CHAPTER

4 Interaction of Chemotherapy and Radiation

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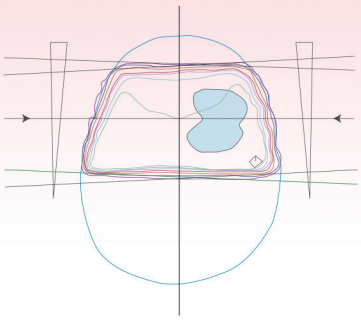


Oncology has increasingly become a multidisciplinary field of medicine: (1) Surgery remains the definitive local treatment modality; (2) Chemotherapy remains the definitive systemic treatment modality; and (3) Radiation therapy is the definitive loco-regional treatment modality. Although, historically, these approaches have predominantly been used exclusively of one another, the past 25 years have seen an explosion of both preclinical and clinical efforts that have sought to combine these therapies for improved outcomes, including improved local and regional control, overall survival, cosmesis, and organ preservation. We have learned a great deal about the interactions between chemotherapy and radiation from clinical trials that have combined these treatment modalities in sequential and concomitant regimens. In addition, laboratory investigations have demonstrated key molecular targets and pathways that can potentially be exploited for improved outcome. Indeed, the combination of chemotherapy and radiation has changed the management approach in several disease sites, which are broadly reviewed here.

HISTORICAL PERSPECTIVE

Radiosensitization and chemosensitization are complex concepts that have many different interpretations and have been used to describe many different interactions.[1,2] The use of radiation and chemotherapy for mutual or even simultaneous sensitization adds to the intricacies of these interactions. Indeed, more than 100 years ago, radiation treatment and benzene systemic therapy were combined for leukemia treatment.[3] However, probably the best historical model of chemotherapy and radiation therapy interaction is that of 5-fluorouracil.

5-Fluorouracil

In the 1950s, the halogenated pyrimidine, 5-fluorouracil (5-FU), was combined with external beam irradiation (EBRT) after this class of drug was determined to have anticancer properties.[4] In the last 50 years, 5-FU has been successfully combined with radiation to treat a variety of gastrointestinal cancers, as well as cervical cancer and head and neck cancers.[5] The route of administration and scheduling of 5-FU has been manipulated many times in an attempt to reduce toxicity and maximize tumor control. What began as bolus delivery at the beginning and end of a fractionated radiation treatment course ("Moertel" regimen) has progressed to protracted venous infusion (PVI) and now to twice daily oral 5-FU analog formulations. These approaches have allowed for an increase in cumulative dose of the drug, decreased chemotherapy toxicity, and improved radiosensitization. Indeed, 5-FU has proven to be a staple drug in the armamentarium of medical oncologists and a key radiosensitizer for the radiation oncologist.

RATIONALE

Limitations in Current Therapeutic Approach

Over the past several decades, we have seen the great technological advances in surgery and radiation while novel systemic agents are being developed at a never-before-seen pace. Nevertheless, cancer morbidity and mortality remain major problems. The advent of combined modality therapy has sought to improve on the limitations that surgery, chemotherapy, and radiation carry independently. For several decades, radiation has complemented surgery by improving loco-regional control. Unfortunately, tumor-specific and patient-specific factors limit both surgical and radiation success. In this chapter, we will focus on the multiple ways that systemic therapies are used in an attempt to overcome the shortcomings of radiation treatment. The presence of micrometastatic disease, disease outside of our treatment fields, and the inability to deliver adequate dose to the target region as a result of normal tissue toxicity risk are some of the most frequently cited reasons. In addition, tumors may contain regions of relative hypoxia or subpopulations of cells with intrinsic or acquired resistance to radiation damage. We will briefly review the current understanding of these topics.

Tumor Detection

If ionizing radiation were without normal tissue toxicity, tumor detection would be immaterial, and radiotherapy could be delivered to the entire body much like chemotherapy. Obviously this is not the case, and much like surgeons, we must be able to identify the tumor so that we can precisely and accurately target it with our radiation akin to "carving out" a tumor with a scalpel. Fortunately, advances in radiology have dramatically improved our ability to detect tumor location and extent. Whereas computed tomography (CT) and magnetic resonance imaging (MRI) provide excellent anatomic information, when combined with biological or functional imaging such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), the radiation oncologist can more confidently define tumor vs. nontumor. Emerging MRI sequences including dynamic contrast enhanced and fast imaging employing steady-state acquisition (FIESTA) ultrafast pulse sequence approaches, and MR spectroscopy are providing improved anatomic (and biologic in the case of MR spectroscopy) imaging for surgeons and radiation oncologists. Nevertheless, the resolution of our current techniques (on the order of 5 mm for PET resolution[6]) and high false-negative rates with small tumors still limit our ability to identify microscopic tumor extent and micrometastatic disease. Future technologies such as PET/MRI as well as novel radiopharmaceuticals may provide improvements.

Inherent and Acquired Resistance

We know, empirically, that certain tumors have inherent radiation resistance pathways that manifest with high rates of local failure following radiation. In some cases, such as in pancreatic cancer, it is difficult to deliver adequate doses of radiation to the target because of the limitations in dose tolerance of surrounding bowel, kidney, and liver. However, there are other tumors with extremely high local failures despite dose escalation. A prime example is glioblastoma multiforme, which has local recurrence rates approaching 100%. Biological factors within the tumor or tumor microenvironment also generate resistance. Figure 4-1 summarizes some of the major

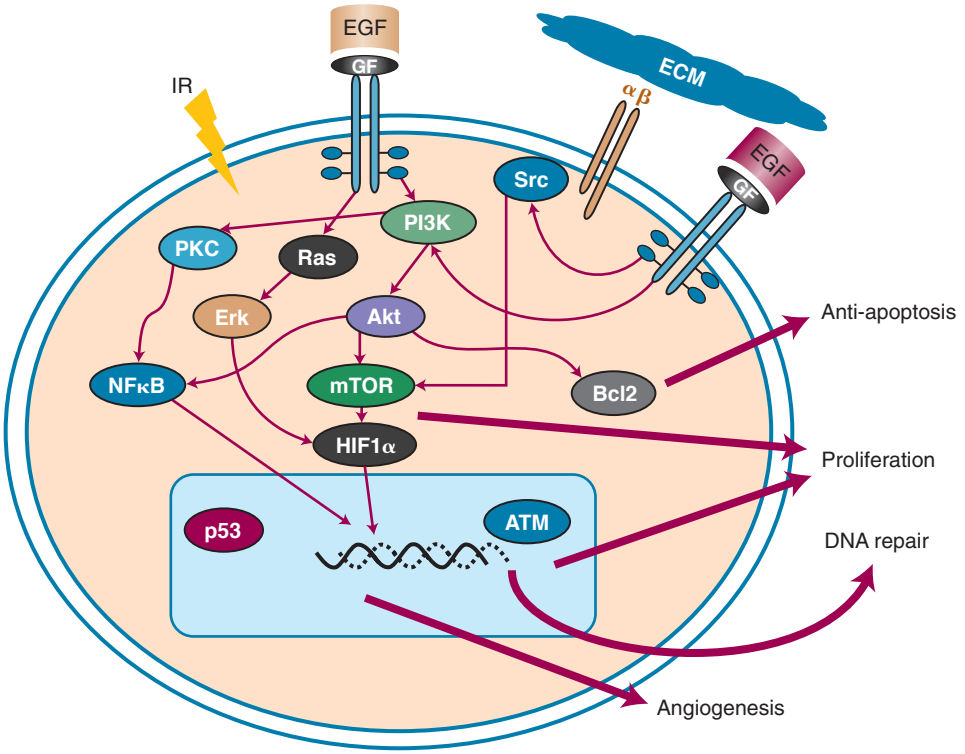


Figure 4-1 Schematic of radiation-induced signal transduction cascades indicating pathways leading to antiapoptosis, proliferation, DNA repair, and angiogenesis.

resistance pathways within tumors. Later in this chapter we will describe how chemotherapeutics can potentially mitigate these resistance pathways.

Increased Toxicity

In the original treatise by Steel and Peckham on combining chemotherapy and radiation,[7] it was assumed that each modality functioned independently in both beneficence and toxicity. However, it is abundantly clear that concurrent chemoradiation has increased toxicity suggesting some level of overlapping toxicity, chemosensitization by radiation, or radiosensitization by the chemotherapy. Because chemoradiation is often used when tumors have wide anatomic extension (thus, precluding surgery), the volume of normal tissue irradiated, and therefore, at risk of toxicity, is larger. In some cases, a patient has comorbid conditions that prevent aggressive therapy as well.

Therapeutic Index

The features described previously generate the need for a metric to determine efficacy relative to toxicity so that newer approaches can be compared. This metric, known as the *therapeutic index* (or therapeutic ratio) refers to the ratio of the probability of tumor control to the probability of normal tissue toxicity. Typically, the ratio is calculated based on the 50% control rate of tumor versus the 50% normal tissue toxicity. These sigmoidal-shaped curves determine the estimated efficacy versus toxicity of treatment. Figure 4-2 depicts an idealized form of these curves. Therapeutic index has been, and will continue to be, the "holy grail" of cancer therapy. For this reason, it is no surprise that it takes careful treatment planning to try to achieve maximal tumor cell kill while also sparing normal tissue in hopes of preserving function. There are a host of technological factors that impact this therapeutic ratio.

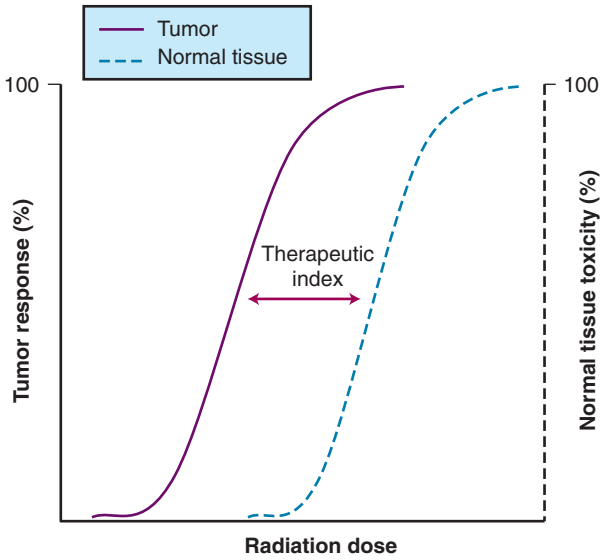


Figure 4-2 Graph of an idealized therapeutic index curve. The therapeutic index is indicated as the difference in probability of tumor response and probability of normal tissue toxicity. The greater the separation of these two curves, the greater the therapeutic index.

Certainly our ability to correctly identify tumor versus normal tissue will affect therapeutic ratio. The expanding use of PET, MRI, and SPECT imaging, as described previously, are allowing radiation oncologists to better differentiate target from nontarget. Obviously, the ability to precisely deliver radiation through techniques such as intensity modulated radiation therapy (IMRT), stereotactic procedures, and proton therapy allow us to avoid normal tissue while targeting tumor.

Moreover, our ability to accurately deliver radiation via image guidance (IGRT) has grown by leaps and bounds, which enables smaller margin expansions and will also limit dose to normal tissue. Nevertheless, based on the anatomical location of the tumor, there are technological limits to what can be accomplished with radiation in and of itself. Therefore, additional improvement will likely rely on the interaction of systemic agents with our technologically advanced radiation delivery methods.

Strategies to Improve Therapeutic Index

The fundamental approach to improving outcomes through combined modality therapy has its basis on the theoretical strategies set forth by Steel and Peckham in 1979.[7] Their seminal paper defined four potential means by which combined therapy could improve the therapeutic index and were described as (1) independent toxicity, (2) normal tissue protection, (3) spatial cooperation, and (4) enhanced tumor response. As will be discussed, the first theoretical concept may not actually function as in the original intent. However, the latter three concepts are relevant for modern strategies of combining drugs with radiation. Additional mechanistic considerations have been identified in recent years that expand on Steel and Peckham's "exploitable mechanisms in combined radiotherapy-chemotherapy" that was described more than three decades ago.[7] These newer concepts of biological cooperation and temporal modulation are impacting current investigative strategies for improving the therapeutic index.

Independent Toxicity

One of the main concepts suggested by Steel and Peckham as a means to improve the therapeutic index is to select a chemotherapeutic regimen with a distinct toxicity profile from that of radiation. This ideal selection of nonoverlapping toxicities could allow for increased tumor cell kill with minimal impact in terms of tissue toxicity. Although this has been pursued in therapy selection, the actual success in finding independent toxicity has been elusive. However, the inverse relationship has been implemented to a great extent. Indeed, the avoidance of drugs with overlapping toxicities is standard of care practice, for instance, avoiding methotrexate with cranial radiation, Adriamycin with breast irradiation, or bleomycin with lung irradiation.

Normal Tissue Protection

The identification of clinically relevant agents that promote normal tissue protection without protecting tumors has provided little in terms of therapeutics. Limited success has been achieved with the free radical scavenging agent, amifostine (WR-2721), which appears to be selectively taken up by normal tissue relative to tumor where it is converted into the active thiol metabolite, WR-1065.[8] Although amifostine has been shown to protect against xerostomia in head and neck cancers treatment (Table 4-1) and to limit renal toxicity from cisplatin, several clinical trials have failed to show an advantage to amifostine use. Undoubtedly, investigations into novel radioprotectors will continue with the potential to impact the therapeutic ratio.

