

Chapter 2

Modern Radiation Therapy Approaches: Targeted and Ablative Strategies

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Introduction

Modern radiation therapy is a therapeutic cancer modality that can achieve local and regional control of malignancy in addition to providing palliation. Radiation therapy exerts its anticancer effect through the accumulation of DNA damage in the tumor cells. The DNA damage leads to either acute cell death or a delayed cell death, known as mitotic catastrophe. For this reason, tumors may shrink months after the completion of radiation therapy.

Principles of Radiation Therapy

The amount of radiation, or dose, that can safely be given to a tumor, is limited by the radiation tolerance of the normal organs surrounding it. There are a number of strategies that can be used to improve the therapeutic ratio of radiation therapy. The *energy* of the radiation beam determines how deeply the radiation penetrates, whereas the amount of radiation absorbed (dose) determines the biologic effects.

Most commonly, high energy megavoltage photons are used to spare skin due to its greater depth of penetration. Multiple beams can be focused from many directions to concentrate the radiation dose in the tumor and spare critical adjacent normal structures. Indeed, side effects occur when the adjacent normal tissues receive too much accumulated radiation. Both the total dose absorbed and the volume of normal tissue irradiated contribute to these side effects.

Similarly, as tumor cells can die either acutely or via a delayed mechanism, so to side effects can be either acute or late. Acute side effects are the ones that occur during the course of radiation and may persist up to a month thereafter. Tissue types prone to this type of damage are generally rapidly proliferating types, for example, mucosal surfaces that can lead to diarrhea or mucositis. In contrast, late effects may happen at any point beyond 6 weeks from the completion of therapy, rather than during treatment. Organ damage such as transverse myelitis from overtreatment of the spinal cord, radiation-induced liver disease (RILD), and radiation pneumonitis are examples of severe long-term late effects.

The field of radiation oncology primarily focuses on balancing the risks of normal tissue toxicity and the effectiveness of therapy. This chapter will focus on the newer technologies of interest to the interventional radiologist.

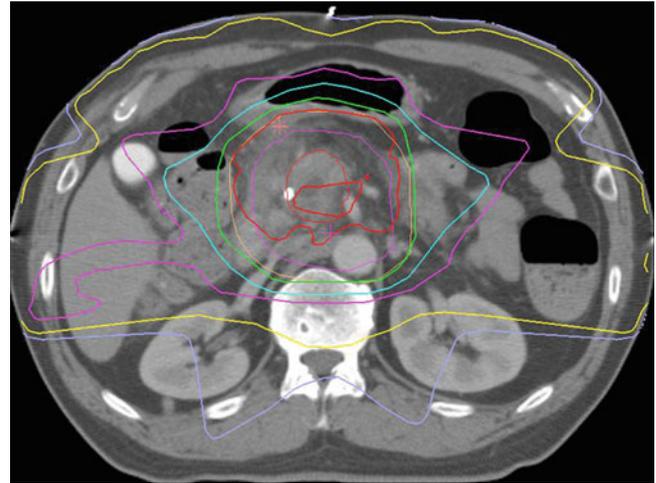
Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) is a form of highly conformal photon-based therapy that uses modulation of the intensity across the radiation beam to create highly conformal treatment plans. In contrast to two-dimensional (2D) or three-dimensional (3D) therapy, which uses multiple static fields, IMRT provides the ability to deliver radiation to targets of unusual, concave shapes, as well as differing radiation doses within a given volume allowing dose intensification

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Fig. 2.1 Intensity-modulated radiation therapy (IMRT) plan for a patient with pancreatic cancer. Note the conformal dose distribution



in selected areas of concern, and sparing of surrounding normal tissues. Improvements in treatment-related morbidity have been described in patients with breast, head-and-neck, and prostate cancer treated with IMRT, as compared to conventionally delivered radiation [1–3].

IMRT represents a technological advance that allows the radiation oncologist to “shape” radiation dose profiles around normal structures while fully dosing the tumor and at-risk nodal regions. Since toxicity from radiation is directly related to the volume of normal tissue irradiated, this ability for improved dose distribution provides the opportunity to reduce the overall toxicity profile associated with radiation therapy.

