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Cancer Concepts and Principles: Primer for the Interventional Oncologist-Part II

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INTRODUCTION

This is the second of two parts of an overview of the fundamentals of oncology for interventional radiologists. The first part focused on clinical trials, basic statistics, assessment of response and overall concepts in oncology. This second part aims to review the methods of tumor characterization, principles of the oncology specialties, including medical, surgical, radiation and interventional oncology, as well as the current treatment paradigms for the most common cancers encountered in interventional oncology along with the levels of evidence that guide these treatments.

TUMOR CHARACTERIZATION AND MANAGEMENT

Staging

Tumor staging reflects the extent of disease, determines treatment and therapeutic options, and has specific prognostic implications. Clinical staging refers to non-invasive staging, including physical examination and imaging evaluation, while pathologic staging refers to findings from tissue specimens and allows for the identification of the microscopic extent of

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disease that may be subclinical, or not apparent, on physical examination or imaging. For this reason, clinically and pathologically staged patient populations are not necessarily identical and comparable in terms of outcomes.

Staging systems vary with tumor types. The International Union Against Cancer (*Union Internationale Contre le Cancer*, UICC) and the American Joint Committee on Cancer (AJCC) systems were unified into a single and one of the most common staging systems, which characterizes cancers according to the TNM classification. Cancers are then divided into stages 0 through IV to guide treatment and prognosis (1). Additional staging systems exist, such as for hepatocellular carcinoma, that will be addressed further in this review.

Systemic and Tissue-Specific Tumor Markers

Tumor markers generally refer to a variety of substances, including gene mutations, proteins and metabolites, that can be measured in tumor tissues, blood or other body fluids. Tumor markers can be produced by both cancerous and normal cells. Certain tumor markers are specific to a type or histology of cancer, whereas others may be elevated in several different cancers. The markers may play a role in cancer detection, diagnosis, staging, prognosis and response assessment. The National Cancer Institute provides a concise summary of the most common tumor markers used in oncology, from which Table 1 is derived (2). Interventional oncologists should be well-versed with these tumor markers, as they play an integral role in cancer management.

Methods of Treatment: Medical, Surgical, Radiation and Interventional Oncology

The anti-cancer armamentarium includes chemotherapeutic agents, biologic therapies that target specific molecules in the cell-signaling pathways, radiation, surgical and interventional oncology. While most cancer treatments utilize a combination of many, if not all, of these modalities, the timing of administration of these treatments can result in synergistic, detrimental or toxic clinical outcomes.

The Physician Data Query (PDQ) of the National Cancer Institute and the National Comprehensive Cancer Network (NCCN) guidelines provide up-to-date information on standard treatment regimens for various cancers and stages, in addition to references to experimental protocols and clinical trials as alternatives to standard regimens (3, 4).

Toxicity is the critical, potentially fatal, limiting factor of any cancer treatment, including chemotherapy and radiation. Therapeutic regimens are designed with toxicity in mind in order to avoid overlapping or synergistic toxicities. Consistently evaluating and addressing treatment toxicities is inherent to the practice of oncology and toxicities should be recognizable to all practitioners involved in the care of cancer patients. The Common Terminology Criteria for Adverse Events (CTCAE) provide a standardized classification of toxicities and side-effects related to chemotherapy released by the National Cancer Institute (5). Toxicities are graded according to severity, in which grade 1 is mild, grade 2 is moderate, grade 3 is severe, grade 4 is life-threatening and grade 5 refers to toxicity resulting in death. In general, only grades 3 or greater are reported, since grades 1 and 2 are considered clinically acceptable toxicities related to treatment. This lexicon should be used when describing toxicities related to any oncologic treatment or intervention. Furthermore, there is often a 30-day cut-off after which, many adverse events are not deemed to be treatment-related.

a) Medical Oncology: Chemotherapy—Chemotherapy is most frequently delivered as a regimen of multiple chemotherapeutics in order to maximize tumor cell kill and while minimizing toxicity. The synergistic effects of multiple agents increase the interaction

between chemotherapy and tumor cells, and reduce the likelihood of tumor cells developing drug resistance. Because bone marrow cells are often the most sensitive to chemotherapy, standard treatment regimens have traditionally been designed with regard to bone marrow recovery in order to prevent myelosuppression (6).

While chemotherapeutics are often administered with the intention to cause tumor cell kill, or cytotoxicity, a number of chemotherapy regimens, and particularly those incorporating the molecularly-targeted therapies discussed subsequently in more detail, provide clinical value in terms of cytostasis rather than cytotoxicity. Effective cytostasis manifests as the inhibition of tumor cell growth or prevention of metastases—namely *stable disease*—as opposed to tumor shrinkage (7).

Classes of chemotherapeutic agents include alkylating agents, platinum analogs, antimetabolites, topoisomerase-interacting agents and antimicrotubule agents. Table 2 lists the most commonly encountered chemotherapeutic agents in interventional oncology.

Chemotherapy use generally occurs in one of four clinical settings. In primary induction, chemotherapy is administered as the initial treatment for advanced cancers for which no alternative treatment, such as surgical resection, exists. Neoadjuvant chemotherapy refers to chemotherapy administered prior to surgical resection in order to reduce the size of the primary tumor or minimize the extent of disease in order to increase the likelihood of an R0 resection, which indicates surgical margins free of tumor. Neoadjuvant chemotherapy can also reduce the extent of disease in order to spare critical organs or tissues that would otherwise be included in the surgical resection. In certain instances, successful neoadjuvant chemotherapy can obviate the need for resection, making the cancer amenable instead to radiation therapy. Response to neoadjuvant therapy is an important indicator of tumor sensitivity to the chemotherapeutic agents and can help guide their use for post-surgical adjuvant therapy. Adjuvant chemotherapy refers to chemotherapy used in conjunction with local treatment, such as surgical resection and radiation therapy. Adjuvant chemotherapy addresses micrometastases in order to reduce the risk of local or distant recurrence. Locoregional chemotherapy is directly administered to an affected organ or site, increasing the tumor-to-systemic chemotherapy ratio, such as in chemoembolization of liver tumors or intra-peritoneal chemotherapy for peritoneal carcinomatosis (6).

Although not specific to chemotherapy, first-line therapy refers to the first set of chemotherapeutic, surgical or radiation treatments provided that is generally accepted as the standard and “best” treatment. If this therapy does not result in a cure, or cannot be tolerated because of severe side-effects, other treatments, referred to as second-line therapy may be used instead. Salvage therapy refers to treatment provided after a failure to respond to other treatments (8). It should be noted that despite being a commonly used term, the definition of a “line” of chemotherapy is nebulous. Chemotherapy regimens for patients may be modified or adjusted in real-time. In such cases, this does not necessarily represent a different “line” of therapy. As an example, in colon cancer, chemotherapies received by a specific patient should be described as exposure to the cytotoxic active agents (5FU, oxaliplatin, irinotecan) and the biologics (see later).

b) Medical Oncology: Molecularly-Targeted Therapies—Molecularly-targeted therapies are designed to interact with specific molecules in cell signal transduction pathways in order to interfere with tumor cell growth or proliferation. Molecular subtyping of cancers has therefore become increasingly important in the era of molecularly-targeted therapies in order to ensure the cancer has a phenotype that will respond to the molecular agent. Common molecular subtyping includes evaluation for the presence of epidermal growth factor receptor mutations in non-small cell lung cancer, KRAS mutations in

colorectal cancer, and HER2/neu amplification in breast cancer (9–11). As shown the Table 1, almost all biomarkers used for molecular-targeted therapies necessitate tumor samples, often performed by interventional radiologists.

Epidermal growth factor receptors (EGFR) may be abnormally activated or expressed in several carcinomas, and the binding of small molecules (ligands) to these receptors initiates a number of signaling pathways via tyrosine kinase activation, which can ultimately affect cell proliferation, survival and invasion (12). Cetuximab is a monoclonal antibody that binds to a specific domain of the EGFR and has shown important antitumor activity and clinical responses in patients with chemotherapy-refractory or resistant colorectal cancers (13–17). However, the presence of a genetically mutated KRAS protein, which is a downstream signaling protein in the EGFR signaling cascade, causes a decreased or lack of response to cetuximab, resulting in a worse prognosis compared to patients with the wild-type KRAS protein (16, 18, 19).

Panitumumab is another monoclonal antibody that binds to the EGFR to prevent cell signaling, thereby inhibiting proliferation and promoting tumor cell apoptosis (20). It has shown significant clinical response when used in patients with chemotherapy-resistant metastatic colorectal cancer, or as an addition to first-line treatments of metastatic colorectal cancer (21, 22). The response to panitumumab is also affected by KRAS mutations (23). Therefore, patients with mutant KRAS protein in the setting of colorectal cancer are frequently not candidates for either cetuximab or panitumumab therapies.

Physiologic angiogenesis generally only occurs during embryogenesis, wound healing and placental development (24). Tumor angiogenesis, required for tumor growth, has generally lost the physiologic balance between positive and negative angiogenetic controls, resulting in neovasculature that is morphologically different from that of normal tissues. Tumor vasculature is leaky, which further affects tumor growth, metastasis, and drug delivery (25).

Bevacizumab is a monoclonal antibody that targets tumor angiogenesis. It binds to one of the vascular endothelial growth factor receptor (VEGFR) ligands, limiting ligand interaction with and activation of the receptor, and ultimately causing regression of tumor microvessels and inhibiting the formation of new tumor vasculature (26). The addition of bevacizumab to standard first- and second-line chemotherapy regimens for metastatic colorectal cancer has shown significant improvements in disease progression and overall survival (27–30), and its addition to standard first-line therapy has shown survival benefits for patients with stage IIIB and IV non-small cell lung cancer (31).