Spatial Cooperation

The concept of spatial cooperation implies that chemotherapy and radiation therapy are independent players with systemic therapy acting systemically, that is, targeting micrometastatic disease, and radiation therapy acting loco-regionally. Because

TABLE 4-1 Possible Drug–Radiation Interactions

Mechanism	Example	Notes
Normal Tissue Protection	Amifostine in head and neck cancers	Reduces xerostomia rates from RT alone
Spatial Cooperation	Early stage breast cancer with adjuvant chemotherapy PCI in SCLC	RT provides locoregional control for breast cancer but no impact on DM SCLC chemotherapy does not effectively cross BBB → RT can effectively treat the brain
Biological Cooperation	Targeted therapies inhibit prosurvival/proliferation pathways within tumors	Kinase targeted agents including tyrosine kinase inhibitors such as dasatinib and sunitinib as well as monoclonal antibodies such as cetuximab and bevacizumab; mTOR inhibitors
Temporal Modulation	Drugs that impact tumor response in between fractions, namely targeting repair, repopulation, reoxygenation, and redistribution.	This is essentially a composite of several of the other mechanisms but requires concomitant delivery of the drug rather than sequential.
Increased DNA Damage	Drugs that incorporate into DNA	5-FU and platinum are classic examples
Inhibition of DNA Repair	DNA intercalators and nucleoside analogs can disrupt repair and enhance radiation cytotoxicity	Alkylators, antimetabolites, platinum, and topoisomerase inhibitors are a few examples
Cell Cycle Effects	Most chemotherapeutics are cell cycle specific (except alkylators) Cell cycle arrest in radiosensitive phases (microtubule targeting agents at M-phase) Elimination of radioresistant cells (S-phase)	Taxanes, epothilones, 5-FU, gemcitabine, and topoisomerase inhibitors are good examples
Targeting Repopulation	Conceivably any systemic agent that has at least cytostatic properties can prevent repopulation	Molecularly targeted agents as well as chemotherapeutics (particularly antimetabolites) can function this way
Hypoxia Targeting	Mitomycin C and tirapazamine selectively targeting hypoxic cells Tumor shrinkage by chemotherapy decreases interstitial pressure and improves oxygenation	Taxanes and other chemotherapies that can produce tumor shrinkage are indirect means (given as induction therapy) whereas mitomycin C and tirapazamine are directly affecting hypoxic cells.
Tumor Microenvironment Targeting	Antiangiogenesis promotes vascular renormalization	Bevacizumab in glioma

5-FU, *5-Fluorouracil;* BBB, *blood-brain barrier;* DM, *distant mets;* PCI, *prophylactic cranial irradiation;* RT, *radiation therapy;* SCLC, *small-cell lung carcinoma.*

these therapies function independently, it could be assumed that a full dose of each will be required to achieve the desired outcome. If the drug and radiation did function completely independently, then concurrent administration should be possible with nonoverlapping toxicities. It is unclear whether a completely independent action can actually be achieved with the chemotherapies that are currently used with radiation treatment, however, because in-field toxicities do occur suggesting some level of localized radiation sensitization. Therefore, sequential therapy is probably the best means to exploit spatial cooperation. Many clinical examples exist for this approach, such as breast cancer with adjuvant chemotherapy followed by radiation, consolidative radiation to bulky disease in lymphoma, or prophylactic cranial irradiation in small cell lung cancer (see Table 4-1).

Enhanced Tumor Response (Cytotoxic Enhancement)

Currently, a tremendous amount of investigative effort is focused on achieving cytotoxic enhancement with combined modality treatment. In other words, the combination of therapies leads to an interaction on some level that generates improved antitumor effect relative to each treatment alone. Interestingly, we have some clinical examples that subtherapeutic, or radiosensitizing, doses of chemotherapy can impact distant disease control suggesting either that increased locoregional control can diminish distant metastatic disease potential or that lower dose chemotherapy can treat micrometastatic disease (i.e., spatial cooperation).

Biological Cooperation

The term, *biological cooperation*, is a newer concept[9] that involves independent targeting of subpopulations of cells within the tumor itself (see Table 4-1). Although similar to the spatial cooperation concept, biological cooperation implies that some portion of the actual radiation target (i.e., in-field) is resistant to radiation, which is the target of the drug given concomitantly. The most prominent example for biological cooperation is hypoxic cell cytotoxins such as tirapazamine. Because hypoxia is a known radiation resistance condition, tirapazamine will target these subpopulations of cells since it is most potent in anoxic conditions. Tirapazamine is discussed in more detail later in this chapter.

Temporal Modulation

The four R's of classical radiobiology, which include reoxygenation, repair, redistribution, and repopulation,[10] refer to factors that are particularly important for fractionated radiation therapy. For example, antiproliferative therapies could prevent accelerated repopulation between fractions, which might not be detectable using single fraction assays, in vitro. Conversely, although DNA damage repair blockade may enhance radiation sensitivity in the tumor, if DNA repair is also inhibited in normal tissue, outcomes may be worse in fractionated therapy.[9] Depending on which factors are most prominent in normal and tumor cells, the therapeutic index can be shifted in either beneficial or detrimental directions. Therefore, temporal modulation implies therapeutics that optimize these four radiobiology factors in between fractionated radiation treatments (see Table 4-1).[9]

POTENTIAL BIOLOGICAL MECHANISMS OF DRUG RADIATION INTERACTION

There are a host of potential mechanisms by which a drug may impact radiation efficacy that are summarized in Table 4-1. Classical definitions of radiosensitizers indicated an enhancement of DNA damage as the critical factor. However, with increased understanding of cancer cell biology, it is apparent that targets other than DNA damage can enhance radiation efficacy. Therefore, a broader defined "radiation enhancer" can impact several potential mechanisms to increase radiation effect.

Increasing Radiation Damage

The classical radiobiology definition of a radiosensitizer implied that the drug would enhance DNA damage. This is accomplished when the drug incorporates itself into the DNA or causes damage to the DNA itself by forming adducts, thereby increasing susceptibility of the DNA to radiation damage. Examples of this type of interaction include 5-FU and cisplatin.

Inhibition of DNA Repair

Cancer cells that can effectively repair DNA damage will have resistance to radiation effect. Therefore, compounds that can interfere with the DNA damage repair signal transduction pathway can potentially enhance radiation damage. Several chemotherapeutics target this process, particularly those that disrupt nucleotide biosynthesis and utilization. Modified nucleotides such as 5-FU, bromodeoxyuridine, gemcitabine, fludarabine, methotrexate, etoposide, hydroxyurea as well as cisplatin fall into this category. Additionally, as will be described, compounds that alter the cell cycle may indirectly inhibit DNA repair.

Cell Cycle Effects

A multitude of preclinical work has identified the G2/M as the most radiation-sensitive and S as the most radiation-resistant phases of the cell cycle.[11,12] In addition, many cytotoxic chemotherapeutics are cell cycle specific. Therefore, agents that can maintain cells in radiation-sensitive phases or eliminate those cells in radiation-resistant phases will cooperate with radiation for enhanced efficacy. Although this is clearly seen in preclinical settings, there is much less direct evidence for this phenomenon in clinical data. Nevertheless, taxanes and nucleoside analogs and modified pyrimidines appear to work in this manner.[13-16]

Repopulation

In normal adult tissue, the rate of cell loss is balanced by that of cell proliferation. When increased cell loss occurs from injury, including radiation treatment, signaling for proliferation occurs resulting in a repopulation. Cancers, however, have an excess of cell proliferation relative to cell loss by their very nature. Therefore, when a subtotal cell loss occurs during fractionated radiation, cancers can also promote increased proliferation. This is known as *accelerated repopulation*. Chemotherapeutics with cytotoxic or even cytostatic effects when given concurrently with radiation, can counteract this repopulation and enhance efficacy.

Hypoxia/Tumor Microenvironment

Solid tumors, particularly those that have grown to any significant size, will contain regions of lower oxygen tension because of the limitations in vascular flow as well as oxygen diffusion within the tumor. Although many tumors trigger angiogenic factors within the tumor, these stimulants manifest as aberrant vasculature often with disorganized architecture. Moreover, larger tumors may have increased interstitial

pressure that leads to further collapse of blood vessels creating hypoxic regions and overt necrosis at times.

Hypoxia is one of the most potent factors of radiation protection known because radiation relies on the production of oxygen free radicals (hypoxia generates two- to threefold less radiation sensitivity).[17] Therefore, drug therapies that mitigate this hypoxia can enhance radiation efficacy. There are four general chemotherapeutic approaches for accomplishing this: (1) chemotherapy can shrink the tumor through cytotoxic action thereby decreasing interstitial pressure. Moreover, because chemotherapy typically targets the fastest proliferating cells, those cells located next to blood vessels are removed bringing the hypoxic regions into closer proximity with the oxygenated region. A good example of this process is demonstrated by taxanes such as paclitaxel.[18] (2) Antiangiogenic therapies such as bevacizumab, an antibody targeting the vascular endothelial growth factor (VEGF), can potentially normalize vascular flow by eliminating the aberrant neovasculature of the tumor. Work by Rakesh Jain[19,20] and others[21,22] provide evidence of this phenomenon. (3) Hypoxic cell targeting agents, such as tirapazamine, can provide biological cooperation by eliminating the most radiation-resistant cells. (4) Hypoxic cell radiation sensitizers can reverse the inherent radiation resistance of the hypoxic cells. Drugs such as misonidazole, a nitroimidazole compound, can mimic the effects of oxygen within the hypoxic regions.[23,24]

Cell Death Pathway Effects

All of the preceding potential mechanisms of drug-radiation interaction display their efficacy through the consequence of cytotoxicity. However, in recent years, it has become clear that there are several ways in which cytotoxicity manifests itself. In 2005, the Nomenclature Committee on Cell Death (NCCD) was created and a classification system based purely on morphological criteria defined four modes of cell death: apoptosis (Type 1), autophagy (Type 2), necrosis (oncosis) (Type 3), and mitotic catastrophe.[25] Although these are distinct forms of cell death, the stimuli and processes involved interrelated. Moreover, there is evidence that ionizing radiation can manifest its cytotoxicity by each type of cell death. Therefore, as our understanding of these cell death pathways improve, novel therapeutics targeting these forms of cell death could enhance radiation efficacy. These cell death mechanisms are briefly described here.

Apoptosis

Apoptosis is the most clearly defined and studied mechanism of cell death. This programmed cell death involves characteristic morphologic changes including chromatin condensation (nuclear pyknosis) and nuclear fragmentation (karyorrhexis). Apoptotic bodies ultimately form and the cell is removed through phagocytosis but without generating inflammatory response. Apoptosis can occur with or without caspase activation[26,27] and does not require DNA fragmentation,[25] although this is a classical hallmark. Apoptosis is considered the major mechanism for chemotherapy-induced cell death. As a mechanism for radiation-induced cytotoxicity, apoptosis occurs readily in "liquid tumors" as opposed to most solid tumors in which apoptosis is a minor component of cell death. As such, drugs targeting the apoptosis pathway may enhance radiation cytotoxicity in solid tumors.

Autophagy

Whereas apoptosis is a clear self-destruct mechanism for the cell, the role of autophagy in cell death is more controversial. Autophagy, literally meaning "self-eating," can provide a protective mechanism for a cell during times of stress (such as nutrient deprivation) because it allows recycling of cellular building blocks through a controlled break down of cytoplasmic components. However, autophagic cell death does occur, which principally differs from apoptosis because of the lack of chromatin condensation.[25]

Necrosis

Type 3 death, or necrosis, is a cell death mechanism in which the cell swells (oncosis), ruptures the plasma membrane, and releases its contents resulting in a local inflammatory response.[25] The best example of this type of cell death is ischemic injury. Large, single fraction radiation, or radio-ablative doses, can produce this type of cell death as seen in stereotactic radiosurgery of brain lesions.

Mitotic Catastrophe

Mitotic catastrophe is a unique form of cell death that involves failed mitotic events.[25] Typically, this is manifest as micronucleation and multinucleation suggesting a series of mitotic divisions occur without cytokinesis that ultimately leads to cell death.

ANALYZING DRUG–RADIATION INTERACTION

Several methodologies for determining the interaction between a drug and radiation have been detailed in the literature. Moreover, several definitions for the possible interactions have also been described. The concept of radiosensitization originated many years ago, and classic radiosensitization has been defined as an increased amount of radiation-induced cell death that results from exposure to a second agent, after correction for the cytotoxicity of this agent. Clonogenic survival assays, that measure all forms of cell death as well as prolonged or irreversible cell cycle arrest, is the most encompassing method of measuring radiation cytotoxicity in vitro (Figure 4-3). Survival curves are generated by plating known quantities of cells on plates and treating them with various doses of radiation or drug and plotting the surviving fraction of colonies formed in a semilogarithmic fashion. Normalization is

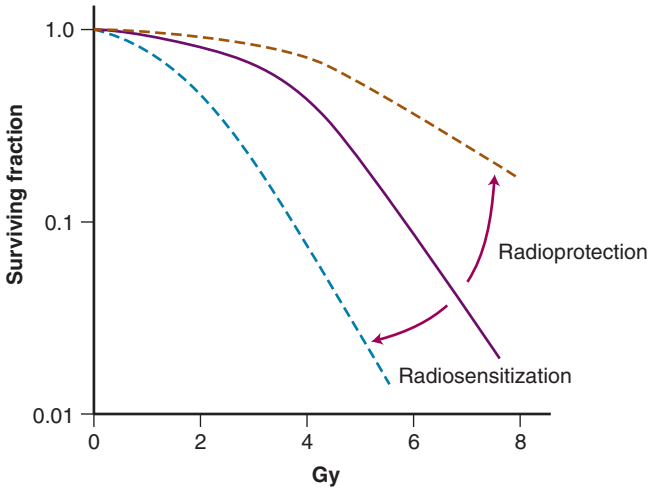


Figure 4-3 Graph of the concept of radiation modulation. The solid line indicates the control clonogenic survival assay plotted as surviving fraction relative to dose in Gy. A combined treatment that causes a rightward shift of the curve indicates a radioprotection effect, whereas a leftward shift of the curve indicates a radiosensitization effect.

performed by dividing the surviving fraction for treated groups by the plating efficiency, which is defined as the surviving fraction of the untreated cells. Modification in radiosensitization, therefore, is demonstrated in clonogenic survival curve data in which a downward or leftward shift of the normalized surviving fraction implies a radiosensitizing interaction, whereas an upward or rightward shift implies a radioprotective shift. Although survival curves can show interaction between chemotherapy and radiation, a better description of radiation modulation is necessary because both chemotherapy and radiation cytotoxicity do not typically follow a linear relationship.

