Practical Guides in Radiation Oncology
Series Editors: Nancy Y. Lee · Jiade J. Lu

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Gastrointestinal Malignancies

A Practical Guide on Treatment Techniques

Springer

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Series editors

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The series *Practical Guides in Radiation Oncology* is designed to assist radiation oncology residents and practicing radiation oncologists in the application of current techniques in radiation oncology and day-to-day management in clinical practice, i.e., treatment planning. Individual volumes offer clear guidance on contouring in different cancers and present treatment recommendations, including with regard to advanced options such as intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT). Each volume addresses one particular area of practice and is edited by experts with an outstanding international reputation. Readers will find the series to be an ideal source of up-to-date information on when to apply the various available technologies and how to perform safe treatment planning.

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Preface

The *Gastrointestinal Malignancies: A Practical Guide on Treatment Techniques* series is intended to be a *Practical Guide* to incorporating and delivering quality radiation therapy in the multimodality treatment of gastrointestinal malignancies *rather than a traditional textbook* addressing background and summaries of landmark clinical trials. It is designed for radiation oncologists, medical physicists, medical dosimetrists, and other oncology professionals such as medical and surgical oncologists with special interest in radiation techniques.

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Contents

Part I

Esophageal Cancer

Proximal/Cervical Esophageal Cancer

1

Anupam Rishi and Jimmy J. Caudell

Contents

1.1 Introduction

The esophagus is a hollow, muscular tube, approximately 25 cm in length, which extends from the lower border of the cricoid cartilage to the cardiac orifice of the stomach. The American Joint Committee on Cancer (AJCC) has divided the esophagus into four regions: cervical, upper (proximal) thoracic, mid-thoracic, and lower thoracic [1]. The cervical esophagus begins at the cricopharyngeus muscle (approximately the C7 level or 15 cm from the incisors) and extends to the thoracic inlet

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(approximately T3 level or 18 cm from the incisors, at the level of the suprasternal notch). Cervical esophageal cancers differ from those at the mid- and lower esophagus or gastroesophageal junction in regard to natural history, patterns of spread, biological behavior, and management. As such, cervical esophageal cancers are managed more similarly to head and neck squamous cell carcinomas rather than for malignancies involving more distal portions of the esophagus. In this chapter, we will discuss the management principles and radiotherapy (RT) delivery techniques for cervical esophageal cancers.

1.2 Management Principles for Cervical Esophageal Cancers

The management of cervical esophageal cancer differs from that of cancers of the remaining esophagus [2]. Due to proximity to critical organs and risk of adjacent anatomical structure invasion, most cervical esophageal cancers are not amenable to surgery, as this would involve functionally devastating resections of portions of the pharynx, larynx, and cervical esophagus (pharyngo-laryngo-esophagectomy). In addition, neck dissections are often required. Therefore, surgery is associated with significant morbidity, mortality, and severely compromised quality of life [3, 4]. Based on various studies, patients treated with definitive surgery had morbidity rates of 60–70%, mortality rates of 7–11%, and a 5-year overall survival rate of 18–27% [5–8] (Table 1.1).

Therefore, RT combined with chemotherapy is preferred as chemoradiation (CRT) offers similar locoregional control and survival as compared to surgical resection, with less functional impairment and better quality of life [13–18]. The FFCD 9102 study showed that locally advanced thoracic esophageal cancer patients who responded to CRT derived no benefit from the addition of surgery after CRT as compared to continuation of additional CRT [19]. Similarly, a German trial compared induction chemotherapy followed by CRT followed by surgery against the same induction regimen (chemotherapy + RT), but without surgery. There was no significant difference in overall survival between the two treatment groups. Treatment-related mortality was significantly greater in the surgery group than in the CRT group [20]. Interestingly, a meta-analysis investigating RT versus surgery within multimodality protocols for esophageal cancer suggested that overall survival was equivalent between surgery and definitive CRT [21]. While these trials were not specific to cervical esophageal cancer, they provide a logical rationale for the selection of definitive CRT.

Table 1.1 Outcome of patients treated with surgery

Study	Year	N Cervical esophagus/ hypopharynx	5-year overall survival (%)	Morbidity *n* (%)	Hospital mortality *n* (%)
Wei et al. [9]	1998	32/37	24	34 (49)	6 (9)
Triboulet et al. [4]	2001	78/131	24	42 (33.1)	10 (4.8)
Wang et al. [10]	2006	15/26	31.5	19 (46.3)	4 (9.8)
Daiko et al. [11]	2007	74/0	33	25 (34)	3 (4)
Tong et al. [12]	2011	43/25	37.6 (2-year)	–	5 (7.1)

1.2.1 Definitive Chemoradiation

Given the location in the neck, cervical esophageal cancers are usually managed similarly to locally advanced head and neck squamous cell carcinoma (HNSCC) [13]. Due to the rarity of cervical esophageal cancers, no large randomized studies have focused exclusively on cervical cancers. The evidence of concurrent chemotherapy in improving survival over RT alone can be extrapolated from randomized trials and meta-analyses targeted to thoracic esophageal or head and neck squamous cell cancers. The landmark Radiation Therapy Oncology Group 85-01 trial using 2-D radiation therapy techniques (2DRT) compared RT alone (64 Gy in 32 fractions over 6.5 weeks) versus concurrent CRT [two cycles of infusional 5-FU (1000 mg/m^2 per day, days 1–4, weeks 1 and 5) plus cisplatin (75 mg/m^2 day 1 of weeks 1 and 5) and RT (50 Gy in 25 fractions over 5 weeks)]. The results showed a significant survival advantage for the CRT arm, i.e., 5-year survival 27% vs. 0% [14, 15, 22]. Although this study included only patients with thoracic esophageal cancer, the study results form the basis of the current non-surgical treatment of patients with esophageal cancer, including cervical esophagus. Various smaller studies of exclusive cervical esophageal cancer have reported a 5-year OS of 30–40% for patients treated with definitive CRT [16–18, 23, 24], which is comparable with OS after surgery alone (24–47%) [4, 10, 11, 13, 25–29]. Previous studies on the efficacy of RT with or without chemotherapy for treating cervical esophageal cancer have reported 3-year survival rates of 22–40% [17, 23, 30–32] (Table 1.2).

Preservation of the larynx and pharynx is an important management concern in cervical esophageal cancer due to the frequency of hypopharyngeal or laryngeal involvement. The negative physical and psychosocial impact of a permanent tracheostomy and loss of natural voice are powerful drivers for patients to choose a treatment that will preserve their laryngeal and swallowing functions. From this perspective of organ preservation, treatment approaches such as RT or concurrent RT and systemic therapy have been used to preserve the functional larynx for patients with laryngeal, hypopharyngeal, or cervical esophageal cancers [37–40]. In the RTOG 91-11 study, the larynx preservation rate was 88% using concurrent CRT [37, 38].

Although CRT for esophageal cancers usually consists of 50.4 Gy in 1.8 Gy per fraction per day, higher doses up to 66–70 Gy may be appropriate for cervical esophageal cancer analogous to the HNSCC [12, 17, 30, 32, 33, 36, 41]. Delivering an adequate RT dose to the tumor is often challenging because of the proximity of the cervical esophagus to vital structures such as the spinal cord, brachial plexus, larynx, pharyngeal constrictors, and lungs. However, with the advances in modern RT techniques, such as IMRT, Volume-Modulated Arc therapy (VMAT), or other rotational radiation delivery techniques, delivery of a more conformal dose to the tumor and improved sparing of nearby organs at risk are possible [42–50]. Preliminary single institution data from use of proton-beam RT (PBT) in cervical esophageal cancers has also shown potentially improved dose distributions [51, 52].

Table 1.2 Outcome of patients treated using radiotherapy

Study	Year	*N*	RT	Dose (Gy)	LRC	2-year overall survival (%)	5-year overall survival (%)
Stuschke et al. [30]	1999	17	2D	60–66	33 (2-year)	24	NA
Burmeister et al. [33]	2000	34	2D	50.4–65	NA	NA	55
Yamada et al. [32]	2006	27	2D	44–73.7	13 (5-year)	38	38
Uno et al. [34]	2007	21	IMRT	60–74	NA	41	27
Huang et al. [23]	2008	71	2D/3D/ IMRT	54 Gy/20 fr (n = 29) 70 Gy/35 fr (n = 42)	NA NA	41 32	NA NA
Tong et al. [12]	2011	21	2D/3D	60–68	NA	46.9	NA
Grass et al. [2]	2014	240	NA	NA	NA	40	28
Cao et al. [35]	2015	115	IMRT	59.4–80	68.3 (2-year)	47.6	NA
Cao et al. [36]	2016	64	IMRT	60–70	74.5 (2-year)	42.5	NA

IMRT intensity-modulated radiotherapy, *LRC* locoregional control

1.2.2 Concurrent Chemotherapy

As cervical esophageal cancers are often managed similar to head and neck squamous cell carcinoma, concurrent high-dose cisplatin-based chemotherapy, consisting of 100 mg/m^2 on day 1, 22, and 43 of RT, may be reasonable [23]. Other commonly used concurrent chemotherapeutic regimens include a combination of cisplatin (75 mg/m^2 day 1 of weeks 1 and 5) and 5-FU (two cycles of infusional 5-FU, 1000 mg/m^2 per day, days 1–4, weeks 1 and 5), as adapted from established regimens in lower esophageal squamous cell cancers (SCC) [53]. No difference in locoregional control and survival outcome has been observed comparing patients treated with high-dose cisplatin versus cisplatin + 5-FU or mitomycin C, but combination therapy can lead to higher toxicity rates when compared with cisplatin alone [23, 54].

Other chemotherapeutic regimens have also been studied with comparable results. Recently, the PRODIGE5/ACCORD17 randomized trial assessed the efficacy and safety of the concurrent FOLFOX regimen (oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, bolus fluorouracil 400 mg/m^2, and infusional fluorouracil 1600 mg/m^2) against standard cisplatin/5FU as part of definitive CRT (50 Gy in 25 fractions) [55]. No significant differences were recorded in the progression-free survival and rates of grade 3 or 4 adverse events in both the arms. Carboplatin and paclitaxel-based chemotherapy, a regimen already used in SCC of the lower esophagus, has been used as an alternative to the cisplatin-based regimen [56].

Overexpression of EGFR has been detected in 30–90% of esophageal cancers and correlates with increased invasion, dedifferentiation, and worse prognosis [57,

58]. Cetuximab, an EGFR targeting therapy, is an established radiosensitizer in HNSCC [59], but its role in cervical esophageal cancers is not established. On the basis of the results of the SCOPE1 trial, a multicenter phase II/III randomized trial comparing CRT versus CRT + cetuximab, the use of cetuximab cannot be recommended due to treatment-limiting toxicity [60]. Recently, a phase III REAL3 trial had to be closed early due to a lack of efficacy [61]. RTOG 0436, a randomized phase III trial, evaluated concurrent chemoradiation [50.4 Gy/1.8 Gy fractions + weekly concurrent cisplatin (50 mg/m^2) and paclitaxel (25 mg/m^2) ± weekly cetuximab (400 mg/m^2 day 1 then weekly 250 mg/m^2)] in nonoperative management of esophageal carcinoma [62]. The preliminary results showed that cetuximab added to chemoradiation did not improve OS [62]. These results add to the growing body of literature, indicating no benefit for current EGFR-targeted agents, and therefore, their use is not recommended outside a trial setting.

1.3 Radiation Therapy Techniques and Planning

The design and delivery of radiation therapy for esophageal cancer requires knowledge of the natural history, anatomy, pattern of spread, and radiobiological principles. Furthermore, the use of proper equipment, implementation of methods to decrease treatment-related toxicity, and close collaboration with the physics and technology staff are essential. The cervical esophagus lies in close anatomical relation to various sensitive organs at risk such as spinal cord, brachial plexus, larynx, pharyngeal constrictors, and lungs. Therefore, key to successful radiation planning is minimizing the dose to these structures while delivering an adequate dose to the primary tumor and regional lymph nodes, which can be aided by techniques such as patient immobilization, modern imaging acquisition, CT-based treatment planning for organ identification, and RT plan optimization.

1.3.1 Setup and Immobilization

Patients are placed in a reproducible supine position with arms laterally and head hyper-extended and immobilized with a thermoplastic head/neck/shoulder mask.

1.3.2 Simulation

A contrast-enhanced Computed Tomography (CT)-based simulation scans are recommended over fluoroscopy for better delineation of target and sparing of organs at risk (OAR).

- The planning CT should encompass the entire neck starting from the base of the skull extending inferiorly through the entire esophagus length to encompass disease with margins.
- Slice thickness of $\leq$3 mm slices should be used, allowing accurate tumor characterization as well as improved quality of digitally reconstructed radiographs.

- Arterial phase IV contrast is generally used to define tumor and nodal basins and to allow the radiation oncologist to discern normal vasculature from other adjacent normal structures, potential adenopathy, etc.
- The tumor and vital structures are then outlined on each slice on the treatment planning system, enabling a 3-dimensional treatment plan to be generated.
- Unlike thoracic esophagus, breathing movements are not significant in cervical esophageal cancer and immobilization using thermoplastic head and shoulder mask sufficiently minimizes interfraction movements. Four-dimensional CT scan, respiratory gating, or breath hold techniques are not routinely recommended for cervical esophageal cancers.

1.3.3 18F-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography (FDG-PET) Planning

As an adjunct to CT, PET-CT can be used in esophageal cancer not only as a routine part of initial staging, but also for RT planning and response assessment.

- For primary tumors, PET scans in esophageal cancer have a sensitivity ranging from 95 to 100% and a specificity of 100% [63, 64].
- Because of its higher accuracy to differentiate malignant and normal tissues, it is recommended to incorporate PET-CT into RT planning to improve the target delineation process and to adapt treatment plans [65–68]. In some studies, the use of PET-CT for tumor delineation results in a difference in target volume when compared to CT and EUS in 10–63% of patients [65]. The discordance between CT and PET-CT was due mainly to differences in defining the longitudinal extent of disease in the esophagus [69].
- If no planning PET is available at the time of simulation, a diagnostic PET can also be fused with the simulation CT to aid target delineation.

1.3.4 Treatment Planning

1.3.4.1 Field Design

- IMRT-based planning has facilitated the treatment of cervical esophageal lesions and is the authors' preferred method for treating these tumors (Fig. 1.1). Strict normal tissue constraints, including normal lung and spinal cord, are important considerations using these techniques.

1.3.4.2 Target Volume

- Supraclavicular and superior mediastinal nodes are irradiated electively. Analysis of nodal involvement in a large series of resected squamous cell carcinoma patients supports the concept of elective mediastinal and supraclavicular node coverage in locally advanced proximal tumors [70].

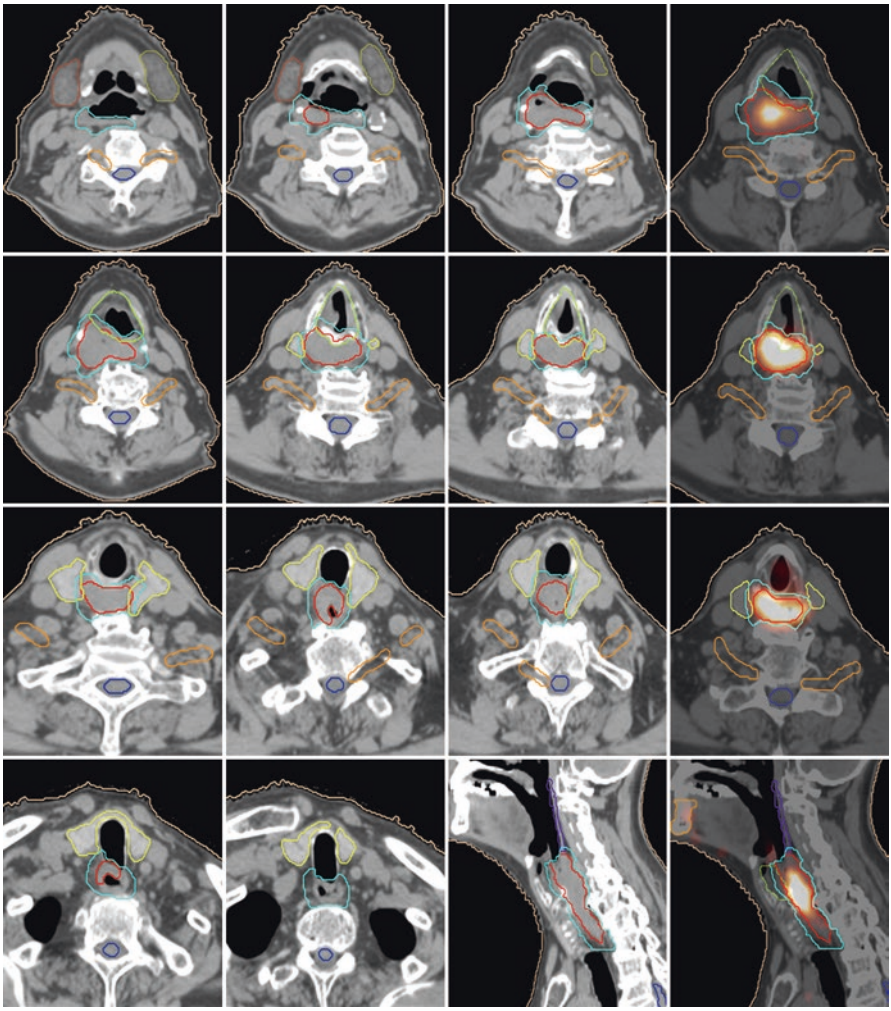

Fig. 1.1 Contouring atlas for a cT3N0M0 cervical esophageal cancer. Delineation of Gross Target Volume (GTV) (*red*), based on CT and PET; Clinical target Volume (CTV) (*skyblue*) expansion accounts for microscopic spread supero-inferiorly; Planning Target Volume (PTV) expansion (3–5 mm) around the CTV to account for setup error and may vary based on IGRT method (Table 1.3). Note the CTV expansion is manually defined to respect anatomic boundaries. *Red* = Gross Target Volume; *Skyblue* = Clinical Target Volume; Normal tissue includes: *Yellow* = thyroid; *Orange* = brachial plexus; mandible (sagittal); *Yellow-green* = larynx; *Blue* = spinal cord; *Brown* = right submandibular gland; *Olive* = left submandibular gland; *Slate blue* = pharyngeal constrictors

- In modern conformal RT practice, treatment volumes are more commonly defined based on the ICRU definitions of clinical target volume (CTV) and planning target volume (PTV). Definitions of GTV, CTV, and PTV are detailed in Table 1.3. Target delineation is shown in Fig. 1.1.

Table 1.3 Definitions of target volumes in RT for cervical esophageal cancer [71]

Type	Description
GTVp	All grossly positive disease of the primary tumor as seen on exam, laryngoscopy, diagnostic and planning CT scans, and PET/CT imaging
GTVn	All grossly involved regional lymph nodes
CTVp[a]	Cranial-caudal: GTV plus 3-cm margin for submucosal extension along the length of the esophagus; or 1 cm above any grossly involved periesophageal nodes, whichever is more cephalad. The upper border should not extend above the level of the cricoid cartilage unless there is gross disease at that level. This margin should be oriented along the esophageal mucosa, instead of being a simple geometric expansion Radially, extend by 1 cm from GTV but respecting anatomic boundaries, such as the vertebral body, trachea, pleura, and vessels, to encompass the periesophageal lymph nodes
CTVn	The nodal CTV should encompass the elective nodal regions, including bilateral levels III, IV, Vb, Vc, VI, and mediastinal nodes, variable coverage of II and Va depending on disease configuration The cranial and caudal limits of the CTV-LN were the caudal edge of the lateral process of the atlas and trachea bifurcation, respectively *Atlas of images illustrating nodal CTV and organs of risk is located at RTOG website: https://www.rtog.org/CoreLab/ContouringAtlases/HNAtlases.aspx)* [72, 73]
PTV	PTV expansion ensures adequate target coverage Defined as per ICRU-62 guidelines and may vary on IGRT method [74] • Portal imaging has been associated with a 5–6 mm setup uncertainty for radiation treatment • With use of CBCT, 3-mm PTV expansion margins appear adequate [75]

GTVp gross tumor volume of primary disease, *GTVn* gross tumor volume of nodal disease, *CTVp* clinical target volume—primary disease, *CTVn* clinical target volume—nodal disease, *PTV* planning target volume, *CBCT* cone-beam CT

[a]CTV should be delineated by radiation oncologists and automatic expansion from GTV is not an acceptable practice

1.3.5 Treatment Delivery Techniques

1.3.5.1 Intensity-Modulated Radiotherapy (IMRT)

With the advent of CT-based 3-dimensional (3D) treatment planning, better anatomic visualization and improved target delineation are feasible for the dose avoidance of normal structures. IMRT utilizes multiple beams (typically 5–9), with each beam modulated further using computer-controlled multi-leaf collimation to dynamically block the path of the radiation when the beam is on. This produces better conformity to the tumor and dose reduction to normal structures [42]. No randomized trial has compared IMRT with 3DCRT in cervical esophageal cancer; however, various studies suggest that these techniques may be useful in the treatment of cervical esophageal cancers [43–46].

1.3.5.2 Volumetric-Modulated Arc Therapy (VMAT) and Helical Tomotherapy (Accuray, Sunnyvale, CA)

Rotational radiation treatment techniques such as Tomotherapy and VMAT allow delivery of a more conformal dose distribution to the tumor and improved sparing of nearby organs at risk, providing an alternative treatment option to conventional IMRT (Fig. 1.2) [47–50]. On dosimetric analysis, tomotherapy plans showed sharper

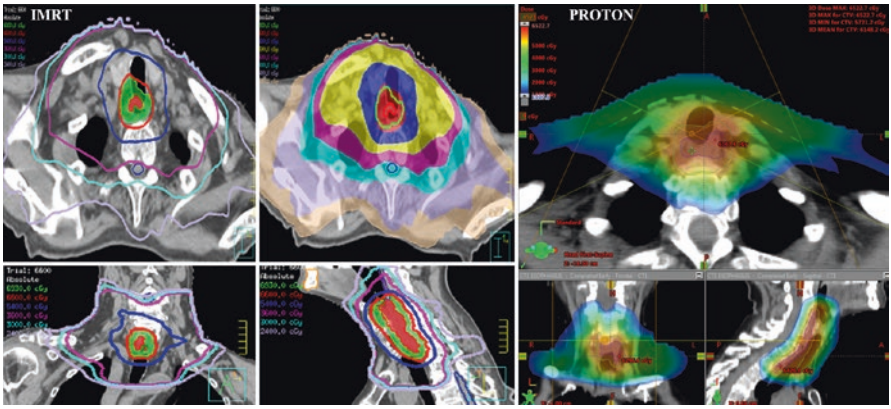

Fig. 1.2 Representative treatment plans for cervical esophagus using IMRT (VMAT) and proton-beam therapy (IMPT). (*Courtesy of Shahed Badiyan, MD, University of Maryland, Maryland Proton Treatment Center, and Michael D. Chuong, MD, Miami Cancer Institute at Baptist Health South Florida). IMRT* intensity-modulated radiotherapy, *VMAT* volumetric-modulated radiotherapy, *IMPT* intensity-modulated proton therapy

dose gradients, more conformal coverage, and better Homogeneity Index for both gross and elective target volume compared with IMRT or 3D-CRT plans. The mean V20 [percentage of the lung volume (with the subtraction of the volume involved by esophageal cancer) which receives radiation doses of 20 Gy or more] of lung was significantly reduced in tomotherapy plans [76]. Compared with static field IMRT, VMAT slightly improves OAR dose sparing and reduces NTCP and monitor units with better PTV coverage [77].

1.3.5.3 Proton-Beam Therapy (PBT)

The interaction between protons and tissue is substantially different than that of photons or electrons [78]. Unlike photon radiation, protons initially traverse matter with minimal loss in energy or attenuation, and the majority of their energy is selectively deposited in the area where they have minimal or essentially no velocity, which is known as the Bragg peak. Importantly, there is essentially no dose deposition distally. Preliminary single institution data from the use of Proton-beam RT (PBT) in proximal esophageal cancers has also shown good dose distributions as the majority of the proton energy is selectively deposited in the area where they have minimal or essentially no velocity, which is known as the Bragg peak (Fig. 1.2) [51, 52].

1.3.5.4 Intensity-Modulated Proton Therapy (IMPT)

Although PBT essentially eliminates exit dose to normal tissues compared with photon therapy, the deposition of high doses proximal to the target is not as highly conformal. In the head and neck regions, the presence of multiple nearby organs at risk that are preferably spared as much as possible makes HNC plans complex. It is therefore especially important in these patients to incorporate robustness in the proton optimization process [79]. Intensity-modulated proton therapy (IMPT) is a more recent technological advancement in which magnets steer the proton beam to cover, or "paint," the target volume layer by layer. Due to the rarity of cervical esophageal cancer, there

Table 1.4 Radiation treatment approaches for proximal/cervical esophageal cancer

Technique	Indication	Fractionation schedules	Beam arrangement	Appropriate chemotherapy
IMRT/ VMAT/ helical tomotherapy	Definitive CRT	50–70 Gy in 25–35 fractions of 2 Gy per fraction; 5 days/week	IMRT: Multiple coplanar isocentric beams VMAT: Volumetrically modulated coplanar arcs	Concurrent Cisplatin/platinum-based chemotherapy[a]
Proton-beam therapy[b]	Definitive CRT	50–70 GyE; 2 Gy per fraction; 5 days per week	Typically, 2–3 fields (AP/PA; lateral or posterior oblique)	Concurrent cisplatin/ platinum-based chemotherapy[a]

[a]See chemotherapy details in Sect. 1.2.2
[b]May be appropriate for selected cases

is no study evaluating the role of protons or IMPT. However, the results can be extrapolated from head and neck cancer treatment. Multiple studies of head and neck cancers have shown the potential benefits of IMPT by comparing proton therapy with photon modalities [80].

Table 1.4 outlines radiation therapy techniques used for the treatment of proximal/cervical esophagus.

1.3.6 Dose and Fractionation

Although the optimal radiation dose is not well-defined, a total dose of 50–70 Gy for definitive CRT in daily 1.8–2 Gy fractions, 5 days per week, is deemed appropriate. We recommend doses of 66–70 Gy.

1.3.7 Treatment Plan Optimization

Regardless of the radiation modality utilized, treatment plans must be optimized for adequate target coverage and minimization of dose received by the dose-limiting critical structures including spinal cord, brachial plexus, larynx, pharyngeal constrictors, and lungs. Several strategies to treatment planning optimization are commonly utilized to improve dose homogeneity within the target and avoidance of high-dose regions within normal structures, including appropriate selection of beam geometry and energy, use of multiple coplanar/ non-coplanar beams, use of beam modification devices (wedges and compensators) to accommodate for irregularities of patient contour, tissue homogeneity correction (lung correction), and the use of dose sculpting techniques to achieve more conformal dose distributions using advanced radiation technologies (IMRT, VMAT, Tomotherapy, IMPT).

We summarized in Table 1.5, the clinically relevant dose-volume constraints to be incorporated as treatment planning objectives for conventional fractionation (1.8–2 Gy per fraction). This information is a “guideline” and each plan should be unique and optimized to accommodate patient and target-specific attributes.

Table 1.5 Dose-volume considerations for treatment planning optimization of conventional fractionation (70 Gy in 35 fractions; 2 Gy per fraction) [81]

Critical structure	Dose/volume parameters	Toxicity rate (%)	Toxicity endpoint
Spinal cord	Max dose (Gy, 0.03 cc) ≤ 50 Gy	0.2	Myelopathy
Lung—PTV	Mean lung dose < 20 Gy V20 ≤ 30% V10 < 40%	<20	Symptomatic pneumonitis
Brachial plexus	Max dose ≤ 66 Gy V60 < 5% (RTOG 0619)	<5	Plexopathy
Larynx	Max dose: 66 Gy Mean dose < 44 Gy V50 ≤ 27%	<20	Vocal dysfunction Aspiration
Pharynx/pharyngeal constrictors	Mean dose < 50 Gy	<20	Symptomatic dysphagia and aspiration
Thyroid	V26 < 20%		Hypothyroidism

1.4 Physics Quality Assurance

- Prospective peer review of treatment plans and detailed attention quality assurance measures before and during treatment is highly recommended.
- ICRU Reports 50, 62, and 83 on prescribing, recording, and reporting photon-beam therapy provide guidance for both 3DCRT and IMRT delivery systems.
  - The American Association of Physicists in Medicine (AAPM) has published the Task Group reports outlining recommendations on quality assurance processes for photon-based 3DCRT and IMRT/VMAT [82–85].
  - For Proton Therapy, ICRU Report 78 provides QA guidance on prescribing, recording, and reporting proton-beam therapy for both passive and scanning beam delivery systems.
  - As image guidance plays a crucial role in targeting, all components need to be comprehensively tested for accuracy [86].

1.5 Summary

- Cervical esophageal cancers are often locally advanced at the time of diagnosis, infiltrating nearby anatomical structures, and often present with lymph node metastases.
- Due to proximity to critical organs, most cervical esophageal cancers are not treatable by surgery, as this would involve functionally devastating resections of portions of the pharynx, the larynx, and portions of the proximal esophagus.
- The management of cervical esophageal cancers is more closely related to head and neck squamous cell carcinomas rather than for malignancies involving more distal portions of the esophagus, and definitive chemoradiotherapy is the standard of care.

- The recommended dose and fractionation include 50–70 Gy for definitive chemoradiation in daily 1.8–2 Gy fractions, 5 days per week.
- Optimal concurrent chemotherapeutic options include cisplatin 100 mg/m^2 IV on days 1, 22, and 43 or 40 mg/m^2 IV weekly for 6–7 weeks.
- We recommend use of newer technologies like IMRT/IGRT for routine treatment as it provides greater precision while minimizing toxicities to adjacent vital organs (spinal cord, brachial plexus, lung).
- Careful consideration should be given while planning to meet the dose constraints for critical surrounding organs without compromising the target dose.

1.6 Treatment Algorithm

See Fig. 1.3.

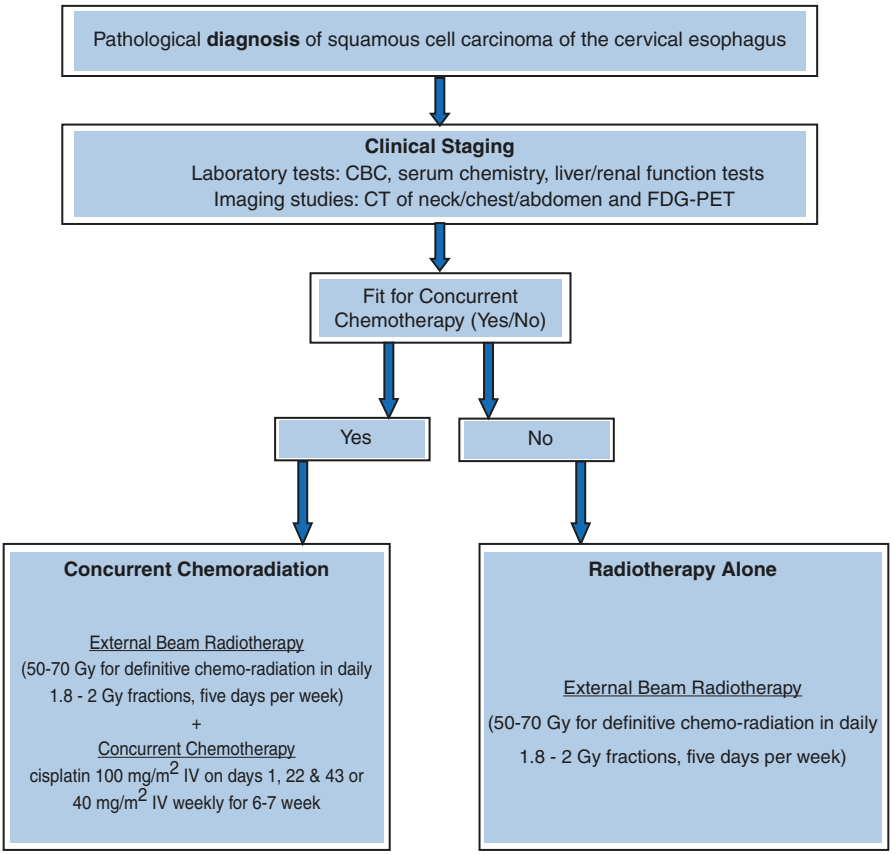

Fig. 1.3 This treatment algorithm is designed to help choose clinical scenarios appropriate for particular treatment modalities in the setting of non-metastatic cervical esophageal cancer

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Mid/Distal Esophageal Cancer and Gastroesophageal Junction Cancer (Siewert Type I and II)

2

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Contents

2.1 Introduction

The esophagus is a hollow, muscular tube, approximately 25 cm in length, which extends from the lower border of the cricoid cartilage at the level of C6 to the stomach. The gastroesophageal junction (GEJ) is near the lower border of vertebra T11. The upper portion of the thoracic/mid esophagus passes behind the

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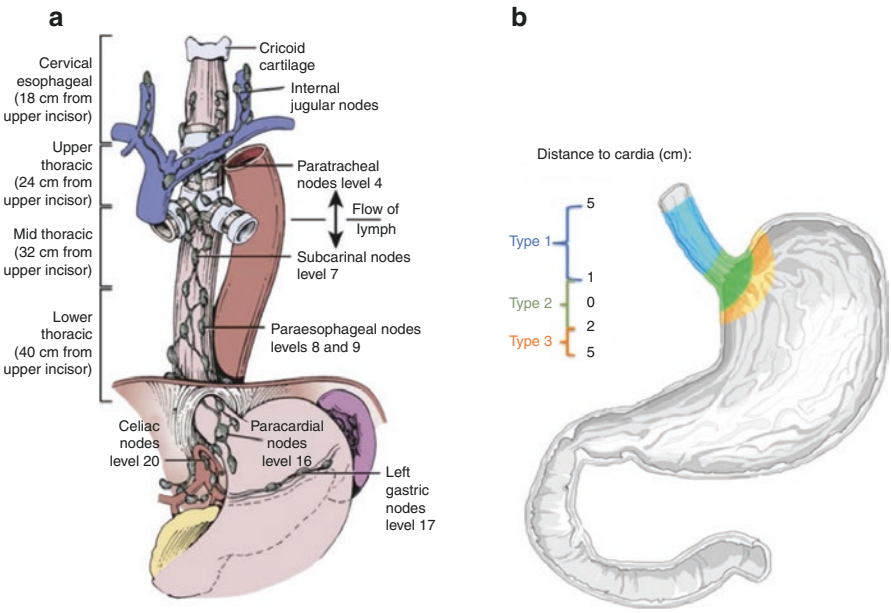

Fig. 2.1 (**a**) Esophagus anatomy (**b**) Siewert-Stein classification for gastroesophageal junction carcinoma (from Matzinger et al. 2009 [1] with permission)

tracheal bifurcation and left main stem bronchus, which corresponds endoscopically 24–32 cm from incisor, and the distal thoracic esophagus is an area approximately 6–8 cm in length from 32 to 40 cm from incisor, merging into the gastroesophageal junction (Fig. 2.1a). Tumors around the GE junction can also be divided using Siewert-Stein classification as type I (adenocarcinoma of distal part of the esophagus with center located within between 1–5 cm above the anatomic GEJ), type II (adenocarcinoma of the real cardia, i.e., within 1 cm above and 2 cm below the GEJ), and type III (adenocarcinoma of the sub-cardiac stomach, i.e., 2–5 cm below GEJ) (Fig. 2.1b). In this chapter, we will discuss the management and treatment techniques for mid/distal and GEJ cancer (Siewert type I and II). Siewert type III, which is considered as stomach cancer, will be discussed in subsequent chapters.

2.2 Management Principles for Mid/Distal Esophagus and Gastroesophageal Junction Carcinoma (Siewert Type I and II)

Surgery has been the standard of care for early-stage esophageal cancer. However, its utility as monotherapy has been challenged. Data from various surgical series report 5-year survival rates of 15–20% with surgery alone [2–5]. Exploration of various therapeutic approaches in randomized trials and meta-analysis led to the

Table 2.1 Treatment recommendation as per NCCN guidelines 2016 [6]

Stage	Recommended treatment
Tis, T1a, superficial T1b and N0	Endoscopic resection and/or ablation, esophagectomy
cT1b, N+ cT2-T4a, N0-N+ and Medically fit	Preoperative chemoradiation [radiotherapy (RT) 41.4– 50.4 Gy + concurrent chemotherapy] → surgery (preferred) or Definitive chemoradiation (for medically inoperable or patients who decline surgery) [RT 50–50.4 Gy + concurrent chemotherapy] or Esophagectomy [T1b-T2 low-risk lesions: <2 cm, well-differentiated] or Preoperative chemotherapy → Esophagectomy or Perioperative chemotherapy (GEJ cancers) → Esophagectomy
cT4b	Definitive chemoradiation [RT 50–50.4 Gy + concurrent chemotherapy]

current standard of care multimodality approach with induction chemoradiotherapy followed by surgical resection for operable disease. For patients with medically inoperable esophageal cancer or who decline surgery, definitive radiotherapy is the treatment of choice for stage T1-2 N0 M0 disease, and concurrent chemoradiotherapy should be considered for locally advanced lesions. Most clinicians treat GEJ (Sievert I & II) as esophageal cancers with preoperative chemoradiotherapy. However, these tumors have been included in many of the trials examining the benefit of adjuvant and neoadjuvant chemotherapy for gastric cancer, and institutional practice varies. The recent NCCN-recommended therapeutic options in different stages are summarized in Table 2.1.

2.2.1 Curative Surgical Techniques

Surgery is usually undertaken for lesions of the mid- to lower third of the thoracic esophagus and gastroesophageal junction and involves a subtotal or total esophagectomy. Esophagectomy may be accomplished by a number of techniques, including a transhiatal esophagectomy, right thoracotomy (Ivor-Lewis), or left thoracotomy [7]. It is vital to know the type of procedure and anastomosis, especially in the context of planning for postoperative radiotherapy.

- Transhiatal Esophagectomy (THE): THE is recommended for tumors anywhere in the esophagus or gastric cardia. THE does not include a thoracotomy, and instead, the stomach is mobilized from the surrounding omentum with blunt dissection of the thoracic esophagus and patients are left with cervical anastomosis. Limitations are the lack of exposure of mid-esophagus and direct visualization and dissection of the subcarinal lymph nodes cannot be performed.

- Transthoracic Esophagectomy (Ivor Lewis procedure): This approach is mainly good for mid to upper esophageal lesions, and patients are left with thoracic or cervical anastomosis.
- Left thoracotomy: appropriate for the lower third of esophagus and gastric cardia, and patients are left with low-to-mid thoracic anastomosis [7].

The optimal surgical approach for esophageal cancer is debatable. Results of a randomized trial and a meta-analysis comparing transhiatal versus transthoracic approach in patients with adenocarcinoma of esophagus revealed no significant differences in 5-year overall and disease-free survival rates, although transhiatal esophagectomy was associated with lower morbidity [4, 8]. Another treatment option for high-grade dysplasia is esophageal mucosal resection (EMR) or esophageal mucosal dissection. EMR dissects the esophageal submucosa to better evaluate and stage early carcinoma [9].

2.2.2 Combined Modality Approach

Prior to the advent of modern radiotherapy delivery techniques and routine use of chemoradiotherapy (CRT), radiation therapy (RT) alone was used (60–66 Gy over a period of 6–7 weeks at 2 Gy per fraction) [10, 11]. Results from numerous randomized trials and meta-analysis did not show any improvement in resectability or overall survival rates from the addition of either preoperative or postoperative radiation alone as compared to surgery alone [12–16]. Five-year overall survival of 0% was seen in RT alone arm in RTOG 8501 as mentioned below [17].

2.2.2.1 Definitive Chemoradiation

For medically inoperable or locally advanced disease, the addition of concurrent chemotherapy has proven to improve survival over RT alone as demonstrated in various randomized trials and meta-analyses. The landmark Radiation Therapy Oncology Group 85-01 trial using 2-D radiation therapy techniques (2DRT) compared RT alone (64 Gy in 32 fractions over 6.5 weeks) versus concurrent CRT [two cycles of infusional 5-FU (1000 mg/m^2 per day, days 1–4, weeks 1 and 5) plus cisplatin (75 mg/m^2 day 1 of weeks 1 and 5) and RT (50 Gy in 25 fractions over 5 weeks)]. The results showed a significant survival advantage for CRT arm, i.e., 5-year survival 27 vs. 0 percent [17, 18]. The dose escalation US Intergroup Study 0123 randomized patients to CRT (cisplatin and 5-FU), but they were randomly assigned to 50.4 Gy vs. high-dose 64.8 Gy arms [19]. The dose escalation arm had higher treatment-related deaths (10% vs. 2%), while there was no difference in median survival (13 vs. 18 months), 2-year overall survival (31% vs. 40%), or locoregional failure (56% vs. 52%). One argument for why higher dose did not result in better survival or locoregional control is the use of dosimetrically inferior 2D radiation delivery techniques. Modern techniques [3-dimensional conformal RT (3D-CRT), intensity-modulated RT (IMRT), image-guided radiotherapy (IGRT) and protons] are associated with precise dose distribution as compared to 2D techniques, and the use of these state of art

radiotherapy techniques with combined CRT has proven to produce a superior outcome over RT alone with manageable toxicities [20].

2.2.2.2 Neoadjuvant (Preoperative) Chemoradiation

Several trials and meta-analyses have demonstrated better survival with the trimodality approach, i.e., preoperative concurrent chemoradiation as compared to surgery alone, and this approach is generally preferred for potentially resectable stage II or III localized cancer of the mid/lower esophagus or GE junction [3, 21–25]. Most recently, the Chemoradiotherapy for Esophageal Cancer Followed by Surgery Study (CROSS) trial, a phase III randomized controlled trial comparing surgery alone versus neoadjuvant RT (41.4 Gy) and concurrent carboplatin/paclitaxel, showed median overall survival was significantly higher in the CRT arm (49.4 vs. 24 months) [26]. The majority of patients (75%) in the CROSS trial had distal esophageal adenocarcinoma, while 11% had the tumor of the GEJ. The long-term outcomes of this trial were recently published, and with a median follow-up of 84.1 months in surviving patients, median OS was significantly better in the CRT arm (48.6 vs. 24 months; $P = 0.003$) [27].

Similar findings were reported for locally advanced squamous cell carcinoma patients in phase III randomized German trial comparing neoadjuvant chemotherapy followed by definitive concurrent chemotherapy and radiation versus preoperative chemotherapy and radiation therapy; trimodality treatment also showed an improved local control and progression-free survival with a trend for improved survival [28]. In the light of CROSS trial, neoadjuvant chemoradiotherapy (NACRT) has become the standard of care in operable esophageal cancers. Adjuvant radiation therapy has not shown benefit in esophageal cancer patients; however, adjuvant chemoradiation in proximal gastric/GEJ tumors has shown encouraging results based on North American Intergroup Trial 0116 [29].

2.2.2.3 Chemotherapy

Multiple randomized trials evaluating the role of neoadjuvant chemotherapy has shown conflicting results [30–35]. The MAGIC trial has shown perioperative chemotherapy (epirubicin, cisplatin, and 5-FU × 3 cycles pre- and postoperatively) to be effective in resectable adenocarcinoma of the GE junction, or lower esophagus. Due to the lack of consistent finding of using chemotherapy alone, and CRT achieving higher rates of pathologic complete responses and complete (R0) resection, it is the preferred strategy [36]. Most frequently used concurrent regimen includes cisplatin (75–100 mg/m^2 on days 1 and 29) plus 5-FU (750–1000 mg/m^2 continuous infusion over 24 h daily on days 1–4 and 29–32). Recent studies are also investigating the role of newer concurrent chemotherapy regimens. In CROSS trial, weekly carboplatin (AUC 2 mg/mL per min) and paclitaxel (50 mg/m^2 of body-surface area) were administered intravenously for five cycles. Although CROSS trial used lower radiotherapy dose (41.4 Gy in 23 fractions of 1.8 Gy), the treatment was well-tolerated with 95% patients completing the entire neoadjuvant chemoradiotherapy regimen and only 8% patients had grade 3 or worse hematological toxicity. Recently, PRODIGE5/ACCORD17 randomized trial assessed the efficacy and safety of the

concurrent FOLFOX regimen (oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, bolus fluorouracil 400 mg/m^2, and infusional fluorouracil 1600 mg/m^2) against standard 5FU/cisplatin as part of definitive chemoradiotherapy (50 Gy in 25 fractions) [37]. No significant differences were recorded in the progression-free survival and rates of grade 3 or 4 adverse events in both the arms.

Epidermal Growth Factor Receptor, a member of the ErbB tyrosine kinase family, is a target that was examined in several studies. Binding of the ligand leads to receptor dimerization and consecutively to activation of downstream signals regulating cell cycle, apoptosis, cell proliferation, and angiogenesis. Overexpression of EGFR was detected in 30–90% of esophagogastric tumors, correlating with increased invasion, dedifferentiation, and worse prognosis [38–40]. Although their use is most commonly limited to metastatic or locally advances setting as an adjunct to systemic chemotherapies, some phase II trials have explored the conjugation of anti-EGFR therapies with chemoradiation. On the basis of the results of the SCOPE1 trial, a multicenter phase II/III trial, randomizing 258 patients between standard CRT and CRT combined with cetuximab, the use of cetuximab cannot be recommended due to treatment-limiting toxicity [41]. Recently, a phase III REAL3 trial had to be closed early due to a lack of efficacy [42]. Similarly, in a phase II trial, the addition of molecular-targeted therapy with bevacizumab and erlotinib to neoadjuvant chemoradiation (paclitaxel/carboplatin/5-FU/radiation) in localized esophageal and GEJ tumors did not demonstrate improved pathologic complete response rate or a survival benefit [43]. The data for the use of targeted therapies in the concurrent setting are sparse and immature, and thus, their use is not recommend outside a trial setting.

2.3 Radiation Therapy Techniques and Planning

The design and delivery of radiation therapy for esophageal cancer requires knowledge of the natural history of the disease, patterns of failure, anatomy, and radiobiological principles. Furthermore, the use of proper equipment, implementation of methods to decrease treatment-related toxicity, and a close collaboration with the physics and technology staff are essential. Radiation oncology, as are other medical specialties, is both an art and a science. Therefore, the recommendations made in this chapter should serve only as a guide, and treatment decision should be based on individualized patient and expertise.

Due to the anatomical complexity of esophagus, various sensitive organs at risk (OAR) are in a close anatomical relation of the esophagus and, depending on the location of the primary tumor, may be in the radiation field. Key to successful radiation planning is minimizing the dose to these structures while delivering an adequate dose to the primary tumor and local/regional lymph nodes, which can be aided by techniques such as patient immobilization, modern imaging acquisition, intratumoral endoscopic fiducial placement if feasible, CT-based treatment planning for organ identification and lung correction, and the use of dose volume histograms.

2.3.1 Setup and Immobilization

Patients are placed in a reproducible supine position with arms up and immobilized with a Vac-Lok™ (Civco Radiotherapy, Orange City, Iowa), Alpha Cradle (Smithers Medical Products Inc., North Canton, OH), T-bar, or equivalent immobilization.

2.3.2 Simulation

Previously, fluoroscopy was used for tumor localization during simulation, but the advent of flexible endoscopy, endoscopic ultrasound (EUS), and contrast-enhanced Computed Tomography (CT) scans has reduced the use of fluoroscopy in radiotherapy planning.

- The planning CT should encompass the entire thoracic cavity starting from the level of the thoracic inlet and extending inferiorly through the entire stomach volume to a point below the celiac axis (T12 in most patients) or at the level of L3 to encompass the entire kidney volume (especially for distal esophagus and/or GE junction tumors).
- A uniform 3 mm slice thickness is recommended.
- Imaging with oral and IV contrast is recommended for visualization of the esophagus and improved delineation of the tumor or tumor bed and adjacent normal structures. Oral contrast can be avoided if intratumor fiducials are placed for their discrete visualization.
- Consideration of 4-dimensional CT (4D CT) or fluoroscopy to evaluate tumor motion
- Normal breathing, inspiratory, expiratory breath hold CTs if fluoroscopy/4D CT not available

2.3.2.1 18F-Fluoro-2-Deoxy-d-Glucosepositron Emission Tomography (FDG-PET) Planning

As an adjunct to CT, PET-CT can be used in esophageal cancer not only as a routine part of initial staging, but also for radiotherapy planning and response assessment

- For primary tumors, PET scans in esophageal cancer have a sensitivity ranging from 95 to 100% and a specificity of 100% [44, 45]. Because of its higher accuracy to differentiate malignant and normal tissues, it is recommended to incorporate PET-CT into RT planning to improve target delineation process and adapt treatment plans (Fig. 2.2) [46–49]. In some studies, the use of PET-CT for tumor delineation results in a difference in target volume when compared to CT and Endoscopic Ultrasound (EUS) in 10–63% of patients [46]. The discordance between CT and PET-CT was due mainly to differences in defining the longitudinal extent of disease in the esophagus [50].
- If no planning PET at the time of simulation, diagnostic PET should be fused with simulation CT to permit accurate target delineation.
- PET-CT can also provide vital radiomics parameters for response prediction, and therefore, can help identifying patients which will most benefit from radiation dose escalation [51].

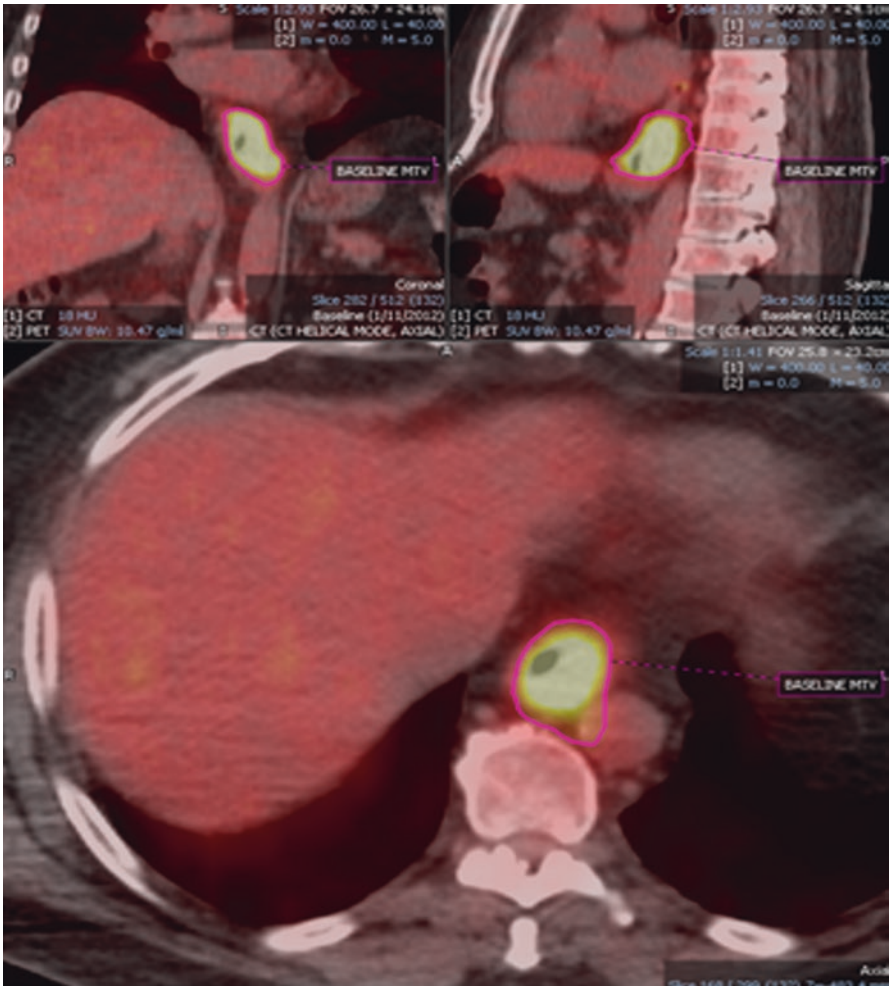

Fig. 2.2 PET/CT scan showing baseline Metabolic Target Volume (MTV) in distal esophageal adenocarcinoma [courtesy: Venkat et al. (2003) with permission]

2.3.3 Motion Management and 4-Dimensional (4D)-CT Simulation

As with other thoracic tumors, both interfraction (mainly due to setup error) and intrafraction (motion from breathing, cardiac motion, esophageal peristalsis or for GEJ tumors, the bowel/stomach distension not accounted for with pretreatment portal imaging) variations are important when considering margin expansions for appropriate target coverage and minimizing geographical miss [52].

Table 2.2 Respiratory motion margins [57]

Motion direction	Motion margin (cm)
Supero-inferior (primary)	1.5
Antero-posterior (primary)	0.75
Left-right (primary)	0.75
Supero-inferior (celiac)	2.25
Antero-posterior (celiac)	1.0
Left-right (celiac)	0.75

- Computed tomography (CT) scans obtained during inhalation and exhalation phases demonstrate radial displacement of the esophagus on the order of 0.8 cm radial and 1.7 supero-inferiorly (Table 2.2) [53]. Lower esophagus and GE junction tend to move more as compared to proximal lesions [54].
  - 4D-CT or fluoroscopy tumor motion data should be considered for defining internal target volume (ITV) expansion to ensure incorporation of all possible respiratory positions of the target for adequate dose coverage of target volumes.
- In general, if breathing movement less than 5 mm motion is noted on fluoroscopic or 4D CT analysis, patients can be treated to an ITV while free-breathing, using the 0 and 50% phases of the respiratory cycle.
- For situations where respiratory motion is observed to be in excess of 5 mm, the use of techniques such as respiratory gating or abdominal compression should be considered.
- Variations in gastric filling may lead to intrafraction differences in the location of perigastric nodes and dose to normal stomach. Although we practice keeping patients NPO for 2–3 h prior to simulation and each treatment in GEJ tumors, there is no definite evidence of gastric filling impacting target coverage when adequate PTV margins are used. Therefore, dietary instructions are not recommended for a routine practice or adaptive planning in mid/lower esophageal or GEJ tumors [55, 56].
- Image-guided radiation therapy (IGRT) using daily pretreatment 2- or 3-dimensional imaging is often used for onboard treatment position verification utilizing the imaging coordinates of the actual radiation treatment plan. This can be accomplished using:
  - Cone-beam computed tomography (CBCT) dataset compared with the planning computed tomography (CT) dataset or by
  - Matching planar kilovoltage (kV) or megavoltage (MV) images with digitally reconstructed radiographs (DRRs) generated from the planning CT.
- Fiducial markers placed in or around the tumor in the tumor bed may be used to enhance localization of target volume.

