

# Chapter 1

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## Overview of Cancer and Cancer Treatment

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### A. Definition of cancer

1. Clinically, cancer is a large group of malignant diseases with some or all of the following characteristics (Eggert, 2010; Merkle, 2011).
  - a) Abnormal cell proliferation caused by a series of cellular and/or genetic alterations or translocations
  - b) Lack of controlled growth and cell division that leads to the formation of tumors and invasion of tissues in proximity to tumor cells
  - c) Ability to spread (metastasize) to distant sites and establish secondary tumors
  - d) Ability to involve any tissue of the body
  - e) Evasion of natural cell death (apoptosis)
2. On the cellular and molecular levels, however, cancer is believed to be only a few diseases (Eggert & Kasse, 2010) that result from faulty or abnormal genetic expression caused by changes in deoxyribonucleic acid (DNA).
  - a) The transcription of DNA into a single strand of messenger ribonucleic acid (mRNA) may be changed.
  - b) When abnormal mRNA exists, the sequence of amino acids is changed, resulting in abnormal protein synthesis.
3. Multiple factors often interact, leading to the development of cancer. Normal cells may undergo changes outlined by Eggert and Kasse (2010) because of
  - a) Spontaneous transformation: No causative agent is identified, but cellular characteristics are typical of cancer cells.
  - b) Exposure to chemical or physical carcinogens: Environmental factors are continuously being studied. Chronic or occupational exposure to substances such as asbestos, benzene, radiation, tobacco, arsenic, nickel, and some chemotherapeutic agents is implicated in cancer development. The National Institute for Occupational Safety and Health (NIOSH) and other organizations have identified more than 100 substances as carcinogens, with the listings continually evaluated and revised (International Agency for Research on Cancer [IARC], 2013; National Toxicology Program, 2011; U.S. Department of Health and Human Services [DHHS], 2012).
  - c) Genetic alterations: Mutations are permanent changes in the sequencing of DNA base pairs resulting in a cell with malignant properties. Some mutations are of no concern, whereas others lead to tumor formation (Eggert & Kasse, 2010; Merkle, 2011).
    - (1) A small percentage of cancers are caused by mutations inherited between generations in germ cells (sperm and ova).
    - (2) Most cancers are sporadic and caused by a series of acquired mutations over time.
  - d) Exposure to viruses: Genetic changes can occur to cells through viral infections. For example, the human papillomavirus (HPV) is the primary cause of cervical cancer (Fair, 2011).

4. Figure 1 provides a summary of genetic changes that may result in tumor formation. The properties of transformed cells are changes in the cytology, cell membrane, and growth and development.

**Figure 1. Clonal Evolution in Cancer**

Figure viewable in purchased book.

*Note.* From "Biology of Cancer" (p. 7), by C.J. Merkle in C.H. Yarbro, D. Wujcik, and B.H. Gobel (Eds.), *Cancer Nursing: Principles and Practice* (7th ed.), 2011, Burlington, MA: Jones and Bartlett. Copyright 2011 by Jones and Bartlett. Reprinted with permission.

## B. Cancer grading and staging

1. Differentiation and grading: Cellular differentiation is based on how closely tumor cells resemble normal cells in their structure and maturity. Differentiation is graded using the following scale.
  - a) GX—grade cannot be assessed
  - b) G1—well differentiated (resembles the parent cell)
  - c) G2—moderately well differentiated
  - d) G3—poorly differentiated (bears little resemblance to the parent cell)
  - e) G4—undifferentiated (impossible to tell which cell is the parent)
  - f) Cells are obtained by biopsy or surgical removal for microscopic examination by a pathologist. Cancer cells appear different from those of the surrounding normal tissue. Tumor differentiation can vary over time, and cells with several grades of differentiation can exist within a single tumor. Tumor grade is a prognostic indicator. The higher the grade, the more aggressive the tumor (American Joint Committee on Cancer [AJCC], 2010; Vogel, 2011).
2. Staging: The purpose of staging is to verify the extent of the disease by assessing the location and size of the primary tumor and determining if it has spread to other tissues or organs. Staging assists in determining prognosis, treatment planning, identification of suitable clinical trials, and treatment response. Staging provides a common language with which the healthcare team can communicate about a patient's case. Staging criteria are unique for each type of cancer (AJCC, 2010; National Cancer Institute [NCI], 2013).
  - a) AJCC (2010) describes three types of staging: clinical (based on physical examination, imaging, and biopsy), pathologic (based on information obtained during surgery), and restaging (completed upon disease recurrence).