Aflibercept is another antiangiogenetic molecule that binds to multiple VEGFR ligands (32). The addition to aflibercept to standard second-line chemotherapy regimens containing irinotecan for metastatic colorectal cancer has shown significant increases in progression-free and overall survival (33).

Sunitinib is a multiple tyrosine kinase inhibitor, including those of the VEGF receptors and platelet-derived growth factor receptors (PDGFR), among others. Its use in advanced pancreatic neuroendocrine tumors has shown significant increases in clinical response and overall survival compared to placebo (34). Sunitinib has shown favorable outcomes in the treatment of metastatic renal cell cancer compared with standard cytokine therapy resulting in significantly prolonged median progression free survival and a strong trend toward improved overall survival (35, 36).

The mammalian receptor of rapamycin (mTOR) is a serine-threonine kinase that plays an important role in autocrine stimulation of cell growth, proliferation and angiogenesis.

Everolimus inhibits mTOR and has shown significant improvements in progression-free survival for patients with progressive advanced pancreatic neuroendocrine tumors (37).

Octreotide is a synthetic analog of the native peptide hormone somatostatin. The native hormone inhibits a number of physiologic functions throughout the gastrointestinal tract. Octreotide binds to various somatostatin receptors and has been shown to have significant anti-proliferation effects in neuroendocrine tumors (38).

Sorafenib is also a multiple kinase inhibitor that causes inhibition of tumor-cell proliferation and angiogenesis, as well as increases the rate of apoptosis. Sorafenib has shown survival benefits for patients with advanced renal cell carcinoma who have failed first-line therapy (39). Its use in advanced hepatocellular carcinoma has resulted in significant increases in overall survival and is now the only standard systemic therapy for advanced HCC (40, 41).

Regorafenib is a multiple kinase inhibitor that has demonstrated significant survival benefits for patients with gastrointestinal stromal tumors (GIST) and metastatic colorectal cancer. For patients with metastatic or unresectable GIST who have failed standard treatment with imatinib or sunitinib, regorafenib has been shown to increase progression-free survival compared to placebo (42). Regorafenib has also demonstrated an increased median survival compared to placebo for patients with metastatic colorectal cancer that has progressed on all standard therapies (43).

c) Surgical Oncology—Surgery has several roles in the diagnosis and treatment of cancer, including tissue diagnosis, definitive surgical treatment for a primary cancer, tumor debulking, resection of metastatic disease with curative intent, treatment of oncologic emergencies, palliation, and reconstruction. The decision for surgical intervention is not only driven by technical feasibility (resectability), but also by the patient's physical condition and ability to undergo surgery (operability). For instance, suboptimal performance status or severe coronary heart disease could preclude major surgery; interventional oncology procedures play a key role in such cases. Hence, non-operability is a frequent pathway leading to interventional oncology therapies.

Curative surgery intends to remove a tumor in its entirety, including an adequate margin of uninvolved tissue in order to eliminate the chance of residual, micro-invasive tumor. The definition of adequate margins of tissue varies from cancer to cancer and is defined by the findings of clinical trials. An R0 resection indicates the complete removal of a tumor and tumor-free margins at surgical pathology. An R1 resection indicates the presence of tumor cells at the margins at surgical pathology (microscopic). An R2 resection indicates that visible (macroscopic) tumor remained at the time of surgical resection (44).

Resection of a single or few metastases can often be curative, particularly for the metastases of solid tumors to the liver or lungs. Resection of solitary pulmonary metastases in certain sarcomas and adenocarcinomas can provide long-term survival rates approaching 30%-70% depending on the cancer of origin (45, 46). Resection of hepatic metastases of colorectal cancer in patients without additional extrahepatic metastases can provide 5-year survival approaching 60% depending on the extent of liver involvement (47, 48). Preoperative scoring prior to resection of hepatic colorectal metastases has been shown to be highly predictive of outcome. Poor long-term outcome was associated with a node-positive primary, a disease-free interval from primary disease to metastasis less than 12 months, more than one hepatic metastasis, the size of the largest hepatic lesion exceeding 5 cm, and a CEA level greater than 200 ng/mL (47).

For certain cancers, tumor debulking, or cytoreductive surgery, which refers to the removal of as much of the primary or metastatic disease as possible knowing that viable tumor is left behind, may prolong survival, or at least offer significant symptom palliation. Resection of functional neuroendocrine metastases in the liver, for example, will not be curative but may prolong survival and improve quality of life by reducing the biochemical and hormonal effects of the functional neuroendocrine tumor cells. Cytoreductive surgery has become standard of care in the treatment of certain advanced ovarian and uterine cancers. Cytoreductive surgery for advanced ovarian cancer, in which successful therapy is defined as removal of all disease >1 cm in size, results in significant prolongation of both progression-free and overall survival (49), while cytoreductive surgery to no gross residual disease in advanced and recurrent endometrial cancer is associated with prolonged overall survival (50).

Surgical oncology for cancer prevention includes prophylactic surgery for the removal of organs prior to evident disease in circumstances of very high risk, such as total proctocolectomy for patients with polyposis syndromes or long-standing ulcerative colitis to prevent colon carcinoma, total thyroidectomy in certain MEN syndromes, and bilateral mastectomy and oophorectomy in the setting of BRCA 1 and BRCA 2 mutations. Palliative surgery in the cancer patient includes surgery to address intractable pain, bleeding, bowel obstruction or infection (8).

Knowledge of the Couinaud segmental anatomy of the liver is critical for understanding oncologic hepatic resections (Figure 1). The eight hepatic segments have their own hepatic arterial, portal venous and biliary supplies with segmental venous drainage to the hepatic veins. In a gross specimen, a line along the gallbladder fossa and inferior vena cava separates the right hepatic and left hepatic lobes, while the falciform ligament divides the medial and lateral segments. Anatomically and on imaging, segments are demarcated by the right, middle and left hepatic veins, and the portal vein. The middle hepatic vein separates the right lobe from the left lobe. Hepatic lobectomies and segmentectomies are performed along these divisions and are defined according to the International Hepato-Pancreato-Biliary Association (IHPBA) Brisbane 2000 Terminology. A right hepatectomy removes segments 5, 6, 7 and 8 while a left hepatectomy removes segments 2, 3 and 4. A right trisegmentectomy removes the right lobe plus the medial left hepatic lobe (segment 4), while a left trisegmentectomy removes the left hepatic lobe plus the anterior sector of the right hepatic lobe (segments 5/8). A left lateral segmentectomy removes the lateral segments of the left hepatic lobe (segments 2, 3). Wedge resection refers to a non-anatomic resection of disease with the extent of resection focused on clean surgical margins (51).

Adjunctive modalities to oncologic hepatic resections include intra-operative ultrasound to help in the detection of metastases and guide anatomic resections, intra-operative radiofrequency or cryoablation—either open or laparoscopic—particularly for disease that is not amenable to percutaneous therapy, and intra-operative radiotherapy for tumors that can only be partially resected (52).

d) Radiation Oncology—Radiation oncology relies on the ability of radiation-induced DNA damage to cause cell death. The interactions between photons or particle radiation and cellular compounds or water generate ionized molecules and free radicals that impart damage onto chromosomal DNA, including DNA strand breakage and the formation of abnormal DNA and molecular crosslinks. The most effective damage to bring about cell death comes from double-strand breaks of DNA (53). Cell death may occur within few cell divisions or be delayed as a response to signaling factors released subsequent to radiation exposure and damage (54).

Cellular oxygen exposure is an important mediator of radiation-induced cell death, as lower oxygen levels can reduce the lethality of radiation exposure. A higher fraction of cells have been shown to survive radiation exposure in a hypoxic environment compared to an aerobic environment (55). The oxygen enhancement ratio (OER) is a ratio of the dose required to produce the same therapeutic effect in hypoxic cells compared to cells at a normal oxygen tension. An OER of 2.5 to 3 for high-dose radiation indicates that hypoxic cells can require up to three times the radiation dose as oxygenated cells in order to bring about the same cell kill (56).

The number of tumor cells killed by ionizing radiation is a function of the radiation dose. The dose required for local control, referred to as the tumor control probability (TCP), is proportional to the logarithm of the total number of tumor cells. Carcinomas may require 60 to 80 Gy of radiation, divided into multiple fractionations, whereas more radiosensitive cancers, such as lymphoma, may require a dose of 20 to 40 Gy (57, 58).

The effectiveness of an administered radiation dose depends on the fraction of the dose given at each treatment and the duration over which the course of radiation is delivered. The total radiation dose to be administered is divided into fractionations, which are delivered over several treatment sessions. Fractionation doses typically fall in the range of 1.8 to 2.0 Gy per day for five days a week (58). Because the repair mechanisms of tumor cells are less effective than the repair mechanisms of normal cells, fractionation relies on the ability of normal cells to recover from radiation-induced cellular damage more quickly and more effectively than tumor cells. Fractionation schemes can be altered depending on the tumor type and curative or palliative goals of therapy, such as with accelerated fractionation, hyperfractionation or hypofractionation (59). In accelerated fractionation, the duration of time over which the course of radiation is delivered is reduced in order to minimize the opportunity for tumor cell regeneration. In a hyperfractionation scheme, the dose given at each fraction is lower, but the total number of dose fractions is increased in order to provide a higher total dose and increase the likelihood of tumor cells being in a radiosensitive phase (58, 59).

