include the vertical growth phase of the primary tumor, if present. Incisional biopsy does not appear to facilitate the spread of melanoma. For suspicious lesions, every attempt should be made to preserve the ability to assess the deep and peripheral margins and to perform immunohistochemistry. Shave biopsies are an acceptable alternative, particularly if the suspicion of malignancy is low, but they should be deep and include underlying fat; cauterization should be avoided. The biopsy should be read by a pathologist experienced in pigmented lesions, and the report should include Breslow thickness, mitoses per square millimeter for lesions ≤1 mm, presence or absence of ulceration, and peripheral and deep margin status. Breslow thickness is the greatest thickness of a primary cutaneous melanoma measured on the slide from the top of the epidermal granular layer, or from the ulcer base, to the bottom of the tumor. To distinguish melanomas from benign nevi in cases with challenging histology, fluorescence in situ hybridization (FISH) with multiple probes and comparative genome hybridization (CGH) can be helpful.

## CLINICAL CLASSIFICATION

Four major types of cutaneous melanoma have been recognized (Table 105-2). In three of these types—*superficial spreading melanoma*, *lentigo maligna melanoma*, and *acral lentiginous melanoma*—the lesion has a period of superficial (so-called radial) growth during which it increases in size but does not penetrate deeply. It is during this period that the melanoma is most capable of being cured by surgical excision. The fourth type—*nodular melanoma* —does not have a recognizable radial growth phase and usually presents as a deeply invasive lesion that is capable of early metastasis. When tumors begin to penetrate deeply into the skin, they are in the so-called vertical growth phase. Melanomas with a radial growth phase are characterized by irregular and sometimes notched borders, variation in pigment pattern, and variation in color. An increase in size or change in color is noted by the patient in 70% of early lesions. Bleeding, ulceration, and pain are late signs and are of little help in early recognition. Superficial spreading melanoma is the most common variant observed in the white population. The back is the most common site for melanoma in men. In women, the back and the lower leg (from knee to ankle) are common sites. Nodular melanomas are dark brown-black to blue-black nodules. Lentigo maligna melanoma usually is confined to chronically sun-damaged sites in older individuals. Acral lentiginous melanoma occurs on the palms, soles, nail beds, and mucous membranes. Although this type occurs in whites, it occurs most frequently (along with nodular melanoma) in blacks and East Asians. A fifth type of melanoma, *desmoplastic melanoma*, is associated with a fibrotic response, neural invasion, and a greater tendency for local recurrence. Occasionally, melanomas appear clinically to be amelanotic, in which case the diagnosis is established microscopically after biopsy of a new or a changing skin nodule. Melanomas can also arise in the mucosa of the head and neck (nasal cavity, paranasal sinuses and oral cavity), the gastrointestinal tract, the CNS, the female genital tract (vulva, vagina), and the uveal tract of the eye.

Although cutaneous melanoma subtypes are clinically and histopathologically distinct, this classification does not have independent prognostic value. Histologic subtype is not part of American Joint Committee on Cancer (AJCC) staging, although the College of American Pathologists (CAP) recommends inclusion in the pathology report. Newer classifications will increasingly emphasize molecular features of each melanoma (see below). The molecular analysis of individual melanomas will provide a basis for distinguishing benign nevi from melanomas, and determination of the mutational status of the tumor will help elucidate the molecular mechanisms of tumorigenesis and be used to identify targets that will guide therapy.

## PATHOGENESIS AND MOLECULAR CLASSIFICATION

Considerable evidence from epidemiologic and molecular studies suggests that cutaneous melanomas arise via multiple causal pathways. There are both environmental and genetic components. UV solar radiation causes genetic changes in the skin, impairs cutaneous immune function, increases the production of growth factors, and induces the formation of DNA-damaging reactive oxygen species that affect keratinocytes and melanocytes. A comprehensive catalog of somatic mutations from a human melanoma revealed more than 33,000 base mutations with damage to almost 300 protein-coding segments compared with normal cells from the same patient. The dominant mutational signature reflected DNA damage due to UV light exposure. The melanoma also contained previously described driver mutations (i.e., mutations that confer selective clonal growth advantage and are implicated in oncogenesis). These driver mutations affect pathways that promote cell proliferation and inhibit normal pathways of apoptosis in response to DNA repair (see below). The altered melanocytes accumulate DNA damage, and selection occurs for all the attributes that constitute the malignant phenotype: invasion, metastasis, and angiogenesis.

An understanding of the molecular changes that occur during the transformation of normal melanocytes into malignant melanoma would not only help classify patients but also would contribute to the understanding of etiology and aid the development of new therapeutic options. A genome-wide assessment of melanomas classified into four groups based on their location and degree of exposure to the sun has confirmed that there are distinct genetic pathways in the development of melanoma. The four groups were cutaneous melanomas on skin without chronic sun-induced damage, cutaneous melanomas with chronic sun-induced damage, mucosal melanomas, and acral melanomas. Distinct patterns of DNA alterations were noted that varied with the site of origin and were independent of the histologic subtype of the tumor. Thus, although the genetic changes are diverse, the overall pattern of mutation, amplification, and loss of cancer genes indicates they have convergent effects on key biochemical pathways involved in proliferation, senescence, and apoptosis. The *p16* mutation that affects cell cycle arrest and the *ARF* mutation that results in defective apoptotic responses to genotoxic damage were described earlier. The proliferative pathways affected were the mitogen-activated protein (MAP) kinase and phosphatidylinositol 3' kinase/AKT pathways (Fig. 105-2).



**TABLE 105-2 HISTOLOGIC SUBTYPES OF MALIGNANT MELANOMA**

| Type | Site | Average Age at Diagnosis, Years | Duration of Known Existence, Years | Color |
|---|---|---|---|---|
| Lentigo maligna melanoma | Sun-exposed surfaces, particularly malar region of cheek and temple | 70 | 5–20 or longer[a] | In flat portions, shades of brown and tan predominate, but whitish gray occasionally present; in nodules, shades of reddish brown, bluish gray, bluish black |
| Superficial spreading melanoma | Any site (more common on upper back and, in women, lower legs) | 40–50 | 1–7 | Shades of brown mixed with bluish red (violaceous), bluish black, reddish brown, and often whitish pink, and the border of lesion is at least in part visibly and/or palpably elevated |
| Nodular melanoma | Any | 40–50 | Months–<5 years | Reddish blue (purple) or bluish black; either uniform in color or mixed with brown or black |
| Acral lentiginous melanoma | Palm, sole, nail bed, mucous membrane | 60 | 1–10 | In flat portions, dark brown predominantly; in raised lesions (plaques), brown-black or blue-black predominantly |

[a]During much of this time, the precursor stage, lentigo maligna, is confined to the epidermis.

***Source:*** Adapted from AJ Sober, in NA Soter, HP Baden (eds): *Pathophysiology of Dermatologic Diseases*. New York, McGraw-Hill, 1984.