Malignant Melanoma

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After completing this article, the reader should be able to:

- Identify common risk factors for malignant melanoma.
- Discuss the challenges in diagnosing and treating malignant melanoma.
- Explain the mechanisms of action of recently approved drug therapies for metastatic disease.
- List the advantages and disadvantages of a variety of imaging modalities used in radiation treatment planning.
- Describe the changing roles of the radiation therapist and medical dosimetrist in treating malignant melanoma.
- Use a simple mnemonic device to remember how to detect skin cancer early.

Skin cancer has been making headlines in recent years, thanks to advances in research and the approval of several new drugs for malignant melanoma, its most deadly form. “It’s an exciting time,” according to Antoni Ribas, MD, PhD, a malignant melanoma expert at the University of California at Los Angeles.

Clinical trials have shown statistically significant improvements in survival among patients treated with new therapies, and, although no one is claiming to have found a cure, some responses have been quite durable. Moreover, the mechanism of action of the new drugs—or how they work in the body—has broad implications for other forms of cancer.

Unfortunately, the new drugs also can have serious and unpleasant adverse effects, according to Catherine Poole, president of the Melanoma International Foundation, a patient advocacy group outside Philadelphia, Pennsylvania. In addition, some of the most effective drugs work only in patients who carry a certain gene mutation, leaving other patients with no new options. In a conversation with Poole (September 2013), she said, “We haven’t hit a home run yet.”

Because malignant melanoma can be so deadly, some of the most sophisticated forms of medical imaging and radiation therapy are used in diagnosis and treatment, including positron emission tomography fused with computed tomography (PET-CT) and stereotactic radiosurgery (SRS). One leading researcher at Memorial Sloan-Kettering Cancer Center in New York City has observed an abscopal effect in certain patients being treated with one of the new drugs. The abscopal effect is a rare phenomenon that occurs when localized radiation therapy delivered to a tumor in a patient with advanced disease leads to shrinkage of tumors outside the radiation field.

Malignant melanoma is the rarest type of skin cancer, but it can be deadly. Recent progress in treatment for malignant melanoma has been rapid, with several new pharmaceutical agents approved since 2011. Malignant melanoma can be diagnosed and staged with a variety of medical imaging modalities, including lymphoscintigraphy, computed tomography, positron emission tomography, and magnetic resonance. First-line treatment is surgery, which may be curative if the lesion is detected early. Advanced cases could require drug therapy, adjuvant radiation, and palliative radiation. Brain metastases are common and often irradiated with advanced techniques.
The Integumentary System

The skin, hair, and nails are all parts of the body’s integumentary system, which also includes hair follicles, sweat glands, oil glands, capillaries, and nerve endings. The function of the skin is to provide mechanical protection against abrasion and punctures, as well as a barrier against microbial invasion. The skin also helps regulate the body’s temperature. In summer, evaporation of perspiration at the skin’s surface dissipates heat, while in winter contraction of surface blood vessels helps the body retain warmth. In bright sunlight, the skin helps to protect underlying tissues from harmful ultraviolet radiation. It also contains important sensory organs that provide information about changing environmental conditions. Skin secretions send olfactory signals that play a role in mating and sexual behavior.3,4

The outermost layer of the skin is called the epidermis (see Figure 1). Dead cells, called keratinocytes, form a thin protective sheet on top. Over the course of about a month, these dead cells are gradually displaced and sloughed off by new generations of cells arising from below. The epidermis can become especially thick in regions that are exposed to frequent abrasion resulting in calluses, such as on the palms of the hands or soles of the feet.3,4

Epidermal tissue is a stratified squamous epithelium, which means it consists of several layers of cells. Cells of the lowermost layer, also called the basal layer or basal membrane, undergo continuous mitoses and produce cells that are pushed upward to renew the layers above.3 Squamous cells typically lie flat atop the basal layer. Roughly 80% of nonmelanoma skin cancers arise from basal cells and are called basal cell carcinomas. The other 20% arise from squamous cells and are called squamous cell carcinomas.5

Below the epidermis lies a thicker layer called the dermis, or true skin. The dermis consists of dense connective tissue containing blood vessels, glands, hair follicles, nerve endings, and pigment cells. The dermis nourishes and supports the epidermis, which has no blood supply. The pigment that gives skin cells their color, and which protects against ultraviolet (UV) radiation, is called melanin. Melanin-containing cells, called melanocytes, are found at the junction of the epidermis and the dermis. UV radiation of the sun causes melanocytes to produce...

Figure 1. Anatomy of the skin. Illustration ©2008 Terese Winslow, U.S. Govt. has certain rights.
more melanin, causing skin to darken. Malignant melanoma originates from melanocytes.\(^4\)

Below the dermis but above the bones or muscles lies a layer of subcutaneous tissue, consisting largely of adipose (fat) cells interspersed with numerous tiny blood vessels. These vessels expand or contract to maintain a constant body temperature. They also intersect with a network of thin-walled lymphatic capillaries, which carry filtered fluid (lymph) throughout the body. The lymphatic system plays a central role in the body’s defense against foreign invasion (see Figure 2). Located at intervals along the lymphatic vessels are numerous lymph nodes, which are concentrated in the neck (cervical nodes), under arm (axillary nodes), and groin (inguinal nodes).\(^3\) Malignant melanoma frequently spreads via the lymphatic system, often starting with the lymph node nearest to the primary lesion.\(^6\)

**Epidemiology and Etiology**

The incidence of malignant melanoma has been rising steadily for at least the past 30 years, and it has now become the fifth most common tumor type among men in the United States and the sixth most common among women.\(^7\) During 2013, an estimated 76,690 new cases were reported, while an estimated 9,480 people died.\(^8\) Basal cell carcinomas and squamous cell carcinomas are far more common than malignant melanoma but much less serious. These lesions are not required to be reported to national cancer registries, and incidence estimates vary widely.