IMRT refers to a specific technique of linear accelerator based photon therapy whereby radiation beams are modulated in such a manner to produce highly conformal dose distributions. A primary objective of IMRT is to reduce dose to selected normal tissue structures in an effort to preserve function, while maintaining full dose delivery to tumor targets. Conventional computed tomography (CT) based radiation therapy, known as 3D-conformal radiation therapy (3D-CRT), uses static beams from two or more angles to target a tumor. These beam angles are chosen by the physician and the physicists and are modulated by a static beam modifier such as a wedge or tissue compensator. In contrast, IMRT is delivered either by multiple modulated static fields (step and shoot) or by a continuously rotating gantry (serial tomotherapy). As the radiation is delivered, specific subsections of each field, known as beamlets, are delivered at different intensities to produce highly conformal dose distribution around irregular shapes.

IMRT planning is conceptually distinct from conventional radiotherapy planning. With 3D-CRT treatment planning, the radiation oncologist will choose beam angles and shape the beam apertures using custom blocking or multileaf collimators (MLC). A generous field margin is used to account for set-up variation and physical characteristics of the beam itself. The radiation dose and profile is then calculated using broad and simple beams in a process known as forward planning. In contrast, IMRT planning requires the up-front designation of specific targets (prostate, gross tumor, elective nodal regions) and avoidance structures (rectal wall, bladder, bowel, spinal cord, salivary glands, optic apparatus, etc.). Dose specifications are then defined for each of the targets and avoidance structures. The computer planning software then creates a series of beam angles with modulation patterns that strive to achieve the physician’s dose prescription goals. This process is known as inverse planning.

IMRT is now routinely used in the treatment of disease sites where high doses are needed for cure such as prostate cancer and cancers of the head-and-neck. Increasingly, IMRT is also being used in other disease sites, such as brain tumors, lung cancer, upper gastrointestinal malignancies like pancreatic cancer (Fig. 2.1), anal cancer, and other historically difficult to treat locations. It should be noted that few head-to-head comparisons of clinical efficacy exist between 3D-CRT and IMRT.

Stereotactic Body Radiotherapy

Conventional radiation therapy is generally given in many small doses. In addition to the dose-volume predictors of radiation toxicity, how much radiation is given in a particular dose, or how the radiation is *fractionated* is also an important predictor of toxicity. Generally, radiation schedules where small doses are given over many fractions leads to fewer late

effects than when large doses are given over few fractions. For this reason, most conventional curative treatments are given over daily treatments of 6–8 weeks. The typical daily dose is between 1.5 and 4 Gy/day.

Stereotactic body radiation therapy (SBRT) is a new, evolving external beam radiotherapy method used to precisely deliver a high dose of radiation to an extracranial target using one to five doses [4]. This treatment is safely deliverable due to high targeting accuracy and rapid dose falloff gradients. This technique requires intensive physics support. Specialized treatment planning is needed to achieve sharp dose falloffs. Image registration of diagnostic scans [dynamic CT imaging or magnetic resonance imaging (MRI)] is often needed to accurately identify the tumor target on the planning CT. Motion management and intensive immobilization, either invasive or noninvasive, are needed to minimize the risk of both geographical miss as well as overtreatment of normal structures. Strategies for motion management include respiratory gating, abdominal compression, or use of a “motion envelope” around the target based on a four-dimensional CT scan. Additionally, internal fiducials, such as gold seeds placed by interventional radiology under CT guidance, may also be used for targeting.

Stereotactic radiation was first developed for intracranial lesions such as brain metastases, and base of skull lesions, with a very high rate of local control and an outstanding safety profile. These sites were treated first due to the lack of internal organ motion and the ability for rigid immobilization, allowing for more accurate setup. Clinical success led investigators to develop the technology for extracranial targets. With this technology, doses of 5–25 Gy can be delivered to each treatment, in contrast to the 1.5–3 Gy mentioned above.

Multiple treatment platforms exist for delivery of SBRT. SBRT may be delivered with either photons or protons (see the next section). Commercial SBRT-specific devices, such as CyberKnife (Accuray, Sunnyvale, CA) and Novalis (Varian, Palo Alto, CA), are integrated photon SBRT delivery systems. CyberKnife uses a linear accelerator mounted on a robotic arm that allows for a delivery of a pencil beam from multiple noncoplanar angles. Unique to CyberKnife is a tumor tracking system, which uses an internally implanted fiducial that can then be tracked by the system.