2.3.4 EUS-Guided Fiducial Marker Placement

The placement of fiducials within tumor allows for more confident and accurate target volume delineation and improved assessment of respiratory tumor motion on 4-dimensional CT simulation for internal target volume delineation. This is

particularly helpful in patients with smaller lesions and for those who received induction chemotherapy with a substantial response. Most fiducials are placed into the submucosa just proximal and distal to the tumor, and not into the lesion itself to mitigate fiducial loss during the course of RT due to probable tumor response (Fig. 2.3). Institutional experience from Moffitt Cancer Center with EUS fiducial is one of the largest studies of its kind using gold fiducial markers measuring 0.75 mm or (0.35 mm) × 10 mm (Visicoil, RadioMed, Inc., Tingsboro, MA) [58].

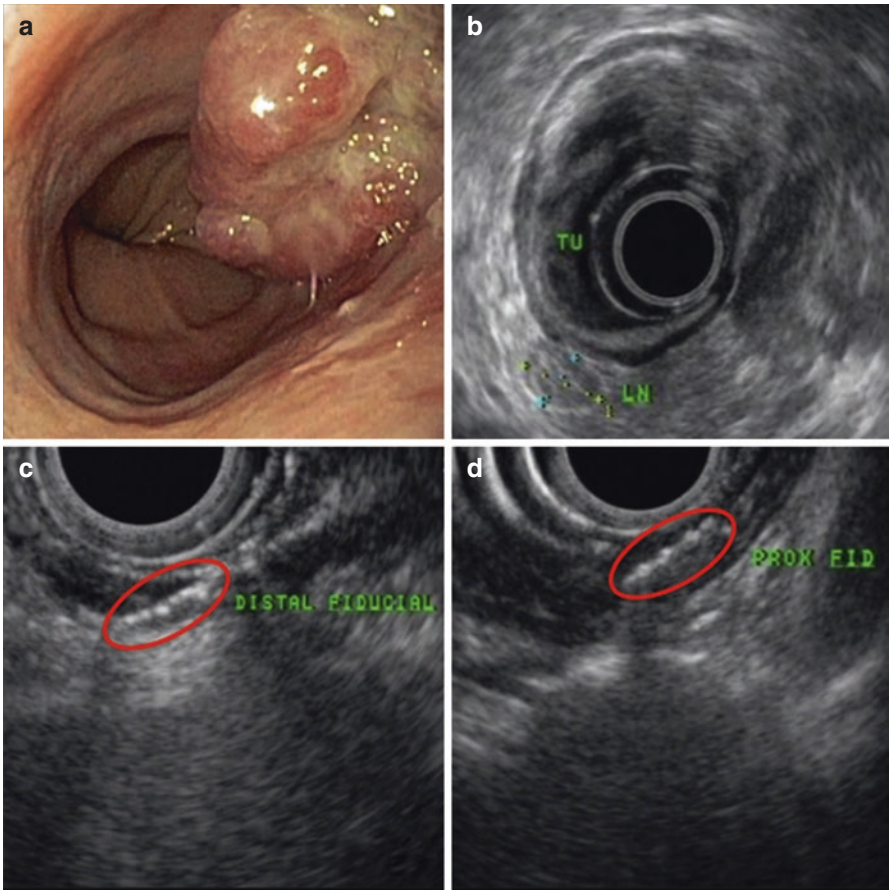

Fig. 2.3 Appearance of a T3N1M0 adenocarcinoma of the distal esophagus at the time of endoscopic ultrasound (EUS) guided placement of two 0.75 mm × 10 mm fiducial markers at the proximal and distal margins of the primary tumor. (**a**) Exophytic primary lesion at esophagogastroduodenoscopy. (**b**) Diagnostic radial EUS revealing a suspicious periesophageal lymph node. Postimplantation radial EUS scanning images confirming placement of fiducial markers at the distal (**c**) and proximal margins (**d**) of the primary tumor [from Fernandez et al. Pract Radiat Oncol. 2013;3(1):32–9, with permission]

In the 60 patients (and 105 fiducial markers), 94% fiducial markers were visible at the time of RT simulation, 88% fiducials were still present posttreatment imaging after implantation, thus confirming its reproducibility (Fig. 2.4). The study showed that in many patients fiducial placement led to smaller treatment margins, and thus, facilitating conformal treatment with image-guided RT techniques.

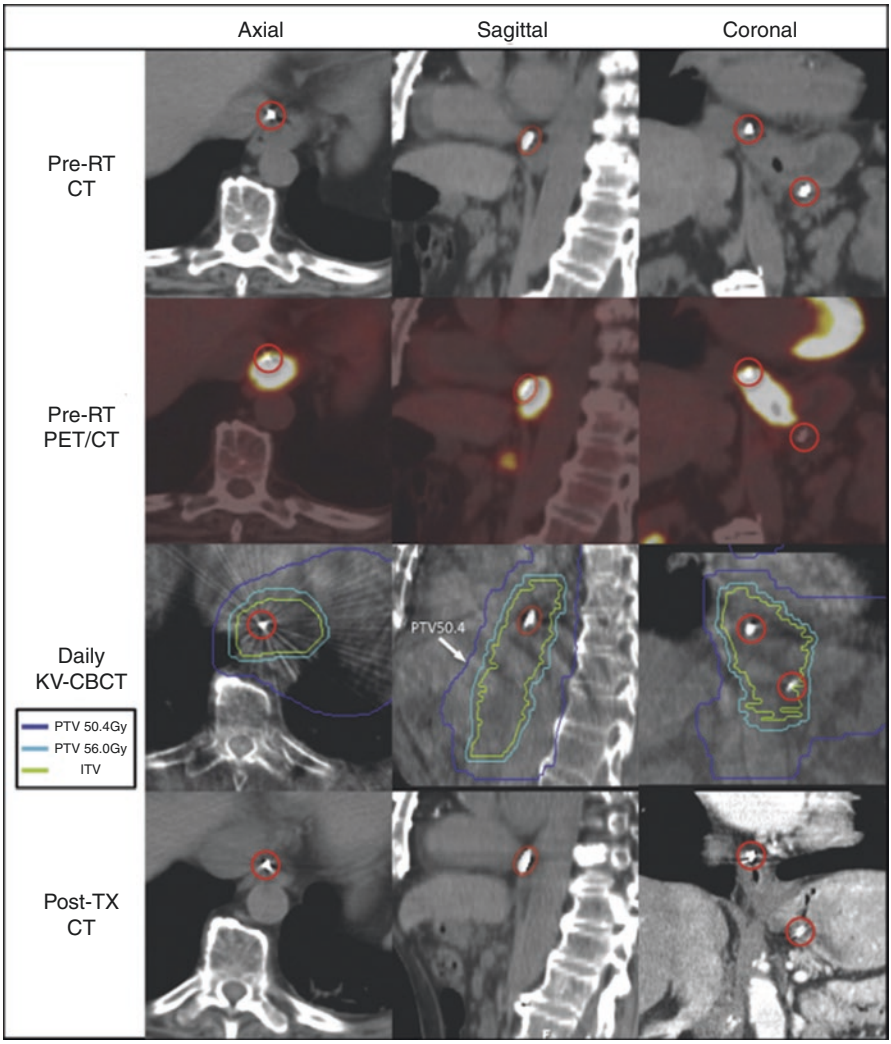

Fig. 2.4 Appearance of implanted fiducial markers on pretreatment computed tomographic (CT), positron emission tomography (PET)-CT, daily kilovoltage cone-beam computed tomography (KV-CBCT), and posttreatment (TX) CT scan performed 54 days after completion of radiation therapy (RT) and 107 days after implantation. *Red* circles indicate fiducial locations. *ITV* internal target volume, *PTV* planning target volumes [from: Fernandez et al. Pract Radiat Oncol. 2013;3(1): 32–9, with permission]

2.3.5 Target Volume Definition

- Traditionally, RT fields have been designed based on 2-D planning, using barium swallow/esophagrams to identify the primary lesion and utilizing geometric expansions and bony landmarks to shape radiation fields. To encompass subclinical disease extension and regional nodal spread, typical field borders were designated by 5 cm expansions proximally and distally beyond apparent tumor along the length of the esophagus, and 2 cm laterally [18, 24].
- In modern radiotherapy practice, treatment volumes are more commonly defined based on the ICRU definitions of clinical target volume (CTV) and planning target volume (PTV).
  - Gao et al. examined surgical specimens of patients undergoing surgery for squamous cell carcinoma of the esophagus (n = 34) or adenocarcinoma of the gastroesophageal junction (n = 32) to determine the CTV necessary for radiation therapy planning both proximally and distally from gross tumor and for lymph node metastasis [59]. Their study showed that extent of microscopic spread within esophagus (recommended CTV margin) was 30 mm in about 94% of cases of esophageal cancer, except for distal microscopic spread in GEJ adenocarcinoma, in which 50 mm was needed to cover about 94% of cases. Based on their study, a consensus cutoff of 4 cm GTV to CTV expansion is used in most cases [60].

Table 2.3 Definitions of target volumes in RT for esophageal cancer

Type	Description
GTVp[a]	All grossly positive disease primary tumor as seen on exam, EGD report, and PET/CT imaging
GTVn[a]	All grossly involved regional lymph nodes
CTV[b]	Superiorly and inferiorly: GTV plus 3–4 cm for submucosal extension along the length of the esophagus and gastric cardia; or 1 cm above any grossly involved periesophageal nodes, whichever is more cephalad. The inferior extension of CTV at the GEJ/stomach should be customized according to anatomy: May cover the lesser curvature (for paracardial and left gastric nodes) and celiac axis nodes for distal/GEJ tumors if these regions are not included as part of the GTV Radially extend by 1 cm from GTV but respecting anatomic boundaries, such as the pericardial sac, vertebral body, pleura, and vessels, to encompass the peri-esophageal lymph nodes. Unless GTV is located at the esophagus/heart interface or liver, it is recommended that the CTV expansion be limited to 0.5 cm. Excluding the liver and heart from the CTV entirely is reasonable if robust motion management (gating or ITV approach) techniques are employed
PTV	CTV plus 0.5–1 cm margin based on the use of daily image guidance[c]

GTVp gross tumor volume of primary disease, *GTVn* gross tumor volume of nodal disease, *CTV* clinical target volume, *PTV* planning target volume, *ITV* internal target volume

[a]GTV is contoured on MIP imaging (if 4D-CT is available) to account for tumor excursion with respiratory motion

[b]CTV should be delineated by radiation oncologists and automatic expansion from GTV is not an acceptable practice

[c]Fiducial markers should be contoured if present. Consider daily image guidance using cone-beam CT (CBCT) which should be matched to the fiducial markers

  - Definitions of GTV, CTV, and PTV are detailed in Table 2.3. However, different margins have been used by various radiation oncology groups, and for better understanding, the technique, margins, and dose used in various important trials are highlighted in Table 2.4. Target delineation of distal esophageal cancer and Sievert II GEJ tumor is shown in Figs. 2.5 and 2.6, respectively.
- Regional Nodes:
  - For mid-thoracic esophagus, the para-esophageal region is considered to be regional (AJCC seventh edition) and should be included in target, but limiting to 3–4 cm proximal/distal margin on gross tumor [60, 61]. It is not necessary to deliberately include superior mediastinal nodal stations electively, other than would be encompassed by 1 cm radial expansion of the esophagus [60].
  - For distal esophageal tumors involving or approaching the GE junction, the CTV should be extended inferiorly to include para-aortic, gastrohepatic ligament (often classified as lesser curvature or left gastric), and celiac lymph nodes (usually T12) [60].
  - The splenic hilar nodes are not considered regional nodes for esophageal cancer, although they may be incidentally covered if the tumor extends significantly into the stomach. With Siewert Type II GE junction tumors with a high pathological risk of lymph node involvement, the inclusion of some or all nodes in the splenic hilum and greater curvature region can be at the discretion of the treating radiation oncologist.

Table 2.4 Technique, margins, and dose used in various important trials

RTOG 85-01 [17]	2D planning CRT arm: entire esophagus to 30 Gy + 20 Gy boost to tumor + 5 cm RT alone arm: tumor + 5 cm to 50 Gy followed by 14 Gy boost with 5 cm margins
RTOG 0246 [62]	Dose 50.4 Gy at 1.8 Gy per fraction, IMRT not used CTV = 3 cm beyond tumor superior and inferior, 2 cm radial Celiac nodes $\leq$ 2 cm allowed
RTOG 0113 [63]	CTV = 4 cm proximal and distal, and 1 cm radial PTV = 1–2 cm around CTV Celiac included for distal lesions
German [28]	3D-CRT CTV = 5 cm proximal and 3 cm distal, and 3 cm radial mucosal in all directions, with 1 cm radial around positive lymph nodes Elective LNs: left and right cardiac, LN along left gastric and lesser curvature, celiac Elective: LN along splenic and hepatic artery (dose: 30 Gy/15)
Walsh [23]	2D planning Tumor + 5 cm superior-inferior and 2 cm radial Dose: 40 Gy in 15 fractions at 2.67 per fraction
MDACC [64]	4D-CT, IMRT planning CTV = GTV + 3 cm proximal/distal and 1 cm lateral margin 4D to ICTV PTV = CTV + 0.5
Cross [27]	41.4 Gy at 1.8 Gy per fraction 3D CRT PTV = GTV + 4 cm proximal and distal (if no stomach), and 3 cm distal if stomach, and 1.5 cm radial

CRT chemoradiation, *RT* radiotherapy, *CTV* clinical target volume, *PTV* planning target volume, *LN* lymph node, *4D-CT* 4 dimension CT, *ICTV* internal clinical target volume

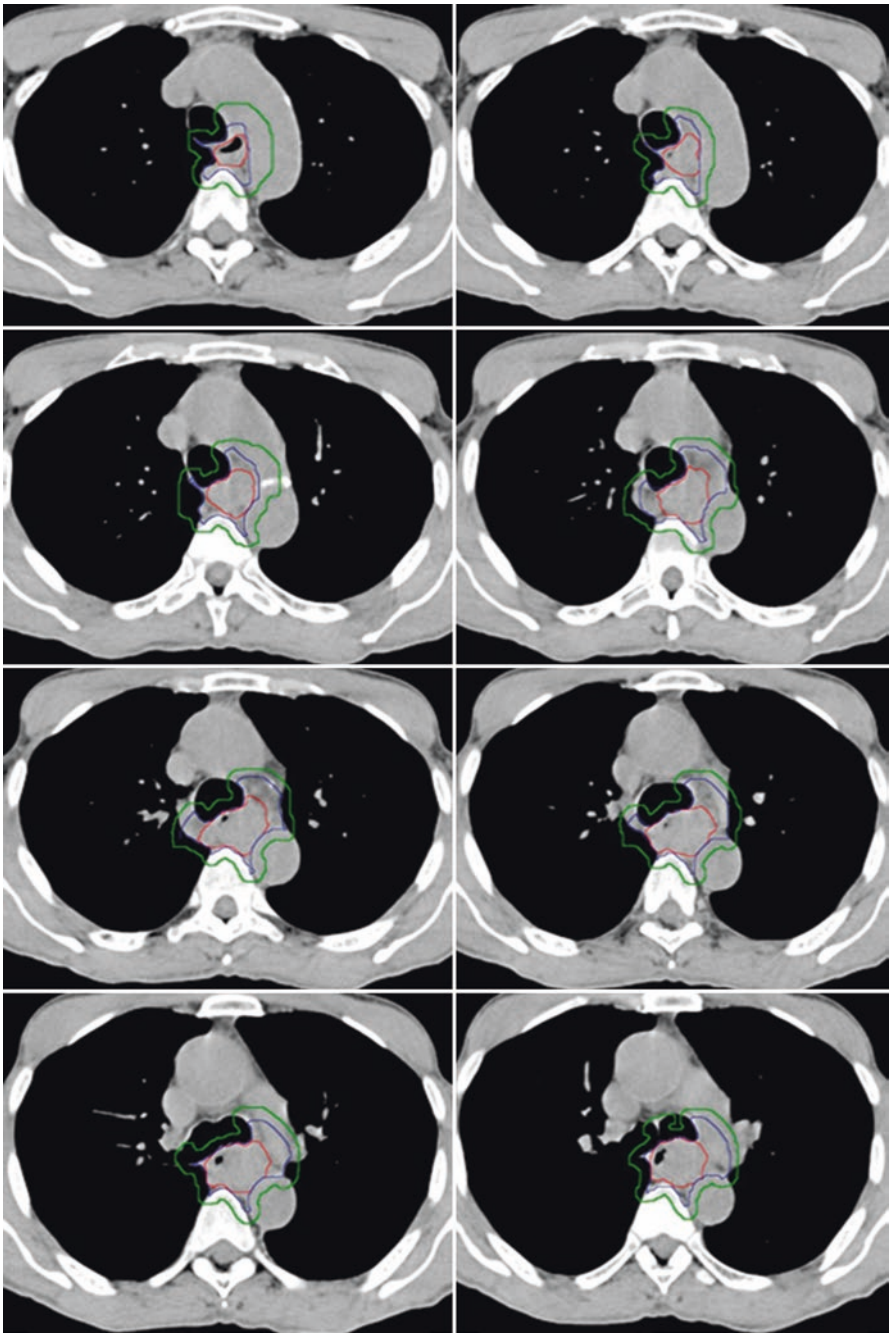

Fig. 2.5 Target delineation of distal esophageal cancer. Delineation of GTV (*red*), based on PET and EGD report; CTV (*blue*) expansion accounts for microscopic spread supero-inferiorly around 4 cm over GTV; PTV (*green*) expansion by 0.5 cm around the CTV to account for setup error. Note the CTV expansion is manually defined to respect anatomic boundaries

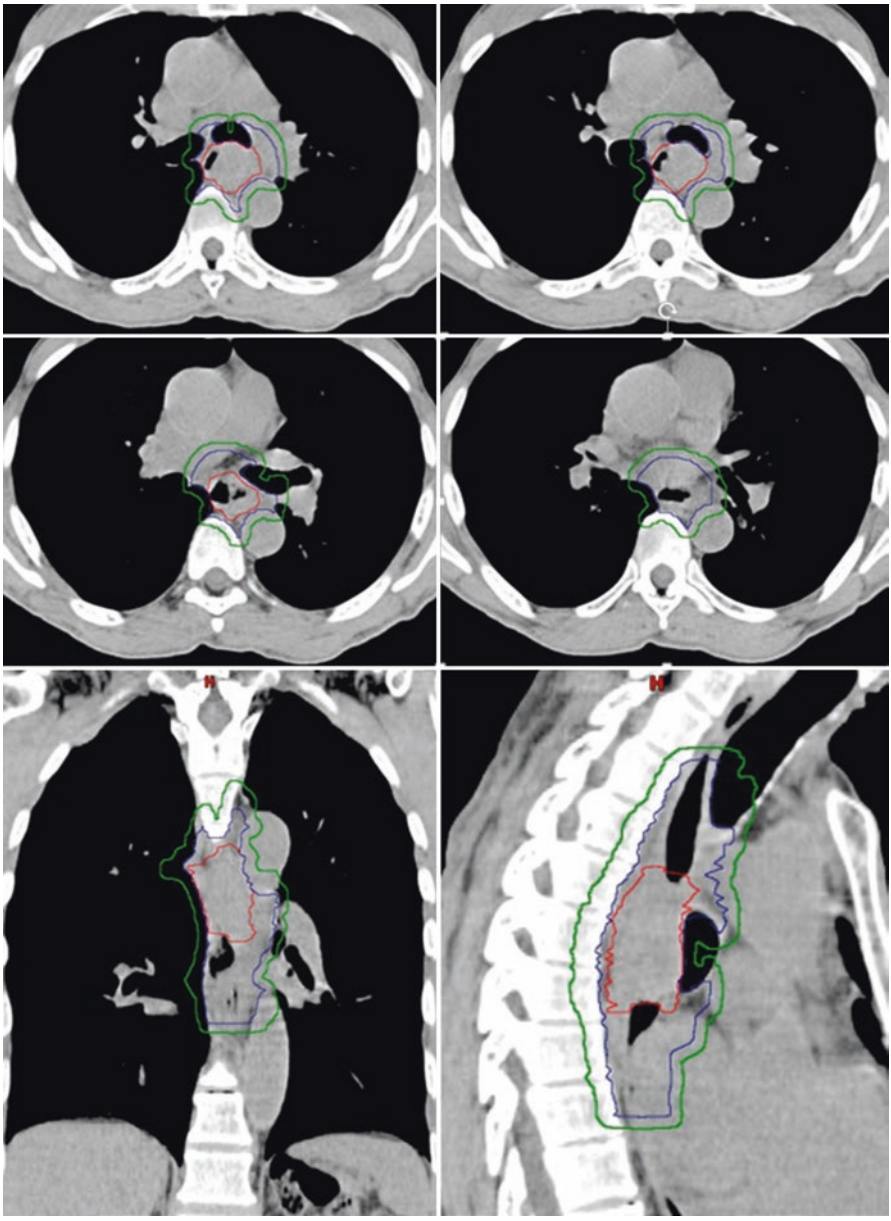

Fig. 2.5 (continued)

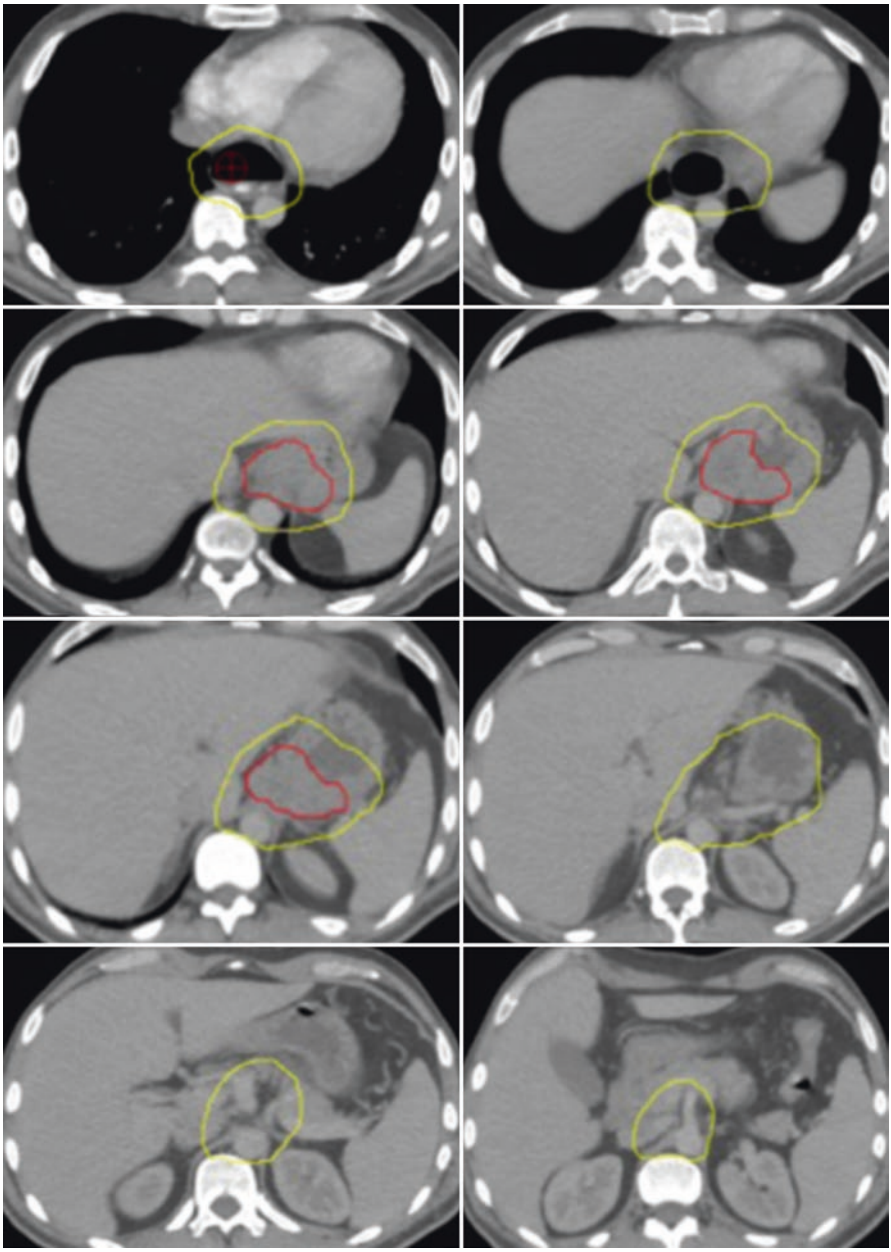

Fig. 2.6 Consensus contours for T3N0, Siewert II GE junction cancer. GTV (*red*), CTV (*yellow*) [adapted from Wu AJ et al. Int J Radiat Oncol Biol Phys. 2015;92(4):911–20, with permission]

2.3.6 Treatment Delivery Techniques

2.3.6.1 Intensity-Modulated Radiotherapy (IMRT)

With the advent of CT-based 3-dimensional (3D) treatment planning, better anatomic visualization and improved target delineation is feasible for the dose avoidance of normal structures. IMRT utilizes multiple beams (typically 5–7), with each beam modulated further using computer-controlled multi-leaf collimation to dynamically block the path of the radiation when the beam is on. This effectively allows the dose to be "painted" with various intensities, thus producing better conformity to the tumor and dose avoidance to the normal structures. As shown in various dosimetric studies, IMRT leads to reduced radiation exposure to normal tissues, especially lungs, leading to favorable toxicity profiles [65].

No randomized trial has compared IMRT with 3DCRT in esophageal cancer. However, with various non-randomized studies having been conducted, IMRT with concurrent chemotherapy is beginning to be explored for the treatment of esophageal cancer [64, 66–68]. A single institution study from Moffitt Cancer Center comparing IMRT vs. 3DCRT among 232 patients (138 IMRT, 94 3D-CRT) treated between 2000 and 2012 showed no difference in outcome, but significantly less toxicity in the IMRT group [69]. The largest study to date is from MD Anderson Cancer Center, which reported a propensity score-adjusted comparison of long-term clinical outcomes between 3D-CRT and IMRT in 676 patients, 413 of which were treated with 3DCRT and 263 IMRT [64]. IMRT was associated with significantly higher locoregional control and overall survival, but there was no difference in cancer-related deaths or pulmonary-related deaths. The key difference was seen in the patients who received 3D-CRT and had a significantly higher cardiac-specific mortality and other-cause deaths. Further support for IMRT in reducing toxicities over 3DCRT comes from a recent analysis of two large cancer registries, encompassing over 2500 elderly patients [70]. Using multivariate propensity score-adjusted analysis, there was a significant improvement in OS, cardiac-specific survival, and "other" (non-cancer, pulmonary, or cardiac-specific)-cause survival in the IMRT group, but not for cancer-specific or pulmonary-related survival. The crude yearly rate of cardiac mortality remained constant over time at about 5% for the 3DCRT cohort, which was almost five times the rate seen in the IMRT cohort. Based on these studies, the use of IMRT is justifiable in mid, lower esophagus including GEJ, due to greater anatomic proximity with the heart. Nevertheless, in the absence of prospective work, these population-based data corroborate high-volume, single-institutional results in support of the clinical utility of IMRT in distal esophageal cancers.

2.3.6.2 Helical Tomotherapy

On dosimetric analysis, tomotherapy plans showed sharper dose gradients, more conformal coverage, and better Homogeneity Index for both gross and elective PTVs compared with IMRT or 3D-CRT plans. The mean V20 [percentage of the

lung volume (with the subtraction of the volume involved by esophageal cancer) which receives radiation doses of 20 Gy or more] of lung was significantly reduced in tomotherapy plans. However, tomotherapy and IMRT plans resulted in larger V10 of lung compared to 3DCRT plans. The heart was significantly spared in tomotherapy and IMRT plans compared to 3D-CRT plans in terms of V30 and V45 [71].

2.3.6.3 Volumetric-Modulated Arc Therapy (VMAT)

Compared with static field IMRT, VMAT slightly improves OAR dose sparing and reduces NTCP and monitors units with better PTV coverage [72]. A greater proportion of the body received low doses (V5 was 18% greater) with VMAT compared to IMRT [73]. VMAT combined with Active Breath Control (ABC) to achieve moderate Deep Inspiratory Breath Hold (mDIBH representing 80% of peak DIBH value) is a feasible approach for radiotherapy of thoracic esophagus and has the potential to effectively reduce lung dose in a shorter treatment time and with better targeting accuracy. VMAT combined with DIBH reduced mean lung doses as well as V20, V30, V40 significantly and also had shorter treatment times [74].

2.3.6.4 Proton-Beam Therapy (PBT)

The interaction between protons and tissue is substantially different than that of photons or electrons [75]. Protons initially traverse matter with minimal loss in energy or attenuation, resulting in lower patient doses proximal to the target of interest. As protons decelerate, the majority of their energy is selectively deposited in the area where they have minimal or essentially no velocity, which is known as the Bragg peak. Importantly, there is essentially no dose deposition distally. This substantially reduces the integral dose, which is a key advantage of PBT over techniques such as IMRT that deliver a low-dose bath to a large volume of normal tissue [76]. The close proximity of critical structures like heart, lungs, spinal cord, liver, and uninvolved stomach makes mid or lower esophageal/GEJ cancer an ideal clinical scenario where the reduction in OAR doses may translate into clinical advantages [77, 78].

There are various comparative dosimetric studies that have demonstrated a significant reduction in cardiopulmonary doses using PBT compared to IMRT and 3DCRT [79, 80]. There are no published prospective studies supporting PBT, but there are data from retrospective single institution clinical experiences. One of the earliest reports was published from the University of Tsukuba in which 51 esophageal squamous cell carcinoma patients were treated with PBT without concurrent chemotherapy who were prescribed a median dose of 80 GyE, most commonly delivered using a combination of photons and protons [81]. The median survival was approximately 21 months and grade 3 esophagitis was reported in only six patients. Subsequently, the same group reported their 40 patient experience of using PBT (60 GyE) with concurrent chemotherapy with cisplatin/5FU [82]. Whereas the 3-year OS was 70% with 2-year locoregional control of 66%, there were importantly no grade 3 or higher cardiopulmonary toxicities. Additional esophageal PBT data was published from the MD Anderson Cancer Center in 2012 [83]. Most of the 62 patients had esophageal adenocarcinoma and the median prescription dose was 50.4 GyE in 28 fractions. A variety of chemotherapy regimens were given concurrently with

PBT. Treatment was well-tolerated with <10% grade 3 toxicities. Notably, postoperative wound, cardiac, and pulmonary complications occurred in just 3%, 8%, and 7%, respectively. The 3-year OS, relapse-free, distant metastatic, and local regional-free survival were 51.7%, 40.5%, 66.7%, and 56.5%, respectively. Pathologic complete response was achieved in 28% of patients who underwent post-NACRT surgical resection. In a second study confined to preoperatively treated patients, the incidence of postoperative pulmonary, cardiac, wound, and gastrointestinal complications was evaluated [84]. During this period, 444 patients were treated with 3DCRT (208), IMRT (164), or PBT (72). Radiation modality used was significantly associated with pulmonary and GI complications. These promising data provide a strong rationale for a randomized trial between protons and photons, and such a trial between IMRT and PBT is currently enrolling patients (NCT01512589).

Despite these promising data, there are some potentially limiting factors that should be considered. First, dose distribution using protons is substantially more sensitive to changes in density within the beam path than photons. PBT planning and delivery must be performed with this in mind. In particular, distal thoracic and GEJ tumors may move significantly with respiration owing to its close relation to the diaphragm and cause significant interplay effects. Despite this, motion robust planning techniques may produce treatment plans that are fairly insensitive to respiration-associated motion [85, 86]. Finally, PBT centers have significant installation, operational, and maintenance costs. It has been debated whether the potential, yet largely unproven, benefits of PBT warrant its high costs. However, with the promising results of the aforementioned retrospective data, which showed decreased clinical toxicities, postoperative complications, and hospital stay, there is a good reason to believe that PBT could be cost-effective for esophageal cancers.

2.3.6.5 Intensity-Modulated Proton Therapy (IMPT)

Although PBT essentially eliminates exit dose to normal tissues compared with photon therapy, the deposition of high doses proximal to the target is not as highly conformal (Fig. 2.7). Pencil-beam scanning, which is also commonly referred to as intensity-modulated proton therapy (IMPT), is a more recent technological advancement in which magnets steer the proton beam to cover, or "paint," the target volume layer by layer.

- Pencil-beam scanning utilization is increasing because of its ability to deliver a dose distribution that conforms to both the distal and proximal edges of the target volume.
- IMPT provides the ability to vary the dose distribution throughout the treatment volume and decreases the integral dose.
  - Beam Scattering—multiple fields can deposit dose from different directions, but requires switching compensators and apertures, increasing treatment time.
  - Beam Scanning—varies proton-beam intensity and/or the speed of the scan to vary the dose distribution over individual voxels and "paints" a non-uniform dose over an area to provide an overall uniform target dose, improve dose conformity, and reduce the integral dose.

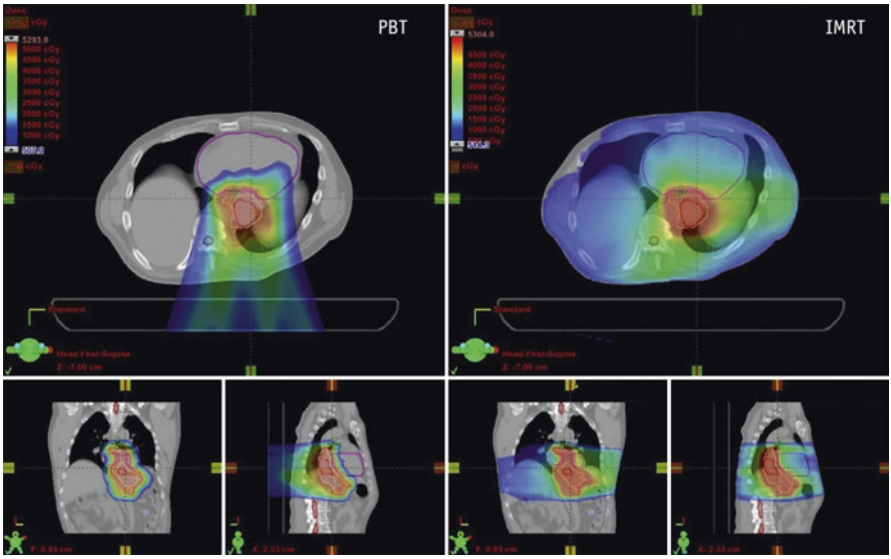

Fig. 2.7 Significant normal tissue sparing is achieved with proton-beam therapy (PBT), which in this case is done with intensity-modulated proton therapy (IMPT), compared with intensity-modulated radiation therapy (IMRT) for distal esophageal cancer [from Chuong MD et al. Int J Radiat Oncol Biol Phys. 2016;95(1):488–97, with permission]

2.3.7 Dose and Fractionation

The optimal radiation dose is not well-defined, although a total dose of 41.4–50.4 Gy for neoadjuvant, and 50–50.4 Gy for definitive RT administered in daily 1.8–2 Gy fractions, 5 days per week, results in reasonable results with acceptable toxicity. Various studies have used different dose/fractionation schedules (Table 2.5). The CROSS trial used 41.4 Gy at 1.8 Gy per fraction with concurrent carboplatin/paclitaxel due to concerns of pulmonary toxicity precipitated by this chemotherapy regimen [26]. No survival benefit with doses greater than 50.4 Gy was demonstrated in the INT 0123 study [20].

With the advent of precision radiation delivery techniques, PBT, and better image guidance, there is a question in the mind of contemporary radiation oncologists whether dose escalation in mid/lower esophageal or GEJ cancers leads to superior control. However, this was challenged in a recent National Cancer Data Base (2004–2012) analysis, which evaluated the effect of radiation dose escalation on overall survival using propensity score matching [87]. Interestingly, the study showed that dose escalation >50.4 Gy did not result in improved OS treated with definitive concurrent radiation and chemotherapy. These data suggest that, despite advanced contemporary treatment techniques, OS for patients with esophageal

Table 2.5 Radiation treatment approaches for mid/lower esophageal and GEJ cancer

Technique	Indication	Fractionation schedules	Beam arrangement	Appropriate chemotherapy
3D-CRT	Neoadjuvant therapy for resectable mid/lower esophageal and GEJ cancers	50.4 Gy in 30 fractions of 1.8 Gy per fraction; 5 days per week	Two fields (AP/PA); Three field boost (anterior and right and left posterior oblique pair or lateral field); or Four field box	Concurrent [cisplatin + 5-FU on week 1 and 4][a]
		41.4 Gy in 23 fractions of 1.8 Gy; 5 days per week [CROSS trial]	Two fields (AP/PA); Three field boost (anterior and right and left posterior oblique pair or lateral field); or Four field box	Induction or concurrent: weekly carboplatin (AUC 2) and paclitaxel (50 mg/m^2) for five cycles[b]
	Definitive chemoradiation for locally advanced or medically inoperable disease	50.4 Gy in 30 fractions of 1.8 Gy per fraction; 5 days/week		Induction and/or concurrent[c]
IMRT VMAT Helical tomotherapy	Neoadjuvant therapy for resectable mid/lower esophageal and GEJ cancers	50.4 Gy in 30 fractions or 41.4 Gy in 23 fractions; 1.8 Gy per fraction; 5 days/week	IMRT: Multiple coplanar isocentric beams VMAT: Volumetrically modulated coplanar arcs	Concurrent
	Definitive chemoradiation for locally advanced or medically inoperable disease	50.4 Gy in 30 fractions of 1.8 Gy per fraction; 5 days/week		Induction and/or concurrent
Proton-beam therapy[d]	Neoadjuvant therapy for resectable mid/lower esophageal and GEJ cancers	50.4 GyE; 1.8 Gy per fraction; 5 days per week[c]	Typically 2–3 fields (AP/PA; lateral or posterior oblique)	Concurrent
	Definitive chemoradiation for locally advanced or medically inoperable disease	50.4 GyE; 1.8 Gy per fraction; 5 days per week	Typically 2–3 fields (AP/PA; lateral or posterior oblique)	Induction and/or concurrent

[a]Cisplatin (75–100 mg/m^2 days 1 and 29) + 5-FU (750–1000 mg/m^2 continuous infusion over 24 h daily on days 1–4 and 29–32)

[b]Weekly carboplatin (AUC 2) and paclitaxel (50 mg/m^2) for five cycles

[c]Dose painting with simultaneous integrated boost (SIB) to the gross primary disease to 56 Gy can be used

[d]May be appropriate for carefully selected patients

Table 2.6 Dose-volume considerations for treatment planning optimization of conventional fractionation schedules for 3D CRT, IMRT, VMAT, and photon therapy (50.4 Gy in 28 fractions; 1.8 Gy per fraction) [88]

Critical structure	Description	Dose/volume parameters	Toxicity rate	Toxicity endpoint
Spinal cord	Spinal cord	Max dose (Gy, 0.03 cc) ≤ 50 Gy	0.2%	Myelopathy
Lung	Lungs—PTV	Mean lung dose < 20 Gy V20 ≤ 30% V10 < 40%	<20%	Symptomatic pneumonitis
Heart	Heart and pericardium	Max dose (Gy, 0.03 cc) ≤ 52 Gy Mean dose < 26 Gy V40 < 50%	<15%	Pericarditis
Kidneys	Bilateral combined kidneys	Mean dose < 15–18 Gy Max dose (Gy, 0.03 cc) ≤ 45 Gy V20 ≤ 32% V23 < 30% V28 < 20%	5%	Clinically relevant renal Dysfunction
Liver	Whole liver—PTV	Mean dose ≤ 28 Gy	5%	Radiation-induced liver disease

cancer remains unaltered by the escalation of radiation dose >50.4 Gy, consistent with the results of the INT-0123 trial. Although local control, not investigated in the study, might benefit from dose escalation, novel therapies are needed to improve the OS of patients with esophageal cancer.

2.3.8 Treatment Plan Optimization

Regardless of the radiation modality utilized, treatment plans must be optimized for adequate target coverage and minimization of dose received by the dose-limiting critical structures including spinal cord, lung, heart, liver, stomach, and bowels. Several strategies to treatment planning optimization are commonly utilized to improve dose homogeneity within target and avoidance of high-dose regions within normal structures, including appropriate selection of beam geometry and energy, use of multiple coplanar/non-coplanar beams, use of beam modification devices (wedges and compensators) to accommodate for irregularities of patient contour, tissue homogeneity correction (lung correction), and use of dose sculpting techniques to achieve more conformal dose distributions using advance radiation technologies (IMRT, VMAT, Tomotherapy, IMPT).

A great promise of modern treatment planning is quantitative correlates of doses/volumes with clinical outcomes and radiation-induced complications. We summarized in Table 2.6 the clinically relevant dose-volume constraints to be incorporated as treatment planning objectives for conventional fractionation (1.8–2 Gy per fraction) mid/lower esophageal and GEJ cancers. This information is a "guideline" and each plan should be unique and optimized to accommodate patient- and target-specific attributes.

- Acute complications may include esophagitis, anorexia, weight loss, fatigue, skin irritation, and nausea/vomiting. Rarely, esophageal perforation may present with substernal chest pain, increased heart rate, fever, and hemorrhage.
- Subacute and late toxicities include radiation pneumonitis, pericarditis, pericardial effusion, esophageal stricture/fistula, and second primary malignancy.
- Radiation pneumonitis (RP) typically occurs sub-acutely in 6 weeks–6 months after RT. RP presents with cough, dyspnea, hypoxia, and fever. Depending on severity, it is treated with NSAIDs or steroids.
- Late stricture is possible, half of which is due to local recurrence. For benign strictures due to postradiation fibrosis, dilation results in palliation in the majority of patients. For malignant strictures, dilation does not work as well.

2.4 Physics Quality Assurance

The safe delivery of radiation therapy was never a simple matter and has now become exceedingly complex. The quality of radiation is associated with improved survival outcome and reduced toxicities, and to improve the quality of radiation, expert-defined target, and normal tissue contouring, guidelines have been developed (RTOG.org website).

- Prospective peer review of treatment plans and detailed attention quality assurance measures before and during treatment is highly recommended.
- ICRU Reports 50, 62, and 83 on prescribing, recording, and reporting photon-beam therapy provide guidance for both 3DCRT and IMRT delivery systems.
- The American Association of Physicists in Medicine (AAPM) has published the Task Group reports outlining recommendations on quality assurance processes for photon-based 3DCRT and IMRT/VMAT.
  - For 3D CRT, it is recommended to perform secondary Monitor Unit (MU) calculation based on Task Group 71 formalism with the discrepancy tolerance thresholds specified by Task Group 114 [89, 90].
  - IMRT/VMAT commissioning, planning, and delivery are guided by Task Groups 82 and 120 [91, 92].

- Phantom-based verification measurements of calculated dose distributions are an essential part of IMRT/VMAT quality assurance and should be performed prior to the first patient treatment.
  - For Proton Therapy, ICRU Report 78 provides QA guidance on prescribing, recording, and reporting proton-beam therapy for both passive and scanning beam delivery systems.
- As image guidance plays a crucial role in targeting, all components need to be comprehensively tested for accuracy [93].

Specific recommendations from an expert panel outline specific quality assurance, infrastructure, personnel requirements, and technical process requirements for safe radiation practice which are detailed in "Safety is No Accident: A Framework for Quality Radiation Oncology and Care" available at the ASTRO.org website.

2.5 Summary

- Management of local-regional cancer of the mid-thoracic, distal esophagus, and GE junction (Sievert I & II) has evolved over the past two decades. For all management purpose, Sievert I & II GEJ cancers are treated as esophageal cancers.
- Several trials and meta-analyses confirm that trimodality therapy provides a survival benefit compared with surgery alone.
- For non-surgical candidates, definitive chemoradiation has resulted in survival outcomes superior to radiation alone.
- The optimal dose fractionation and drug combination have not been definitively established.
  - For neoadjuvant approach, we suggest lower-dose radiotherapy (41.4 Gy in 23 fractions of 1.8 Gy) with weekly carboplatin plus paclitaxel regimen as per CROSS trial or 50–50.4 Gy at 1.8–2 Gy per fractions with two courses of cisplatin plus 5-FU.
  - The recommended dose for patients treated with definitive chemoradiation remains 50.4 Gy administered in 28 daily fractions.
- With the advent of newer technologies like IMRT/IGRT and proton-beam therapy, it is now possible to deliver radiotherapy with great precision, while minimizing toxicities to adjacent vital organs (i.e., heart, lung, spinal cord, liver).
  - In single-institutional studies, IMRT has been suggested to provide a survival advantage over conventional 2D/3D-CRT and should be considered a standard treatment option.
- Intrafraction organ movement should be taken into account using 4D-CT, and we use EUS-guided intratumoral fiducial marker placement for all our patients.
- Careful consideration should be given while planning to meet the dose constraints for critical surrounding organs without compromising the target dose.

2.6 Treatment Algorithm

See Fig. 2.8.

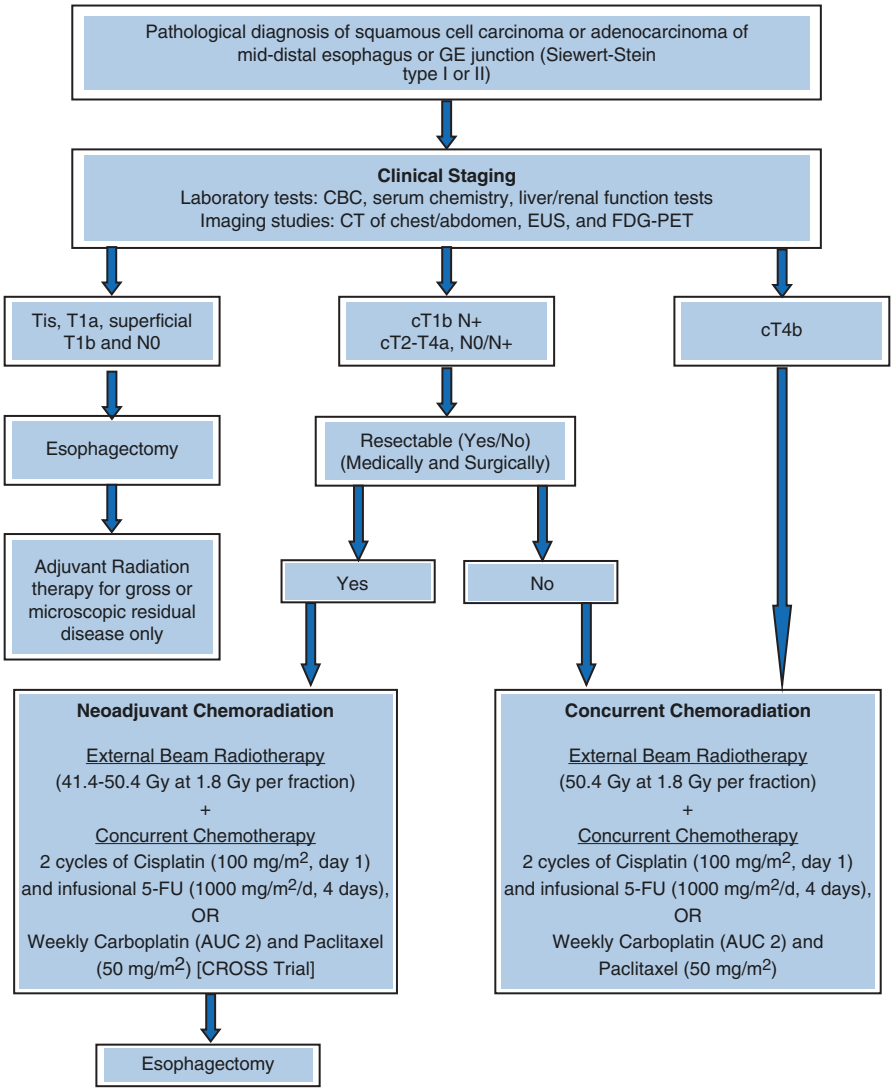

Fig. 2.8 This treatment algorithm is designed to help choose clinical scenarios appropriate for particular treatment modalities in the setting of non-metastatic mid/distal esophageal or GE junction (Siewert-Stein type I or II) cancer

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Part II

Stomach Cancer

Gastric Cancer (Siewert Type III)

3

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3.1 Introduction

Gastric cancer is an aggressive malignancy with high rates of metastatic progression and cancer-specific death, despite the use of valiant surgical and adjuvant therapies. Numerous risk factors have been identified including obesity, chronic reflux disease, diets high in salt or nitrates (smoked foods), H pylori, or EBV infection. The worldwide incidence of gastric carcinoma has decreased over the last several decades (with the exception of proximal tumors which have actually increased over the last 30 years). However, the incidence remains seven- to tenfold higher in many developed Asian countries compared to European and North American nations. The epidemiological differences between Eastern and Western patients with gastric adenocarcinomas require some consideration. Long-term survival outcomes are consistently better in published Asian series than in Western studies. These survival differences are observed in both primary surgical and adjuvant series. The reason for these survival differences is almost certainly multifactorial. Some authors suggest that these reflect technical differences in disease management between Asian and western centers. Operative mortality and postoperative morbidity have consistently been lower in published series from high-volume Asian treatment centers [1, 2]. Asian patients also tend to present with early stage disease which may partially reflect stage migration with active screening in high-risk countries [3, 4]. At the same time, there is evidence to suggest that a large proportion of western and Asian gastric carcinomas may be pathologically distinct entities. There appears to be a strong dietary correlation with mid and distal carcinomas in Asian patients where as many westerners present with more proximal tumors related to obesity, diabetes, and chronic mucosal inflammation [5–7]. These discrepancies have greatly complicated interpretation of the literature as it is not clear how to generalize results from eastern studies with western patients (and vice versa). As described in this chapter, there are many viable adjuvant treatment strategies and it is currently unclear how the efficacy of these approaches compares to one another, particularly in specific subsets of patients.

Surgical resection is considered the only potentially curative treatment for localized gastric cancer, even though resection alone results in 5-year overall survival rates of approximately 40–60% [8–10]. Patterns of failure observed following surgery alone for treatment indicate the need for additional therapies. Surgery followed by adjuvant treatments results in an improvement in outcomes, although response rates to different regimens are variable and randomized studies demonstrate relatively modest survival advantages associated (see Table 3.1). Preoperative and perioperative chemotherapy is considered an acceptable alternative approach in adequately staged resectable gastric cancer [11, 12]. Neoadjuvant treatment is an attractive approach as it potentially allows for in vivo assessment of tumor response and provides treatment of subclinical or radiographically undetectable metastases prior to surgery. The potential role of preoperative chemoradiotherapy for gastric cancers is largely based on randomized studies of lower esophageal/GEJ tumors

Table 3.1 Randomized studies comparing preoperative radiotherapy, chemotherapy, or CRT to surgery alone

Study	Patients	Preoperative treatment	Postop adjuvant therapy	Outcomes	Notes
Zhang [43]	Non-metastatic carcinomas of the gastric cardia *N* = 370 1978–1989	40 Gy (20 fractions)	None	*R0 resection* RT + S: 89% S: 79% *5-year OS* CRT + S: 30% S: 20%	Recommended RT fields included distal esophageal, celiac, paracardial, and paragastric nodes along the lesser curvature
Walsh [13]	Non-metastatic lower esophageal, GEJ, or gastric cardia *N* = 113 1990–1995	40 Gy (15 fractions) with concurrent 5FU (days 1–5) and cisplatin (day 7)	None	*pN+* CRT + S: 42% S: 82% *5-year OS* CRT + S: 32% S: 6%	35% of patients had primary gastric tumors (cardia)
CROSS[14]	T1 N1 or T2–3 N0-N1 esophageal or GEJ carcinomas *N* = 366 2004–2008	41.4 Gy (23 fractions) with concurrent weekly carbo/taxol	None	*R0 resection* CRT + S: 92% S: 69% *Median OS (Mo)* CRT + S: 49 S: 24	Significant esophageal extension was required for enrollment
EORTC 40953 [69]	Non-metastatic UICC stage III–IV[a] gastric or GEJ carcinoma *N* = 144 1994–2004	Weekly cisplatin (weeks 1, 2, 4) and 5FU/folinic acid × 2 six week cycles	None	*R0 resection* C + S: 82% S: 67% *Median OS (Mo) (NS, P = 0.46)* C + S: 64 S: 52	93% D2 resection 92% completed planned chemo
Dutch FAMTX [68]	Non-metastatic non-cardial gastric carcinomas *N* = 59 1993–1996	MTX and 5FU (day 2), leucovorin (days 3–4), doxorubicin (day 15) × 4 four week cycles	None	*R0 resection* C + S: 67% S: 66% *5-year OS (NS, P = 0.17)* C + S: 21% S: 34%	44% completed planned chemotherapy

(continued)

Table 3.1 (continued)

Study	Patients	Preoperative treatment	Postop adjuvant therapy	Outcomes	Notes
MRC MAGIC [11]	Non-metastatic distal esophageal, GEJ, or proximal gastric carcinomas *N* = 503 1994–2002	Epirubicin and cisplatin (day 1), continuous IV 5FU (days 1–21) × 3 cycles	Same as preop	*R0 resection (NS)* Periop C + S: 69% S: 66% *5-year OS:* Periop C + S: 36% S: 25%	74% gastric primaries 27% D2 resection 87% completed preop chemo 42% complete postop chemo
ACCORD [12]	Non-metastatic distal esophageal, GEJ, or gastric carcinomas *N* = 224 1995–2003	Cisplatin (day 1), continuous 5FU (days 1–5) × 2–3 four week cycles	Same as preop 3–4 cycles	*R0 resection* Periop C + S: 84% S: 73% *5-year OS:* Periop C + S: 38% S: 24%	25% gastric primaries 78% completed 2 cycles preop chemo 50% received any postop chemo

[a]Previous UICC stage IV included non-metastatic T4, N+ or N3

including a subset of patients with gastric cardia tumors [13, 14]. Several recent studies have reported promising results using neoadjuvant chemoradiation approaches, but preoperative chemoradiation for non-cardial gastric carcinomas is still considered a current topic of investigation [15–18]. This chapter focuses on incorporation of radiation therapy in the multimodality treatment of resectable gastric cancer with emphasis on radiation treatment planning technique in the adjuvant (postoperative) setting. Neoadjuvant chemoradiation for GE junction and gastric cardia tumors is managed similarly to mid-distal esophageal cancer, which has already been outlined in Chap. 2.