Race disparities are pronounced in this tumor type (see Figure 3). Malignant melanoma is 23 times more common among non-Hispanic whites than among African Americans. In addition, malignant melanoma is 1.4 times more common among men than among women.\(^8\) Mortality rates also are highest among non-Hispanic whites (see Figure 4). A family history of malignant melanoma, more than 50 nevi (moles), fair skin, a history of serious childhood sunburns, and previous malignant melanoma have been cited as risk factors.\(^7\)

The precise cause of malignant melanoma remains uncertain and somewhat controversial. Incidence rates are rising fastest among older white men, and the most commonly suggested explanation is increased exposure to UV radiation from the sun.\(^9\) Two genes have been

![Figure 2. The lymphatic system.](image)

2 cm of the primary tumor. In-transit metastases are defined as lesions more than 2 cm from the primary tumor but within the regional lymph node basin. Distant metastases can form elsewhere in the skin, gastrointestinal tract, lungs, liver, and other soft tissue. 6 Malignant melanoma spreads to the brain more often than any other form of cancer. 13

Diagnosis, Staging, and Work-up

A diagnosis of malignant melanoma typically is made following biopsy and pathologic examination of the suspicious lesion. According to the National Comprehensive Cancer Network, the pathology report should consider these factors 13:

- Breslow thickness.
- Ulceration status.
- Mitotic rate.
- Clark level.
- Peripheral and deep margin status.
- Microsatellite status.
- Histologic subtype.

Breslow thickness, expressed in millimeters, measures the extent of a tumor’s penetration into the underlying skin. The tumor is measured from the top

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Histologic Subtypes of Malignant Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>subtype</em></td>
<td>% of Cases</td>
</tr>
<tr>
<td>Superficial spreading melanoma</td>
<td>70</td>
</tr>
<tr>
<td>Nodular melanoma</td>
<td>15-25</td>
</tr>
<tr>
<td>Lentigo melanoma</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Acral lentiginous melanoma</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Nevinal melanoma</td>
<td>Rare</td>
</tr>
<tr>
<td>Desmoplastic melanoma</td>
<td>Rare</td>
</tr>
</tbody>
</table>

identified that confer susceptibility to malignant melanoma, but their contribution appears to be minor because their combined effect accounts for a minority of familial malignant melanomas. 6 Patient advocates, the American Cancer Society, and the International Agency for Research on Cancer all contend that commercial tanning salons, which use ultraviolet radiation, are carcinogenic to humans and hazardous to the public health. 7,10

Clinical Presentation

There are several different subtypes of malignant melanoma. Their prevalence, usual locations, and appearance are summarized in Table 1. Most malignant melanomas grow slowly, over a period of years. They spread outward and remain superficial at first, in what is known as the radial growth phase, and are confined to the epidermis. If a lesion is detected and treated at this stage, the patient’s prognosis is excellent. 12 Left untreated, however, lesions might enter the vertical growth phase and invade the dermis, subcutaneous layer, and other tissues. 11

Malignant melanoma first spreads through the lymphatic system. Satellite lesions are those found within...
row of cells to the bottom. If the tumor is ulcerated, the measurement is taken from the base of the ulcer to the deepest tumor cells. Mitotic rate, expressed as number of mitoses per square millimeter, has come to the forefront in recent years as a prognostic factor in melanoma patients. Higher mitotic rates correspond with shorter survival times. Rates usually fall within a range of 0 to 20, and they generally increase as tumors thicken and become ulcerated. Mitotic rate is considered the second most important prognostic factor, after tumor thickness.

The Clark level describes the degree of a tumor’s penetration into underlying tissue. Level I describes a cancer that remains on the epidermis. Level II describes a cancer that has begun to invade the papillary dermis, or thin top layer of the dermis. Level III describes a cancer that has invaded the papillary-reticular dermal interface, which lies between the papillary dermis and the reticular dermis, the thicker bottom layer of the dermis. A level IV tumor is one that has invaded the reticular dermis. A level V tumor is one in which the cancer has invaded subcutaneous tissue. A recent study showed that the Clark level is not as reliable as mitotic rate in determining a prognosis, but the Clark level continues to appear on many pathology reports.

Margin status describes the edges of the biopsied tissue. If the margins test positive for the presence of tumor cells, the pathologist infers that the excision did not remove the entire tumor. Deep margins describe the bottom edge, or deepest part, of the biopsy, while peripheral margins describe the lateral boundaries.

In melanoma, microsatellites are minute (< 1 mm) clusters of tumor tissue located next to the main tumor but separated by healthy collagen or subcutaneous fat. While uncommon, they might sometimes be detected during the initial biopsy or wide excision. If present, microsatellites should be reported because they place patients within a prognostic category similar to stage III disease (see Table 2). Traditionally, malignant melanomas have been divided into groups based on histologic subtypes, and these continue to appear on pathology reports. Recently, however, it has also become important to use DNA sequencing technologies to identify mutations in key genes, such as NRAS (a gene involved in regulating cell division), BRAF (a gene that makes a protein involved in sending signals within cells and in cell growth), and c-kit (a type of receptor tyrosine kinase and a tumor marker). This genetic information can then be used by medical oncologists to determine the best targeted therapies for subgroups of patients.

The extent of any work-up depends heavily on the clinical presentation and how the cancer is staged. The current staging system for malignant melanoma is published and updated periodically by the American Joint Committee on Cancer. The system proceeds through 4 stages, with higher stages corresponding to more advanced disease. Historically, the American Joint Committee on Cancer staging system has been based on 3 main variables: tumor size (T), lymph node status (N), and presence or absence of distant metastases (M). TNM staging widely is used, with certain adaptations, to describe the growth and progression of many types of solid tumors. In malignant melanoma, tumor thickness and ulceration are considered together as part of the T component. Primary lesions that are thin (< 1 mm) and not ulcerated, with no nodes involved, require little more than a history and physical examination, while a patient with lesions thicker than 1 mm, a high mitotic rate, or signs of nodal involvement, typically requires chest radiography, blood tests, PET-CT imaging of the entire body, and brain magnetic resonance (MR) imaging.

**Treatment**

**Surgery**

Various surgical techniques are used to remove skin cancers, depending on a number of factors, including the type of cancer, the size of the lesion, its anatomic location, available resources, and patient preferences.

One of the simplest and quickest methods to remove small low-risk tumors is cryosurgery using liquid nitrogen (see Figure 5). The technique can be used in a single visit, without anesthesia, and is especially useful for patients with bleeding disorders or other medical conditions that make other types of surgery impossible.