One of the early attempts at providing a more descriptive system was provided by Tyrell,[28] which may be a better starting point for describing various interactions among therapies:

Antagonism: used in all cases in which the action of two treatments is less than would be expected from the addition of the two treatments given independently.
Zero interaction: used when two treatments lead to the effect expected from the addition of the two treatments given independently.
Positive interaction: used in all cases in which the action of two treatments is greater than would be expected from the addition of the two treatments given independently.
Synergism: a special case of a positive interaction; strictly, used when kinetic data are available.

These terms seem to have been supplanted by the "additivity" descriptors including supraadditive, additive, and infraadditive. Once again, the classic paper by Steel and Peckham[7] describes the construction of an "envelope of additivity" for evaluating the interaction of two treatments using isobologram analysis. This envelope of additivity is constructed from cytotoxicity data by calculating a mode 1 curve that assumes that both agents have completely independent mechanisms of action as well as a mode 2 curve that assumes that the two agents have exactly the same mechanism of action. When plotting combination therapy data points on the isobologram, they can either fall between mode 1 and 2 (additive interaction—within the envelope), above mode 1 (infraadditive), or below mode 2 (supraadditive, or synergistic). An idealized isobologram is shown in Figure 4-4 and a step-by-step method for constructing an isobologram is included in the Expert Consult Website.

Additional text available at https://expertconsult.inkling.com/ for a step-by-step method for constructing an isobologram.

Median Dose Effect Principle

A mathematical modeling system that has gained fairly widespread use for interactions of cytotoxic agents is the median effect principle of Chou and Talalay.[29-31] This system was derived from Michaelis-Menten equations and basic mass-action law considerations. This system has been useful for describing competitive enzyme interactions and interactions of cytotoxic agents. The primary relationship of the median effect principle is described by the following equation: $f_a/f_u = (D/D_m)^m$, in which D is dose, f_a is the fraction affected, f_u is the fraction unaffected, D_m is the dose required to produce the median effect (50%), and m is a Hill-type coefficient used to describe the sigmoid nature of the curve. For first-order Michaelis-Menten kinetics, m = 1.

The following manipulation of this equation can be performed, with surviving fraction (SF) substituted for fraction unaffected in the last step:

$$\log(f_a/f_u) = \log[(D/D_m)^m]$$

$$\log(f_a/f_u) = m\log(D) - m\log(D_m)$$

$$\log[(1/SF) - 1] = m\log(D) - m\log(D_m)$$

The general equation is $y = mx + b$.

A plot of log[(1/SF) – 1] on the *y*-axis and log(D) on the *x*-axis results in a line with a slope of *m* and a *y*-intercept of $m\log(D_m)$. The survival curves for the individual agents and for the combination treatment (the individual agents given together in some fashion) can be fitted to the equation for a line by linear regression. If the interaction of two agents is assessed, three lines (i.e., median effect plots) are produced: one for each agent and one for the combination treatment. A graph of the median effect plots for mock individual agents A and B and for the combination of A and B is shown in Figure 4-5. For the combination treatment, D is the sum of the doses of the two agents given concomitantly; it is helpful to perform the experiments with the two agents given together in a fixed ratio of doses (e.g., 1:2). By using various total doses (i.e., the sum), with the agents given in the same ratio, it is possible to determine the contribution of the individual agents to the combination treatment in a later calculation.

This concept can be visualized in Figure 4-5. For instance, in the case of $\log[(1/SF) - 1] = 0$, where SF is surviving fraction, the corresponding log(D), D indicating the sum of the doses of the two agents, can be calculated from the median effect plot for the combination treatment. An example of an actual combination treatment that has been assessed in this manner is radiation followed by a 24-hour exposure to etoposide.[29] In this example, a set of experiments was performed with the dose ratio fixed as 32 Gy to 1 μg/mL of etoposide. In this example, the dose D that resulted in log[(1/SF) – 1] equaling a given value was a combination of radiation and etoposide given in the ratio of 32:1. The radiation and etoposide components could be discerned, from the median effect plot of the combination treatment, by dividing the resulting dose into the appropriate components based on the ratio of delivery of the two agents.

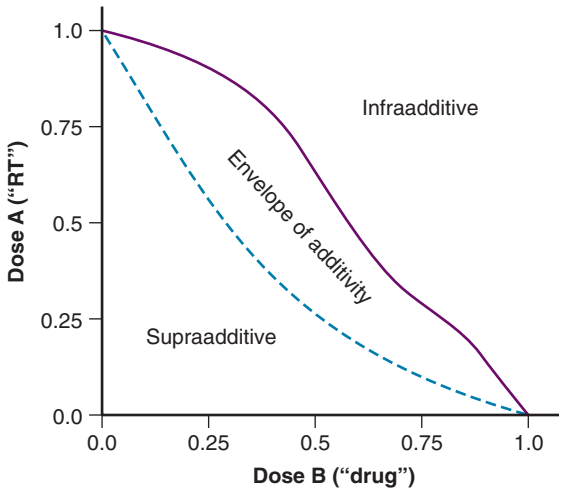
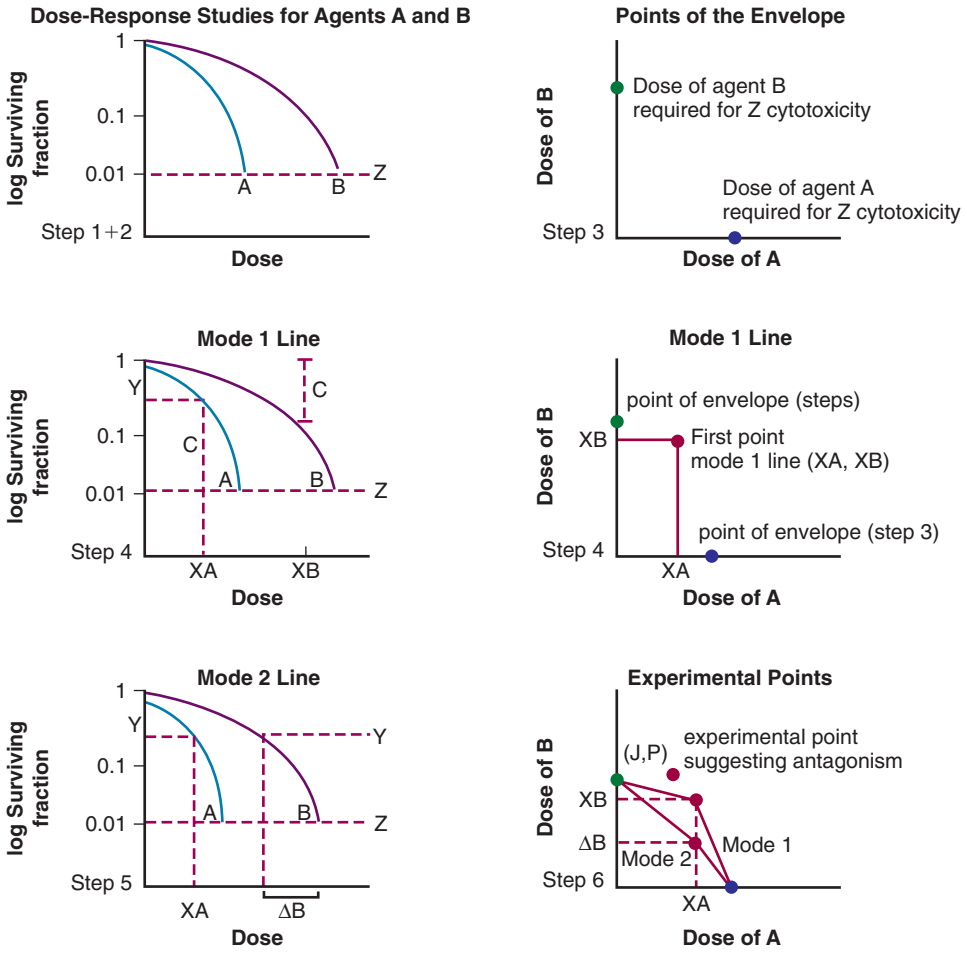


Figure 4-4 Graph of an isobologram for examining the interaction of radiation (RT) and a drug. Isoeffective doses of A (RT) and B (drug) are indicated on the axes. This diagram shows regions of infraadditivity, supraadditivity, as well as an envelope of additivity.



eFigure 4-1 Step-by-step construction of an isobologram to define an envelope of additivity for two cancer treatments. Isobologram analysis is used to evaluate the interaction of two treatments, and it requires the construction of an envelope of additivity that is bordered by mode 1 and mode 2 lines. The mode 1 line assumes that the two agents have completely independent mechanisms of action, whereas the mode 2 line assumes that the two agents have the same mechanism of action.

The following is a step-by-step procedure for calculating isobolograms using Steel and Peckham's method[7,29] (see eFigure 4-1).

Step 1. The investigator must choose to make the assessments at one level of cytotoxicity (e.g., construct an isobologram that represents the interaction of the agents for a cumulative cytotoxicity of 50%, 10%, or 1%). The example in Figure 4-3 depicts the chosen level of cytotoxicity as horizontal line Z: 1% cytotoxicity (0.01 surviving fraction) in this case.

Step 2. Plots are made of dose-response data for both agents. In eFigure 4-1, the dose-response data for the two agents are represented by curves A and B.

Step 3. The extreme points of the envelope of additivity are determined. Initially, a separate cartesian graph is created. The *y*-axis represents the dose of agent B, and the *x*-axis the dose of agent A. The first extreme point of the envelope is placed on the *y*-axis at the dose of agent B alone that causes a specific level of cytotoxicity, as determined by the dose-response curve of agent B, at the intersection of line Z (see eFigure 4-1). The second extreme point of the envelope is placed on the *x*-axis, at the dose of agent A alone that results in that level of cytotoxicity at the intersection of the dose-response curve with line Z (see eFigure 4-1).

Step 4. The mode 1 line is constructed assuming that the agents function independently. The individual dose-response curves are used for this construction. After exposure to dose X of agent A (XA), a level of cytotoxicity is obtained at a point on the dose-response curve that is above line Z. This level of cytotoxicity is identified as Y. Next, the dose of agent B (XB) that is required to produce cytotoxicity equal to the difference in cytotoxicity at line Z and point Y (identified as C) is determined. The cartesian coordinate (XA, XB) is plotted and becomes a point on the mode 1 line. The entire mode 1 line is constructed in this manner by varying the dose of agent A (for a resulting level of cytotoxicity that falls above line Z) and subsequently calculating the appropriate complementary dose of agent B as described.

Step 5. The mode 2 line is constructed assuming that the two agents have the same mechanism of action. As for mode 1 line construction, exposure to dose X of agent A (XA) results in a level of cytotoxicity identified as Y. The dose-response curve for agent B is then examined. The dose of agent B required for cytotoxicity equivalent to Y is determined and identified as YB. The change in dose of agent B that is required to increase cytotoxicity from YB to line Z is determined and labeled ΔB. The cartesian coordinate (XA, ΔB) is plotted. Similar points are calculated for various initial doses of agent A, and the mode 2 line is formed. The mode 2 line varies in shape depending on whether agent A or agent B is selected first for step 5. Generally, the mode

2 line that results in the greatest separation from the mode 1 line is chosen for the envelope of additivity.

Step 6. The two agents are given concomitantly, and a dose-response curve for concomitant treatment is obtained (typically by holding the dose of one agent constant while varying the dose of the other). The doses of the individual agents that result in combined cytotoxicity equivalent to the level represented by line Z are plotted (J, P).

This procedure allows for characterization of experimental data. The experimental point (J, P) represents an antagonistic interaction if the point falls above the envelope of additivity. The effect of the combination treatment is less than would be expected if the agents had completely independent mechanisms of action. An experimental point that falls directly on the mode 1 line suggests that the agents have independent mechanisms of action and the interaction is additive. An experimental point that falls below the mode 2 line suggests a synergistic interaction between the two agents for the particular concomitant treatment used.

The most difficult result to interpret is an experimental point that falls within the envelope of additivity. In some respects, the envelope of additivity is a misnomer because experimental points that fall in this range display an interaction that is greater than the additive effect that is achieved if the agents function by completely independent mechanisms. The interaction between the agents may be positive if the agents have independent mechanisms of action, or it may be negative if they have identical mechanisms of action.

Although the isobologram analysis is useful, it is somewhat limited because interactions in each analysis are investigated at a single level of cytotoxicity. The investigation of interactions at several levels of cytotoxicity requires the construction of several envelopes of additivity. The ambiguity associated with experimental points that fall within the envelope can be disconcerting and may lead to erroneous conclusions, especially if several levels of cytotoxicity are not investigated. Other mathematical modeling systems have been developed to assess the interaction of agents that cause cytotoxicity. These assessments aim to account for the kinetics of cytotoxicity of the involved agents and to assess multiple levels of cytotoxicity.