3.1.1 Surgical Management

Surgical resection of the primary tumor and nodal volumes at risk remains the primary therapy for potentially curable gastric cancers. Several surgical principles are worth highlighting, particularly for understanding how the surgical details of adjuvant therapy trials may affect their interpretation. First, when possible, subtotal gastrectomy is the procedure of choice [19]. Many retrospective and randomized trials have demonstrated that total gastrectomy is associated with higher rates of operative morbidity and equivalent or even worse survival than more limited resections [20–23]. Accordingly, subtotal gastrectomy was the preferred operation in virtually every surgical or adjuvant therapy trial discussed in this chapter. However, as noted above, patients in Western series are more likely to receive a total or near-total

gastrectomy because they are more likely to have a proximal primary tumor location and more extensive disease.

While still somewhat controversial, the role of extended lymphadenectomy in the resection of gastric adenocarcinomas has been clarified somewhat over the last 20 years. The conventional surgical nomenclature for the extent of nodal resection is based on nodal staging described by the Japanese Research Society for Gastric Cancer [24]. This system defined nodal staging based upon the location of involved nodes as opposed to the currently utilized AJCC system, which is based on the number of involved nodes. In the Japanese system, N1 corresponds to involved paragastric nodes (stations 1–6). N2 staging involved nodes along the celiac artery or its first three branches (stations 7–12). A D1 resection involves the resection of paragastric nodes, whereas a more extended D2 resection also involves the resection of nodes around the celiac artery and its major branches. The definition of D3 or greater resection is less consistent, but involves a D2 resection plus the resection of additional nodal stations including the retropancreatic region and superior mesenteric vein.

Multiple series, both Eastern and Western, have clearly demonstrated high rates of local-regional nodal recurrence following surgical resection [8, 9, 25–28]. Based on these observations, it was widely accepted among high-volume Asian centers that extended lymphadenectomy (D2 or greater) should be the operation of choice. In contrast, Western opinion on the matter has largely been based on the initial reports of two western studies that did not support the use of extended resections. The British MRC trial randomized 400 patients to D1 vs. D2 resection with no adjuvant therapy [29]. Importantly, the MRC protocol recommended hemipancreaticosplenectomy for tumors involving the middle and upper third of the stomach (66% of the D2 arm vs. 3% of the D1 arm). With a median follow-up of 6.4 years, there was no difference in overall survival (OS) based on the extent of resection (approximately 40% 5-year survival in both groups). Importantly, operative mortality was quite high in this study: 3 vs. 10% for D1 and D2 resections, respectively. The Dutch intergroup trial randomized 739 patients to D1 vs. D2 resection with no adjuvant therapy [10, 30]. At the time of initial publication in 1999, extended resection was associated with higher operative mortality (4 vs. 10%), but no improvement in survival. However, a more recent publication of the mature data with a median follow-up of over 15 years demonstrated that D2 resection was associated with improved clinical outcomes including a non-significant trend toward improved OS (28 vs. 22%, $p = 0.34$), significantly decreased local recurrence rates (41 vs. 30%), and significantly improved cancer-specific survival (51 vs. 60%) with extended resection.

Interpretation of survival data from these Western surgical series is limited by the excessive operative mortality in the D2 resection arms (10 vs. 3–4%). With these large differences in operative mortality, the absolute survival advantage associated with extended resection (among patients surviving surgery) would need to be at least 10–15% to reach statistical significance. It is reasonable to postulate that technical limitations of these studies could have masked significant improvements in survival with D2 resection. Subgroup analysis of the MRC trial may support this

hypothesis. Pancreaticosplenectomy is no longer recommended as superior survival outcomes are achieved with pancreas-preserving approaches [31–33]. Limiting the survival analysis of the MRC data to patients undergoing pancreas-preserving surgery demonstrated a roughly 10% improvement in 5-year OS with D2 resection compared to D1 resection [9].

The role of D2 or greater resections has not been extensively studied in randomized trials in Asian centers because the practice has been considered standard of care for decades. Large retrospective studies from Japanese, Chinese, Korean, and Taiwanese centers have consistently demonstrated improved survival and decreased local recurrence following extended lymphadenectomies (D2–D3 vs. D1) on the order of about 10% [5]. One relatively small Taiwanese trial randomized 221 patients to D1 vs. D3 resection (D2 + hepatoduodenal, retropancreatic, and SMA nodes) and demonstrated statistically improved 5-year OS (59 vs. 53%) with extended resection [8]. Retrospective support for D2 or greater resection is not limited to Asian studies. Review of 1654 patients in the German Gastric Cancer Study Group demonstrated better median survival in patients who underwent D2 resection (including at least 25 nodes) with no increases in surgical complications [34]. Another study compared outcomes at different high-volume treatment centers and demonstrated that overall survival for 1038 patients undergoing resection at MSKCC in the US (which performs D2 resections approximately 80% of the time) is comparable to patients treated at NCC (Japan) and SNUH (Korea) and superior to typical American outcomes reported to SEER [35]. The bulk of the available data suggest that D2 resection, when performed by experienced surgeons, is associated with improved clinical outcomes and acceptably low rates of operative morbidity and mortality. Referral to high-volume surgical centers is highly recommended.

Patients should be appropriately staged prior to therapy for adequate assessment necessary for treatment recommendations. All patients should have preoperative CT or PET/CT of the chest and abdomen. Endoscopic ultrasound (EUS) can improve detection of pathologically involved regional lymph nodes and depth of primary tumor invasion [36]. EUS can be very helpful in identifying patients who may be eligible for endoscopic resection and should also be considered to pathologically stage patients prior to undergoing neoadjuvant therapies. However, the added value of EUS in patients with evidence of T3–4 invasion or N+ disease on EGD or radiographic imaging is unclear [37]. Laparoscopic evaluation (including peritoneal washings) can improve the detection of occult metastatic disease and is recommended for patients with radiographic/ultrasound evidence of T3–4 or N+ disease [38]. Laparoscopic evaluation is often recommended to obtain a pathologic baseline in patients undergoing neoadjuvant therapies prior to initiating neoadjuvant treatment. Finally, all patients should undergo adequate nodal sampling at the time of gastrectomy which includes the pathologic evaluation of at least 15 nodes [39]. As discussed above, the exact definition of a D2 resection is highly variable. All efforts should be made to identify which nodal stations were pathologically evaluated and/or involved with tumor metastases to properly identify the areas at highest risk. All contouring/management options outlined in this chapter assume that patients have been adequately staged and surgically managed.

3.2 Neoadjuvant Treatment Approaches

3.2.1 Preoperative Radiation and Chemoradiation

There are four randomized trials of preoperative radiotherapy (20–40 Gy) vs. surgery alone and all four demonstrated improvements in local control and OS. Three of these were Russian trials which also incorporated concurrent modalities including hyperthermia and inhaled oxygen with radiation and their application to Western trials is not clear [40–42]. There is an additional randomized trial from China including 390 patients with tumors of the gastric cardia which [43] randomized patients to preoperative radiotherapy (40 Gy in 20 fractions) followed by surgical resection 2–4 weeks later compared to surgery alone. Preoperative radiation improved 5-year OS (30 vs. 20%), locoregional control (61 vs. 48%), and radical (curative) resection rates (80 vs. 62%). Operative mortality was low in both treatment groups (<2.5%).

The potential role of preoperative chemoradiotherapy for gastric cancers is mostly based on indirect evidence from several high-profile randomized studies of lower esophageal/GEJ tumors, which also included a subset of patients with tumors of the gastric cardia. The European trial by Walsh et al. included the greatest percentage of patients with gastric primary tumors (roughly 50%) [13]. This study randomized 113 patients to surgery alone or preoperative radiation with concurrent cis-platinum/5FU. Preoperative chemoradiation markedly improved 3-year (32 vs. 6%) and median (32 vs. 11 months) OS. Similarly, encouraging results were obtained in the CROSS [14] and US GI intergroup (CALGB 9781) trials [44]. These studies are highlighted in full detail in the esophageal chapters of this book. While preoperative chemoradiotherapy has largely become the preferred standard of care for esophageal and GEJ tumors, this approach is not frequently utilized for primary gastric cancers except in patients in whom upfront complete resection is unlikely. However, this is an area of ongoing research. Multiple early phase studies published in the last five years have demonstrated the feasibility of upfront chemoradiation in patients with resectable gastric cancers [17, 45–48], including the use of concurrent carbo/taxol similar to the CROSS trial [17]. The Australian Gastrointestinal Trials Group (AGITG) has opened the TOPGEAR trial that aims to directly compare the efficacy of perioperative chemotherapy with neoadjuvant chemoradiotherapy. This trial will randomize 632 patients with gastric or GEJ cancers to perioperative ECF (as in the MAGIC trial discussed below) or 2 cycles of ECF followed by 5 FU-based chemoradiotherapy prior to surgical resection.

3.2.2 Intraoperative Radiation Therapy (IORT)

The use of IORT has been extensively studied, particularly by Asian physicians, since the 1960s. Several randomized studies, as well as a number of earlier phase trials, have consistently demonstrated a survival benefit following 20–35 Gy of radiation delivered to the areas at highest risk of local recurrence (body of pancreas, celiac trunk, perigastric/pancreatic nodal regions) at the time of surgery compared to surgery alone [49–54]. The magnitude of this survival benefit closely mirrors the

observed improvements in local control with IORT. As examples, one Japanese trial randomized 211 patients with stages II-IV gastric cancer to surgery alone or surgery plus IORT (28–35 Gy) and observed a roughly 15–25% improvement in OS for patients of all stages (84 vs. 62% for stage II and 15 vs. 0% for stage IV (which previously included T4 N+ and N3 patients)) [49]. Ogata et al. also observed a roughly 20% increase in 8-year OS (55 vs. 35%) with IORT to the celiac axis compared to surgery alone [50]. Several phase II trials have demonstrated the feasibility of combining conventional preoperative EBRT (approximately 45 Gy) with IORT at the time of resection [55–58].

The benefit of IORT in the era of modern systemic therapy has been questioned. None of the early trials demonstrating a survival of IORT included postoperative chemotherapy, which would now be considered standard of care. While not supported by robust data, we and others advocate that IORT (+/− preop EBRT) may still play a role in the management of gastric cancers. When performed by experienced centers, this modality is very well-tolerated with minimal increases in operative complications. The relative magnitude of local control conferred by IORT is generally greater than that observed with adjuvant chemotherapy or even EBRT. It is reasonable to postulate that improvements in local control may become clinically more meaningful when combined with adjuvant strategies which improve systemic disease control. At least one study has demonstrated that IORT followed by adjuvant chemotherapy and EBRT is feasible and improves local control compared to adjuvant EBRT and chemotherapy alone [59]. Additional studies combining IORT with adjuvant chemotherapy have been proposed, but no data is yet available.

3.2.3 Preoperative and Perioperative Chemotherapy

Gastric cancer is often a systemic disease with high rates of metastatic progression following resection of what appear to be localized tumors. Consequently, there is strong interest in investigating regimens that lead with intensive chemotherapy regimens in hopes of eradicating micrometastatic disease and improving rates of long-term cure. The feasibility of this approach has been demonstrated in multiple early phase trials utilizing various chemotherapy regimens including FOLFOX [60], EOX (epirubicin/oxaliplatin/capcitabine) [61], XELOX [62], cisplatin/epirubicin/paclitaxel [63], docetaxel/cisplatin/S1 [64], docetaxel/S1 [65, 66], and docetaxel/cisplatin/fluorouracil (TCF) [67]. Several important observations can be made from these studies. First, the use of neoadjuvant chemotherapy does not prevent many patients (albeit from highly selected populations) from undergoing potentially curable resections as >90% of patients underwent resection in the majority of these studies. Second, pathologic complete response rates range from approximately 10% to as high as 35% and R0 resection rates are increased by 15–20% with preoperative chemotherapy. These are potentially promising end points which have correlated with improved DFS in other gastrointestinal malignancies. Unfortunately, the results of several small randomized trials suggest that improvements in these endpoints may not translate into improvements in overall survival.

One Dutch study randomized 59 patients to four cycles of FAMTX (5FU/methotrexate/doxorubicin) before surgery or surgery alone [68]. Pathologic down-staging was observed in 32% of patients in the preoperative chemotherapy arm, but this did not translate into improved long-term survival. There was, instead, a trend towards decreased median OS in the preoperative chemotherapy arm (18 vs. 30 months). Similar results were obtained in EORTC 40953 which randomized 144 patients to preoperative PLF (cisplatin/5FU/folinic acid) or surgery alone [69]. Preoperative chemotherapy was associated with higher rates of R0 resection (82 vs. 67%) and lower rates of pathologic nodal involvement (61 vs. 77%), but with a median follow-up of 4.4 years, OS was not significantly different between the two treatment arms (65 vs. 53 months, $p = 0.45$). Basi et al. randomized 61 patients to preoperative DCF (docetaxel/cisplatin/5FU) or surgery alone and observed higher RO resection rates (87 vs. 61%), but similar short-term survival rates [70].

The use of neoadjuvant or induction chemotherapy in potentially resectable gastric cancers is an area of ongoing research. Numerous early phase trials aim to compare the efficacy of various chemotherapy regimens in terms of pathologic endpoints (complete responses or R0 resection). While the existing randomized trials of neoadjuvant chemotherapy vs. surgery are limited in size, it is worth noting that disease-specific survival following neoadjuvant chemotherapy, but no other adjuvant therapy, is not particularly encouraging. Another treatment approach which has been studied fairly carefully is perioperative chemotherapy (combination pre- and postoperative chemotherapy). Support for perioperative chemotherapy is largely based on the results of two randomized studies. In the British MRC MAGIC trial, 503 patients (of whom 75% had gastric cancer) were randomized to ECF chemotherapy × 3 cycles followed by resection and then three additional cycles of ECF chemotherapy [11]. The extent of nodal resection was not specified and only 27% of patients underwent D2 or greater resection. Perioperative ECF chemotherapy improved both OS (36 vs. 25% at 5 years) and PFS survival compared to surgery alone. The French FNLCC/FFCD ACCORD trial randomized 224 patients (25% gastric) to 2–3 cycles of preoperative cisplatin + fluorouracil, followed by surgery and 3–4 additional cycles of cisplatin + fluorouracil [12]. Perioperative chemotherapy was associated with improved OS (38 vs. 24% at 5 years), PFS (34 vs. 19%), and rates of RO resection (84 vs. 73%).

The MAGIC and ACCORD trials have been criticized on two fronts. First, the majority of patients, particularly on the MAGIC trial, underwent D1 or D0 resection. Some critics argue that the survival benefits of perioperative chemotherapy in these studies reflect a "making up" for poor surgical resections. Second, these regimens are not particularly well-tolerated. In the MAGIC trial, 80% of patients completed all three cycles of neoadjuvant ECF and only 42% of patients completed adjuvant ECF. Nonetheless, perioperative chemotherapy has been widely adopted.

Numerous early phase studies have examined different perioperative regimens including DCF (docetaxel/cisplatin/5FU) [71, 72], DCX (docetaxel/cisplatin/capcitabine) [73], paclitaxel/S1 [74], docetaxel/S1 [75], FOLT (oxaliplatin/5FU/leucovorin/docetaxel) [76], and FOLFOX [77, 78]. The majority of these specifically included patients with planned D2 resection. Several of these regimens appear to be

much better tolerated than ECF as completion rates with FOLFOX and S1-containing regimens approached 60–80% (compared to 42% in the MAGIC trial). Ongoing studies have been designed to compare the efficacy and tolerability of various perioperative chemotherapy regimens. In practice, many medical oncologists in the US already utilize non-ECF or cis/FU regimens in favor of regimens such as FOLFOX.

Trimodality therapy, which incorporates neoadjuvant chemotherapy with postoperative chemoradiotherapy, also deserves mention. As discussed in detail below, postoperative chemoradiotherapy is supported by multiple randomized trials. However, none of these trials incorporated neoadjuvant therapies. Several groups have speculated that the addition of neoadjuvant chemotherapy to adjuvant chemoradiotherapy could further improve long-term survival by improving both local and systemic disease control. Limited early phase trials suggest this approach is feasible [60, 79], but as of yet there are no quality data supporting its efficacy. The ongoing European CRITICS trial will try to assess the value of adding postoperative radiotherapy to perioperative chemotherapy by randomizing patients to three cycles of ECC (epirubicin/cisplatin/capcitabine) before and after resection or three cycles of ECC followed by surgery and postoperative chemoradiotherapy (45 Gy with concurrent cisplatin and capecitabine).

3.3 Postoperative Treatment Approaches

3.3.1 Postoperative Radiation Therapy

EBRT has not been extensively studied as a single-modality adjuvant therapy for gastric cancer. The British Stomach Cancer Group randomized 432 patients to undergo surgery followed by observation, adjuvant radiation, or adjuvant chemotherapy (mitomycin, doxorubicin, and fluorouracil) [80]. Five-year OS was 17% and neither chemotherapy nor radiation improved survival compared to observation (12% for RT, 19% for chemotherapy, 20% for observation). There was, however, less locoregional failure with radiation (10%) compared to chemotherapy (19%) or observation (27%). Interpretation of these results is complicated by the fact that approximately 40% of the patients had at least microscopically positive surgical margins (18% R1, 20% R2). At present, there are no quality data demonstrating that postoperative radiation alone can prolong survival.

3.3.2 Postoperative Chemotherapy

The benefit of postoperative chemotherapy was not established for some time. A number of small randomized trials utilizing various chemotherapy regimens were performed in the 1980s with mixed results. Meta-analyses of 11 of these studies (including 2096 patients) demonstrated a hazard ratio of 0.88 in favor of postoperative chemotherapy, but this did not reach statistical significance (95% CI 0.78–1.08) [81]. A large randomized Japanese trial also failed to demonstrate a benefit to adjuvant chemotherapy. Nakajima et al. randomized 579 patients with T1 or T2 tumors to surgery

alone or surgery plus mitomycin/5FU followed by oral S-1 therapy for 18 months [82]. Chemotherapy did not significantly improve 5-year OS compared to surgery alone (86 vs. 83%). Survival analysis is greatly limited by the very good outcomes in T1 patients (> 30% in both arms). There was a trend towards improved OS with postoperative chemotherapy in patients with T2 tumors (83% vs. 77%). The generalizability of this trial to patients who present with more advanced disease is unclear.

Many authors initially pointed to the MAGIC and ACCORD perioperative chemotherapy trials as supporting adjuvant chemotherapy, though as discussed above most of these patients underwent D0 or D1 resection. The role of chemotherapy in maximally resected patients remained unclear until the publication of the Japanese SCTS GC trial. This trial randomized 1059 patients with stage II–III gastric cancer after D2 resection to observation or adjuvant S1 oral fluoropyrimidine chemotherapy [83]. Accrual was stopped early following interim analysis. OS at 3 years was superior in the adjuvant S1 group compared to observation (80 vs. 70%). The Asian CLASSIC trial was similar in design except that adjuvant chemotherapy was comprised of capecitabine and oxaliplatin [84]. This trial also demonstrated improvements in OS at 5 years (78 vs. 69%) and DFS (68 vs. 53%) with adjuvant chemotherapy. Postoperative chemotherapy is now considered a reasonable standard of care following maximal resection (R0, D2) of stage II–III gastric adenocarcinoma.

3.3.3 Postoperative Chemoradiation

Postoperative chemoradiotherapy has been examined in several randomized trials. The SWOG9008/INT-0116 trial was the first trial that demonstrated the benefit of postoperative chemoradiation for patients with gastric and GEJ tumors. The final analysis included 556 patients, of whom 80% had gastric tumors and 20% had GEJ tumors. All patients had tumors that were amenable to complete resection of gross disease, including involved nodes. The extent of nodal resection was not specified per protocol. Rates of D0, D1, and D2 nodal resections were 54, 36, and 10%, respectively. After resection, patients were randomized to adjuvant therapy (5FU/leucovorin × 1, followed by 45 Gy RT plus concurrent 5FU/leucovorin, followed by two additional cycles of 5FU/leucovorin) or observation. At initial publication (median follow-up of 5 years), adjuvant chemoradiation improved median survival (36 vs. 27 months) [27]. Three-year RFS (48 vs. 31%) and local control (81 vs. 71%) were also improved with adjuvant chemoradiotherapy. Benefits in OS were maintained with greater than 10 years of follow-up [28].

The clear survival benefit seen in the SWOG9008/INT-0116 trial established the role of postoperative chemoradiotherapy for the management of gastric and GEJ tumors. However, there are several important limitations which have restricted the broader acceptance of this approach. First, the treatment regimen utilized is quite toxic and not a typical regimen by modern standards. This study delivered 5FU/leucovorin chemotherapy over 5 consecutive days per cycle, which is more toxic than weekly dosing. Fifty-six percent of patients in the SWOG9008/INT-0116 trial experienced grade III toxicity and approximately 17% of patients had to discontinue treatment early due to toxicity. Several groups have since demonstrated the feasibility of

alternative "gentler" regimens, including cis/5FU before and after radiation with concurrent single-agent fluoropyrimidine.

Another frequently cited limitation to the SWOG9008/INT-0116 trial is the limited lymphatic resection. Over half (54%) of the patients underwent D0 resection and only 10% underwent D2 or greater lymphadenectomy. Critics questioned if chemoradiotherapy would prove beneficial in patients who were more appropriately managed surgically. At least one observational Korean trial argued against this assertion. Kim et al. compared the outcomes of 446 patients who underwent R0, D2 resection alone with 544 patients who also underwent R0, D2 resection and the same chemoradiotherapy paradigm utilized in the SWOG9008/INT-0116 [85]. Even in maximally resected patients, overall survival (57 vs. 51%) and DFS (55 vs. 48%) were higher in patients who received postoperative chemoradiotherapy compared to surgery alone.

Finally, critics of adjuvant chemoradiation point to the now proven survival benefit of adjuvant chemotherapy in maximally resected patients. The SWOG9009/INT-0116 and similar trials randomized patients to adjuvant chemoradiotherapy or observation. None of them included an adjuvant chemotherapy arm. Some have questioned if the survival advantage seen with adjuvant chemoradiotherapy can be attributed to chemotherapy and not radiotherapy. This question has been most directly addressed by the Korean ARTIST trial [86, 87]. This trial randomized 458 patients who underwent at least D2 lymphadenectomy to adjuvant chemotherapy (cisplatin + capecitabine × 6 cycles) or adjuvant chemoradiation (cisplatin + capecitabine × 2 cycles followed by radiotherapy concurrent with single-agent capecitabine and then two additional cycles of cisplatin + capecitabine). At a median follow-up of 53 months, there was a trend towards improved 3-year OS with adjuvant chemoradiotherapy (78 vs. 74%, $p = 0.08$). Unplanned subset analysis limited to node-positive patients (which included 91% of the entire cohort) demonstrated a significant improvement in 3-year DFS (77 vs. 72%, $P = 0.03$). The trend towards improved survival among all patients and the significant improvement in DFS for node-positive patients was maintained with >7 years of follow-up.

A similar Korean study randomized 90 maximally resected patients with locally advanced (stage III or IV) gastric cancer to five cycles of fluorouracil/leucovorin or the same chemotherapy regimen with concurrent radiation (45 Gy) during cycles 2 and 3 [88]. The addition of radiotherapy significantly improved locoregional control (93 vs. 66%) and strongly trended towards an improvement in DFS for stage III patients (74 vs. 55%, $p = 0.056$). These Korean studies demonstrate that very favorable survival outcomes can be achieved with the addition of adjuvant chemotherapy or chemoradiotherapy in patients who have undergone maximal (R0, D2) resection. The ongoing ARTIST II trial will attempt to further elucidate the benefit of chemoradiotherapy in high-risk patients by randomizing node-positive patients to adjuvant S1 or S1 and oxaliplatin +/− radiation following D2 lymphadenectomy.

At present, the optimal adjuvant chemoradiotherapy regimen for resected gastric cancer is not clear. Very few physicians utilize the MacDonald regimen (daily 5FU/leucovorin) and instead opt for better tolerated alternatives including cis/5FU, or taxane-containing regimens [89–92]. Very little published data supports the use of one regimen over another and there is no consensus on the exact choice of chemotherapeutics or dosing regimens (Table 3.2).

Table 3.2 Adjuvant chemoradiation regimens for resected gastric cancer

Study	Patients	Surgery	Postop adjuvant therapy	Outcomes	Notes
Nakajima [82]	cT1-T2 non-metastatic gastric carcinomas *N* = 579 1988–1992	Not specified per protocol (70% subtotal)	MMC and 5FU (twice weekly for 3 weeks) then daily oral S1 × 18 months	*5-year OS* *T1 (NS)* S + C: 92% S: 95% *T2 (NS)* S + C: 83% S: 77%	33% pT1, 56% pT2 92% completed prescribed chemo
Japanese SCTS [83]	Stage II–III gastric carcinomas *N* = 1059 2001–2004	R0, D2	Daily oral S1 (4 weeks on, 2 weeks off) for 12 months	*3-year OS* S + C: 80% S: 70%	Only 4% received pancreatectomy
CLASSIC [84]	Stage II–III gastric carcinomas *N* = 1035 2006–2009	R0, D2 Minimum 15 nodes examined	Oxaliplatin (day 1), oral capcitabine (days 1–21) × 8 cycles	*5-year OS* S + C: 78% S: 69%	Pancreatectomy not recommended 67% completed prescribed chemo
SWOG9008/INT-0016 [27]	Non-metastatic gastric (80%) or GEJ (20%) *N* = 556 1991–1998	D2 recommended but not required	5FU/leucovorin daily for days 1–5 (28 day cycles) × 1 cycle 45 Gy radiation (25 fractions) daily 5FU/leucovorin on days 1–4 and 23–25 of RT followed by 2 additional 28 day cycles	*3-year OS* S + CRT: 50% S: 41% *Median OS (months)* S + CRT: 27 S: 19 *Local Control* S + CRT: 76% S: 64%	10% D2 or greater resection 54% D0 resection 64% completed prescribed chemo Grade 3+ toxicity: 56%

(continued)

Table 3.2 (continued)

Study	Patients	Surgery	Postop adjuvant therapy	Outcomes	Notes
ARTIST [87]	Stage IB-IV[a] non-metastatic gastric carcinoma *N* = 458 2004–2008	R0, D2	Chemo only: Cisplatin (day 1), twice daily capcitabine (1000 mg/m^2, days 1–14) × 6 three week cycles CRT: Two cycles followed by 45 Gy RT (25 fractions) with twice daily capcitabine (825 mg/m^2 twice daily) followed by two more cycles of full-dose cis/capcitabine	*3-year OS* *All patients (NS, P = 0.08)* S + CRT: 78% S + C: 74% *3-year DFS* *pN +* S + CRT: 77% S + C: 72%	91% of patients were pN+ unplanned subset analysis
Kim [88]	Stage III–IV[a] non-metastatic	R0, D2	Chemo only: 5FU/leucovorin daily for days 1–5 (28 day cycles) × 5 cycles CRT: same as SWOG9008/INT-0016	*5-year OS (NS)* S + CRT: 65% S + C: 55% *5-year LC* S + CRT: 84% S + C: 63%	Treatment completion: CRT: 87% Chemo only: 93%

[a]Stage IV tumors in previous staging systems included non-metastatic patients with T4+ or N3

3.4 Summary of Adjuvant Therapies

Multiple randomized trials from high-volume centers have demonstrated that adjuvant therapy with chemotherapy or chemoradiotherapy can improve overall survival even in patients who have undergone optimal surgical resection. However, there currently is little data available to guide the selection of a particular modality for individual patients. Modern practice patterns vary by region. Postoperative chemotherapy is very commonly utilized in Asian medical centers, whereas postoperative chemoradiotherapy or perioperative chemotherapy is more commonly used in the west. Most preoperative approaches (with the exception of perioperative chemotherapy) are considered experimental. There are several ongoing multi-institutional studies that aim to directly compare the efficacy of different adjuvant treatment approaches. These include the Australian TOPGEAR, the European CRITICS, and the Korean ARTIST II trials. However, there is a high likelihood that these trials may do little to solidify any one modality as "the" preferred treatment modality. The TOPGEAR and CRITICS trials have already been criticized for utilizing ECF and ECC chemotherapy regimens. Barring a very clear survival benefit in favor of one modality, critics will almost certainly question the generalizability of the results.

3.5 Treatment Planning

3.5.1 Patient Setup

Patients should be simulated in a supine position with the arms positioned overhead. Immobilization should be achieved by an immobilization device such as a Vac-Loc (Orange City, IA) to enable reproducible patient positioning.

3.5.2 Simulation

Simulation of patients for adjuvant gastric cancer radiotherapy requires consideration of multiple factors to improve target delineation and account for both inter- and intrafractional sources of variability. Sources of intrafractional motion include both regular (respiratory-related) and random (organ deformation, gastric filling, etc.) sources. Patients should generally be scanned from the carina (whole chest for GEJ tumors) to the top of the iliac wings (though the exact field of view should be guided by the tumor location and treatment targets) using CT simulation with 2–3 mm thin slices. The following recommendations should also be considered:

- Imaging with IV contrast (100–150 mL of iodinated contrast delivered over 30 s) is recommended for delineation of targets and normal vasculature.
  - Consider fusion of contrasted diagnostic CT scan if available or unable to perform contrasted CT simulation.

  - Any image fusions used for treatment planning should be registered and fused on central vasculature structures such as the SMA and celiac artery as those often represent treatment targets
- Oral contrast/water immediately before simulation may also help with target delineation and positioning for preoperative radiotherapy.
  - Stomach distention can vary day-to-day and the consumption of controlled amounts of water can help reduce this variation.
  - Consider the use of 200–250 cc of water before treatment daily to ensure consistent gastric filling.
  - Advise patients to avoid eating or drinking at least 2 h before treatment with particular attention to avoiding carbonated beverages.
- Gastric filling before simulation or treatment is not recommended for postoperative gastric radiation.
- 4DCT simulation, Cine MRI, or fluoroscopy should be considered to evaluate the extent of patterned movements of targets and OARs related to respiration.
  - Studies comparing 4D CT with fluoroscopy and MRI suggest 4DCT likely underestimates tumor motion by up to 2–5 mm in the abdomen [93, 94].
  - Tumor motion is minimal for distal esophageal and GEJ tumors and 4D imaging is generally unnecessary for primary tumors in these locations.

3.5.3 Motion Management

Individualized assessment of tumor motion needs to be considered for each patient as the degree of tumor motion in the postop abdomen can be quite variable. It is generally accepted that the motion of nodal targets surrounding central vascular structures (celiac, SMV, etc.) is <5 mm [95]. However, the degree of motion of parenchymal structures can on occasion be measured in centimeters (though this degree of motion is relatively uncommon) [96, 97]. Assessment of the degree of respiratory motion with fluoroscopy, Cine MRI, or 4DCT simulation is highly recommended to assess the need for additional target expansions or methods to address motion management.

- In general, if regular (patterned) target motion is less than approximately 5 mm, then patients can be treated using an internal target volume while free-breathing by combining GTVs. (or CTVs if no gross disease) using the 0 and 50% phases of the respiratory cycle
- If target motion is >5 mm, use of an ITV may still be appropriate depending on the proximity of the mobile portion of the target to critical structures. However, consideration of motion management techniques should be considered to help minimize target volumes
- Respiratory motion management techniques may be useful to minimize the degree of motion, assuming that their potential shortcomings are considered. *The use of any respiratory management technique requires careful evaluation of the reliability of patient setup and rigorous quality assurance of treatment delivery*

  - Abdominal compression devices can minimize target movement related to respiratory motion in the abdomen [98, 99].
    A major limitation to this approach is that abdominal compression may position OAR in closer proximity to target volumes and may bring additional targets (small bowel) into the treatment field.
    If abdominal compression is considered, patients should be simulated with and without abdominal compression to compare relative target and OAR locations.
  - Breath hold techniques including spirometry-based active breathing coordination [100] (ABC, Elekta, Stockholm, Sweden) or deep inspiratory breath hold (DIBH) [101] can alternatively be used to reduce respiratory motion.
    A potential advantage of these techniques is that they are generally performed at or near maximal inspiration, which may improve separation of targets from OARs.
    Potential disadvantages include the technical difficulties of confirming respiratory position during treatment as well as patient difficulty holding this position for long periods of time (multiple breath holds are required).
    External patient positioning can be monitored to confirm deep inspiration by several systems including the video-based RPM system (Varian, Palo Alto, CA) or external belt-based systems [102, 103].
    Reliability of target localization/patient positioning should be confirmed with frequent pretreatment evaluation if breath hold techniques are utilized.
- Daily image-guidance (CBCT etc.) for the first week of treatment is a reasonable consideration.
  - Real-time respiratory gating techniques such as the RPM or similar systems can also be utilized to modulate radiation delivery throughout the respiratory cycle [104–107]

3.6 Motion Evaluation

Consideration for the methods and frequency of confirming patient/target positioning is critical to determining marginal expansions. Though frequently advocated for, the routine use of daily pre-treatment positional evaluation (IGRT) with tight margins for postoperative gastric cancer radiation has potential disadvantages.

- Delineation of CTVs in the postoperative abdomen is inherently subjective and necessitates generous target delineation and expansion.
- All of the data supporting adjuvant radiation for gastric cancer utilized daily fraction sizes of approximately 180 cGy to a total dose of 45–50.4 Gy, which should be well-tolerated by many OARs in a reasonably optimized plan.
- The balance of adequate coverage of areas at risk vs. clinically meaningful normal tissue toxicity in many instances may be better achieved by accepting uncertainty and utilizing generous margins.

We provide the following recommendations:

- For patients with acceptable levels of target motion (<5 mm) on 4DCT imaging, patient evaluation with CBCT or matched planar KV/MV images compared to CT treatment plan or DRRs generated from CT simulation before the first treatment and then weekly is reasonable.
  - Consideration of more frequent patient evaluation with IGRT should be considered in the following instances:
    The use of a respiratory management system (DIBH, abdominal compression, etc.) is utilized to reduce respiratory motion.
    There is significant target motion that can't be adequately addressed by other means.
    The PTV or beam edge is in very close proximity to a critical OAR such as the spinal cord.
    Patient setup/target localization is variable to an unacceptable degree.
    In the setting of prior radiation.
  - Daily imaging with CBCT or planar images in these instances may be necessary. However, if daily imaging demonstrates that set up and/or target localization are reliable, then conversion to less frequent imaging may be appropriate.

3.7 Dosimetric Treatment Planning

3.7.1 Target Volumes

Gross tumor volume (GTV): Includes gross disease in the primary site and any pathologically involved nodes (>1 cm on CT or MR-based imaging). In the postoperative setting, there is usually no gross disease at the time of simulation.

- Evaluation of pretreatment location of gross disease (base on imaging, procedural (EGD), and operative reports) is critical for determining locations at highest risk of recurrence.
- However, the routine fusion of preoperative images to postoperative treatment planning scans for target delineation is not usually helpful as there are often significant differences in anatomic locations of targets following resection.

Clinical treatment volume (CTV): defining the CTV for resected gastric cancers is more difficult than in many other anatomic locations. In addition to anatomical changes in organ position following a sizable resection, there are many nodal locations which may be at risk including (Fig. 3.1):

- Mediastinal
- Paracardial
- Paraesophageal
- Perigastric

- Celiac
- Gastrohepatic
- Portahepatic
- Splenic/splenic hilar
- Suprapancreatic
- Pancreaticoduodenal

The inclusion of all of these nodal stations requires very large treatment fields which is not well-tolerated and is not recommended.

Routine coverage of the entire gastric remnant in the CTV is also not recommended as a routine. While inclusion of the entire gastric remnant was used in early studies [27] and is still referenced in the literature [108], routine inclusion of the entire gastric remnant was specifically not recommended in recent RCTs including the ARTIST

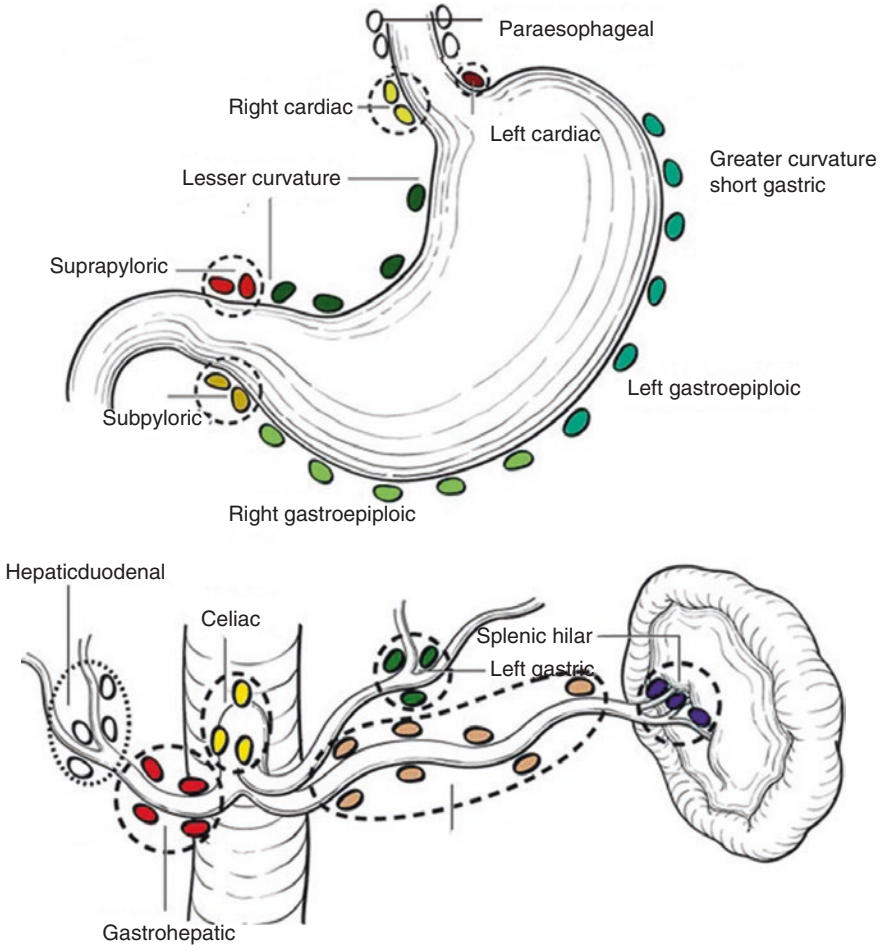


Fig. 3.1 Schematic of regional nodes at risk in gastric cancer

trial [87]. Retrospective analyses suggest that, depending on the extent of the initial tumor and the extent of resection, the exclusion of a portion of the remnant stomach from the radiation field is not associated with decreased local control [109].

Idealized clinical treatment volumes that take into account pathologic findings including depth of invasion, extent of nodal involvement, and primary tumor location have been proposed by us and others. Table 3.3 provides a generalized framework for use in treatment planning. However, it must be emphasized that these are guidelines and not high-level evidence-based recommendations. Physicians need to consider individual patient factors to devise the most realistic plan which best balances treatment tolerability with probability of disease control.

A representative contouring atlas has been provided in Fig. 3.2. In addition, we have provided examples of clinical treatment volumes for the same patient assuming different clinical scenarios (Figs. 3.3 and 3.4). Figure 3.3 shows the CTV (red) and 3DCRT fields (AP/PA and opposed laterals) for a patient with a locally advanced T3 N3 cancer of the middle third of the gastric body and pathologic involvement of >20 nodes. In this case, coverage of all of the nodal regions at risk requires inclusion of the entire gastric remnant, porta hepatis, celiac vessels, as well as the proximal duodenum and the head of the pancreas. These fairly extensive treatment volumes can be compared to an idealized CTV and treatment fields for the same patient, assuming that they had a more localized T2 N1 cancer of the cardia with the involvement of a single proximal perigastric node (Fig. 3.4). In this case, the CTV does not include the entire gastric remnant as there is no need to cover all of the perigastric nodes (particularly those along the distal greater curvature). The CTV also does not include the porta hepatis or the head of the pancreas as the associated regional nodes have a relatively low risk of involvement. See figure legends for more detailed descriptions.

Internal Target Volume (ITV): If necessary because of significant (>5 mm) target motion on 4D imaging, an ITV can be generated on a free-breathing image as the union of GTV or CTVs contoured on 0 and 50% phases of expiration.

If an ITV is generated from a 4DCT, consider an additional PTV expansion of 3–5 mm as 4DTCT may underestimate abdominal organ motion associated with respiration [93].

Planning Target Volume (PTV): As per the ICRU-62 guidelines, it should comprise an expansion of the CTV (or ITV) to account for target motion and setup errors. Recommended PTV margins vary based upon target motion and the type of image-guidance utilized to assess patient setup.

- Portal imaging has been associated with uncertainty of 5–6 mm, whereas CBCT is generally associated with <4 mm of uncertainty in any one plane.
- PTV expansions of 5–10 mm are generally acceptable.
- PTV expansions should not be uniform in all directions in the presence of significant intrafractional motion. For example, if there is significant superior-inferior displacement but minimal axial displacement, then a non-uniform PTV expansion of 7 mm superior-inferior expansion and 5 mm in other directions may be appropriate.

Table 3.3 General recommendations for clinical treatment volumes based on tumor location and TNM staging (assuming adequate pathologic nodal sampling)

Anatomic location	TNM staging	Included local structures	Gastric remnant	Included nodal stations
GEJ or esophageal extension (preoperative)	T2 N0- omission of RT is reasonable assuming R0 resection with adequate nodal sampling	Distal 3–5 cm of esophagus, proximal body of pancreas +/− medial left hemidiaphragm	NA	None. Optional includes distal paraesophageal, proximal perigastric, paracardial
	T3-T4 N0	Same as for T2 plus sites of adhesion (T4) with adequate margins[a]	NA	Distal paraesophageal, paracardial, celiac, and intervening perigastric[b]
	N1	Same as above	NA	Same as for N0 plus all radiographically involved nodal stations
	N2-N3	Same as above	NA	Same as N1 plus suprapancreatic
Cardia (postoperative)	T2 N0- omission of RT is reasonable assuming R0 resection with adequate nodal sampling	Distal 2–3 cm of esophagus, proximal body of pancreas +/− medial left hemidiaphragm	Routine inclusion of entire remnant is not recommended This may be unavoidable if patient is s/p near-total gastrectomy	None[c]. Optional: distal paraesophageal, paracardial, celiac, and intervening perigastric
	T3-T4 N0	Same as T2 N0 plus sites of adhesion (T4) with adequate margins respecting extent of resection[b]	Same as for T2 N0	Distal paraesophageal, paracardial, celiac, and intervening perigastric
	N1	Same as above	Same as for N0	Same as for N0 plus all involved nodal stations If involved nodes were distal perigastric or celiac, consider inclusion of suprapancreatic and pancreaticoduodenal nodal stations
	N2–3	Same as above	Entire remnant will usually be included	Distal paraesophageal, paracardial, paragastric, and celiac. Suprapancreatic and pancreaticoduodenal stations may also be reasonable if there is distal nodal involvement

(continued)

Table 3.3 (continued)

Anatomic location	TNM staging	Included local structures	Gastric remnant	Included nodal stations
Body or middle third (postoperative)	T2 N0- omission of RT is reasonable assuming R0 resection with adequate nodal sampling	Body of pancreas (+/− tail)	Routine inclusion of entire remnant is not recommended	None. Optional stations include distal (intervening) perigastric, celiac, splenic hilar, suprapancreatic, and pancreaticoduodenal
	T3-T4 N0	Body of pancreas (+/− tail) plus sites of adhesion (T4) with adequate margins respecting extent of resection	Same as for T2 N0	Distal (intervening) perigastric, celiac, splenic hilar, suprapancreatic, pancreaticoduodenal
	N1	Same as N0	Sparing of some of the gastric remnant is generally possible as coverage of all perigastric nodal stations is not recommended	Distal (intervening) and involved perigastric, celiac, splenic hilar, suprapancreatic, portal, pancreaticoduodenal
	N2–3	Same as for N0	Adequate nodal coverage generally includes all of the gastric remnant	Perigastric, celiac, splenic hilar, suprapancreatic, portal, pancreaticoduodenal

Antrum, pylorus	T2 N0- omission of RT is reasonable assuming R0 resection with adequate nodal sampling	Head of pancreas +/− first and second parts of duodenum	Routine inclusion of entire remnant is not recommended	None. Optional include distal perigastric, celiac, suprapancreatic, pancreaticoduodenal
	T3-T4 N0	Head of pancreas +/− first and second parts of duodenum plus sites of adherence (T4) with adequate surgical margins	Same as for T2 N0	Distal perigastric, celiac, suprapancreatic, pancreaticoduodenal
	N1	Same as N0	Sparing of some of the gastric remnant is generally possible as coverage of all perigastric nodal stations is not recommended	Distal and involved perigastric, celiac, suprapancreatic, pancreaticoduodenal, portal
	N2–3	Same as N0	Adequate nodal coverage frequently includes the entire remnant	Perigastric, celiac, suprapancreatic, pancreaticoduodenal, portal +/− splenic hilar

[a]CTV margins should always consider the likelihood of involvement/risk of recurrence. None to relatively small margins (1.5–2 cm) are recommended if surgical confidence in location(s) of involvement and extent of resection are high. Larger margins (3–5 cm) may be warranted if there is uncertainty as to the extent of involvement or adequate resection could not be achieved

[b]Most perigastric nodal stations are (or will be) adequately resected at the time of surgery and have a low risk of recurrence. Routine coverage of uninvolved perigastric nodal stations is not recommended in the absence of a high nodal burden or suboptimal (D0) resection. Intervening perigastric nodes refer to the perigastric nodal stations located between the tumor bed and more distal nodal stations (celiac, etc.), which are to be included in the CTV

[c]Other sources recommend perigastric nodal coverage. Coverage of the postoperative bed will invariably include adjacent perigastric nodal stations. However, since these nodal stations are surgically absent, we do not recommend the inclusion of perigastric nodal stations which are not within the CTV margins of the postoperative bed

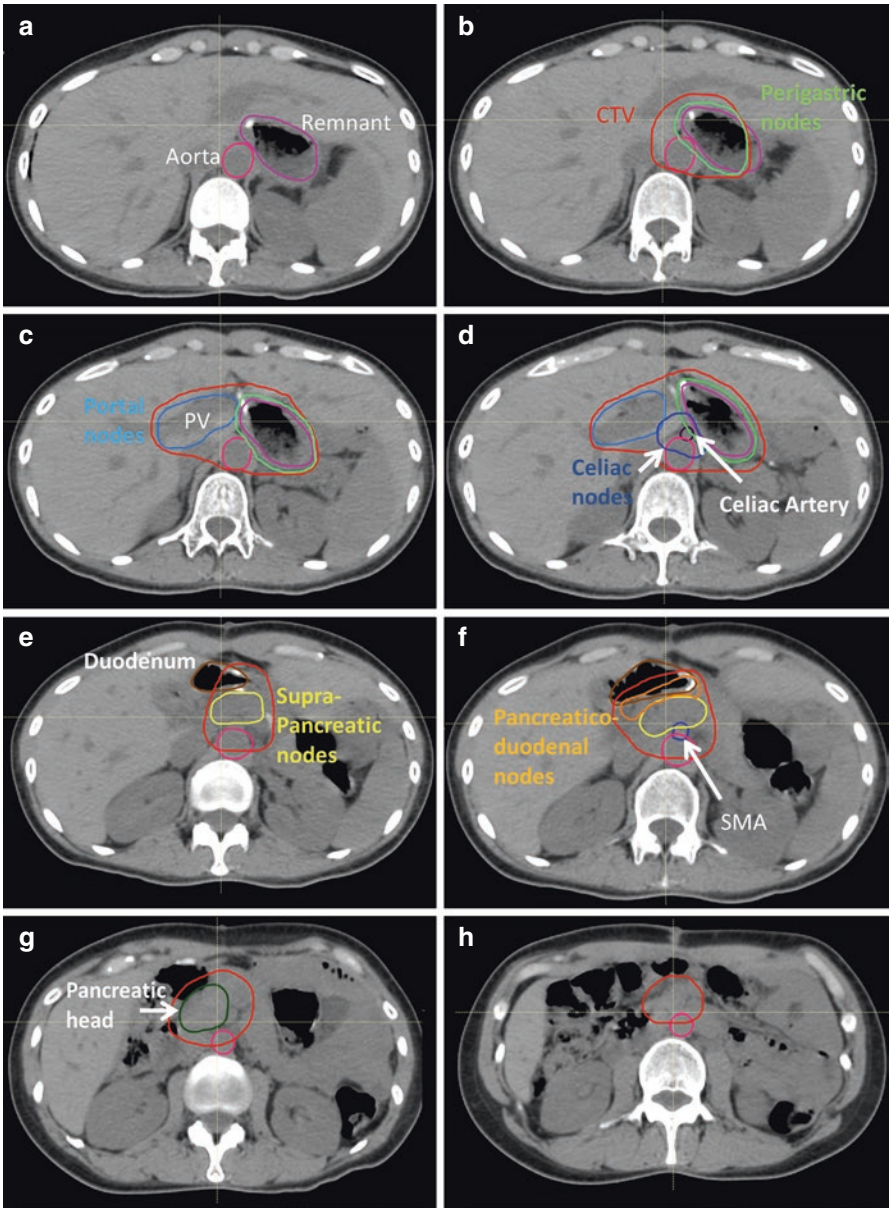


Fig. 3.2 Representative Contouring Atlas for Target Used for Adjuvant Treatment for a T2N2M0 Gastric Antrum Cancer (involving 3/26 nodes; 2 distal perigastric, 1 celiac). *CTV* (*red*) includes head of pancreas (*purple*) +/− first and second parts of duodenum (*brown*) with adequate surgical margins. CTV should also include the following nodal stations at risk: distal and involved perigastric (*green*), celiac (*blue*), suprapancreatic (*yellow*), portal (*teal*), and pancreaticoduodenal (*orange*). Routine inclusion of entire gastric remnant (*pink*) to cover perigastric nodes is not recommended if patients undergo adequate pathologic nodal sampling (>15 nodes) as these are surgically absent and at a low risk of local recurrence. Proximal and lateral gastric remnant was not included in the CTV as this patient underwent adequate pathologic nodal evaluation (**a**, **b**). Additional axial sections are included at the level of the portal vein (**c**), celiac artery (**d**), duodenal-gastric junction (**e**), SMA (**f**), pancreatic head (**g**), and just inferior to the pancreatic head (**h**)

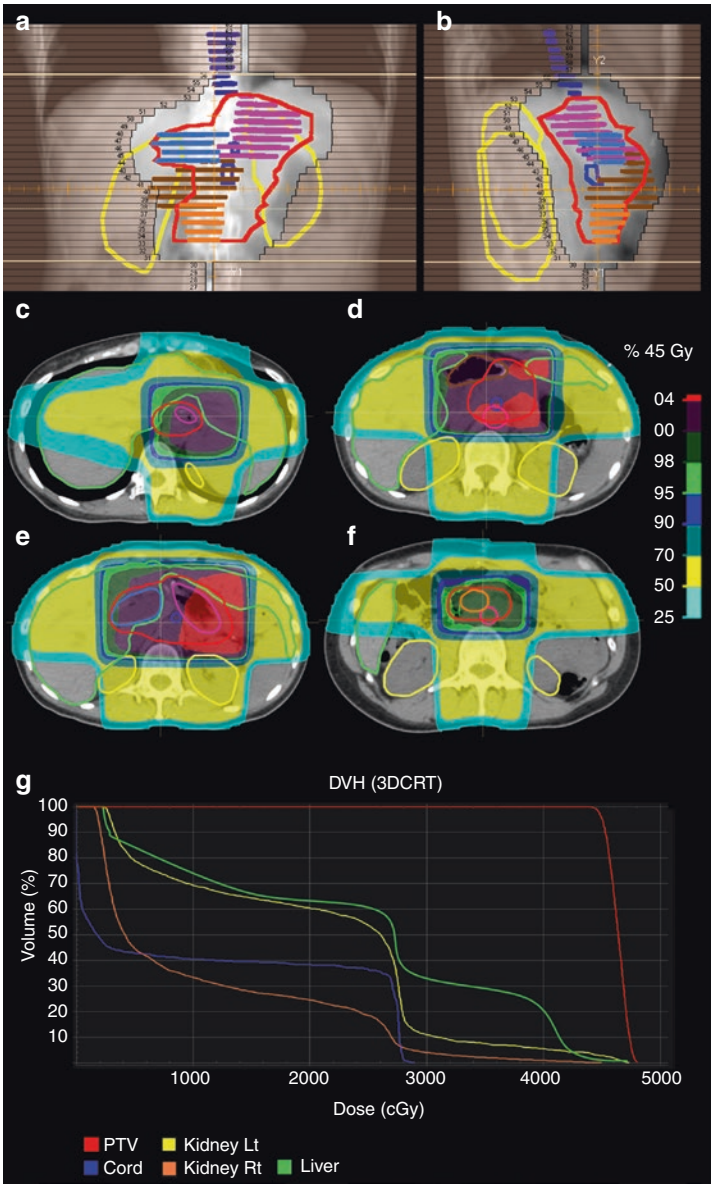
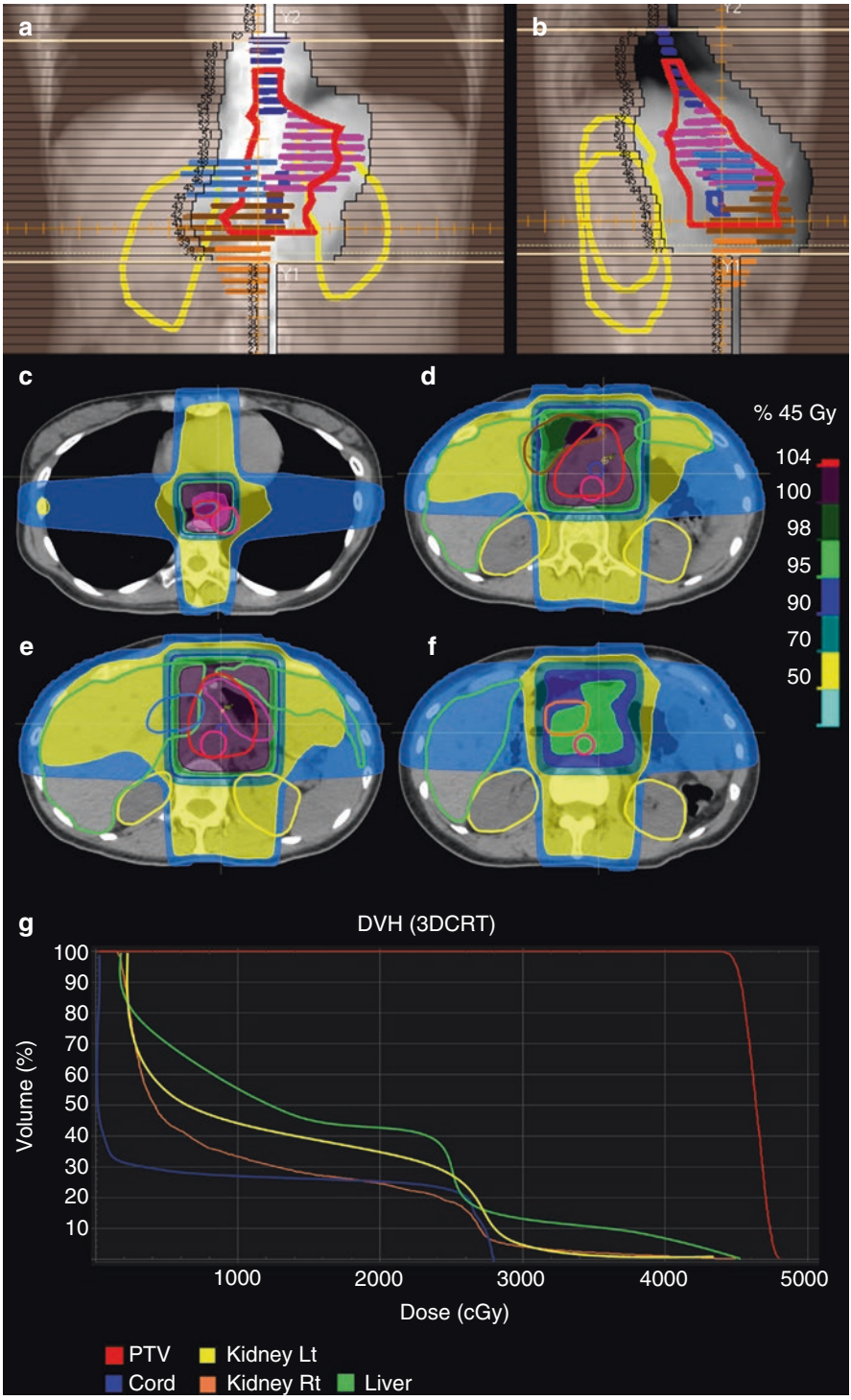


Fig. 3.3 Postoperative clinical treatment volumes and 3DCRT fields for a patient with locally advanced T3 N3 adenocarcinoma of the middle third of the stomach pathologically involving >20 nodes (25/32). Beams eye view of AP (**a**) and right lateral (**b**) fields superimposed on digitally reconstructed radiographs from CT simulation. Note that the coverage of all nodal regions at risk (paragastric, gastrohepatic, celiac, portahepatic, suprapancreatic, and pancreaticoduodenal) within the CTV (*solid red line*) required coverage of the entire gastric remnant (*pink segmented*), portal nodes (*light blue segmented*), celiac artery and SMA (*solid dark blue*), and the pancreatic head (*orange segmented*). The block edge was set at 1.5 cm from the CTV. Panels **c**–**f** show axial images at the level of the proximal gastric remnant (**c**), celiac artery (**d**), SMA (**e**), and distal pancreatic head (**f**). Contoured structures include CTV (*red*), gastric remnant (*pink*), esophagus (*dark blue*), liver (*light green*), celiac artery and SMA (*blue*), kidneys (*yellow*), first and second duodenal segments (*brown*), pancreatic head (*orange*), and aorta (*fuchsia*). Panel **g** shows the dose-volume histogram for the spinal cord, kidneys, and liver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3000
4000
5000
Dose (cGy)
PTV
Cord
Kidney Lt
Kidney Rt
Liver

Fig. 3.4 Postoperative clinical treatment volumes and 3DCRT fields for a patient with a T2 N1 adenocarcinoma of the gastric cardia and pathologic involvement of a single paragastric node (1/28). Beams eye view of AP (**a**) and right lateral (**b**) fields superimposed on digitally reconstructed radiographs from CT simulation. Note that nodal coverage is much less extensive than in patients with a high nodal burden (see Fig. 3.1). Nodal regions covered within the CTV (*solid red line*) include distal paraesophageal, medial paragastric, medial portal and gastrohepatic, celiac, and suprapancreatic. Lateral paragastric nodes were specifically excluded to spare some of the gastric remnant (*pink segmented*). The exclusion of lateral portal (*light blue segmented*) and distal pancreatic/pancreaticoduadenal nodes with low risk of involvement also significantly reduces the filed size and improves sparing of the liver and right kidney. The block edge was set at 1.5 cm from the CTV. Panels **c**–**f** show axial images at the level of the distal esophagus (**c**), celiac artery (**d**), SMA (**e**), and distal pancreatic head (**f**). Contoured structures include CTV (*red*), gastric remnant (*pink*), esophagus (*dark blue*), liver (*light green*), celiac artery and SMA (*blue*), kidneys (*yellow*), first and second duodenal segments (*brown*), pancreatic head (*orange*), and aorta (*fuchsia*). Panel **g** shows the dose-volume histogram for the CTV, spinal cord, kidneys, and liver

Organs at Risk (OAR): In addition to the clinical target volumes, the following normal tissues should be contoured on the CT images for use in treatment planning optimization.

