The Rationale for Fractionation in Radiotherapy

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The use of radiotherapy as a cancer treatment is common, so an appreciation of the biologic effects of radiation at a cellular level is essential to help nurses prepare their patients for the challenging journey ahead using appropriate lay language. The four Rs of radiotherapy (repair, redistribution, reoxygenation, and repopulation) are well established with regard to the principles of radiotherapy; however, these concepts appear undeveloped in nursing literature. The current article aims to succinctly explain how radiation impacts cancer and provides rationale as to why radiation treatment is delivered during a number of sessions. Through receipt of this knowledge, oncology nurses will be better equipped to communicate more efficiently and effectively with their patients.

Using radiation to treat cancer is not a recent innovation; in fact, radiotherapy was used successfully for the first time in 1899 to cure a patient with basal cell epithelioma (Abeloff, Armitage, Niederhuber, Kastan, & McKenna, 2008). Despite yielding success, early treatments often involved very large single doses in a bid to completely eradicate tumors; this was met with many complications, including extensive skin toxicities. Henri Coutard was the first to use smaller doses of radiation therapy delivered over several weeks to overcome the acute toxicity induced by a large single fraction. By about 1934, Coutard’s work became the basis of what is known today in clinical oncology as fractionation (Souhami & Tobias, 2008).

Cellular kill occurs when critical targets within the cell are damaged by radiation and the cell is unable to repair the damage. DNA is most likely to be a critical target for the biologic effects of radiation (Damrot et al., 2009). That has been established following measurement of DNA damage after radiation, which consistently correlates with cell death (McMillan, Tobi, Mateos, & Lemon, 2000). Studies also indicate that cells that are inhibited from repairing DNA damage, or that are naturally deficient in DNA repair enzymes, show distinct radiosensitivity (Kühne et al., 2004).

Direct and indirect damage can break bonds in DNA. These broken bonds can result in damage to one or both strands of DNA. Single-strand DNA breaks are repaired relatively easily using the opposite strand as a template. Therefore, single-strand breaks are not strongly related to cell killing. Double-strand breaks, however, represent the most important factor in determining cell kill. In double-strand breaks, the chromatin is destroyed in two places, which ultimately results in cell death because the cell is unable to repair the damage. Radiation also can work by inducing apoptosis, which is also known as programmed cell death (Rothkamm, Krüger, Thompson, & Löbrich, 2003). Radiation is, therefore, an established and appropriate method to kill cancerous cells.

Radiation’s Effect on Cell Replication

The biologic basis of fractionation in radiation therapy takes advantage of what are known as the “four Rs” of radiobiology: repair, redistribution, reoxygenation, and repopulation.

Repair

Cells have complex mechanisms responsible for repairing radiation-induced damage. One of the clearest demonstrations of the cell’s ability to repair radiation damage is the phenomenon called sublethal damage repair (Heideker, Lis, & Romesberg, 2007). Following radiation exposure, cells can repair any sublethal or indirect damage. As explained earlier, direct DNA damage can be rare; the more exposures to small doses of radiation, the more likely direct DNA damage will accumulate (Pajonk, Vlashi, & McBride, 2010). With sufficiently high doses comes increased cell destruction, but this comes with a price of increased toxicities to normal cells and tissue, as well. Small doses of radiation will allow normal cells to repair, thereby reducing toxicity. According to Corner and Bailey (2008),
cancerous cells repair at a slower rate than normal cells; therefore, with fractionated regimens, all cells can be damaged, but cancerous cells specifically repair slower, thereby decreasing their number in the body.