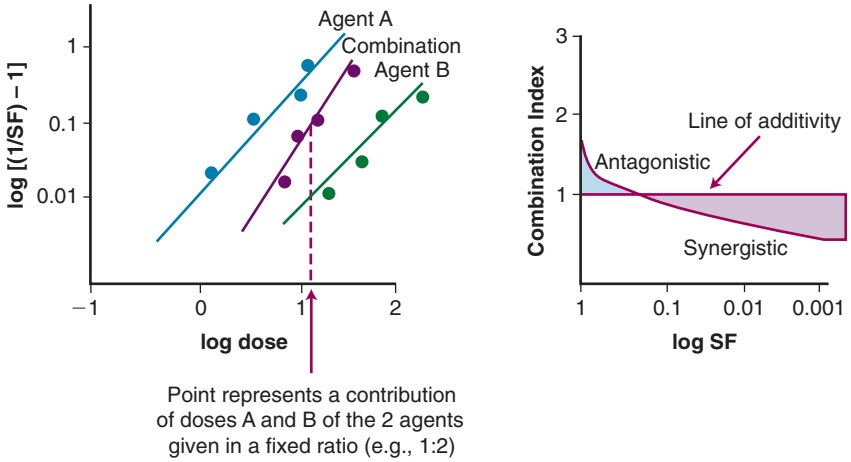


Figure 4-5 The hypothetical graph *(left)* demonstrates the median effect principle analysis for agents A and B given alone or in combination. The combination treatments are given in a fixed ratio so that the individual contribution of each agent to the combined effect can be calculated. The combination index *(right)* is then calculated at various levels of cytotoxicity as measured by surviving fraction (SF). The areas of antagonism, additivity, and synergism are indicated.

Definitions used in the median effect principle include the following:

Mutually exclusive: the agents of interest have similar modes of action and do not act independently.
Nonmutually exclusive: the agents of interest have different modes of action or act independently.
Combination index (CI): the derivation of this index is beyond the scope of this chapter. Calculation of CI allows characterization of an interaction as synergistic (CI <1), antagonistic (CI >1), or a summation (CI = 1). Chou and Talalay[31] provide a full description.

CI can be calculated for any surviving fraction and for mutually exclusive or mutually nonexclusive interactions. For a mutually exclusive interaction,

$$CI = [D_1/(Dx)_1] + [D_2/(Dx)_2]$$

For a mutually nonexclusive interaction,

$$CI = [D_1/(Dx)_1] + [D_2/(Dx)_2] + [D_1D_2/(Dx)_1(Dx)_2]$$

in which

$(Dx)_1 = D_m[(1/SF) - 1]^{1/m}$, solving the general equation for agent 1 given alone in a dose x.
$(Dx)_2 = D_m[(1/SF) - 1]^{1/m}$, solving the general equation for agent 2 given alone in a dose x.
$(Dx)_{1,2} = D_m[(1/SF) - 1]^{1/m1,2}$, solving the general equation for the agents given in combination for dose x, which represents the sum of the doses of the agents given in a fixed combination.
$D_1 = (Dx)_{1,2} \times$ (fraction of the mixture that is agent 1).
$D_2 = (Dx)_{1,2} \times$ (fraction of the mixture that is agent 2).

CI represents the doses of the agents required for a given effect when they are given together, divided by the doses required when the agents are given alone; in this way, CI less than 1 represents a synergistic interaction. A diagram of a CI plot for various levels of surviving fraction is shown in Figure 4-5.

Despite the advent of these robust statistical tools for determining the additivity relationship between treatments, the applicability outside of in vitro models is limited based on time and expense necessary to complete dose response experiments for both drug and radiation. Therefore, preclinical in vivo experimentation typically involves the use of a single drug dose at a concentration that can be achieved clinically.

CHEMOTHERAPY AND RADIATION AND COMBINATIONS OF CYTOTOXIC AGENTS

General Concepts

From the Bench to the Clinic

Occasionally, the process of quantifying interactions of chemotherapy and radiation has frustrated clinicians attempting to interpret in vitro and in vivo laboratory information, as exemplified by Charles Moertel (quoted by Tannock[32]) in his keynote speech at the first International Conference on Combined-Modality Therapy in 1978:

> *Based on the results of various individual studies, I could conclude that it is most ideal to administer the nitrosourea 15 hours before irradiation, 2 hours before irradiation, simultaneously with irradiation, or 6 hours after irradiation. While we will continue to cheer our radiation biology colleagues on from the sidelines, I am afraid that we are not yet at the stage where we can comfortably incorporate their results into our clinical practice.*

This was not meant as disrespect for the radiobiology community but to point out that, at that time, the laboratory models were potentially quite different from the clinical setting. Because it has been difficult to extrapolate from laboratory results to clinical results, many clinicians have used combination treatments on a trial-and-error basis. However, the reverse order of study has occasionally been fruitful, and efficacious combinations of treatment demonstrated in clinical studies have inspired laboratory investigations that revealed interesting molecular bases of interaction.[29,30] Translational research ideally occurs with a concept that arises from laboratory findings and subsequently is shown to have clinical efficacy. However, preclinical model systems have not always allowed investigators to take findings from the laboratory to the clinic, as indicated by the quotation of Moertel and by many of the early hypoxic cell sensitizer studies.

Therapeutic Benefits

Tannock[32] mentioned another problem with translating findings from the laboratory to the clinical setting, emphasizing that investigators must not merely explore combinations of therapeutic agents to find synergistic interactions but must also find interactions that will produce a therapeutic benefit (e.g., provide greater cytotoxicity in tumor cells than in normal cells). To categorize potentially exploitable differences, Tannock[32] described three main categories of biologic diversity between tumor cells and normal cells: tumor cells may display

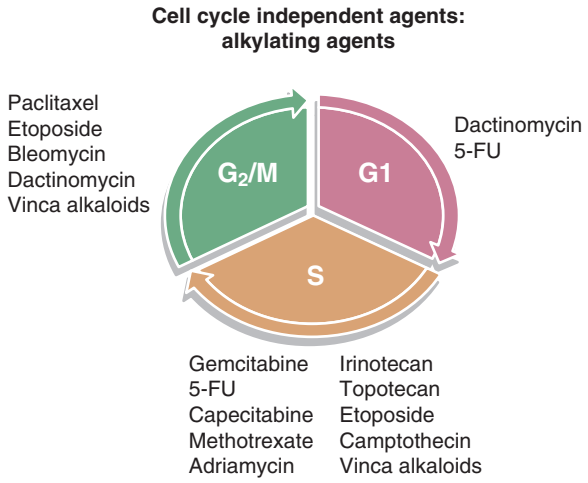


Figure 4-6 Diagram of the cell cycle with the cell cycle phase dependence of various chemotherapeutics.

genetic instability compared with normal tissues; tumor cells and normal cells may be different with respect to cellular proliferation or proliferation that occurs after treatment; and environmental factors such as oxygenation and pH may affect tumor cells and normal cells differently. As findings are translated from the laboratory to the clinical setting, it is important to consider the effects of the host mechanisms on these three areas.

Chemotherapeutic Classes

In the next section, several classes of systemic agents will be presented followed by a brief review of clinical data describing combination treatment of these agents with radiation. There are a host of chemotherapeutic classes that are used in patients that will undergo radiation treatment. Although not all of these agents are used concurrently with radiation, it is helpful to understand their predominant mechanism of action. A brief description of several of the major classes of chemotherapeutics with some information regarding possible means of interaction with radiation follow. In addition, Figure 4-6 summarizes the cell cycle phase specificity of these agents.

Antimetabolites

The origin of antimetabolite chemotherapy dates back to the 1940s when aminopterin was used to treat pediatric leukemia.[33] Since then, a large number of antimetabolite chemotherapeutics have been developed with tremendous success. The targets for these drugs include folate metabolism and nucleoside analogs. The major antimetabolites are presented here.

Fluoropyrimidines: Fluorouracil, Fluorodeoxyuridine, and Capecitabine

The fluoropyrimidines, as the name implies, are halogenated pyrimidines that function as antifolates by inhibiting thymidylate synthesis. As mentioned previously in historical perspectives, 5-FU is one of the most established drugs used in combination with radiation. It has been used in both a bolus infusion as well as a continuous venous infusion when combined with radiation and appears to target the radioresistant cells in S-phase.[16] The two delivery methods have some differences in terms of side effect profile, but both seem to have good efficacy. In a phase III rectal cancer postoperative adjuvant chemoradiation trial, concurrent continuous infusion 5-FU during EBRT was more effective than the bolus delivery.[34] Moreover, data shows that 5-FU plasma levels and intracellular metabolite levels are rather short-lived,[35] also suggesting a need for continuous administration of the drug to be effective with radiation. Because of this, oral formulations have been developed, most notably capecitabine, a fluoropyrimidine carbamate prodrug of 5-FU, which must be converted through the action of thymidine phosphorylase. In addition to the improved patient comfort of taking an oral medication rather than having an infusion pump, another potential advantage of capecitabine in combination with radiation is that it appears that radiation increases thymidine phosphorylase levels in tumors, which allows potential bioaccumulation of active metabolite within irradiated tumor.[36,37]

Gemcitabine

Gemcitabine is an analog of deoxycytidine that specifically functions during the S-phase by preventing the dNTP production. There is both preclinical and clinical evidence demonstrating dramatic radiation sensitizing properties to combined gemcitabine and radiation.[38-41] In fact, a significant amount of toxicity has been demonstrated in clinical trials for pancreatic cancer[42] necessitating either decreased dose of gemcitabine or limited field size for radiation treatment ports.

Antifolates: Methotrexate, Trimetrexate, and Pemetrexed

The antifolate, methotrexate, tightly binds dihydrofolate reductase (DHFR) thereby inhibiting folate metabolism. Through this inhibition, thymidylate synthesis is blocked, and thus, purine biosynthesis. In addition, some amino acid synthesis is impaired through blockade of this enzyme resulting in cytotoxicity.[43] Pemetrexed is a pyrrolopyrimidine that functions as an antifolate that inhibits multiple enzymes including thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyl-transferase, and aminoimidazole carboxamide formyl-transferase in a cell cycle independent manner. Pemetrexed is effective against many solid tumors and has shown radiosensitizing propertied in preclinical systems.[44,45,46]

Alkylating Agents

Alkylating agents are composed of several classes of electrophilic compounds that share the antitumor characteristic that they form covalent bonds with ("alkylate") DNA bases. Some alkylators interact with a single strand of DNA, whereas others can cross-link two strands. The induced DNA damage leads to the cytotoxicity of these agents. The various classes of alkylators that are potentially used with irradiation are briefly presented here.

Nitrogen Mustard: Chlorambucil and Melphalan

The first of a long series of alkylating agents developed for clinical use, mustard gas was discovered based on clinical observations of people and animals exposed to mustard gas during World War I, particularly the effect on bone marrow.[33,47] Later, nitrogen mustards were developed for lymphoma therapy as mechlorethamine or Mustargen, eventually used in the MOPP (Mustargen, vincristine [Oncovin], procarbazine, prednisone) regimen for Hodgkin's lymphoma. The most commonly used nitrogen mustards are chlorambucil and melphalan (L-phenylalanine mustard) and are principally used for the treatment of chronic lymphocytic leukemia and multiple myeloma, respectively. Because of the bone marrow effect of these drugs, caution should be used when irradiating large volumes of bone marrow.

Oxazaphosporines: Cyclophosphamide and Ifosfamide

The oxazaphosphorines are nitrogen mustard-like compounds that include cyclophosphamide and its structural isomer,

ifosfamide. These agents are used in combination with radiation in both pediatric and adult cancer treatment.

Mitomycin C

Mitomycin C is an antibiotic with alkylating characteristics derived from *Streptomyces*. This agent, is an aziridine ring–containing compound that resembles nitrogen mustard as well. This drug blocks DNA synthesis but also causes cell cycle arrest during G2/M phase transition.[48,49] Mitomycin C has also been shown to function well as a hypoxic cell radiosensitizer,[50] which may help explain why mitomycin C-based chemoradiation is so effective in anal cancer treatment,[51,52] as discussed later in the chapter.

Triazenes: Procarbazine, Dacarbazine, and Temozolomide

Temozolomide has revolutionized the treatment of high-grade gliomas in combination with irradiation. It effectively crosses the blood-brain barrier. (The cerebrospinal fluid [CSF] can achieve 30% of plasma levels).[53] Temozolomide generates DNA damage through methylation of DNA at the O-6 position of guanine. Interestingly, the O-6 methylguanine DNA-methyltransferase (MGMT) is a p53 DNA repair enzyme that can be regulated epigenetically silenced by promoter methylation, which appears to predict for response to temozolomide-based chemoradiation because of the inability of the cancer cell to remove the O-6 methylguanine causing cytotoxicity.[54] Indeed, this DNA alkylation/methylation from temozolomide triggers the mismatch repair pathway with a G2/M phase arrest yielding apoptosis and radiosensitive cells.[55] Ongoing clinical trials are examining the importance of MGMT status and combining temozolomide with other agents.[54,56]

Nitrosoureas: BCNU, Methyl-CCNU, CCNU, and Streptozotocin

Several members of the nitrosourea group of alkylating agents are capable of crossing the blood-brain-barrier and cross-linking DNA. BCNU, or carmustine, has been used to treat brain tumors, predominantly gliomas, but it has also been used for multiple myeloma and high-dose transplant regimens. Gliadel (BCNU impregnated wafer) can be placed in a glioma resection cavity, which biodegrades slowly to release the chemotherapeutic. CCNU, or lomustine, is a related compound with increased lipid solubility also used for brain tumors.[57]

Platinums: Cisplatin, Carboplatin, Oxiliplatin, and Satraplatin

Cisplatin, (cis-Diammine dichloroplatinum[II]), the prototypical and most widely studied member of the platinum family, has been used for decades as an anticancer treatment. Preclinical work in the late 1970s by Soloway et al[58] demonstrated radiosensitization in a murine model of transitional cell carcinoma. Since then, a host of both clinical and preclinical data suggests several mechanisms of interaction between cisplatin and radiation. Potential cooperation between the two modalities can occur at the level of DNA because radiation often causes repairable single-stranded breaks in DNA, which can be converted to lethal double-stranded breaks when they occur close to cisplatin-DNA adducts (intra- and interstrand cross-links). This may also be as a result of the ability of cisplatin to function as a free-electron scavenger that impairs the DNA repair mechanism, thus, "fixing" the radiation-induced DNA damage.[59] In addition, radiation may enhance the uptake of cisplatin into the cell as well as help generate active platinum metabolites.[1] The other family members, carboplatin, oxiliplatin, and the orally active, satraplatin, appear to have similar mechanisms of action though differences among the members may be because of the three-dimensional structure of the DNA adducts that each platinum generates, which influences binding to various polymerases and DNA repair enzymes.[60] For these reasons, the platinums function independent of the cell cycle phase.