Clinical Indications

SBRT is primarily used as an ablative alternative to surgery. The most commonly treated sites are the lung and the liver. However, there is increasing interest in expanding SBRT to other difficult clinical scenarios.

Lung Tumors

SBRT has been studied extensively in medically inoperable stage I non-small cell lung cancer (NSCLC). A study from Timmerman and colleagues reported the 70-patient phase II study results of SBRT in patients with medically inoperable lung cancer [5]. Patients with T2 tumors received 66 Gy divided over three fractions. Patients with T1 tumors received 60 Gy divided over three fractions. With a median follow up of 18 months, the 2-year local control was 95%, with an overall survival of 56%. Most deaths were due to intercurrent disease rather than disease progression. Of note, severe toxicity was seen in patients with tumors within 2 cm of the bronchial tree. Based on this observation, SBRT is primarily now offered to patients with peripheral tumors.

This single-institution experience was followed by a multicenter study conducted by the Radiation Therapy Oncology Group (RTOG) [6]. In this study, 59 patients with T1/2 N0 M0 NSCLC were treated to 54 Gy divided in three fractions. Patients with central tumors, as described above, were excluded. The 3-year local control was 98%. The 3-year overall survival was 56%. There were only two Grade 4 toxicities with no treatment-related deaths.

Based on these prospective results, as well as other retrospective data, SBRT is a reasonable approach for peripheral, medically inoperable non-small cell lung cancer. Ongoing studies are further characterizing the optimal treatment schedule.

Liver Tumors

SBRT represents a potential treatment modality for the management of hepatic metastases. Historically, radiotherapy for unresectable liver tumors has been limited by the risk of radiation-induced liver disease (RILD). RILD is a clinical diagnosis that occurs within 3 months of liver radiation characterized by anicteric ascites with elevated liver function tests (LFTs) with alkaline phosphatase elevated out of proportion to transaminases. However, a strong relationship between the volume of liver irradiated and the risk of RILD spurred investigators to explore the feasibility SBRT for liver tumors.

Two large prospective multi-institutional series were published in 2009. The first study by Rusthoven and colleagues [7] evaluated 47 patients with 63 lesions in a phase I/II study of SBRT. Eligibility was restricted to up to three lesions with maximal size of 6 cm. In the phase I portion, dose was escalated from 36 Gy (12 Gy/fraction) to 60 Gy (20 Gy/fraction). In the phase II portion, patients received a dose of 60 Gy. Sixty nine percent of patients had at least one prior systemic regimen. Radiation therapy was delivered with SBRT techniques in three fractions. In total, 45% of patients had extrahepatic disease at the time of study entry. The median tumor size was 2.7 cm (0.4–5.8 cm). Local control in lesions \leq 3 cm in size was 100%, with a median survival of 20.5 months. There was only one Grade 3 toxicity noted of soft tissue breakdown in a patient whose chest wall received 48 Gy (16 Gy/fraction). There were no episodes of RILD.

Since frequently unresectable tumors are larger in size, in the second study, Lee and colleagues placed no size limit on tumor size but instead utilized an individualized approach [8]. In this multi-institutional phase I study, patients with up to four lesions (no size limit) were included. An individualized dose escalation was performed that took into account the differing volumes of normal liver irradiated given the heterogeneity in tumor size. Using the previously validated RILD risk model developed at the University of Michigan, three “isotoxic” risk groups were identified based on “effective volume” (Veff). Veff is a radiobiological model by which the heterogenous dose distribution of an organ is expressed as what fractional volume of the organ receiving the prescription dose produces the same biological effect. The three risk strata were low Veff <0.22 , mid Veff $0.22\text{--}0.51$, and high Veff >0.51 . For the low-risk Veff stratum, the dose was escalated from 54 to 57 Gy to 60 Gy in six fractions over 2 weeks as the RILD risk was estimated to below 5%. For the mid- and high-risk Veff stratum, the dose was escalated based on an increasing normal tissue complication probability (NTCP) for RILD of 5, 10, and 20%. Patients were planned for six fractions. At the highest dose level (20% risk), the median dose/fraction was 8 Gy for the mid-risk Veff stratum and 6 Gy for the high-risk Veff stratum. In total 68 patients were treated: 13 patients in the low-risk stratum, 25 in the mid-risk, and 20 patients in the high-risk stratum. Median gross tumor volume (GTV) size was 75.2 cm³ (range, 27.7 to 3,090 cm³). Only one patient experienced a Grade 3 toxicity (2%). The most common side effect was fatigue (Grade 2 18%), followed by gastritis (Grade 2 4%). Subacute liver pain occurred in six patients. There were no incidents of RILD. Local control at 1 year was 71%, and median overall survival was 17.6 months.