Traditionally, a linear-quadratic model of cell-survival after radiation is used to predict tumor response and normal tissue toxicity from fractionated radiation (Cox & Ang, 2002). The model describes the amount of cell killing following radiotherapy and illustrates the range of the amount of cell death for both tumor cells and normal tissue cells. The model is particularly useful in radiobiology, as it can provide an overview to clinicians regarding the amount of tumor cell kills versus the amount of normal tissue cell kills. Oncologists try to find a level of radiotherapy that balances tumor cell kill and normal tissue cell kill. Although the linear-quadratic model has its limitations, including the overestimation of cell killing from radiation (Guerrero & Li, 2004), it does provide insight into predicting tumor control and normal tissue toxicity. The linear-quadratic model often is used as the basis for determining fractionation schemes (Jones, Dale, Finst, & Khaksar, 2000). The Royal College of Radiologists’ (2006) radiotherapy dose-fractionation guidelines provide fractionation schemes for different organs based on research. Various organs have different sensitivity to radiation, so the same fractionation schedule cannot be used in all cancers because different tissues repair at different rates. Figure 1 provides a hypothetical illustration of the linear-quadratic model.

Generally, normal tissue effects are more greatly impacted by fraction size than are acute effects, which is why 1.8–2 Gy fractions are considered standard in the irradiation of most diseases in which the patient is expected to survive long enough to potentially experience late radiation-induced toxicity (Royal College of Radiologists, 2006). The linear-quadratic model is well placed to illuminate the short- and medium-term effects of radiotherapy on normal tissue cells; however, with regard to long-term effects, the linear-quadratic model is less effective because the radiation damage to slower-responding tissues (e.g., thyroid, bone) is not evident until much later (e.g., more than five years) (Cox & Ang, 2002; Glastein, 2008). That illustrates an element of unpredictability in planning if long-term effects of irradiation cannot be estimated regardless of fraction size. These sentiments are echoed by Milano, Constine, and Okunieff (2008).

**Redistribution**

The radiosensitivity of human cells varies according to the position in the cell cycle. Cells in mitosis or late G2 phase generally are the most sensitive. Cells late in the DNA-synthetic stage, or late S, are more resistant (Cox & Ang, 2002). When exposed to a single large dose of radiation, most of the surviving cells are likely to be in the resistant phases of the cell cycle. An immediate second dose of radiation, therefore, would be less effective than the first, as the population is resistant. Radiotherapy that takes place over multiple sessions is more effective because it allows the cells in the G2 phase of the cell cycle to move around to mitotic phase of the cycle (Harrington, Jankowska, & Hingorani, 2007). Fractionation benefits as doses of radiation timed apart can target previously resistant cells (Pawlik & Keyomarsi, 2004).

**Reoxygenation**

According to the oxygen fixation hypothesis, in the absence of oxygen, the chemical changes produced in the target molecule may be repaired; if oxygen is present, the damage is fixed (i.e., made permanent and irreparable) (Fyles et al., 2002). Many tumors of various histologic types have been evaluated in different animal species and, according to Cox and Ang (2002), the proportion of hypoxic cells in these tumors usually ranges from 10%–15%. Hypoxia in tumors can result from two quite different mechanisms. Chronic hypoxia results from the limited distance that oxygen can diffuse in respiring tissues. Regions of acute hypoxia within a tumor, by contrast, result from a temporary blockage to the blood vessel. If the blockage were permanent, the cells downstream would eventually die and be of no further concern (Fyles et al., 2002). However, evidence suggests that tumor blood vessels open and close randomly and, thus, that different regions of the tumor become hypoxic intermittently. At the moment when a radiation dose is delivered, some proportion of the tumor cells may be hypoxic; if radiation were to be delayed, a different group of cells may be hypoxic (Chan et al., 2008).

When a tumor that consists of a mixture of oxygenated and hypoxic cells is irradiated, the oxygenated cells are more likely to be killed because of their greater sensitivity to radiation. The survivors, therefore, will most likely contain hypoxic cells (Nordsmark et al., 2005). The situation is not static because over time, after irradiation, the proportion of hypoxic cells tend to shift and return to a preirradiation level. That shift is a result of reoxygenation (Nordsmark et al., 2005).