- b) The tumor, node, metastasis (TNM) staging system is maintained jointly by AJCC and the Union for International Cancer Control. It is used commonly with solid tumors and classifies cancers by the following three criteria. Additional information about cancer staging is available online at [www.cancerstaging.org](http://www.cancerstaging.org) (AJCC, 2010; Vogel, 2011).
- (1) T—tumor (local involvement, invasion): The primary tumor is measured to document its size and to determine the depth of invasion.
  - (2) N—node (nodal involvement): Lymph nodes in the area of the primary tumor are examined for evidence of tumor cells. Lymph node size, number, and location are documented.
  - (3) M—metastasis: Studies are done to determine if the primary tumor has metastasized to a distant location.
- c) Lymphomas, leukemias, and multiple myeloma are hematologic malignancies that are staged according to other systems. For example, the Ann Arbor staging classification is used to stage Hodgkin lymphoma (HL), and the International Staging System is used for multiple myeloma (Gospodarowicz, 2009; Tariman & Faiman, 2011; Vogel, 2011).
- d) Childhood cancers may be staged by the TNM system or by criteria from the Children’s Oncology Group (COG), which conducts clinical trials in pediatric oncology (NCI, 2013).
- e) Some gynecologic cancers are staged using the International Federation of Gynecology and Obstetrics, or FIGO, system.
- f) Prognostic information is provided by an increasing number of non-anatomic factors that may predict the effectiveness of specific therapies. Gender, overall health status, and specific biologic properties of tumor cells are characteristics that may affect patient outcomes and have been incorporated into some staging algorithms (AJCC, 2010).

### C. Cancer treatment modalities

1. Table 1 summarizes the history of cancer therapy. A variety of modalities are used to treat cancer. Treatment may include one or more of the following interventions.

Table 1. History of Cancer Therapy	
Period	Events
Pre-20th century	1500s: Heavy metals are used systemically to treat cancers; however, their effectiveness is limited and their toxicity is great (Burchenal, 1977). 1890s: William Coley, MD, develops and explores the use of Coley toxins, the first nonspecific immunostimulants used to treat cancer.
World War I	Sulfur-mustard gas is used for chemical warfare; servicemen who are exposed to nitrogen mustard experience bone marrow and lymphoid suppression (Gilman, 1963; Gilman & Philips, 1946).
World War II	Congress passes National Cancer Act in 1937, establishing the National Cancer Institute (NCI). Alkylating agents are recognized for their antineoplastic effect (Gilman & Philips, 1946). Thioguanine and mercaptopurine are developed (Guy & Ingram, 1996). 1946: NCI-identified cancer research areas include biology, chemotherapy, epidemiology, and pathology. 1948: Divisions within NCI and external institutions are identified to conduct research (Zubrod, 1984). Folic acid antagonists are found to be effective against childhood acute leukemia (Farber et al., 1948). Antitumor antibiotics are discovered.
1950s	1955: The National Chemotherapy Program, developed with Congressional funding, is founded to develop and test new chemotherapy drugs. 1957: Interferon is discovered. The Children’s Cancer Group, the first cooperative group dedicated to finding effective treatments for pediatric cancer, is formed.

(Continued on next page)

Table 1. History of Cancer Therapy (Continued)