Based on these two studies, SBRT for liver tumors may be a viable option for unresectable metastases. However, while these prospective, multi-institutional studies are compelling, the concept requires further validation. Specifically, the second study of individualized SBRT is particularly interesting as it more closely reflects the clinical reality that unresectable lesions are often larger in size with fewer competing options than the lesions described in earlier studies of liver SBRT.

Pancreatic Tumors

There has been significant interest in the use of SBRT in the management of locally advanced pancreatic cancer. Early reports suggested modest median survival with high rates of duodenal toxicity [9]. A more recent retrospective from Beth Israel Deaconess in Boston evaluated 36 patients treated with sequential gemcitabine chemotherapy and SBRT with CyberKnife [10]. With a median follow up of 24 months, the median overall survival was 14.3 months. The treatment was well-tolerated, with a 14% Grade 3 toxicity rate. Figure 2.2 shows a CyberKnife pancreas treatment plan.

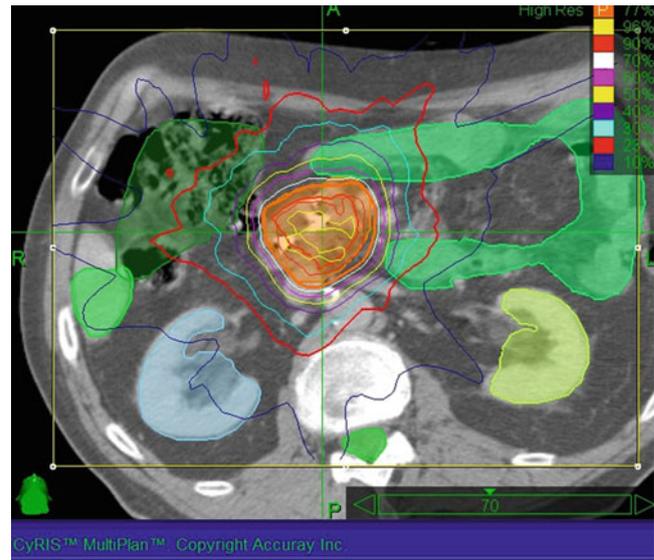
One reason for the modest results with SBRT is the difficulty in visualizing the target accurately. In a study by Arvold and colleagues, 97 consecutive resected patients who underwent preoperative pancreas protocol CT were evaluated for correlation between CT size and pathologic size of the tumor [11]. Tumors were found to be larger on pathology by a median of 7 mm but up to 43 mm larger. Additionally, 79% of patients had nodal involvement not seen and 72% of patients had invasion into the duodenum, which is an avoidance structure for SBRT. Thus, the modest results may be the result of inadequate coverage of the entire tumor volume. This highlights an important consideration of SBRT – the targeting is only as reliable as the imaging.

Spinal Tumors

The spine is one of the most common sites of metastases for cancer. However, the limited tolerance of the spinal cord to radiation therapy limits the ability to give a high enough dose of radiation required for durable tumor control. Additionally, as progression happens, retreatment options are frequently limited. For this reason, SBRT is an attractive approach for tumors of the vertebral bodies.

There is limited prospective data on the use of SBRT for spinal metastases. In a phase I/II study from MD Anderson, 63 patients with 74 spinal metastases were treated with SBRT to either 30 Gy in five fractions or 27 Gy in three fractions.

Fig. 2.2 CyberKnife
(Accuray, Sunnyvale, CA)
plan for a patient with locally
advanced pancreatic cancer



Out of 63, 35 patients had prior radiation in the sites of interest. No patient developed Grade 3 or higher toxicity. The 1-year freedom-from-radiographic progression was 84% [12]. Another phase II study from the University of Florida reported on 21 patients with 25 lesions in which 43% of patients had pain relief, and the crude local control was 96% [13].

Because of the limited data, SBRT for spine metastases is still investigational. Its greatest utility may be in the setting progression after prior radiation therapy.