Each dose of radiation reduces the oxygenated cells of the tumor, having little effect on the hypoxic cells. If the interval between radiation doses is long enough to allow reoxygenation to take place, then hypoxic cells can be targeted. Few hypoxic cells are killed with each dose of radiation, but they are more potently destroyed after they have been exposed to oxygen. Single-dose radiation is ineffective because of the resistance of the hypoxic cells; however, if the radiation is split into fractions delivered over time, with the interval between fractions being sufficient for reoxygenation, the presence of hypoxic cells will have a minimal effect (Zöller & Streffer, 2002).
Repopulation

Repopulation is the last of the four Rs and it refers to the increase in cell division that is seen in both normal and malignant cells at some point after radiation has been delivered (Harrington et al., 2007). As the total treatment time to deliver a dose of radiation lengthens, cells within a tissue have the ability to repopulate.

Cell-kill increases as radiation dose increases. Early-responding tissues such as skin, mucosa, bone marrow, and tumor cells are likely to experience acute toxicities, which occur during the radiation course or within a few weeks thereafter. They exhibit rapid cell turnover from surviving stem cells. The intensity of the toxicity in these tissues reflects the balance between cell killing and the regeneration of cells from surviving stem cells (Suwinski et al., 2003). That balance depends primarily on accumulation of radiation dose. Larger fraction sizes are a factor in determining the severity of acute toxicities, with larger fraction sizes resulting in higher toxicity than smaller ones.

Dose rate not only correlates with tumor killing but also with toxicity. That double-edged sword means that stronger doses mean greater killing potential but, combined with acute toxicities, could mean the patient may not be able to complete the radiotherapy program because of toxicities. That may allow for accelerated tumor repopulation.

Delaying initiation of treatment is advocated to be better than forcing delays during treatment. If overall treatment time is too long, the effectiveness of later dose fractions will be ineffective because of the triggering of rapid repopulation (Bese, Sut, & Ober, 2005).

The enhanced tumor cell division that occurs during a course of radiotherapy is generally viewed negatively as the driving force behind accelerated repopulation, but it may also serve to make a tumor more susceptible to radiation-induced death by causing it to enter mitosis with unrepaired DNA damage, a situation Harrington et al. (2007) termed a mitotic catastrophe.

Effects of Radiotherapy Fractionation

Certain tissues manifest evidence of radiation effects in a matter of hours to days, and these are classified as acutely responding tissues (see Table 1). Acutely responding tissues include the bone marrow, ovary, testis, lymph node, salivary gland, small bowel, stomach, colon, oral mucosa, larynx, esophagus, arterioles, skin, bladder, capillaries, and vagina.

Tissues that do not reveal acute effects of clinical significance but show evidence of damage in a matter of weeks to a few months after radiotherapy often are termed subacutely responding tissues. Those tissues include lung, liver, kidney, heart, spinal cord, and brain.

If given sufficient doses of radiation, all tissues can manifest late effects. However, several tissues are characterized as showing little, if any, evidence of acute effects but have well-recognized late effects. Those tissues include lymph vessels, thyroid, pituitary, breast, bone, cartilage, pancreas, uterus, and bile ducts.

Systemic effects of ionizing radiation are determined by the proportion of the body irradiated, the specific organs included, and the dose received. Doses of 100 Gy or higher cause patient death in a matter of hours from effects on the central nervous system and cardiovascular collapse; intermediate doses of 10–20 Gy result in cell death in several days, caused by elimination of the intestinal epithelium with diarrhea. Lower doses, from 1–5 Gy, result in depopulation of hematopoietic stem cells; cell death can occur several weeks after the exposure from infection or bleeding. According to Cox and Ang (2002), individuals can survive large doses with supportive treatment, including antibiotics and transfusions of blood products. However, side effects exist in virtually all patients.