The effects of radiation therapy on tumor cells must be carefully balanced against its effects on uninvolved tissues. Normal tissue responses to radiation exposure can be divided into the early effects, which occur within days to weeks of exposure, and late effects, which occur months to years after the radiation treatment (60). Certain organs may be more susceptible to acute toxicities and are referred to as early responding tissues (61). Late responding tissues may not manifest toxicities until well after the radiation exposure. Radiation effects on tissue are determined by the total radiation dose delivered, the magnitude of the fractionated doses, the duration of the course of radiation therapy, the time interval between fractionations, and the radiosensitivity of the tissue exposed (58, 62).

Radiosensitization from chemotherapy is an important concept for patients receiving chemotherapy and radiation therapy concomitantly or within short intervals of each other. Several chemotherapeutic agents, particularly the antimetabolites 5-FU and gemcitabine, platinum compounds such as cisplatin, and taxanes such as paclitaxel and docetaxel, augment the effects of chemotherapy and radiation compared to either therapy administered alone (63–65). The synergistic effects of radiation and radiosensitizing chemotherapies have led to their implementation as standard-of-care treatments for certain head and neck, lung and gastrointestinal cancers. However, radiosensitization also increases the risk of chemotherapy- or radiation-associated toxicities. Amifostine may be administered in such circumstances for its radioprotective effects through free-radical scavenging, DNA protection and acceleration of DNA repair. Its protective effects on non-malignant as

opposed to tumor cells is believed to be due differences in the cells' pH environment and differential expression of an activating enzyme (66).

In general, external beam radiation offers the advantage of being non-invasive. It is of particular interest in very large, unresectable tumors, or in non-operable patients as an alternative to best supportive care. Advances in radiation oncology delivery technologies have allowed external beam doses to be modified according to the distribution of viable tumor. Information on the distribution of tumor metabolic activity, as provided by PET imaging, can more precisely define the target volume. Multileaf collimators and intensity modulation are devices and algorithms used to improve the conformality of the radiation beam with the target volume in order to reduce irradiation of uninvolved tissues (67).

With 3-D conformal radiotherapy (3D-CRT), the radiation beam is shaped to match the target volume of the tumor using multiple beams and multileaf collimators. Intensity-modulated radiation therapy (IMRT) further increases radiation precision to optimize radiation doses to an irregularly shaped tumor volume. Computer algorithms and treatment simulations are used to formulate a pattern of radiation delivery and modulate the energy of the radiation beam to create non-uniform dosing according to the tumor dimensions. Radiation beams can be arranged to enter the patient at different locations in order to concentrate the beam on the targeted tumor volume while minimizing exposure to normal tissue (68, 69).

As opposed to conformal radiation delivered to a specific target volume over the course of multiple sessions, such as with 3D-CRT and IMRT, stereotactic radiosurgery (SRS) generally refers to the use of high-dose conformal radiation delivered to a tumor volume in a single session. Stereotactic radiotherapy (SRT), also called stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR), refers to the delivery of high-dose focused radiation in one to five fractions with individual doses typically exceeding 5 Gy (70). The total dose and fractionation range from 30 Gy delivered in one fraction up to 60 Gy delivered in three to five fractions; however, the biologic effective dose of the radiation delivered is greater than the absolute value of the dose. A dose of 60 Gy delivered in three fractions has approximately the same effective dose as 150 Gy delivered in conventional 2 Gy fractions (71). SRS and SBRT technologies include Gamma knife, Cyberknife and proton beam therapies. Gamma knife stereotactic radiosurgery employs an array of precisely collimated beams to create a spherical treatment volume of variable diameters and is specific to intracranial lesions (67). Cyberknife and other similar linear-accelerator-based stereotactic radiosurgery technologies rely on modifications of the standard linear accelerator devices to achieve capabilities such as real-time target volume tracking, as well as radiation beam shaping and intensity modulation. Orthogonal radiographs obtained immediately prior to radiation delivery are cross referenced with stereotactic tracking software to establish the radiation beam alignment (72).

Proton beam radiosurgery uses protons instead of photons to deliver a radiation dose and relies on the principle that a proton beam will stop at a depth proportional to the energy of the beam, thereby eliminating a dose to the tissues beyond the targeted volume (73, 74). Because the Bragg peak of protons, which is the point of maximum energy transfer and therefore dose deposition, occurs in the last few millimeters of the proton beam's range, tumor volume can be targeted with high radiation doses while minimizing doses to the deeper normal tissues (58).

Brachytherapy refers to an altogether different mode of radiation delivery in which a radioactive source, usually with short radius of cytotoxic activity, is placed close to or

within the tumor, allowing very high local tumor doses that decline rapidly with distance according to the inverse-square law (75).

Intracavitary brachytherapy applicators may be placed within a body cavity or surgical site. For example, in the balloon-based brachytherapy systems used to provide accelerated partial breast irradiation (APBI), a balloon-catheter is implanted in the lumpectomy cavity at the time of surgery and afterloaded with a radioisotope (76). Permanent low dose-rate brachytherapy seeds implanted in the prostate gland for the treatment of localized prostate cancer are a form of interstitial brachytherapy (77). A line source of radioactivity within the lumen or duct of an organ, such as those placed within transhepatic biliary stents for the treatment of unresectable cholangiocarcinoma, are referred to as trans- or intraluminal brachytherapy (78).

Intra-operative radiotherapy (IORT) refers to the administration of a single dose of external beam radiation at the time of open surgery as opposed to multiple fractionations of external beam radiation. It is most commonly described in head and neck, breast, pelvic and unresectable biliary malignancies (52, 79, 80).

e) Interventional Oncology—Interventional oncology offers a broad scope of percutaneous and transcatheter endovascular cancer therapies that provide unequivocal clinical benefits and are clearly unique from medical, surgical and radiation oncologic treatments, thereby establishing interventional oncology as the fourth pillar of cancer care.

Percutaneous therapies consist of non-thermal and thermal ablative technologies. Nonthermal technologies include chemical ablation and irreversible electroporation (IRE), while thermal ablative technologies include radiofrequency ablation, cryoablation and microwave ablation. In a manner analogous to achieving an R0 resection in surgical oncology, ablative therapies aim to ablate a circumferential margin of healthy tissue measuring approximately 0.5 to 1.0 cm, often referred to as an “A0” ablation.

Chemical ablative therapies, including percutaneous ethanol injection (PEI) and percutaneous acetic acid injection, cause protein denaturation and thrombosis of the tumor microvasculature. Primarily used for hepatocellular carcinoma, the soft nature of the tumor compared to the surrounding cirrhotic liver favors diffusion confined to the tumor itself. While inexpensive and efficacious, chemical ablative techniques may be limited by the predictability of their response and the smaller upper limit of tumor sizes (< 2 cm) that can be adequately treated.

Irreversible electroporation (IRE) is a non-thermal ablation technique that induces cell death by disrupting the electric potential gradient across cell membranes, leading to the formation of permanent nanopores through the plasma membrane, altering cellular transport and ultimately cell homeostasis (81). The effects of IRE are dependent on a number of tissue and electrical field parameters, which allow for precise mathematical modeling and treatment planning (82). Furthermore, IRE appears to be free from perfusion-mediated tissue cooling and heating issues that affect the thermal ablative therapies and has been shown to be safe for use on hepatic tumors adjacent to hepatic veins and portal pedicles (83, 84).

Radiofrequency ablation causes tissue heating due to the frictional energy generated by polar molecules, particularly water, that vibrate in attempt to remain aligned with the direction of an alternating current, as well as resistive heating generated as an electric current passes through ionic tissue (85). Microwave ablation causes tissue heating by causing polar water molecules to continuously realign with an oscillating electromagnetic field that emanates from the microwave antenna. The propagation of microwaves is not

limited by low electrical conductivity, high tissue impedance or low thermal conductivity as can be the case with radiofrequency ablation (86). With both technologies, tissue heating induces coagulation necrosis and subsequent cell death. Cryoablation causes rapid cooling of the target tissue, resulting in intracellular ice- crystal formation that destroys organelle and cell membranes, and induces membrane pore formation that disrupts the electrochemical gradient. Cellular tonicity is also disturbed, causing lethal transmembrane fluid shifts. If these changes do not cause immediate cell death, they often initiate apoptosis (87). The ability to visualize ice-ball formation, the edge of which marks the 0°C isotherm, in cryoablation on several imaging modalities is a particular benefit.

High intensity focused ultrasound (HIFU) is a non-invasive ablative modality that can cause coagulation necrosis of tumors at a specific focal length due to controlled local heating. Although data are limited, favorable outcomes have been reported for ultrasound-guided HIFU in the treatment of hepatic, pancreatic, renal, breast and bone tumors (88). HIFU has been reported to cause complete necrosis for tumors adjacent to major blood vessels without damage to the vessels (89).

Intra-arterial chemoinfusion therapy traditionally required surgical placement of chemotherapy ports, but advances in technology have now allowed for minimally invasive port placement by interventional radiologists (90, 91). Intra-arterial chemoinfusion allows for increased local concentration and therapeutic response for chemotherapeutics with first-order kinetics and a steep dose-response curve (92).

Transcatheter endovascular therapies of interventional oncology rely on embolization in its various manifestations. Embolization may be used to selectively treat a tumor via its nutrient arterial supply with bland, chemo- or radioembolization, or to induce liver hypertrophy in order to increase the functional liver remnant prior to tumor resection in portal vein embolization.