- Spinal cord
- Esophagus
- Liver
- Gastric remnant
- Duodenum
- Small bowel
- Kidneys (right and left as separate structures)

It may also be useful to contour the following to help with target delineation:

- Celiac artery
- SMA
- Pancreatic head
- Pancreatic body/tail
- Porta hepatis

Dose-volume considerations for OARs with conventional (1.8–2.0 Gy) fractionation are provided in Table 3.4.

Table 3.4 Dose-volume considerations for treatment plan optimization of standard with standard fractionation schedules[a]

OAR	Quantec consensus guidelines				Authors' institutional recommendations
	Volume	Dose/volume	Toxicity rate	Endpoint	
Duodenum	NA				Max <54 Gy
Esophagus	Mean	<34 Gy	<20%	Grade 3+ acute esophagitis	Max <60 Gy
	V30	<50%	<30%	Grade 2+ acute esophagitis	
	V50	<40%	<30%	Grade 2+ acute esophagitis	
	V70	<20%	<30%	Grade 2+ acute esophagitis	
Kidneys (bilateral)	Mean	<15–18 Gy	<5%	Clinical Dysfunction	Mean < 15 Gy V20 < 32%
		<28 Gy	50%	Clinical Dysfunction	
	V12	<55%	<5%	Clinical Dysfunction	
	V20	<32%	<5%	Clinical Dysfunction	
	V23	<30%	<5%	Clinical Dysfunction	
	V28	<20%	<5%	Clinical Dysfunction	
Liver	Mean	<30 Gy	<5%	RILD (normal liver)	Mean < 20 Gy V30 < 30% V15 < 66%
		<42 Gy	<50%	RILD (normal liver)	
		<28 Gy	<5%	RILD (CP-A, cirrhosis)	
		<36 Gy	<50%	RILD (CP-A, cirrhosis)	
Small bowel (Individual loops)	V15	<150 cc	<10%	Grade 3+ late toxicity	Max <45–50 Gy
Spinal cord	Max	50 Gy	<1%	Myelopathy	Max <50 Gy
		60 Gy	6%	Myelopathy	
		69 Gy	50%	Myelopathy	

[a]Volumetric data is adapted from Marks et al. [110] unless otherwise stated

Table 3.5 Overview of radiation treatment modalities utilized in the adjuvant treatment of gastric cancers

Modality	Dose/fractionation	Beam arrangement
3DCRT	45–50.4 Gy; 1.8 Gy per fraction; 5 days per week	3–4 fields (AP/PA with opposed laterals)
IMRT	45–50.4 Gy; 1.8 Gy per fraction; 5 days per week	Conventional IMRT: multiple coplanar or non-coplanar isocentric beams Tomotherapy: multiple non-isocentric coplanar beamlets VMAT: volumetrically modulated isocentric coplanar arcs
IORT[a]	15–20 Gy if no EBRT 10–15 Gy following preoperative EBRT or if postoperative EBRT is planned; Single fraction delivered at the time of surgery to high-risk vascular and nodal regions or gross disease after organs at risk are displaced from the treatment field	En face electrons

[a]May be appropriate for carefully selected patients

3.8 Treatment Modalities

3DCRT and IMRT are both utilized for the adjuvant treatment of gastric cancer. IORT has also been utilized and will also be described briefly herein. SBRT and proton therapy for gastric cancer have also been recently evaluated [111–113], but published clinical experience with these modalities is limited and they will not be discussed here. Table 3.5 provides an overview of the major radiation modalities along with recommended dose schedules and beam arrangements.

3.9 Treatment Optimization

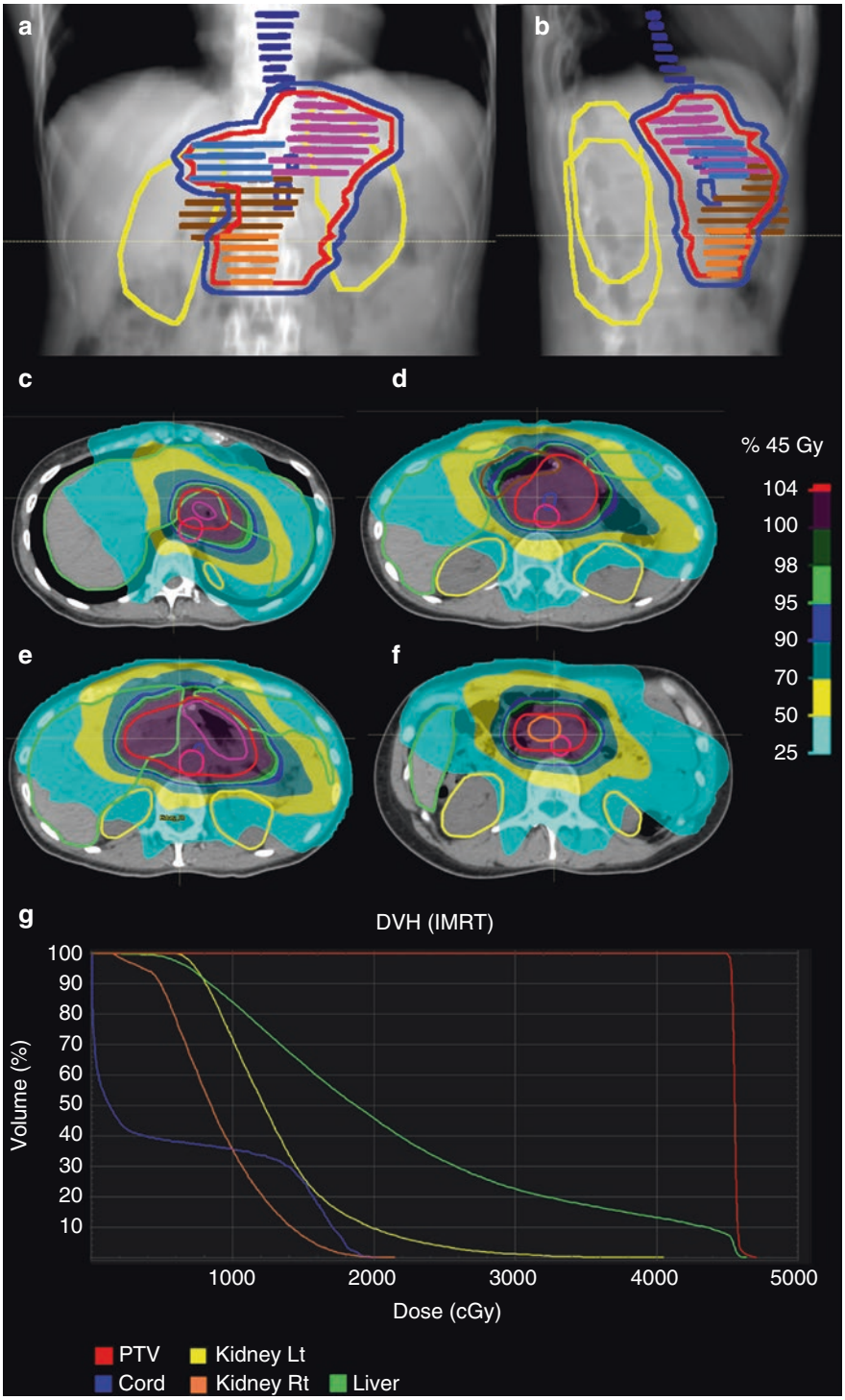
Optimization of all treatment plans, whether 3DCRT or IMRT, entails maximizing target coverage, while minimizing the risk of treatment toxicity (by minimizing dose to OARs). Normal tissue tolerances to conventional dose radiation (1.8–2 Gy daily) have been examined previously and consensus guidelines have been published. Recommended tolerances are shown in Table 3.4.

The choice between 3DCRT and IMRT requires consideration of individual patient characteristics. Undoubtedly, optimized IMRT plans usually do a better job (on paper at least) of minimizing high-dose exposure to adjacent OARs without compromising PTV coverage and there are cases in which adequate PTV coverage can't be achieved without accepting clinically meaningful risks using 3DCRT. Many institutions regularly utilize IMRT for all postoperative gastric cancer cases. However, the translation of better dosimetric distributions into clinical benefits with IMRT in the upper abdomen have been inconsistent and are mostly limited to decreases in low-grade physician-assessed (CTCAE, etc.) toxicities [114–116]. At present, there are no quality data to suggest that the regular use of IMRT for tumors of the upper abdomen can improve disease control or significantly decrease the incidence of toxicity. There are potential advantages to using 3DCRT which deserve consideration.

- 3DCRT delivers a lower integral dose to the patient.
- There is ample uncertainty as to the accurate definition of areas at risk in the postop abdomen and IMRT planning is inherently less forgiving than 3DCRT with regard to marginal dosing adjacent to clinical target volumes.
- IMRT can be more sensitive than 3DCRT to under-dosing of the PTV as a result of small errors in patient/target positioning.
- Treatment time with 3DCRT may be shorter than that with IMRT.
- IMRT is more expensive than 3DCRT.

Ultimately, the choice between 3DCRT and IMRT needs to be tailored to the individual patient and factor important variables including physician and institutional experience. In the absence of quality data which clearly justifies one modality over the other, both modalities are reasonable options for the treatment of most patients. Figs. 3.5 and 3.6 compare optimized 3DCRT and IMRT plans for the same patient.

Fig. 3.5 Postoperative clinical treatment volumes and IMRT fields for a patient with locally advanced T3 N3 adenocarcinoma of the middle third of the stomach pathologically involving >20 nodes (25/32). These images show treatment volumes and optimized dose-distribution of an IMRT plan for the same patient in Fig. 3.1. Contoured treatment volumes and normal structures are superimposed on digitally reconstructed AP (**a**) and right lateral (**b**) radiographs from CT simulation. Coverage of all nodal regions at risk (paragastric, gastrohepatic, celiac, portahepatic, suprapancreatic, and pancreaticoduodenal) within the CTV (*red solid*) required coverage of the entire gastric remnant (*pink segmented*), portal nodes (*light blue segmented*), celiac artery and SMA (*solid dark blue*), and the pancreatic head (*orange segmented*). The PTV (*dark blue solid*) is a 5 mm isotropic expansion of the CTV (*red solid*). Panels **C**-**F** show axial images with dose distribution at the level of the proximal gastric remnant (**c**), celiac artery (**d**), SMA (**e**), and distal pancreatic head (**f**). Contoured structures include CTV (*red*), gastric remnant (*pink*), esophagus (*dark blue*), liver (*light green*), celiac artery and SMA (*blue*), kidneys (*yellow*), first and second duodenal segments (*brown*), pancreatic head (*orange*), and aorta (*fuchsia*). Panel **g** shows the dose-volume histogram for the spinal cord, kidneys, and liver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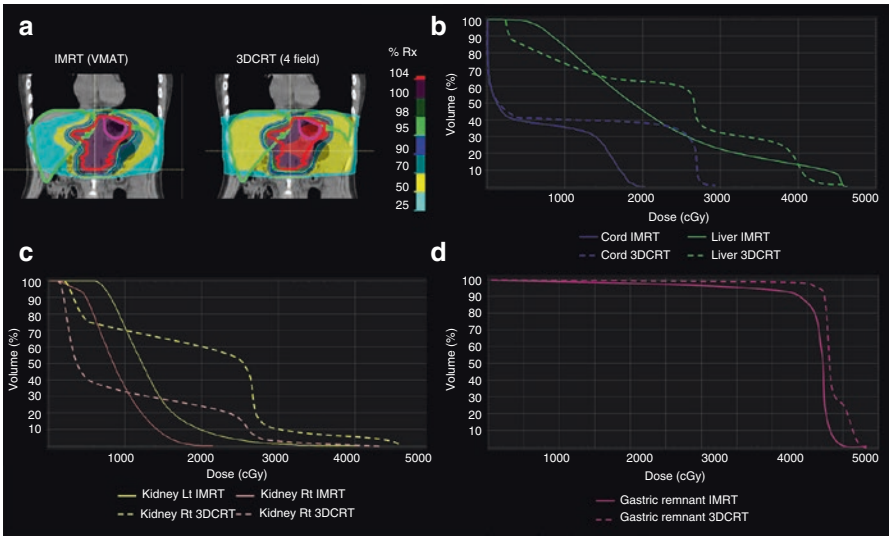

Fig. 3.6 Comparison of dose-volume histograms from optimized IMRT (VMAT) and four fields 3DCT plans for the same patient as in Figs. 3.1 and 3.3. Dose distribution for IMRT (*left*) and 3DCRT (*right*) imposed on a coronal slice of the planning CT is shown in panel **a**. Both plans utilized the same CTV (*red*) and were prescribed to 45 Gy in 25 fractions. The field edges were placed 1.5 cm from the CTV for the 3DCRT plan. The CTV was isotropically expanded to generate a PTV (*dark blue*) for IMRT planning. Contoured structures including liver (*green*), gastric remnant (*pink*), and kidneys (*yellow*). DVHs for cord and liver (**b**), kidneys (**c**), and gastric remnant (**d**) are shown below. Solid lines represent IMRT values and dashed lines represent 3DCRT values. Volumetric dosing for the cord (*blue*) is lower at all dose levels in the optimized IMRT plan (**b**). Neither plan has equal or lower liver (*green*) volumes at all dose levels (**b**). Liver volumes receiving between 15 and 40 Gy are higher in the 3DCRT plan. However, volumes receiving less than 15 or more than 40 Gy are higher in the IMRT plan. The increased liver volume receiving >40 Gy is a consequence of minimizing dose to the gastric remnant and right kidney. For bilateral kidneys (*pink* and *yellow*), the optimized IMRT plan achieved lower volumes receiving greater than approximately 12 Gy, but higher volumes receiving between approximately 5 and 12 Gy (**c**). The entire gastric remnant was included within the 3DCRT field edges and 99% received at least the 45 Gy prescription dose with approximately 25% receiving between 100 and 106% (**d**). In contrast, the PTV for the IMRT plan did not contain the entire gastric remnant and approximately 15% of the remnant received less than prescription dose with the IMRT plan. Note that, despite the large CTVs, dosing to all OARs was well below tolerance limits and the clinical significance of most of the dosimetric differences between the plans is likely insignificant

3.10 Summary

Treatment options for patients with resectable gastric cancer include perioperative chemotherapy and postoperative chemoradiation. Neoadjuvant chemoradiation for GE junction and gastric cardiac tumors is managed similarly to mid-distal

esophageal cancer with neoadjuvant chemoradiation. Both 3DCRT and IMRT are acceptable treatment approaches, which should be determined based on patient factors and physician/institutional experience. Treatment plans should be individualized taking into consideration anatomic location, nodal involvement, extent of nodal resection, and anatomical changes in organ position following resection. Details to reproducibility of patient set up, organ motion, and daily variations of stomach distension are important components influencing accurate delivery of radiation treatment. A treatment algorithm based of tumor staing and pathologic/clinical response to theraphy is provided in Fig. 3.7.

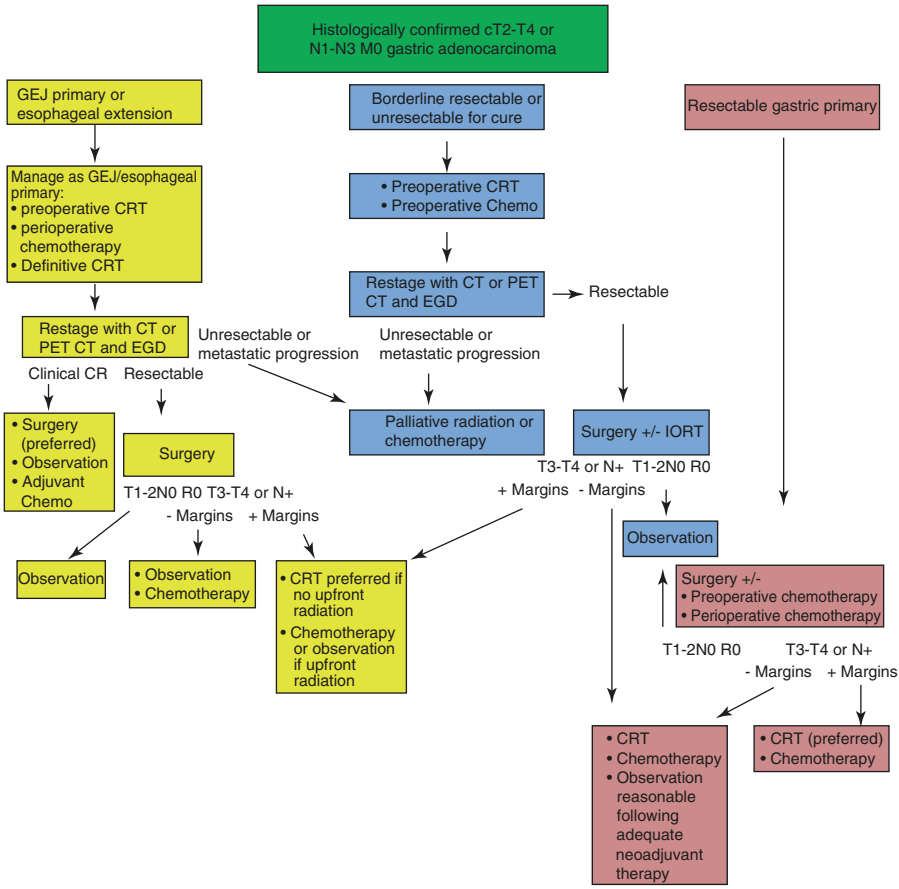

Fig. 3.7 Treatment algorithm

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Part III

Hepatobiliary Malignancies

Primary Liver Tumors: Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma

4

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4.1 Introduction

4.1.1 Liver Histology and Anatomy

The histologic and anatomic make-up of the liver has unique properties compared to sites of other gastrointestinal cancers, typically arising from tubular structures lined with mucosa. In contrast, the liver is made up primarily of hepatocytes, which serve synthetic and energy storage functions, detoxify a variety of compounds, and secrete these oxidized and/or conjugated by-products into the biliary ductal system. This excreted material includes conjugated bilirubin and bile salts and tracks through an extensive ductal system, collecting in the left and right hepatic ducts. Tumors that arise from hepatocytes are most commonly hepatocellular carcinomas (HCC). Tumors that arise from the mucosa of the biliary tree within the liver are termed intrahepatic cholangiocarcinomas (IHCC). Tumors that arise distal to the start of the common hepatic duct are extrahepatic cholangiocarcinomas (EHCC). Although IHCC and EHCC are similar biologically, surgically they require different surgical procedures depending on the anatomical location and extent. Normal liver has a dual blood supply, with over 75% of blood volume coming from the portal vein and the rest coming from hepatic arteries. Venous blood drainage is through the hepatic veins which coalesce into the inferior vena cava. The liver is divided into eight segments (I–VIII) based on surgical landmarks. The right hepatic vein divides the right lobe into anterior and posterior segments. The middle hepatic vein divides the liver into right and left lobes. This plane runs from the inferior vena cava to the gallbladder fossa. The left hepatic vein divides the left lobe into medial and lateral parts. The portal vein divides the liver into upper and lower segments. For radiation oncologists, however, cross-sectional imaging is used so that the CT- and MR-based landmarks can be used to understand how these regions relate to the surgical segments. The dual blood supply of the liver is critical to understanding the therapeutic advantage of arterial-based liver-directed cancer therapies. Both primary and secondary liver tumors are angiogenic, and thus, draw a disproportionate amount of their blood supply from the arterial system. Another unique property of the liver is its ability to regenerate, which makes very aggressive surgical and radiotherapeutic approaches possible. If a liver is not cirrhotic, part of the liver can be removed or obliterated and compensatory regeneration can take place. However, most cases of HCC occur along with cirrhosis, which makes their treatment especially challenging.

4.1.2 Hepatocellular Carcinoma (HCC)

The most common risk factor for HCC is cirrhosis, which can be caused by hepatitis B or C, alcohol, hemochromatosis, non-alcoholic fatty liver disease, autoimmune primary biliary cirrhosis, or alpha-1-antitrypsin deficiency. Hepatitis B carriers are also at risk for HCC, even without clinically evident cirrhosis. Patients at high risk for HCC should be screened using a combination of ultrasound and alpha-fetoprotein (AFP), a sensitive tumor marker for HCC. Suspicious nodules or rising AFP can be

further evaluated by triple-phase CT or MRI. Unlike most other cancers, HCC can be diagnosed by imaging alone by assessing for classic enhancements, namely arterial hyper-enhancement and venous washout. When a lesion cannot be diagnosed by imaging characteristics alone, core biopsy can be done to confirm the diagnosis; however, attempts to avoid biopsy, if possible, are warranted due to the risk of contamination of the extrahepatic biopsy. There are several standardized imaging evaluation guidelines to help radiologists determine how to handle nodules over 1 cm.

Staging of HCC is roughly based on liver transplant criteria, and the AJCC TNM staging criteria are shown in Table 4.1 [1]. In addition to staging, it is important to also calculate patients' Child-Pugh score, an indicator of liver disease used to estimate survival and operative risk, based on total bilirubin, serum albumin, prothrombin time, ascites, and hepatic encephalopathy as shown in Table 4.2 [2].

Table 4.1 AJCC version 8 staging for HCC by TNM

Primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor </= 2 cm, or >2 cm without vascular invasion
T1a	Solitary tumor </= 2 cm
T1b	Solitary tumor > 2 cm without vascular invasion
T2	Solitary tumor > 2 cm with vascular invasion, or multiple tumors, not > 5 cm
T3	Multiple tumors, at least one of which is >5 cm
T4	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
Regional lymph nodes (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

Table 4.2 Child-Pugh Scoring System

Points	1	2	3
Encephalopathy (grade)	None	1–2	3–4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds over control) INR	<4 <1.7	2–3 1.7–2.3	>3 >2.3
Bilirubin (mg/dL)	<2	2–3	>3

Class A (well-compensated): 5–6 points; Class B (significant compromise): 7–9 points; Class C (decompensated): 10–15 points

Table 4.3 Barcelona Clinic Liver Cancer (BCLC) Staging system for HCC

BCLC stage	Performance status	Tumor status	Liver function
Stage A: early			
A1	0	Single, <5 cm	No portal hypertension, normal bilirubin
A2	0	Single, <5 cm	Portal hypertension, normal bilirubin
A3	0	Single, <5 cm	Portal hypertension and abnormal bilirubin
A4	0	3 tumors <3 cm	Child-Pugh A-B
Stage B: intermediate	0	Large multinodular	Child-Pugh A-B
Stage C: advanced	1–2	Vascular invasion or extrahepatic spread	Child-Pugh A-B
Stage D: end-stage	3–4	Any	Child-Pugh C

Although the MELD (model for end stage liver disease) score is used to determine priority on liver transplant lists, Child-Pugh scores are more commonly used to make liver radiotherapy decisions. Another commonly used treatment algorithm is the Barcelona Clinic liver cancer (BCLC) staging system, which incorporates tumor factors, performance status, and liver function and is summarized in Table 4.3 [3]. In addition to the labs required to calculate the Child-Pugh score, complete blood counts, platelets, electrolytes, liver function tests, AFP, and hepatitis panels should be assessed. In additional to cross-sectional abdominal imaging, CT of the chest should be performed to evaluate for spread to the lungs. The most important decision point for management of HCC is the assessment for operability, which can be curative, either by orthotopic liver transplantation (OLT) or partial hepatectomy with negative margins. The advantage of OLT is that it also can cure the underlying liver disease, in addition to both radiographically visible and invisible HCC. Because donor livers are a precious resource, strict criteria are used to determine who is eligible. The UNOS (United Network for Organ Sharing)/Milan criteria require a solitary tumor </= 5 cm or up to 3 tumors all </= 3 cm without any macrovascular involvement or extrahepatic disease. In addition, patients who are eligible for resection by partial hepatectomy are not eligible for OLT. One common use of liver-directed therapies is to convert or maintain patients within transplant criteria with so-called bridging therapies. These are aimed at limiting progression without adversely affecting liver function. Bridging therapies can include radiofrequency ablation, microwave ablation, percutaneous ethanol injection, cryoablation, transarterial embolization, TACE, sorafenib, or radiation (discussed in more detail below).

Systemic therapy for HCC has had less of a prominent role in the past as standard cytotoxic chemotherapies have not been particularly beneficial. More recently, sorafenib, a small molecule tyrosine kinase inhibitor, demonstrated an OS benefit over placebo in the SHARP trial [4] and has been used in select

patients. Its use is often limited by the toxicity profile, and alternate biologic therapies are being explored. The FDA did grant approval for the use of the anti-angiogenic kinase inhibitor, regorafenib, in HCC patients who had previous treatment with sorafenib.

4.1.3 Intrahepatic Cholangiocarcinoma (IHCC)

IHCCs are relatively rare with an incidence in the U.S. of ~2500 cases per year. Unique risk factors for IHCC include primary sclerosing cholangitis and history of liver fluke infection. Unlike HCC, IHCC is not as strongly associated with a history of cirrhosis. However, biologically, it has commonality with other cancers of the biliary tree, including gallbladder cancer and extrahepatic cholangiocarcinoma, with significant rates of lethal metastatic disease. Where HCCs infrequently have extra-abdominal distant metastatic disease, cholangiocarciomas frequently spread to regional lymph nodes as well as abdominal and other distant metastatic sites. IHCCs typically present with biliary obstructive signs and symptoms. Work-up includes complete blood counts, serum chemistries, coagulation studies, and liver function tests. The tumor markers that may be helpful in IHCC are CA 19–9 and CEA, although it is common to obtain AFP and hepatitis serologies. Cross-sectional triple-phase imaging with CT and/or MRI can show characteristic enhancement patterns with delayed enhancement (~15 min). Chest CT should be done to evaluate for pulmonary metastases. Cholangiography, either with magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatogram (ERCP), can help define lesions with high resolution. ERCP is typically only done if drainage or decompression is required. Additional endoscopic imaging of the upper and lower GI tracts is recommended. The staging for intrahepatic bile duct tumors is shown in Table 4.4 [5].

The role of biopsy in liver tumors is complicated, as described above for HCC. Biopsies of intrahepatic malignancies should be considered when there are no pathognomonic imaging findings to support a diagnosis of HCC, namely to explore the possibility of IHCC. Cholangiocarcinomas can be stubbornly difficult to diagnose pathologically with fine needle aspirates, core biopsies, and/or ERCP brushings. As the procedures to obtain these biopsies are not without risk, the decision to proceed with cancer treatments in the absence of confirmed pathology should be weighed carefully. As with HCC, margin-negative surgical resection provides the best chance of cure. For potentially resectable patients, a staging laparoscopy may be considered to evaluate for occult abdominal metastases. The resectability of tumors depends on medical fitness as well as location. Involvement of bilateral hepatic ducts, main portal vein involvement, and inadequacy of remaining liver to support required liver function all can render a patient inoperable. The general approach for patients with IHCC is to first determine resectability with a goal of a negative margin. Surgical resection of IHCC often requires removing large proportions of the liver; however, in non-cirrhotic patients, the liver does have the ability to regenerate. This property can be harnessed by using preoperative portal venous

Table 4.4 AJCC 8th edition staging for intrahepatic bile duct tumors by TNM

Primary tumor (T)	
T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intraductal tumor)
T1	Solitary tumor without vascular invasion, ≤ 5 cm or >5 cm
T1a	Solitary tumor ≤5 cm without vascular invasion
T1b	Solitary tumor >5 cm without vascular invasion
T2	Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral
T4	Tumor involving local extrahepatic structures by direct invasion
Regional lymph nodes (N)	
N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present
Distant metastasis (M)	
M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

embolization to the lobe that will be resected. This results in a compensatory hypertrophy of the non-diseased liver. Once this occurs, a partial hepatectomy may be more safely pursued, with an attempt to remove all gross and microscopic disease. This includes adequate margin on the biliary tree itself, given the proclivity of cholangiocarcinomas to spread by periductal infiltration.

Lymph node sampling is usually performed in order to determine if regional spread has occurred. Left-sided IHCCs typically drain to the gastrohepatic nodes followed by the celiac nodes. Right-sided IHCC (and extrahepatic cholangiocarcinomas) drain to the perihilar and periportal nodes, followed by drainage to the portacaval and peri-aortic lymph nodes. For resected patients, the decision for adjuvant therapy is generally guided by pathologic findings.

There are no randomized prospective trials to guide the decision about adjuvant therapy, so most of the useful data are retrospective or population-based. A meta-analysis of adjuvant therapy studies published between 1960 and 2010 suggested that adjuvant therapy had the biggest impact in node-positive and R1 disease [6]. The same meta-analysis found that either chemotherapy or chemoradiation outperformed radiation alone, so like many other GI cancers, chemoradiation is preferred if radiation is to be given at all. A more modern systematic review and meta-analysis of prognostic factors specific to IHCC was performed based on studies published between 2000 and 2013 [7]. With regard to the impact of adjuvant therapy, they found that adjuvant chemoradiation was associated with longer OS in 3/10 studies, but worse OS in 1 study of perioperative chemotherapy alone. This meta-analysis did find that multiple tumors, lymph node metastasis, poor tumor differentiation, and

vascular invasion were strong negative prognostic factors on OS. A National Cancer Database study of 638 resected IHCC patients diagnosed between 1998 and 2006 showed that presence of lymph node metastasis, unexamined nodes, and positive margins were associated with worse OS [8]. Multivariate analysis showed that adjuvant chemotherapy (HR 0.73, $p = 0.038$) or chemoradiation (HR 0.77, $p = 0.038$) was associated with better OS. In the 248 node-negative patients, the impact of adjuvant therapy was not significant, although the hazard ratios still favored chemotherapy (HR 0.57, $p = 0.06$) or chemoradiation (HR 0.79, $p = 0.28$) compared to observation. For node-positive patients, both chemotherapy alone and chemoradiation were highly beneficial compared to observation (HR both close to 0.5). Similarly, chemotherapy and chemoradiation were both significantly associated with improved survival in margin-positive patients, but not in margin-negative patients.

In spite of the lack of prospective, randomized data, the above studies suggest an apparent benefit of adjuvant therapy for node-positive and margin-positive patients. For patients with no nodal metastases and an R0 resection, observation or adjuvant chemotherapy alone is an reasonable option. The other tumor-specific risk factors may tip oncologists in the direction of offering adjuvant chemotherapy, such as vascular invasion, multiple tumors, or poor differentiation. For vascular invasion, node-positive and/or R1 resections, chemotherapy, or chemoradiation should be strongly considered. Given the variability of preoperative location and other patient factors, the decision between chemotherapy alone vs. chemoradiation will depend on anticipated toxicities of proposed radiation volumes and other patient factors. When chemotherapy alone is to be used, the most common modern regimen is gemcitabine and cisplatin, based on superior efficacy over gemcitabine alone in the metastatic setting [9].

If resection is not possible, then the location and number of lesions will determine therapy. If there is diffuse disease that lies within the distribution of a safely targetable hepatic arterial branch, TACE is a common first approach if the bilirubin is below 3 g/dL. There are limited data on radioembolization in IHCC, which are summarized in the section "Radioembolization" below. For unresectable localized disease, ablative therapies or radiation therapy with or without concurrent chemotherapy can be employed. In the setting of more diffuse disease or metastatic disease, patients may be treated with systemic chemotherapy (e.g., gemcitabine/cisplatin or gemcitabine/capecitabine) or best supportive care.

4.2 Liver-Directed Therapies

When disease is entirely or predominantly limited to the liver, liver-directed therapies may be more appropriate than systemic therapies. This decision may be due to the potential toxicity of available systemic therapies and greater response rates of liver-directed therapies over systemic therapy. There are numerous approaches to focus therapy on tumors in the liver, which are employed in both primary liver tumors like HCC and IHCC and metastatic disease to the liver. Techniques are generally similar when treating primary or metastatic lesions, even if the intents of the treatments are

different. One intriguing question for ablative liver-directed therapies is whether they can exact a cure without surgery. The most common liver-directed treatments are outlined below and can be used as alternatives or in concert with liver-directed radiation.

Radiofrequency ablation (RFA) is a semi-invasive technique where a needle electrode is inserted into a tumor, either percutaneously or intraoperatively. High frequency alternating current is used to heat the surrounding tissue and induce necrosis in the tumor. RFA is most commonly used for smaller lesions (≤3 cm) where local failure rates are ~10% [10]. For larger tumors, the local failure rate is higher, which is thought to be due to technical limitations in the ablative radius. In addition to size, other selection criteria are related to tumor location. Tumors near major vessels are challenging to treat due to the heat sink effect of circulating blood, thus making the therapy less effective. Lesions near bile ducts can increase the risk for complications like biloma or bile leaks. Percutaneous RFA is technically challenging for lesions in the dome, although these may be approached intraoperatively. Alternative ablative techniques such as microwave ablation or cryoablation may overcome some of the limitations of traditional RFA.

Arterially directed therapies are a mainstay of liver-directed therapies and require cannulization of the hepatic artery. As described above, the liver is an unusual organ due to its dual blood supply. The primary blood supply to the normal liver is through the portal vein and its tributaries. In contrast, the hepatic arterial system delivers a small minority of the blood to the normal liver, in addition to supplying the biliary tree. Hepatic malignancies are predominantly supplied by the hepatic arterial system, due to the neovascularization required to support growth. Arterially directed therapies can target large lesions as well as multifocal lesions supplied by the same hepatic artery branch. Embolization through the hepatic arteries can be in the form of bland transarterial embolization (TAE), transarterial chemobolization (TACE), or by radioembolization (described below). The mechanisms of TAE and TACE are to reduce blood flow to the tumor, resulting in ischemia and necrosis. Compared to conservative treatment, TACE has been shown to improve overall survival (OS) in carefully selected Child-Pugh A/B HCC patients [11]. The main exclusions for TACE are elevated bilirubin (>3 mg/dL), main portal vein thrombosis, and Child-Pugh C. Although a number of embolic agents have been used, including gelatin sponges, polyvinyl alcohol particles, and microsphere, the oil-based contrast agent, ethiodized oil (Lipiodol®), has been used widely as an embolic agent and chemotherapy carrier since the early 1980s [12]. When TACE is used with ethiodized oil, the embolized regions are radiographically dense; this density may be used as fiducial marking for image-guided radiotherapy that may follow TACE (described below in further detail).

In sum, there are multiple interventions that can be performed on patients with liver cancers by a host of specialists. Some of these specialists will have had extensive oncologic training, but some will have had more of an emphasis on technical training. Ablative therapies can be performed by interventional radiologists and surgeons. Many patients will have sequential liver-directed therapies for the same or nearby tumors. For radiation oncologists, it is important to understand these various procedures in order to interpret images, optimize radiation treatment strategies, and to manage these complicated cancer patients in the multidisciplinary realm.

4.2.1 Radioembolization

As in chemoembolization, the hepatic arterial system may be harnessed in order to deliver radiation to liver tumors. This procedure may be performed using Yttrium-90-labeled microspheres and is referred to as radioembolization. Unlike in chemoembolization, the much smaller radioactive microspheres produce a more limited ischemic effect. Yttrium-90 is a beta emitter with maximum decay energy of 2.28 MeV and half-life of 64.1 h. Two commercial formulations are available, one that uses glass spheres and one that uses resin spheres. Although the two formulations are similar in size, the glass spheres are labeled with approximately 50 times the activity per sphere, meaning that there is the possibility of delivering substantially more activity to the liver before completely embolizing the vessel being used for delivery. In addition, the methods of prescription are different for each type of spheres. In general, these prescriptions depend heavily on the total volume of liver being treated and are impacted less by the volume of tumor to be treated. Unlike other radiation treatments, there is no ability to target the dose to a tumor, as this dose is being delivered intravascularly by the interventional radiologist. The treatment may be delivered in a lobar or segmental fashion, depending on the distribution of the tumor. A lobar treatment may be repeated sequentially (usually after an interval of at least 4 weeks) in order to treat the entire liver.

Although radiation oncologists are not involved in radioembolization treatments at all centers, the comprehensive oncologic training that a radiation oncologist possesses may be beneficial in selecting the appropriate treatment strategy for a patient with a hepatic malignancy and ensuring that the appropriate activity of microspheres is being delivered. In particular, patients must have vascular anatomy that prevents off-target treatment; therefore, a staging or mapping angiogram must be performed prior to treatment. The gastroduodenal artery may be embolized as part of this procedure. At the completion of the angiogram, a small dose (2–4 mCi) of Tc99m macroaggregated albumin is injected and SPECT imaging is performed in order to determine the shunt to the lungs due to arteriovenous malformations. Patients with elevated shunt percentages may require dose adjustments, and shunt fractions that are too high (typically over 20%) are not suitable for treatment with radioembolization. Additionally, this study can ensure that there is no expectation of off-target treatment by examining upper gastrointestinal structures for unexpected activity. Other important selection criteria include preserved liver function, with a bilirubin under 2.0 mg/dL. In particular, as there may be several weeks between the decision to treat and actual treatment, it may be useful to recheck liver function immediately prior to treatment. Additionally, patients with main portal venous thrombosis and prior radiotherapy to the liver should be approached cautiously. While there are limited randomized prospective data to guide us in treating HCC or intrahepatic cholangiocarcinoma patients with radioembolization, there are numerous small prospective and retrospective reports that demonstrate its efficacy and describe its toxicity.

The activity of Yttrium-90 must be prescribed prior to the procedure. Several different prescription methodologies exist for the two formulations and have developed empirically over time. This prescription will be somewhat foreign to a radiation

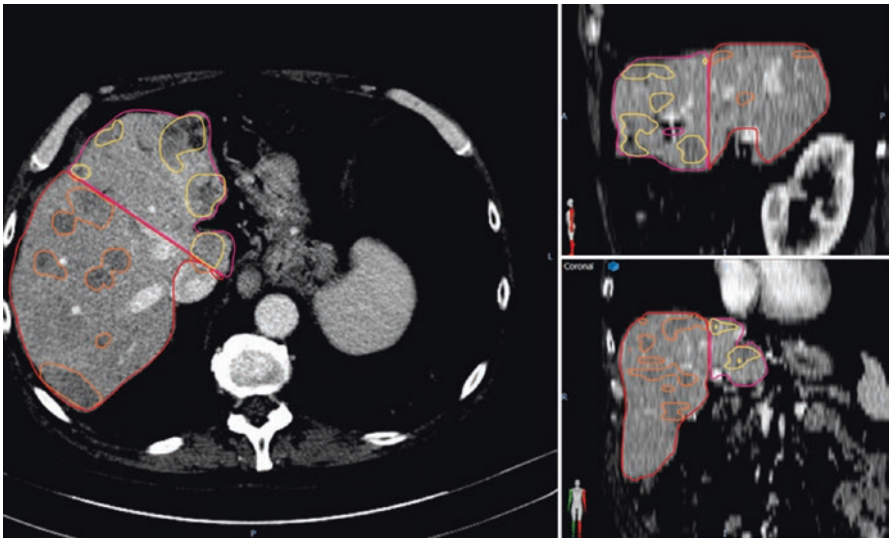

Fig. 4.1 Radioembolization planning. Contours of the left and right lobes of the liver as well as tumor in each lobe are shown. The left and right lobes are divided anatomically by the middle hepatic vein

oncologist who expects to know exactly where a dose will be delivered in three dimensions. The prescription takes into account variables such as body surface area, liver volume, vascular treatment volume, tumor volume, lung shunt percentage, and anticipated waste in tubing. The specifics of the calculations may be found in this review by Kennedy and colleagues [13]. In order to prescribe dose, the normal liver and tumor are typically contoured, as shown in Fig. 4.1. Occasionally, decisions about prescription are more complicated, such as after prior radiotherapy, significant hepatic resection, or other liver-directed therapy. This is where a radiation oncologist's familiarity with dose-volume relationships may allow thoughtful integration of multiple modalities of treatment.

A small randomized study of radioembolization (resin microspheres) versus chemoembolization was performed at multiple European centers [14]. Twenty-eight patients with BCLC A-C HCC were randomized to a single radioembolization procedure (N = 13) or a median of two TACE procedures (N = 15). Both treatments were well-tolerated, with 23% of patients experiencing treatment-related adverse events in the radioembolization arm and 33% in the TACE arm. There were no significant differences in adverse events or serious adverse events. Rates of partial response in target lesions (using RECIST 1.0 criteria) were 13% for chemoembolization and 31% for radioembolization. The median progression-free survival was under 4 months for both arms, and 1-year OS was 46 and 67% for the radioembolization and chemoembolization arms, respectively.

A prospective study of radioembolization (resin microspheres) was performed in Korea of 42 patients who were ineligible for curative therapies, had ECOG performance status of 0–1, and were Child-Pugh class A or B [15]. Patients were excluded

with serum albumin <3.0 g/dL, total bilirubin >2.0 mg/dL, extrahepatic disease, or main portal vein thrombosis. Ninety percent of patients were Child-Pugh class A and 95% were ECOG performance status 0, with the vast majority BCLC stage A or B. Except for abdominal pain, which was mostly grade 1, adverse events were uncommon. The response rate at 3 months was 58%. Three-year OS was 75%, and median time to progression (TTP) was 18 months.

A phase II prospective study was performed by a group in Milan, Italy, treating 52 patients with intermediate or advanced HCC with radioembolization (glass microspheres) [16]. All patients were ECOG performance status 0–1 and Child-Pugh class A-B7. The most common toxicities reported included anorexia (15%), ascites (10%) and elevated bilirubin (27%), elevated alkaline phosphatase (19%), and decreased lymphocyte count (15%). The authors did not report attribution, and it is difficult to know which of these signs and symptoms were resultant from the treatment. The median TTP was 11 months, and median OS was 15 months. There were non-significant differences in TTP and OS in favor of patients without portal vein thrombosis. The objective response rate was 40%, and 10% had a complete response. On multivariable analysis, tumor response was the only variable that effected TTP; Child-Pugh class and tumor response impacted OS.

A prospective study of radioembolization (glass microspheres) for patients with portal vein thrombosis was conducted on 30 patients [17]. Four patients (13%) developed grade 2–4 toxicity. Median OS was 13 months, and time to progression (TTP) was 9 months in this poor prognosis group. Multivariate analysis demonstrated an ECOG performance status of 0, Child-Pugh class A, and a lung shunt fraction under 10% predicted for increased OS and TTP.

Twenty patients with Child-Pugh score up to B8 and, without extrahepatic disease, vascular invasion, performance status over 2 or contraindications to sorafenib use were enrolled in a small prospective study, randomized to either radioembolization (glass microspheres) or radioembolization + sorafenib, with a goal of successfully bridging patients to liver transplantation [18]. Seventeen out of 20 patients underwent transplantation at a median time of 7.8 months. There was no difference in survival in the two arms, but there were increased peri-transplant biliary complications and a trend toward increased acute rejections in the sorafenib arm. Authors suggested caution in using this targeted therapy along with radioembolization in the setting of planned transplantation.

A large retrospective study was published by Salem and colleagues that analyzed 291 patients who underwent 526 treatments [19]. The authors highlight the importance of Child-Pugh score and the presence or absence of portal vein thrombosis in predicting TTP and OS. Median TTP for patients without portal vein thrombosis was 15.5 months for Child-Pugh A patients and 13.0 months for Child-Pugh B patients. Portal vein thrombosis decreased these times to 5.6 and 5.9 months, respectively. Twelve percent of patients underwent curative surgery, impacting OS times. However, OS was largely determined by Child-Pugh class and portal vein thrombosis. Child-Pugh A patients without portal vein thrombosis had a median OS of 22.1 months versus 10.4 months with portal vein thrombosis. Child-Pugh B patients without thrombosis had a median OS of 14.8 months, compared to 5.6 months with

portal vein thrombosis. The authors note that the value of radioembolization is questionable in Child-Pugh B patients with additional poor prognostic factors such as portal vein thrombosis or metastatic disease due to the competing risk of death.

A modest number of small prospective and retrospective studies have been performed utilizing radioembolization for IHCC. Eleven studies were systematically reviewed by Al-Adra and colleagues, including five retrospective and six prospective studies [20]. Response rates at three months ranged from 24 to 100% and median OS ranged from seven to 22 months. Commonly reported toxicities included fatigue, abdominal pain, and nausea, as well as elevation of bilirubin, AST, and Alkaline Phosphatase.

Radioembolization is a specialized technique that requires expertise from interventional radiologists, hepatologists, and ideally radiation oncologists. Given the numerous factors that impact the decision to deliver radioembolization, a specialized multidisciplinary tumor board team should help decide who should receive this therapy. While no level I data exist supporting the treatment of HCC with radioembolization, the available evidence suggests that this modality is well-tolerated, with outcomes comparable to TAE/TACE.

4.2.2 External Beam Radiation for HCC and IHCC

Common indications for external beam radiation include liver tumors where local control is desired as an alternative to liver-directed therapy either after failure or in planned combination, and in transplant candidates bridging to transplant. In general, radiation is limited to patients with Child-Pugh A and some favorable B, but extreme caution should be used in B9 and C patients. From our institutional experience, the use of external beam radiation for primary liver tumors has been on the rise (Fig. 4.2). Most have attributed this to rapidly developing technologies that have been able to deliver high-doses to tumor safely without causing major liver damage, but may also reflect the increasing incidence of HCC. In fact, the use of palliative RT in the management of HCC has been shown to be associated with improved OS in a National Cancer Database study [21]. Despite the improvement in technology, there are likely still medical communities that rarely refer primary liver cancer patients for radiation due to perceptions that HCCs are radioresistant or that the liver is extremely sensitive to radiation, usually from older studies of whole-liver tolerance. One example is Korea, where only 3.7% of HCC patients received RT (alone or combined with other therapies) for initial therapy in 2012 [22]. In fact, use of RT actually declined from 2009 to 2012 in these patterns of care study.

One of the most important myths about liver radiation is that the liver is extremely sensitive to radiation side effects. Radiation-induced liver disease (RILD) is a veno-occlusive phenomenon characterized by a subacute (2–16 weeks post-RT) development of anicteric ascites, hepatomegaly, and fatigue. Laboratory studies typically reveal alkaline phosphatase elevations (three to tenfold increases) that are well out of proportion to the transaminase increase (less than twofold increase). Bilirubin and lactate dehydrogenase are minimally elevated if at all. A dose escalation study (RTOG

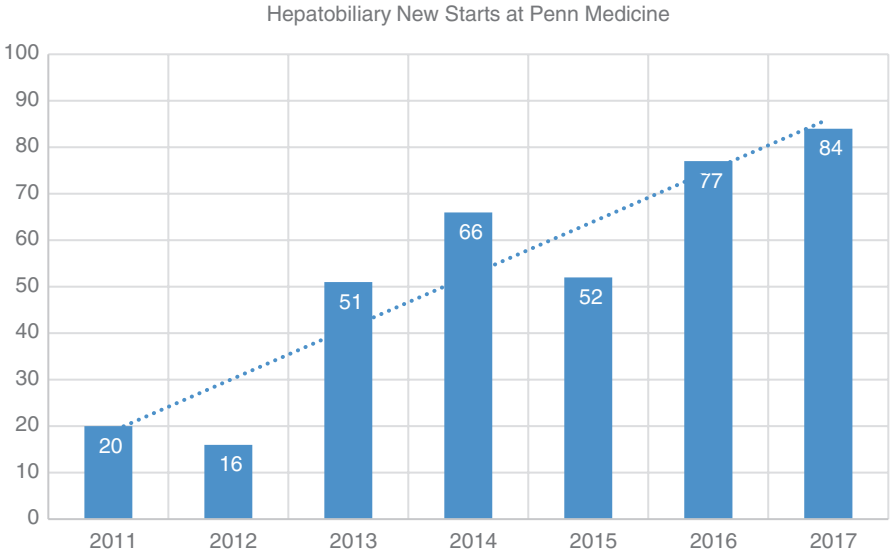

Fig. 4.2 Trend in the use of radiation for liver tumors at a single academic center. New starts in the Department of Radiation Oncology by fiscal year (July–June) at Penn Medicine for "hepatobiliary" diagnoses. Note that 2017 is estimated based on Q1–3 trend. Trend line is a linear fit. Courtesy Dr. James Metz

8405) testing whole liver, twice-daily RT for metastases showed that no patients treated with 27 Gy (n = 53) or 30 Gy (n = 69) developed RILD; however, 5 of 51 patients treated with 33 Gy developed RILD [23]. In a series of prospective studies conducted at the University of Michigan, the partial volume tolerance of the liver to escalated doses was tested. It was discovered that the partial liver tolerance (up to 90 Gy) well exceeded the total liver tolerance (~30 Gy). A normal tissue complication probability (NTCP) model was derived from their accumulated experience [24]. No cases of RILD were observed if the *mean* liver dose was under 31 Gy (Fig. 4.3). This model was used to deliver individualized radiation doses in a prospective trial of 128 patients with intrahepatic malignancies (35 with HCC) [25]. The radiation dose was prescribed based on the NTCP model (allowing risk of 10–15% RILD) with doses ranging from 40 to 90 Gy, delivered with concurrent hepatic arterial fluorodeoxyuridine. They found that RT dose was the most important predictor of OS, with doses over 75 Gy resulting in median OS of 23.9 months vs. 14.9 months for lower doses. Of note, the rate of Grade 3 or higher RILD was 6.4%, demonstrating that intensifying RT doses could potentially improve tumor control without causing high rates of RILD.