Proton Beam Therapy

There has been an unprecedented interest in proton beam therapy. The basis for the advantages of proton beams lies in the physical laws that determine the absorption of energy in tissues exposed to photon or proton beams. In a specific tissue, photons are absorbed exponentially, whereas protons have a finite range dependent upon the initial proton energy. Therefore, the depth dose characteristics of the two beams are qualitatively different. Protons lose their energy in tissue mostly by coulombic interactions with electrons in the constituent atoms; however, a small fraction of energy is transferred through nuclear collisions. The energy loss per unit path length is relatively small and constant as the proton traverses the tissue until near the end of the proton range where the residual energy is lost over a short distance (approximately 0.7 cm in width at 80% of the maximum dose) and the proton comes to rest, resulting in a distinctive sharp rise in the tissue absorbed dose (energy absorbed per unit mass) – known as the Bragg peak. In physical terms, the magnitude of the transfer of energy to tissue per unit path length traversed by the protons is inversely proportional to the square of the proton velocity. The low-dose region between the entrance and the Bragg peak is called the plateau of the dose distribution, and the dose there is 30–40% of the maximum dose.

These physical characteristics lead to a lack of “exit dose.” Where standard high-energy photons penetrate through the entire body, protons can stop at a depth chosen by the physician. Hence, the overall all normal tissue exposure is 30–60% less. This technology affords the opportunity for higher doses, and theoretically greater tumor control, with fewer side effects.

One flaw of proton beam therapy is the significant cost of a proton facility. A cyclotron or synchrotron, which can deliver beam to two to five rooms, is approximately 50 times the cost of a single linear accelerator. Thus, it is cost-prohibitive for most medical centers to use proton beam therapy.

Proton beam therapy has primarily been studied in intracranial/base of skull tumors and in pediatrics due to the greater importance on protecting normal tissues as well as the relatively small number of cases per year. For these patients, standard radiation schedules of 6–8 weeks are used. However, there has been growing interests in using protons for nonsurgical, potentially curative indications. Primary liver tumors (hepatocellular carcinoma and intrahepatic cholangiocarcinoma) represent one such indication, which is discussed below.

Primary Hepatoma

Many patients with primary hepatobiliary cancer are not surgical candidates due to anatomic location or size of the tumor, concurrent cirrhosis, or medical inoperability. Therefore, an important role exists for a treatment that can provide the equivalent of tumor excision, but with minimal morbidity.

The treatment of unresectable hepatocellular or locally recurrent hepatocellular cancer and cholangiocarcinoma has been palliative. Standard treatment modalities have included transarterial chemoarterial embolization (TACE), radiofrequency ablation, or systemic chemotherapy/targeted therapy with few long-term survivors. TACE is useful in patients with multiple lesions, but is not considered an ablative approach. Similarly, systemic therapy does not produce more than anecdotal complete responses.

Radiofrequency ablation (RFA) is the most commonly employed ablative technique for nonsurgical candidates at many institutions. However, the use of RFA can be limited by location. An adjacent large vessel can act as a heat sink and limit the efficacy of therapy. Treatment of dome lesions near the diaphragm carries the risk of diaphragmatic perforation, and treatment of deep lesions near bowel loops may be associated with bowel perforation. Radiofrequency ablation can be highly effective for small lesions, with local control of 75% or greater. However, this local control falls off steeply beyond 3–5 cm in maximum diameter.

Because of the limited tolerance of the liver to external beam irradiation when the whole liver is irradiated, experience with radiation has been limited. However, several studies have demonstrated that the tolerance of liver significantly increases when smaller volumes of the liver are irradiated. A study from the University of Michigan reported the results of 22 patients with unresectable hepatocellular carcinoma and cholangiocarcinoma treated by high-dose irradiation employing conformal 3D techniques using 10 MV X-rays and hepatic artery fluorodeoxyuridine. These patients were observed to have a 4-year survival of 20% and no late hepatic toxicity [14]. Total radiation doses were determined by the fraction of normal liver treated to 50% of the isocenter dose. If 33% of the normal liver received 50% of the dose, the patient was treated to 66 Gy; if 33 to 66% of the liver received 50% of the dose, the patient received 48 Gy; and if 66% of the liver received 50% of the dose, the patient received 36 Gy. Treatment was given daily at 1.8 Gy per fraction 5 days per week. The tumor response exhibits strong dose-dependence with the response rate for tumor doses above 60 Gy twice as high as for tumor doses below 50 Gy [15–17]. Similarly encouraging results of dose escalations studies using three-dimensional conformal radiotherapy have recently been reported by groups from Korea (183 patients) and Taiwan (93 patients) [18, 19]. These studies demonstrated that the overall median survival could also be significantly improved with higher doses. The chief cause of mortality was progression of underlying severe cirrhosis and not tumor or treatment-related causes.