Period	Events
1960s–1970s	<p>Development of platinum compounds begins.</p> <p>Multidrug therapy improves remission rates without severe toxicity; mechlorethamine, vincristine, procarbazine, and prednisone (MOPP), the first combination chemotherapy, is used and found to be curative against Hodgkin disease (Noonan, 2007).</p> <p>Clinical trials of bacillus Calmette-Guérin and <i>Corynebacterium parvum</i>, nonspecific immunostimulants, begin.</p> <p>Chemotherapy is used with surgery and radiation as cancer treatment.</p> <p>Development of hybridoma technology begins.</p> <p>NCI starts its Biological Response Modifiers Program.</p> <p>Tamoxifen is synthesized in 1962 and first used in 1969.</p>
1970s	<p>The National Cancer Act of 1971 provides funding for cancer research; NCI director is appointed by and reports to the president of the United States.</p> <p>Doxorubicin phase I trials begin.</p> <p>Adjuvant chemotherapy begins to be a common cancer treatment (Bonadonna et al., 1985; Fisher et al., 1986).</p>
1980s	<p>Community Clinical Oncology Programs are developed in 1983 to contribute to NCI chemotherapy clinical trials.</p> <p>Use of multimodal therapies increases (Eilber et al., 1984; Marcial et al., 1988).</p> <p>Focus turns to symptom management to alleviate dose-limiting toxicities related to neutropenia, nausea and vomiting, and cardiotoxicity.</p> <p>Clinical trials for dexrazoxane (ICRF-187) as a cardioprotectant begin (Speyer et al., 1988).</p> <p>New chemotherapeutic agents are available.</p> <p>Scientists begin to investigate recombinant DNA technology.</p> <p>Trials of monoclonal antibodies and cytokines begin.</p> <p>Effector cells (lymphokine-activated killer cells and tumor-infiltrating lymphocytes) are grown ex vivo.</p> <p>1986: U.S. Food and Drug Administration (FDA) approves interferon alfa.</p> <p>1989: FDA approves erythropoietin.</p>
1990s	<p>New classifications of drugs (e.g., taxanes) are developed.</p> <p>In clinical trials, paclitaxel is found to be effective against ovarian and breast cancers (Rowinsky et al., 1992).</p> <p>FDA approves granulocyte–colony-stimulating factor and granulocyte macrophage–colony-stimulating factor, interleukin-2, interleukin-11, rituximab, trastuzumab, and denileukin diftitox.</p> <p>Clinical trials of gene therapy and antiangiogenic agents begin.</p> <p>FDA approves filgrastim for use in bone marrow transplantation and chemotherapy-induced neutropenia, severe chronic neutropenia, and peripheral blood stem cell transplantation.</p> <p>FDA approves ondansetron for prevention of chemotherapy-induced nausea and vomiting; other 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) receptor antagonists are in clinical trials (Perez, 1995).</p> <p>As a result of improved symptom management, dose intensity becomes a focus.</p> <p>FDA approves new analogs (e.g., vinorelbine) (Abeloff, 1995).</p> <p>Scientists focus on the sequencing of agents (Bonadonna et al., 1995).</p> <p>The genetic basis of cancers becomes an important factor in cancer risk research (e.g., <i>BRCA1</i> for breast cancer, renal cell cancer) (Gnarra et al., 1995; Hoskins et al., 1995; Miki et al., 1994).</p> <p>Aromatase inhibitors are approved for breast cancer treatment. This marks a step forward for hormonal therapy.</p>
2000–present	<p>The Children's Oncology Group, a cooperative group combining the efforts of several groups, is formed to further the advancement of cancer treatment for children (<a href="http://www.childrensoncologygroup.org">www.childrensoncologygroup.org</a>).</p> <p>Scientists complete a working draft of the human genome (American Society of Clinical Oncology [ASCO], n.d.).</p> <p>Theory of immune surveillance continues, and biotherapy is used to target and mount a defense against certain antigens on malignant cells (e.g., gemtuzumab ozogamicin binds to CD33 on leukemic cells, rituximab binds to CD20-positive non-Hodgkin lymphoma cells).</p> <p>Radioimmunotherapy is used to deliver radioactivity directly to select tumor cells, avoiding damage to healthy tissue (e.g., ibritumomab tiuxetan, tositumomab I-131).</p> <p>FDA approves targeted therapies attacking epidermal growth factor receptor for lung cancer (gefitinib and erlotinib) and colon cancer (cetuximab and panitumumab) (ASCO, n.d.).</p> <p>FDA approves antiangiogenic agents (bevacizumab was the first) (ASCO, n.d.).</p> <p>Neurokinin-1 antagonist (aprepitant) is used in combination with other antiemetic drugs to prevent chemotherapy-induced nausea and vomiting.</p> <p>Therapeutic vaccine trials are begun for existing cancers (e.g., OncoVAX<sup>®</sup>, an autologous tumor cell vaccine, is in phase III studies for stage II colon cancer), and FDA approves a prophylactic vaccine (Gardasil<sup>®</sup>) for the prevention of human papillomavirus infections that cause cervical cancer (ASCO, n.d.).</p> <p>2010: Affordable Care Act is signed into law.</p>