Microtubule Targeting

Because microtubule polymerization and depolymerization are critical for spindle formation and chromosome segregation during mitosis, microtubule targeting agents have the ability to enhance radiation effect by creating a cell cycle blockade during M-phase, which is a radiation-sensitive phase of the cell cycle. Moreover, these agents promote apoptosis as well. The three predominant classes of microtubule targeting agents are discussed here.

Estramustine

Estramustine is an interesting hybrid molecule that is derived from both nitrogen mustard and 17β-estradiol. Estramustine effectively blocks microtubules by binding β-tubulin and microtubule associated proteins resulting in destabilization of microtubules. This targets the mitotic spindle and leads to cell cycle arrest during M-phase causing radiosensitization.[61] This drug has been approved for hormone-refractory prostate cancer for almost three decades.

Vinca Alkaloids: Vincristine, Vinblastine, and Vinorelbine

The vinca alkaloids have been used as anticancer agents for more than 40 years and function by targeting microtubules. They are able to force depolymerization of microtubules and, thus, disrupt the mitotic spindle resulting in an M-phase blockade.[62] These drugs have been used for a wide variety of malignancies, both pediatric and adult. In terms of radiosensitization, vincristine, vinblastine, and vinorelbine impact cell cycle effects and DNA damage repair.[9,62]

Taxanes: Paclitaxel, Docetaxel, and Albumin-Bound Paclitaxel

As opposed to the vinca alkaloids, the taxanes stabilize microtubules and promote further tubulin polymerization, which inhibits centrosome mechanics during mitosis. In terms of enhancing radiation effect, the taxanes appear to manipulate several of the factors listed in Table 4-1. First, the taxanes will block the metaphase-anaphase cell cycle checkpoint, which could allow for accumulation of cells in the radiosensitive G2/M phase.[62,63] Furthermore, taxanes can cause tumor shrinkage,[64,65] thereby decreasing interstitial pressure and allowing for improved oxygenation.[18] In addition, taxanes can manipulate signal transduction cascades involved in radiation response.[66]

Epothilones (Epothilone B, Aza-Epothione B [Ixabepilone])

The epothilones are considered next-generation microtubule targeting agents that function similar to taxanes but are derived from mycobacterium. They are able to stabilize microtubules with high potency and halt mitosis similar to taxanes.[62] These drugs were developed to be independent of the p-glycoprotein efflux resistance mechanisms that target taxanes and vinca alkaloids.[62,67] These drugs will likely become a popular choice for concurrent chemoradiation regimens in the future.

Topoisomerase Inhibitors

Topoisomerases are critical enzymes in DNA replication of all cells because of their ability to unwind DNA. There are two major classes of topoisomerases in mammalian cells that are

clinically relevant for oncology therapeutics, topoisomerase I and II. Topoisomerase I (TopI) is involved in DNA replication fork movement and unwinding supercoils during DNA transcription, whereas topoisomerase II (TopII) is important for untangling DNA during transcription and remodeling chromatin.[35,43] These classes are named based on how many DNA strand breaks are created during enzymatic action, a single-stranded break for TopI and double-stranded break for TopII.[43] These breaks are required for TopI and II to unwind and disentangle DNA, but they are temporary because the enzyme will reconnect the broken strands (religation). TopI/II inhibitors have cytotoxicity by disrupting the process and generating DNA double-stranded breaks.

Topoisomerase I Inhibitors (Camptothecins—Irinotecan, Topotecan)

Camptothecin is a naturally occurring alkaloid derived from the plant *Camptotheca acuminata* that was identified in an anticancer drug discovery screen in the 1960s.[68] Camptothecin is believed to form a stable ternary complex that prevents normal DNA religation and a collision of the complex with the replication fork occurs leading to a DNA double-stranded break and cytotoxicity.[69] The S-phase specificity of this drug class provides some of the rationale for radiosensitization. The drug was unsuccessful in the clinic because of severe urinary complications, though camptothecin is still used as a research tool and positive control for cytotoxicity and apoptosis. However, derivatives of camptothecin, notably irinotecan and topotecan, are used as chemotherapeutics. Irinotecan is FDA approved for colorectal cancer, but data related to concomitant administration with radiation has been generated in patients with both small cell[70-72] and non–small cell lung carcinoma.[73,74] Topotecan is approved for ovarian, small cell, and cervical cancer, but it has been combined with radiation in glioblastoma clinical trials.[75,76]

Topoisomerase II Inhibitors

Podophyllotoxins: Etoposide, Etoposide Phosphate, and Teniposide. The plant extract, podophyllotoxin, has microtubule binding activity, yet, the clinically used derivatives do not function through microtubule action but actually are TopII poisons.[77] These epipodophyllotoxins, most notably etoposide and teniposide, are glycoside derivatives that are used in both childhood and adult tumors.[35] In addition, these drugs have been used with radiation in both sequential and concomitant regimens.[78-81]

Anthracyclines: Idarubicin, Doxorubicin, Epirubicin, and Daunorubicin. Anthracyclines are naturally occurring substances that intercalate into the DNA when they target TopII leading to DNA double-stranded breaks.[35,82] These drugs have a wide range of clinical indications, including both liquid and solid tumors. In terms of radiation sensitization, the interaction of doxorubicin and radiation are well known such that concurrent administration is generally avoided. In fact, when doxorubicin is given after radiation, an inflammatory reaction known as "radiation recall" can occur.[83,84]

Others: Mitoxantrone and Dactinomycin. Mitoxantrone is an anthracenedione that was designed to function like an anthracycline but have less cardiotoxicity[85] because it is less likely to form free radicals[35] and may affect calcium release differently.[86] Like anthracyclines, mitoxantrone can intercalate in DNA and poison TopII to form DNA double-stranded breaks. This drug is approved for hormone-refractory prostate cancer. Dactinomycin is a *Streptomyces* derived antibiotic that can intercalate in DNA, block TopII and cause DNA double-stranded breaks.[35] Dactinomycin is used in pediatric sarcoma therapeutic regimens, including rhabdomyosarcoma.

CHEMORADIATION CLINICAL EXAMPLES

An all-encompassing review of the clinical examples of the use of chemoradiation is beyond the scope of this chapter. More comprehensive information regarding disease site-specific trials are included in the individual chapters devoted to each site. What follows is merely a brief account of some of the landmark trials that have demonstrated improved organ preservation, local control, and overall survival in the modern era. Specifically, aerodigestive, genitourinary, gynecological, and central nervous system cancer examples are presented.

Gastrointestinal Cancers

Anal Cancer

A classic example of the evolution of an efficacious interaction of chemotherapy and radiotherapy is combined modality treatment for anal cancer. In the early 1970s, it was discovered that anal cancer could be treated successfully with a combination of 5-FU, mitomycin C (MMC), and irradiation.[52] In 1974, Nigro et al[52] reported on three patients who received variations of these three treatments, with excellent responses to the preoperative therapy (eTable 4-1). This article became a classic in the oncology literature, and the regimen became prominent in the treatment of anal cancer. Because of this regimen, many patients were spared abdominal perineal resection.

After the initial report of Nigro et al,[52] several other groups confirmed the efficacy of chemotherapy and irradiation (without surgery) as the standard treatment for primary anal cancer (Table 4-2).[52,87-89] Subsequently, an intergroup effort was undertaken by the Radiation Therapy Oncology Group (RTOG) and Eastern Cooperative Oncology Group (ECOG) to determine whether MMC could be removed from the regimen because its inclusion resulted in increased toxicity compared with that of 5-FU and radiation without MMC. With 5-FU, however, fewer patients were able to avoid colostomy (see Table 4-2).

Additional attempts at replacing MMC with less toxic concurrent chemotherapy have been undertaken, most notably in the U.S. GI Intergroup study (see Table 4-2) coordinated by RTOG (RTOG 98-11). This trial compared an induction chemotherapy (5-FU and cisplatin) regimen followed by the same chemotherapy concurrently with radiation versus standard concurrent chemotherapy (5-FU and MMC) with radiation. The hypothesis was that the induction chemotherapy would decrease tumor bulk making radiotherapy more effective and thus improving local control and that the additional cycles of induction chemotherapy may improve overall survival (OS) by decreasing distant metastases. However, these hypotheses were disproven because the cisplatin arm not only failed to show a benefit in terms of local control, disease-free survival (DFS), and OS, but was clearly inferior to MMC in terms of colostomy-free survival (CFS).[51] Long-term followup of trial results not only confirmed initial results regarding CFS but, more importantly, demonstrated a statistically significant superior DFS and OS with 5-FU and MMC compared to induction and concurrent 5-FU and cisplatin.[90] Therefore, the combination of 5-FU, MMC, and irradiation remains the standard regimen for anal cancer. IMRT strategies combined with 5FU-MMC based chemoradiation have been investigated by multiple groups and demonstrate a reduction in normal tissue toxicities.[91-93]

Additional text available at https://expertconsult.inkling.com/ for a discussion of how the laboratory investigations followed the clinical data.

eTABLE 4-1 Combined-Modality Treatment for Anal Cancer: A Study of Three Patients

Patient	RT	Chemotherapy	Results
1	34.7 Gy/5 wk	Concomitant 5-FU*/porfiromycin (50 mg)	APR 9 wk after RT, NED
2	30.6 Gy/17 Fx	Concomitant 5-FU*/mitomycin (30 mg)	Clinically free of disease, patient refused APR
3	30 Gy/15 Fx	None	APR 8 wk after RT, NED

Data from Nigro ND et al.[52]

5-FU, *5-Fluorouracil;* APR, *abdominoperineal resection;* Fx, *fractions;* NED, *no evidence of disease;* RT, *radiation therapy.*

**Dose of 1500 mg of 5-fluorouracil in the form of a continuous 24-hour infusion for 5 days.*

The clinical finding of the efficacious combination of 5-FU, mitomycin C, and radiation led to laboratory studies. Dobrowsky et al[94] performed a complex isobologram analysis using the same agents reported by Nigro et al.[52] The assessment by Dobrowsky et al,[94] using an in vitro system of a squamous tumor cell line, illustrated some of the difficulties with the ideal progression of taking laboratory discoveries to the clinic. Two different endpoints were used: colony formation (cells plated after treatment and allowed to form colonies) and viable cells per flask (obtained by multiplying the cell number per flask at 96 hours by the surviving fraction, as stipulated by a standard colony formation assay). In an attempt to duplicate the clinical treatment of Nigro et al,[52] mitomycin C was given as a 1-hour exposure and 5-FU as a 4-day exposure after initial radiation.

The first experiments assessed the interaction of 5-FU and mitomycin C without radiation. Initially, a single dose of mitomycin C (0.5 μg/mL for 1 hour) was combined with various doses of 5-FU. Isobolograms were constructed for the colony formation endpoint at a surviving fraction of 0.04. Isobologram construction showed that the combination treatment resulted in an experimental point below the envelope of additivity at this level of cytotoxic assessment. Isobolograms also were constructed for the viable cells per flask endpoint at the 1% viability level; the experimental point for combined 5-FU and mitomycin C was directly on the mode 2 line. This endpoint was included because it was believed to account for the cytotoxic and cytostatic effects of the treatment.

Because the results of this synergy analysis varied with the endpoint used, the optimal endpoint, whether colony formation or viable cells per flask, is not known. That the use of these slightly different endpoints produced slightly different isobologram results illustrates some of the problems in interpreting in vitro data and in attempting to extrapolate this information to the clinical setting. In the future, it may be possible to assess which endpoints may be most useful for various cytotoxic agents and various tumors on the basis of the relative contribution of cytotoxic and cytostatic effects for a given situation.

On the basis of the experiments without irradiation, specific concentrations of mitomycin C (0.5 μg/mL) and 5-FU (0.15 μg/mL) were selected for subsequent experiments involving radiation[94]; these concentrations resulted in 60% and 80% surviving fractions, respectively. With colony formation as the endpoint, it was discovered that the interaction of irradiation and 5-FU or irradiation and mitomycin C (at the levels of cytotoxicity assessed) produced experimental points below the envelope of additivity. These results corroborated those reported previously by Byfield et al,[95] in which some level of 5-FU cytotoxicity was required for a positive interaction with irradiation. However, the results of radiation in conjunction with mitomycin C were not entirely consistent with those of previous reports, which had suggested that a positive interaction of these agents did not exist.[96]

The previous example illustrates several important points. If the protocol of Nigro et al[52] had been designed on the basis of laboratory studies (if all of the aforementioned studies had existed in 1974), it would have been difficult to assess where to begin. First, the investigator would need to decide which in vitro endpoint would be most relevant to anal cancer (viable cells per flask or colony formation), and this decision would affect whether one believed that 5-FU and mitomycin C interacted synergistically. Second, the investigator would need to decide which assessment of mitomycin C and radiation was most relevant to the treatment of anal cancer because authors disagreed about whether this interaction was synergistic. This example also illustrates the challenges that are faced when interpretations of in vitro or in vivo experimental data are used to guide the design of clinical trials. These challenges can be exciting as we learn more about the significance of various endpoints at the molecular level and how these molecular events may be manipulated in a particular tumor.