Transarterial embolization procedures are loco-regional therapies for the treatment of primary and metastatic hepatic malignancies. Bland embolization refers to the infusion of embolic materials via the nutrient artery in order to cause occlusion of the tumor arterioles. Chemoembolization involves selective infusion of chemotherapeutic agents via the nutrient arterial supply, followed by an embolic agent, in order to attain higher intra-tumoral chemotherapy concentrations by preventing chemotherapy washout, in addition to inducing ischemic tumor necrosis. Transarterial chemoembolization with drug-eluting beads (DEB-TACE) is an adaptation of this concept in which biocompatible, non-resorbable beads are loaded with a chemotherapeutic agent and then administered through selective catheterization of the tumor's nutrient arterial supply. The beads are intended to deliver higher and more sustained doses of the chemotherapeutic agent to the tumor and reduce systemic exposure in order to maximize tumor cell kill while minimizing systemic toxicities (93).

Transarterial radioembolization refers to the selective intra-arterial delivery of glass or resin microspheres loaded with the radioisotope yttrium-90 (⁹⁰Y). Deposition of the radioactive microspheres within the tumor allows for the safe administration of radiation doses that may exceed 150 Gy, whereas the likelihood of developing severe radiation-induced liver disease (RILD) may exceed 50% for external-beam radiation doses greater than 40 Gy (94, 95). Radiation segmentectomy further builds on the concept of selective radiation administration in that high doses of radiation are delivered to an even smaller volume of one or two hepatic segments in order to maximize tumor irradiation and minimize exposure of the normal liver parenchyma. Indeed, calculated segmental radiation doses have been reported in excess of

500 Gy with calculated tumoral doses greater than 1200 Gy with a very low incidence of biochemical toxicities (96).

Portal vein embolization (PVE) involves selective embolization of a portion of the liver prior to partial hepatic resection in order to redirect portal venous flow to the intended future liver remnant (FLR). This causes hypertrophy of the non-embolized portion of the liver and improves functional hepatic reserve. Patients with normal livers with a planned resection of more than 80% of their functional liver mass, or patients with existing liver disease in addition to the resectable tumor with a planned resection of more than 60% of their functional liver mass, are at highest risk for postoperative complications. By inducing preoperative hypertrophy of the FLR, PVE allows otherwise unsuitable patients to become surgical candidates by reducing the postoperative morbidity and mortality associated with major hepatic resections (97). Changes similar to PVE have also been observed during long-term follow-up of patients having received unilobar ^{90}Y radioembolization, with significant volumetric decreases in the treated hepatic lobe and concomitant significant volumetric increases in the untreated lobe. This atrophy-hypertrophy complex, termed radiation lobectomy, has resulted in a volumetric increase of the untreated lobe of approximately 40%, which compares to 30% hypertrophy of the liver remnant seen following extensive hepatic resection and approximately 15% hypertrophy of the future liver remnant following portal vein embolization. (98).

DISEASE-SPECIFIC REVIEW AND LEVELS OF EVIDENCE

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related deaths in the world (99), most often occurring in patients with chronic liver disease, either from viral hepatitis, alcohol-induced liver disease or non-alcoholic steatohepatitis. Several organizations, including the American Association for the Study of Liver Disease (AASLD), the United States Veterans Administration, and the European Association for Study of the Liver (EASL), recommend screening for HCC in all patients with cirrhosis and certain patients with hepatitis B infection even in the absence of cirrhosis. Screening includes a liver ultrasound and serum alpha fetoprotein levels every 6 to 12 months (100–102).

According to the EASL and AASLD practice guidelines, the diagnosis of HCC is based either on imaging or pathology. In cirrhotic patients, the presence of a lesion measuring greater than 1 cm with hallmark features on either four-phase CT or dynamic contrast-enhanced MRI is diagnostic of HCC (level 2D evidence). Hallmark features are hypervascularity on the arterial phase with washout on portal venous or delayed phases. If hallmark features are not seen on one modality, imaging with the second modality is recommended. Biopsy is reserved for suspicious lesions that do not demonstrate typical imaging characteristics of HCC. Serum AFP level is no longer part of the diagnostic criteria of HCC, and is an imperfect indicator of HCC as approximately 40% of HCC less than 2 cm in size and 28% of HCC between 2 and 5 cm will not have an elevated AFP (102, 103).

The Barcelona-Clinic Liver Cancer (BCLC) staging system for HCC is the most widely accepted staging system in both clinical practice and clinical trials, and it is the recommended staging system for prognosis prediction and treatment allocation (level 2A evidence). BCLC divides patients into very early (0), early (A), intermediate (B), advanced (C) and terminal (D) stages based on performance status, Child-Pugh scoring, and tumor characteristics. Treatment recommendations are based on the BCLC stage, including curative treatments for very early and early HCC (BCLC 0 and A), palliative treatments for intermediate and advanced HCC (BCLC B and C), and symptomatic treatment for terminal HCC (BCLC D). As reflected in the BCLC staging system, the natural history of HCC

depends heavily on tumor liver function, functional status and tumor characteristics. Untreated, intermediate stage patients have a one-year survival of approximately 50%, while advanced and terminal stage HCC patients have one-year survival rates of 25% and 11%, respectively (104). BCLC is the only system that associates a stage with a recommended treatment strategy.

Surgical resection is the first-line treatment for patients with solitary tumors and preserved liver function (level 2A evidence). Resections should be anatomic and delineated by the Couinaud hepatic segments (level 3A evidence). There is no consensus on the necessary width of a negative surgical margin, and recurrence and survival analyses have reported acceptable outcomes for margins ranging from 0.5 to >2 cm (105–107). Preserved liver function is indicated by a normal bilirubin and either a hepatoportal venous pressure gradient (HVPG) < 10 mmHg or a platelet count > 100,000 with associated splenomegaly. However, fewer than 10% of patients with HCC are eligible for resection according to these criteria (102).

For patients who are not candidates for surgical resection, liver transplantation is the first-line treatment if the tumor characteristics fall within transplant criteria (level 2A evidence). The Milan criteria are the most commonly utilized criteria worldwide, which limit eligibility to a single tumor measuring ≤ 5 cm or no more than three tumors, each ≤ 3 cm (108). In the United States, the Organ Procurement and Transplantation Network (OPTN) and United Network for Organ Sharing (UNOS) define transplant-eligible HCC as T2 disease, the tumor size and number criteria of which are identical to the Milan criteria (109). The University of California San Francisco has expanded criteria to include a solitary tumor ≤ 6.5 cm or up to three tumors ≤ 4.5 cm with a total tumor diameter ≤ 8 cm (110). The Model for End-Stage Liver Disease model (MELD) uses the values of total bilirubin, international normalized ratio (INR) and creatinine to calculate a score that predicts survival probability for patients with end-stage liver disease. Liver transplant candidates with HCC receive a MELD score increase (“exception points”) as well as an additional 10% increase every three months until the candidates receive a transplant or are no longer eligible for transplant due to disease progression (109).

For patients with early stage HCC who are not surgical candidates, ablative treatments, both non-thermal and thermal, are options with very favorable response profiles. Percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) have been shown to be equally effective for tumors < 2 cm, but the effects of RFA are more predictable (level 1 evidence) (103). Radiofrequency ablation has demonstrated 5-year survival rates in early stage HCC ranging from 50 to 64%. RFA results are most favorable for tumors < 3 cm, with rates of successful ablation decreasing as tumors exceed 3 cm. For patients with tumors ≤ 2 cm, complete sustained response has been shown in 97% of patients with a 5-year survival rate approaching 70%, which is comparable to survival rates following surgical resection (111). Indeed, data suggest that for small, solitary, early stage HCC, RFA offers similar survival rates to surgical resection and may arguably represent an equivalent alternative to surgical resection as first-line treatment (111, 112).

Recent data indicate that tumor necrosis following RFA initiates a T-cell mediated immune response that provides prolonged immune response and protection against recurrent HCC (113).

The zone of ablation should include a circumferential ablative margin of 0.5 to 1 cm (114). However, even with small tumors, tumor location has a substantial impact on the ability to achieve complete tumor necrosis. The presence of a large vessel (> 3 mm) abutting the tumor decreases the rate of complete tumor necrosis to < 50% due to a “heat-sink” effect (115).

Furthermore, a subcapsular location is associated with an increased risk of incomplete ablation and tumor progression (116).

Recurrence after surgical resection or ablation occurs in approximately 80% of patients by five years. Approximately one-half of these recurrences are early recurrences, occurring within two years, and are considered recurrences due to primary tumor dissemination. Late recurrences are considered de novo tumors arising in an oncogenic liver (117, 118).

Preoperative bridging therapies such as ablation and embolization can be considered if the transplant waiting list is expected to exceed 6 months (level 2D evidence) (103, 119). Ablation of HCC in transplant-eligible patients must be undertaken with caution, since, at follow up imaging, the zone of ablation, which includes the ablative margin, will exceed the original tumor size. Since transplant criteria often take absolute lesion size into account, not tumor viability, a complete necrotic response may nonetheless push a lesion beyond the size limitations for transplant eligibility. Bland, chemo- and radioembolization also provide acceptable bridging or down-staging strategies for patients on the transplant waiting list.