It is not likely that all parts of the liver and biliary system are equally sensitive to radiation, and attempts have been to make the models more sophisticated. In addition to accounting for liver tissue that may have been compromised by other liver-directed therapies, it has been hypothesized that the "central zone" may be uniquely sensitive. The central zone has been defined as an isotropic 1.5 cm expansion of the portal vein, as it extends from the splenic confluence to the first bifurcation of the

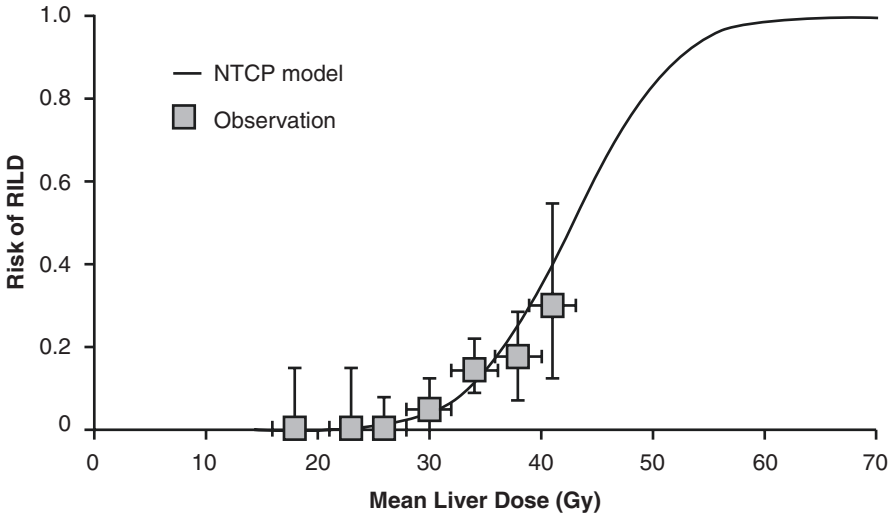

Fig. 4.3 Partial volume liver tolerance to radiation-induced liver disease (RILD) with fractionated radiation therapy. Normal tissue complication probability (NTCP) model fit to clinical data from University of Michigan experience. Reproduced with permission from Dawson et al. [9]

left and right portal vein, including any biliary stents if present [26]. Delivering high doses to central zone when treating primary liver tumors may increase the risk of hepatobiliary toxicity. In particular, it is recommended to keep $V_{BED10}40 < 37$ cc and $V_{BED10}30 < 45$ cc during liver stereotactic body radiotherapy (SBRT) [27]. The authors proposed nomogram tool is available on a website [28]; however, this nomogram has yet to be independently validated. It remains to be seen if prospective trials will use these dose constraints moving forward, but most of the published studies have used the simplified NTCP models.

The use of an isotoxic dose prescription has been used for a fractionated proton therapy dose intensification trial where the prescribed dose was varied based on NTCP models [29]. This multi-institutional trial enrolled 83 patients (44 HCC, 37 IHCC, 2 mixed) with unresectable disease and Child-Pugh A or B liver function. The goal was to deliver 67.5 Gy in 15 fractions for peripheral tumors (>2 cm from porta hepatis) or 58.05 Gy in 15 fractions for central tumors (within 2 cm of porta hepatis). Dose de-escalation occurred based on NTCP models, and the median delivered dose was 58 Gy. Although the median tumor size was fairly large (5 cm for HCC and 6 cm for IHCC), 2-year local control was 94.8% for HCC and 94.1% for IHCC. The mean liver-GTV dose ranged from 3.2 to 29.5 GyE (mean 19.2 GyE), and one patient developed liver failure and ascites. Together, these studies suggest that modern imaging and radiotherapy techniques can be used to deliver the high doses needed to control primary liver cancers with acceptable toxicity as long as sufficient functioning liver is spared. Ultimately, the myth that HCC and IHCC are radioresistant has been debunked, but it is still an ongoing challenge to educate all members of the multidisciplinary team.

4.2.3 Stereotactic Body Radiotherapy (SBRT)

Advances in imaging, immobilization, and beam delivery have allowed radiation oncologists to target liver tumors with stereotactic body radiotherapy (SBRT), frequently called stereotactic ablative radiotherapy (SABR). A number of studies have been published showing excellent local control and toxicities with SBRT. A report of prospective trials escalating doses (with dose and fraction number adjusted by target volume) showed that the SBRT dose over 42 Gy in three fractions was an independent predictor of OS on multivariate analysis [30]. This study reported on mostly smaller tumors (ITV < 50 cc), where the doses were escalated from 39 to 57 Gy in three fractions. A systematic review of HCC treated with radiation therapy, including SBRT, demonstrated that SBRT is associated with improved local control over conventional photon radiotherapy [31]. The relevant partial volume liver tolerance using SBRT-style fractionation has been explored [32]. These authors found that 33% developed Grade 2 or higher hepatic toxicity and 11% had worsened Child-Pugh class, which they argue is an important endpoint as it may limit further therapy. Their analysis showed that the volume of liver receiving under 18 Gy was associated with progression of Child-Pugh class. They recommended a limit of at least 800 cc receiving under 18 Gy. Other groups, including the authors, have used a limit of 700 cc receiving under 15 Gy [30]. Similar to the isotoxic dose intensification protocol using fractionated radiation performed at University of Michigan [25], Dawson and colleagues performed a 6-fraction SBRT trial using a "Veff" model that de-escalated radiation dose based on the effective volume of normal liver irradiated [33]. This lead to a Phase II trial using a Veff strategy with dose assignments shown in Table 4.5.

The combined outcomes of 102 Child-Pugh A HCC patients treated with this approach were updated and showed excellent local control (87% at 1 year) with an observed dose response [34]. There were seven deaths possibly related to treatment and 29% at 3 months had progression of their Child-Pugh class, although it should be noted that the median size of the largest lesions was 7.2 cm, ranging from 1.4 to 23.1 cm. The concepts have been adopted for the SBRT specifications in the ongoing NRG Oncology RTOG 1112 trial testing sorafenib alone vs. SBRT + sorafenib, but adapted for routine use in the U.S. where SBRT billing codes only allow for five (or fewer) fractions. The 5-fraction dose allocation strategy used mean liver dose (MLD) as well as an optional liver Veff parameter (Table 4.6).

Table 4.5 Veff dose allocation strategy for phase II trial of 6-fraction SBRT in HCC [5]

Liver Veff (%) (Gy)	Dose per fraction/total dose
</=25	9/54
>25–30	7.5/45
>30–40	6.5/39
>40–50	5.5/33
>50–60	5/30
>60	Not suitable

Table 4.6 Dose allocation strategy for 5-fraction SBRT on RTOG 1112

Liver Veff (%), optional	Allowed mean liver dose (Gy)	Planned prescription dose per fraction/total dose(Gy)
<25	13	10/50
25–29	15	9/45
30–34	15	8/40
35–44	15.5	7/35
45–54	16	6/30
44–64	17	5.527.5

4.2.4 Proton Therapy

Primary liver cancer has become one of the predominant GI indications for proton beam therapy (PBT), as evidenced by the recommendations in the ASTRO Model Policy on Proton Beam Therapy. Primary hepatocellular cancer treated with hypofractionation is considered a Group 1 recommendation, meaning PBT is medically necessary based on published clinical data. The use of PBT in liver tumors has been thoroughly reviewed [35]. The decision to use PBT versus photon radiation can be aided by a clinical decision tool that modeled various tumor sizes and locations within the liver [36]. PBT most notably outperformed photons in dome and central tumors that were >3 cm. In general, PBT was able to deliver lower MLD in tumors >5 cm, suggesting a role for PBT where the MLD threshold may limit the prescription dose. In reality, the use of PBT is dependent more on availability and insurance coverage than clinical decision tools. As mentioned above, the use of external beam radiation has been historically marginalized due to toxicity concerns and the dominance of other liver-directed therapies. PBT may be an appealing alternative to liver-directed therapies if minimal normal liver is radiated, thus leaving room for other therapies. An interesting randomized study at Loma Linda randomized HCC patients between PBT and TACE as a bridge to OLT [37]. At the interim analysis, they found that PBT trended toward increased pathologic complete responses and fewer hospital days. If both PBT and photons are available, the importance of volumetric image guidance (e.g., CBCT) can direct the decision. If the advantage of accurate IGRT with volumetric imaging outweighs the dosimetric benefits of PBT, then photons may be more advantageous, such as when SBRT is indicated. At Penn Medicine, PBT is reserved for fractionated radiotherapy (at the time of this writing), and SBRT is done exclusively with photons due to limited on-board imaging in the proton treatment rooms. As newer proton therapy clinics are built, on-board imaging will likely be more common and extreme hypofractionation with PBT may become more common.

4.2.5 Practical Decisions When Using SBRT and Fractionated Radiation

In practice, when the risk of liver injury appears to be higher than acceptable with SBRT, strategies to lower the risk include use of more fractionated radiation, lowering the total dose and introducing a treatment break. Alternate fractionation

regimens, which are often used to decrease the dose per fraction to bowel or stomach, require use of different partial volume liver tolerances as described in the QUANTEC paper devoted to the liver [38]. For therapeutic partial liver RT attempting to keep RILD risk <5%, the authors recommend a mean liver minus GTV dose (MLD) of <28 Gy for primary liver cancer and <32 Gy for liver metastases when 2 Gy fractions are used. In our practice, we use the Child-Pugh score to generate a sliding scale for the constraint on liver-GTV, keeping the MLD < 28 Gy for A, <27 Gy for B7–8, and <24 for B9. Other factors that may influence the "acceptable" MLD are the total liver volume—GTV and other prior decrements in liver function after a prior liver-directed therapy. Depending on the intent of therapy, the goal should be to achieve a minimum BED intensity (~100) while avoiding overly prolonged courses. When SBRT is not tenable, we typically start with the 15 fraction/67.5 Gy regimen used by Hong et al. [29] and work down to a 22 fractions/55 Gy. A less intense regimen should be considered palliative, which may affect the overall management of the patient. If patients have significant cirrhosis, we have used split course radiation with 2/3 of the dose delivered, followed by a 1 month break before delivering the remaining 1/3 of the course. The use of a planned split course may run counter to teaching on package time described in other cancer sites, but the opportunity to see if a patient "teetering" on the edge of progressive liver disease may allow judicious use of what is usually palliative radiotherapy. Bringing a patient back after a planned break with repeat of laboratory studies and an evaluation scan on the CT simulator to assess for ascites or the need to replan can help select patients who are either obviously progressing or would not tolerate the full dose. In the Penn 5-fraction SBRT for HCC series, 35% of the 43 SBRT courses were delivered with a planned 1 month break after three fractions without any obvious decrement in local control (the one local failure was in non-split course) (Baumann BC et al. manuscript submitted ASTRO 2017 reference needed or personal communication). Ultimately, the final decision to radiate a patient should be made after treatment planning, and radiation oncologists should be prepared to abort radiation plans if the risk-benefit ratio is not favorable.

4.3 Treatment Planning

4.3.1 Patient Setup and Immobilization

Fiducial placement is placed by interventional radiology prior to simulation with 2–3 markers. This is important for measuring motion by 4DCT, but is critical for systems that use them for motion tracking. Some patients may not require new fiducial markers to be placed if they have radiopaque Lipiodol or surgical clips already present in the liver adjacent to the target. Depending on the location of the target and patients' body habitus, liver contour edge may be used if there are reproducible structures nearby, depending on the breathing system being used.

Patients should first be assessed for their ability to tolerate motion-management devices, such as breath-hold (where available) and compression devices. Patients

with compromised liver function often struggle with breath-hold techniques, so this may be assessed prior to CT simulation in a fluoroscopic simulator if available. In addition to breath-hold device, compression devices should be assessed for patient tolerance and the impact on target motion. The right hemi-diaphragm is often a good surrogate for the liver. In order to minimize overly large ITVs, some form of motion management should be employed. Patients are positioned supine with an immobilization device such as Vac-Lok™ (Civco Radiotherapy, Orange City, Iowa) or Alpha Cradle (Smithers Medical Products Inc., North Canton, OH) with arms up. For SBRT, a full length body bag is used.

4.3.2 Simulation

The planning CT should encompass the entire abdominal cavity with a uniform 3 mm slice thickness. Four-dimensional CT (4DCT) is required to define the ITV and should be imaged with any abdominal compression device in place. Oral and IV contrast is recommended for visualization of primary liver tumors. Images may be acquired in multiple phases of contrast, namely arterial phase (~25 s) and venous phase (55–70 s), to enhance the ability to accurately define tumor. When breath-hold is planned, these scans are timed with the breath-hold position if possible. In practice, timing breath-hold and contrast is difficult to achieve, so the breath-hold planning CT is fused to non-breath-hold scans with contrast, focusing on the liver.

Ideally, a contrast-enhanced MRI is done in the treatment planning position; however, this requires MR compatibility of immobilization devices such as abdominal compression devices. Otherwise, separately obtained diagnostic abdominal MRI is fused to the planning CT. Fusions of MRI with planning CTs should focus on liver anatomy (liver-to-liver fusion).

4.3.3 Motion Evaluation

As described above, breath-hold is ideal for radiotherapy for liver tumors. End-expiration breath-hold devices are preferred as the position is more stable. Deep-inspiration breath-hold devices are an alternative, but there is no particular advantage anatomically for liver radiation. In fact, if patients do have ascites, the deep breath-hold position may be less comfortable.

4DCT scans should be evaluated for motion, whether or not compression devices are used. Because liver tumors are typically difficult to visualize on non-contrast 4D CT scans, definition of the tumor on individual phases of the scan is quite challenging. General motion patterns can be evaluated based on structures that can be visualized close to the tumor as a motion surrogate, such as a fiducial marker. Non-uniform expansions to account for motion may be used to expand CTV to ITV if the target cannot be easily seen on individual phases of the 4D scan.

4.3.4 Motion Management for Optimized Treatment Delivery

Motion management is dependent on whether breath-hold can be performed. Image guidance in liver treatment differs from many other disease sites since the liver is not tethered to bones or other structures visible on matching planar kilovoltage (kV) imaging. In addition, the liver can rotate and change position and shape depending on bowel/stomach filling. Therefore, direct image guidance is required if PTV expansions are to be small. If fiducials are used, gating can be implemented. On-board volumetric imaging is optimal for fractionated external beam radiation and is required for SBRT.

4.3.5 Dosimetric Treatment Planning

4.3.5.1 Target Volumes

For breath-hold simulation, the GTV should be contoured on the breath-hold scan using all available contrast phases of the CT and fused MRI. If using 4D free breathing (or abdominally compressed) scan, the GTV should be contoured on all phases of the breathing cycle to create an internal GTV. In the case of HCC with tumor thrombus, the GTV should include both parenchymal and vascular tumor.

Non-tumor thrombi are not included as GTV. Expansion from GTV to CTV is a point of some controversy in liver tumors. Based on pathologic data, it has been suggested that HCC may extend microscopically as far as 5 mm from a radiographically evident primary. Thus, 5 mm GTV to CTV expansions are used by some. However, some do not expand 5 mm, as is the case for RTOG 1112, which only allows for CTV expansion into sites that may be at high risk for microscopic disease like RFA ablation or TACE sites. This expansion may need to be larger for IHCC depending on the radiographic appearance of the primary. Some use a CTV expansion for fractionated RT, but no expansion for SBRT due to the high dose per fraction used in SBRT. Metastases do not require an expansion from GTV to CTV/ITV. Definition of GTV can be challenging when ideal imaging is not available, and even then there can be disagreement by experts [39]. A study of several expert radiation oncologists, some aided by abdominal radiologists, demonstrated that contouring concordance decreased as the cases became more complicated and contrast-enhanced imaging was less than ideal. Variability was greatest between contouring radiation oncologists when liver thrombus needs treatment. PTV expansion is dependent on motion management, setup, and image guidance. Typically, a 4–7 mm expansion is used and can be asymmetric if appropriate.

Organs at risk should be contoured as shown in the contouring atlas (Fig. 4.4). The central zone is a 1.5 cm expansion of the portal vein (from the splenic confluence to the first bifurcation) [26].

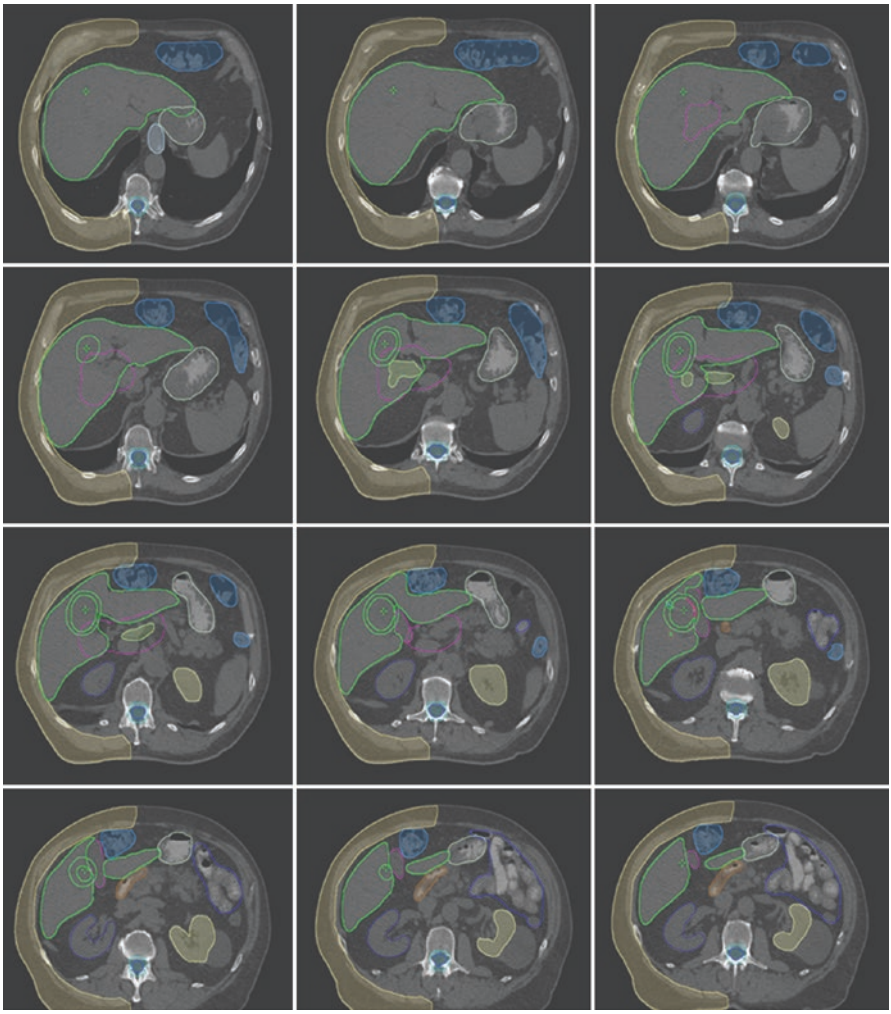

Fig. 4.4 Contouring atlas for liver SBRT. Liver-GTV and PTV are green. Two fiducials are contoured (*green* and *blue*) with a 3 mm expansion to be used as an on-board imaging guide. Portal vein (*yellow*) is expanded 1.5 cm to create the central biliary tract or central zone (*pink*). Other OARs contoured are chest wall (*yellow*), kidneys (*blue* and *yellow*), stomach (*light green*), duodenum (*brown*), small bowel (*dark blue*), large bowel (*light blue*), spinal cord (*dark blue*), 5 mm expansion of the spinal cord (*light blue*), and gallbladder (*pink*)

4.3.6 Treatment Modalities

As discussed above, the choice of treatment modality depends on several parameters, including tumor size and location as well as uninvolved liver size and function.

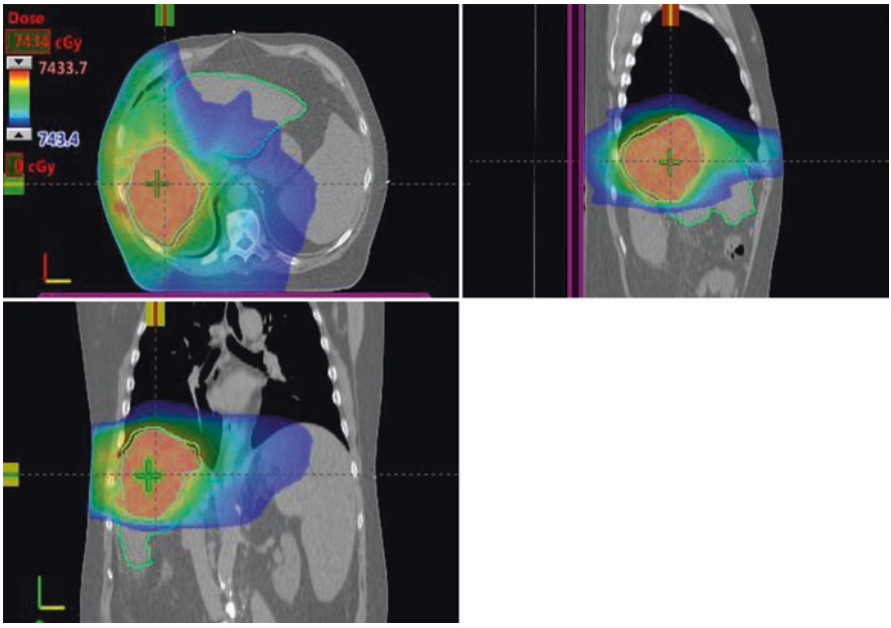

Fig. 4.5 Representative fractionated VMAT treatment plan for a large HCC. This is a patient Child-Pugh A5 with a 10 × 8 cm mass refractory to TACE treated with 15 fractions to a total dose of 67.5 Gy. Liver is *green*, PTV is *light blue*. MLD (Liver-GTV) was 23 Gy

4.3.6.1 IMRT/VMAT

The choice of beam angles and/or arcs is critical for photon-based planning. When using VMAT, multiple partial arcs, including non-coplanar arcs, may be useful for covering the target while maintaining OAR constraints. A representative VMAT treatment plan is provided in Fig. 4.5 for a patient with a 10 cm mass refractory to TACE treated with 15 fractions to a total dose of 67.5 Gy. The decision between extreme hypofractionation (SBRT) and more fractionated treatments depends on the ability to meet dose constraints. In our experience, SBRT is more suited for small tumors (5 cm or less); however, larger tumors can certainly be treated with SBRT depending on tumor location. In fact, the Phase I/II trial of SBRT treated many large tumors with the median tumor size over 7 cm [34].

Larger tumors can be treated with SBRT, but fractionated RT may be safer. At Penn Medicine, we generally use SBRT only on tumors that are 5 cm or smaller; however, many institutions routinely treat larger tumors. A representative SBRT with linear accelerator-based VMAT for a small HCC is provided in Fig. 4.6.

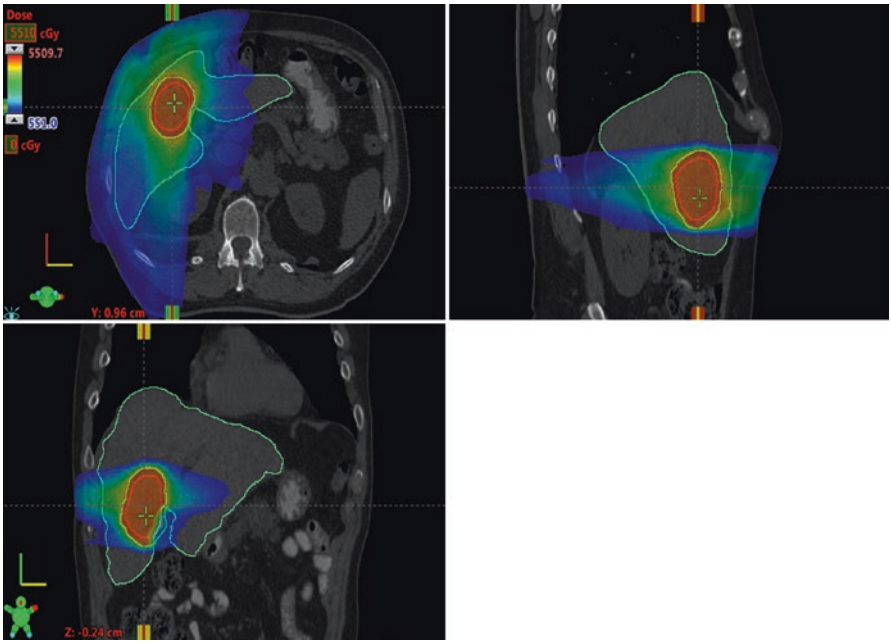

Fig. 4.6 Representative SBRT with linear accelerator-based VMAT for a small HCC. This is a medically inoperable patient, Child-Pugh A5 with a 1.4 cm mass treated with five fractions to a total dose of 50 Gy. Liver is *green*, GTV is *red*, PTV is *green*. MLD (Liver-GTV) was 8.9 Gy

4.3.6.2 Proton Beam Therapy

As discussed above, PBT can be used to maintain dose intensity while keeping MLD low, even for very large tumors. Figure 4.7 provides a representative PBT treatment plan using pencil beam scanning (PBS) and abdominal compression motion management for a large segment VI IHCC. Due to proximity of the stomach and bowel, the medial aspect of the ITV is undercovered, but still gets a high dose. The prescription dose is 70 Gy in 3.5 Gy fractions and the MLD (liver-GTV) is 28.9 Gy, which was accepted as this patient did not have impaired liver function.

As previously described, there are a number of radiation treatment delivery methods that can be considered for the treatment of primary liver tumors. Table 4.7 describes the various radiation options and indications.

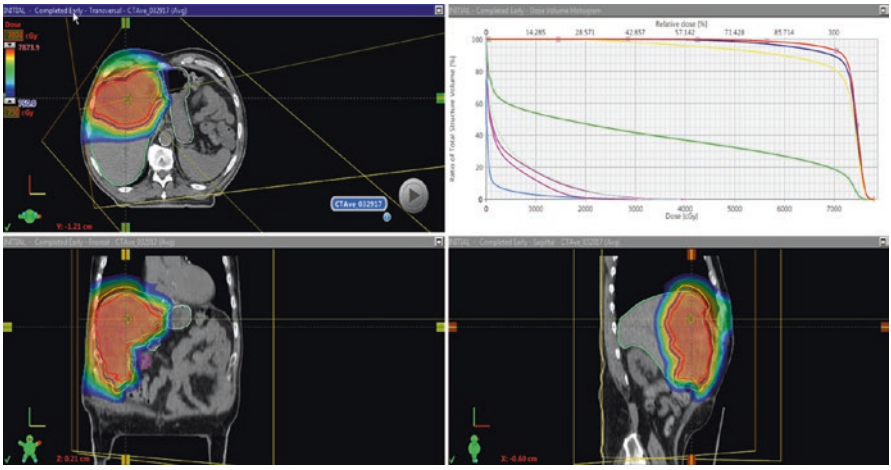

Fig. 4.7 Representative PBT treatment plan for a large IHCC. Two PBS beams (RAO and RPO) are used to treat this large segment VI mass. GTV (*red*), ITV (*dark blue*), and pencil beam scanning PTV (*yellow*) are the targets, which are undercovered due to the presence of the stomach adjacent to the target. Liver-GTV (*green*) is shown on the DVH and the MLD is 28.9 Gy. Duodenum and duodenum-PTV are in *pink*. Large bowel is *light blue*.

Table 4.7 Radiation treatment approaches for primary liver tumors

Technique	Indication	Fractionation schedules	Beam arrangement	Appropriate chemotherapy
3D CRT	Palliation (HCC/IHCC)	30 Gy; 3 Gy per fraction; 5 days per week. Alternate palliation fractionations as appropriate	3 or 4 fields	
IMRT VMAT	Liver-directed therapy for HCC/IHCC	67.5 Gy; 4.5 Gy per fraction, 5 days per week. Decrease dose per fraction to meet constraints as below	IMRT: multiple coplanar isocentric beams VMAT: volumetrically modulated coplanar partial arcs	Sorafenib, regorafenib (not concurrent)
	Liver-directed therapy for HCC with compromised liver function	Consider 70 Gy; 3.5 Gy per fraction. 55 Gy; 2.5 Gy per fraction. 45 Gy; 3 Gy per fraction. 50 Gy; 2 Gy per fraction. Consider planned break	As above, consider non-coplanar beams/arcs in order to keep MLD within tolerance	

(continued)

Table 4.7 (continued)

Technique	Indication	Fractionation schedules	Beam arrangement	Appropriate chemotherapy
Proton therapy	Large HCC/IHCC, central or dome tumors where MLD is difficult to achieve with intensified prescription dose	67.5 Gy (RBE); 4.5 Gy per fraction; Central Tumors: 58.05 Gy (RBE); 3.87 Gy per fraction; 5 days per week [29]	At least 2 beams; avoid treating through bowel or stomach; avoid overlap on skin	
	Bridge to transplant (HCC)	70.2 Gy (RBE); 4.68 Gy per fractions; 5 days per week [37]		
SBRT	Definitive. Smaller HCC/IHCC, up to 3 tumors	50 Gy; 10 Gy per fraction; over 1–2 weeks (every day or every other day). Consider planned break for impaired liver function	Linac-based: IMRT: multiple coplanar isocentric beams VMAT: volumetrically modulated coplanar partial arcs Cyberknife: multiple non-coplanar nonisocentric beams	
SBRT[a]	HCC as bridge to transplant	40 Gy; 8 Gy per fraction. Every other day over 2 weeks	Linac-based: IMRT: multiple coplanar isocentric beams VMAT: volumetrically modulated coplanar partial arcs Cyberknife: multiple non-coplanar nonisocentric beams	
Radioembolization	More than 3 tumors, Tbili <2.0. Main portal vein involvement is relative contraindication	Staged bilobar treatment can be done		

[a]May be appropriate for carefully selected patients

4.3.7 Treatment Plan Optimization

Treatment planning optimization requires attention to organ at risk (OAR) radiation dose constraints to minimize risk of toxicity. 3D CRT, VMAT/IMRT, and proton therapy for larger HCCs and IHCCs commonly utilize more "conventional" or "mildly" fractionation regimens and are listed in Table 4.7 (3D CRT, IMRT/VMAT, Proton Therapy). An example of OAR planning constrains considered for mildly fractionated liver radiation is provided in Table 4.8.

With SBRT, the key objective is to maintain liver function while targeting the tumor. The dose constraints with extreme hypofractionation are different from fractionated radiation. Some common goals for liver are to spare ≥700 cc of normal liver from receiving ≥15 Gy; spare ≥500 cc of normal liver from receiving ≥7 Gy; and limit the mean dose to the liver to ≤15 Gy [27]. Table 4.8 provides a list dose constraints for liver SBRT. As discussed above, a constraint may also be placed on the central zone to keep the $V_{BED10}40 < 37$ cc and $V_{BED10}30 < 45$ cc [27]. Although the risk of compromising liver function is a major concern, injury to bowel and stomach has been seen in multiple trials of liver radiation and often limit the dose that can be prescribed to liver tumors.

SBRT used for the treatment of smaller HCCs and IHCCs commonly utilizes more aggressive fractionation regimens (Table 4.9). SBRT may be considered for the treatment of carefully selected larger tumors using a more protracted dose fractionation. Commonly used SBRT dose fractionation regimens are provided in Table 4.7 and an example of OAR planning constrains considered for SBRT liver radiation is provided in Table 4.8.

Table 4.8 Planning constraints for mildly fractionated liver radiotherapy from University of Pennsylvania

Serial tissue	Max point dose (Gy)	Endpoint (>/=Gr 3)
Cord	35 Gy	Myelitis
Heart	35 Gy	Pericarditis
Gallbladder	35 Gy	Ulceration
Stomach	35 Gy	Ulceration/fistula
Duodenum	40 Gy	Ulceration
Small bowel	40 Gy	Enteritis/obstruction
Large bowel	40 Gy	Colitis/fistula
Parallel tissue	**Dose constraint**	**Endpoint (>/=Gr 3)**
Liver-GTV	Child-Pugh Score: A: Mean < 28 Gy B7–8: Mean < 27 Gy B9: Mean < 24 Gy	Basic liver function
Kidney total	50% less than 15 Gy	Basic renal function

Table 4.9 Planning constraints for liver SBRT from University of Pennsylvania

Serial tissue	Volume	Volume max (Gy)	Max point dose (Gy)	Endpoint (>/=Gr 3)
Cord	0.1 cc <0.35 cc <1.2 cc	25 Gy 23 Gy (4.6 Gy/fx) 14.5 Gy (2.9 Gy/fx)	30 Gy (6 Gy/fx)	Myelitis
Esophagus	<5 cc	19.5 Gy (3.9 Gy/fx)	35 Gy (7 Gy/fx)	Stenosis/fistula
Heart/ pericardium	<15 cc	32 Gy (6.4 Gy/fx)	38 Gy (7.6 Gy/ fx)	Pericarditis
Chest wall/rib	<30 cc	35 Gy (7 Gy/fx)	43 Gy (8.6 Gy/ fx)	Pain or fracture
Skin	<10 cc	36.5 Gy (7.3 Gy/fx)	39.5 Gy (7.9 Gy/fx)	Ulceration
Stomach	0.1 cc <10 cc	27.5 Gy 18 Gy (3.6 Gy/fx)	32 Gy (6.4 Gy/ fx)	Ulceration/fistula
Duodenum/ gall bladder	0.1 cc <5 cc <10 cc	30 Gy 18 Gy (3.6 Gy/fx) 12.5 Gy (2.5 Gy/fx)	32 Gy (6.4 Gy/ fx)	Ulceration
Small bowel	<5 cc	19.5 Gy (3.9 Gy/fx)	35 Gy (7 Gy/fx)	Enteritis/obstruction
Large bowel	<20 cc	25 Gy (5 Gy/fx)	38 Gy (7.6 Gy/ fx)	Colitis/fistula
Parallel tissue	**Critical volume**	**Critical volume dose max**		**Endpoint (>/=Gr 3)**
Lung total	1500 cc 1000 cc	12.5 Gy (2.5 Gy/fx) 13.5 Gy (2.7 Gy/fx)		Basic lung function Pneumonitis
Liver-GTV	700 cc	15 Gy (3 Gy/fx)		Basic liver function
Kidney total	200 cc	17.5 Gy (3.5 Gy/fx)		Basic renal function

4.3.8 Special Treatment Planning Consideration for Proton Therapy

Compared to photon-based radiation, PBT is more sensitive to changes in density in the beam path. If an air replaces soft tissue in the beam line compared to the time of simulation, the dose will travel further in the body, possibly treating tissue that was originally beyond the end of the spread-out Bragg peak (SOBP). For liver cases, this could be a loop of bowel between the abdominal wall and a cirrhotic liver. This is one of the reasons that selection of beam angles is critical for treatment planning. Regions of potential change in proton stopping power (like loops of bowel or the stomach) are avoided when selecting beams. The converse problem of increased tissue density between the surface and the target can lead to undercoverage of the distal part of the target. For example, accumulation of ascites between the abdominal wall and the liver would result in a beam that travels less far, leaving a cold spot distally. Most of the planning algorithms are built in potential errors such as these for improved robustness. The longer the beam path, the greater the amount of uncertainty for all types of error. Despite trying to account for error, there are other changes in the target anatomy that can negatively impact that dose distribution.

Another important concern for PBT is excessive motion. This is relevant for passive-scatter PBT where target coverage is sensitive to motion in the beam path, but even more important for PBS. The impact of target motion, defined as 80th percentile of perpendicular motion, has been studied using PBS for liver tumors [40]. The authors found that for small motion (<5 mm), motion mitigation was not needed, but for moderate motion (7–10 mm), abdominal compression was helpful. For patients with large motion (>10 mm), some kind of motion management, like abdominal compression, was required for robust target coverage. In general, repainting with multiple beams and multiple fractions (as few as 3–4) helps mitigate issues arising from the interplay effect. As proton therapy centers become more sophisticated with PBS and volumetric on-board imaging, more challenging cases may be attempted, treating large tumors while sparing liver function.

4.3.8.1 Proton Delivery Techniques

Most of the older proton therapy centers have used passive-scatter PBT therapy. This has been used in most of the literature reporting outcomes of liver tumors treated with PBT. Its main limitation is conformality proximal to the target, since the only OAR proximal to the liver in right-laterally oriented beams has historically been the skin, ribs, and chest wall. When using dose intensification, it is therefore important to try to space beams out without overlap on skin, since the entrance dose with passive-scatter PBT is relatively high. Passive scatter is relatively robust with respect to motion, as discussed above. PBS-only facilities have been on the rise. A technique for treating liver tumors with PBS has been described [40]. Although PBS is more sensitive to motion, it does have potential advantages with respect to conformality. In particular, PBS can be used (like IMRT) to dose paint. This allows for intensification of dose in the majority of the target while deescalating close to serial OARs, such as the duodenum or stomach. In theory, true IMPT could be used for liver PBT where each beam does not cover the entire target volume. This may be of use in lowering dose to the central zone or a loop of bowel when targeting concave liver tumors.

4.3.8.2 Special Considerations for Proton Dosimetry and Quality Assurance

The input of experienced proton physicists and dosimetrists is crucial to an effective and safe PBT program for liver tumors. Potential pitfalls in planning can compromise robust plans. At present, PBT in most centers is limited by lack of on-board cross-sectional imaging for IGRT. Verification CT scanning in the treatment position with forward planned dose evaluation is an integral part of the quality assurance program. Figure 4.8 demonstrates an example of a patient with HCC in segments II and III planned for PBT using PBS. The stomach was an important OAR as it lies adjacent to the liver. A verification CT was done and the original plan was superimposed on the new CT, where it was noted that the stomach was more distended, especially with gas. This had the effect of rotating the liver laterally and interposing stomach tissue into the end of the SOBP where the most medial aspect of the target

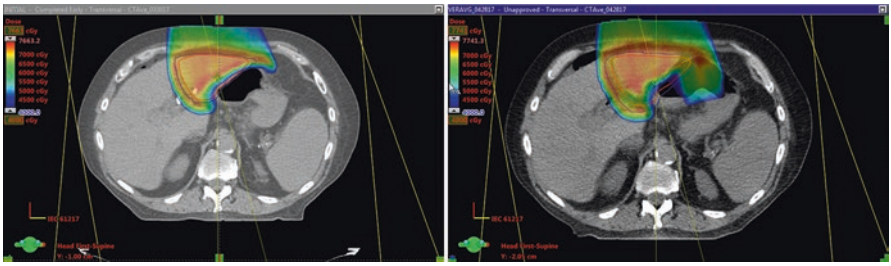

Fig. 4.8 Example of how anatomy changes can alter PRT dose distribution. A patient was simulated with abdominal compression and an ITV was created based on 4DCT scan. The segment II/III mass was planned with two pencil-beam-scanned beams using SFUD (AP and RAO). A verification scan showed that the stomach was more distended, resulting in overdose to the stomach. The plan was modified to lower the total dose and decrease the daily fractionation

had been. The result was to dramatically increase the volume of stomach treated with high radiation doses. This is an example of where the originally prescribed hypofractionated, dose intense prescription was altered, using more protracted fractionation and a lower total dose.

Verification CT scans are an important part of the quality assurance program for using PBT for GI sites. This is especially important when there are suspected changes in the patient's anatomy, as with changes in ascites, weight changes, or prolonged treatment breaks (planned or unplanned). We have found that routine verification scans in liver patients treated with PBT is useful for all patients with the initiation and frequency dependent on the total number of fractions. Additional scans are done ad hoc.

4.4 Summary

Radiotherapy is an important component of the multidisciplinary treatment of localized primary liver tumors. External beam radiation, including IMRT/VMAT, SBRT, and proton therapy can be used to deliver high doses to liver tumors, while sparing other organs.

4.4.1 HCC (Fig. 4.9)

- Radiation can be used with curative intent for isolated lesions as an alternative to excision
- Radiation can be used as a bridge to transplant
- Palliative radiation can be used as an alternative to other liver-directed therapies or systemic therapies

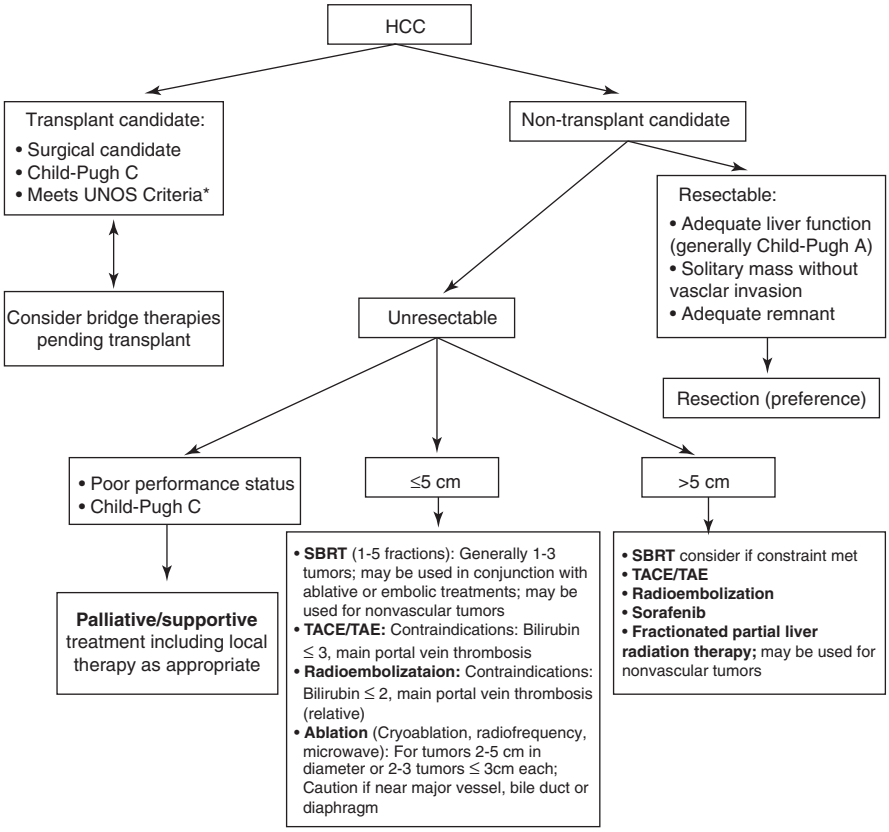

Fig. 4.9 Treatment algorithm for HCC

4.4.2 IHCC (Fig. 4.10)

- Adjuvant radiation, often used with chemotherapy, following surgery with curative intent
- Definitive radiation, often used with chemotherapy, can be used to treat unresectable tumors

Radiotherapy for liver tumors has been enabled due to improved understanding of the partial volume radiation tolerance of the liver as well as advances in imaging and radiation delivery techniques. In particular, the development of SBRT, image-guided therapy with fractionated IMRT/VMAT, and proton therapy has provided new opportunities to treat patients safely. There is an emerging role for radiation in primary HCC, in the definitive setting, as a bridge to transplant, and as palliation. Although surgery remains the mainstay of curative treatment for HCC, either by partial hepatectomy or OLT, radiation is emerging as an important and versatile tool in the management of HCC and IHCC. The appropriate combinations and sequence of external beam radiation in respect to other ablative and embolic liver-directed therapies is evolving. Radioembolization has a unique role for more diffuse liver disease, with

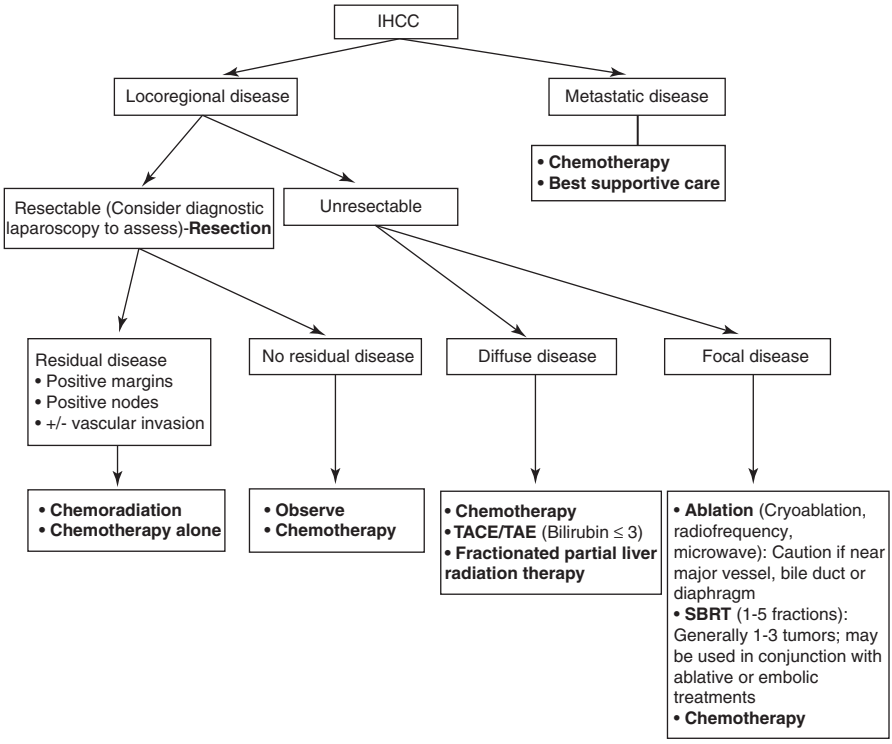

Fig. 4.10 Treatment algorithm for IHCC

eligibility criteria different from TACE and TAE. The radiation oncologist plays a key role in the multidisciplinary team to understand liver reserve and the impact of proposed radiation-containing regimens. In addition, radiation oncologists can help dispel the myths that primary liver tumors are radioresistant and that the liver is too sensitive for therapeutic radiation. Through risk-adapted dose intensification, radiation can be used more judiciously with a higher rate of tumor control.

As many practicing radiation oncologists did not have the opportunity to treat a lot of liver tumors during their formal education, continuing education is critical. We should pay close attention to pitfalls in contouring liver tumors, which may have confusing patterns of enhancement/washout on various phases of contrasted scans and MR sequences. Consultation with abdominal radiologists is highly recommended while on the steep part of the learning curve. In addition, the role of the medical physicist cannot be understated when attempting complicated treatments like respiration gated SBRT or proton therapy. Adherence to dose-volume limits, with appropriate adjustment of the total dose and/or dose per fraction, will help minimize toxicities. Ultimately, radiotherapy for liver tumors requires team work both in the multidisciplinary clinic for optimal patient selection and with the radiation oncology team for high quality, safe radiation delivery.

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Gallbladder Cancer and Extrahepatic Cholangiocarcinoma

5

Rachit Kumar, Gary Walker, Lauren Rosati, Sweet Ping Ng, and Joseph Herman

Contents

5.1 Introduction

5.1.1 Gallbladder Cancer (GBC)

The work-up for gallbladder cancer typically includes volumetric imaging of the chest and abdomen (computed tomography [CT] or magnetic resonance imaging [MRI]) with intravenous (IV) contrast, labs including liver function tests, carcinoembryonic antigen (CEA), and carbohydrate antigen 19–9 (CA19–9). Positron

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emission tomography (PET)/CT is generally reserved for patients with questionable findings in other volumetric imaging [1]. A staging laparoscopy should be considered in all patients, as it can reveal occult disease, particularly in patients with locally or regionally advanced disease [2]. Multidisciplinary evaluation is recommended for all patients with input from a surgical oncologist, medical oncologist, radiation oncologist as well as imaging and pathology review. Preoperative jaundice is a relative contraindication for radical resection, as these patients tend to have a very poor prognosis [1, 3].

Patients who are diagnosed with an incidental finding of carcinoma after a cholecystectomy are typically observed if staged T1a and the margins are negative. Patients with an incidental finding of stage T1b or higher cancer, lymph node-positive disease, or who have a mass on imaging should first be evaluated for resectability in a multidisciplinary setting. One multi-institutional retrospective study from Europe demonstrated that re-resection increased 3-year survival from 20 to 54% [4]. A survival benefit for re-resection has not been demonstrated in T1a disease [5].

Patients whose tumors are deemed resectable and do not involve metastatic disease should undergo a cholecystectomy with en bloc hepatic resection and lymph node dissection with consideration of bile duct excision. While radical resection has been shown to improve survival [6, 7], it is generally not beneficial in patients with positive celiac, superior mesenteric artery (SMA), or para-aortic lymph nodes (N2); thus, consideration of sampling these areas prior to radical surgery should be considered [8, 9]. Port site resection is not routinely indicated.

The benefit of chemoradiation therapy following surgery has been established by multiple retrospective studies. Wang et al. developed a nomogram to estimate the benefit of adjuvant chemoradiation therapy using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database [10, 11]. While this benefit may be related to selection bias and variability in surgical expertise in the community, the survival benefit associated with chemoradiation has been demonstrated in high-volume centers [12–14]. Adjuvant chemoradiation therapy is generally recommended for advanced T-stage, node-, or margin-positive disease [14]. Chemoradiation is usually delivered with concurrent 5-fluorouracil (5-FU) or capecitabine. The Southwest Oncology Group (SWOG) 0809 phase II trial examined the role of adjuvant therapy in extrahepatic cholangiocarcinoma (EHCC) or gallbladder cancer with stage pT2–4, N1–2, or positive resection margins with M0 disease [15]. Patients received four cycles of gemcitabine and capecitabine followed by chemoradiation with capecitabine (45 Gy to regional lymphatics; 54–59.4 Gy to tumor bed). The median survival was 35 months with a 2-year survival for all patients of 65% (48% for gallbladder) and an acceptable toxicity profile.

Patients with unresectable GBC should proceed with systemic chemotherapy and/or chemoradiation therapy. Gemcitabine plus cisplatin has been shown to improve survival compared to gemcitabine alone in the ABC-02 prospective phase II trial, although it did have worse toxicity [16]. Patients with poor performance status may be treated with gemcitabine alone. Patients with T3/T4 or N1 disease should be considered for neoadjuvant therapy [1]. This can be followed with

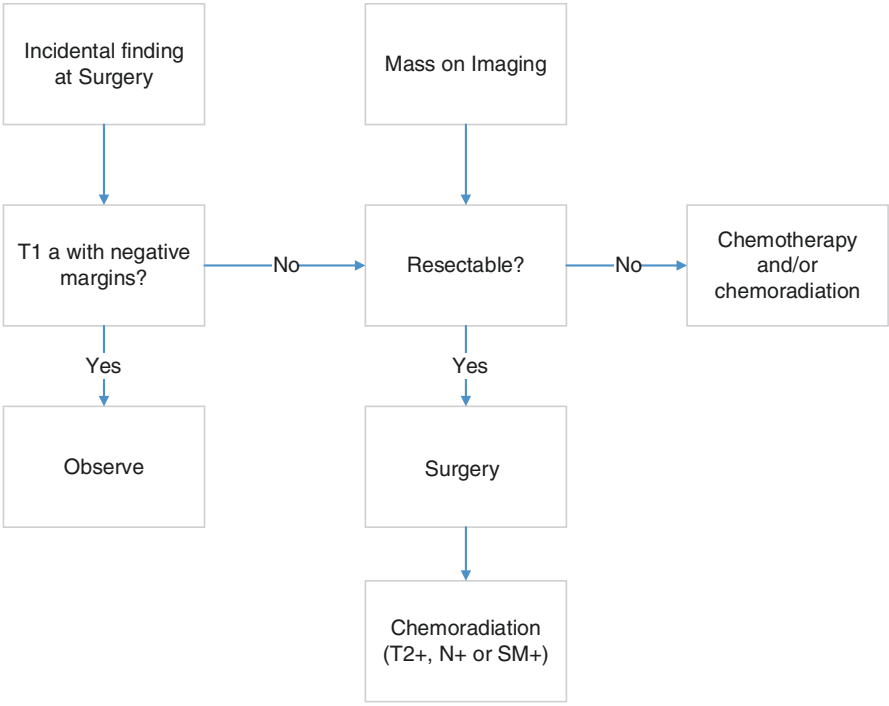

Fig. 5.1 Treatment algorithm for the management of gallbladder carcinoma

consideration of local therapy in those patients who do not develop metastatic disease. Stereotactic body radiation therapy is limited to case reports [17]. A treatment algorithm for the management of patients with GBC can be found in Fig. 5.1.

5.1.2 Extrahepatic Cholangiocarcinoma (EHCC)

Although transabdominal ultrasound may initially help diagnose EHCC by identifying a biliary stricture, detailed imaging of the chest and abdomen (CT or MRI) with IV contrast is the preferable imaging modality. When available, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous transhepatic cholangiopancreatography (PTC) allow for accurate detection of the location and extent of biliary tree involvement. In the case of ERCP and PTC, tissue sampling may also be performed. FDG-PET has demonstrated high rates of sensitivity and specificity in determining both malignant disease within the bile ducts and malignant lymphadenopathy [18]. Standard labs should include liver function tests, CEA and CA19–9. A staging laparoscopy should be considered. Multidisciplinary evaluation is recommended for all patients with input from a surgical oncologist, medical oncologist, radiation oncologist as well as imaging and pathology review.

Patients with a good performance status should be evaluated for resectability, and a pancreaticoduodenectomy is advised in patients without distant metastases. The goal of surgery is to obtain a margin-negative (R0) resection, as an R0 resection is associated with higher rates of disease-free and overall survival. The 5-year overall survival following pancreaticoduodenectomy is 20–54% [7, 19, 20]. However, even in the setting of an oncologic resection, both local recurrence and metastatic dissemination are common. Approximately two thirds of patients with EHCC will develop a local recurrence following surgery, and 59% of patients will have a local failure as the site of first recurrence [21]. As a consequence, multiple groups have reported the results of the role of adjuvant chemotherapy and chemoradiation. A meta-analysis of ten retrospective studies involving adjuvant radiation in cholangiocarcinoma, eight of which specifically addressed EHCC, investigated the role of surgery alone versus adjuvant radiation [22]. Despite the fact that patients receiving radiation were more likely to have positive surgical margins (69 vs. 31%, $p < 0.001$), the hazard ratio for overall survival favored the addition of radiation (0.62).

As mentioned previously, the publication of the SWOG clinical trial 0809 prospectively investigated the role of adjuvant chemotherapy and chemoradiation in patients with EHCC and GBC [15]. This study enrolled 54 patients with EHCC, resected with a pancreaticoduodenectomy to pathologic T2–4, node-positive, or margin-positive disease, received adjuvant gemcitabine and cisplatin, followed by chemoradiation to a dose of 45 Gy with concurrent capecitabine. Seeking a 2-year overall survival of 65% for patients with an R0 resection and 45% for patients with an R1 resection, the investigators found the overall survival to be 68% for all EHCC patients. The 2-year disease-free survival was 54% for patients with EHCC, with a local recurrence rate of only 13%. Intriguingly, three (30%) of the ten patients enrolled that did not receive radiation developed a local recurrence. Based on the results of the SWOG protocol, adjuvant chemotherapy and chemoradiation is indicated in patients with T2–4, node-positive, or margin-positive disease.