TABLE 4-2 Concomitant Radiation and Chemotherapy for Anal Cancer

Study	Regimen	Outcome
Nigro et al[52] (1987), Wayne State University	RT (30 Gy/15 Fx) with CI 5-FU (1000 mg/m^2) for 4 days × 2 cycles and mitomycin C (15 mg/m^2) on day 1	Of 104 patients, 31 required APR
Sischy et al[89] (1989), RTOG/ECOG	RT (40 Gy/20 Fx) with CI 5-FU (1,000 mg/m^2) for 4 days × 2 cycles and mitomycin C (10 mg/m^2) on day 2	Of 79 patients, 8 required APR
Flam et al[88] (1996), RTOG/ECOG	RT (45 Gy/25 Fx) with CI 5-FU during weeks 1 and 4, with randomization to mitomycin C (10 mg/m^2) on days 1 and 29 vs. no mitomycin C	Colostomy-free survival improved with MMC, 71% vs. 59% (p = 0.014)
Bartelink et al[87] (1997), EORTC	RT (60-65 Gy*) alone vs RT plus 5-FU (750 mg/m^2 on days 1-5, 29-33) and mitomycin C (15 mg/m^2) on day 1	Improved event-free survival with RT and chemo compared with RT alone (p = 0.03)
Ajani et al[51] (2008), Gunderson et al[90] (2012); RTOG 98-11 (GI INT)	RT (55-59 Gy) with CI 5-FU CI 5-FU (1000 mg/m^2, for 4 days, wks 1 & 5) and MMC (10 mg/m^2 on days 1 and 29) vs CI 5-FU (1000 mg/m^2) + cisplatin (75 mg/m^2 on days 1 and 29) with induction chemotherapy	(N = 682); Improved DFS and OS at 5 y (67.8% vs. 57.8%; p = 0.006 and 78.3% vs. 70.7%; p = 0.026, respectively) for MMC arm

5-FU, *5-Fluorouracil;* APR, *abdominoperineal resection;* chemo, *chemotherapy;* CI, *continuous infusion;* ECOG, *Eastern Cooperative Oncology Group;* EORTC, *European Organization for Research and Treatment of Cancer;* Fx, *fractions;* GI INT, *gastrointestinal intergroup;* MMC, *mitomycin-C;* N, *total number of patients;* RT, *radiation therapy;* RTOG, *Radiation Therapy Oncology Group.*
**Surgery 6 weeks after initial 45 Gy if no response.*

Esophagus/Esophago-Gastric Junction

Esophageal/esophago-gastric junction cancer remains a challenging cancer to treat, primarily because of the locally advanced stage that is typically found at diagnosis. For nonsurgical approaches to treatment, radiation alone has been shown to be quite limited in terms of controlling the disease. Indeed, chemoradiation has been clearly shown to be the treatment of choice following several landmark trials comparing chemoradiation to radiation alone. The Intergroup trial coordinated by RTOG (85-01) originally published by Herskovic et al[97] and later updated by Cooper et al[98] randomized patients to either 64 Gy radiation alone at 2 Gy/fraction or 50 Gy in 2 Gy/fraction concurrent with 5-FU (1000 mg/m^2/day for days 1-4) and cisplatin (75 mg/m^2 on day 1). In the concurrent arm, the chemotherapy was given every 28 days during radiation and then every 21 days thereafter for two additional cycles. This trial established that radiation alone was inferior to combined modality chemoradiation (5 year OS 0% vs. 26%, p = 0.0001).[98] A meta-analysis by Wong et al[99] confirmed that concurrent chemoradiation was beneficial in terms of survival with a hazard ratio of 0.73, 95% confidence interval of 0.64-0.84, p < 0.0001. Sequential chemotherapy and radiation did not show a statistically significant benefit, however.[99]

The role of trimodality therapy with neoadjuvant chemoradiation followed by surgery has also been investigated. Tepper et al[100] published the results of the U.S. GI Intergroup study (CALGB 9781) that randomized patients to neoadjuvant cisplatin/5-FU/EBRT (50.4 Gy) before esophagectomy versus esophagectomy alone. Although the trial was closed early because of poor accrual, the 56 patients enrolled were analyzed on an intent-to-treat analysis. This revealed a significant difference in median and 5-yr OS with trimodality treatment and surgery alone (median: 54 vs. 21.6 mo.; 5-yr OS: 39% vs. 16%, p = 0.002).[100] More recently, the CROSS group completed a large randomized phase III study of 366 analyzable patients comparing neoadjuvant carboplatin/paclitaxel/EBRT (41.4 Gy) before esophagectomy and esophagectomy alone.[101] Results of this study revealed that preoperative chemoradiation improved OS (median, 49.4 vs. 24 mo.; 5-yr OS 47% vs. 34%; p = 0.003; hazard ratio, 0.657) without significant increases in acute side effects or postoperative complications. Pathologic complete response was noted in 29% of patients with neoadjuvant therapy. A complete resection of the tumor (R0 resection) was accomplished in 92% of patients who underwent neoadjuvant therapy compared to 69% in patients who had surgery alone.

Combining molecularly targeted agents with standard chemotherapies with radiation have also been tested. Most heavily investigated has been the addition of EGFR targeting agents to standard chemoradiation regimens. Results from the SCOPE1 trial, a European multicenter phase II/III trial evaluating the addition of cetuximab to concurrent cisplatin, capecitabine, and radiation (50 Gy), has revealed a lack of benefit and possible detriment with the addition of cetuximab.[102] Initial reports of RTOG 0436, a randomized phase III trial evaluating the addition of cetuximab to concurrent cisplatin, paclitaxel, and daily radiation (50.4 Gy), also confirm these findings with little or no benefit of cetuximab as evidenced by no improvement in OS or clinical complete response.[103]

Gastric

The U.S. GI Intergroup 0116 phase III trial, reported by McDonald et al, compared adjuvant postoperative chemoradiation to surgery alone for patients with resected high-risk gastric or gastroesophageal cancers. Bolus 5-FU/leucovorin was given before EBRT (one 5-d cycle), concurrently with EBRT (2 cycles: 4-d wk 1, 3-d wk 5), and after EBRT (2 additional 5-d cycles). A survival advantage of concurrent chemoradiation was shown (3-yr OS—50% vs. 41%, p = 0.005; 3-yr relapse free survival—48% vs. 31%, p = 0.001),[104] and this treatment has been the standard of care for gastric cancer in the United States. In the United Kingdom, the MAGIC trial established a nonradiation regimen that involves perioperative (neoadjuvant and adjuvant) epirubicin, cisplatin, and 5-FU (ECF) chemotherapy as an appropriate standard of care for resectable gastric cancer.[105] The logical followup study was a postoperative adjuvant U.S. GI Intergroup phase III trial (CALGB 80101) that essentially married the INT-0116 and the MAGIC trial by investigating the role of chemoradiation in the setting of more modern ECF chemotherapy as the experimental arm versus the control arm of GI INT 0116. Although the experimental arm did not improve survival, the ECF regimen had a more favorable toxicity profile.[106]

Rectal

Although rectal cancer is a surgically managed disease, the addition of adjuvant therapy is well recognized as a vital

TABLE 4-3 Randomized Trials of Neoadjuvant Concomitant Radiation and Chemotherapy for Rectal Cancer

Study	Regimen	Outcome
Boulis-Wassif et al[108] (1984)	Preop RT (34.5 Gy at 2.3 Gy/fx) ± 5 FU 10 mg/kg/d day 1-4 followed by surgery	Trend toward improved 5 y OS (59% vs. 46%, $p = 0.06$)
Bosset et al[107] (2006)	4 arm study: preop RT (45 Gy) + S vs. preop CT-RT with 5 FU (325 mg/m^2/d)/LV (20 mg/m^2/day) d1-5, 28-32+ S vs. preop RT + S + adjuvant 5 FU/LV vs. preop CT-RT + S + adjuvant 5 FU/LV	5 y LR was worse in the RT only arm (17.1% vs. 8.7%, 9.6%, and 7.6% in the CT containing arms; $p = 0.002$)
Bujko et al[109] (2006)*	Preop RT (25 Gy at 5 Gy/fx) + S vs. Preop CT-RT (50.4 Gy at 1.8 Gy/fx with 5 FU(325 mg/m^2/d)/LV (20 mg/m^2/day) d1-5, 28-32 + S	No difference in LC, OS, or late toxicity, but CT-RT had more early toxicity (8.2% vs. 3.2%; $p < 0.001$)
Gerard et al[110] (2006)	Preop RT (45 Gy at 1.8 Gy/fx) ± 5 FU (350 mg/m^2/d d1-5 days + LV) followed by S + adjuvant 5 FU (350 mg/m^2/d d1-5 days + LV)	Improved pCR (11.4% vs/ 3.6%; $p < 0.05$) and less LR (8.1% vs. 16.5%; $p < 0.05$) with CT-RT

5-FU, *5-Fluorouracil;* CT, *chemotherapy;* CT-RT, *concurrent chemoradiation;* fx, *fractions;* LR, *local recurrence;* LV, *leucovorin;* pCR, *pathologic complete response;* RT, *radiation therapy.*

**Not a true comparison of adjuvant EBRT ± concurrent chemo as used markedly different adjuvant EBRT regimens*

component of therapy. Four randomized trials[107-110] investigating the addition of chemotherapy to neoadjuvant EBRT in Stage II and III rectal cancer is summarized in Table 4-3 (the Bujko trial did not use the same dose/duration of EBRT so it is not a true comparison of EBRT ± concurrent chemotherapy). Furthermore, a meta-analysis reviewed these four trials.[111] Although this analysis showed improved complete pathological response rate and local control with the addition of chemotherapy to preoperative radiation, no benefit was found in terms of sphincter preservation, DFS, or OS. Of note, preoperative chemoradiation was found to produce increased grade 3 and 4 toxicity compared to preoperative EBRT alone.

The current standard of care approach, however, was defined in the phase III German Rectal Trial.[112] Preoperative chemoradiation was shown to be superior to postoperative chemoradiation in terms of local control, sphincter preservation rates, and toxicity.

As in other disease sites, more recent trials are investigating the addition of molecularly targeted agents to the standard preoperative chemoradiation regimen. The antivascular endothelial growth factor antibody, bevacizumab, has shown promising results in phase I/II trial in which all 32 patients showed tumor regression following neoadjuvant therapy with an actuarial 5-year DFS of 75%.[113] In addition, EGFR targeted agents have shown promise in KRAS wild-type tumors.[114,115] However, these agents remain investigational in this setting.

Head and Neck Cancers

Head and neck cancers management for locally advanced tumors were traditionally managed with surgery and postoperative radiation. However, over the past two decades, an explosion of chemoradiation trials shifted the management toward an organ preservation approach (summarized in Table 4-4). One of the most impressive results for a randomized trial in head and neck cancers was that of Intergroup 0099 (RTOG 8817) originally published by Al-Sarraf et al in 1998.[116] In this trial of patients with nasopharyngeal cancer, radiation alone (70 Gy at 2 Gy/fx) versus radiation with concurrent cisplatin with adjuvant cisplatin/5-FU demonstrated a dramatic 67% to 37%, respectively, 5-year OS advantage in favor of the chemoradiation arm. More than 90 randomized clinical trials have been performed examining chemoradiation in head and neck cancers. Several meta-analyses have been published showing an absolute survival benefit to chemoradiation. Indeed, the most recent update of the MACH-NC in 2009 analyzed more than 17,000 patients in 93 randomized trials and showed an absolute OS benefit of 6.5% at 5 years.[117] Although two large randomized trials of neoadjuvant chemotherapy followed by radiation have shown a benefit in terms of laryngeal organ preservation,[118,119] subsequent studies, including RTOG 9111,[120] and the MACH-NC[117] suggest that concurrent chemoradiation is more effective than sequential administration.

As mentioned previously, the RTOG 9111 was a landmark Intergroup trial for patients with what would currently be staged as T2 and T3 glottic and supraglottic squamous cell carcinomas.[120] This trial randomized patients to one OS was not different between the groups, the DFS and local-regional control favored the concurrent chemoradiation arm.[120] This benefit is not restricted to organ preservation studies. Indeed, two trials published in the same issue of the *New England Journal of Medicine* detailed the RTOG[124] and EORTC[123] trials randomizing patients to postoperative radiation with or without concurrent chemotherapy. Although the two trials had slight differences in their inclusion criteria, they both established the importance of adjuvant chemoradiation in the setting of high-risk postoperative patients. A pooled data analysis from the two trials identified positive margins and extracapsular extension as the two significant risk factors for combining chemotherapy with radiation in the adjuvant setting.[127]

Recently, the question regarding whether induction chemotherapy followed by concurrent chemoradiation is superior to concurrent chemoradiation alone in locally advanced head and neck cancers was addressed in the PARADIGM trial.[128] In this study, patients were randomized to receive either induction chemotherapy with docetaxel, cisplatin, and 5-FU followed by concurrent chemoradiation with docetaxel or carboplatin compared to concurrent chemoradiation using cisplatin. Although the trial was terminated early because of poor patient accrual, results suggest no difference in overall survival between the two groups. However, a greater incidence of febrile neutropenia was noted in patients who received induction followed by concurrent chemotherapy compared to concurrent chemoradiation alone.