Conventional transarterial chemoembolization (TACE), specifically emulsified chemotherapy and lipiodol followed by embolization, is the recommended first-line therapy in intermediate stage (BCLC B) without vascular invasion, cancer-related symptoms or extra-hepatic spread, and is now considered the standard of care (102). Two landmark prospective randomized trials have demonstrated improved overall survival for TACE compared to best supportive care in patients with HCC and preserved liver function (level 1A evidence). In one study, patients treated with TACE had 1-, 2- and 3-year survival rates of 57%, 31% and 26%, respectively, compared to 32%, 11% and 3% in the control group (120). In a second study, the trial was stopped early when sequential inspection demonstrated that TACE had a significantly improved survival compared to conservative treatment. One- and 2-year survival rates for chemoembolization were 75% and 50%, respectively, compared to 63% and 27% for the control group (121). The median survival for untreated intermediate-stage HCC is approximately 16 months, whereas survival following TACE has been shown to approximate 20 months (102). Chemoembolization with doxorubicin-loaded drug-eluting beads (DEB-TACE) has been shown in a randomized trial to have similar results to conventional TACE, but with higher administered doses of doxorubicin, and significantly reduced serious liver toxicity and doxorubicin-related adverse events (level 1D evidence) (93).

Radioembolization is an alternative transarterial treatment option for intermediate-stage HCC and has been shown to be safe and efficacious for patients with portal vein invasion (122). Yttrium-90-loaded glass or resin beads are infused via selective hepatic arterial catheterization. Because of the hypervascular nature of HCC, which derives the vast majority of its blood supply from the hepatic arteries, there is preferential deposition of the radioactive microspheres within the tumor. There are no randomized controlled trials comparing survival following radioembolization to TACE, but studies have shown median survival times of approximately 17 months in patients with intermediate stage HCC and 12 months for advanced HCC with portal vein invasion (level 2A evidence) (122–124). A comparative effectiveness analysis of more than two hundred patients treated at the same institution with radioembolization and chemoembolization indicated similar survival times for the two therapies with a significantly reduced toxicity profile for radioembolization. The authors conclude that more than 1000 patients would have to be enrolled in a randomized controlled trial in order to achieve sufficient statistical power to demonstrate equivalence of survival times for the two therapies (125).

Sorafenib, a multi-tyrosine kinase inhibitor, is an oral, molecularly targeted therapy for hepatocellular carcinoma and is the only systemic therapy that has demonstrated a survival advantage for advanced HCC. The SHARP trial, a randomized, double-blind, placebo-controlled phase III trial for patients with advanced HCC demonstrated a median overall survival of 10.7 months in the sorafenib group compared to 7.9 months for the placebo group, as well as a significantly longer time to tumor progression for the sorafenib group (5.5 months vs. 2.8 months) (40). The Asia-Pacific trial, in which the majority of patients had hepatitis B infection, median overall survival was 6.5 months for the sorafenib group compared to 4.2 months for the placebo group (41). Shorter median survival times in the Asia-Pacific trial compared to the SHARP trial reflect the more advanced stage of disease for patients included in the Asia-Pacific trial. Sorafenib is therefore recommended as standard systemic therapy for patients with preserved liver function (Child-Pugh A) but advanced tumor (BCLC C), or for patients with progression following loco-regional therapy (level 1A evidence) (102).

Response assessment for HCC should follow necrosis methodologies, either the EASL or modified RECIST (mRECIST) criteria, which measures viable tumor as indicated by enhancing tissue (level 2B evidence). Multiphase CT or dynamic contrast-enhanced should be performed one month after surgical resection, ablation, locoregional therapy or initiation of systemic therapy (level 1A evidence). In order to evaluate for TTP, cross-sectional imaging is recommended every 6 to 8 weeks. In order to evaluate for recurrence, repeat cross-sectional imaging should occur every 3 months for the first year and every 6 months for the second year (102).

In summary, the BCLC staging system is currently the most widely accepted staging system for HCC and provides an algorithm to guide treatments; however, there is significant variability in treatment paradigms in different parts of the world and throughout the United States. The use of chemoembolization for intermediate stage HCC (BCLC B) without vascular invasion, cancer-related symptoms or extra-hepatic spread, and the use of sorafenib for advanced HCC are based on level 1A evidence. Surgical resection, ablation and transplantation are primarily based on non-randomized cohort analyses, while the use of bland and radioembolization are based on phase II cohort studies. Other HCC systems to be familiar with include the Cancer of the Liver Italian Program (CLIP), Okuda, Chinese University Prognostic Index (CUPI), Japanese Integrated Score, Taiwanese scoring as well as United Network for Organ Sharing (UNOS).

Colorectal Cancer

Colorectal cancer is the second leading cause of cancer death in the United States. When localized to the bowel, the cancer is highly treatable and often curable. Penetration through the bowel wall, involvement of regional lymph nodes and distant metastases determine prognosis and are reflected in the staging systems. Elevated serum CEA carries a negative prognostic significance (126).

Patients at highest risk for the development of colorectal cancer include those with hereditary conditions such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (also known as Lynch syndrome), or inflammatory bowel disease such as ulcerative colitis or Crohn disease (127). A personal history of adenomas, first-degree relatives with colorectal cancer or adenomas, and a personal history of breast, ovarian or endometrial cancer also increase risk (128). However, these risk factors account for less than 40% of incident colorectal cancers.

Colorectal cancer is staged according to the AJCC TNM classification. In order to confirm the absence of nodal involvement, at least 12 lymph nodes should be included in the surgical

pathological examination. Stage I disease does not extend beyond the muscularis propria, stage II disease extends beyond the colon and may be locally invasive. The presence of regional lymph node metastases indicates stage III disease while distant metastases characterize stage IV disease.

Without evidence of distant metastatic disease, surgical resection of the primary tumor and en bloc removal of regional lymph nodes is the standard of care (NCCN category 2A recommendation), with laparoscopic-assisted colectomy having been shown to be as effective as open colectomy (NCI level 1A evidence) (129). The use of adjuvant chemotherapy for stage II disease is controversial and may be limited to stage II disease at high-risk for recurrence (130). Radiation therapy may be considered for locally invasive disease (131).

Metastatic disease confined to regional lymph nodes denotes stage III disease, and patients with fewer than four lymph nodes involved carry a better prognosis than patients with four or more of lymph nodes involved (132). Stage III disease should be treated with fluorouracil-based (5-FU) chemotherapy combined with oxaliplatin (NCCN category 1 recommendation; NCI level of evidence 1A). 5-FU, given concomitantly with leucovorin (folinic acid) is administered intravenously, while capecitabine is an oral fluoropyrimidine that is enzymatically converted to 5-FU within tumor cells. Disease-free survival is equivalent for patients receiving oxaliplatin with either intravenous 5-FU-leucovorin (FOLFOX) or oral capecitabine (CapeOx) (NCI level of evidence 1D) (133).

Distant metastases characterize stage IV disease and will occur in 50% of patients with colorectal cancer, either at the time of initial presentation or due to disease recurrence (134). Isolated hepatic metastases that are limited in number and have no major vascular involvement may be candidates for surgical resection, resulting in 5-year survival rates from 40–60% (NCI level 3D evidence) (47, 48). Similar survival rates may be achieved with resection following neoadjuvant chemotherapy (135). For patients who are not surgical candidates, 5-year survival rates following percutaneous radiofrequency ablation approach but do not equate to or exceed those of surgical resection for tumor < 4 cm (level 3D evidence) (136). In a randomized, phase II trial, radiofrequency ablation added to systemic chemotherapy for unresectable colorectal metastases increased median progression-free survival by nearly 7 months (16.8 vs. 9.9 months) (level 1D evidence). The study was not powered to evaluate for differences in overall survival (137).

First-line treatment for stage IV disease includes either 5-FU/leucovorin with oxaliplatin (FOLFOX) or 5-FU/leucovorin with irinotecan (FOLFIRI) (NCI level 1D evidence) with or without the addition of molecularly targeted therapies. Capecitabine is an acceptable alternative to infusional 5-FU for oxaliplatin-based therapy (level 1D evidence) (138). First-line treatment regimens with molecularly targeted therapies include the addition of bevacizumab to FOLFOX (or CapeOx) or FOLFIRI, the addition of panitumumab to FOLFOX or FOLFIRI, or the addition of cetuximab to FOLFIRI (NCCN Category 2A recommendation, NCI level 1 evidence) (131). Patients receiving panitumumab or cetuximab must have wild-type KRAS, as carriers of mutant KRAS have worse outcomes (22, 139). Second-line therapy for patients starting with FOLFOX or CapeOX regimens generally includes switching to an irinotecan-based regimen with bevacizumab, ziv-aflibercept, cetuximab or panitumumab. Second-line therapy for patients starting with FOLFIRI regimens includes cetuximab or panitumumab with irinotecan only, or FOLFOX (CapeOx) with bevacizumab (NCCN category 2A). The molecularly targeted drug regorafenib may be considered in patients with mutant KRAS who have progressed on second-line therapy or patients with wild-type KRAS who have progressed on second- and third-line therapies.