The following are just a few common possible side effects of radiotherapy. These are by no means comprehensive and serve only to illustrate the destructive potential of radiation. Depending on the area irradiated, side effects include erectile dysfunction, dysuria, fistula formation, hematuria (Pinkawa et al., 2010), oral mucositis (D’haese et al., 2005), fatigue (Brunner & Scott-Brown, 2010), tooth decay (Corner & Bailey, 2008), nausea and vomiting (Soulami & Tobias, 2008), radiation pneumonitis, radiation fibrosis, nonproductive chronic cough formation (Goldman, Wennberg, Svane, Bylund, & Lind, 2010), cerebral edema and cognitive dysfunction (Baujat et al., 2010), dysphasia (Carroll et al., 2008; Peponi, Glanzmann, Willi, Huber, & Struder, 2011), blindness, hearing loss (Petsuksiri et al., 2011), acute nephritis, cystitis, and vaginal stenosis (Cairns, Harry, Sarkar, & Parkin, 2008).

In one of the largest studies of its kind ever conducted, Brenner, Curtis, Hall, and Ron (2000) used data to evaluate the outcome of 51,584 men with prostate cancer treated with radiation and 70,539 treated with surgery. The study showed that the men who were treated with radiotherapy were 6% more likely to develop any form of cancer at any time compared to the group who did not have radiation. The risk of second malignancy grew to 34% after 10 years. The large study presented a correlation between rate of second malignancy and treatment with radiation. Radiation can cause chemical changes in a cell that, in turn, cause a mutation leading to additional cancers.

Radiation has been shown to be a double-edged sword to patients with cancer. On one hand it represents cure or symptom control, but on the other it represents a high probability of some degree of toxicity. Fractionation has been demonstrated to improve the therapeutic ratio relating to patients with cancer, whereby complications are reduced and tumor kill has been increased.

Hyperfractionation Versus Hypofractionation

Advanced technologies provide an opportunity for the acceleration of treatment without excessive risk to normal tissue (Vikram, Coleman, & Dey, 2009). Also provided is the prolongation of treatments, which can have the advantage of avoiding acute reactions and allowing adequate reoxygenation in tumors. However, excessive prolongation can decrease acute reactions without necessarily sparing late injury, and it may
allow surviving tumor cells to proliferate or repopulate during treatment. Two separate fractionated strategies are hyperfractionation and hypofractionation.

Hyperfractionated treatment, the delivery of radiation in small-dose fractions (e.g., 2–3 times per day), aims to improve the therapeutic ratio, reducing the dose given in each fraction, so as to reduce the late side effects while also permitting an increased total dose to the tumor. Bajaj et al. (2010) determined that, based on 6,515 patients from 15 trials, hyperfractionation provided the greatest benefit to patients with head and neck cancer because of a decrease in late-stage toxicity associated with the regimen.

Hypofractionated treatment gives a smaller number of radiation fractions, but the dose per fraction is increased. The total dose is lower than conventional treatments because of enhanced late side effects. Hypofractionated regimens often are used for palliative treatments so that the course of treatment can be shorter. That has been supported by Cochrane Reviews written by Lester, MacBeth, Toy, and Coles (2009) investigating non-small cell lung cancer and McQuay, Collins, Carroll, and Moore (2008) investigating bone metastases.

Salminen et al. (2011) hasten to warn that the avoidance of late effects relating to hypofractionation obviously cannot be confirmed without long and careful follow-up. Several trials of hypofractionation in common cancers have shown comparable clinical outcomes to conventional fractionation. Common cancers such as breast cancers can be successfully treated in three weeks rather than in five weeks (Dewar et al., 2007). In a Cochrane Review by James et al. (2010), it was found that of the 7,095 women studied, no significant differences existed in survival rates or tumor recurrences, but skin toxicity was significantly reduced in patients undergoing hypofractionation because of shorter radiation exposure. Fujii et al. (2008) and Guenzi et al. (2010) also showed favorable results using hypofractionation. Additional recommended hypofractionated regimens were reported by Brenner (2003), Nedzi (2008), Shen et al. (2010), and Uematsu et al. (2005).