Another option for low-risk lesions is curettage and electrocautery. Typically carried out under topical anesthesia, the physician uses a curette to scrape off the abnormal growth and an electrocautery needle to remove additional tissue and control bleeding.
### Table 2

#### Melanoma Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Image</th>
<th>Description</th>
<th>Work-up</th>
</tr>
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<tbody>
<tr>
<td><strong>Stage 0</strong></td>
<td><img src="image1.png" alt="Image" /></td>
<td>Both normal and abnormal melanocytes and melanin are present in the epidermis.</td>
<td>No further studies required.</td>
</tr>
<tr>
<td><strong>Stage IA</strong></td>
<td><img src="image2.png" alt="Image" /></td>
<td>Tumor is ≤ 1 mm thick, with no ulceration or break in the skin.</td>
<td>Depending on mitotic rate, further studies might be required.</td>
</tr>
<tr>
<td><strong>Stage IB</strong></td>
<td><img src="image3.png" alt="Image" /></td>
<td>One tumor is ≤ 1 mm thick, with ulceration. A second tumor is more than 1 mm thick but ≤ 2 mm thick, with no ulceration.</td>
<td>–</td>
</tr>
<tr>
<td><strong>Stage IIA</strong></td>
<td><img src="image4.png" alt="Image" /></td>
<td>One tumor is &gt; 1 mm thick but ≤ 2 mm thick, with ulceration; the other tumor is &gt; 2 mm thick but ≤ 4 mm thick, with no ulceration.</td>
<td>Blood work to determine lactate dehydrogenase (LDH) levels along with baseline whole-body imaging might be ordered.</td>
</tr>
<tr>
<td><strong>Stage IIB</strong></td>
<td><img src="image5.png" alt="Image" /></td>
<td>One tumor is &gt; 2 mm but ≤ 4 mm thick, with ulceration; the other tumor is &gt; 4 mm thick, with no ulceration.</td>
<td>–</td>
</tr>
<tr>
<td><strong>Stage IIC</strong></td>
<td><img src="image6.png" alt="Image" /></td>
<td>A tumor that is &gt; 4 mm thick, with ulceration.</td>
<td>–</td>
</tr>
</tbody>
</table>
Surgical excision with local anesthesia also can be performed. The physician removes the entire growth along with a surrounding border of normal skin, called a margin, to be sure all abnormal cells have been removed. The wound is then closed with stitches and allowed to heal. Depending on the size of the wound and the resulting scar, this technique might not be appropriate for larger tumors or those in cosmetically important areas, such as the face.  

Mohs micrographic surgery is the surgical method with the highest cure rate and best cosmetic effects. However, it can be costly and time-consuming, so this technique usually is reserved for riskier lesions and those in critical areas around the eyes, nose, lips, and ears (see Figure 6). While the patient is under local anesthesia, the surgeon first removes a very thin layer of tissue and examines it immediately under a microscope to determine whether cancerous cells are present. If they are, the surgeon continues to remove tissue. The procedure is repeated until the last tissue section is cancer-free. The wound is either allowed to heal on its own or reconstructed using plastic surgery.
The standard treatment for localized malignant melanoma is called **wide local excision**, and this has become first-line therapy for stages I to III. This technique requires the surgeon to remove the primary lesion as well as surrounding tissue, allowing for precision diagnosis based on a pathology report as well as accurate staging based on microscopic examination of cells. The amount of tissue to remove has been determined by several clinical trials, and the recommended margins are now 1 cm for thin (<1 mm) lesions and 2 cm for thick (>2 mm) lesions. For lesions of intermediate thickness (1-2 mm), recommended margins are 1 to 2 cm. These margins might be adjusted slightly for anatomic or cosmetic reasons.

A biopsy of the first draining lymph node, sometimes called the **sentinel lymph node**, might be ordered to detect signs of metastasis. Identifying the sentinel lymph node frequently involves a well-established nuclear medicine imaging procedure called **lymphoscintigraphy** (see Figure 7). This procedure involves intradermal injection of a radiopharmaceutical such as technetium Tc 99m sulfur colloid at multiple sites around the primary lesion to help visualize lymphatic drainage patterns. Immediately after the radiopharmaceutical is administered, the patient is placed beneath a nuclear medicine gamma camera, which detects the radioactive emissions from the radiopharmaceutical, and 2 to 3 sets of dynamic images are acquired. Because lymphatic drainage patterns are unpredictable, a review of these images by the attending physician might lead to changes in surgical management.

The status of the sentinel lymph node is crucial, as it provides important prognostic information, helps physicians make subsequent treatment decisions, and can help identify patients who are candidates for clinical trials. If biopsy of the sentinel lymph node is negative, no treatment might be recommended beyond wide local excision and complete physical examinations every 3 to 12 months for the next 5 years. Thus, a sentinel lymph node biopsy can spare the patient removal and dissection of all local lymph nodes, which can be major surgery if inguinal or lumbar nodes are removed. However, if the sentinel lymph node

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**Figure 6.** Mohs micrographic surgery typically is performed by a trained specialist. The specialist removes a very thin layer of skin and immediately stains and examines it under a light microscope (not shown here). If cancer cells are detected in the sample, additional tissue is removed and inspected. The process is repeated until the last layer examined under the microscope tests negative for tumor tissue. Illustration ©2009 Terese Winslow, U.S. Govt. has certain rights.
biopsy proves positive, then in addition to wide local excision, the attending physician might order surgical removal of selected local lymph nodes, systemic therapy, baseline imaging, nodal irradiation, or all of the above.6,11,12

**Systemic Therapies**

For many years there was little hope for patients with advanced metastatic malignant melanoma. Median survival ranged between 6 to 9 months, and patients almost always died within a year. As recently as 2010, only 2 systemic therapies had been approved by the FDA. Dacarbazine and interleukin-2 both had low response rates (< 20%) and frequently showed minimal effect on tumor progression or overall survival; dacarbazine was well-tolerated, but interleukin-2 was so toxic it could be administered only in special centers with experienced staff. Interferon, temozolomide, taxanes, and various platinum-containing drugs also were used occasionally, as well as various combinations of these agents, but none proved superior to dacarbazine in randomized clinical trials.6

The treatment landscape suddenly changed for the better in 2011, when decades of painstaking research began to bear fruit. Medical oncologists now have a variety of regimens to choose from (see Box 1).

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**Box 1**

**Systemic Therapy Options for Advanced or Metastatic Melanoma**

**Preferred Regimens**

- Ipilimumab
- Vemurafenib
- Dabrafenib
- High-dose interleukin-2
- Clinical trial

**Other Active Regimens**

- Trametinib
- Imatinib for c-kit mutated tumors
- Dacarbazine
- Temozolomide
- Albumin-bound paclitaxel
- Dacarbazine- or temozolomide-based combination, including cisplatin and vinblastine with or without interleukin-2, interferon-α
- Paclitaxel
- Paclitaxel/carboplatin
Breakthroughs occurred on 2 fronts: molecular targeted therapy and immunotherapy. The FDA approved 2 new malignant melanoma drugs in 201114 and 2 more in 201315; additional approvals might come in 2014 as more agents receive accelerated review and advance through late-stage clinical trials.