Radioembolization has shown favorable outcomes in patients with unresectable hepatic metastases of colorectal cancer. The use of radioembolization for the treatment of chemotherapy-resistant or -refractory disease remains category 3 according to the NCCN guidelines. The addition of ^{90}Y radioembolization to chemotherapy has shown significantly prolonged times to tumor progression compared to chemotherapy alone [(15.9 months vs. 9.7 months, $P<0.001$ (140)) and (18.6 vs. 3.6 months, $P<0.0005$ (141))] with a trend toward prolonged 2-year survival in one study (39% vs. 29%, $P=0.06$ (140)) and statistically significant longer median survival in a second study (29.4 vs. 12.8 months, $P=0.02$ (141)) (level I and level 2 evidence). A randomized phase III trial of chemotherapy with and without radioembolization demonstrated a significantly prolonged time to liver progression (5.5 vs. 2.1 months, $P=0.003$) and time to tumor progression (4.5 vs. 2.1 months, $P=0.03$) but no significant difference in median overall survival (10.0 vs. 7.3 months, $P=0.80$), although greater than 40% of the control arm crossed over to receive radioembolization upon disease progression (level 1D evidence) (142). A matched-pair study of radioembolization for patients with chemotherapy-refractory disease showed a prolonged median survival (8.3 vs. 3.5 months, $P<0.001$) compared to best supportive care (level 3A evidence) (143).

Hepatic arterial embolization using drug-eluting beads preloaded with irinotecan (DEBIRI) has shown favorable outcomes compared to a systemic FOLFIRI. Results of a randomized trial comparing DEBIRI to systemic FOLFIRI demonstrated statistically significant prolonged overall survival, median survival (22 vs 15 months, $P=0.006$), progression free survival, and duration of quality of life improvement (8 months vs. 3 months, $P=0.00002$) for the patients receiving DEBIRI (level 1A evidence) (144).

Direct hepatic arterial chemoinfusion has been most often reported for the treatment of metastatic colorectal cancer. Many randomized trials have compared outcomes of hepatic arterial to systemic intravenous administration of 5-fluorodeoxyuridine (floxuridine), and more recently infusional 5-FU with leucovorin. Several of these studies have demonstrated significantly and markedly improved response rates for patients receiving the arterial infusion. However, survival analyses were limited by substantial patient cross-over (145–147), the inclusion of patients with extra-hepatic metastases in the hepatic infusion group (147), or a majority of patients not receiving or prematurely terminating arterial infusion due to catheter malfunction (148). Two additional studies did not show a survival advantage for patients receiving hepatic arterial chemoinfusion, while another demonstrated a survival advantage only in subgroups analysis of patients with hepatic tumor burden $<25\%$ (149). One of the most recent studies comparing hepatic arterial to systemic 5-FU with leucovorin did demonstrate a statistically significant increase in overall survival, hepatic response rate and physical functioning for the patients receiving hepatic arterial chemoinfusion, although time to extra-hepatic progression in this group was significantly shorter (150).

In summary, the use of chemotherapy and molecularly targeted therapies in the treatment of metastatic colorectal cancer is based on level 1A evidence. There is level 1 evidence to support the use of transarterial therapies in the treatment of metastatic colorectal cancer. Surgical metastatectomy, ablative and radiation therapy, are based on non-randomized cohort analyses. It should be noted that, while surgical resection may provide survival benefit compared to other available treatments for hepatic metastases, the use of survival after metastatic resection as a benchmark against which other therapies are compared is inherently flawed, given that surgical resectability, particularly in colorectal cancer, reflects a selection bias of early detection.

Neuroendocrine Tumors

Neuroendocrine tumors arise from the neuroendocrine cells of the embryologic fore-, mid- and hindgut, the most common of which are carcinoid and pancreatic neuroendocrine tumors. Pancreatic neuroendocrine tumors arise from the endocrine tissues of the pancreas, while carcinoid tumors most frequently arise in the lungs, small intestine, appendix or rectum. Except when associated with genetic syndromes such as multiple endocrine neoplasia (MEN) types 1 and 2, neuroendocrine tumors are relatively rare with sporadic incidence.

Neuroendocrine tumors are classified based on tumor histology, specifically differentiation and grade, and are generally separated into three different categories: G1 (well differentiated, low-grade), G2 (well differentiated, intermediate-grade), and G3 (poorly differentiated, high-grade). Cancers are staged according to the American Joint Committee on Cancer (AJCC) TNM staging system (151). Pancreatic neuroendocrine tumor staging follows the TNM staging system for pancreatic exocrine carcinoma, whereas carcinoid tumor staging differs according to the organ of involvement.

Pancreatic neuroendocrine tumors represent 1% of incident pancreatic cancers (152). The majority (70%) of functioning pancreatic neuroendocrine tumors are insulinomas, but nearly 90% of these are benign. Gastrinomas and somatostatinomas represent 10% of the functioning NETs but have the highest risk for metastases. Survival rates for metastatic pancreatic neuroendocrine are approximately 20–25% in population-based studies (153), but have been reported as high as 57% at a dedicated cancer institute (154). The 5-year survival rate for metastatic carcinoid tumors at dedicated cancer centers is approximately 75% (155).

Cross-sectional multiphase imaging is important for the diagnosis of primary and metastatic NETs. Because many NETs express high-affinity receptors for somatostatin, nuclear medicine imaging using a somatostatin analog (^{111}In -DTPA-octreotide) can be an important imaging tool for tumor localization and indicates the ability to treat with octreotide, a somatostatin analog that inhibits tumor growth. Chromogranin A is a serum marker that may be elevated with NETs, allowing its use as a tumor marker (NCCN category 3), but may also be elevated in patients taking proton-pump inhibitors and those with gastritis, hypertension, and renal or liver failure (151). The serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) may be used as a tumor marker for some cases of carcinoid tumor.

Excision or surgical resection with curative intent is generally recommended for NETs (NCCN category 2A; NCI level of evidence 3D). Depending on the location of the primary tumor and its size, with 2 cm frequently being the cutoff, surgical resection with local lymph node dissection should be performed.

For NETs with limited hepatic disease, surgical resection of the primary tumor as well as hepatic metastases is an option (NCI level of evidence 3D). Nearly all patients will have recurrence within five years following hepatic resection, but five- and ten-year survival rates exceed 70% and 50%, respectively (156). Nonetheless, most patients with metastatic disease are not candidates for surgical resection. For patients with unresectable but asymptomatic disease with a low tumor burden, observation is recommended with clinical and imaging assessment every 3 to 12 months until there is evidence of significant disease progression.

Patients with symptomatic but unresectable disease, clinically significant tumor burden or clinically significant progressive disease, several treatment options exist. For metastatic carcinoid tumor, patients should receive octreotide (NCCN category 2A) (157). Octreotide may be considered in patients with pancreatic NETs expressing somostatin receptors (NCCN category 2B). Additional treatment options include systemic treatment with

molecularly targeted therapies, such as everolimus or sunitinib (NCCN category 2A, NCI level of evidence 1D for pancreatic NET) (34, 37), cytotoxic chemotherapy (NCCN category 2A pancreatic NET; category 3 carcinoid), thermal ablative therapy (NCCN category 2B recommendation) or hepatic arterial therapies including bland embolization, chemoembolization or radioembolization (NCCN category 2B recommendation, NCI level 3D evidence). There are no prospective randomized trials comparing bland, chemo- or radioembolization for the treatment of progressive, unresectable carcinoid or neuroendocrine tumors. Bland embolization and chemoembolization of hepatic metastases have been shown to provide significant symptomatic and radiologic responses in a majority of patients with encouraging progression-free survival (158). Radioembolization has been reported to provide a complete response in up to 18% of patients, although survival times do not differ significantly from those seen following bland embolization or chemoembolization (159, 160).

Liver transplantation has been performed for patients with metastatic neuroendocrine tumors confined to the liver; however, liver transplantation in this setting is still considered investigational and not part of the standard treatment algorithm (151).

In summary, the use of chemotherapy for the treatment of metastatic neuroendocrine tumors with systemic agents is based on randomized studies with surrogate markers for overall survival. Surgical resection, ablative therapies and transcatheter arterial therapies are based on non-randomized cohort studies.

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma arises from the bile duct epithelium peripheral to the confluence of the right and left hepatic ducts and is a relatively rare malignancy, although with an increasing incidence. Most patients present with advanced disease, and those who are surgical candidates usually recur despite surgery. Risk factors include chronic biliary inflammation, including primary sclerosing cholangitis, liver fluke infestation, hepatolithiasis and cirrhosis (161). There is recent evidence that hepatitis C infection may also increase the risk of cholangiocarcinoma (162).

Staging of intrahepatic cholangiocarcinoma used to be identical to the staging of HCC; however, modifications to the most recent (7th) edition of the AJCC TNM staging system has distinguished intrahepatic cholangiocarcinoma from HCC and focus on the number of tumors, the presence of vascular invasion and lymph node metastases. Tumor size has not been shown to have an independent effect on survival (163). Surgical resection is the only curative therapy for intrahepatic cholangiocarcinoma, with 5-year survival rates of approximately 20–30%, but most patients are not surgical candidates at presentation (164). In general, multiple tumors and lymph node metastases preclude surgical resection.

Patients with R0 resection may receive observation alone or adjuvant chemotherapy in the setting of a clinical trial. Patients with R1 or R2 surgical resections may receive additional resection when feasible, loco-regional therapy, chemoradiation with a radiosensitizing fluoropyrimidine, or a fluoropyrimidine- or gemcitabine-based chemotherapy. Combination therapy with gemcitabine and cisplatin has been shown to increase progression-free and overall survival compared to gemcitabine alone and is now the recommended chemotherapy for unresectable or advanced cholangiocarcinoma (165).