2. Surgery (Drake & Lynes, 2010; Gillespie, 2011)
  - a) Is a precise local treatment
  - b) May remove all or a portion of the primary tumor
  - c) Can be used to obtain specimens for cytopathology
  - d) May be the only treatment a patient requires
  - e) May be preceded or followed by other modalities
  - f) May be used in the palliative setting to alleviate or lessen intolerable symptoms
3. Radiation therapy (Gosselin, 2011; Kelvin, 2010)
  - a) Is a local treatment in which energy is precisely directed at a specific target
  - b) May follow surgery to prevent recurrence of the primary tumor
  - c) Is more effective for some diseases than others
  - d) Is sometimes used after chemotherapy because radiation can permanently damage bone marrow, making it impossible to give chemotherapy in the doses needed for curative therapy
  - e) Is often given in combination with chemotherapy (chemoradiation)
  - f) May be given as radioimmunotherapy (RIT), combining a radioisotope and a monoclonal antibody (mAb)
4. Chemotherapy/hormonal therapies (Levine, 2010; Tortorice, 2011)
  - a) Are systemic therapies, rather than local treatments, as drugs are distributed throughout the body by the bloodstream
  - b) May be used as single agents or, more commonly, in combination
  - c) Are limited by toxic effects on normal tissues
  - d) May have a tumoricidal effect in hormone-sensitive tumors because of reduction or blockage of the source of the hormone or receptor site where hormone is active
5. Biotherapy/targeted agents (Lapka & Franson, 2010)
  - a) Are systemic treatments
  - b) May modify the patient's own immune defenses
  - c) May be so specific as to target a single receptor on the surface of tumor cells or an enzyme within the cell
  - d) May cause side effects and toxicities different from those of other antineoplastic agents
  - e) May be combined with other treatment modalities
  - f) May promote tumor regression
  - g) May stimulate hematopoiesis

#### D. Treatment approaches

1. Neoadjuvant therapy: The use of one or more treatment modalities prior to the primary therapy (e.g., chemotherapy before surgery). Goal is to shrink the primary tumor to improve the effectiveness of surgery or decrease the likelihood of micrometastases (Otto, 2007). In cases of locally advanced breast tumors, using neoadjuvant therapy may increase the possibility for breast conservation.
2. Adjuvant therapy: Therapy following the primary treatment modality (e.g., chemotherapy or radiation after surgery). The goal of adjuvant therapy is to target minimal disease or micrometastases for patients at high risk for recurrence (Otto, 2007).
3. Conditioning or preparative therapy: Administration of chemotherapy, sometimes with total body irradiation, to eliminate residual disease or empty the marrow space prior to receiving a stem cell transplant (also referred to as *myeloablation*).
  - a) Myeloablation: Obliteration of bone marrow with chemotherapeutic agents typically administered in high doses in preparation for peripheral blood stem cell or bone marrow transplantation (BMT). Myeloablative therapy does not allow for spontaneous marrow recovery because

- of the lethal doses of agents used; therefore, it must be followed by stem cell transplantation to prevent death. An example of myeloablative therapy is cyclophosphamide plus total body irradiation or busulfan plus cyclophosphamide (National Marrow Donor Program, 2012).
- b)* Nonmyeloablative: Reduced-intensity conditioning using doses that are not lethal to bone marrow (Poliquin, 2007). Use of nonmyeloablative regimens has expanded the number of patients eligible for transplantation (National Marrow Donor Program, 2012).
4. Immunosuppression: Administration of chemotherapy at doses sufficient to blunt a patient's immune response. This is done prior to transplantation to prevent graft rejection in allogeneic stem cell transplant recipients. Agents such as methotrexate are given post-transplantation to prevent graft-versus-host disease (GVHD). Certain agents are given for immunosuppression to treat noncancerous conditions, such as autoimmune diseases.