With the lack of exit dose and greater potential for liver sparing, protons are a natural fit for primary liver tumors, especially in light of the underlying cirrhosis (Fig. 2.3). The use of protons for liver tumors has been extensively studied in Asia. Chiba and colleagues reported 162 patients with hepatocellular carcinoma (HCC) treated with proton radiotherapy. All treatments were delivered using hypo-fractionated regimens (3.5–5 Gy), and total doses ranged between 50 Gy (10 fractions) and 84 Gy (24 fractions) [20]. A total of 192 lesions were treated. Median tumor size was 3.8 cm (1.5–14.5 cm). The median dose was 72 cobalt gray equivalent (CGE) in 16 fractions. At a median follow-up interval of 31.7 months (range 3.1–133.2 months), the 5-year local control rate was 86.9% and corresponding overall survival rate was 23.5%. Survival appeared to be impacted by the level of liver dysfunction with over 50% dying without tumor progression (usually complications of liver cirrhosis). The acute side effects were limited primarily to elevation in liver enzymes (9.7%) and only five patients had Grade 2 or higher late toxicity. Among a subset of 50 patients with solitary tumors and Child Class A cirrhosis, the observed 5-year survival rate of 53.5% rivals similar to that of surgery. Similarly favorable outcomes have been observed in patients with unfavorable features and limited treatment options [21–25]. In particular, one study of 22 patients with HCC larger than 10 cm in size (median 11 cm, range 10–14 cm) treated with proton beam showed a 2-year local control of 87% with no acute or late Grade 3 toxicity [25].

Patients with portal venous thrombosis might benefit especially from proton radiotherapy, because they tend to have larger tumors and many, if not most, of these patients have few viable ablative treatment options. However, because of the size, extent, and location of the disease, conventional photon radiotherapy at higher doses may not be feasible. In a series of 35 of these patients, Sugahara and colleagues found that treatment to 50–72 CGE led to local control rates of 45% at 2 years, but with only three patients developing severe acute toxicity [26]. As noted previously, the excellent conformality of proton radiotherapy offers the possibility of retreatment if new HCCs arise within the liver further away from the originally treated HCC. The Tsukuba proton radiotherapy group has reported on the safety, feasibility, and efficacy of repeated courses of proton radiotherapy in a series of 27 patients with 68 lesions [27]. With a median interval of 24 months between the first and second courses, and a median dose of 66 CGE in 16 fractions for the retreatment, they reported a 5-year overall survival of 56% and a 5-year local control rate of 87.8%.