In 2006, Bonner et al published the results of a randomized phase III trial incorporating a molecularly targeted therapy with radiation in locally advanced head and neck cancers.[125] This trial used cetuximab, which is a monoclonal chimeric (mouse and human) antibody to EGFR. This trial showed not only a local control benefit but also an overall survival benefit when cetuximab was combined with radiation, including altered fractionation schedules. In addition, the incidence of serious toxicity (other than rash and transfusion reactions) was similar between the groups, which is in stark contrast to chemoradiation regimens that invariably have increased toxicity. These results have held up at the most recently published update[126] showing a 49-month median survival in the

TABLE 4-4 Selected Concomitant Radiation and Chemotherapy for Head and Neck Cancers

Study	Regimen	Outcomes
INT 0099 (1998)[116]	RT (70 Gy) vs. RT (70 Gy) + cisplatin (100 mg/m^2 q3 wks × 3) with adjuvant cisplatin (80 mg/m^2)/5-FU (1 g/m^2/d for 96 h q 4wks × 3)	At 5-yr update, PFS (58% vs. 29%), DFS (74% vs. 46%), and OS (67% vs. 37%) favors the CT-RT arm ($p < 0.001$)
Brizel et al (1998)[121]	RT (75 Gy at 1.25 Gy BID) vs. RT (70 Gy at 1.25 Gy BID) with concurrent cisplatin (12 mg/m^2/d) and 5-FU (600 mg/m^2 days 1-5) on weeks 1 and 6.	3-yr LRC favored CT-RT (70% vs. 44%, $p = 0.01$). 3-yr OS trends in favor of CT-RT (55% vs. 34%, $p = 0.07$).
RTOG 9111 (2003)[120]	3 arm trial of glottic and supraglottic cancer patients: RT(70 Gy) vs. sequential chemo (cisplatin 100 mg/m^2 + 5-FU g/m^2/d for 120 h q3wks × 3) then RT(70 Gy) vs. concurrent ChemoRT (cisplatin 100 mg/m^2 q3wks × 3)	No difference in OS but concurrent arm had superior local control (2-yr: 78% vs. 61% sequential vs 56% RT alone; $p \leq 0.003$) and highest organ preservation rate (88% vs. 75% vs. 70%; $p \leq 0.005$)
Adelstein et al (2003)[122]	3 arm trial: RT (70 Gy) vs. concurrent RT (70 Gy) + cisplatin (100 mg/m^2 q3wks × 3) vs. split course RT (30 Gy with cycle 1 and 30-40 Gy with cycle 3) + concurrent 5-FU (1 g/m2/d for 96 h) and cisplatin (75 mg/m^2) q4wks	The concurrent non-split cisplatin/RT arm had superior 3-ry OS (37% vs. 27% in split course CT-RT vs. 23% in RT alone; $p = 0.014$). Concurrent cisplatin/RT had highest rate of grade 3+ toxicity (89% vs. 77% vs 52%; $p < 0.0001$)
EORTC 22931 (2004)[123]	Postoperative RT (up to 66 Gy) vs. postoperative CT-RT (up to 66 Gy with cisplatin 100 mg/m^2 q3wks × 3) for potential high-risk head and neck cancer patients (Stage III/IV except T3N0 or T1-2N0-1 with +margins, +PNI, +ECE, +VSI, OC/OP primary with + LNs at levels 4-5)	Improvement in 5-yr OS (53% vs. 40%; $p = 0.02$), 5-yr PFS (47% vs 36%; $p = 0.04$), and 5-yr LRC (82% vs. 69%; $p = 0.007$) with CT-RT; Grade 3/4 mucositis was higher in CT-RT arm (41% vs. 21%; $p = 0.001$)
RTOG 9501 (2004)[124]	Postoperative RT (up to 66 Gy) vs. postoperative CT-RT (up to 66 Gy with cisplatin 100 mg/m^2 q3wks × 3) for potential high risk head and neck cancer patients (2 or more +LNs, +ECE, + margins)	Improvement in 2-yr DFS (54% vs. 44%; $p = 0.04$) and LRC (82% vs. 72%; $p = 0.01$) with trend toward better OS (63% vs. 57%, $p = 0.19$); Higher rate of grade 3 or greater acute toxicity in chemoRT arm (77% vs. 34%; $p < 0.001$)
Bonner et al (2006[125] and 2010[126])	Once Daily RT (70 Gy at 2 Gy/d), concomitant boost (72 Gy in 42 fxs) or hyperfractionated (72-76.8 Gy at 1.2 Gy BID) ± cetuximab (given 1 week before RT at 400 mg/m^2 then given weekly at 250 mg/m^2 × 7 wks)	Improvement in MS (49 vs. 29.3 months) and 5-yr OS (45.6% vs. 36.4%) in the cetuximab arm (HR of 0.73; $p = 0.018$). No difference in grade 3 or 4 toxicity, including mucositis, (except acneiform rash and infusion reaction).
MACH-NC meta-analysis[117]	Meta-analysis of 93 randomized trials of CT in head and neck cancer, with 17,346 patients.	Concomitant CT-RT provides absolute 5-yr OS benefit of 6.5% whereas induction chemo showed only 2.4% (HR of 0.81; $p < 0.0001$).

5-FU, *5-Fluorouracil;* BID, *twice per day;* CT, *chemotherapy;* CT-RT, *chemoradiation;* DFS, *disease-free survival;* ECE, *extracapsular extension;* EORTC, *European Organization for Research and Treatment of Cancer;* INT, *intergroup;* LN, *lymph nodes;* LRC, *loco-regional control;* MACH-NC, *meta-analysis of chemotherapy in head and neck cancer;* MS, *median survival;* OC/OP, *oral cavity/oropharynx;* OS, *overall survival;* PFS, *progression-free survival;* PNI, *perineural invasion;* RT, *radiation therapy;* RTOG, *Radiation Therapy Oncology Group;* VSI, *vascular space invasion.*

cetuximab arm and 29.3 months in the radiation alone arm. Five-year OS was 45.6% in the cetuximab group and 36.4% in the radiation alone group (hazard ratio, 0.73; $p = 0.018$).

Several trials are accruing or recently closed combining cetuximab with chemoradiation including the Phase III RTOG 0522 randomizing patients with stage III and IV squamous cell carcinoma of the oropharynx, hypopharynx, and larynx to cisplatin (100 mg/m^2 every 3 weeks) with or without a 1-week pretreatment (400 mg/m^2) and concurrent (250 mg/m^2/week) cetuximab with accelerated fractionation. Initial reports suggest the addition of cetuximab to concurrent chemoradiation does not improve clinical outcomes.[129] Final results should be forthcoming.

The human papilloma virus (HPV) has been implicated as a major cause of head and neck cancers.[130] Interestingly, patients with HPV-associated head and neck cancers have improved outcomes over patients with cancers not associated with HPV. It has been suggested that this may be as a result of an inherent DNA repair defect in HPV-associated head and neck tumors. Thus, efforts by ECOG and RTOG are under way to deescalate therapy in attempts to reduce the morbidities of therapy. The ECOG E1308 is a phase II trial, which tests the efficacy of reducing radiation doses and using concurrent cetuximab rather than chemotherapy in patients who have achieved a complete response to induction chemotherapy. Initial results are promising, with an 86% overall response rate observed in enrolled patients, and more importantly, decreased toxicities compared to historical controls.[131] The RTOG 1016 is a phase III trial randomizing patients to concurrent chemoradiation or cetuximab/radiation. This study is currently nearing completion of accruing the necessary number of patients.

Non–Small Cell Lung Carcinoma

Non–small cell lung carcinoma (NSCLC) is the number-one cause of cancer death in the United States, which is at least partly the result of the late presentation that typically occurs with this disease. As such, most patients will present with stage III disease or stage IV.

The treatment of stage III NSCLC has evolved over the past two decades. For unresectable stage III patients, EBRT alone produced poor 2-year OS, on the order of 20%. A modest improvement (up to 29%) was achieved with more intense radiation schedules such as the continuous hyperfractionated accelerated radiotherapy (CHART) regimen.[132]

To improve on these outcomes, the approach that was most heavily tested was the addition of systemic agents to EBRT, which is summarized in Table 4-5. Three major trials of

TABLE 4-5 Concomitant Radiation and Chemotherapy for Non–Small Cell Lung Cancer

Study	Regimen	Outcome
Dillman et al[133] (CALGB 8433 updated[141])	Sequential cisplatin (100 mg/m^2 d1 and 29) and vinblastine (5 mg/m^2 weekly × 5) followed by RT (60 Gy) vs. RT alone (60 Gy)	Improved MS (13.7 vs. 9.6 mo.; p = 0.012) with CT-RT
Sause et al[134] (RTOG 8808 updated[142])	Three-arm trial: sequential cisplatin (100 mg/m^2 d1 and 29) and vinblastine (5 mg/m^2 weekly × 5) followed by RT (60 Gy) vs. HyperFx RT (69.6 Gy at 1.2 Gy BID) vs. RT alone (60 Gy)	Improved MS (13.2 vs. 12 vs. 11.4 mo.; p = 0.04) with CT-RT
Furuse et al[138]	Chemo of cisplatin (80 mg/m2 on d1 and 29), vindesine (3 mg/m^2 on d1, 8, 29, and 36), and mitomycin C (8 mg/m^2 on d1 and 29) given either concurrently with split course RT (28 Gy × 2, 10 days apart) or sequentially with RT (56 Gy)	Improved MS (16.5 vs. 13.3 mo.; p = 0.03998) with concurrent CT-RT
Curran et al[137] (RTOG 9410)	Three-arm trial: cisplatin (100 mg/m^2) and vinblastine (5 mg/m^2) given before (Arm 1) or concurrently with once daily RT (Arm 2, 60 Gy), or concurrent cisplatin (50 mg/m^2) and oral etoposide (50 mg BID) with HyperFx RT (Arm 3, 69.6 Gy at 1.2 Gy BID)	Improved MS (17 mo.) in concurrent once daily CT-RT arm (arm 2) va. 15.6 mo (arm 3) va. 14.6 mo. (arm 1) (p = 0.038)
Albain et al[143] (INT 0139)	Stage IIIA patients received two cycles of chemo: cisplatin (50 mg/m^2 on d1, 8, 29, and 36) and etoposide (50 mg/m^2 on d1-5 and 29-33) plus 45 Gy. If no progression, they were randomized to surgery or 16 Gy boost. All patients received 2 adjuvant cycles of cisplatin/etoposide	No difference in MS, or 5-yr OS; improved median PFS in trimodality arm (12.8 vs. 10.5 mo.; p = 0.017); in subset analysis, improved OS in patients who underwent lobectomy vs. CT-RT, but CT-RT was better if patient underwent pneumonectomy.
Thomas et al[144] (GLCCG)	Patients received three cycles of cisplatin and etoposide and were randomized to CT-RT with concurrent carboplatin and vindesine followed by S or S followed by RT alone.	Preoperative CT-RT resulted in increased pathological response but no improvement in PFS. For patients requiring pneumonectomy, preop CT-RT had trend to increased Tx-related mortality (14% vs. 6%; p = 0.14)

BID, *Twice daily;* CALGB, *Cancer and Leukemia Group B;* CT-RT, *chemoradiation;* INT, *intergroup;* GLCCG, *German Lung Cancer Cooperative Group;* HyperFx, *hyperfractionation;* mo., *months;* MS, *median survival;* OS, *overall survival;* PFS, *progression-free survival* RT, *radiation therapy;* RTOG, *Radiation Therapy Oncology Group;* S, *surgery;* Tx, *treatment.*

sequential chemotherapy followed by radiation were published in the 1990s that showed improvement with the addition of platinum-based chemotherapy.[133-135] Around the same time, a meta-analysis demonstrated a small, but significant improvement with the addition of chemotherapy.[136] However, because the various trials included many different sequences of chemotherapy and radiation, it was unclear what would be the best regimen. Therefore, several randomized phase III trials compared sequential to concurrent chemoradiation.[137-140] In all but one trial,[140] the concurrent arm showed a significant improvement relative to sequential chemotherapy and irradiation. This established concurrent chemoradiation as the treatment of choice. What was not clear, however, was whether adjuvant chemotherapy could be added to concurrent chemoradiation regimens, and if so, if it was better to administer the chemotherapy neoadjuvantly or adjuvantly.

A phase II trial called the Locally Advanced Multimodality Protocol (LAMP) trial attempted to determine what would be the best approach.[145] The three arms in this trial included (1) neoadjuvant chemotherapy followed by radiation, (2) neoadjuvant chemotherapy followed by concurrent chemoradiation, and (3) concurrent chemoradiation followed by adjuvant chemotherapy. Although the concurrent followed by adjuvant arm had the best outcome, the trial had some limitations including insufficient power to determine the best regimen.[145]

Although concurrent chemoradiation is the standard approach for stage III NSCLC, there are certain instances in which surgery can be combined with chemoradiation in a trimodality approach. Two major randomized trials have been published regarding this trimodality approach, which are also included in Table 4-5 (U.S. Lung Intergroup 0139[143] and the German Lung Cancer Cooperative Group[144] trials). Both trials appeared to show that trimodality therapy was feasible, but that preoperative chemoradiation should be avoided if a pneumonectomy would be performed due to excessive treatment related mortality.

Cervical Cancer

One of the clearest clinical examples demonstrating improved outcomes of combined chemoradiation is in locally advanced cervical cancer. Cisplatin-based regimens have had clear success in a series of randomized phase III trials showing not only improvement in local-regional control but in also OS. This series of clinical trials (summarized in Table 4-6) had differing inclusion criteria and various treatment approaches, yet, these trials presented convincing evidence that cisplatin, when combined with radiation, improves outcome in locally advanced cervix cancer. An excellent review of the historical context and remaining controversies regarding these trials is available,[146] so they will only briefly be discussed here.