For medically or technically unresectable EHCC patients, Ghafoori and colleagues at Duke University reported on their retrospective results of 37 patients treated definitively with radiation [23]. The reported 1- and 2-year overall survival rates were 59 and 22%, respectively. Local control at 1 and 2 years was 90% and 71%, respectively. These data are similar to a smaller series reporting a median progression-free survival of 7.2 months with a median overall survival of 12.0 months; the most common site of failure was distant [24]. Though limited, this series demonstrated that local control is possible for patients treated using radiation and may be considered for palliation of local symptoms.

A dearth of data regarding the results of neoadjuvant chemoradiation in EHCC is present in the literature. However, two very small series show high rates (>90%) of R0 resections following a neoadjuvant chemoradiation approach [25, 26]. Additionally, despite having more advanced tumors, patients treated neoadjuvantly lived longer than patients treated with upfront surgery (5-year overall survival of 53% vs. 23%) [26]. Neoadjuvant therapy presents an intriguing option for EHCC patients and deserves prospective assessment. A treatment algorithm for the management of patients with EHCC can be found in Fig. 5.2.

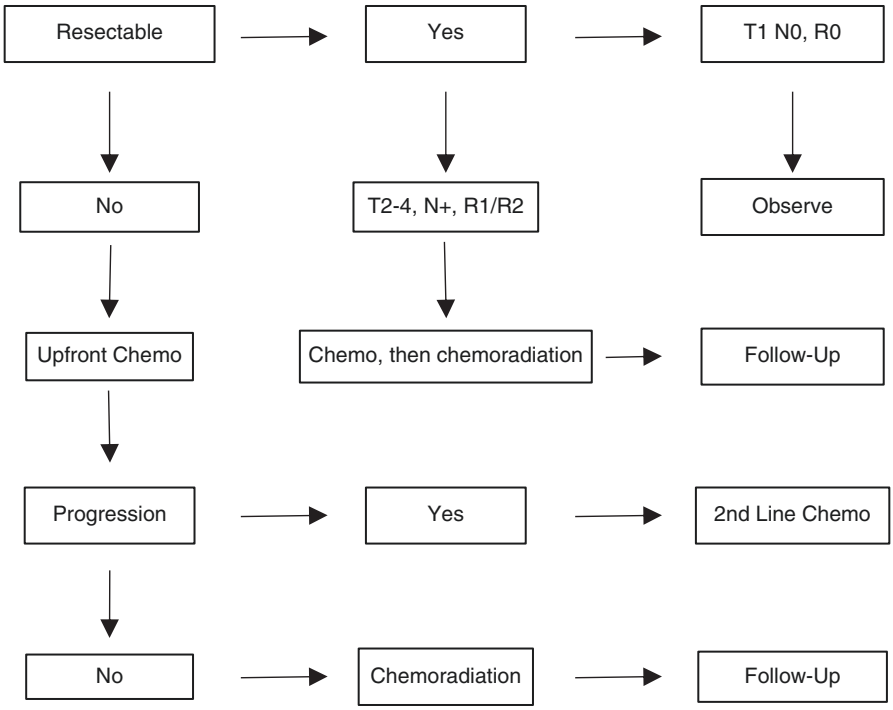

Fig. 5.2 Treatment algorithm for extrahepatic cholangiocarcinoma

5.2 Treatment Planning

Patients should be placed in a supine position with arms up, immobilized in a Vac-Loc (Civco Radiotherapy, Orange City, Iowa), Alpha Cradle (Smithers Medical Products Inc., North Canton, OH), or equivalent immobilization device.

5.2.1 Simulation

Patients are scanned from the carina through the top of the pelvis using CT simulation (thin slices, 2–3 mm, through the tumor bed and locoregional nodal basins)

- Imaging with oral contrast/water and with and without IV contrast strongly recommended for improved delineation of the tumor or tumor bed and adjacent normal structures.
- Tumor or tumor bed position can vary depending on the amount of gastric distension, which should be accounted for during simulation and treatment. Patients should not eat or drink 3 h (in some cases, longer) before simulation or treatment. Consider the use of 200–250 cc of oral contrast (simulation) or water (treatment) consumed and immediately prior to treatment to ensure consistent filling.

- Motion evaluation of interfraction (due to set-up error) and intrafraction (breathing or bowel/stomach distension not accounted for with pretreatment portal imaging) variations is important when considering margin expansions.
- Consideration of four-dimensional CT (4D CT) to evaluate tumor or tumor bed motion and define an internal target volume (ITV) expansion to ensure that tumor motion is incorporated into treatment planning margins for adequate dose coverage of target volumes
- Normal breathing, inspiratory, expiratory breath-hold CTs if 4D CT not available.
- Free-breathing treatment should be avoided if target motion exceeds 1.5 cm.
- Motion management should be considered using either of the two following approaches:
- Immobilization using *reliable* abdominal compression devices, breath-hold techniques including active breath control (ABC), or self-held deep inspiration breath-hold (DIBH) techniques.
- Physiologically monitoring tumor motion (tracking or gating) which allows the radiation beam to follow tumor motion and requires fiducial markers (surgical clips or implantable fiducials).

5.2.2 Radiation Planning

5.2.2.1 Gallbladder Cancer

CT simulation imaging should be carefully reviewed along with preoperative volumetric imaging. A virtual gross tumor volume (GTV) should be delineated to include the preoperative gross disease in the gallbladder fossa, including any lymph node disease, respecting postoperative anatomical changes. Details from the operative report can aid contouring. For those patients deemed to have unresectable tumors, all gross disease, including any nodal disease, should be included in the GTV.

Two clinical target volumes (CTV) are recommended: a microscopic (CTV1) and macroscopic (CTV2) volume. CTV1 is generally to include the GTV or tumor bed including the cystic lymph nodes, as well as the retropancreatic/pancreaticoduodenal, celiac, and common hepatic/portal vein/hilar node basins [27]. Nodal regions should include a 1–1.5 cm expansion around the retropancreatic space, the pancreaticoduodenal space, the proximal 1–1.5 cm of the celiac axis, proximal 2.5–3 cm of the superior mesenteric artery (SMA), the portal vein segment that runs anteromedial to the inferior venal cava to the bifurcation at the liver, and the liver hilum. CTV2 includes the GTV or tumor bed, enlarged nodes, and areas of positive margin. Typically, a 5–10 mm expansion around target volumes to create a CTV is sufficient. The CTV should be appropriately adjusted to account for extension into nearby normal tissues. When indicated, an ITV to account for target motion should be employed, using a 4D CT scan and/or fluoroscopy.

A representative contouring atlas for a patient with resected GBC is presented in Fig. 5.3.

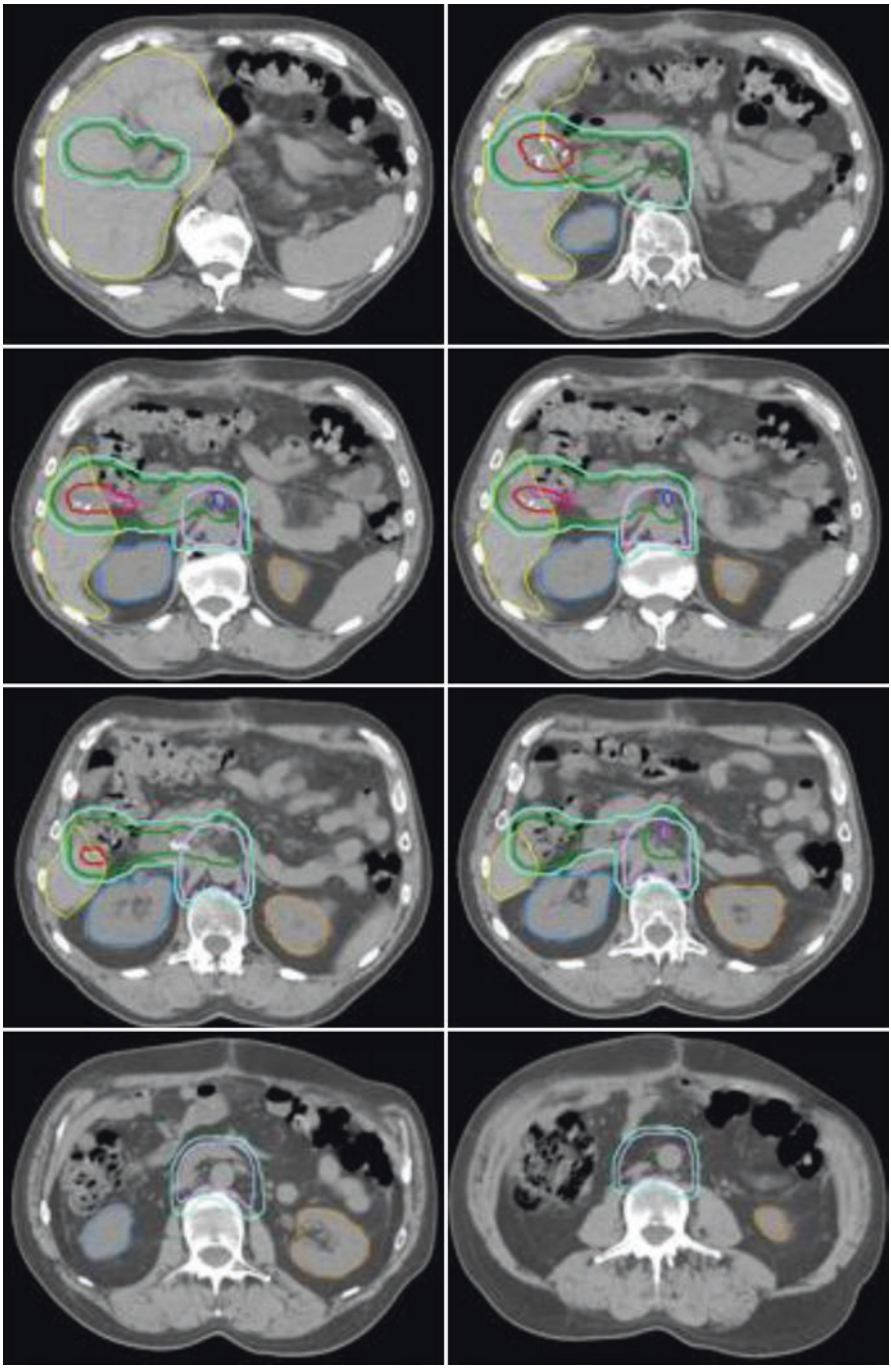

Fig. 5.3 Representative contouring atlas for a resected gallbladder cancer

Finally, a planning target volume (PTV) margin to account for set-up and equipment error up to 1 cm should be applied. However, for facilities using motion management, a 5 mm radial and 7 mm superior-inferior expansion is recommended based on Southwest Oncology Group Protocol 0809. With daily cone-beam CT scans, smaller PTV margins are reasonable based on facility-specific physics quality assurance.

A representative treatment plan for a patient with resected GBC is presented in Fig. 5.4, and corresponding DVH is shown in Fig. 5.5.

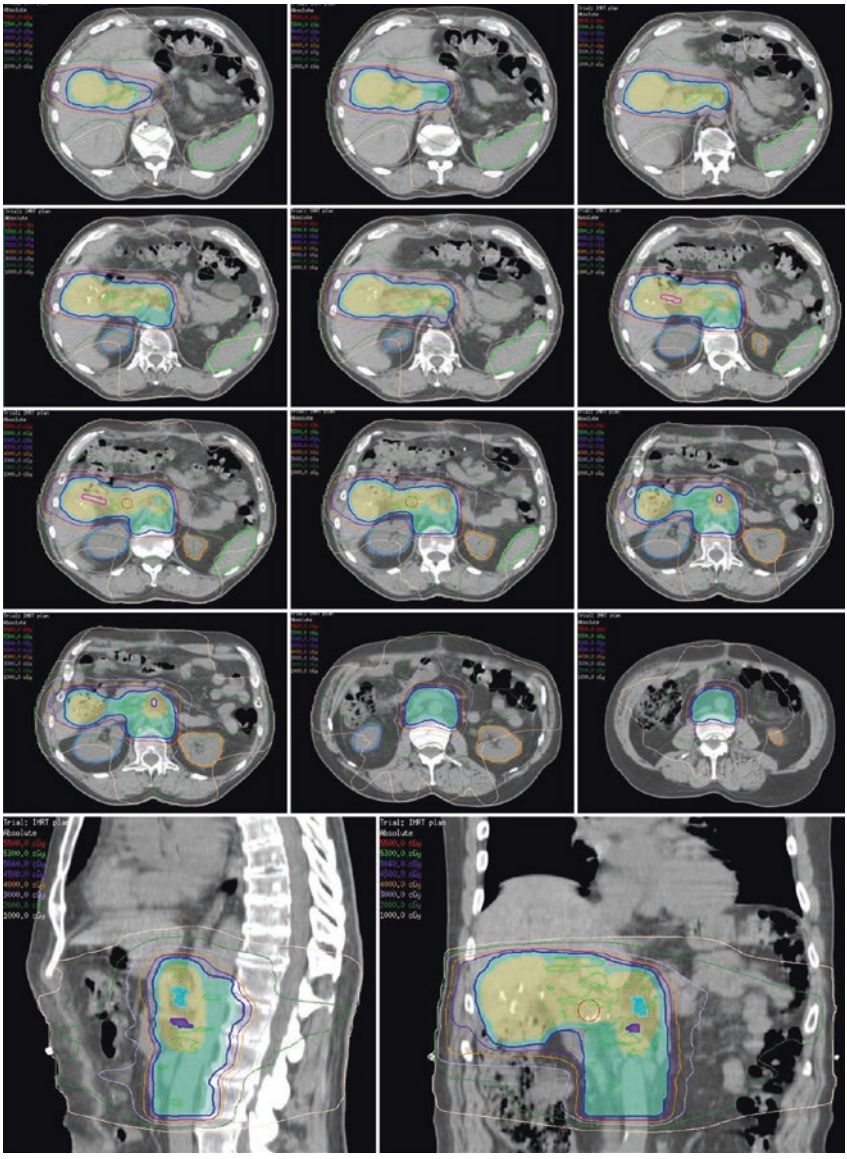

Fig. 5.4 Representative IMRT treatment plan for resected gallbladder cancer

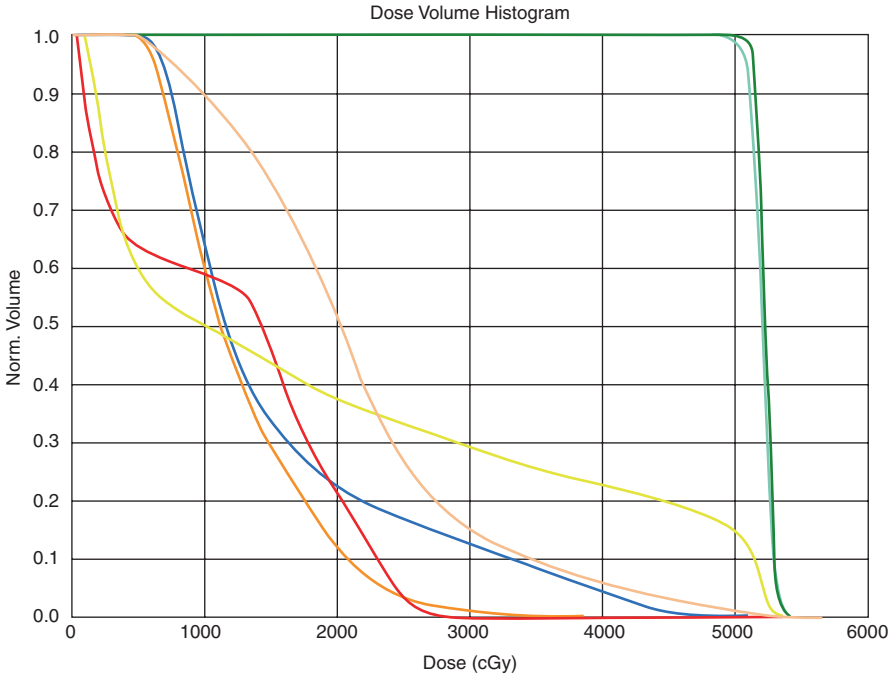

Fig. 5.5 Dose-volume histogram for IMRT plan for resected gallbladder cancer. *Cyan*—PTV, *Green*—CTV, *blue*—right kidney, *orange*—left kidney, *khaki*—small bowel, *yellow*—liver, *Red*—spinal cord

5.2.2.2 Extrahepatic Cholangiocarcinoma

For appropriate planning, all available imaging should be obtained and reviewed with pertinent multidisciplinary team members, including radiologists and surgeons. If available, diagnostic imaging should be reviewed and fused with the simulation CT scan. In postoperative patients, the preoperative imaging should be fused with the CT simulation.

For patients with intact (unresectable) disease, the GTV consists of all visible disease using available imaging. This is to include primary disease, enlarged lymphadenopathy, and PET-avid areas. In the postoperative setting, the presurgical imaging volume is identified and a "virtual" GTV is delineated by the physician, with assistance from the multidisciplinary team as needed. As anatomical changes are expected in the postoperative setting, incorporation of surgical anastomoses should be completed with radiation planning.

Two CTV are recommended: a microscopic (CTV1) and macroscopic (CTV2) volume. CTV1 is generally to include the GTV or tumor bed, retropancreatic, celiac, and portal vein nodes. Nodal regions should include a 1–1.5 cm expansion around the retropancreatic space, the pancreaticoduodenal space, the proximal 1–1.5 cm of the celiac axis, proximal 2.5–3 cm of the superior mesenteric artery (SMA), the portal vein segment that runs anteromedial to the inferior venal cava to the bifurcation at the liver, and the liver hilum. CTV2 includes the GTV or tumor bed, enlarged nodes, and

areas of positive margin. Typically, a 5–10 mm expansion around target volumes to create a CTV is sufficient. The CTV should be appropriately adjusted to account for extension into nearby normal tissues. When indicated, an ITV to account for target motion should be employed, using a 4D CT scan and/or fluoroscopy. Free-breathing treatment should be avoided if target motion exceeds 1.5 cm.

A representative contouring atlas for a patient with unresectable EHCC is presented in Fig. 5.6.

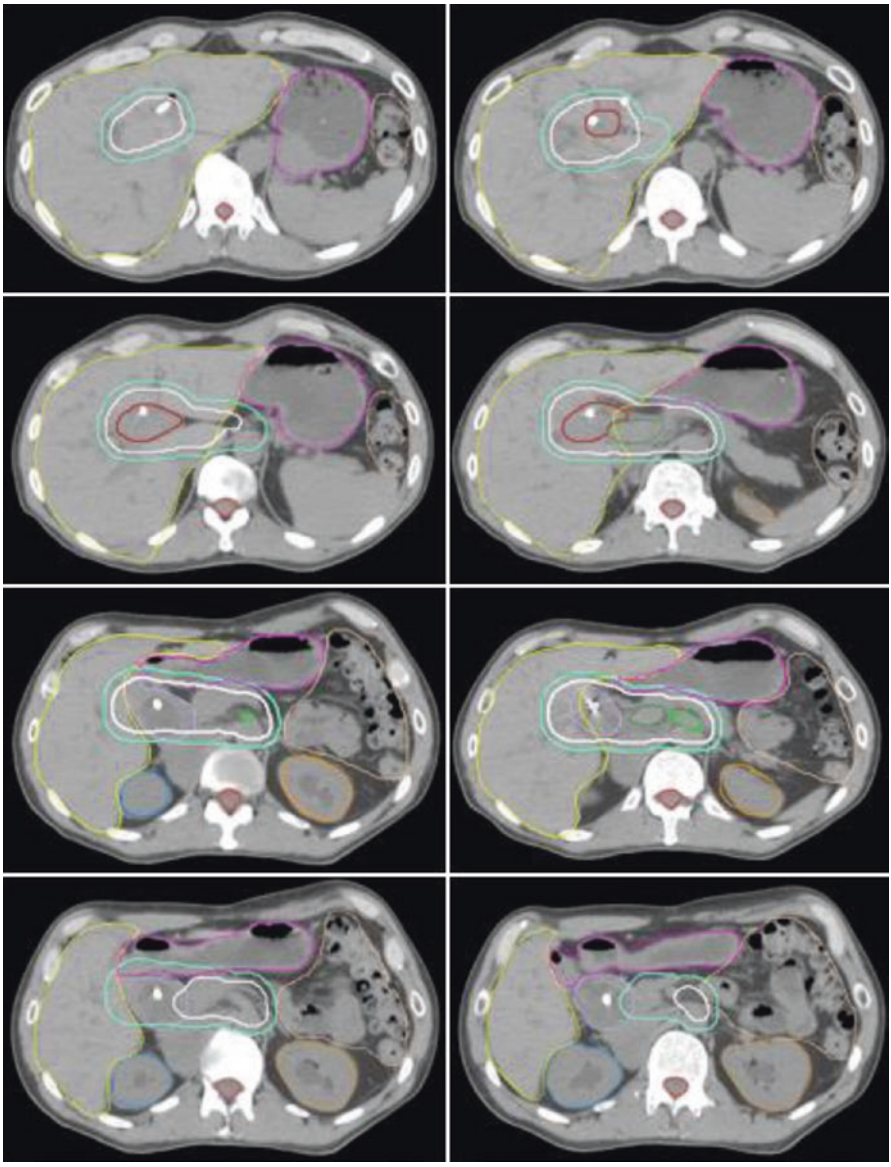

Fig. 5.6 Representative contouring atlas for a patient with unresectable EHCC

A PTV margin to account for set-up and equipment error up to 1 cm should be applied. However, for facilities using motion management, a 5 mm radial and 7 mm superior-inferior expansion is recommended based on Southwest Oncology Group Protocol 0809. With daily cone-beam CT scans, smaller PTV margins are reasonable after discussing with the facility's physics team.

A representative treatment plan for a patient with unresectable EHCC is presented in Fig. 5.7, and corresponding DVH is shown in Fig. 5.8.

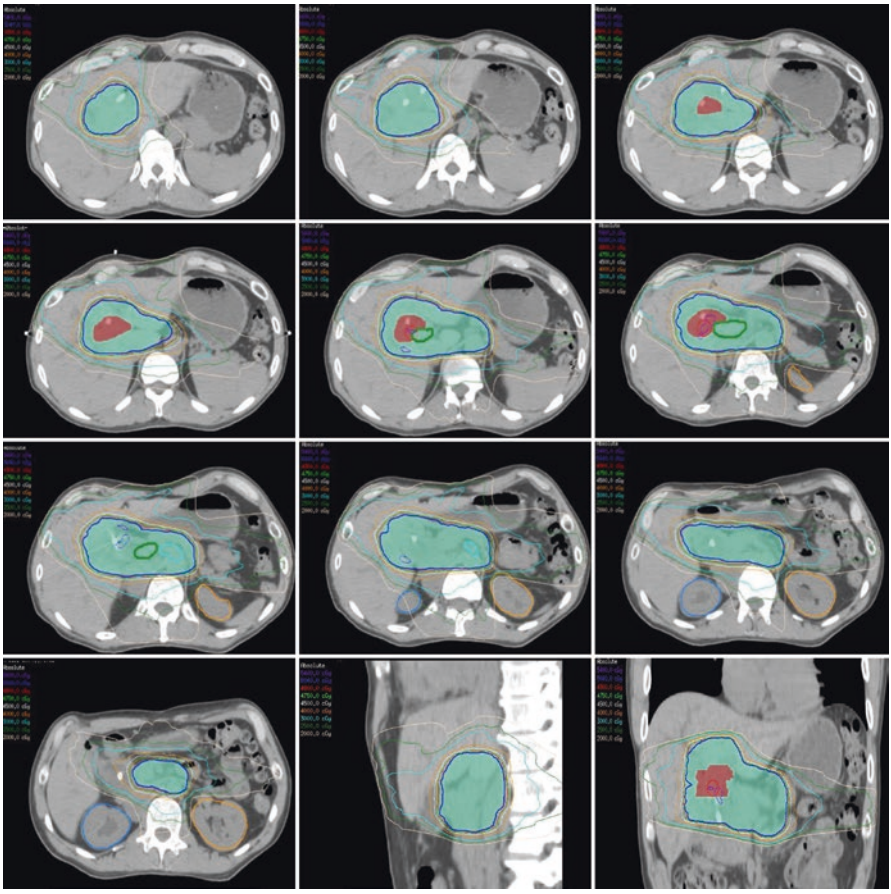

Fig. 5.7 Representative IMRT treatment plan for unresectable hilar cholangiocarcinoma

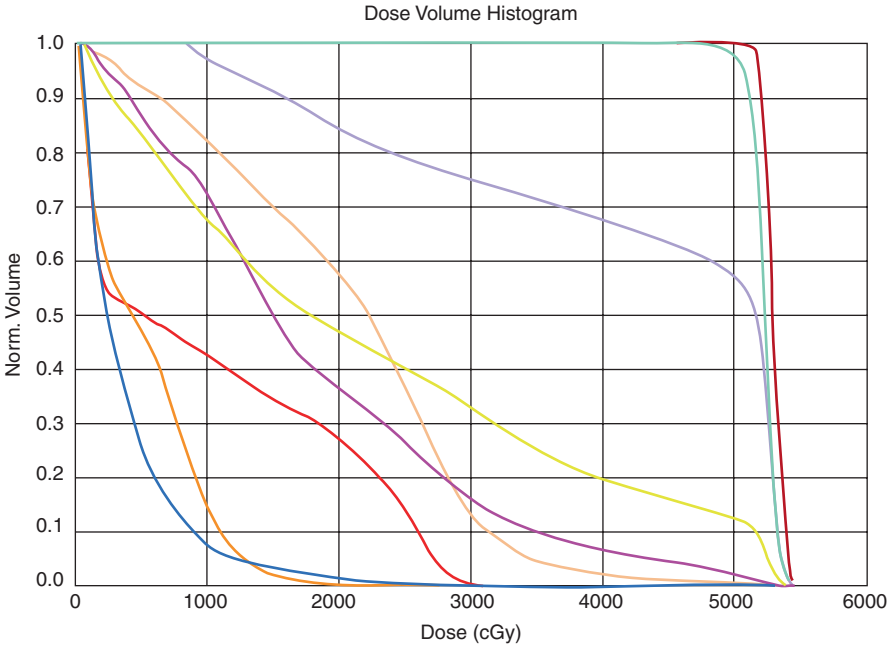

Fig. 5.8 Dose-volume histogram for IMRT plan for unresectable EHCC

5.2.3 Radiation Dose and Technique

While 3D planning is appropriate, intensity-modulated radiation therapy (IMRT)/volumetric arc therapy (VMAT) may allow for dosimetric improvements in normal tissue sparing, as is seen with pancreatic adenocarcinoma. If 3D planning is utilized, beam wedging and 2–4 fields will be needed, in whichever format helps increase homogeneity and reduce dose to the adjacent normal tissues. Dosing varies depending on the usage of 3D planning or IMRT/VMAT.

(a) 3D conformal 45 Gy in 25 fractions to PTV1, *then an additional*

– 9 Gy in 5 fractions to PTV2 (if R0 resection), *or*
– 14.4 Gy in 8 fractions to PTV2 (if R1 resection), *or*
– 14.4–18 Gy in 8–10 fractions to PTV2 (if gross disease)

(b) IMRT/VMAT *Using simultaneous integrated boost technique (SIB)*

– 45 Gy in 25 fractions to PTV1
– 52.5 Gy in 25 fractions to PTV2 (if R0 resection), *or*
– 55 Gy in 25 fractions to PTV2 (if R1 resection), *or*
– 60–66 Gy in 25 fractions to PTV2 (if gross disease).

5.2.4 Organs at Risk

Adjacent normal structures should be contoured including both kidneys, liver, stomach, small intestine, and spinal canal. Normal-tissue constraints are specified in SWOG Protocol 0809 (Tables 5.1 and 5.2).

Table 5.1 IMRT normal-tissue dose-volume constraints per SWOG 0809

Structure	Constraints
Kidney (L and R)	Max dose ≤20 Gy; not more than 10% of the volume can be between 18 and 20 Gy
Liver	Mean dose <30 Gy
Spinal cord	Max dose ≤45 Gy
Stomach Small bowel	Max dose ≤55 Gy; 25% of the volume can be between 45 and 55 Gy; 2% of the volume can be between 50 and 55 Gy
Duodenum	Max dose ≤55 Gy; not more than 33% of the volume can be between 45 and 55 Gy; not more than 10% of the volume can be between 54 and 55 Gy

Table 5.2 3D conformal normal-tissue dose-volume constraints per SWOG 0809

Structure	Constraints
Kidney (L and R)	The equivalent of 90% of one kidney must receive ≤18 Gy
Liver	Mean dose <30 Gy
Spinal cord	Max dose ≤45 Gy

5.2.5 Dosimetry/Physics

For 3D conformal radiation, the 95% isodose line must encompass 99.5% or greater of the PTV, and hot spots >105% are not allowed. For IMRT/VMAT, SIB is recommended, and dose heterogeneity of −5% to +10% is permitted provided that normal-tissue constraints are met. The mean dose must be within ±2% of the prescribed dose.

5.3 Summary

5.3.1 Gallbladder Cancer

Multidisciplinary evaluation at a high-volume center is essential for the appropriate management of GBC. Patients with an incidental finding of carcinoma are typically observed, if T1a and negative margins. Patients with resectable disease should undergo oncologic resection followed by chemoradiation therapy. Patients with unresectable disease should be treated with chemotherapy and/or chemoradiation therapy. The operative bed and nodal regions are typically treated using a 3D or IMRT technique to a dose of 45–54 Gy using adequate motion management techniques and special attention to avoiding adjacent normal tissues.

5.3.2 Extrahepatic Cholangiocarcinoma

As with GBC, a multidisciplinary evaluation is critical to determine both medical and technical resectability. Early-stage EHCC patients with negative nodes, negative margins, and no distant disease may be observed. However, the presence of more advanced disease, positive margins, and/or positive lymph nodes should be considered for adjuvant therapy using chemotherapy and chemoradiation as consolidation. Patients in whom surgery is not a reasonable possibility should be considered for upfront chemotherapy and/or chemoradiation; radiation alone should be limited to the palliative setting. The radiation oncologist should utilize motion management at the time of simulation and treatment to minimize normal-tissue injury.

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Non-Colorectal Liver Metastases

6

Adam C. Mueller, William A. Stokes, Dale Thornton, and Tracey Schefter

Contents

6.1 Section 1. Local Therapy to Non-Colorectal Metastases

The liver is a common site of metastases of multiple malignant neoplasms, and progressive liver dysfunction through invasion and replacement of its parenchyma is one of the mechanisms by which cancer frequently leads to morbidity and mortality. The traditional paradigm has been that once cancer progresses beyond its primary site and lymph nodal basins to metastasize in distant organs, the primary mechanism to deal with the disease is chemotherapy, with little to no role of surgical and radiation-based local therapies. Over the last few decades though, there have

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been advances in chemotherapy, which have slowed disease progression and allowed for prolonged survival in the metastatic setting, particularly with isolated metastases. These, combined with improvements in techniques of surgery, radiotherapy, and interventional radiology, have allowed us to reconsider the role of local therapy in slowing or halting cancer progression and delaying organ dysfunction. It has been postulated that in certain cases of metastatic cancer, there is an intermediate or "oligometastatic" state, between local and widely disseminated systemic disease, in which local therapies can be directed at metastatic sites with curative or life-prolonging intent [1]. Given its propensity to spread to the liver in limited numbers of metastases, and its slow average rate of disease progression on first line chemotherapy, most of the initial data on local therapies as potential curative approaches to liver metastases have been in colorectal adenocarcinoma. Several studies of cohorts treated with surgery for colorectal liver metastases found 25–40% 5-year survival, suggesting this approach could be used to prolong lifespan when faced with a limited disease burden among surgical candidates [2–4]. The development of more advanced techniques in interventional radiology, as well as SBRT in the realm of radiation therapy, has allowed high levels of local control to be achieved among patients with isolated liver metastases who are not candidates for surgery [5, 6]. More recently, these approaches have begun to be applied to non-colorectal cancer varieties, and with the correct screening and patient selection, are becoming a part of the oncological armamentarium in slowing the progression of metastatic disease while maintaining quality of life.

6.1.1 Surgical Approaches to Non-Colorectal Liver Metastases

Surgical resection has been the traditional approach to isolated colorectal metastases, though only 20% of these patients are surgical candidates with resectable tumors [7]. Still, among this population, surgery is a good option, with excellent local control and 5-year survival between 27 and 37%, compared to below 3% 5-year survival for patients with liver metastatic colorectal carcinoma that do not receive resection in some series, although this could be a result of selection bias [8, 9]. Additionally, there is an established role for surgical resection in the case of liver metastatic neuroendocrine tumors, which often present with liver metastases, but have an indolent disease course and 5-year survival rates of greater than 70% if surgically managed [10]. While comparatively sparse in relation to the literature on colorectal liver metastases, there is a growing body of literature from retrospective studies examining surgical resection in cancers of non-colorectal origin, which is now suggesting that in the appropriate patient population and clinical scenario, it may be a good tool to prevent liver progression and extend survival in certain instances. Patient selection in these cases is of utmost importance, requiring assessment of performance status, determination of whether extrahepatic disease is present, an understanding of the biological behavior of the cancer type, including rate of progression and response to treatment, and technical resectability of the tumor itself.

One of the earlier studies examining this approach in non-colorectal metastases, by Adam et al., in 2006 collected outcomes from 41 centers performing hepatic resections of non-colorectal metastases, between 1983 to 2004, including 1452 patients over that time period. They found that among these patients, postoperative mortality was low (2.3%), and overall survival at 5 and 10 years was 36 and 23%, respectively, suggesting a possible utility in providing long-term survival by including this approach. There was variability in outcomes based on histologic type, with longer survival for breast, urologic, gynecologic, and gastrointestinal tumors, and with poorer survival in the cases of melanoma, pancreatobiliary, and lung primary tumors. Additionally, a longer disease-free interval at presentation of liver metastases, absence of extrahepatic disease, and response to chemotherapy conferred a more positive prognosis [11].

A systematic review by Uggeri et al. found that across 30 studies, including a total of 3849 patients, mean overall survival at 5 years after resection of liver metastases from non-colorectal, non-neuroendocrine, non-sarcoma origin was 32.3%, with 5 and 10-year overall survival ranging from 19 to 42% and 23 to 25%, respectively. R0 resection when reported was achieved in 71% of cases. When performing subgroup analysis, it was found that histological subtype was a very important prognostic factor, suggesting tumor biology is an important consideration for patient selection. Patients with cancers of breast, kidney, ovarian, testicular, ampulla of vater, and adrenal gland origin had high rates of 5-year survival, over 30%. Patients with cancers of gastric and duodenal origin had 5-year survival rates between 15 and 30%, while patients with liver metastases from cancers arising in the lung, pancreas, esophagus, and anus had 5-year survival below 15%. Additionally, size of metastases below 5–6 cm and number of metastases of 3–4 and below were independent positive prognostic factors. Also, a period between initial presentation and development of liver metastases greater than 1 year suggested longer 5-year survival following liver resection [12].

6.1.2 Interventional Approaches to Liver Metastases

Due to the limited number of patients who are surgical candidates at the time of presentation of hepatic metastases, surgery as a local therapeutic approach is only pursued in a minority of cases, but there remain several other options for local ablation of hepatic metastases. A number of these approaches utilize percutaneous interventional techniques to access tumors and ablate them through a variety of physical, chemotherapeutic, and radiologic mechanisms. These methods include the ablative therapies radiofrequency ablation(RFA), cryotherapy, irreversible electroporation, laser-induced thermotherapy (LITT), and microwave ablation (MWA), as well as the embolization therapies transcatheter chemoembolization, bland embolization as well as yttrium 90 radioembolization [5].

These ablative therapies are appropriate for patients with liver-confined disease, and with a small number of lesions below 3 cm in diameter. They all involve insertion of a probe using image guidance to ablate the tumor by generation of heat in the

case of RFA, microwave ablation, and LITT, freezing the tumor in the case of cryotherapy, or by electroporation which irreversibly perforates the tumor cell membranes. These methods have generally had similar good rates of local control in non-colorectal metastases, though inferior to surgical resection [5]. A series examined these thermal ablation techniques in breast cancer patients with liver metastases and found local progression rates among appropriately selected candidates ranging, 13.5–58% for RFA, from 9.6% for MWA and 2.9% for LITT, with similar 5-year survival rates of 27–35% [13], suggesting a potential local control advantage trend for LITT. Another series which examined LITT in patients with a variety of oligometastatic non-colorectal cancers found a median survival of 37.6 months, and a 5-year overall survival of 33%, with prognostic factors including the number and volume of metastases, suggesting benefit is greater in those with a lesser hepatic disease burden [14].

Transcatheter embolization-based approaches can be used in cases where there are tumor volumes that are larger than are amenable to percutaneous ablative techniques. These approaches involve access to liver tumors through the hepatic artery, clogging tumor vasculature with particles to cut off blood flow and deliver cytotoxic agents to the tumor. The more dense and disordered nature of tumor microvasculature allows particles released upstream of tumor to concentrate and lodge in the tumor, preventing systemic release. Bland embolization is the most basic of these techniques, clogging tumor microvasculature with inert particles, but is rarely used in the metastatic setting. Chemoembolization can be performed by transcatheter administration of a chemotherapy emulsion, followed by bland embolization with a particulate mixture, in order to deliver highly concentrated chemotherapy to the local tumor area, for a prolonged exposure time while limiting systemic exposure to chemotherapy agents [15]. Newer drug eluting particles are becoming available that release chemotherapy over time, which further can reduce systemic release of the chemotherapy agents [16].

Yttrium-90 radioembolization, also called selective internal radiotherapy (SIRT), is a technique that uses Yttrium-90-conjugated microspheres to deliver radioisotopes that become lodged in tumor microvasculature and radiate the surrounding tumor parenchyma over a period of weeks [17]. Similar to chemoembolization techniques, it relies on delivery through the hepatic artery and the dense, disorderly tumor vasculature to cause the particles to become trapped within the tumor [18]. There have been few case series examining the effect of SIRT in non-colorectal metastases, but those that have show promise for its use in certain patients. Select studies examining SIRT in chemoresistant breast cancer liver metastases have found median survival as high as 14 months, particularly in patients with <25% of liver involvement [17]. This is greater than the historical median survival from presentation of liver metastases which has ranged from 3 to 10 months [19]. SIRT has also shown some promise in treating melanoma liver metastases, with median overall survival ranging from 7.6 to 10.1 months in several series [20–22], compared to the historical value of 3 months [23]. This technique does appear to have utility in treating liver metastases of multiple etiologies, though many of these approaches need further study to stratify patients who will derive the most benefit.

6.1.3 External Beam Radiation-Based Approaches to Non-Colorectal Liver Metastases

Historically, treatment of liver lesions with external beam radiation had been limited by toxicity to the organ from the treatment techniques available. Traditionally, liver treatment was through 2D whole liver treatment, which could not deliver meaningful doses of radiation to tumor without excessive toxicity to the liver. Among patients receiving whole liver radiation, radiation-induced liver disease (RILD) was a dose-limiting side effect, consisting of elevated liver enzymes, anicteric hepatomegaly, and ascites, occurring 3 months following treatment [24]. The whole liver dose escalation study RTOG8405 found rates of RILD increasing from 0 to 10% when increasing whole liver dose from 30 to 33 Gy, making whole liver treatment of metastases of little use, given the low doses that it took to generate unacceptable liver toxicity. Because the liver is a large organ composed of redundant (though relatively radiosensitive) subunits, the advent of 3D planning made it possible to treat smaller areas of the liver to higher doses, offering the opportunity to deliver meaningful biological doses of radiation while circumventing the consequences of irradiating the whole liver. Later studies examining partial liver irradiation found that RILD could essentially be avoided as long as the mean dose of radiation to the whole liver did not surpass 31 Gy [25, 26], allowing partial liver doses of 70–90 Gy to be reached in 1.5 Gy BID fractions without inducing RILD [26]. However, despite this dose escalation, rates of local control using traditionally fractionated radiation to the liver were poor [27], suggesting a different approach would be necessary for it to be a frequently used modality in treating liver metastases.

High-dose ablative radiation, delivered in a highly focused and conformal manner, has long been used in the treatment of brain metastases with a high rate of local control. Over the last 20 years, these concepts have been translated to the treatment of isolated metastases to extracranial organs, particularly the lung and liver. Doses per fraction of greater than 10 Gy have the potential to cause different types of damage than more fractionated radiation and have been shown to cause vascular injury in mouse xenograft models [28]. Treatment of extracranial metastases with high-dose radiation has a number of practical considerations including increased difficulty of target delineation relative to local anatomy, radiosensitive normal structures, immobilization techniques, and prevention of interfraction setup variability. Newer technologies incorporating image guidance, using fiducial markers for target delineation, and respiratory gating have allowed levels of precision to be attained, which have facilitated the ability to deliver single and multi-fraction SBRT to abdominal tumors without high grade toxicity, with appropriate planning constraints.

Multiple trials have been conducted examining the safety and efficacy of SBRT directed towards liver metastases and concluded that it is in fact safe and effective in gaining a high level of local control when used appropriately. In the last 20 years, there have been several series and early stage trials examining both single fraction high-dose conformal radiation to reach ablative doses to oligometastases as well as hypofractionated SBRT to liver metastases. Most of these series included several tumor histologies, primarily colorectal, but also many included non-colorectal

metastases. One of the initial trials by Blomgren and colleagues at the Karolinska institute examined 1–4 fraction high-dose conformal radiation to solitary metastases in the lung, liver, or peritoneal space, achieving local control rates of 80% and response rates of 50% with a mean dose of 30.2 Gy to the PTV [29]. This established a potential role for this type of radiation in treating solitary metastases, particularly among non-surgical candidates. A similar study was conducted by Wulf and colleagues at the University of Wurzburg, achieving a local control rate of liver metastases at 1 and 2 years of 76% and 61%, respectively [30].

In the United States, the first multi-institution phase 1 dose escalation trial of safety of multi-fraction liver SBRT was conducted by Schefter and colleagues at the University of Colorado and Indiana University [31]. Eighteen patients, including 12 with non-colorectal metastases, were treated for 1–3 liver metastases, with tumors below 6 cm in diameter, and healthy liver functions. Initially, patients were treated with 36 Gy in 3 fractions, with doses escalating up to 60 Gy in 3 fractions after there were no observed grade 3 or above liver or intestinal toxicities. Constraints were utilized to ensure that at least 700 mL of normal liver received a dose below 15 Gy, which has since been employed in other trials examining liver SBRT. The population included patients with metastases of bladder, breast, colorectal, esophageal, head and neck, lung, ovarian, and pancreatic origin. They found no grade 3 or 4 toxicity among all of the patients, and no incidence of RILD, suggesting that doses of 60 Gy in 3 fractions could safely be used to treat metastases from a number of histologic types.

This study was followed up by a phase 2 trial by Rusthoven and colleagues examining 47 patients with 63 liver metastases, to determine whether durable local control could be achieved using liver SBRT [6]. The patients included had primary tumors of colorectal, lung, breast, ovarian, esophageal, and several other primary origins. The results of this study were impressive 1- and 2-year local control rates of 95% and 92%, respectively. Median overall survival was 20.5 months with a 2-year survival rate of 30%. They stratified these patients into unfavorable primary sites, including lung, ovarian, and non-colorectal GI, and found that these patients had a median overall survival of 12 months, compared to 32 months for patients with colorectal, breast, renal, carcinoid, GIST, and sarcoma primary cancers. For these favorable tumor types, 2-year local control was 97%, resembling that of surgery [32]. The primary predictor for local control was tumor size, with 100% 2-year local control for tumors below 3 cm in diameter and 77% for tumors greater than 3 cm but less than 6 cm. Altogether, these results suggested that SBRT to liver metastases of multiple etiologies could achieve robust local control with appropriate patient selection. Also, though certain tumor histologies conveyed a much poorer prognosis than others, these patients would typically have never been considered surgical candidates and SBRT was able to achieve local control and longer survival than historical norms even in these cases.

Goodman and colleagues alternatively performed a phase 1 dose escalation study of single fraction SBRT to patients with liver tumors, including hepatic metastases,

intrahepatic cholangiocarcinomas, and recurrent hepatocellular carcinomas in their cohort. They examined doses from 18 to 30 Gy delivered in a single fraction to tumors up to 5 cm in diameter. They observed 1-year local failure rates of 23% and 1- and 2-year overall survival rates of 71 and 53%, respectively [33]. Thirty-five percent of patients experienced grade 1 toxicities, primarily nausea, with three patients developing duodenal ulcers 3 months following treatment, one of which had received reirradiation to the area. No grade 3 toxicities were seen. This suggested single fraction SBRT to the liver could deliver good local control and overall survival in appropriate patients, though maybe with a higher risk of duodenal ulcer formation.

Another phase 1 study of SBRT for both primary and metastatic liver tumors was conducted by Romero and colleagues between 2002–2006 among 25 patients who were not candidates for surgery or other local ablative therapies. They treated patients predominantly with 3, 12.5 Gy fractions and were able to achieve a 1-year local control rate of 94%, with some high-grade toxicities, seen primarily in cirrhotic patients. They did find acute high-grade toxicity in 4 of 25 patients, with one late toxicity seen. Most of these patients had colorectal metastases, but this series did include histologies of breast and lung cancer as well, which did not show a greatly different local control rate [34]. Since then several case series have been reported showing similarly promising local control and survival results, with minimal high-grade acute toxicities, and with dose delivered as the highest predictor of local control.

Rule and colleagues performed a phase 1 dose escalation study in patients with hepatic metastases of multiple histologic types and found a direct relationship between increasing dose and increasing local control across tumor types. They found that delivery of 60 Gy in 5 fractions provided 1- and 2-year local control rates of 100%, compared to 100% and 89% for 50 Gy in 5 fractions, and 56% and 56% for patients treated with 30 Gy in 3 fractions [35]. There were no treatment-related grade 4 or above toxicities at any of the dose levels used in the trial, and one occurrence of grade 3 transaminitis in the 50 Gy group. The conclusions reached by this trial is that 60 Gy in 5 fractions delivered similarly high local control as previous trials treating with a similar dose in 3 fractions and was a safe dose to use with similar dose constraints (critical volume model, >700 mL with mean <15 Gy). This 5 fraction regimen may be more appropriate for centrally located tumors to theoretically reduce toxicity to more sensitive structures close to the central liver (namely biliary and gastrointestinal tract). The central liver near the hilum, where the biliary system, portal vein, and hepatic artery coalesce, resembles a serial functional-anatomical arrangement compared to the parallel functional-anatomical arrangement of the more peripheral liver parenchyma. Damage to these structures can result in damage to the remaining liver parenchyma and biliary toxicity. For treatment planning purposes, the central liver zone is defined as the course of the portal vein to its bifurcation within the liver expanded by 2 cm. Figure 6.1 represents central liver zone target volume for treatment planning.

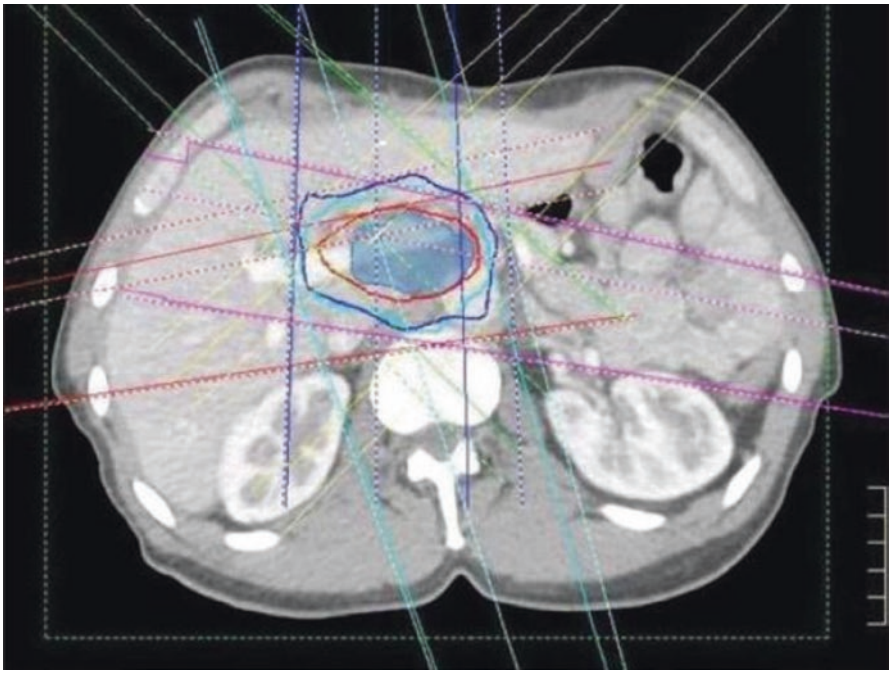

Fig. 6.1 Representative treatment plan identifying central liver zone target volume. *Light blue* represents the central liver zone PTV; *Red* and *Dark blue* represent 100% and 90% treatment planning isodose lines. (Hoffe SE, Finkelstein SE, Russell MS, et al. Nonsurgical options for hepatocellular carcinoma: evolving role of external beam radiotherapy. *Cancer Control*. 2010;17(2):100–10. Reprinted with permission of Moffitt Cancer Center)

6.1.3.1 Radiosensitivity Index

The utility of SBRT for oligometastases is subject to the biology of the tumor type of origin, its response to chemotherapy, likelihood of widely disseminated microscopic disease at the time of oligometastatic progression, rate of proliferation, as well as its radiation sensitivity. This final point is of importance given the impact of biological equivalent dose (BED) delivered in achieving local control, with advantages seen with dose escalation in most studies examining SBRT in this context and whether an effective BED can be reached without unacceptable toxicity to the liver and nearby organs of interest. A recent study utilized a genetic model termed the radiosensitivity index, which examines expression levels of ten genes [36], for predicting radiosensitivity between multiple tumor types in samples collected from patients who underwent resection of liver metastases [37]. They found wide variability in RSI between tumor histologies, with high RSI predicting poor response to radiation in GIST and melanoma, intermediate RSI in colorectal and pancreatic neuroendocrine, colorectal adenocarcinoma histologies, and lower RSI predicting higher sensitivity in breast, lung, and pancreatic adenocarcinoma, as well as anal squamous cell carcinoma and small intestine neuroendocrine histologies. They then identified a prospective cohort of patients, including 27 patients with colorectal and 11 with non-colorectal patients, including breast adenocarcinoma, anal squamous cell carcinoma, and lung

adenocarcinoma patients, and treated them with SBRT, examining local control and survival at 1 and 2 years. They found that local control among the non-colorectal metastases, which corresponded to histologies with lower RSI, was 100% at 1 and 2 years, whereas it was 79% and 59% at 1 and 2 years, respectively, for colorectal metastases, which reached statistical significance. However, there was no significant difference in overall survival, with a trend for better survival among the colorectal patients; 1 and 2-year survival for non-colorectal cancers was 82% and 73% versus 100% and 73% for colorectal cancers, respectively. This suggests that even better local control can be obtained in more radiosensitive tumor histologies than colorectal cancers, with posttreatment median survival duration long enough to warrant liver-directed therapy.

6.1.3.2 SBRT for Non-Colorectal Liver Metastases

Liver metastases are a morbid consequence of many tumors, and local therapies to target these lesions, particularly surgery, have only been available to a select few high performance status patients with anatomically feasible surgical approaches. Percutaneous interventions and trans catheter interventional approaches have increased the number of patients who have local therapies available to them, though with variable rates of local control, and still requiring technically feasible approaches and with a limit to the size of treatable lesions. SBRT has emerged as a noninvasive, minimally toxic, and highly effective method of achieving local control of liver metastases of multiple etiologies. Appropriate patient selection remains of import when choosing whether to treat these lesions, as favorable tumor histology can portend long overall survival after treatment, whilst more aggressive tumors, such as lung or esophageal cancer, are more likely to have metastases arising in multiple other locations, making the benefit of local therapy a subject of more debate despite achievability of local control. Additionally, the radiosensitivity of tumors can come into play when predicting local control, though this effect may be overcome with dose escalation as long as appropriate constraints are used. With the use of appropriate planning, modern daily imaging, fiducial markers, and respiratory gating, SBRT can accurately target metastatic liver lesions with great precision and should be in the armamentarium of radiation oncologists treating gastrointestinal malignancies.

In total, these techniques present a powerful array of tools for specific clinical scenarios where patients present with isolated liver metastases or isolated progression of individual metastases. These cases should be discussed before a multidisciplinary tumor board to determine the appropriate patient-centered approach. Surgery remains the gold standard, but interventional and radiation oncology techniques can provide good local control independently and in conjunction with each other, with limited toxicity and more flexibility in targeting anatomically difficult to access lesions. The role of the radiation oncologist in this setting is crucial, as sophisticated delivery of SBRT to non-colorectal isolated liver metastases is rapidly becoming an important and well-tolerated tool, in lieu of, or in conjunction with surgical and interventional therapies.

Table 6.1 outlines potential treatment options for non-colorectal liver metastases during different clinical scenarios.

Table 6.1 Radiation *(and non-radiation)* treatment approaches for non-colorectal hepatic metastases

Technique	Indication	Target	Typical dose schedule
3D CRT	Palliative control of symptoms	Whole or partial liver	30 Gy in 10 daily fractions 20 Gy in 10 daily fractions 8 Gy in 1 fraction
IMRT/VMAT	Palliative control of symptoms	Whole or partial liver	20–30 Gy in 5–10 daily fractions
SBRT	Durable local control of limited number of metastases (≤5 lesions) not amenable to surgery but <6 cm, and limited extrahepatic disease	Gross tumor	54 Gy in 3 fractions over 1–2 weeks 50 Gy in 5 fractions over 1–2 weeks
SIRT	Durable local control of limited or modest number of metastases not amenable to surgery, particularly larger tumors, and limited extrahepatic disease	Segment(s), lobe, or whole liver	≥120 Gy in 1–2 fractions separated by 30–45 days
Resection/RFA	Durable local control of limited number of metastases amenable to surgical approach	Gross tumor or segment	
Systemic therapy	Significant hepatic or extrahepatic disease burden		

6.2 Section 2. Planning Considerations and Treatment of Non-Colorectal Metastases

6.2.1 Treatment Techniques

6.2.1.1 Conventionally Fractionated Techniques

Three-dimensional conformal radiotherapy (3D–CRT) entails a forward-planning process wherein the clinician specifies beam shape, direction, profile, and intensity. The clinician then manually adjusts these parameters for each beam according to clinical discretion until a satisfactory treatment plan is achieved. The high degrees of conformality and dose heterogeneity offered by 3D–CRT can generate steep dose gradients that both allow both dose escalation to the tumor and facilitate normal tissue sparing. This enhancement of the therapeutic ratio is essential in SBRT.