#### E. Treatment strategies

1. Combination versus single-agent therapy (Tortorice, 2011): A combination of drugs is more effective in producing responses and prolonging life than the same drugs used sequentially. With combination therapy, more cancer cells are exposed in a sensitive phase, resulting in higher tumor cell kill. Moreover, "with rare exceptions, . . . single drugs at clinically tolerable doses have been unable to cure cancer" (Chu & DeVita, 2013, p. 3).
- a)* Tumor cell populations are heterogeneous; therefore, a combination of agents with different mechanisms of action is able to increase the proportion of cells killed at any one time.
- b)* Combination agents with different mechanisms of action also reduce the possibility of drug resistance, theoretically minimizing the chances for outgrowth of resistant clones (Skeel, 2011a).
- c)* Agents selected for use in combination chemotherapy have proven efficacy as single agents.
- d)* Combination chemotherapy may use the principle of drug synergy to maximize the effects of another drug. Synergy is affected by the rate of tumor cell proliferation and by timing of drug administration (sequential or simultaneous; for example, leucovorin potentiates the cytotoxicity of 5-fluorouracil [5-FU]) (Brown, in press). Combinations can be used to provide access to sanctuary sites for reasons such as drug solubility or affinity of specific tissues for a particular drug type (Skeel, 2011a).
- e)* Drugs with similar toxicities generally are avoided, although this is not always possible. For example, both paclitaxel and cisplatin can cause peripheral neuropathy as single agents but often are used together (Argyriou et al., 2007).
2. Dosing of chemotherapy
- a)* Treatment cycles are designed to permit recovery from damage to normal tissues and organs. Because the average white blood cell (WBC) nadir is 10–14 days, many regimens are based upon this time frame.
- b)* Administering a drug such as 5-FU at a steady concentration over a period of time increases cell kill (Howland & Mycek, 2006).
- c)* *Dose density* refers to the drug dose per unit of time. Higher dose density is achieved by shortening the intervals between treatments (Freter, 2012). Reducing the time between chemotherapy cycles may diminish tumor regrowth. This strategy has resulted in longer survival for patients with breast, ovarian, and colon cancers and lymphoma (Tortorice, 2011). The prophylactic use of the myeloid growth factor pegfilgrastim has allowed for administration of dose-dense chemotherapy regimens that would otherwise result in unacceptable neutropenia (Burdette-Radoux et al., 2007; von Minckwitz et al., 2007).

- d) *Dose intensity* is the amount of drug that is delivered over time. Nurses should be aware that dose reduction or delay resulting from chemotherapy side effects, scheduling conflicts, or any other reason reduces dose intensity and may negatively affect patient survival (Tortorice, 2011). Optimal cell kill is achieved by delivering sufficient doses of chemotherapy at planned intervals.
- e) *Relative dose intensity* is calculated by comparing the received dose to the planned dose of the standard regimen. Proactively managing symptoms and educating patients on the importance of maintaining the prescribed dosing schedule are paramount. (See Chapter 7 for further discussion of dosing concepts.)

F. Goals of cancer therapy: Treatment planning includes discussion with patients about their goals of therapy and whether those goals are realistic (Skeel, 2011b).

1. Prevention (Mahon, 2010)

a) Primary cancer prevention: Measures taken to avoid carcinogen exposure and promote health. Steps taken to prevent disease development (e.g., avoidance of tobacco products, immunization against HPV).

(1) Chemoprevention: The use of selected pharmacologic agents to prevent cancer in high-risk individuals, such as the administration of tamoxifen to women whose personal health history indicates they are at a statistically increased risk for developing breast cancer (Brown, in press).

(2) There has been discussion related to the role of nutritional epidemiology in the identification of nutritional or chemopreventive approaches to colon cancer, but that has yet to be confirmed (Marshall, 2009).

b) Secondary cancer prevention: Early detection and treatment of cancer

c) Tertiary cancer prevention: Monitoring for and/or preventing recurrence of the original cancer or secondary malignancies

2. Cure: Defined as the prolonged absence of detectable disease. This is the desired outcome for all patients but is not always achievable.

3. Control: When cure is not possible, the goal is to allow patients to live longer than if therapy had not been given (Skeel, 2011b). Treatment often extends life and may prevent the growth of cancer cells without complete elimination of disease or may reduce existing disease (Goselin, 2011).

4. Palliation: Palliative cancer care is the integration of therapies that address the multiple issues that cause suffering in patients with cancer and their families. In 2009, the American Society of Clinical Oncology (ASCO) Board of Directors advocated that palliative care be offered to all patients from the time of diagnosis to death (Ferris et al., 2009). Palliation involves reduction of side effects and symptoms, including pain (Brown, in press; Gaddis & Gullatte, in press). It may include surgery, radiation therapy, chemotherapy, or biotherapy, individually or in combination (Otto, 2007).