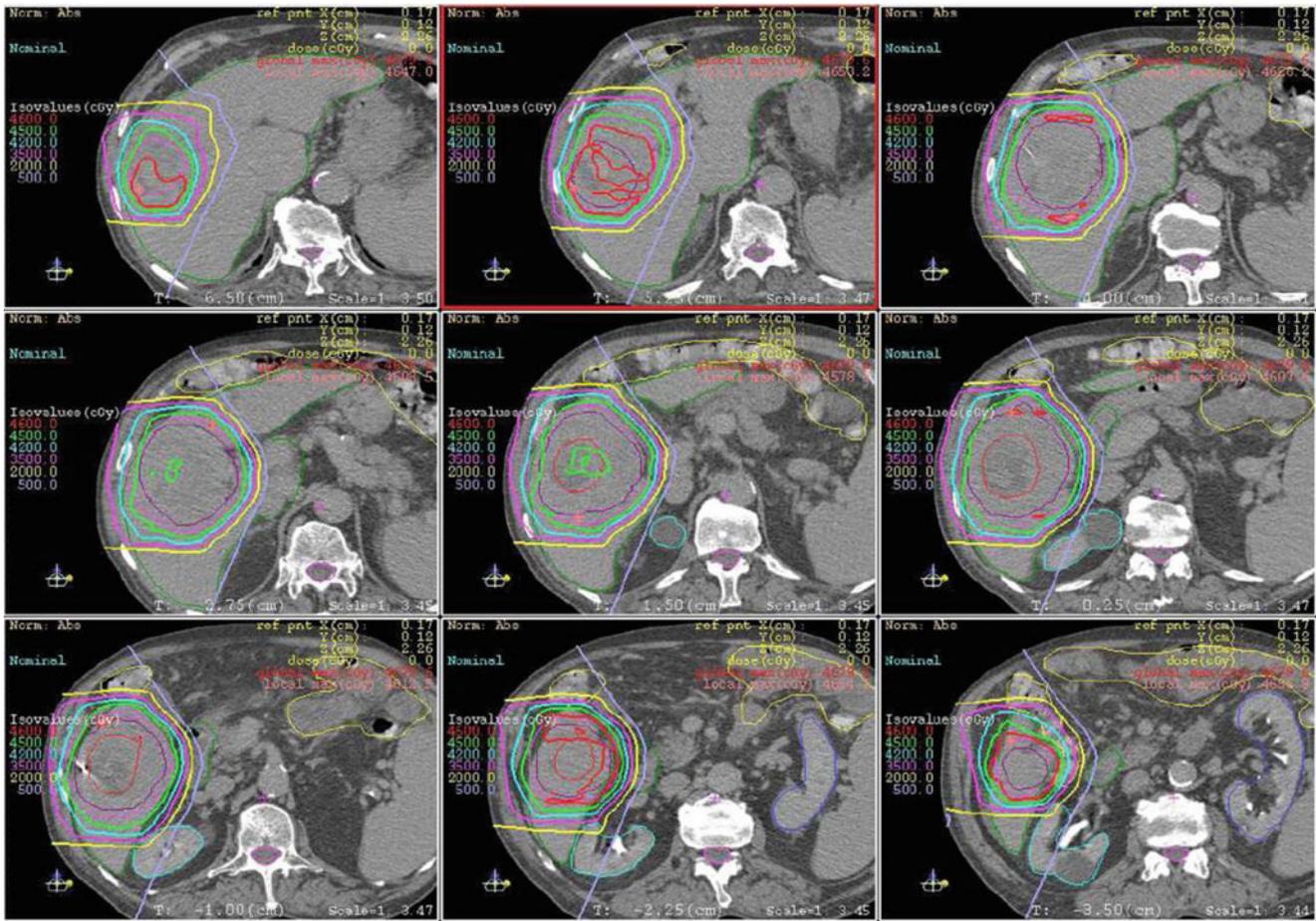


Fig. 2.3 Proton plan for a liver tumor. In contrast to the photon plans of Figs. 2.1 and 2.2, note the lack of radiation beyond the entry paths of the beam

Similarly, in a phase II trial, Kawashima and colleagues reported overall survival rates of 66% in cirrhotic patients after proton radiotherapy to 76 CGE in 3.8 CGE daily fractions [28]. In this study, 20% of patients developed hepatic insufficiency, with a rate of Grade 3 toxicity of about 40%.

Data regarding outcomes and toxicity with the use of protons in populations where hepatitis B vaccine (HBV) is non-endemic is much more limited. In a phase II trial of proton radiotherapy for HCC, Bush and colleagues treated 34 cases of unresectable HCC to 63 CGE in 15 fractions [29]. In this study, the 2-year overall survival was 55%, with local control rates of 75%. No RILD was seen in this study; however, 60% of patients were noted to have mild acute toxicity due to radiotherapy. Furthermore, less than 10% of these patients experienced a gastrointestinal bleed, which was due, in large part, to the proximity of gross disease to the colon or duodenum. Finally, of these patients, six went to liver transplant and of these two patients had a complete response after pathological review.

In summary, proton beam therapy may have a role in treating patients with underlying hepatic dysfunction, large tumors, and portal vein thrombosis not amenable to other ablative therapies. Further investigations are ongoing.

Summary

Advanced radiation techniques such as IMRT, SBRT, and proton therapy have the potential to expand the range of ablative options for the cancer patients. These modalities are complementary to the arsenal of tools available to the interventional radiologist.

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