Intensity-modulated radiotherapy (IMRT) refers to an inverse-planning process with the clinician defining high-dose regions covering the tumor or subclinical disease and regions containing OARs to which dose should be constrained. A computer then utilizes an automated iterative algorithm that aims to achieve acceptable dose coverage while maintaining OAR dose constraints in order to produce an optimized treatment plan. Like 3D–CRT, IMRT offers highly conformal dose distributions that can achieve high doses to the tumor while sparing critical structures (see Fig. 6.2).

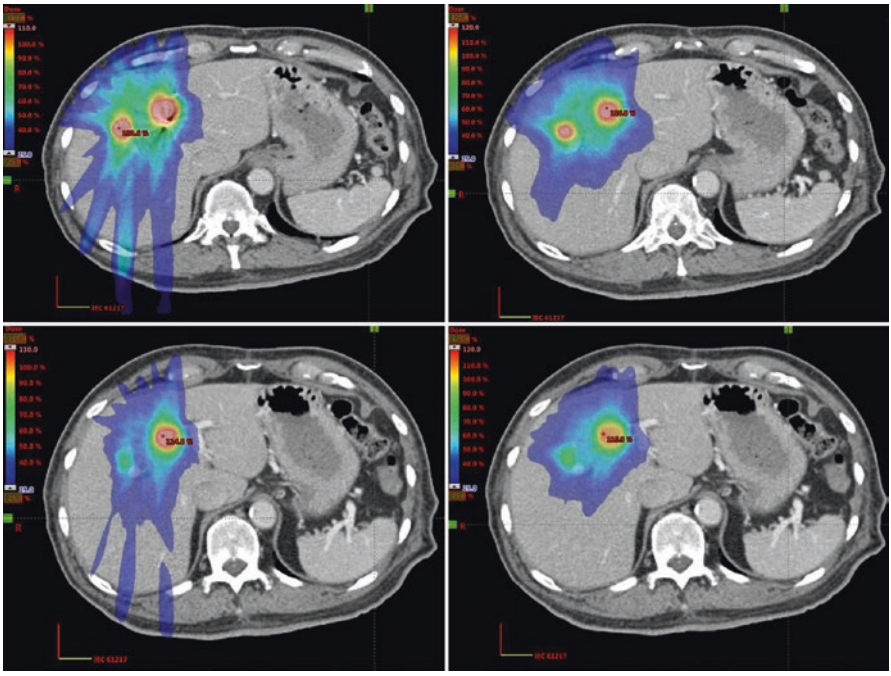

Fig. 6.2 Comparison of 3D–SBRT (*left*) vs. VMAT-SBRT (*right*) plans for treatment of two liver metastases. Dose wash diagram showing higher conformality of VMAT/IMRT plan

Volumetric intensity-modulated arc therapy (VMAT) is a specific type of IMRT that allows rapid conformal delivery of radiotherapy via simultaneous rotation of the gantry through an arc, collimation of leaves within the gantry, and variation in beam intensity.

Helical Tomotherapy is another continuous rotational platform for IMRT delivery that consists of a linear accelerator mounted to a ring gantry with a binary collimator and megavoltage CT (MVCT) scanner. The gantry delivers a fan beam of radiation as it continuously rotates around the couch as it translates through the machine. While the large number of gantry angles (51 angles assumed per rotation) is advantageous for conformal planning, the on-board MVCT is limited by a lack of soft tissue contrast [38].

In comparison to static IMRT, rotational therapies such as VMAT and Tomotherapy produce plans that are more conformal in high-dose regions and tend to reduce treatment time; however, they also entail delivery of low doses to larger volumes of normal tissue, thereby producing a higher integral dose. In contrast, static IMRT delivers comparatively high doses to smaller volumes of normal tissue [39].

6.2.1.2 Stereotactic Body Radiotherapy

Stereotactic body radiotherapy (SBRT) allows delivery of high doses of radiotherapy to target lesions in a highly conformal manner over a small number of fractions (typically fewer than five). It offers the benefit of durable local control

without the invasiveness of a surgical, percutaneous, or endovascular intervention. This ablative effect stems from both the DNA damage from high cumulative doses of radiotherapy and a separate postulated effect of the high dose-per-fraction on endothelial cells that triggers microvascular collapse within the target region. SBRT is therefore thought to enhance the therapeutic ratio as compared to conventionally fractionated radiotherapy by increasing the effective target dose while excluding normal tissue (see Fig. 6.3 for an example SBRT plan using fiducial markers to target two hepatic metastases with a highly conformal dose distribution).

The parallel arrangement of the liver's functional subunits renders the organ a suitable target for SBRT, as the functional redundancy ensures that the remaining healthy tissue can compensate for the ablated portion of the liver parenchyma.

The past century has witnessed a shift in stereotactic localization technique from frame-based to image-guided approaches. This has resulted in a move away from stereotactic body frames to less restrictive immobilization devices and towards on-board imaging, which has been enabled by X-ray and CT technology equipped on modern linear accelerators. In contrast to lesions in the lung, which are relatively easy to discern on cone-beam CT (CBCT), visualization of liver lesions is comparatively difficult. For this reason, placement of fiducial markers (discussed below) leads to improved target localization. CBCT is usually limited for target localization within the hepatic parenchyma, and fiducials can facilitate patient setup before each treatment and allow intrafraction assessment of motion in real-time.

The precise delivery of radiotherapy offered by SBRT would not be possible without recent technological advances allowing precise target localization, treatment planning, motion control, image guidance, and radiotherapy delivery. Each of these constitutes an essential component of a high-quality liver SBRT program.

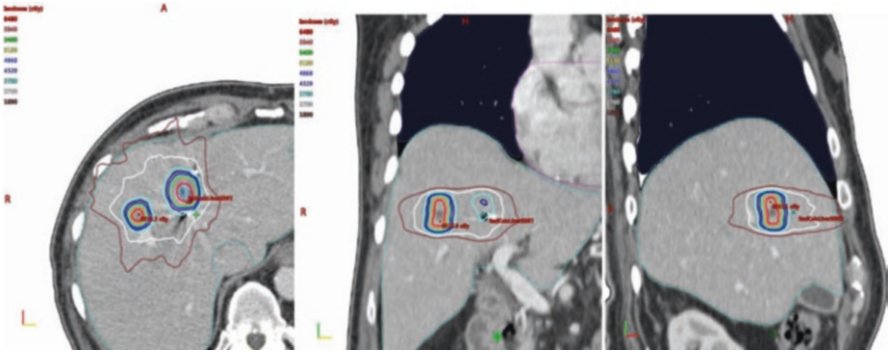

Fig. 6.3 SBRT plan for 78-year-old man with oligometastatic GIST. Note fiducial marker placement for treatment setup and respiratory gating. Patient was treated to 5400 cGy in 3 fractions to PTV, with GTV taken to 6400 cGy. Liver constraints were met with >1500 ccs with dose below 15 Gy. Patient-tolerated treatment well with no side effects experienced during or after treatment, with good local control on follow-up scans

6.2.1.3 Selective Internal Radiotherapy

Selective internal radiotherapy (SIRT) has emerged as an alternative radiotherapeutic modality for non-colorectal hepatic metastases. This technique, typically performed in conjunction with an interventional radiologist, entails percutaneous injection of radioisotope-embedded microspheres into the arterial supply of targeted liver segments. These spheres then become trapped in the hypervascularized tumor locale, where they exert both microembolic and radiotherapeutic effects. The microspheres are composed of either resin (SIR-Spheres) or glass (TheraSpheres) loaded with yttrium-90 (^{90}Y), a pure β-emitting isotope with a relatively short half-life of 64 hours.

SIRT offers potential advantages over external beam radiotherapy. First, hepatic metastases tend to derive the majority of their blood supply from the hepatic arterial circulation, in contrast to the normal hepatic parenchyma, which is predominantly supplied by the portal venous system [40]. This distinct blood supply, in addition to the limited tissue penetration of ^{90}Y into surrounding tissue, can lead to a brachytherapy-like dose distribution and a favorable therapeutic ratio.

As the logistics of SIRT delivery are distinct from those for EBRT, the planning process differs, as well. In addition to the typical work-up for hepatic metastases including physical examination, imaging, and laboratory studies, patients should also undergo mesenteric angiography with attention to the hepatic vasculature, extrahepatic vasculature, and any liver-to-lung shunts. Prophylactic embolization of extrahepatic vessels is recommended to reduce the risk of nontarget microsphere deposition. Careful calculation and planning of dose distribution should be performed, taking into account microsphere type, vascular anatomy, liver function, tumor burden, and potential for nontarget deposition.

Infusions can be targeted at specific lesions, segments, lobes, or the entire liver, and they can be delivered in single or sequential fractions separated by at least 4 weeks. Typical prescription doses approach or exceed 120 Gy. Infusions take place an outpatient basis. For improved tolerance and toxicity mitigation, short courses of PPI, antiemetic, anti-inflammatory, and analgesic medications can be prescribed before and after infusions.

6.2.2 Simulation

Prior to simulation, placement of fiducial markers is recommended to allow for precise target localization and motion assessment. Our institutional practice is to have 2–3 gold fiducial markers placed under fluoroscopy via a percutaneous transhepatic approach in or around the lesion. Gold markers are preferred as they are readily visualized by kilovoltage (kV) imaging. Placement should take place at least 3–5 days before simulation in order to allow for any fiducial migration and resolution of postprocedural inflammation. Dedicated fiducial markers may not be necessary if existing surgical clips from prior interventions are close enough to the lesion to provide adequate localization. In situations where it is not possible to implant fiducial markers or use existing surgical clips, anatomic landmarks

appreciable on kV imaging, such as the hepatic margin or dome of the diaphragm, can be used.

The overarching goal of simulation is to establish reference conditions for a patient's radiation treatment that are readily reproducible. Computerized-tomography (CT)-based simulation is typically performed with the patient in the supine position with arms extended overhead and immobilized from the thighs to the thorax, with an overarching goal of achieving a setup that can be duplicated during each fraction. Intravenous contrast can facilitate delineation of both target and normal anatomy, with most metastases best visualized in the portal venous phase. Oral contrast given approximately 30 minutes prior to simulation can enhance visualization of small bowel and stomach. We utilize four-dimensional (4D) CT simulation in order to delineate lesion motion with the respiratory cycle. This entails a modified CT scanning protocol that synchronizes couch translation through the CT bore with the respiratory pattern of the patient, resulting in the acquisition of the entire respiratory cycle at each table position. The patient's respiratory cycle is then reconstituted and divided into phases, each associated with a distinct 3D reconstruction of the patient and assigned a percentage value, with end-inspiration corresponding to 0% (and 100%) and end-expiration to 50%.

Given their hypodense appearance on CT, liver lesions may not be adequately visualized on the simulation study. In this situation, additional imaging modalities such as diagnostic CT with multiphasic contrast enhancement, magnetic resonance imaging (MRI), or fluorodeoxyglucose positron-emission tomography (FDG-PET) can be obtained to facilitate target delineation. Care must be taken when fusing and registering diagnostic studies, typically acquired with free-breathing, to simulation images, which may be acquired with the motion management techniques discussed below.

6.2.3 Motion Management

Despite the enhanced accuracy afforded by fiducial markers and multiple imaging modalities, uncompensated organ motion can nevertheless compromise precise treatment delivery, especially if smaller fields are utilized as in SBRT. In one study [41], liver tumor motion attributed to the free-breathing respiratory cycle averaged 0.9 cm craniocaudally, 0.5 cm anteroposteriorly, and 0.4 cm mediolaterally, but extended as high as 1.9 cm, 1.2 cm, and 1.2 cm, respectively. Greater motion was observed among lesions in the left lobe, those in cirrhotic livers, and those in post-surgical livers. Liver motion secondary to the cardiac cycle was comparatively negligible at an average of 0.2 cm. Beyond movement induced by the respiratory and cardiac cycles, additional motion can result from variable gastric and duodenal filling and even variation in setup of abdominal compression. Liver motion is therefore complex and must be taken into account when planning conformal radiotherapy. As a result, motion management constitutes an integral component of a high-quality liver SBRT program.

Motion management techniques can be broadly categorized as either motion restricting or motion compensating.

Motion restriction methods are designed to limit diaphragmatic movement and include abdominal compression and active breathing control. The former consists of a paddle or inflatable belt that compresses the abdominal cavity, increases intra-abdominal pressure, and limits diaphragmatic excursion, thereby resulting in reductions in liver motion amplitude of roughly 50% [42, 43], typically to fewer than 10 mm. Treatment is then delivered in a continuous fashion. Active breathing control [44] requires the patient to hold his or her breath at a specified phase of the breathing cycle, typically maximal inspiration, thereby arresting diaphragmatic excursion and liver motion. This technique requires patient adherence to predictable respiration patterns and video tracking to ensure treatment delivery at the desired phase of the breathing cycle.

Motion compensation typically entails cyclical delivery of radiotherapy during specific intervals of time when the tumor passes through a known space. Respiratory gating systems track chest wall movement as a surrogate for tumor position and trigger the beam to deliver radiation only during specified portions of the respiratory cycle. Multiple systems have been developed to track the respiratory cycle, including Varian's Real-time Position Management (RPM) system, which uses external infrared markers on the patient that are tracked via a special camera (Fig. 6.4). Of note, respiratory gating triggers treatment delivery by movement of the chest wall rather than by detection of fiducials or

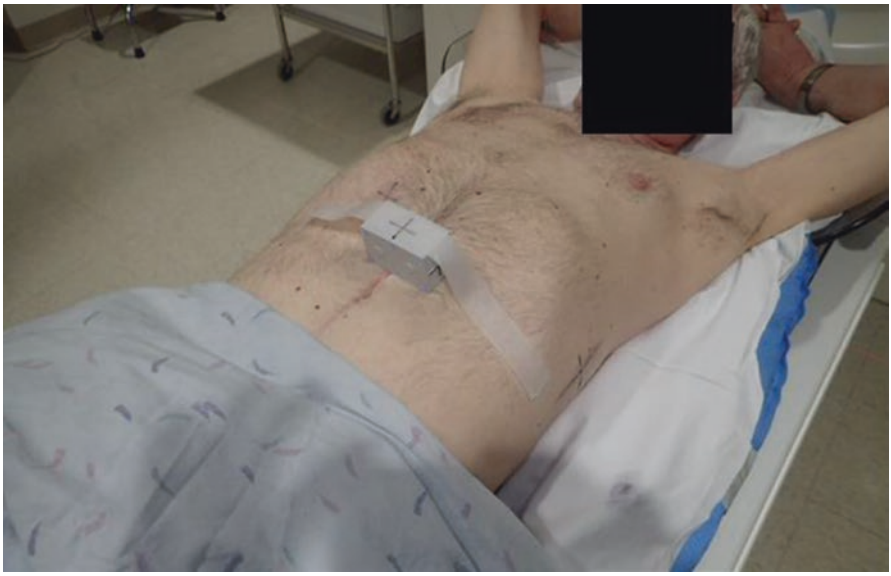

Fig. 6.4 Patient setup using Varian RPM respiratory gating. Note supine position with arms overhead. Beam cycled on at end-expiratory phase of breathing cycle, tracked by position of infrared marker

tumor. For this reason, the beam is typically cycled on during end-expiration (typically between the 40 and 70% phases of the cycle), as motion is smallest within this window. Some systems utilize fluoroscopy to monitor tumor motion in relation to chest wall motion. Other motion compensation systems track the tumor more directly, such as that utilized by CyberKnife®, which localizes fiducial markers in real-time.

Motion management techniques, especially restrictive methods that alter or limit normal respiratory excursion, can cause significant patient discomfort. Clinicians may wish to consider prescribing a small quantity of benzodiazepines, which can help alleviate this discomfort, ensure a reproducible breathing pattern, and in a randomized trial modestly reduced liver motion [45].

6.2.4 Contouring

After the CT acquired at time of simulation is fused with any additional diagnostic imaging (multiphasic CT, MRI, FDG-PET), the entire extent of the lesion appreciable in these studies should be contoured as gross tumor volume (GTV). If respiratory gating is used, GTV should be defined on an end-expiratory image. A clinical treatment volume (CTV) to account for subclinical disease is not typically utilized in SBRT planning.

If motion restriction techniques such as abdominal compression are to be employed, an internal tumor volume (ITV) should be contoured that encompasses the entire motion of the tumor during the respiratory cycle. The generation of a maximum-intensity projection (MIP) or minimum-intensity projection (MinIP) may facilitate ITV delineation. Alternatively, if motion compensation techniques such as respiratory gating are to be used, the ITV should be contoured on scans corresponding to the gated phases (i.e., 40–70% phases).

Expansion to planned tumor volume (PTV) depends on the motion management approach. With motion restriction, appropriate margins can range from 5 to 10 mm [33], while with motion compensation, adequate image guidance afforded by 4DCT planning and intrafractional motion assessment may preclude the need for a PTV expansion of greater than a few millimeters.

Organs-at-risk including normal liver (excluding GTV), spinal cord, small bowel (either individual loops or the entire peritoneal cavity), stomach, and both kidneys should be contoured on the end-expiration breath-hold scan (Fig. 6.5).

Fiducial markers should be contoured at the 50% phase (end-expiration) and on the first phase of the gating window (i.e., 40% if gate opens at 40% phase), if gating is to be used.

6.2.5 Dose Prescription

A variety of dose-fractionation schedules have been reported, including single fractions of 14–30 Gy [33, 46, 47], two fractions of 10–20 Gy [29], three fractions of

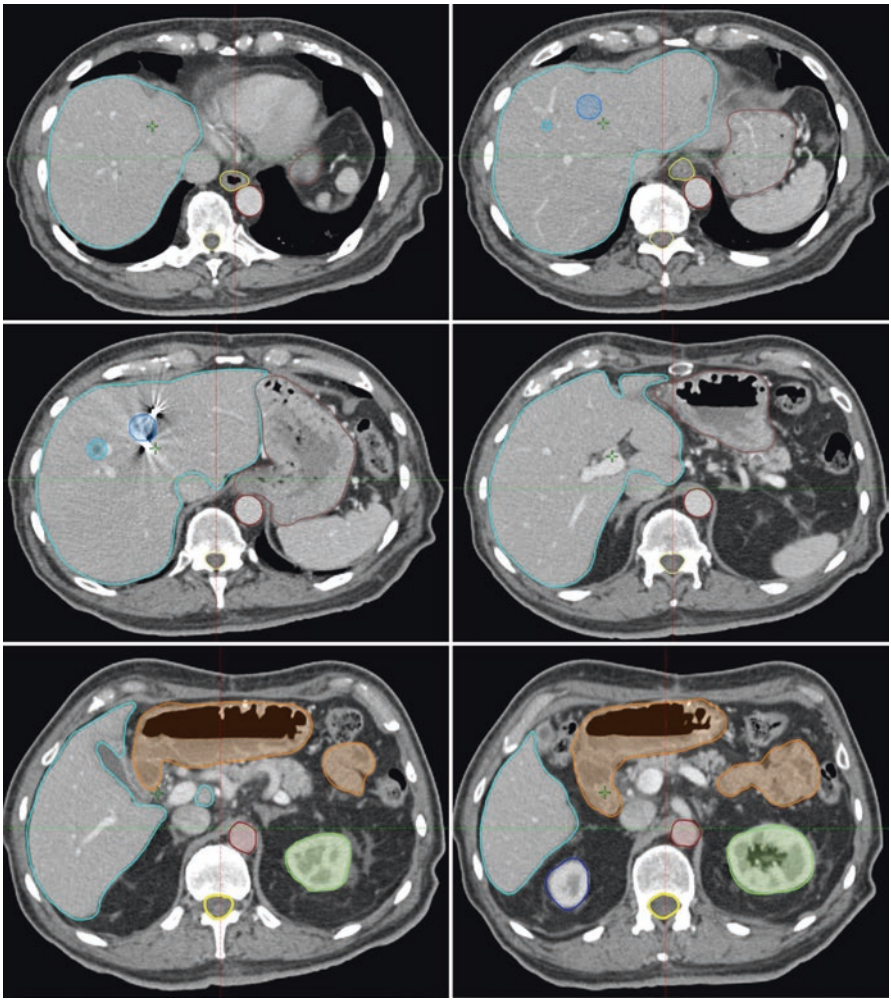

Fig. 6.5 OAR contours for liver SBRT. Liver in *cyan*, small bowel in *orange*, stomach in *brown*, aorta in *maroon*, spinal cord in *yellow*, left kidney in *green*, right kidney in *blue*, tumor PTVs delineated in *light blue* and *cyan*

9–20 Gy [29–31, 47], four fractions of 7–10 Gy [29, 30, 47], five fractions of 5–12 Gy [35, 47], and six fractions of 9–10 Gy [48].

RTOG 0438 was a single-arm dose escalation trial evaluating the maximum-tolerated dose of ten hypofractionated treatments, starting at 4 Gy fractions and proceeding up to 5 Gy fractions. Results presented in abstract form [49] demonstrated no dose-limiting toxicities within 90 days of radiotherapy. While these findings indicate that 5 Gy × 10 is a feasible and safe regimen for liver metastases, data supporting its efficacy are lacking.

Table 6.2 Commonly used dose constraints

Organ at risk	QUANTEC	RTOG 1112 (5 fractions)	RTOG 0438 (10 fractions)
Liver (liver—GTV)	Standard fractionation: mean < 32 Gy 3 fractions: mean < 15 Gy 3–5 fractions: $V_{15\ Gy}$ < 700 cc 6 fractions: mean < 20 Gy	Mean ≤ 13 Gy (Child-Pugh A)	$V_{27\ Gy} \leq 30\%$ $V_{24\ Gy} \leq 50\%$
Spinal cord	Standard fractionation: Max dose ≤50 Gy 1 fraction: Max <13 Gy	Max dose ≤25 Gy to 0.5 cc (cord + 5 mm)	Max dose ≤34 Gy
Stomach	Standard fractionation: Max dose <45 Gy SBRT: $V_{22.5\ Gy} \leq 4\%$ & $V_{22.5\ Gy} \leq 5$ cc 3 fractions: Max dose <30 Gy	Max dose ≤30 Gy to 0.5 cc	$V_{37\ Gy} \leq 1$ cc
Small bowel	Standard fractionation: $V_{45\ Gy\ (peritoneal\ cavity)}$ < 195 cc OR $V_{15\ Gy\ (bowel\ loops)}$ < 120 cc 1 fraction: $V_{12.5\ Gy\ (bowel\ loops)}$ < 30 cc (avoid circumferential) 3–5 fractions: Max dose to loops <30 Gy	Max dose ≤30 Gy to 0.5 cc	$V_{37\ Gy} \leq 1$ cc
Kidney (bilateral)	Mean dose <15–18 Gy	Mean dose <10 Gy	$V_{18\ Gy} \leq 33\%$ (normal renal function) $V_{10\ Gy} \leq 10\%$ (renal dysfunction)
Chest wall		Max dose ≤50 Gy to 0.5 cc	
Esophagus	Standard fractionation: mean < 34 Gy	Max dose <32 Gy to 0.5 cc	
Heart	Standard fractionation: mean < 26 Gy	Max dose <30 Gy to 30 cc	

At our institution, our schedule of choice is 18–20 Gy × 3; however, for tumors in the vicinity of critical structures including the central liver zone (portal vein to its bifurcation within the liver expanded by 2 cm), we tend to use a more fractionated schedule of 10–12 Gy × 5.

Recent and current prospective trials of liver SBRT specify that the prescription dose be prescribed to various isodose lines, ranging 65–90% [31, 33, 35, 46].

Common dose constraints are shown in Table 6.2.

6.2.6 Complications/OARs/Strategies to Reduce Toxicity

6.2.6.1 Hepatotoxicity

Preserving functional liver should be a paramount goal in the management of hepatic metastases. Based on surgical series, up to 80% of the liver parenchyma

can be resected without clinical liver failure [50, 51]. In comparison, radiotherapy historically had a limited role in the management of liver metastases due to the significant risk of radiation-induced liver disease (RILD) associated with whole liver doses insufficient to achieve meaningful tumor control. However, the advent of more conformal techniques has allowed delivery of higher doses to defined targets while sparing an adequate amount of hepatic parenchyma.

RILD, also known as radiation hepatitis, refers to acute changes in the liver including veno-occlusive disease in the hepatic sinusoids that lead to congestion, hemorrhage, and necrosis. Onset typically occurs within 4–8 weeks after radiotherapy and manifests with fatigue, hepatomegaly, ascites, and abnormal liver function tests. Most patients recover within 6 months; however, a minority progress to fibrosis and chronic hepatopathy. The incidence of RILD following SBRT is low, typically occurring in fewer than 5% of patients [52]. In models of radiation-associated liver injury and dose constraints, it is presumed that the functional contribution of any liver tumor is negligible, and therefore, the liver OAR is considered to be the functional component, defined as total liver volume minus all GTV's, and also referred to as effective liver volume (V_{eff}).

It is important to note that the recommended dose constraints for hepatic metastases are more permissive than those applicable in the treatment of primary liver lesions. Primary liver tumors tend to arise in the background of cirrhotic livers, which tend to have less functional reserve and therefore reduced tolerance to radiotherapy. Most patients with hepatic metastases do not have underlying cirrhosis, and their livers are therefore thought to be less susceptible to RILD [53]. Most prospective trials of liver SBRT exclude patients with Child-Pugh class B or worse. In parallel phase I studies of liver SBRT for primary and metastatic tumors conducted at the same institution, 17% of patients with primary tumors progressed from Child-Pugh class A to class B within 90 days of SBRT and 12% developed grade 3 LFT abnormalities [54], compared to 6% and 3%, respectively, among patients with metastases [48].

A constraint implemented in an early dose escalation trial of 3-fraction SBRT for liver metastases specified $V_{15\,Gy} < 700$ cc and resulted in no grade 3 or higher hepatotoxicity [31], under the premise that a minimum critical volume of functional liver must be spared significant dose in order to preserve adequate hepatic function. This metric was subsequently adopted by QUANTEC for courses of 3 to 5 fractions [52]. Additional recommendations for SBRT for hepatic metastases from QUANTEC include mean dose <15 Gy in 3 fractions and mean dose <20 Gy in 6 fractions. In the setting of Child-Pugh B disease, mean dose <6 Gy in 4 to 6 Gy fractions is recommended.

Other proposed volumetric constraints include $V_{15\,Gy} \leq 50\%$ and $V_{21\,Gy} \leq 30\%$ in 3 fractions [55], and $V_{17.1\,Gy} \leq 700$ cc and $V_{21\,Gy} < 700$ cc in 5 fractions [56].

When standard fractionation is to be used in the management of liver metastases, a mean dose <32 Gy has been modeled to yield a < 5% risk of RILD [25].

6.2.6.2 Enteral Toxicity

Treatment of lesions in proximity to the stomach and small bowel can place patients at risk for erosive gastritis/enteritis, bleeding, stricture, ulceration, and perforation. An early report of SBRT reported a single episode of hemorrhagic gastritis (in a patient with premorbid gastritis) when the stomach $V_{14\,Gy} \leq 30\%$ in 2 fractions and a single episode of symptomatic gastritis where the stomach wall likely fell into the high-dose region of a 3-fraction course [29]. In another series containing 44 patients undergoing SBRT to liver metastases, one patient developed colonic perforation requiring surgery and two experienced duodenal ulcerations managed conservatively [57]. In each case, dose to the affected organ exceeded 30 Gy.

An early phase I trial of 3-fraction liver SBRT specified a maximum dose to the stomach or small intestine of 30 Gy [31], a metric also adopted by QUANTEC. Others have proposed more conservative constraints such as max doses of 24 Gy in 3 fractions and 32 Gy in 5 fractions for both the stomach and duodenum [35, 56], which have translated to negligible luminal toxicity.

It is our practice when planning SBRT for lesions in the medial aspect of the liver to prescribe a short course of proton-pump inhibitor therapy to reduce the risk of enteral toxicity. While the application of these medications in SBRT is not supported by randomized evidence, it is reasonable to assume that the efficacy of these medications in preventing and treating other etiologies of luminal mucosal injury extends to radiation-induced injury, as well.

6.2.6.3 Chest Wall Toxicity

While inflammation of muscles, bones, nerves, and connective tissue in the chest wall (CW) is a relatively common and transient phenomenon manifesting in mild to moderate pain, rib fractures can be quite painful but are fortunately rare. The most common dosimetric parameter used for the CW in the management of peripheral lung lesions is $V_{30\,Gy}$ [58–60]. One analysis of 60 patients undergoing three to five fractions reported 0% incidence of pain or fracture when the corresponding $V_{30\,Gy} < 30$ cc, which increased to 30% incidence when the $V_{30\,Gy}$ exceeded 35 cc [60]. Another analysis of patients undergoing 3–5 fractions for non-small cell lung cancer identified significant increased incidence of grade 2 CW pain when $V_{30\,Gy} > 70$ cc [61].

6.2.7 Special Considerations for Dosimetry and Physics QA

Beyond the treatment planning and delivery considerations above, several additional factors must be taken into account in the development and implementation of a liver SBRT program. First, all staff involved in the planning and delivery process must have appropriate education and experience. As the large doses, small target volumes, and limited number of fractions associated with SBRT leave a

small margin for error, team members must be well-versed in setup procedures, planning parameters, and delivery protocols. Rather than a single episode taking place during the on-boarding of each new team member, training should be a continuous process undertaken by the entire team at regular intervals. These strategies will ensure that the impact of uncertainties in this rapidly evolving technique is minimized.

Next, all systems and devices employed in SBRT delivery must be commissioned and maintained to an appropriate standard. Given the small fields used in SBRT, even minor errors in commissioning data measurements can significantly impact the ultimate dose delivered [62], and therefore, regular verification of mechanical accuracy of the linear accelerators and dosimetric verification of the treatment-planning models must be performed. The importance of commissioning also extends to ancillary systems including on-board or in-room imaging modalities and motion management devices such as abdominal compression and respiratory gating equipment. Task Group Report 101 [63] details appropriate testing for various systems relevant to an SBRT program.

Another consideration is quality assurance. This process should take into account data from commissioning and regularly benchmark system performance to this baseline. Isocenter verification should be performed daily, and more intensive testing should take on a less frequent basis. While many of these procedures are part of routine quality assurance for linear accelerators delivering standard fractionation schedules, the requirements for SBRT delivery are more stringent [64].

6.3 Summary

As discussed, there is a growing set of tools to treat liver metastases in the so-called oligometastatic setting. These tools, when used appropriately depending on tumor biology, location, surgical candidacy, performance status, and responsiveness to systemic therapy, have the potential to confer high local control, correlating with longer survival than historically possible. These cases should be discussed before multidisciplinary tumor boards at high volume institutions with experience treating these lesions. Patient selection remains key, particularly as surgical resection remains the gold standard for local control of liver metastases, though with the efficacy in obtaining local control and tolerability of SBRT and interventional ablative techniques now very high, more patients are candidates for ablative therapy to solitary liver metastases, solo and in combination. SBRT is a powerful tool for the radiation oncologist, which when using appropriate constraints, fiducial placement, motion management, and dose escalation, can provide excellent local control with minimal complications in this setting (Fig. 6.6).

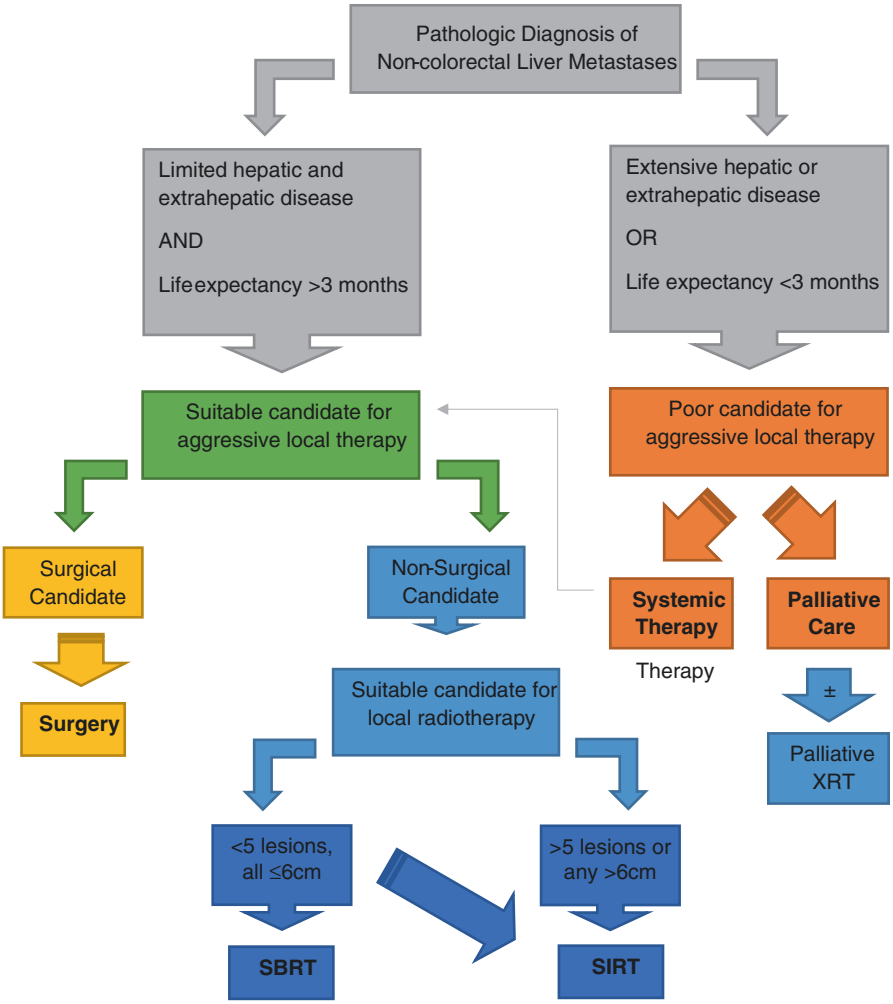

Fig. 6.6 Treatment algorithm

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Proton Beam Therapy for Hepatic Malignancies

7

Smith Apisarnthanarax, Rosanna Yeung, Stephen Bowen, and Tobias R. Chapman

Contents

7.1 Introduction

Historically, external bream radiation therapy for liver cancers was regarded as unsafe due to high rates of radiation-induced liver disease (RILD) that resulted when delivering definitive doses to tumors [1]. Advances in technology and biological understanding of liver radiation tolerances, however, have led to the development of more conformal radiotherapy techniques allowing for partial liver irradiation while significantly reducing the risk of RILD [2, 3].

PBT has emerged over the last couple of decades as a promising treatment modality for primary and metastatic liver tumors due to its distinct dosimetric advantages compared to conventional photon radiotherapy [4]. Photons are absorbed exponentially in tissue and deposit dose along the path of the beam, resulting in exit dose to adjacent normal tissues, particularly the surrounding normal (non-tumor) liver. In contrast, protons exhibit a finite range in tissue. The energy loss of a proton beam per unit length is small until at the end of the beam range. Near the end of the beam range, the residual energy of a proton beam is lost over a very short distance

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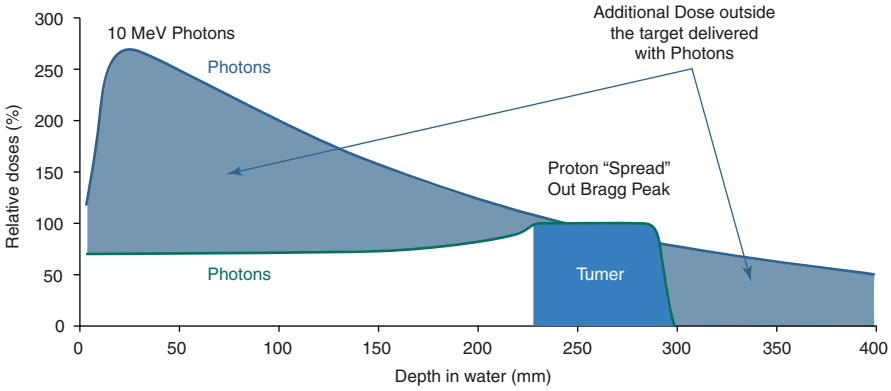

Fig. 7.1 Depth-dose characteristics of photons compared to protons (single beam displayed). Due to the spread out Bragg Peak, protons deliver less radiation dose proximal and distal to tumors

and comes to a rest, resulting in a distinct sharp rise in absorbed dose called the "Bragg peak" and a sharp dose falloff (Fig. 7.1).

The risk of RILD is found to be particularly dependent on the volume of liver receiving low doses [5, 6]. As such, the lack of exit dose with PBT offers a dosimetric advantage over photon therapy by reducing the liver volume irradiated to low doses, thereby potentially decreasing the risk of RILD while still allowing for tumor dose escalation [4, 7] (Fig. 7.2).

Dose escalation has been associated with improved OS in primary liver tumors [8, 9]. For hepatocellular carcinoma (HCC), the liver-sparing characteristic of PBT is particularly advantageous for tumor dose escalation while minimizing RILD, as most patients have impaired liver function due to cirrhosis and/or have received prior liver-directed therapies [8]. In the case of unresectable or medically inoperable intrahepatic cholangiocarcinoma, PBT delivered in a dose-escalated hypofractionated manner may potentially allow for improved outcomes with a shortened treatment duration and less acute toxicity compared to conventionally fractionated chemoradiation with photons [9, 10]. Although there is less data regarding the use of PBT for treatment of liver metastases, PBT may be considered for large tumors not amenable to stereotactic body radiotherapy (SBRT) and/or in patients with increased risk of RILD due to prior history of liver-directed or systemic therapies.

There are no consensus guidelines for choosing the appropriate radiation modality for patients with liver malignancies who are eligible for PBT and photon-based treatment such as SBRT; this topic is an active area of investigation. HCC data from Japanese trials have suggested a specific benefit for PBT in treating very large (> 10 cm) tumors, severely cirrhotic (Child-Pugh class C) patients, elderly patients (>80 years old), and patients with portal vein tumor thrombosis [11–13]. Clinical outcomes of studies from Japan and the United States for PBT in HCC have demonstrated excellent 2- to 5-year local control rates ranging from 88% to 95% [10,

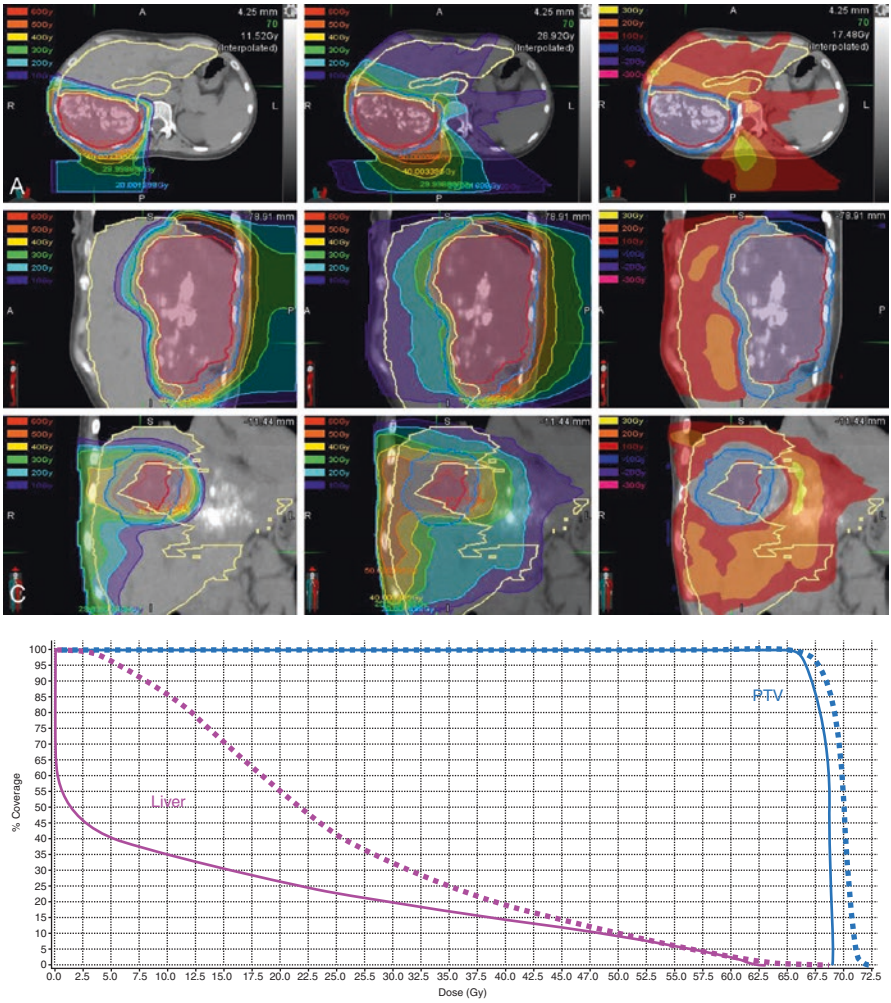

Fig. 7.2 (**a**–**d**) A 36 y/o female with a large (15 cm) multinodular BCLC stage B hepatocellular carcinoma in the setting of hepatitis B-related Child-Pugh A6 cirrhosis s/p transarterial chemoembolization with persistent, viable disease treated with hypofractionated proton beam therapy to 67.5 GyE in 15 fractions using a posterior and right anterior oblique beam approach. Row **a**, axial views of proton beam therapy with pencil-beam scanning plan (*left column*), photons with volumetric-modulated arc therapy plan (*middle column*), and dose difference map (*right column*) depicting additional dose delivered with photons (*red-yellow* color scale). Row **b**, sagittal views. Row **c**, coronal views. GTV, *red* color wash. PTV, *blue* color wash. Liver minus GTV, *khaki* line. **d**, DVH analysis of proton (*solid lines*) and photon (*dashed line*) plans

14–17]. A cooperative group randomized trial comparing SBRT and PBT for unresectable HCC (NRG-GI003) has recently been opened which should provide more insight on identifying which patients may benefit from PBT [10].

7.2 Proton Beam Therapy Approaches

7.2.1 Simulation

7.2.1.1 Motion Assessment

As the liver is located directly under the diaphragm, it is subject to movement during respiration. Although the movement is most substantial in the cranial-caudal direction, studies have demonstrated that movement in other directions may also be significant [18, 19]. The American Association of Physicists in Medicine Task Group 76 recommends motion management techniques in tumors that move >5 mm [20]. Because the proton range is highly dependent on tissue density, treating moving targets within an inhomogeneous medium can lead to overdosing normal tissues or underdosing tumor targets. This effect is pronounced in the liver, due to the air and soft tissue interface near the dome of the diaphragm, and to a lesser extent the bone-soft tissue interface near ribs. Furthermore, PBT delivery techniques that rely on active pencil-beam scanning are susceptible to a destructive interplay between the time-interval over which the target dose is delivered and the similar time-interval over which the patient breathes. This degradation in radiation dosimetry is known as the interplay effect [21]. Assessment of motion when treating liver tumors with PBT, therefore, is particularly critical and arguably even more important for PBT than photon-based treatments.

At most institutions, motion assessment is performed with a 4D–CT scan acquired during free breathing. Dependent on the location of the target, various surrogates have been used to assess tumor motion, particularly in tumors that are not well seen on non-contrast scans (e.g., HCC tumors). Fiducial marker placement, typically performed percutaneously by ultrasound-guidance, is generally recommended whenever feasible, and particularly important in proton systems lacking on-board volumetric imaging capabilities (CBCT) [18]. Other surrogates have also been used including diaphragmatic excursion, previous stents, surgical clips, or lipiodol stains [19, 22–24]. Markers in closest proximity to the target should be used as studies have demonstrated increased difference in the absolute range of target motion with increased distance between markers [19]. There is no consensus on which form of motion management is recommended, although published literature has suggested that these methods should be considered when treating tumors with motion >1 cm [25].

Proton beam range is highly dependent on the stopping power of tissues along the beam path. As stopping power is calculated from the Hounsfield Units of tissues (HU), it has been demonstrated that presence of lipiodol stains can result in an underestimation of the proton beam range by treatment planning systems. Thus, when lipiodol stains are present, HUs should be overridden and replaced by the HU of surrounding normal (liver) tissue for more accurate range calculations during treatment planning [22]. The same principles apply to implanted hardware, which include fiducials such as gold seeds or titanium clips. For permanent implants that will be present during treatment, it is advisable to override to the

known density and material composition of the fiducial. In any implanted metal, surrounding metal shadowing artifacts should be overridden to the neighboring mean tissue density.

For liver malignancies where proximity to normal tissues (such as bowel or stomach) limits the deliverable radiotherapy dose, surgical placement of a tissue spacer to achieve separation prior to radiotherapy may be considered. Preliminary studies have demonstrated feasibility of this approach with open or laparoscopic placed biologic mesh spacers [26].

7.2.1.2 Motion Management

Tumor motion may be accounted for by either passive or active methods. The following are the most common types of motion management utilized in PBT of liver malignancies:

(a) Free-breathing with Internal Target Volume (ITV): *Passive*

Patients are simulated with and planned on a 4D–CT scan. Gross tumor volume (GTV) is contoured on all respiratory phases of the 4D–CT scan. The sum of GTV volumes (or CTV volumes if applicable) in all respiratory phases results in an internal target volume (ITV) that covers all possible positions of the tumor during respiration.

(b) Volumetric Rescanning of ITV: *Passive*

This method applies only to PBS techniques and is recommended at our institution for tumor motion between 5 and 10 mm. Following generation of a motion-encompassing plan on the 4D–CT scan, each original beam is split into at least two beams with identical weights/monitor units. This lengthens the time during which the tumor is scanned with PBS and thereby reduces the interplay effect with respiratory-induced target motion. Other methods such as layered rescanning involve rescanning of individual proton energy layers, though this can still lead to degradation in tumor radiation dosimetry along the beam path at the interface between energy layers. Rescanning techniques may be able to mitigate motion-related dose inhomogeneity for tumors with motion $\leq$10 mm to some degree, but other motion mitigation strategies are recommended for tumor motion >10 mm [27].

(c) Breath Hold: *Active*

In this method, patients are instructed to hold their breath during treatment to reduce tumor motion. This results in smaller margins required in the expansion of the target volume to account for tumor motion. Previous studies have demonstrated superior reproducibility of end-expiration breath hold compared to end-inspiration breath hold, and many institutions therefore favor end-expiration breath hold treatment [28, 29].

Breath hold may be accomplished either: (1) voluntarily, by the patient voluntarily holding their breath at the predefined phase of their respiratory cycle or (2) involuntarily by the aid of a commercial device (such as an active breathing control [ABC] device) which imposes a breath hold.

Breath hold treatment poses specific challenges with regard to PBT compared to photons. The delivery of PBT, either through passive uniform scanning (US) or active PBS, is through consecutive layers of dose from most distal to proximal edge of the target, and there is an inherent delay between delivery of each layer. For a single energy cyclotron-produced beamline, PBS layer switching times are on the order of 3–5 s. Beam delivery times, therefore, generally are longer for US/PBS PBT (200–500 s) versus photons (100–200 s) and patients can only interrupt their breath hold between layers. Length of beam delivery is even longer with PBS compared to US due to the duration of energy tuning between layers (*see Passive versus Active Techniques*). In general, treatment plans that reduce the number of energy layers, and to a lesser extent, those that reduce the number of spots required to provide clinically sufficient target coverage will improve the duty cycle of PBT delivery under breath hold conditions. In addition, uncertainties related to breath hold reproducibility and/or setup may be more pronounced and problematic compared to photon-based treatment (*see Breath Hold Reproducibility and Uncertainties*).

(d) Abdominal Compression: *Active*

The use of an abdominal compression belt encourages shallow breathing, thereby reducing diaphragmatic excursion and thus liver motion. The same pressure setting and placement of the abdominal belt is used during CT simulation and treatment to ensure reproducibility. Specifically, for PBT, reproducibility of belt diaphragm positioning is important, as alterations in positioning can not only result in differences to liver positioning, but also differences in body surface contours which can impact the robustness of the proton beam. Larger compression devices, such as compression plates, may physically limit the number of optimal beam angles.

(e) Respiratory Gating: *Active*

In respiratory gating, the beam is switched on during a specific phase of the respiratory cycle. Thus, only tumor motion during gated phases needs to be accounted for, resulting in smaller margins around target volumes. The greater mechanical complexity of a cyclotron compared to a linear accelerator makes implementation of respiratory gating strategies even more complicated for PBT versus photon therapy. Recent studies, however, have described feasibility and successful implementation of this technique with PBT [25, 30]. Fifteen patients with liver malignancies were treated at Massachusetts General Hospital on a prospective institutional trial evaluating the feasibility of a respiratory gated delivery of PBT [30]. Targets were contoured on the 50% end-exhale phase of a 4DCT scan and an internal motion margin was customized based on the tumor motion in the gating window (between 40 and 60% end-exhale phases). Respiratory gating was then performed using a real-time position monitoring (RPM) device, and beam-on time was configured for 30% centered on the 50% end-exhale phase. Orthogonal radiographs were acquired at end-exhale to confirm patient treatment position.

Our institutional guidelines for motion assessment categorize patients in the following manner for motion management:

- Peak-inhale to end-exhale displacement <5 mm: treatment planned on free-breathing 4D–CT scan, with delivery under free-breathing conditions and no motion management.
- Displacement 5–10 mm: treatment planning and delivery robustness to motion assessed and incorporated, particularly when utilizing PBS technique (*see Volumetric Rescanning of ITV).*
- Displacement >10 mm: active motion management required with treatment planned either under breath hold on helical CT or under abdominal compression on 4D–CT. Special attention should be given to the location of largest tumor motion as it relates to the tumor volume and shape. Tumors with high amplitude motion perpendicular to the proton beam direction generally require the greatest degree of motion mitigation.

7.2.2 Treatment Planning

7.2.2.1 Dose Fractionation Regimens

(a) Hepatocellular Carcinoma (HCC)

In terms of dose fractionation schedules for HCC, two general treatment approaches have been used that both utilize PBT alone primarily in a hypofractionated manner and are tailored according to the location of the tumor in relation to surrounding organs at risk (OAR) (Table 7.1).

Table 7.1 Common dose fractionation regimens for PBT in liver malignancies

Tumor type	Dose fractionation		
Hepatocellular carcinoma	>2 cm from GI tract or porta hepatis	≤2 cm of porta hepatis	<2 cm from GI tract
	• 66 GyE in 10 fractions [15] ($EQD2_{\alpha/\beta10}$ 91.3 Gy) • 67.5 GyE in 15 fractions [10] ($EQD2_{\alpha/\beta10}$ 81.6 Gy) • 63 GyE in 15 fractions [14] ($EQD2_{\alpha/\beta10}$ 74.6 Gy) • 70.2 GyE in 15 fractions [31] ($EQD2_{\alpha/\beta10}$ 85.9 Gy)	• 72.6 GyE in 22 fractions [16] ($EQD2_{\alpha/\beta10}$ 80.5 Gy) • 58.05 GyE in 15 fractions [10] ($EQD2_{\alpha/\beta10}$ 67.1 Gy)	77 GyE in 35 fractions [17] ($EQD2_{\alpha/\beta10}$ 78.3 Gy)
Intrahepatic cholangiocarcinoma	>2 cm from GI tract or porta hepatis	≤2 cm of porta hepatis	
	67.5 GyE in 15 fractions [10] ($EQD2_{\alpha/\beta10}$ 81.6 Gy)	58.05 GyE in 15 fractions [10] ($EQD2_{\alpha/\beta10}$ 67.1 Gy)	
Liver metastasis	60–72.6 GyE in 10 to 22 fractions [32, 33] ($EQD2_{\alpha/\beta10}$ 80–80.5 Gy)		

(i) University of Tsukuba Approach

For tumors located more than 2 cm from gastrointestinal tract: 66 GyE in ten fractions (6.6 GyE per fraction) is suggested. Reported institutional 5-year local control (LC) and overall survival (OS) were 88% and 39%, respectively, with this fractionation scheme [15]. For tumors located within 2 cm of the porta hepatis: 72.6 GyE in 22 fractions (3.3 GyE per fraction) is recommended to reduce risk of late bile duct stenosis. Reported 3-year LC and OS were 86% and 45%, respectively [16]. For tumors located within 2 cm of the gastrointestinal (GI) tract: 77 GyE in 35 fractions (2.2 GyE per fraction) is recommended with field reduction after 40–50 GyE to avoid excess dose to GI OARs. Reported 4-year LC and OS were 88% and 34%, respectively [17].

(ii) United States Approach

A multicenter phase II trial of PBT for HCC and intrahepatic cholangiocarcinoma utilized a dose of 67.5 GyE in 15 fractions for peripheral tumors (>2 cm from porta hepatis) and 58.05 GyE in 15 fractions for central tumors (within 2 cm of porta hepatis) [10]. The 2-year LC and OS rates were 95% and 64%, respectively. At Loma Linda University, an alternative 15 fraction regimen was used: 4.2 GyE for 15 fractions to 63 GyE. Median progression-free survival rate was 36 months for all patients and a 3-year progression-free survival rate was 60% for patients within the Milan criteria [14]. A more recent study from Loma Linda randomizing patients to chemoembolization versus PBT employed a 70.2 GyE in 15 fractions of 4.68 GyE regimen [31].

(b) Intrahepatic Cholangiocarcinoma (ICC)

The above multicenter U.S. phase II study employed the same fractionation scheme for ICC tumors [10]. The 2-year LC and OS were 94% and 47%, respectively. It should be noted that four additional local recurrences occurred in ICC patients after 2 years, suggesting that late local failures in ICC are possible. It remains to be seen with longer follow-up if these hypofractionated doses are adequate for long-term durable tumor control (at 3–5 years) and if other measures, such as adding concurrent chemotherapy or higher dose escalation, are warranted for ICC tumors.

(c) Liver Metastasis

There is limited published data surrounding PBT therapy for liver metastasis. Retrospective studies have utilized a range of dose and fractionation schemes from 60 to 72.6 GyE in 10–22 fractions [32, 33]. University of Tsukuba treated 140 patients with metastatic liver cancers, mainly with colorectal and pancreatic primaries, with PBT doses ranging from 9 to 77 GyE (most commonly with 72.6 GyE in 22 fractions [$EQD2_{\alpha/\beta 10}$ 80.5 Gy]) [32]. Five-year OS was 24% in all patients and 30% in patients with disease confined to the liver

treated with curative intent. Compared to most photon SBRT data for metastatic liver tumors, 2-year LC was relatively suboptimal at 66%, raising the question of the role of PBT for liver metastases if photon SBRT treatment is an option. Currently, there is a prospective phase I–II study of stereotactic body proton radiation therapy open at the Loma Linda, which will provide more data on treatment of liver metastasis with PBT [33].