G. Measuring response

1. Measuring tumor response

a) Objective tumor response is assessed through a quantitative measurement such as surgical examination, imaging studies, or serum tumor markers. Measurements recorded at the time of diagnosis are compared to those recorded after treatment completion. In 1981, the World Health Organization (WHO) first published tumor response criteria with overall assessment of tumor burden. Response to therapy may be measured by survival, disease-free survival, ob-

jective change in tumor size or in tumor product, and subjective change (Skeel, 2011a). With neoadjuvant therapy, tumor response and resectability are partial determinants of effectiveness (Skeel, 2011a). The current end point for assessing response to therapy in solid tumors is measuring change in tumor size (Kumar, Halanaik, & Dahiya, 2010).

b) Tumor response has historically been classified using the following system (Wahl, Jacene, Kasamon, & Lodge, 2009).

- (1) Complete response: Absence of all signs and symptoms of cancer for at least one month using objective criteria (e.g., quantitative bidimensional tumor measurement)
- (2) Partial response: At least a 50% reduction of measurable tumor mass for one month without development of new tumors
- (3) Stable disease: A reduction in tumor mass of less than 50% or less than a 25% increase in tumor growth
- (4) Progressive disease: Growth of 25% or more or development of new tumors. Note that this definition of *progressive* is negative, in contrast to the standard English usage of the term.
- (5) Relapse: After complete response, a new tumor appears or the original tumor reappears. Following partial response, a new tumor appears or the original tumor increases in size. See Table 2 for further information.

c) Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were developed in 1999 by an international task force including the European Organization for Research and Treatment of Cancer (EORTC), NCI, and the National Cancer Institute of Canada Clinical Trials Group. The criteria were revised in 2008 and notated as RECIST 1.1.

- (1) Guidelines are intended to facilitate communication between researchers and clinicians (Therasse, Eisenhauer, & Buyse, 2006).
- (2) Considerable variation exists between the original RECIST and WHO criteria for evaluating response (Mazumdar, Smith, & Schwartz, 2004; Schwartz et al., 2006), as well as subsequent editions of RECIST. These variations create a challenge for evaluating the effectiveness of therapies being studied in clinical trials. For example, RECIST criteria may show tumor progression more slowly than WHO criteria, and RECIST 1.1 criteria result in a higher complete response rate than the original RECIST criteria (Wahl et al., 2009).

2. WHO (Therasse et al., 2000) recognizes that diagnostic technologies (e.g., computed tomography [CT] scans, magnetic resonance imaging

**Table 2. Comparison of WHO and RECIST Criteria for Tumor Response**

Response	WHO	RECIST 1.1
Complete response	Absence of all known disease for at least 4 weeks	Disappearance of all target lesions
Partial response	≥ 50% reduction of measurable tumor mass for ≥ 4 weeks without development of new tumors	30% reduction in the sum of the diameters of target lesions compared to the baseline
Progressive disease	Growth of ≥ 25% or more, or development of new tumors	20% increase in the sum of diameters of target lesions
Stable disease	Unable to meet criteria for either partial response or progressive disease	Unable to meet criteria for either partial response or progressive disease

RECIST—Response Evaluation Criteria in Solid Tumors; WHO—World Health Organization  
 Note. Based on information from Eisenhauer et al., 2009; Wahl et al., 2009.



[MRI]) have led to confusion regarding three-dimensional measurement of disease. As a result, the reported response criteria vary among research groups. See Table 2 for a comparison of WHO and RECIST criteria.