Molecular Targeted Therapy

This type of therapy is not limited to malignant melanoma but is becoming widely used in many other tumor types. A targeted therapy is designed to limit its cytotoxic effects to tumor cells; earlier forms of chemotherapy killed all rapidly dividing cells in both cancerous and healthy tissues, often resulting in hair loss, nausea, diarrhea, and other adverse effects. In theory, targeted therapy should avoid these toxicities, but in practice, some familiar adverse effects continue, along with several new ones. Targeted therapy sometimes is called personalized therapy, as patients are selected for treatment based on their tumor’s particular genetic makeup, as determined by a DNA sequencing test.

The first targeted therapy to be approved by the FDA for melanoma was vemurafenib, which is now indicated for patients whose tumors express a gene mutation called BRAF V600E. The BRAF gene codes for a protein that is an important part of the mitogen-activated protein kinase intracellular signaling pathway. The mitogen-activated protein kinase pathway controls cell growth, and in malignant melanoma this pathway’s growth signals have been activated far beyond normal limits. An estimated 40% to 60% of malignant melanoma patients carry this mutation.16

In the pivotal phase III trial that resulted in FDA approval in 2011, investigators compared vemurafenib with dacarbazine in 675 patients with previously untreated metastatic malignant melanoma with the BRAF V600E mutation. After 6 months, overall survival was 84% in the vemurafenib group and 64% in the dacarbazine group. Response rates were 48% for vemurafenib and 5% for dacarbazine. After an interim analysis and safety check, patients were encouraged to cross over from dacarbazine to vemurafenib, and investigators concluded vemurafenib significantly improved both overall survival and progression-free survival. However, a number of adverse effects were noted, including arthralgia, rash, fatigue, and dermatologic complications, including unusual outbreaks of squamous cell carcinoma.17

A second BRAF inhibitor, called dabrafenib, was approved by the FDA in 2013. In the pivotal phase III trial leading to approval, 250 patients were randomly assigned to receive either dabrafenib (187 patients) or dacarbazine (63 patients). Median progression-free survival was 5.1 months for dabrafenib and 2.7 months for dacarbazine, which was deemed statistically significant. Response rate was reported at 52% among patients treated with dabrafenib and 17% for patients treated with dacarbazine. The median duration of response was approximately 5 months in both groups, and there was no significant difference in overall survival. The most common adverse effects with dabrafenib were skin-related toxicities, fever, fatigue, arthralgia, and headache.18

While response rates to BRAF inhibitors have been encouraging—some even call them spectacular—most responses have not been durable, and patients appear to develop resistance in less than a year. In an effort to overcome this resistance, agents are being developed to block a second step along the mitogen-activated protein kinase pathway. This step involves a gene called MEK, which appears to be farther along the chain of interactions from the BRAF gene. By delivering a 1-2 punch, investigators hope to prolong response rates and improve outcomes.

The first MEK inhibitor to be approved by the FDA was trametinib. In the pivotal phase III trial leading to approval in 2013, investigators randomly assigned 322 patients with the BRAF mutation to receive either trametinib or standard chemotherapy in a 2:1 ratio. Standard chemotherapy could be either dacarbazine or paclitaxel. Patients in the standard chemotherapy group whose tumors progressed were permitted to use trametinib. The median progression-free survival was 4.8 months in the trametinib group and 1.5 months in the chemotherapy group. After 6 months, the rate of overall survival was 81% in the trametinib group and 67% in the standard chemotherapy group, despite many patients crossing over. Rash, diarrhea, and peripheral edema were the most common adverse effects in the trametinib group. Notably, secondary skin growths were not observed.19

Investigators now are using the combination of dabrafenib and trametinib in an early-stage clinical trial.20
Preliminary results reported at the 2013 American Society for Clinical Oncology annual meeting were promising. Dabrafenib and trametinib can be safely combined at normal doses. Progression-free survival was reported at 9.4 months for the combination vs 5.8 months for monotherapy; response rates were reported at 76% for the combination vs 54% for monotherapy. Fever was more common among patients treated with the combination. Secondary skin cancers appeared less common in the combined therapy group, although the difference did not attain statistical significance.35 Dr Ribas, the malignant melanoma expert at the University of California at Los Angeles quoted at the opening of this article, noted that the combination of dabrafenib and trametinib is “one of the few times in the history of medicine…that you put 2 drugs together and they work better together, and are less toxic.”

A second MEK inhibitor, called cobimetinib, is being tested in combination with vemurafenib in a large phase III clinical trial scheduled for completion in 2016.36 The trial is being conducted at 197 locations worldwide, including hospitals in 21 states.

Immunotherapies

Technically, interleukin-2 is a form of immunotherapy, but low response rates (<16%) and high toxicities left investigators searching for improvements. A breakthrough came in 2011, with FDA approval of ipilimumab. This monoclonal antibody was engineered to bind and block a molecule called cytotoxic T-lymphocyte antigen 4, commonly found on the surface of activated T-cells. In so doing, ipilimumab works as a brake release, allowing the body’s immune system to do its job and attack tumor cells. For this reason, ipilimumab and other agents in its class are sometimes called T-cell stimulants or immune checkpoint blockers.37

The pivotal trial leading to FDA approval was reported in 2010. A total of 676 patients with advanced melanoma were randomly assigned, in a 3:1:1 ratio, to receive ipilimumab plus a tumor vaccine, ipilimumab alone, or the vaccine alone. Overall survival for both patient groups receiving ipilimumab was 10 months, compared with 6 months among patients receiving the tumor vaccine alone. However, serious adverse effects were more common in patients receiving ipilimumab, including diarrhea and colitis.37 Other sources reported increased rates of dermatitis and hepatitis.

With the success of ipilimumab, investigators were encouraged to find other ways to release the brakes on the immune system. One promising candidate appears to be nivolumab, a monoclonal antibody that binds to the programmed death-1 receptor. In 2013, investigators at Memorial Sloan-Kettering Cancer Center in New York reported promising results from a small trial combining ipilimumab and nivolumab. Tumor reduction of 80% or more was reported in 53% of patients. However, serious adverse effects also were reported in 53% of patients, although these were considered manageable.38

Another alternative might be lambrolizumab, which also enhances antitumor immunity by targeting the programmed death-1 receptor. Ribas and other investigators at the University of California reported in 2013 that a trial of lambrolizumab among 135 patients resulted in response rates as high as 52%. Responses were considered durable, with a median follow-up of 11 months among patients whose tumors responded to treatment. Perhaps even more promising, fewer serious adverse effects were reported.39

Radiation

The first tumor ever treated with radiation was skin cancer. In 1903, doctors reported the successful use of radium to treat 2 Russian patients.40 Today, surgery has become the method of choice to treat early-stage melanoma, but radiation remains an important treatment option in advanced cases.