Locoregional therapies for intrahepatic cholangiocarcinoma have been shown to be safe and effective in small series, although there have been no randomized clinical trials. Radiofrequency ablation has been reported to provide good local tumor control of patients with unresectable cholangiocarcinoma, with the optimal results in tumors <5 cm. Reports of

median overall survival following RFA range from 20 to 38.5 months (166, 167). RFA for recurrent tumors, also <5 cm, following curative resection has also been reported, with median overall survival after ablation of 27.4 months (level 3 evidence) (168). In a study of 24 patients treated with ⁹⁰Y radioembolization, six patients (27%) had partial response and 15 patients (68%) had stable disease with median survival of 14.9 months. Seventeen patients (77%) in this cohort had >50% tumor necrosis and two patients (9%) had complete tumor necrosis (level 3 evidence) (169). In a report of 25 patients with unresectable intrahepatic cholangiocarcinoma treated with ⁹⁰Y, six patients (24%) achieved a partial response and 11 patients (48%) had stable disease with median survival after treatment of 9.3 months (level 3 evidence) (170). In a study of 62 patients treated with chemoembolization using a combination of cisplatin, doxorubicin and mitomycin-C, 11% had a partial response and 64% had stable disease with median overall survival after treatment of 15 months (level 3 evidence) (171).

In summary, the evidence for resection of localized, resectable cholangiocarcinoma is based on non-randomized cohort studies. For unresectable cholangiocarcinoma with or without metastatic disease, gemcitabine/cisplatin is the standard of care based on randomized data with improvement in survival.

Lung Cancer

Lung cancer is the leading cause of cancer death in the United States and comprises several histologic subtypes, including small cell lung cancer (SCLC) and the non-small cell lung cancers (NSCLC) such as squamous cell carcinoma, large cell carcinoma, adenocarcinoma and neuroendocrine tumors of the lung. Classifications for adenocarcinoma have recently been updated, eliminating the use of bronchioloalveolar cell carcinoma (BAC) and mixed subtype adenocarcinoma from the classification system. The new categories include adenocarcinoma in situ (AIS, formerly BAC), minimally invasive adenocarcinoma (MIA), invasive adenocarcinoma (formerly non-mucinous BAC), and variants of invasive adenocarcinoma. Immunohistochemical staining is used to differentiate small cell lung cancer from non-small cell lung cancer, primary from metastatic adenocarcinomas, and to differentiate adenocarcinoma from malignant mesothelioma, as well as to determine the neuroendocrine status of lung tumors (172).

Stage I disease includes tumors <5 cm. Stage IIA disease includes tumors 7 cm without lymph node involvement and <5 cm with ipsilateral peribronchial or hilar lymph node involvement, while IIB disease includes tumors 5–7 cm with ipsilateral peribronchial or hilar lymph node involvement, tumors >7 cm without lymph node involvement, or tumors with local invasion. Stage IIIA disease includes tumors of any size with ipsilateral mediastinal or subcarinal lymph node involvement, or invasion of critical structures with lymph node involvement limited to the ipsilateral peribronchial or hilar regions. Any nodal involvement of the supraclavicular lymph nodes or contralateral lymph nodes denotes stage IIIB. Stage IV disease includes separate tumor in a contralateral lobe, pleural nodules, malignant effusion and distant metastases (173).

Molecular analysis has an important role in guiding the treatment of lung cancers. The two most common EGFR mutations found in NSCLC are associated with sensitivity to molecularly targeted therapy with the tyrosine kinase inhibitors erlotinib and gefitinib. The presence of an EML4-ALK gene rearrangement may indicate the use of the tyrosine kinase inhibitor crizotinib. Levels of expression of ERCC1 can help predict sensitivity to platinum-based chemotherapies. KRAS mutations are associated with shorter survival than wild-type KRAS, and the use of erlotinib in patients with KRAS mutations may reduce the efficacy of chemotherapy (174, 175).

Chemotherapy, surgery and radiation therapy are the mainstays of NSCLC treatment. Surgery offers the best chance of cure, and lung cancer resection with complete ipsilateral mediastinal lymph node dissection (CMLND) is indicated for patients with stage I, II and IIIA disease (NCCN category 2A, NCI level 1A evidence) (175, 176).

Chemotherapy may be used for neoadjuvant and adjuvant therapy, or for advanced or metastatic disease. Platinum-based chemotherapies are the foundation of lung cancer care, but the ultimate chemotherapeutic regimen is determined by tumor histology and clinical parameters. Patients with resected stage II and IIIA disease benefit from cisplatin-based adjuvant chemotherapy (NCI level 1A evidence) (176). Chemotherapy with radiation is the standard treatment algorithm for patients with unresectable stage III disease (NCI level 1A evidence), and combination chemotherapy for patients with stage IV disease improves survival and palliates disease-related symptoms (NCI level 1A evidence).

The addition of bevacizumab to standard first line chemotherapy has shown benefits in certain patients with advanced stage IIIB or stage IV NSCLC (NCCN level 2A, NCI level 1A evidence). The EGFR inhibitors gefitinib and erlotinib in place of platinum-based therapies have shown improved progression free survival for patients with advanced stage disease and corresponding mutations (NCI level 1D evidence) (177–180).

Radiation therapy is used as adjuvant therapy for resectable disease, primary local treatment for patients with inoperable or unresectable disease, or for palliative therapy in incurable disease (NCCN category 2A, NCI level 1 evidence).

For patients with inoperable or unresectable disease, SABR, in which high-dose radiation (>5 Gy) is delivered in few fractions, is an option (175). For medically inoperable stage I NSCLC (tumor <5 cm), tumor and local (tumor and involved lobe) control rates approaching 98% and 91%, respectively, at three years have been reported with three-year disease-free and overall survival at 48% and 56%, respectively (181).

Radiofrequency ablation is an option for treatment of localized, node-negative lung cancers in patients who refuse surgery or would not tolerate surgery due to poor performance status, limited cardiopulmonary reserve or other comorbidities. RFA is also an option for the treatment of tumors arising in previously irradiated tissue. A large, multi-center, prospective study of RFA for primary and metastatic lung cancers measuring >3.5 cm in patients who were not candidates for surgery, chemotherapy or radiotherapy showed complete responses lasting at least one year in 88% of patients without a significant difference in primary versus metastatic lung cancers. Overall 1-year and 2-year survival for patients with NSCLC were 70% and 48%, respectively. One-year and 2-year overall survival was 89–92% and 64–66%, respectively, for patients with colorectal and other metastases to the lungs (level 3 evidence). A different study compared outcomes for patients with stage I NSCLC who were unable to undergo lobectomy and instead received sublobar resection, radiofrequency ablation or cryoablation. There was no significant difference in the probability of 3-year survival based on therapy received with 3-year cancer specific survival ranging from 87–91% and cancer-free survival ranging from 46–61% (level 3 evidence) (182). While these results are not directly comparable to outcomes from surgical or radiation therapies due to the fact that these patients had comorbidities precluding such treatments, the outcomes do compare well to reported outcomes of external-beam and stereotactic radiotherapies in similar populations (183).

In summary, the evidence for resection of early stage lung cancer is based on non-randomized phase II data (level 2 evidence). For more advanced disease in patients with metastatic disease, treatment with chemotherapy is based on randomized evidence with

survival as the endpoint (level I). SABR and ablative therapies for inoperable lung cancer are based on level 3 data.

Renal Cancer

Renal cancer represents approximately 2–3% of all malignancies in the United States with an increasing incidence. The vast majority of renal cancers are renal cell carcinomas. Stage I disease includes renal masses ≤ 7 cm confined to the kidney. Renal masses larger than 7 cm but still confined to the kidney are considered stage II disease. Extension into the major veins or perinephric tissue, or nodal involvement indicates stage III disease. Stage IV disease includes tumors extending beyond Gerota's fascia or into the ipsilateral adrenal gland (184).

Surgical resection, which includes radical nephrectomy and nephron-sparing partial nephrectomy, is the mainstay of early stage renal cancer with the significant long-term survival benefits. Stage II and III renal cancers are treated with radical nephrectomy, while stage IV disease may be treated with molecularly targeted therapies (NCCN category 1, NCI level 1D evidence), cytokine immunotherapy (NCCN category 2A, NCI level 1A evidence), or the combination of cytokine immunotherapy and bevacizumab (NCCN category 1, NCI level 1D). Systemic chemotherapy for unresectable or stage IV disease, with the choice of agents depending on the histologic subtype of the renal cell carcinoma, has shown modest responses and remains a NCCN category 3 recommendation. (184, 185)

For patients with T1 renal tumors (≤ 7 cm) but substantial medical comorbidities or limited life expectancy, active surveillance or thermal ablation are alternatives to surgical resection. With active surveillance of T1 renal cancers, patients are monitored and treated upon progression (185). The American Urological Association includes thermal ablation as an acceptable treatment option for T1 renal masses (≤ 7 cm) in high-risk surgical patients with the understanding that, while thermal ablative therapies have shown similar distant recurrence-free survival rates to surgery, there may be an increased risk of local recurrence, particularly for T1b tumors (4–7 cm) (level 3 evidence) (186, 187). Tumor size and location are the critical factors in choosing which thermal ablation modality to use. Although a meta-analysis comparing radiofrequency ablation to cryoablation appears to indicate that RFA has higher rates of local recurrence compared to cryoablation (12.9% vs. 5.2%, $P < 0.0001$), resulting in a higher rate of repeat ablation (8.5% vs. 1.3%, $P < 0.0001$) (188), the study has been criticized for the heterogeneity of the patient cohorts. For tumors smaller than 3 cm, both RFA and cryoablation are highly effective. A large retrospective review at a single institution reports no significant difference in outcomes between RFA and cryoablation for renal tumors ≤ 3.0 cm with regard to technical success, local recurrence and complications. Specifically, local recurrence following RFA occurred in 3.2% of treated lesions, whereas local recurrence following cryoablation occurred in 2.8% of treated lesions (189). However, rates of effective local tumor control with RFA do decrease as tumor size exceeds 3 cm. In a study of 100 tumor radiofrequency ablations, RFA resulted in complete tumor necrosis for all tumors < 3 cm, whereas 44% of tumors > 3 cm required repeat ablation (190). In a study of 125 tumor radiofrequency ablations, RFA provided complete tumor necrosis for all tumors < 3.7 cm while 30% of the larger tumors had residual viable tumor on follow-up (191). Cryoablation, on the other hand, has demonstrated effective local tumor control for tumors > 3 cm (192). In addition to size > 3 cm, a central location near the renal hilum can result in incomplete tumor necrosis with RFA due to the heat sink effect of the hilar vessel, while cryoablation has been shown to be both safe and effective for tumors in this location (190, 193–195).