### 3. RECIST 1.1 guidelines

- a) Response to a clinical trial is used to decide whether an agent or regimen demonstrated results promising enough to warrant further testing (prospective end point).
- b) Baseline lesions are characterized as measurable or nonmeasurable. At baseline, tumors must be measurable in at least one dimension (using metrics) by calipers or a ruler. Baseline measurements must be obtained within four weeks of initiating therapy. Lesions may be measured using CT or MRI, but CT is preferred in most cases because of variability in MRI scan parameters. In the original RECIST, nonmeasurable lesions included bone lesions, ascites, pleural or pericardial effusions, leptomeningeal disease, and inflammatory breast cancer. RECIST 1.1 now accepts bone metastases and soft tissue masses measuring 10 mm or larger as target lesions (Costelloe, Chuang, Madewell, & Ueno, 2010).
- c) The same method and technique used at baseline must be used to evaluate response for reporting and follow-up.
- d) If the primary end point is response to treatment, the patient must have at least one measurable lesion at baseline. If only one measurable lesion is present, it must be confirmed by cytology or histology.
- e) Measurable lesions, up to 5 per organ or 10 in total, are identified as *target lesions*.
  - (1) Lesions selected are the longest in diameter and suitable for follow-up measurement.
  - (2) The sum of the longest diameters for all target lesions is designated as the *baseline sum longest diameter*. This sum is used as the reference to compare response (Skeel, 2011b).
  - (3) All other nontarget lesions are measured and recorded if possible. Their presence or absence can be noted for follow-up but is not included in the response evaluation. For example, effusions cannot be measured, nor can lesions with necrotic centers (Skeel, 2011b).
- f) Using RECIST criteria: See Table 2.
  - (1) Time to progression is a valuable indicator in cases when treatment results in disease stability despite failure to produce measurable shrinkage. This can be used as an indicator of disease status when there is no measurable disease at the start of therapy, given the limitations of current RECIST 1.1 criteria (Skeel, 2011b).
  - (2) Follow-up should be protocol specific.
    - (a) Every other cycle (six to eight weeks) is reasonable for follow-up.
    - (b) Patients who discontinue therapy because of deterioration of their health condition without evidence of progressive disease are identified as *symptomatically deteriorated* and not included in the partial response, stable disease, or progressive disease groups.
    - (c) At the conclusion of treatment, follow-up tests and schedules are based on the goal of the study. If time to a specific event, such as recurrence or death, is the primary end point of the study, measurements must be compared to the baseline.
    - (d) The duration of overall response is measured from when the measurement criteria were met for complete or partial response until the first date a recurrence or progressive disease was measured.



2. Tumor burden: The inverse relationship between the number of tumor cells and response implies that the smaller the tumor, the higher the rate of response (Tortorice, 2011). As tumor mass increases, the growth rate slows, decreasing the effectiveness of antineoplastic therapy. Additionally, large solid tumors may have inadequate blood flow, which inhibits the ability of the chemotherapy to reach the entire tumor (Tortorice, 2011).
3. Rate of tumor growth: *Tumor doubling time* (time for the tumor to double in mass) and *growth fraction* (proportion of proliferating cells in relation to the total number of tumor cells) are important factors affecting

**Table 3. Performance Status Scales**

The Karnofsky Performance Status scale has been used in oncology, hospice, case management, and other healthcare settings since 1949. It is a tool for classifying patients on a scale from 0 to 100 according to their level of functional impairment. The Karnofsky scale is designed for patients age 16 and older.

Rating	Description
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Able to carry on normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance but able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission indicated although death not imminent
20	Very sick; hospital admission necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

The Eastern Cooperative Oncology Group, World Health Organization, and Zubrod Performance Status scales also are used to classify patient responses to treatment. These scales are designed for patients age 16 and older.

Grade	Description
0	Fully active; able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

The Lansky Performance Scale is used to classify pediatric patients (younger than 16 years old) according to functionality.

Score	Description
100	Fully active
90	Minor restriction in physically strenuous play
80	Restricted in strenuous play; tires more easily, otherwise active
70	Both greater restrictions of and less time spent in active play
60	Ambulatory up to 50% of time; limited active play with assistance/supervision
50	Considerable assistance required for any active play; fully able to engage in quiet play
40	Able to initiate quiet activities
30	Needs considerable assistance for quiet activity
20	Limited to very passive activity initiated by others (e.g., watching TV)
10	Completely disabled, not even passive play

Note. Based on information from National Marrow Donor Program & Medical College of Wisconsin, 2009; Skeel, 2011b.

response. Cytotoxic chemotherapy agents are most effective if given during the growth phase of the tumor, when a high percentage of cells are susceptible to the effects of that agent (Skeel, 2011a; Tortorice, 2011).