Adjuvant Radiation

Irradiation might be recommended as an adjuvant to surgical resection of locally advanced lesions.41 However, the use of radiation in this context is rare and usually confined to patients with desmoplastic lesions known to have a high risk of local recurrence. Adjuvant radiation also might be recommended when surgical margins are narrower than recommended for safety, or when margins test positive.42

Regional radiation is more frequently recommended for patients who have had involved lymph nodes surgically removed. Patients in this category are at high risk of relapse, but a recent Australian study indicated this risk can be reduced substantially with adjuvant irradiation.43
Patients in the Australian study received 48 Gy of radiation in 20 fractions with 5 fractions per week. Recurrence of disease within the lymph node field was significantly less frequent for patients who received radiation, but there was no improvement in overall survival.12,41 Patients usually tolerate this sort of adjuvant radiation well; however, exceptions have been reported. In the Australian study, serious edema was noted in both the treatment group and the control group, but radiation dermatitis was confined to the treatment group.44

Erythema with patches of moist skin desquamation, especially near the axilla and groin, are common. Mucositis and parotiditis also are common following irradiation of the cervical nodes.11 Extensive edema of the extremities can occur, especially after surgery to the groin, and can be managed with physical therapy, compression garments, or both.11 In one study, swelling was observed after surgery but before initiation of radiation therapy, leading investigators to conclude that swelling was not caused solely by radiation.45

Care must be exercised when combining adjuvant radiation therapy with systemic therapy, as certain combinations might increase adverse effects. For example, patients who receive interferon plus radiation following surgery can experience serious skin reactions and radiation-induced myelitis. In addition, special care should be taken when the spinal cord is included in the radiation field.43

Conversely, temozolomide routinely is administered concurrently with radiation for brain metastases. In this circumstance, toxicities are considered manageable and survival might be prolonged.44 In rare cases, the combination actually might be beneficial. Jedd Wolchok, MD, PhD, of the Memorial Sloan-Kettering Cancer Center, reported in 2012 the case of a patient who was treated with radiation while also receiving ipilimumab. Wolchok’s team irradiated one tumor that was causing the patient pain, and the tumor shrank. Surprisingly, other tumors outside the radiation field, in the right lung and spleen, also regressed. This abscopal benefit lasted at least 10 months until the next CT scan, suggesting the combined treatment might have stimulated a systemic immune response.2

Radiation Techniques

The target volume for adjuvant radiation following lymph node dissection typically includes the primary site scar with a 3- to 4-cm margin.11 Techniques vary slightly according to the location of lymph nodes that have been removed.

After lymph nodes have been removed surgically, adjuvant radiation therapy of the regional nodal basin sometimes is ordered to reduce the risk of local recurrence. This particularly is true for patients with positive surgical margins. Radiation can decrease the rate of local recurrence up to 50% but cannot be expected to prolong the patient’s life.6

When surgery has been performed on nodes in the head and neck region, the target volume includes the primary lesion, the preauricular and postauricular lymph nodes, and the ipsilateral nodes, including the ipsilateral supraclavicular fossa.11

When surgery has been performed in the axillary region, radiation fields usually include the axillary lymph nodes, the supraclavicular fossa, and the low cervical nodes.11

The entire surgical scar always is included in the radiation field following resection of groin lymph node metastases. The well-documented increased toxicity of groin irradiation and the likelihood of clinically significant lymphedema means clinical judgment must be used when including adjacent nodal regions (see Table 3). This especially is true for obese patients (body mass index > 25 kg/m2).11

Setup, Schedule, and Patient Care

Following removal of cervical nodes, the setup for adjuvant radiation requires an open neck position to provide access to the primary site as well as the parotid and cervical lymphatics. A 6- to 9-MeV electron field superiorly can cover the primary site, and an abutting 9-MeV electron field is used to irradiate the parotid and lower neck nodes. Tissue-equivalent bolus material can be used to protect the temporal lobe and the thyroid. The thickness of the bolus depends on the intensity of energy used.11

In the United States, a typical total dose for adjuvant radiotherapy following removal of lymph nodes ranges between 30 and 48 Gy in as few as 5 fractions or as many as 20. Lower total doses and fewer fractions are favored in the United States; higher doses and more numerous fractions are favored in Australia.11,41

Following removal of axillary nodes, a common position for treatment requires the patient to be
immobilized in a supine position with his or her arm akimbo, with one hand on the hip and the elbow pointed outward. Reproducibility of the treatment setup is accomplished by aligning the patient using surface markings to the in-room lasers. To ensure the upper and lower torso are aligned correctly, the marks on the patient often are placed at superior and inferior points along the torso. Typically, higher photon energies are used. For example, 18-MV photon fields are used to deliver energy to the axillary lymph nodes. Multileaf collimators can be used to shape the treatment field; this excludes tissue outside of the desired treatment area and also aids in dose homogeneity.

Following removal of inguinal nodes, patients might be set up with an immobilization device in a unilateral frog-leg position. For this general area of treatment, the setup should be established in such a way as to minimize skin folds. The nodal basin might be irradiated using a mixed-beam technique of high energy electrons, such as 16- or 20-MeV electrons, and high energy photons, such as 18-MV photons. Deeper iliac nodes often require separate anterior and posterior photon fields. Lower-energy electron fields, which are used to treat more superficial depths, can be used superior and inferior to the nodal treatment area to irradiate the entire extent of the scar. Special care must be taken to limit the dose to the patient’s small bowel; doses usually are limited to less than 24 Gy.

For all treatment areas, patient care and follow-up procedures might include the application of topical products, such as hydrogen peroxide solution to treat or prevent secondary infection in areas where moist desquamation occurs. During follow-up visits to check for local relapse, a number of late adverse effects might be observed, including hypopigmentation, hyperpigmentation, and subcutaneous tissue atrophy. After cervical irradiation, it is important to monitor for hypothyroidism and hearing loss. Lymphedema of the extremities affected by radiation treatment can be managed with physical therapy and compressive devices.

### Palliative Radiation

Brain metastases are common in patients with melanoma. Men with primary lesions on the trunk or head and neck are at especially high risk. SRS commonly is used to irradiate these intracranial tumors.