The Gynecological Oncology Group (GOG) had three positive trials for chemoradiation as a component of treatment. The GOG 85 trial investigated two different concurrent chemotherapy regimens (hydroxyurea and cisplatin/5-FU) with radiation for patients with locally advanced cervix cancer.[147] This trial demonstrated that concurrent cisplatin/5-FU was superior to hydroxyurea (5-yr OS 62% vs. 50%, p = 0.018). GOG 120 was a three-arm trial that compared radiation alone to two different cisplatin containing regimens (one with cisplatin alone and the other with cisplatin plus 5-FU and hydroxyurea).[148] The two cisplatin-containing arms were superior to the control arm (3-yr OS for both cisplatin based arms of 65% vs. 47%, $p < 0.005$). Since the cisplatin alone arm was less toxic than the 5-FU/hydroxyurea combination, the concurrent cisplatin/radiation approach was preferred. The GOG also

TABLE 4-6 Concomitant Radiation and Chemotherapy for Cervix Cancer

Study	Regimen	Outcome
GOG 85 (1999)[147]	IIB-IVA patients; RT + HU (3 g/m^2 twice per week) vs. RT + Cisplatin (50 mg/m^2)/5-FU(4 g/m^2/96 h)	Improved PFS (RR of 0.79, $p = 0.033$) and improved OS (5-yr: 62% vs. 50%, RR of 0.74, $p = 0.018$) in cisplatin containing arm
GOG 120 (1999)[148]	IIB-IVA patients; three arms: Cisplatin (40 mg/m^2/week) vs. Cisplatin (50 mg/m^2)/5-FU (4 g/m^2/96 h) with HU (2 g/m^2 twice per week) vs. HU (3 g/m^2 twice per week)	Improved PFS (RR of 0.57 and 0.55, $p < 0.001$) and improved OS (3-yr: 65% vs. 47%, RR of 0.61 and 0.58, $p < 0.005$) in both cisplatin containing arms
GOG 123[149]	IB (tumors ≥4 cm) patients; RT ± cisplatin (40 mg/m^2/week)	Improved PFS (RR of 0.51, $p < 0.001$) and improved OS (3-yr: 83% vs. 74%, RR of 0.54, $p < 0.008$) in cisplatin containing arm
SWOG 8797 (2000)[150]	I-IIA patients after hysterectomy with high-risk features (positive nodes, positive margins, or parametrial involvement); RT ± cisplatin(70 mg/m^2)/5-FU(4 g/m^2/96 h)	Improved PFS (HR of 2.01, $p = 0.003$) and improved OS (4-yr: 81% vs. 71%, HR of 1.96, $p = 0.007$) in cisplatin containing arm
RTOG 9001[151]	IB-IIA (≥5 cm), IIB-IVA (or positive pelvic nodes) patients; RT ± cisplatin (75 mg/m^2)/5-FU(4 g/m^2/96 h)	Improved 5-yr DFS (67% vs. 40%, $p < 0.001$) and improved 5-yr OS (73% vs. 58%, $p = 0.004$) in cisplatin containing arm
NCIC[152]	IB-IIA (≥5 cm), IIB-IVA (or positive pelvic nodes) patients; RT ± cisplatin (40 mg/m^2/week)	No difference in PFS or OS

5-FU, *5-Fluorouracil;* DFS, *disease-free survival;* GOG, *Gynecological Oncology Group;* HR, *hazard ratio;* HU, *hydroxyurea;* NCIC, *National Cancer Institute Canada;* OS, *overall survival;* PFS, *progression-free survival;* RR, *relative risk;* RT, *radiation therapy;* RTOG, *Radiation Therapy Oncology Group.*

investigated the importance of chemotherapy with radiation for patients in bulky stage IB treated with hysterectomy in GOG 123. In this trial, the patients were randomized to radiation alone versus radiation plus weekly cisplatin before undergoing hysterectomy.[149] Once again, the cisplatin-containing arm was superior (3-yr OS 83% vs. 74%, $p = 0.008$).

In the 1990s, the RTOG also examined the importance of cisplatin with radiation for patients with locally advanced cervix cancer. RTOG 9001 compared extended field radiation alone to pelvic radiation plus cisplatin and 5-FU.[150] The chemoradiation arm was superior to the extended field irradiation (5-yr OS 73% vs. 58%, $p = 0.004$).

The fifth trial to support concurrent cisplatin/radiation was the Intergroup 0107/SWOG 8797, which tested chemoradiation in the adjuvant setting for patients that underwent hysterectomy with high-risk features at time of surgery including positive pelvic nodes, positive margins, and parametrial involvement.[151] Patients were randomly assigned to receive radiation alone or radiation with cisplatin/5-FU. The chemoradiation group was again superior (4-yr OS 81% vs. 71%, $p = 0.007$).

Only one major trial, from National Cancer Institute of Canada (NCIC), failed to demonstrate an OS benefit for this approach.[152] However, that trial has been criticized because of the small size and wide confidence intervals that may have prevented a difference from being detected.

The next generation of chemoradiation trials is adding molecularly targeted agents, including cetuximab and tirapazamine, to standard cisplatin-based regimens.

Genitourinary Cancer

Chemoradiation is established as the standard bladder preserving management strategy for muscle invasive bladder cancer. Shipley et al[153] published a single institution experience using a neoadjuvant chemoradiation approach similar to the larynx preservation trials discussed previously in which a cisplatin-containing chemoradiation regimen is given (following a maximal transurethral resection of bladder tumor [TURBT]), an evaluation for tumor response is then performed followed by either surgery (for anything less than a complete response) or consolidative chemoradiation. With this approach, the 5-year OS is comparable to surgical series at 54%. Bladder preservation rates without invasive local recurrence are ~50%.

Another genitourinary example involving the use of hormone ablation therapy plus EBRT for high-risk prostate cancer demonstrates a local control, DFS, biochemical DFS, and possibly an OS benefit based on both RTOG[154-156] and EORTC[157,158] experience. It has been postulated that androgen-deprivation therapy used in concomitant radiation regimens not only provides a spatial cooperation interaction but also a biological cooperation function. Currently, the RTOG is investigating the addition of TAK-700 (Orteronel), which suppresses adrenal androgen production, to concurrent EBRT and standard androgen deprivation therapy for high-risk prostate cancer patients (RTOG 1115) in attempts to maximally suppress androgen production.

Glioblastoma

The treatment of glioblastoma has dramatically changed in recent years based on the encouraging findings from the phase III trial from EORTC and NCIC. This trial, first published by Stupp et al in 2005[159] and updated with 5-year data,[160] demonstrated a remarkable improvement in median survival (14.6 vs. 12.1 months) and OS (9.8% vs. 1.9% at 5 years; hazard ratio, 0.63; $p < 0.0001$) with the use of concurrent temozolomide and radiation with adjuvant temozolomide. Prognostic[161-163] and possibly predictive[164] information can be garnered from evaluating the MGMT promoter methylation status because it has been shown that patients whose tumors have MGMT epigenetic silencing as a result of promoter hypermethylation do better.

FUTURE DIRECTIONS

Molecular Prediction

One of the current ideals for the medical field is to develop personalized or "precision" medicine for patients. For the oncology field, the identification of biomarkers for prognosis and response to therapy is of critical importance for achieving this ideal. Perhaps the most promising strategy toward personalized medicine in oncology has been the investigation of synthetic lethal interactions between two distinct pathways, which can be exploited therapeutically.[165] This concept of synthetic lethality is one in which mutation or loss of either of the two pathways individually has no effect on survival; however, mutation or loss of both leads to cell death. To this end, inhibitors of poly(ADP)-ribose polymerase (PARP) have come to the forefront for patients with BRCA-associated cancers.[166,167] PARP is involved in the base excision repair of single-stranded DNA

damage, which if left unrepaired, is converted into a double-stranded DNA break that can be repaired by the homologous recombination repair pathway mediated by BRCA. In patients with BRCA-associated tumors, which are homologous recombination repair defective, inhibition of PARP leads to significant cytotoxicity of tumors while sparing normal tissues, which are proficient in homologous recombination repair. This exciting therapeutic strategy has shown promise in multiple clinical trials and exemplifies the ultimate goal of personalized therapy—that is, to maximize therapeutic ratio.

The predominant investigative tools for biomarker discovery are related to genomics and proteomics, the study of global gene expression and protein expression, respectively. An emerging science is that of kinomics in which global kinase activity is determined. These expression or activation patterns of individual tumors can be correlated to outcomes including treatment response and survival endpoints. The hope is that diagnostic tests can be developed that will guide clinicians in selection of therapy. A brief description of each discovery tool is found here.

Genomics/Transcriptomics

The most actively studied component of molecular prediction uses genomic technology. Genomics refers to the genome-wide evaluation of individual gene expression. Pharmacogenomics refers to the study of genetic information to predict treatment response. There are a host of platforms for analyzing genetic information within a biologic specimen. One means is through evaluation of polymorphisms, which refers to a variation within a gene such that at least two alleles occur in 1% or more of the general population. When the variation occurs at a single nucleotide, this is termed a *single nucleotide polymorphism*, or SNP. Several groups have identified SNPs within DNA synthesis/DNA repair genes that could potentially serve as markers of response to radiation,[168] chemotherapy,[169] or chemoradiation.[170] Genome-wide SNP arrays are commonly used these days and have been applied to translational studies. Historically, though, the most widely used approach has been microarray-based, such as the GeneChip from Affymetrix (Santa Clara, CA). These arrays enable the analysis of relative expression of more than 38,000 genes on a single chip. However, with the advent of next-generation sequencing (NGS or "deep sequencing") ushering in lower costs and higher throughput, NGS approaches are largely replacing microarray-based methods. For example, the RNASeq approach can provide gene expression information (transcriptome) but also provide information about genomic alterations (at least for the expressed genome). Focused exome NGS is being used to identify drug-targetable mutations in patient tumors. NGS approaches are now the methodology of choice for The Cancer Genome Atlas (TCGA) project that is cataloging molecular data on 20 tumor types that has already identified many molecular subtypes among several cancer types.[171]

No matter what platform is used, the identification of genomic/transcoptomic differences between good and poor responders may eventually guide therapy decisions. A significant amount of work has been done in predicting breast cancer response to chemotherapy in vivo.[172] Similar studies for radiation and chemoradiation response are in various stages of development.

Proteomics

Proteomics is becoming an established platform for biomarker discovery. The predominant approach involves mass spectrometry to identify levels of proteins based on peptide fragments generated from enzymatic digestion of all of the proteins within a biologic specimen such as a biopsy, tissue sample, blood, urine, etc. This approach has been used for prognostic purposes in NSCLC[173] as well as prediction of sensitivity to chemoradiation in cervical cancer patients.[174] Miniaturization with nanofluidic assays[175] and novel dynamic-proteomics[176] approaches are providing more information and understanding regarding cellular response to drugs.

Kinomics

Although genomic and proteomic strategies are being used in translational components of several clinical trials with RTOG and other cooperative groups, these technologies have significant difficulty in detecting transient signaling events such as kinase activation. This is as a result of the fact that kinases are predominantly regulated posttranslationally, that is, they are subject to phosphorylation events, conformational changes, subcellular translocation, binding partnerships, etc. Kinomics, thus, refers to the global detection of kinase signaling events within a cell or tissue. There is a tremendous amount of preclinical data that demonstrates robust but transient activation of kinase-based resistance pathways downstream of ionizing radiation and chemotherapy.[177-181] Arguably, the most prominent class of next-generation therapeutics for oncology is kinase-targeted agents. In the near future, there may be a large repertoire of available kinase inhibitors that are available for therapy if we could only identify the patients most likely to benefit from them. Kinomic analysis may help guide therapy by identifying the critical kinase activations that predict for sensitivity or resistance to particular drugs. Although this technology is still in its infancy, kinomics may one day provide a complementary clinical tool to the genomic and proteomic strategies that are making their way into oncology practice. Indeed, the TCGA selected reverse phase protein arrays (RPPA) as their platform technology for functional proteomic evaluation of tumors.[182] Other translational research examples include kinomic profiling of pediatric brain tumors,[183] chondrosarcomas,[184] preclinical xenograft treatment response prediction,[185] chemoradiation response prediction in locally advanced rectal cancer patients,[186] and even for identification of novel radiation modulators.[187]

Patient-Derived Xenografts

One potential strategy to improve molecular prediction is to use better preclinical model systems for combination testing. Patient-derived xenografts (PDX, xenolines, or tumor avatars) have been increasingly used as preclinical model systems. PDX appear to more faithfully represent clinical reality because they are passaged within immunocompromised mice rather than cultured in plastic with high levels of serum. "-Omic" characterization and therapy response data have shown considerable promise leading many pharmaceutical companies and some academic institutions to incorporate PDX into their preclinical testing program. Indeed, several companies specializing in PDX production and therapy testing have emerged in recent years. One potential strategy for integrating PDX into therapeutic development is the concept of a "parallel mouse" clinical trial that can be performed in conjunction with an actual human clinical trial. The incorporation of the parallel mouse trial allows for a larger cohort of tumor specimens to be available for molecular characterization and biomarker development. The potential for PDX-informed clinical decision making could be possible with this approach.

SUMMARY

Multimodality therapy has become the mainstay of the vast majority of solid malignancies. Understanding the interaction between chemotherapy and radiation is, therefore, vital to improving patient care. With the addition of biologically targeted agents to the armamentarium of anticancer therapy, it

may be better to refer to chemotherapeutics and biologics simply as systemic agents. It is expected that clinical investigation will help validate as well as generate novel strategies in the laboratory. In addition, the establishment of useful biomarkers will hopefully usher in a new era of personalized oncologic medicine. In this way, exploitable differences between tumor tissue and normal tissue will be optimized for each patient.

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