 based on a comprehensive analysis of over 17,000 patients with melanoma. In this analysis it became obvious that some prognostic factors (Clark level) were not particularly useful, while others (ulceration) had a dramatic effect on survival. Jade Honsi and colleagues consider these changes and present the current state of knowledge on biologic factors such as angiogenesis, mitotic rate, and newer molecular markers. Thus, while some factors such as Clark level have fallen out of favor, ulceration of the primary tumor has been recognized as a determinant of outcome that is ranked on a par with lymph node involvement presaging aggressive biology. Molecular alterations such as BRAF mutations underlie up to 70% of all melanoma. The authors consider the import of these findings and their applicability to clinical relevance and prognosis. Some other features such as vasculogenesis and mitotic rate may be important in forthcoming refinements of prognostic classifications.

Melanoma is a curable disease when detected early. Thin primary melanoma (1 mm in thickness) has a 5-year median overall survival rate of over 90%. In this group of patients, surgical management is key to their cure and sur-

vival. Sentinel lymph node biopsy has been widely adopted for thicker melanoma, but its performance is controversial for thin lesions. While some experts believe that melanoma larger than 0.75 mm but smaller than 1.0 mm should be considered in the same fashion as thicker lesions, Christopher Puleo and coauthors suggest that several prognostic factors should be considered in developing individualized treatment regimens for patients with thin lesions.

Once melanoma has been diagnosed and risk factors are evaluated, some discussion of adjuvant therapies is warranted. The most commonly prescribed adjuvant therapy (and the only therapy currently approved by the Food and Drug Administration) is interferon alpha. This topic has been extensively discussed elsewhere; essentially, interferon has been proven to reduce recurrence but has not been shown definitively to improve survival. Interferon alpha is associated with significant toxicity and is expensive. These features and the year-long duration of treatment make it inappropriate for many patients with high-risk melanoma. What are the alternatives? David Lawson describes the state of knowledge regarding these treatment options. While many of these treatments are currently under investigation, several are in clinical use, and he provides a thoughtful context for these therapies.

The final article in this melanoma series by Matthew Kienstra and Tapan Padhya addresses head and neck melanoma. While the pathogenesis of melanoma in this location is no different from other cutaneous primary lesions, the anatomy of this particular region is reviewed. Sentinel lymph node dissection presents unique challenges in this richly lymphatic region. Wide local excision with adequate margins demands specialized techniques for cosmesis.

The last issue of *Cancer Control* that focused on melanoma was published in January 2002. That issue discussed the promises of new technologies and therapies for this disease. Since then, some of these promises have been realized. We are finally seeing glimpses of the biological behavior of this capricious cancer in a way that may enable us to provide better treatments in the future.

We have included two additional papers in this issue that relate to subjects other than melanoma. The first of these discusses alpha-fetoprotein as the most commonly used tumor marker for hepatocellular carcinoma, but especially in cases diagnosed in the United States it suffers from a lack of sensitivity and specificity. Motawa Elshemy

and coauthors discuss their experience in enhancing the detection of hepatocellular carcinoma using combinations of several tumor markers, specifically alpha-fetoprotein, vascular endothelial growth factors, insulin-like growth factor-2, and alpha-L-fucosidase, to improve the detection sensitivity of hepatocellular carcinoma. In the second article, Nasim Khan and colleagues review the use of FDG-PET in patients with medullary or anaplastic thyroid carcinoma. Oncologists generally encounter patients with these diseases only occasionally. It is difficult, therefore, to remain au courant with advances in imaging to monitor and follow patients with these diseases. To help fill this knowledge gap, the authors present their experience with the use of FDG-PET with medullary and anaplastic thyroid carcinoma.

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