Typically, patients with newly diagnosed brain metastases might be considered for surgical resection or some form of radiation to relieve pain and reduce symptoms. Although palliative therapy can be successful temporarily, prospects for recovery among patients in this group are poor: Median survival from the time of diagnosis of brain metastasis is 4 months, and only 14% to 19% of patients survive 1 year.

Alternative forms of radiation in this case include whole-brain radiation therapy, stereotactic irradiation using convergent beams, or both. Reports of adverse effects of whole-brain radiation therapy on cognitive function favor the use of stereotactic techniques. Since the first stereotactic machine in the United States was installed at the University of Pittsburgh in 1987, these systems have become more common and affordable. Increasingly, stereotactic radiation systems are found in private hospitals and freestanding clinics, not just in academic medical centers.

Stereotactic radiation can be delivered 2 ways: via stereotactic radiotherapy or SRS. Stereotactic radiotherapy is the use of more than one fraction, typically 2 to 5, using small fields and relatively high doses per fraction (5 to 20 Gy). SRS is the use of a single-fraction, small-field, high dose (> 12 Gy) of highly focused radiation in patients with a small number (< 6) of small intracranial tumors. Advanced systems with the proprietary names
Case Study

A 74-year-old woman presented in the fall of 2009 with a flesh-colored lesion on the vertex of her scalp. She had been previously diagnosed with metastatic melanoma involving the lungs and mesenteric lymph nodes.

The woman presented again in June of 2010 with a left arm motor seizure that generalized to tonic-clonic (grand mal) seizure. She awakened with postictal Todd paralysis, a brief period of paralysis after a seizure. A computed tomography (CT) scan of the brain showed an area of high attenuation. A magnetic resonance (MR) imaging scan confirmed 3 lesions consistent with metastatic disease. There also was evidence of hemorrhage within the right parietal lobe (see Figure 8).

The patient was started on a course of steroids and an anticonvulsant. Three days later, the patient underwent her first round of stereotactic radiosurgery (SRS) with high-dose radiation to all 3 lesions. The right parietal lesion was treated with 2000 cGy, the left insula lesion was treated with 2200 cGy, and the right frontal lesion was treated with 2200 cGy. The radiation oncologist wrote the prescription for all lesions to 50% isodose surface (see Figure 9).

Steroids were discontinued after 2 weeks. The patient had no prior history of systemic therapy. Her oncologist prescribed 3 cycles of dacarbazine, infused over 5 to 10 days every 3 to 4 weeks.

In September, a second round of cranial imaging showed 2 of the 3 original brain lesions had regressed (see Figure 10). However, a new intracranial lesion in the occipital region was found on a screening MR scan, and a whole-body CT showed progressive disease with worsening pulmonary nodules.
Box 2 (continued)

Case Study

The patient then underwent a second round of SRS the next month, during which 2 tumors seen on an MR scan were treated. The right frontal lesion, which had been treated during the first round and was now smaller but still visible, was retreated with 2200 cGy. The newly discovered right occipital lesion was treated with 2000 cGy (see Figure 11). The prescribed course of dacarbazine had ended, and the patient’s oncologist prescribed a 5-week course of ipilimumab.

The patient began receiving 3 cycles of ipilimumab at 3 mg/kg. However, she developed ipilimumab-related colitis requiring hospitalization and a course of infliximab. A body CT scan in December 2010 showed a mixed response to the ipilimumab, with overall improvement in the pulmonary nodule. In the spring of 2011 she was taken off ipilimumab and placed on a combination of carboplatin and paclitaxel at reduced doses. She continued on this combination through September 2011, at which point treatment was discontinued because of tumor progression. Her oncologist placed her on a clinical trial of pidilizumab (CT-011) in December 2011.

Final imaging of the patient’s cranium in May 2012 showed near-complete resolution of all 4 irradiated brain metastases (see Figure 12). Nevertheless, the patient was withdrawn from the clinical trial after 5 doses of pidilizumab because of disease progression elsewhere in her body. She died in June 2012 at 77 years of age.

Gamma Knife, CyberKnife, and Novalis all can deliver SRS to brain metastases (see Box 2).48-51

SRS is a minimally invasive alternative to surgery, which requires opening the skull and comes with the risk of related complications. Patients who show the greatest survival benefit are young, have smaller tumors, and have better performance status.19 Because of the high accuracy required for SRS, treatment includes immobilization of the target (see Figure 13) along with careful planning that includes treatment simulation and imaging studies.
PET scans can be used to assess metabolic rates within tumors compared with healthy tissues using radioactive tracers. The most common tracer is fluorodeoxyglucose (FDG), a glucose analog whose rate of uptake by cells corresponds with metabolic rate. A key benefit of FDG-PET is that malignant melanoma is associated with one of the highest accumulation rates of this tracer. Like MR spectroscopy, FDG-PET can be used to delineate the most promising area for biopsy. When combined with CT, MR, or both, FDG-PET becomes a potent method to detect metastatic melanoma and is more sensitive than CT alone. However, the use of PET scans is limited by the cost of computer equipment required to merge PET scans with outputs from CT and MR and the availability of radiopharmaceuticals.

Craig McKenzie, CMD, and a board member of the American Association of Medical Dosimetrists who is affiliated with the University of Florida Proton Institute, considers PET-CT to be the current standard for treatment planning in many U.S. radiation oncology suites. In a January 2014 telephone interview, McKenzie said PET-MR is newer and not yet as widely accepted. However, combining the power of PET to illustrate metabolic processes in real time with the power of MR to produce high-resolution anatomic images can be “even more helpful” than PET-CT, McKenzie said. Applications of PET-MR are numerous in the field of oncology, allowing imaging of 4 key processes related to cancer therapy: cell death, formation of new blood vessels, cellular proliferation, and metastasis. Because of the high costs and technical challenges related to the strong magnetic fields required by MR imaging, equipment capable of combining both imaging modalities in a single scan is not yet widely available, McKenzie said. A clinical trial comparing PET-CT to PET-MR in childhood cancer is being conducted at the Massachusetts General Hospital’s advanced imaging facility in Boston. Meanwhile, GE Healthcare is sponsoring a clinical trial to carry out premarket testing on a new PET-MR scanner.

Defining normal tissues and their locations is an essential part of treatment planning as it allows the treatment team to avoid or minimize dose delivery to nearby critical structures. Treatment planning prior to SRS requires precise calculation of dose delivery to the target as well as adjoining structures. Conformal beams allow for treatment of irregularly shaped lesions (see Figure 14). Within

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**Figure 13.** A mask used in a frameless delivery system. Other systems require a metal frame to be surgically attached to the patient’s head and removed after treatment has been completed. Image courtesy RAS Radiation Oncology Center, Carmichael, CA.
the cranium, key structures to consider when calculating dose-volume histograms include the brain stem, the optic nerves, the optic chiasma, and the cochlea (see Table 4).