Arterial embolization of renal cell tumors may be used for palliation of symptoms resulting from the primary tumor or due to ectopic hormone or cytokine production. Preoperative

arterial embolization may also be used to decrease blood loss during partial nephrectomy or facilitate surgery in cases of limited access to the renal hilar vessels (184, 196).

In summary, the evidence for resection of early RCC treated with resection is based on non-randomized long-term cohort analyses. For the treatment of metastatic disease, the majority of evidence is based on randomized evidence with PFS as the endpoint. The only exception to this is temsirolimus, where a survival advantage has been demonstrated in randomized studies (197).

Osseous Metastatic Disease

The skeleton is the third most common site of metastatic disease and affects 30–95% of patients with breast, prostate, lung, bladder and thyroid cancers (198). While external-beam radiation is the standard of care for the treatment of painful osseous metastases, symptom relief can often be prolonged and transient (199). Limitations of radiation dose exposure to the surrounding normal tissue may also preclude repeat radiation for persistent or recurrent pain (200). Both radiofrequency and cryoablation of painful osseous metastases have been shown to consistently provide significant and prolonged pain improvement (201), (202), (203). Multiple probes can be used to treat large tumors, and ice-ball visualization with cryoablation provides an important benefit when treating tumors adjacent to critical structures (200).

Cementoplasty, including vertebroplasty and kyphoplasty, play an important role in treating painful vertebral compression fractures in patients with cancer. Metastatic disease, in addition to prior radiation therapy, hormone and steroid treatments, and poor nutritional status, increase cancer patients' risk of developing painful vertebral compression fractures (204). The prospective, multicenter, randomized CAFE trial demonstrated that, compared to non-surgical management, balloon kyphoplasty provided statistically significant reduction in pain, analgesic use and disability, as well as significant improvement in quality of life (level 1C evidence) (205).

Combining radiofrequency ablation with either vertebroplasty or kyphoplasty can provide local tumor control and may reduce the risk of procedure-related complications. In addition to tumor necrosis, thermal effects can change the tumor consistency to optimize cement distribution within the lesion, and vessel thrombosis within the ablation zone may reduce the risk of venous cement leakage that can result in radiculopathy (epidural and neural foraminal veins) or pulmonary embolism (206, 207). When combined with kyphoplasty, RFA may reduce the likelihood of cement leakage by allowing for a low-pressure infusion of cement into a preformed cavity, particularly in circumstances in which the lesion is close to critical structures or in the presence of vertebral body cortical defects (207). Cementoplasty is contraindicated in patients with spinal cord compression, spinal instability as evidenced by a severe kyphotic deformity or vertebral body subluxation, and osteomyelitis. Posterior wall defects and epidural tumor spread are relative contraindications requiring careful consideration (208, 209).

CONCLUSION

Cancer treatment comprises the broadest range of medical disciplines and requires the collaboration of numerous specialists in order to provide patients with optimal care and outcomes. Such effective collaboration demands a precise understanding of the disease entities and their standard of care treatments, as well as an expert comprehension of the rationale, levels of evidence and controversies that underlie the treatment decisions. A mastery of the fundamentals of oncology is the foundation of such knowledge and the

necessary first step in further advancing the specialty of interventional oncology. We hope that these fundamentals were provided in this review.

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Figure 1.

Table 1

Common tumor markers, source and clinical applications

Marker	Cancer	Source	Clinical Use
ALK Gene Rearrangement (anaplastic lymphoma kinase)	<ul style="list-style-type: none"> Non-small cell lung cancer Anaplastic large cell lymphoma 	Tumor tissue	<ul style="list-style-type: none"> Treatment planning Prognosis
AFP (alpha-fetoprotein)	<ul style="list-style-type: none"> Primary liver cancer Germ cell tumors 	Blood	<ul style="list-style-type: none"> Response assessment (Liver) Staging, prognosis, response assessment (germ cell)
-hCG (beta-human chorionic gonadotropin)	<ul style="list-style-type: none"> Choriocarcinoma Ovarian Testicular Gastric Liver Lung 	Blood	Staging <ul style="list-style-type: none"> Prognosis - Response assessment (choriocarcinoma, testicular cancer)
CA 19-9 (cancer antigen)	<ul style="list-style-type: none"> Cholangiocarcinoma Gallbladder carcinoma Gastric Pancreatic adenocarcinoma 	Blood	Response assessment
CA 125	Ovarian cancer	Blood	<ul style="list-style-type: none"> Response assessment Monitor for recurrent disease
CEA (carcinoembryonic antigen)	<ul style="list-style-type: none"> Colorectal cancer Breast cancer Add'l adenocarcinoma 	Blood	<ul style="list-style-type: none"> Prognosis (colorectal) Response assessment Monitor for recurrent disease
CgA (chromogranin A)	<ul style="list-style-type: none"> Neuroendocrine tumors Small cell lung cancer Prostate cancer 	Blood	<ul style="list-style-type: none"> Diagnosis Response assessment Monitor for recurrent disease
C-kit Mutation	Gastrointestinal stromal tumors	Tumor tissue	<ul style="list-style-type: none"> Treatment planning with molecularly targeted therapy
ERCC1 (endonuclease excision repair cross- complementing 1)	<ul style="list-style-type: none"> Gastric cancer Ovarian cancer Non-small cell lung cancer (NSCLC) 	Tumor tissue	<ul style="list-style-type: none"> Associated with resistance to cisplatin (gastric, ovarian) Treatment planning with docetaxel, cisplatin (NSCLC)
EGFR Mutation (epidermal growth factor receptor)	<ul style="list-style-type: none"> Non-small cell lung cancer 	Tumor tissue	<ul style="list-style-type: none"> Treatment planning with molecularly targeted therapy Prognosis

Marker	Cancer	Source	Clinical Use
HER2/neu (human epidermal growth factor receptor 2)	<ul style="list-style-type: none"> Breast Gastric Esophageal Ovarian 	Tumor tissue	<ul style="list-style-type: none"> Treatment with trastuzumab
KRAS (v-k-ras Kirsten rat sarcoma viral oncogene homolog)	<ul style="list-style-type: none"> Colon cancer Lung cancers Pancreatic cancer 	Tumor tissue	<ul style="list-style-type: none"> Treatment planning with molecularly targeted therapy (colon: mutation associated with poor response to cetuximab and panitumumab) (3),(4)
Ki-67	<ul style="list-style-type: none"> Breast Cancer Pancreatic neuroendocrine tumors 	Tumor tissue	<ul style="list-style-type: none"> Prognosis
PSA (prostate specific antigen)	Prostate Cancer	Blood	<ul style="list-style-type: none"> Diagnosis Response assessment Monitor for recurrent disease

Table 2

Common chemotherapeutics encountered in interventional oncology

Class	Agent(s)	Mechanism of Action
Antimetabolite	5-fluorouracil (5-FU)	Inhibits thymidylate synthase (TS), the enzyme providing only de novo source of thymidine for DNA synthesis (10) Leucovorin increases 5-FU toxicity by optimizing 5-FU metabolite binding to TS
	Capecitabine	Oral pro-drug converted to 5-FU by thymidine phosphorylase, which is found in higher concentrations in tumor tissue compared to normal tissue (11)
	Gemcitabine	Metabolites interfere with DNA polymerase and are incorporated into DNA strands resulting in early strand termination (12)
Platinum-based	Cisplatin Carboplatin Oxaliplatin	DNA damage caused by various DNA-DNA and DNA-protein crosslinks, which inhibit DNA replication and transcription, cause strand breaks and lead to apoptosis (13) FOLFOX : folinic acid (leucovorin), 5-FU, oxaliplatin). Oxaliplatin increases toxicity of 5-FU by inhibiting its intracellular breakdown (14)
Taxanes	Paclitaxel Docetaxel	Disrupt cell mitosis and progression through the cell cycle by interfering with the centrosomes, spindles and microtubules required for chromosomal organization and rearrangement during cell division (15)
Topoisomerase Inhibitor	Irinotecan	Targets DNA topoisomerase I, which is essential to reducing natural DNA twisting that occurs during DNA transcription and replication. Causes double-strand DNA breaks and arrest of DNA replication (16) FOLFIRI : folinic acid (leucovorin), 5-FU, irinotecan
	Doxorubicin Epirubicin	Target topoisomerase II, increasing double-strand DNA breaks, insertions, deletions and aberrant recombinations (17)
Antibiotic	Mitomycin C	Derived from the <i>Streptomyces</i> bacterium. Biologically active in anaerobic conditions resulting in alkylation and cross-linking of DNA that inhibits DNA synthesis (18)