Acceleration of treatment is another mechanism employed, but it can be difficult because the acute effects become limiting. In a study of 900 patients, Overgaard et al. (2010) found that an accelerated treatment relating to patients with head and neck cancer yielded no significant late effects; however, acute late effects were in some cases almost doubled, with 10% in the accelerated group reporting severe reactions compared to almost 5% in the control group. In some accelerated treatments, a rest period is imposed in the middle of the treatment or the dose must be reduced slightly, with acute effects being the limiting factor (START Trialists’ Group, 2008a, 2008b). The intent of any accelerated treatment is to reduce repopulation in rapidly proliferating tumors. Late effects should show little or no change because the number of fractions and dose per fraction is unaltered (Njeh, Saunders, & Langton, 2010).

The concept of fractionation extends beyond a simplistic definition of giving smaller doses of treatment over time. Hyperfractionation, hypofractionation, and accelerated fractionation are just some regimens employed by radiobiologists that can prove more effective than standard fractionation on specific tumor sites, thereby improving therapeutic outcome for patients with cancer.

### Implications for Nursing Practice

Many oncology nurses are unaware of the key concepts of radiobiology because of its complexity. The current article should provide some insight into how radiation impacts not only a cellular level but a human level. To provide patients with cancer with the best care, nurses must be aware of the rationale for radiotherapy treatments being spread across a number of days. Knowing the treatment area and daily and total radiation dose also is helpful. In addition, nurses must be able to articulate to a patient, in lay language, why the type of radiotherapy they receive is not always the same. That knowledge will enable a nurse to discuss, with confidence, the process of being treated with radiotherapy to the patient.

### Conclusion

Little doubt exists that fractionation provides a more therapeutic means of delivering radiation to patients with cancer (Bibault et al., 2011). Its volatile nature is advantageous in killing tumor cells; however, its enormous potential for toxicity should never be underestimated. The prospect of radiotherapy adds considerably to the fear and anxiety already present following a cancer diagnosis. Fear, misunderstandings of the use of radiation treatment, and negative attitudes regarding its effectiveness

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**TABLE 1. Acute Effects Related to Radiotherapy**

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<tr>
<th>Organ or System</th>
<th>Symptom</th>
<th>Management</th>
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<tbody>
<tr>
<td>Bladder</td>
<td>Dysuria</td>
<td>Analgesia</td>
</tr>
<tr>
<td>Bowel</td>
<td>Nausea</td>
<td>Antiemetics</td>
</tr>
<tr>
<td>Hematopoietic</td>
<td>Anemia</td>
<td>Transfusion</td>
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<tr>
<td>Liver</td>
<td>Radiation hepatitis</td>
<td>Fluids, antiemetics, analgesia</td>
</tr>
<tr>
<td>Lung</td>
<td>Pneumonia</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Oral mucosa</td>
<td>Ulceration</td>
<td>Analgesia</td>
</tr>
<tr>
<td>Rectum</td>
<td>Bleeding</td>
<td>Corticosteroid suppositories</td>
</tr>
<tr>
<td>Skin</td>
<td>Erythema</td>
<td>Aqueous cream</td>
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*Note. Based on information from Souhami & Tobias, 2008.*

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<th>Implications for Practice</th>
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<td>▶ With a better understanding of the 4 Rs of radiobiology, nurses will be better placed to provide insight on the impact of radiotherapy, not only at a cellular level, but also at a human level.</td>
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are abundant in the literature, as presented by Hammick, Tutt, and Tait (1998), whose qualitative study indicated more than 30% of adults interviewed perceived radiotherapy in a negative light. Holistic patient care involving all disciplines, coupled with adequate information given relating to the treatment course, can greatly supplement radiotherapy and enhance the effectiveness of the treatment, thereby making it more therapeutic (Lenzi, Baile, Constantini, Grassi, & Parker, 2011).

References


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