**Treatment Team Roles**

A series of alarming stories in *The New York Times* about harmful or fatal medical radiation errors, followed by a U.S. Congress hearing in 2010, have focused public attention on safety in the radiation oncology suite. As part of this renewed emphasis on safety, some of radiation oncology’s most prominent professional organizations published new reports and guidelines delineating the roles of various members of the treatment team. For example, the American Society for Radiation Oncology (ASTRO), with support from the American Society of Radiologic Technologists and 10 other professional associations, published a 52-page report titled *Safety Is No Accident* calling for a clearer definition of roles. The American College of Radiology (ACR), with cooperation from ASTRO, published a clinical practice guideline concerning SRS. These 2 documents set out in detail the roles of the medical dosimetrist and the radiation therapist when

**Table 4**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Volume (cc)</th>
<th>Total Dose (Gy)</th>
<th>Max Point Dose (Gy)</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal brain parenchyma</td>
<td>10</td>
<td>10</td>
<td>–</td>
<td>Necrosis</td>
</tr>
<tr>
<td>Brain stem</td>
<td>0.5</td>
<td>10</td>
<td>15</td>
<td>Cranial neuropathy</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>1.2</td>
<td>7</td>
<td>14</td>
<td>Myelitis</td>
</tr>
<tr>
<td>Optic pathway</td>
<td>–</td>
<td>–</td>
<td>8-10</td>
<td>Blindness</td>
</tr>
<tr>
<td>Cochlea</td>
<td>–</td>
<td>–</td>
<td>9</td>
<td>Hearing loss</td>
</tr>
</tbody>
</table>

*For parallel structures, subtract the volume that receives the listed dose from the total size of the organ and verify it is less than the volume listed. For example, a patient’s liver is 2000 cc. An integral dose-volume histogram shows 55% receives 9.1 Gy. This means 45% of the liver (100-55) has been spared from 9.1 Gy. Because 900 cc equals 45% of this patient’s liver—more than the listed 700 cc volume—the plan would meet this liver objective. Note that the dose-volume histogram point used for IMRT optimization in this case would be (2000-700)/2000 = 65% volume and 9.1 Gy dose.*
conducting SRS and other forms of potentially dangerous radiation treatment. The report and the guideline indicate how these leading professional organizations envision the proper functioning of the treatment team.

The ACR recommends the team should include, at a minimum, a radiation oncologist, a neurosurgeon, and a medical physicist. When applicable, the team also should include a radiation therapist and a medical dosimetrist. ACR According to the ACR, the radiation therapist must fulfill state licensing requirements and should have American Registry of Radiologic Technologists certification in radiation therapy. The role of the radiation therapist includes:

- Preparing the treatment room for the SRS procedure.
- Assisting the treatment team with patient positioning and immobilization.
- Operating the treatment unit after the clinical and technical aspects of beam delivery are approved.

Medical dosimetrists are not required to be state licensed. According to the ACR, the role of the medical dosimetrist includes:

- Contouring clearly discernible normal structures.
- Ensuring proper orientation of volumetric patient image data on the radiation therapy treatment planning system (from CT and other fused image data sets).
- Designing and generating the treatment plan under the direction of the radiation oncologist and medical physicist.
- Generating all technical documentation required to implement the treatment plan.
- Being available for the first treatment and assisting with verification for subsequent treatments as necessary.

*Safety Is No Accident* contains an even more complete discussion of the roles of the treatment team, including the radiation therapist and the medical dosimetrist (see Table 5). According to this report, the team also includes nonphysician providers such as nurse practitioners, physician assistants, and oncology nurses. Here, duties of the dosimetrist align closely with the duties of the supervising medical physicist.

As technology advances, the roles of treatment team members might need to change. ASTRO has tried to indicate what the future holds for radiation therapists and medical dosimetrists. For example, the traditional role of the dosimetrist has been treatment planning and software quality assurance. In the future, dosimetrists will be more involved in image cataloging and manipulation, especially fusing or merging images obtained via multiple technologies such as CT, MR, and PET. They also will be called upon to assist with the quality assurance of equipment used in intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT). They will encounter professional and educational challenges, including adequate instruction in anatomy and proper use of emerging technologies.

For example, the program in medical dosimetry at the University of Texas MD Anderson Cancer Center specifies 8 semester credit hours of instruction in anatomy.
and physiology prior to admission, plus 1 semester credit hour in anatomy for radiation oncology, including study of sagittal, transverse, and coronal section planes. Moreover, the medical dosimetry curriculum published in 2012 by the Joint Review Committee on Education in Radiologic Technology requires instruction in cross-sectional anatomy, as well as instruction in SRS, stereotactic body radiation therapy (SBRT), IMRT, IGRT, proton therapy, craniospinal irradiation, total body irradiation (TBI), and total skin electron irradiation (TSEI). Cross-sectional anatomy, as well as TBI, TSEI, SRS, and SBRT are all covered in the 2014 certification examination administered by the Medical Dosimetrist Certification Board.

The traditional role of the radiation therapist has been to provide safe and effective delivery of radiation as prescribed by the attending physician, along with performing daily quality assurance checks on equipment and new patient treatments. In the future, the radiation therapist might be called upon more to assess 2-D and 3-D images to make decisions concerning patient treatment, mobility, and alignment. Professional challenges are expected to include the safe and proper use of additional imaging and treatment delivery systems.

Outcomes and Survivorship

The number of cancer survivors in the United States is growing rapidly. As of January 2012, their number was estimated at 13.7 million. This number is projected to increase by approximately 30%, to almost 18 million by 2022. Malignant melanoma survivors accounted for roughly 7% of the total in 2012.

The number of malignant melanoma survivors is projected to grow even faster than survivors of other types of cancer. In 2012, malignant melanoma had the highest annual percent change in incidence among 16 types of cancer measured by the National Cancer Institute. One recent research study predicted the number of melanoma survivors would grow from 1.2 million in 2010 to between 1.7 million and 2 million in 2020, which would be an increase in the range of 40% to 67%. The higher numbers assume the recent extraordinary rise in malignant melanoma incidence rates will continue. The higher estimate also assumes a slight improvement in long-term survival rates as a result of advancing treatment techniques.