#### 4. Hormone receptor status

a) Presence of estrogen receptors (ERs) and/or progesterone receptors (PRs) is prognostic for breast cancer. Patients who are ER/PR positive demonstrate better overall survival rates (Yackzan, 2011). Tumors that grow more rapidly in the presence of a specific hormone may be suppressed with an antihormonal agent.

b) Hormone receptor status has become increasingly important in cancer therapy.

#### 5. Drug resistance: Many patients experience relapse because tumors become resistant to the drugs used to treat them (McDermott, Downing, & Stratton, 2011).

a) Genetic instability of tumor cells and the emergence of drug resistance are currently considered the most significant determinants of tumor response to treatment (Tortorice, 2011).

b) Complex biochemical pathways involving a multitude of receptors and enzymes are implicated and depend upon the type of cell and chemotherapy agent (Tortorice, 2011).

c) Research points to a complex interaction among cytotoxic agents, chemical messengers (transporters that deliver drugs to the tumor), and the genetic ability of malignant cells to avoid chemotherapy-induced apoptosis because of their high rate of genetic instability (Gaddis & Gullatte, in press; Tortorice, 2011).

d) Genomic changes, originally presenting in small subclones of cancer cells, often underlie acquired resistance, such as *ABL* mutation in chronic myeloid leukemia and *MET* in non-small cell lung cancer. Genomic differences have an important role in determining how a given cancer will respond to treatment (McDermott et al., 2011).

e) Tumor cells may be inherently resistant to antineoplastic agents or develop resistance after drug exposure because of the emergence of resistant clones. Single-agent resistance or multidrug resistance (MDR) can occur and may be caused by a number of factors.

(1) Insufficient dosing may lead to the development of resistant cell clones arising from random mutations in cellular DNA.

(2) Chemotherapy may kill sensitive cells while sparing cells resistant to treatment administered (Tortorice, 2011).

(3) MDR occurs when malignant cells are exposed to cytotoxic agents possessing dissimilar mechanisms of action and appears to be caused by mutations in the malignant cells' regulatory system (Tortorice, 2011). Several pathways are thought to be responsible for MDR, including alterations in the metabolism of chemotherapy within the tumor, the ability of tumor cells to repair damaged DNA (thus bypassing apoptosis), and decreased uptake by formerly susceptible cells (Tortorice, 2011). MDR pathways include the following.

(a) Overexpression of the *MDR1* gene, which encodes for the cell membrane efflux pump P-glycoprotein (P-gp), is believed to cause resistance by its ability to remove toxic molecules (e.g., chemotherapy) from inside the cell before the drug can reach the DNA. The presence of P-gp is a poor prognostic indicator (Gonzalez-Angulo et al., 2007; Tortorice, 2011).

(b) Resistance to topoisomerase drugs (e.g., doxorubicin) can occur when the tumor develops the ability to change the binding properties of topoisomerase enzymes (Tortorice, 2011).

- (c) MDR can occur from increased levels of normally protective enzymes (e.g., glutathione S-transferase), which facilitate the elimination of platinum compounds and alkylating agents from malignant cells (Tortorice, 2011).
- (4) Impaired metabolism may result in reduced drug activation or increased drug deactivation.
- (5) Other types of resistance
  - (a) Acquired resistance is the result of further mutations after exposure to additional drugs and nongenetic mechanisms (Lackner, Wilson, & Settleman, 2012). *KRAS* mutations contribute to the acquired resistance of colorectal cancers treated with agents targeted against epidermal growth factor receptor (EGFR). *KRAS* mutations account for 40%–50% of relapses among patients with colorectal cancers (Azvolinsky, 2012).
  - (b) Emergent resistance occurs after the affected cells survive an exposure to an environmental carcinogen (e.g., tobacco).
  - (c) Cells may be temporarily less responsive because of changes in environment or stimuli or may have permanent resistance (Freter & Goldie, 2012).
  - (d) Poor blood supply to the tumor may cause temporary resistance, which prevents delivery of a therapeutic dose of drug (Tortorice, 2011).
- (6) Overcoming drug resistance remains a high priority. Recurrences are presumably attributed to the inability to assess which tumors are resistant to treatment when administering in an adjuvant setting (Dawood et al., 2008). Researchers continue to look for ways to deactivate P-gp in malignant cells and to identify new agents that alter the apoptotic pathways, increase the effectiveness of current chemotherapy, and interact with specific characteristics associated with the DNA in malignant cells (Barton-Burke & Wilkes, 2006).

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