the tumor cells seem to lack the capacity to metastasize. Tumors in radial growth phase fall into several clinicopathologic classes, including: **lentigo maligna**, usually presenting as an indolent lesion on the face of older men that may remain in the radial growth phase for several decades; **superficial spreading**, the most common type of melanoma, usually involving sun-exposed skin; and **acral/mucosal lentiginous** melanoma that is unrelated to sun exposure.

After a variable (and unpredictable) period of time, melanoma shifts from the radial phase to a **vertical growth phase**, during which the tumor cells invade downward into the deeper dermal layers as an expansile mass (Fig. 25-8*C*). **The vertical growth phase is often heralded by the appearance of a nodule and correlates with the emergence of a tumor subclone with metastatic potential.** Unlike melanocytic nevi, "neurotization" is absent from the deep invasive portion of melanoma. The probability of metastasis in such lesions correlates with the depth of invasion, which by convention is the distance from the superficial epidermal granular cell layer to the deepest intradermal tumor cells; this measurement is known as the **Breslow thickness**. Other histologic features that correlate with outcome include the number of mitoses and the presence of ulceration; these and other prognostic factors are discussed later.

Individual melanoma cells are usually considerably larger than normal melanocytes or cells found in melanocytic nevi. They have large nuclei with irregular contours, chromatin that is characteristically clumped at the periphery of the nuclear membrane, and prominent red (eosinophilic) nucleoli (Fig. 25-8*D*). The appearance of the tumor cells is similar in the radial and vertical phases of growth. While most nevi and melanomas are easily distinguished based on their appearance, a tiny fraction of "atypical" lesions fall in a histologic gray zone and have been termed melanocytic tumors of uncertain malignant potential; such lesions require complete excision and close clinical follow-up.

Prognostic Factors. Once a melanoma is excised, a number of clinical and pathologic features are used to gauge the probability of metastatic spread and prognosis. One model used to predict outcome is based on the following variables: (1) tumor depth (the Breslow thickness); (2) number of mitoses; (3) evidence of tumor regression (presumably due to the host immune response); (4) ulceration of overlying skin; (5) the presence and number of tumor infiltrating lymphocytes; (6) gender; and (7) location (central body or extremity). Determinants of a more favorable prognosis in this model include thinner tumor depth, no or very few mitoses (< 1 per mm^2), a brisk tumor infiltrating lymphocyte response, absence of regression, and lack of ulceration. Since most melanomas initially metastasize to regional lymph nodes, additional prognostic information may be obtained by performing a sentinel lymph node biopsy; as in breast cancer (Chapter 23), this involves the identification, removal, and careful examination of the lymph node (or nodes) that is the initial site of drainage of intratumoral lymphatic vessels. Microscopic involvement of a sentinel node by even a small number of melanoma cells (micrometastases) confers a worse prognosis (Fig. 25-7*D*, *inset*). The degree of involvement and the total number of lymph nodes involved correlate well with overall survival.

Clinical Features. **The most important warning signs, sometimes called the ABCDEs of melanoma, are (1) *a*symmetry; (2) irregular *b*orders; and (3) variegated *c*olor, (4) increasing *d*iameter, and (5) *e*volution or change over time, especially if rapid.** Because locally advanced melanomas often metastasize, early recognition and complete excision are critical. Melanoma of the skin is usually asymptomatic, although itching or pain may be early manifestations. The majority of lesions are greater than 10 mm in diameter at diagnosis. The most consistent clinical signs are changes in the color, size, or shape of a pigmented lesion. Other features of pigmented lesions that should raise concern are a diameter greater than 6 mm, any change in appearance, and new onset of itching or pain.

Molecular insights into the pathogenesis of melanoma have spawned attempts to treat this cancer with drugs that target the RAS and PI3K/AKT pathways (Fig. 25-8). Such approaches are urgently needed, as metastatic melanoma is resistant to both conventional chemotherapy and radiation treatment. Ultimately, it is likely that these types of targeted therapies will be used in combinations tailored to fit the oncogenic molecular lesions found in individual tumors. This idea is based on the observation that a high fraction of tumors with BRAF mutations respond to BRAF inhibitors, whereas tumors belonging to other molecular subtypes do not.

More recently, recognition that melanoma is inherently immunogenic has spawned interest in therapies such as anti-CTLA4 blocking antibodies or, even more promising, anti-PD1 blocking antibodies that enhance host recognition of melanoma-specific antigens. Such treatments have produced encouraging results in early clinical trials. This clinical paradigm of taking the brakes off the immune system is one that may be applicable to other cancers as well (Chapter 7). Ultimately, it may be that such agents will be used in combination with targeted therapies such as BRAF antagonists.

KEY CONCEPTS

Melanocytic Lesions, Benign and Malignant

- Most *melanocytic nevi* have activating mutations in *BRAF* or less often *NRAS*, but the vast majority never undergo malignant transformation
- Most sporadic *dysplastic nevi* are best regarded as markers of melanoma risk rather than premalignant lesions. They are characterized by architectural and cytologic atypia and are associated with germline mutations in genes encoding cell cycle regulators (p16/INK4a, CDK4) and telomerase.
- *Melanoma* is a highly aggressive malignancy linked to sun exposure; risk of spread is predicted by a number of tumor characteristics, particularly the vertical thickness of excised tumors
- Melanoma is associated with mutations in cell cycle regulators (p16/INK4a, CDK4), pro-growth signaling factors (growth factor receptors [e.g., KIT], RAS, BRAF), and telomerase
- Melanoma often incites a host immune response and sometimes shows dramatic responses to antibody therapies that enhance T-cell immunity