Prevention

All types of skin cancer are highly curable if detected and treated early. Even malignant melanoma is curable when caught in its earliest stages. The 5-year relative survival rate for malignant melanoma patients is 91%, and the 10-year rate is 89%. When melanoma is detected before it spreads, the 5-year survival rate is 98%, but this rate declines to 62% if regional lymph nodes are involved and 15% if the tumor has begun to metastasize.

Despite these clear links between early detection and greatly improved outcomes in malignant melanoma, no randomized clinical trials support routine skin cancer screenings for the general population. Educational efforts by the American Cancer Society, government agencies, and patient advocacy organizations aim to help clinicians and the public to improve the early recognition of suspicious lesions. These efforts appear to bear fruit: According to the American Cancer Society’s Cancer Facts & Figures 2013 showing data from 2005 to 2009, the death rate among whites younger than 50 years declined by 2.8% per year among men and by 2.0% per year among women.

A widely used mnemonic device for early skin cancer detection while inspecting nevi refers to the ABCDs:
- A – asymmetry.
- B – border irregularity.
- C – color variation.
- D – diameter greater than 6 mm (see Table 6).

The best prevention remains limited sun exposure and heightened vigilance through periodic skin checks. The American College of Preventive Medicine recommends reducing exposure to the sun, especially at midday, along with protective clothing, hats, and sunscreen with a sun protective factor (SPF) of at least 15. The American Cancer Society recommends sunscreen with an SPF of at least 30, along with avoiding sunbathing, sun lamps, and indoor tanning. An effective skin cancer screening takes only 3 minutes and involves a visual inspection of the entire body, including scalp, hands, and soles of the feet.

Conclusion

Nonmelanoma skin cancer is the most common type of cancer diagnosed, and one estimate placed the number of new cases diagnosed annually in the United States at more than 3 million—roughly double the annual number of new cases of all other cancer types combined.
Americans. Even advanced forms of the disease have recently become more treatable. However, some of these treatment advances benefit only certain subgroups of patients based on their precise genetic makeup, and much work remains to be done to find options for all patients. In the meantime, the most effective prevention methods appear to be avoiding sunburns and keeping a close watch on large moles or skin blemishes.

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References


Fortunately, skin cancers rarely are serious, and basal cell carcinomas and squamous cell carcinomas are quickly and easily removed in the clinic. Although rarer, malignant melanoma is much more serious. Its incidence has been rising steadily among whites, although it is much less of a concern among minorities, especially African Americans. Even advanced forms of the disease have recently become more treatable. However, some of these treatment advances benefit only certain subgroups of patients based on their precise genetic makeup, and much work remains to be done to find options for all patients. In the meantime, the most effective prevention methods appear to be avoiding sunburns and keeping a close watch on large moles or skin blemishes.
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Malignant Melanoma

Read the preceding Directed Reading and choose the answer that is most correct based on the article.

1. The ______ is a rare phenomenon that occurs when localized radiation therapy delivered to a tumor in a patient with advanced disease leads to shrinkage of tumors outside the radiation field.
   a. tumor lysis syndrome
   b. abscopal effect
   c. spontaneous remission
   d. immunotherapeutic remission

2. Roughly 80% of nonmelanoma skin cancers arise from:
   a. subcutaneous tissue.
   b. melanin.
   c. squamous epithelium.
   d. basal cells.

3. Melanin-containing cells, called melanocytes, are found:
   a. on top of the epidermis.
   b. below the subcutaneous layer.
   c. at the junction of the epidermis and dermis.
   d. in the adipose (fat) tissue.

4. Malignant melanoma frequently spreads via which body system?
   a. lymphatic
   b. central nervous
   c. circulatory
   d. endocrine

5. Malignant melanoma mortality rates are highest among which racial and ethnic group?
   a. Hispanic whites
   b. African Americans
   c. American Indians
   d. non-Hispanic whites

6. Which of the following is not a risk factor for malignant melanoma?
   a. cosmetics use
   b. fair skin
   c. history of serious childhood sunburns
   d. family history

continued on next page
13. The first tumor ever treated with radiation, more than a century ago, was ______ cancer.
   a. lung
   b. skin
   c. breast
   d. bone

14. Regional radiation frequently is recommended for patients who have had:
   a. involved lymph nodes surgically removed.
   b. a primary lesion surgically removed but no nodes.
   c. a sentinel lymph node biopsy.
   d. recurrent disease.

15. Adverse effects of combined adjuvant radiation therapy and systemic therapy following surgery include:
   1. serious skin reactions.
   2. radiation-induced myelitis.
   3. edema.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

16. The target volume for adjuvant radiation following lymph node dissection typically includes the primary site scar with a ______-cm margin.
   a. 1- to 2
   b. 2- to 3
   c. 3- to 4
   d. 4- to 5

17. In the United States, a typical total dose for adjuvant radiation therapy following removal of lymph nodes ranges between:
   a. 30 to 48 Gy, given in 8 to 10 fractions.
   b. 25 to 34 Gy, given in 8 to 10 fractions.
   c. 25 to 34 Gy, given in a single treatment.
   d. 30 to 48 Gy, given in 5 to 20 fractions.
18. Because of the high accuracy required for stereotactic radiosurgery, treatment includes:
   1. imaging studies for target definition.
   2. treatment simulation.
   3. immobilization of the target.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

   a. positron emission tomography (PET)
   b. magnetic resonance (MR)
   c. CT
   d. PET-CT

20. ______ might be used to assess metabolite concentrations within tumors and normal tissue to help distinguish between neoplasms and radiation necrosis.
   a. CT
   b. MR spectroscopy
   c. Functional MR imaging
   d. PET

21. When calculating dose-volume histograms within the cranium, which of the following structures is not typically considered?
   a. cochlea
   b. optic nerves
   c. soft palate
   d. brain stem

22. According to the American Society for Radiation Oncology, which of the following professionals calculates dose-volume constraints?
   a. medical dosimetrist
   b. radiation therapist
   c. radiation oncologist
   d. neurosurgeon

23. In the future, the ______ might be called upon more to assess 2-D and 3-D images to make decisions concerning patient treatment, mobility, and alignment.
   a. medical dosimetrist
   b. radiation therapist
   c. radiation oncologist
   d. neurosurgeon

24. When melanoma is detected before it spreads, the 5-year survival rate is ______ %.
   a. 66
   b. 75
   c. 88
   d. 98

25. In the widely used A-B-C-D mnemonic device for early skin cancer detection while inspecting nevi (moles) on the skin, the “A” stands for:
   a. area.
   b. arrangement.
   c. asymmetry.
   d. atypical.