(d) Stereotactic Proton Radiation Therapy

Although planning studies have demonstrated improved liver-sparing with proton-based stereotactic body radiotherapy (SBRT) compared to photon-based SBRT [34, 35], currently no clinical data is available on the safety and efficacy of proton SBRT. Due to depth-dose characteristics of PBT, volumetric image guidance is of critical importance and is increasingly so when used in a stereotactic approach. Most early PBT systems have KV-imaging for image guidance and do not have on-board volumetric image verification, which is recommended for SBRT. Newer systems have begun to incorporate this technology, making proton-based SBRT more technically feasible.

At our institution, we generally treat HCC and ICC tumors using the 15 fraction approach used in the multicenter U.S. phase II study. Doses of 60–67.5 GyE are prescribed if OAR constraints are met. If situations where these doses are not deliverable (e.g., close proximity to GI OARs), a simultaneous-integrated boost (SIB) or cone-down approach is used (*see Uniform Scanning and Pencil-beam Scanning*). PBT with SIB has also been described in literature as effective and safe for treatment in HCC with tumor vascular thrombosis [36].

7.2.2.2 Target and Organ at Risk Delineation

GTV should encompass all gross disease seen on the planning and diagnostic scans. If clinically indicated, a margin of 0.5–1.0 cm can be applied to the GTV to generate the clinical target volume (CTV). An ITV should be generated from the GTV or CTV (if applicable) to account for tumor motion. A planning tumor volume (PTV) margin of 0.5–1.0 cm is commonly used to account for setup error. At a minimum, OARs including liver, heart, esophagus, stomach, duodenum, small bowel, large bowel, kidneys, and spinal cord should be contoured based on established consensus guidelines [37]. Suggested dose constraints to OAR utilized at our center are presented in the table below for 15 fraction course of hypofractionated PBT based on the multicenter U.S. phase II trial (Table 7.2) [10].

As previously mentioned, early PBT systems do not have on-board volumetric image verification. At our institution, planning OAR volumes (PRVs) are used for treatment planning when calculating the Dmax (to 0.5 cc volume) to GI OARs (esophagus, stomach, duodenum, small bowel, large bowel). Margins of 5 mm are added to GI OARs to create these PRVs [38].

Table 7.2 Proposed OAR dose constraints for a 15 fraction PBT regimen

Organ at risk	Dose constraint
Liver-GTV	Mean ≤ 24 GyE V30 < 30%[a] V20 < 40%[a]
Spinal cord + 5 mm	Dmax <37.5 GyE
Stomach	Dmax <42 GyE V36 < 5 cc[a]
Duodenum	Dmax <45 GyE V36 < 5 cc[a]
Small bowel	Dmax <45 GyE V36 < 5 cc[a]
Large bowel	Dmax <45 GyE V36 < 5 cc[a]
Kidneys (bilateral)	V14 < 30% Mean < 12 GyE
Heart	V40 < 10% Dmax 45 GyE[a]
Chest wall	V60 < 5 cc[a]

Dmax = dose to 0.5 cc volume
[a]Recommended, but not mandatory

7.2.2.3 Proton Beam Angle Selection

Once target and OAR volumes have been delineated, PBT treatment planning begins in the context of all information gathered at the time of simulation. The individual patient characteristics related to tumor motion, tumor location, tumor size, prior treatment history, and liver function, among others, are collated to inform on the appropriate treatment planning technique. This choice then determines beam angle selection, which in turn specifies the requirements for successfully mitigating beam-specific setup and proton range uncertainties. This is fundamentally different from photon treatment planning where uncertainties are assumed to contribute equally from all beams and are accounted for by target and OAR margins. PBT planning utilizes few beams in order to leverage the absence of exit dose beyond the distal edge of the target and the lower integral dose to normal tissue for the same dose to tumor as compared with conventional photon therapy. The angles and paths of these few beams are therefore carefully selected to maximize dosimetric advantage. The following are key considerations when selecting proton beam angles:

- Beam robustness vs. target dose conformality: this is a tradeoff between the ability to irradiate the tumor with low uncertainty and the ability to conformally irradiate the tumor's geometric shape. Selecting a beam angle that is robust may require irradiating more volume of normal liver tissue, while selecting a beam that can conform to the tumor and avoid other normal organs may introduce more proton range uncertainty. Compromises in beam selection should be individualized and reached to maintain sufficient target dose coverage under beam-specific uncertainties while meeting clinical constraints on OAR doses.
- Organ sparing priority: assigning priority weighted to normal tissues will help to narrow the space of clinically safe beam angles. For example, maximum dose constraints on the spinal cord, stomach, bowel, and duodenum may dictate certain

beam angles through portions of the liver while meeting volumetric constraints on the liver dose.

- Extent and directionality of target/organ motion relative to beam direction: motion that is parallel to the beam direction can generally be mitigated effectively through sufficient proton range and energy/range modulation, particularly in the liver where such motion does not lead to significant changes in tissue density along the beam path. However, motion that is perpendicular to the beam direction, even if accounted for with target margins, can lead to underdosing the tumor or overdosing normal tissue in the presence of density changes. This is most pronounced for liver lesions at the dome that experience substantial diaphragmatic motion and reside at the interface between lung and soft tissue. Under these circumstances, protons will range through low density lung at peak-inhale (diaphragm inferior) and irradiate the heart, esophagus, and/or stomach (*see Breath Hold Reproducibility and Uncertainties*).

Examples of beam angle selection for tumors in different locations of the liver as treated at our institution are discussed below:

- Right lobe tumors: posterior and lateral beams are frequently utilized to treat lesions residing in the right lobe that descend posteriorly due to their superior robustness compared to other beam angles (Fig. 7.3a). Combined with typically reduced motion and the ability to avoid ranging through bowel, stomach, and spinal cord, posterior proton beams should always be considered first when planning. Obliquity of the posterior beam angle should be minimized in order to avoid intersecting the table edge or irradiating parallel to a bone-tissue interface, both of which increase the beam-specific uncertainty of the treatment plan. Once a posterior beam is in place, selection of an orthogonal beam (e.g., right lateral) can provide several dosimetric advantages. These include reduction of skin and/or chest wall dose and mitigation of range uncertainty errors introduced by the posterior beams. Specifically, uncertainty in the posterior beam distal falloff can be offset by lateral falloff of the orthogonal beam.

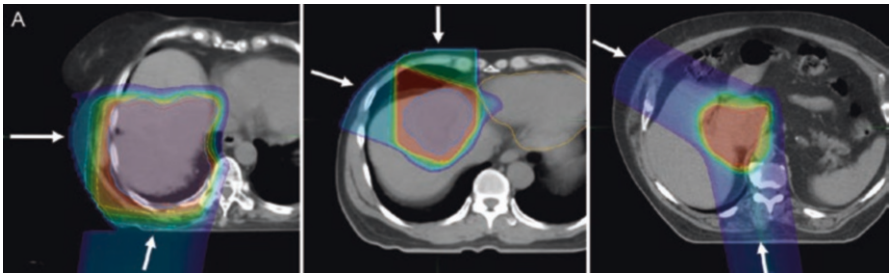

Fig. 7.3 (**a**) Hepatocellular carcinoma in segments 6 and 7 treated with PBS right posterior oblique and right lateral beams. Note how right lateral beam avoids the right breast, which would result in significant uncertainties. (**b**) Hepatocellular carcinoma in segment 8 treated with US anterior-posterior (AP) and right anterior oblique beams. Note that the AP beam was necessary to avoiding irradiating the heart. (**c**) Hepatocellular carcinoma in the caudate lobe (segment 1) treated with simultaneous-integrated boost PBS left posterior oblique and right anterior oblique (RAO) beams. Note how the RAO beam avoids stomach and bowel

- Anterior tumors: anterior beams that preferentially avoid irradiating bowel, stomach, heart, or other air interfaces are preferred (Fig. 7.3b). Further, anterior beams are chosen to enter through a reproducible segment of the patient's skin, in which no skin folds or irregular surfaces persist. Lastly, angular separation of at least 40° between beams is typically respected to reduce beam overlap at the skin and chest wall, thereby mitigating toxicity. Unless absolutely necessary, lateral beams that pass perpendicular to the lung-liver diaphragm interface are not favored.
- Central location: (Fig. 7.3c). central lesions pose the most demanding challenge for beam selection, as they are often surrounded by GI organs. In addition to the critical OAR dose tolerances, beam-specific range uncertainties propagate to higher magnitudes when reaching deep-seated lesions. While there are no single set of optimal beams for treating central lesions, combinations of posterior oblique and anterior oblique beams should be evaluated on a case-by-case basis, using a minimum of two fields.

No matter the selected beam angle, care should be exercised to characterize all material that resides in the beam path. Whether overriding fiducial markers, metal shadow artifacts, transient air-filled bowel, contrast in stomach, and planning dose through these structures should be undertaken cautiously and in a manner that most realistically represents the patient state at the time of treatment delivery is to been considered.

7.2.2.4 Passive Versus Active Planning Techniques

Passive scattering and active scanning techniques can both be utilized for liver PBT planning, each with distinct advantages and disadvantages (Table 7.3). The double scattering technique, in which a broadly scattered and flattened proton beam irradiates the entire tumor volume, has been in clinical use the longest and provides arguably the most robust delivery to motion and setup uncertainties for a given beam configuration. US (passive) and PBS (active) are utilized at our institution and their application to liver PBT is described below:

(a) Uniform Scanning (US)

US scatters a small pencil beam to a moderately sized 3–5 cm spot and raster scans it rapidly to produce a uniform field of a given proton energy. The uniform rectangular field is shaped by a patient-specific brass aperture, and the range of each proton from the uniform field is defined by a patient-specific compensator that matches the distal edge of the tumor. Each uniform field layer is sequentially delivered from highest energy/deepest range to lowest energy / shallowest range necessary to cover the tumor by passing the beam through steps of a range-modulator wheel. The use of physical custom-shaped devices offers the potential for sharp lateral falloff, but comes at the expense of neutron and scattered proton dose produced in the beam line. It also lacks the ability to modulate the shape of the beam dynamically to conform to the proximal shape of the tumor, thus resulting in unnecessary irradiation of normal tissues proximal to the tumor. Any integrated boosts must be planned as separate fields with modified patient devices, reducing planning flexibility and increasing patient treatment times. This field-in-field technique typically consists of maintaining

Table 7.3 Comparison of uniform scanning (US) and pencil-beam scanning (PBS) delivery techniques

	Uniform scanning	Pencil-beam scanning
Physical dose properties	− Less proximal dose conformality	+ Dose conformality in three dimensions from single beam (lateral, distal/proximal edges)
	− Secondary neutron scatter dose	+ Deviceless beam shaping
	+ Sharper lateral dose falloff from patient-specific aperture field edge	− Shallower lateral dose-off from scanning magnet field edge (larger penumbra at lateral edges)
Delivery properties	+ Faster raster-scanned delivery with lower degree of interplay/interference relative to respiratory motion	− Slower pencil-beam spot delivery due to energy layer tuning with higher degree of interplay/interference relative to respiratory motion
	− Increased air gap between aperture/compensator and patient surface for clearance increases scatter dose to patient skin	+ Deviceless beam shaping improves doses at shallow depths and does not require narrow air gap
	− Practical field size limitation due to weight of brass apertures	+ Flexible field sizes
Advanced planning approaches	Field-in-field technique utilizing patient-specific devices to shape each boost field	Dose painting (simultaneous-integrated boost) technique in which individual or sets of boost fields can be optimized to different doses per fraction

(+) are pros and (−) are cons

similar range and modulation while modifying the patient-specific devices. The aperture and compensator of the boost fields are shaped so as to shrink the field off critical structures, typically the stomach, bowel, and duodenum (Fig. 7.4).

(b) Pencil-beam Scanning (PBS)

PBS magnetically scans a small pencil beam and modulates the intensity of the beam at each spot location through dwell time. Each proton energy layer is individually tuned by the cyclotron degrader (or synchrotron directly), allowing the shape and modulation to be entirely optimized in three dimensions. These additional degrees of freedom allow seamless integration of boosts within the same field or set of fields without the need for beam collimation devices. By removing all patient-specific devices, the neutron dose and proton scattered dose is drastically reduced, but this advantage comes at the expense of a blurrier field edge defined by the scanning magnets as compared to the brass aperture. PBS boosts are planned using a dose painting technique, which simultaneously integrates dose to higher levels per fraction from single or multiple fields. Unlike photon dose painting plans in which multiple fields are optimized to different doses per fraction, proton dose painting plans can consist of individual beams that are each independently optimized to a different prescribed dose per fraction (Fig. 7.5).

At our institution, the complexity of the case is a large determinant for the treatment planning and delivery technique. Lateralized lesions with few proximal critical structures but significant motion and tissue heterogeneity tend to benefit from

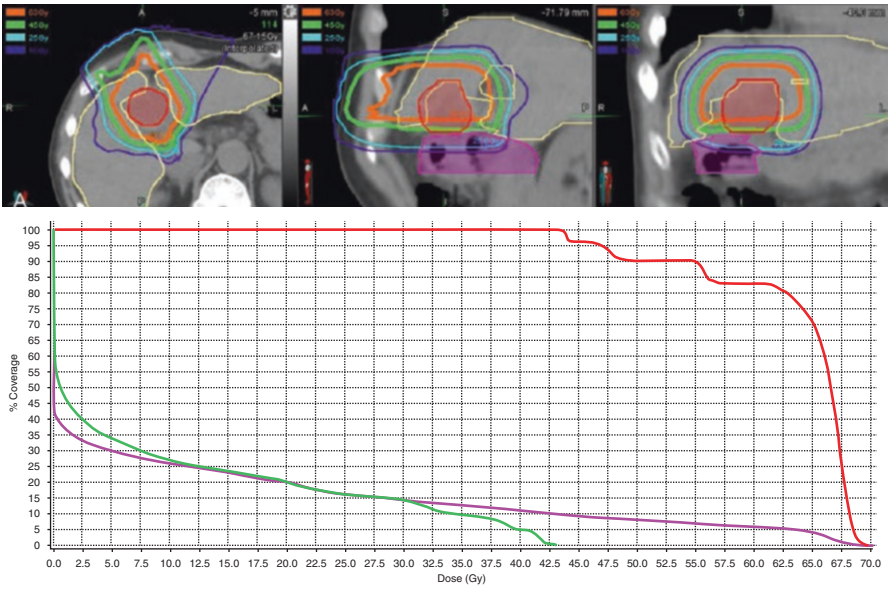

Fig. 7.4 (**a**, **b**) A 64 y/o male with a medically inoperable segment 4B intrahepatic cholangiocarcinoma in the setting of hepatitis C-related Child-Pugh A5 cirrhosis. Proton beam therapy with uniform scanning plan using a field-within-field technique to deliver 45 and 67.5 GyE in 15 fractions. Left anterior oblique and right anterior oblique fields delivered 45 Gy to a larger volume that overlapped with the duodenum and smaller right lateral and right anterior oblique fields that spared the duodenum were used to concurrently deliver additional dose to the GTV. Row **a**, isodose line distribution showing the 45 Gy line (*green*) avoiding overlap with the duodenum (*shaded magenta*) and a subregion of the GTV (*shaded red*) receiving 63 GyE (*orange line*). **b**, DVH analysis

US planning using 2–3 beam arrangements. Such US plans are optimized to cover the GTV/CTV with beam-specific margins that equate to 2.5% of the highest range + 2 mm water-equivalent thickness. Central lesions, lesions near critical structures, and lesions planned to higher integrated peak prescribed doses often require the flexibility to optimize beam-specific dose in three dimensions with PBS planning. In these cases, beam-specific uncertainties due to motion and heterogeneity are properly accounted for during the plan optimization and delivery process.

PBS inverse planning spans a spectrum of optimization techniques, since PBT can deliver all or portions of the prescribed dose to tumor from a single field in a manner impossible to achieve with photon therapy. Due to the delivery uncertainties associated with tumor motion, liver deformation, and surrounding organ density heterogeneity, our institution frequently utilizes single field optimization (SFO) to uniform dose. This places a simple constraint on each field of the treatment plan to deliver uniform dose to the tumor, most often with equal weighting across all fields. In cases where an integrated boost is required using the dose painting described above, the boost target can be given uniform dose from each field while allowing dose to falloff into the adjacent larger low-dose target. The SFO plan can be achieved with objectives to the PTV, or with objectives to the CTV that directly incorporate range/setup uncertainties in the optimization. Robust CTV-based optimization is

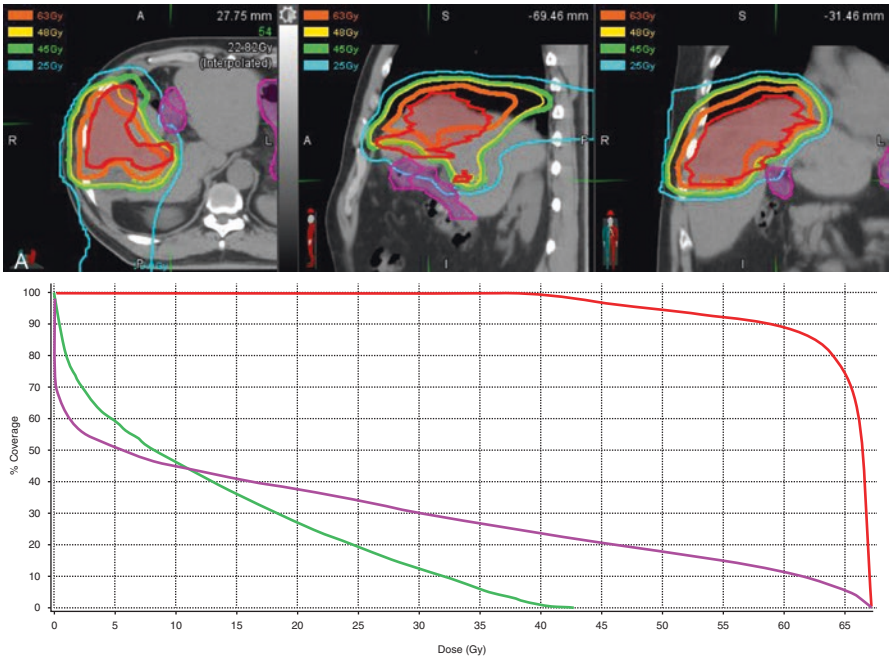

Fig. 7.5 (**a**, **b**) A 72 y/o male with a BCLC stage C hepatocellular carcinoma in the setting of hepatitis B-related Child-Pugh A5 cirrhosis s/p multiple liver-directed therapies (surgery, multiple radiofrequency ablations, transarterial chemoembolization) with persistent disease in segment 8 and left branch portal vein tumor thrombus. Proton beam therapy with pencil-beam scanning plan (posterior and right lateral beams) using a simultaneous-integrated boost technique to deliver 45 GyE, 48 GyE, and 67.5 GyE in 15 fractions to dose escalate subregions of the GTV, while meeting dose constraints of surrounding GI OAR (e.g., duodenum). Row **a**, isodose line distribution showing 45 GyE line (*green*) avoiding overlap with stomach and duodenum (*shaded magenta*) and subregion of GTV (*shaded red*) receiving 63 GyE (*orange line*). **b**, DVH analysis

most useful in cases where there is a high degree of tissue heterogeneity, and PTV margins do not sufficiently encompass range uncertainties in the beam path [39, 40]. The robust plans, however, will tend to decrease the conformality to the PTV as part of the tradeoff described above. In practice, it is convenient to utilize PTV objectives initially and supplement with robust CTV objectives as needed to meet clinical target coverage goals.

It is important to note that while proton treatment planning is evolving towards active PBS technique with robust multi-field optimization (MFO) for GTV/CTV coverage and OAR sparing, there are still many cases in which the degree of uncertainty warrants consideration for passive double scattering or US techniques.

7.2.2.5 Special Considerations

(a) Range Uncertainty

Range uncertainty is automatically accounted for in passive US planning through increased range and modulation to cover >95% of the GTV/CTV with prescribed dose. We utilize a range uncertainty margin of 2.5% + 2 mm. In PBS

planning, range uncertainty can be automatically accounted for through robust GTV/CTV objectives during inverse planning, though this is less common for liver PBS planning where PTV margins sufficiently encompass the range uncertainty.

(b) Robustness Testing

Specific to PBS technique, the robustness of an optimized plan to range and setup uncertainty are explicitly tested. Range uncertainty is simulated by systematically shifting all densities up/down 3% and recalculating the planned dose. Increasing the density by 3% will decrease the proton range, while decreasing it will increase the proton range. Setup uncertainties are tested by shifting the beam isocenter position relative to the patient anatomy. Typically, 3–5 mm shifts are performed to be consistent with daily setup variation averaged over the 15 fraction treatment regimens. Future robustness testing will involve disease site-specific uncertainties that are derived from image-guided positional variation and tissue heterogeneity.

7.2.3 PBT Delivery Using IGRT Technique

Image guidance during PBT delivery is a clinical standard that bears several forms. The majority of proton centers utilize daily orthogonal kV planar X-ray imaging for patient alignment prior to beam delivery, while a growing minority of modern single and multi-room proton therapy facilities incorporate volumetric CBCT for localization. In liver cancer, the use of kV X-ray planar imaging permits initial alignment to bony anatomy and, if applicable, followed by subsequent shifts to match fiducial marker position. The X-ray images should be acquired at cardinal angles (e.g., sagittal and coronal views) whenever possible rather than at oblique angles where discernment of bony anatomy can be challenging.

At our institution, fiducial marker contours are also displayed on the fusion of the treatment planning CT-derived DRR and the daily X-ray for further guidance. When establishing proton IGRT setup tolerances, one must account for target margins and the plan robustness to shifts in anatomy, particularly near bone/tissue/air interfaces. Liver PBT plans should be designed to be robust to such anatomic shifts, through appropriate beam selection, margin design, and setup uncertainty evaluation. Once daily shifts are applied, verification X-rays are acquired to provide information on residual (e.g., random) setup error. If the residual error falls within the setup tolerance, typically on the order of 5 mm, then treatment field delivery can proceed. In cases that require couch angular shifts between fields, another set of X-ray images are acquired and any additional shifts are applied as needed to comply with setup tolerances.

With the advent of CBCT in newer proton facilities, IGRT workflows will consist of soft tissue and/or fiducial marker alignment and volumetric matching of planning target and normal tissue structures. As applied to PBT, CBCT-based IGRT may also include beam-specific evaluation of motion, setup, and range uncertainty.

7.2.4 QA Verification Plan and Adaptive PBT

The increased sensitivity of proton dosimetry to anatomic changes requires plan verification QA prior to and during therapy. In the absence of daily CBCT at most proton therapy centers, this can be practically achieved through serial QA CT imaging on the simulator. For liver cancers, QA scanning consists either of a slow CT scan protocol, which reduces the x-ray tube rotation speed and current in order to generate and time-averaged image during free-breathing conditions, or a complete respiratory-correlated 4D–CT protocol. The latter provides superior anatomic and dosimetric accuracy, but increases imaging dose to the patient.

At our institution when treating with a 15 fraction regimen, weekly QA slow CT scans are conducted, which are co-registered to the original planning phase-averaged 4D–CT. Following rigid registration or under special circumstances deformable registration, target and normal structures are transferred to the new QA CT anatomy, manual contour modifications are made, and the original proton beams are recalculated to the equivalent beam isocenter. The QA verification plan is then reviewed for significant deviations in target coverage and normal tissue dose constraints. Great care must be given when the evaluation is performed in order to rule out dosimetric changes caused by image artifacts on the QA CT that could mislead a decision to adapt the plan.

In the event that a QA verification plan does not meet the original clinical goals, PBT plans can be adapted in a number of ways. US liver plans are adapted in order of increasing complexity by (1) increasing/decreasing the range or modulation without modification to patient devices, (2) modifying the aperture to increase target coverage or reduce OAR dose, (3) modifying the patient aperture and compensator to reshape beam transverse and distal profiles, (4) selecting an entirely new beam. US plan adaptation via (1) or (2) occurs in approximately 10% of all cases, while adaptation via (3) or (4) is rare unless ill-advised beams were selected initially for planning. While adaptation of US plans is encumbered by new device fabrication, PBS plan adaptation is relatively straightforward. As an inverse planning technique, PBS plans can be re-optimized to modified targets and current patient anatomy, and the new treatment fields under patient-specific QA in an analogous manner to IMRT QA.

7.2.4.1 Interfractional OAR Geometric Uncertainties

Figure 7.6 illustrates an example case in which the position of the large bowel on a QA verification CT scan after ten fractions has moved into the radiation field, thereby significantly increasing the daily bowel dose. Uncertainties in interfractional OAR geometry support the utilization of planning risk volumes (PRV), which are analogous to the PTV concept for OAR. Specifically, patient-specific and beam-specific geometric uncertainties can be incorporated into OAR margins. Interfractional variation in OAR position, among other sources of variability, can be accounted for during planning by imposing dosimetric constraints on the PRV in addition to those on OAR. Meeting planned dose constraints to PRV structures will increase the likelihood that these constraints will be met throughout the entire course treatment. This has practical implications, as ensuring reproducible dose to critical structures leads to safer treatments, while reducing the frequency and burden of adaptive replanning. Undercoverage of target volumes is possible, however, and must be balanced with the concern for these geometric uncertainties.

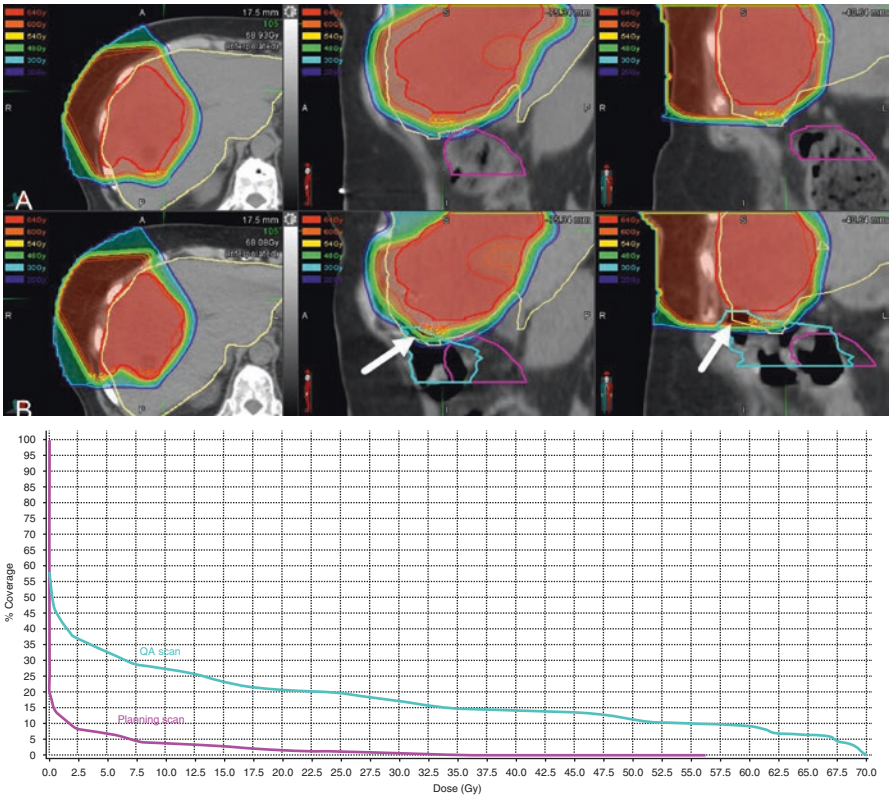

Fig. 7.6 (**a**–**c**) A 75 y/o female with a BCLC stage B hepatocellular carcinoma involving segments 5 and 8 in the setting of NAFLD-related Child-Pugh A5 cirrhosis. Proton beam therapy with uniform scanning to deliver 58.05 GyE in 15 fractions using a right lateral and right anterior oblique beam approach. Row **a**, isodose line distribution of original plan from treatment planning CT. The large bowel (*magenta*) is adequately spared. Row **b**, quality assurance (QA) scan after ten fractions shows different positioning of the large bowel (*cyan*) that results in overdosing of the large bowel. The 48 GyE line (*green*), dose constraint for large bowel, is shown overlapping with the large bowel (*white arrows*, middle and right column). **c**, DVH analysis showing differences in large bowel dose between the initial plan (*magenta line*) and QA plan (*cyan line*)

7.2.4.2 Breath Hold Reproducibility and Uncertainties

Figure 7.7 illustrates the challenges associated with breath hold reproducibility throughout a treatment course. A QA verification CT scan performed under breath hold after ten fractions shows a 1.2 cm inferior displacement of the liver dome under breath hold, indicating that the same breath hold volume was not achieved successfully. This results in proton dose ranging farther through lung tissue and depositing higher dose to the esophagus. Special care must be given to QA breath hold devices and to implement QC programs that standardize breath hold coaching technique, including documentation of all relevant breath hold parameters.

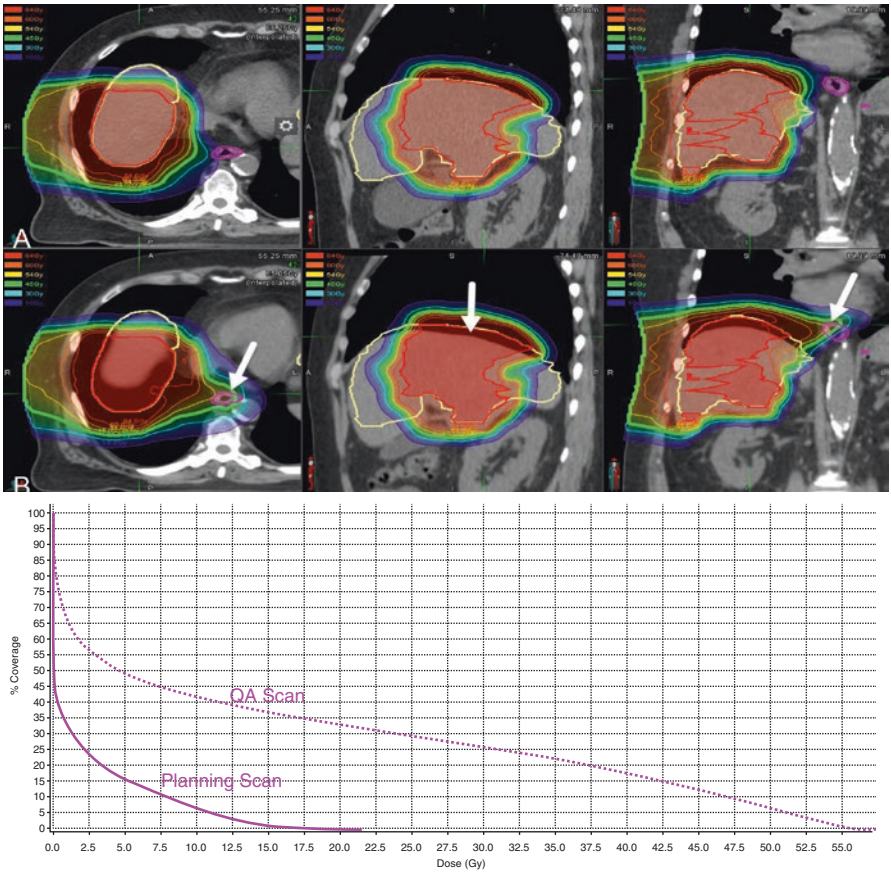

Fig. 7.7 (**a**–**c**) A 64 y/o male with a BCLC stage C hepatocellular carcinoma involving multiple segments and the left and main portal vein in the setting of hepatitis C-related Child-Pugh A6 cirrhosis s/p sorafenib. Proton beam therapy with pencil-beam scanning plan to deliver 67.5 GyE in 15 fractions using a single right lateral beam with volumetric rescanning and an active breathing coordinator (ABC) end-exhale breath hold technique. Row **a**, isodose line distribution of original plan from treatment planning CT. The esophagus (*shaded magenta*) is adequately spared. Row **b**, quality assurance (QA) scan after ten fractions shows different positioning of the liver dome of approximately 1.2 cm (*white arrow*, middle column) that results in over-ranging of the proton beam and overdosing of the esophagus. The 45 GyE line (*green*), dose constraint for duodenum, is shown overlapping with the esophagus (*white arrows*, left and right column). **c**, DVH analysis showing differences in esophagus dose between the initial plan (*solid line*) and QA plan (*dashed line*)

7.2.5 Toxicities and Complications of Liver PBT

The most significant OAR of toxicity for any course of RT delivered to the hepatobiliary system is the liver. In addition to liver toxicity, other OAR at risk from the delivery of definitive doses of PBT include the GI tract, chest wall, and biliary structures. Each of these is discussed in detail below.

7.2.5.1 Liver

Classic RILD (cRILD) is seldom seen with modern PBT techniques for HCC. Kawashima et al. reported on predictors of hepatic toxicity in 60 patients treated with PBT for HCC. Seventy-eight percent of patients were CP-A, and 82% had HCV cirrhosis with 60% receiving prior liver-directed therapy (LDT) [41]. The majority received 76 GyE in 20 fractions, and eight patients experienced transient G3 transaminase elevation during treatment. Pretreatment liver function was objectively measured using indocyanine green retention at 15 min (ICG R15), which had previously been shown to predict liver toxicity in prior work [42]. Eleven patients (18%) developed proton-induced hepatic insufficiency (PHI; anicteric ascites or asterixis in the 6 months after treatment in the absence of disease progression), of which seven died. No patients with an ICG R15 < 20% had PHI, whereas 75% of those >50% died of PHI. Of patients with an ICG R15 of 21–49%, the V_{30GyE} was the strongest predictor of PHI, with a cut off of 25% (0% vs. 45% risk). Critically, the occurrence of PHI was significantly associated with an increased risk of death on multivariate analysis, as was pretreatment CP score, underscoring the importance of pretreatment assessment of liver function in HCC patients.

The majority of liver toxicity data reported are non-classic RILD (ncRILD) endpoints, including a large body of work from Tsukuba University in Japan on the PBT treatment of HCC. In a recent publication that specifically addressed changes in normal liver function after PBT, 259 patients are described retrospectively [6]. The majority of patients had cirrhosis secondary to HCV infection (73%), and 76% were CP-A. Sixty-three percent had prior LDT and were treated with their standard treatment protocol based on proximity to GI structures or the porta hepatis. As compared to baseline, on the final day of PBT treatment, 18% of patients had an increase in CP score of 1 and 1% ≥2. At 6 months, this was 11% and 9%, respectively, and at 12 months 16% and 11%. Of the patients who had CP score progression of ≥2 at 12 months, 50% died of liver failure without tumor progression. Increases in CP score ≥ 1 (defined as an "adverse event") were associated with various dosimetric factors (V0–30, aV0–20) and pretreatment CP score. In contrast to these studies, other groups report a relatively low incidence of ncRILD, with Bush et al. describing no significant elevation in a panel of liver enzymes [14], and Hong et al. just a 4% CP class change rate [10]. While PHI is clearly associated with survival, there is an unclear relationship between the various ncRILD metrics, and further work is needed in this area.

7.2.5.2 Biliary Structures

The biliary system is an important OAR when treating liver malignancies with PBT, particularly when the target necessarily includes these structures, as with cholangiocarcinoma. Two Japanese institutions report significant late biliary toxicity in small patient cohorts treated for advanced cholangiocarcinoma with median doses of 68.2–72.6 GyE. Ohkawa et al. describe biliary tract infection requiring stent placement in 14% (2/14) of patients [43], and Makita et al. report 28% (8/28) of patients with G2–3 cholangitis or bile duct stenosis, a number of which required intervention [44]. This is in contrast with the limited data in HCC, with Chiba et al. reporting just one biliary stricture and two bilomas in 162 patients treated with a median 72 GyE [45]. Given the small patient numbers, no DVH dose constraints have been established for PBT, in contrast to SBRT [46].

7.2.5.3 GI Tract

Given the proximity of the stomach, duodenum, and bowel to potential treatment fields, GI toxicity is a clinically relevant risk in PBT of the liver and has been described in cohorts from multiple institutions. Of 60 unresectable HCC patients treated with 60–76 GyE (10–26 fractions) in a study by Kawashima et al. three patients developed ≥G2 gastrointestinal toxicity, including hemorrhagic duodenitis, hemorrhagic ulceration of the colon, and esophagitis, two of which required surgical intervention [42]. Other investigators have reported an approximately 1–2% risk of ≥G2 gastrointestinal toxicity in both HCC and mixed populations [10, 45, 47]. In addition, 7% (5/76) of patients treated at Loma Linda developed grade 2 bleeding, inflammation, or ulceration of the GI tract [14]. This led to increased bowel avoidance after the first 30 patients, with no toxicity after that, which reinforces the need to tailor dose/fractionation schemes when the PTV is in the proximity of bowel to mitigate this risk (see Tsukuba protocol above).

7.2.5.4 Chest Wall

Given the potential proximity of liver tumors to the chest wall, particularly peripherally located ones, rib fracture and chest wall pain syndrome are potential toxicity risks [48], which can adversely affect the quality of life of cancer patients [49]. There is limited data regarding the risk of chest wall toxicity in patients treated with PBT for liver malignancies, with many studies not reporting incidence or severity. The recently published phase II prospective study of Hong et al. reported a 4% risk of CTCAE MSK/Soft Tissue toxicity in 92 patients treated for HCC or IHCC with a maximum dose of 67.5 GyE in 15 fractions, none of which were >G2 [10]. In addition, a recent detailed analysis of the University of Tsukuba experience reports rates of rib fracture in 67 HCC patients treated with 66 GyE in ten fractions [50]. They found 11 patients with rib fracture (16%), in 27 of 310 irradiated ribs (8.7%). Three patients were symptomatic with chronic chest wall pain and the median time to rib fracture was approximately 2 years. While all DVH parameters were higher in fractured than non-fractured ribs, V_{60} Gy_3 (BED) was most predictive of fracture, with a cut off of 4.48 cm^3 having a 26 vs. 1.4% risk of fracture.

7.2.6 Summary

PBT is a treatment modality that offers promising potential by providing optimal normal liver tissue sparing from radiation for hepatobiliary cancer patients, particularly those with chronic liver dysfunction. When delivered in a hypofractionated regimen, PBT offers the ability to deliver dose-escalated treatment in a shortened duration with minimal acute toxicity and potentially less radiation-induced hepatotoxicity. Treatment planning and delivery of liver PBT is relatively more complex than liver photon-based treatment. Special considerations including comprehensive motion assessment and management, beam angle selection, and a myriad of uncertainties (range, OAR geometric uncertainties) must be taken into careful account. Currently, it is unclear which hepatobiliary cancer patients derive the greatest clinical benefit from PBT. Until results from future and ongoing randomized trials become available to provide more clarity on patient risk stratification and selection for PBT, a summary algorithm of proposed guidelines for patient selection and treatment planning workflow in HCC patients is presented in Fig. 7.8.

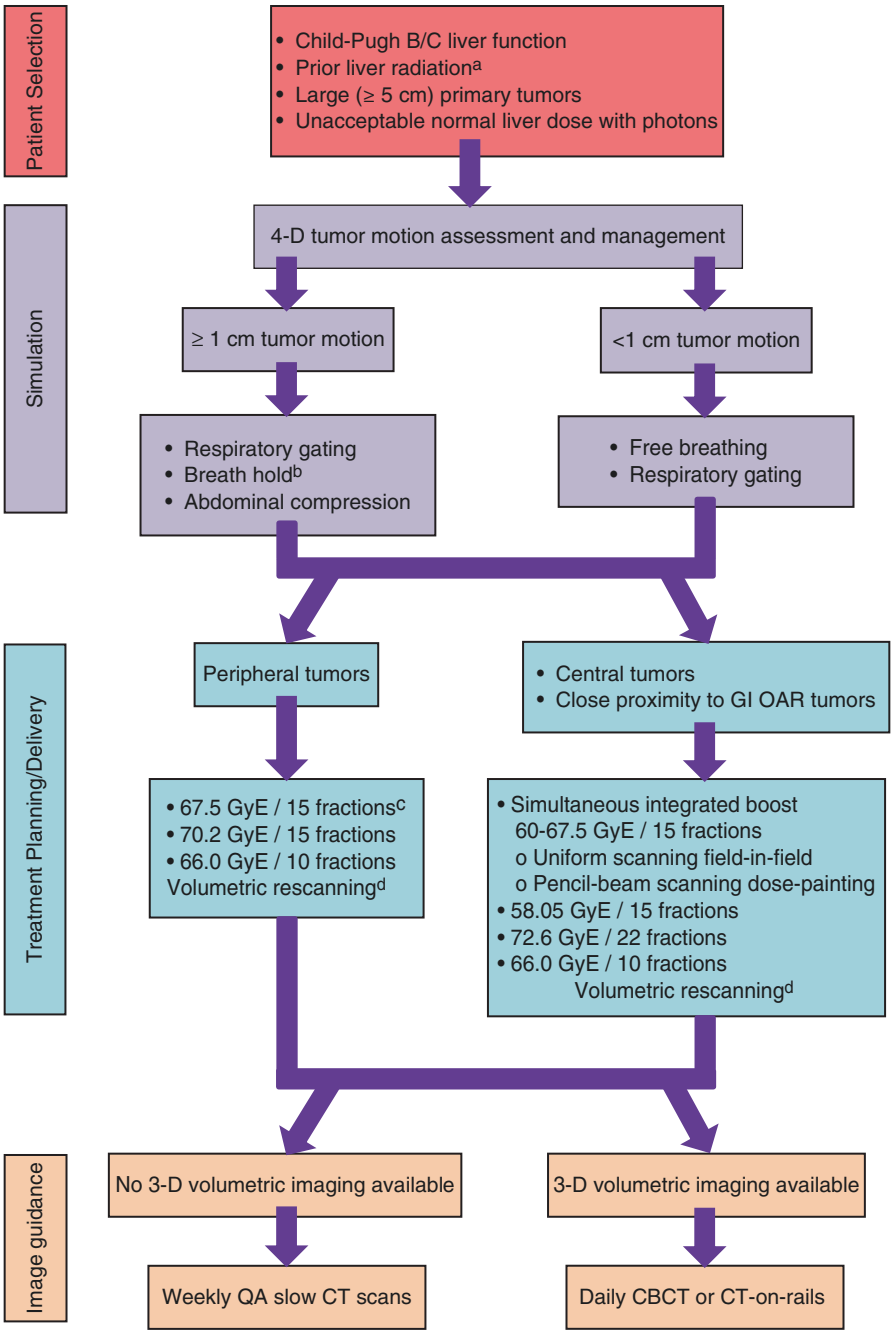

Fig. 7.8 Summary algorithm of proton beam therapy for primary liver cancers. [a]External beam or internal (transarterial radioembolization) radiation therapy. [b]End-exhale recommended. Generally, more feasible with uniform scanning due to the increased time duration of energy tuning between layers with pencil-beam scanning. [c]Preferred fractionation regimen at our institution. [d]May be considered and applied in conjunction with any of the above motion management strategies for tumor motion >5 mm.

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Part IV

Pancreatic Cancer

Resectable and Borderline Resectable Pancreatic Cancer

8

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8.1 Introduction

Surgical resection is considered the only potentially curative treatment for localized pancreatic cancer, even though resection alone results in median overall survival rates of approximately 20 months [1, 2]. Patients who undergo surgical resection with curative intent followed by adjuvant chemotherapy with or without radiation have recurrence rates as high as 77% [3]. Patterns of failure observed following surgery alone for treatment of pancreatic cancer indicate the need for additional therapies. Surgery followed by adjuvant treatments results in disappointing outcomes, in part due to the mortality and morbidity risks of pancreatic surgery and to the limited efficacy of adjuvant treatment. Response rates to adjuvant therapies are variable and randomized studies demonstrate only modest survival advantages associated with adjuvant therapy for resectable pancreatic cancer [4, 5]. The two major factors that contribute to poor outcome following surgical resection of pancreatic cancer include the limitation of staging techniques to distinguish patients with truly localized disease amenable to surgery and the lack of therapeutic agents that are effective against micrometastatic disease.

Neoadjuvant treatment is an attractive approach as it potentially allows for in vivo assessment of tumor response, provides treatment of subclinical or radiographically undetectable metastases prior to surgery, and improves the chance of obtaining a margin-negative (R0) resection. While disease progression still occurs in 45 to 74% following neoadjuvant chemoradiation [6–9] and 30–78% following neoadjuvant chemotherapy [10], reevaluation for progressive disease following neoadjuvant therapy potentially avoids futile surgery and the associated morbidity in the subset of patients who develop early metastatic disease. Neoadjuvant therapy has been associated with improved R0 resection rates [6, 11–14] without increases in operative morbidity and mortality [11]. Prospective trials demonstrate that patients who achieve an R0 resection have improved survival compared to patients with positive margins following surgery [15, 16]. Furthermore, a meta-analysis has demonstrated that the use of neoadjuvant therapy in pancreatic cancer has the potential to increase the number of operative candidates by converting initially borderline or locally advanced unresectable tumors to resectable [17]. In this study, approximately one third of patients with unresectable tumors were converted to operative candidates and demonstrated similar survival rates as patients with initially resectable disease.

The ability to accurately stage pancreatic cancer is essential for the development and evaluation of stage-specific therapies to maximize outcome and quality of life, and the lack of a standard definition of surgical resectability has confounded outcome data for many pancreatic cancer treatment studies. Hence, accurate identification of potentially resectable disease by evaluating the relationship of tumor to vessel and presence or absence of extrapancreatic disease utilizing high-quality cross-sectional imaging [18, 19] is critical prior to considering up-front surgery versus a neoadjuvant treatment approach. Thin-section, multi-phase, contrast-enhanced computed tomography (CT) is typically used evaluating the relationship of tumor with adjacent vascular structures and predicting R0 resections in 73% of

cases. The American Joint Committee on Cancer (AJCC) staging system focuses on the relationship of tumor to vessels to emphasize the importance of resectability by predicting the ability to perform margin-negative resection. Currently, there are many proposed systems for defining resectability criteria, the most widely adopted being: the National Comprehensive Cancer Network [20], M.D. Anderson Cancer Center (MDACC) [21, 22], and the Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology /Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT) [23, 24]. For the purposes of this manuscript, we will focus on definitions of potentially resectable, borderline resectable and unresectable locally advanced pancreatic cancer used in the recent ALLIANCE A021101 trial as described in Table 8.1 [19].

It is highly recommended that determination of resectability and overall treatment approach be addressed prior to initiating therapy in a multidisciplinary setting. If neoadjuvant therapy is subsequently recommended, several treatment approaches should be considered as follows:

Table 8.1 ALLIANCE A-021101 definitions of potentially resectable, borderline resectable, and unresectable pancreatic cancer as defined by CT/MRI [19, 25]

	Potentially resectable	Borderline resectable	Unresectable and/or locally advanced
SMV and portal vein	Tumor-vessel interface <180° of vessel wall circumference	Tumor-vessel interface ≥180° of vessel wall circumference, and/or short-segment occlusion amenable to resection or reconstruction with normal vein proximal and distal to interface	Occlusion of the SMV or portal vein without sufficient cuff or normal vein above or below the interface for venous reconstruction
SMA	No radiographic interface between tumor and artery	Tumor-vessel interface <180° of vessel wall circumference	Tumor interface ≥180° of vessel wall circumference
Aorta	No radiographic interface between tumor and aorta		Interface between tumor and aorta
Celiac axis	No radiographic interface between tumor and celiac axis		
Nodes	Absence of suspicious lymph nodes outside of surgical field		
Hepatic artery	No radiographic interface between tumor and artery	Reconstructable short-segment interface of any degree between tumor and vessel wall with normal artery proximal and distal to interface	Long-segment interface of any degree or major tributaries with insufficient artery proximal or distal to the interface for reconstruction

Note: Presence of distant (including non-regional lymph nodes- aortocaval, distant abdominal) or ascites defines metastatic disease

8.2 Resectable Disease

8.2.1 Adjuvant Treatment Strategies

Both adjuvant chemotherapy and chemoradiation (5-fluorouracil (5-FU) or gemcitabine-based) have been associated with a survival advantage over observation after surgical resection in prospective and retrospective studies. Although clinical trials have demonstrated a clear benefit to the use of adjuvant chemotherapy (without radiation), the optimal adjuvant treatment strategy remains unclear. Adjuvant chemoradiation is considered an option for patients with margin-positive or margin-close resection who are at increased risk of locoregional failure.

8.2.1.1 Adjuvant Chemotherapy (Without Radiation) for Resectable Disease

The Charite Onkologie Study (CONKO)-001 trial randomized patients following R0 or R1 surgical resection to observation or 6 cycles of gemcitabine and demonstrated improved median disease-free survival compared with the observation arm with an improvement in overall survival at 5 years [26]. These results have established gemcitabine-based chemotherapy as an important component of adjuvant treatment. The European Study Group for Pancreatic Cancer (ESPAC)-3 trial randomized patients following R0 or R1 resection to receive either adjuvant 5-FU/leucovorin or gemcitabine for six cycles. Adjuvant gemcitabine and 5-FU/leucovorin demonstrated similar median OS (23.6 months versus 23.0 months, respectively; $p < 0.39$) and median progression-free survival (PFS) (14.3 months versus 14.1 months, respectively), but less high-grade treatment-related toxicity was observed in the gemcitabine arm, leading to recognition as the preferred adjuvant chemotherapy regimen over 5-FU [3]. The ESPAC-4 trial compares survival outcomes for patients receiving adjuvant gemcitabine with or without capecitabine, and early results suggest improvement with combination chemotherapy [27]. Other systemic treatment regimens that have demonstrated survival benefit in the metastatic setting including the combination of 5-FU, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) as well as gemcitabine/nab-paclitaxel are also being evaluated in the adjuvant setting.

8.2.1.2 Adjuvant Chemoradiation for Resectable Disease

Historically, adjuvant chemoradiation was considered the established standard of care by the early Gastrointestinal Tumor Study Group (GITSG) 1985 randomized trial [28], which demonstrated an overall survival advantage with the addition of adjuvant bolus 5-FU-based chemoradiation over surgery alone for resectable disease. However, this study was criticized for small patient numbers and use of older techniques. A similar survival benefit was observed in three other large retrospective studies comparing adjuvant 5-FU-based chemoradiation with or without maintenance chemotherapy [29–31]. Other studies including ESPAC-1 [16] and EORTC 40891 [15] have failed to demonstrate a survival benefit associated with chemoradiation in the adjuvant setting. Results similar to the initial GITSG study were

observed in the subsequent EORTC 40891 randomized trial using a continuous infusion 5-FU chemotherapy regimen with split course radiation, although small patient numbers influenced the ability to demonstrate a survival benefit [15].

Older studies evaluating the benefit of adjuvant chemoradiation have been criticized for not only trial design, but also the use of older chemotherapy regimens. Subsequently, adjuvant chemoradiation strategies using modern chemotherapy drugs have been evaluated in the clinical setting. The Radiation Therapy Oncology Group 9704 randomized trial demonstrated safety and comparable survival of adjuvant chemoradiation using gemcitabine by randomizing patients to receive either adjuvant 5-FU or gemcitabine for 3 weeks followed by 5-FU-based chemoradiation followed by additional chemotherapy following surgical resection [32]. The prospective randomized phase II EORTC 40013/FFCD 9203/GERCOR study was designed to compare adjuvant gemcitabine alone with or without concurrent radiation following surgery. The study demonstrated feasibility of gemcitabine-based adjuvant chemoradiation and improved local control with the addition of radiation, but similar survival and distant progression rates [33].

Interestingly, the results from a large retrospective analysis of patients who had R0 and R1 resections for localized pancreatic cancer receiving either adjuvant chemotherapy or chemoradiation were analyzed for relapse and survival outcomes. Locoregional control was improved for patients receiving radiation as a component of their treatment compared to those receiving only adjuvant chemotherapy (80% vs. 68%, respectively; $p < 0.0001$), and locoregional relapse was associated with worse overall survival (45.8% no local relapse vs. 33.6% local relapse; $p = 0.02$), indicating the importance of local control following surgery [34].

The role of radiation in the adjuvant setting remains unclear in the absence of prospective randomized studies. The Radiation Therapy Oncology Group (RTOG) 0848 trial is an ongoing randomized trial designed to determine whether gemcitabine plus erlotinib improves survival over gemcitabine alone, and whether the addition of radiation using modern treatment planning techniques and dose fractionation schedules to radiosensitizing doses of concurrent 5-FU or capecitabine adds benefit. The results of this trial should provide additional insight into the role of adjuvant chemoradiation in the modern era. Currently, adjuvant chemoradiation should be considered in patients with high-risk features following surgery and adjuvant chemotherapy (close R0, R1 and R2 surgical margins, or multiple nodes positive).

8.2.1.3 Adjuvant Radiation Considerations

When using a chemoradiation for the treatment of pancreatic cancer, drug-radiation interactions and concomitant treatment related sequelae should be considered. The use of combined modality approaches in pancreatic cancer is especially associated with increased gastrointestinal toxicity, especially when utilizing conventional three-dimensional conformal radiation treatment (3D CRT) [32]. Modification of concurrent chemotherapy doses and schedules (compared to those used without concurrent radiation) and special attention to dose-volume constraints using sophisticated dose-sculpting techniques such as intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) are typically used to mitigate dose to normal

tissue and the associated risks of early and late side effects of concomitant therapy [35, 36]. Proton therapy has also been used in the adjuvant setting [37].

8.2.1.4 Intraoperative Radiation Therapy (IORT) for Resectable Disease

In certain instances, IORT delivered at the time of surgical resection is considered in the treatment of initially resectable pancreatic cancer, ideally in cases in which surgical resection may result in close or positive margins. The delivery of high doses of conventionally fractionated external beam radiation therapy in pancreatic cancer may have the potential to improve local control, but is limited by dose tolerance limits of small bowel, spinal cord, stomach, kidney, and liver. Incorporation of focal IORT has the potential to reduce normal tissue doses, simultaneously allowing for radiation dose escalation with attempt to enhance locoregional control. Studies have demonstrated that IORT can be delivered safely with surgical resection for pancreatic cancer, although late complications have been reported [38].

Data evaluating the role of IORT in initially resectable pancreatic cancer is limited mostly to retrospective series comparing patient cohorts who received IORT versus those who have not. A local control benefit between 40 and 80% has been reported with the addition of IORT, without increase in operative morbidity or mortality [39–44]. In an older, small, prospective, randomized trial of 24 patients with stages II–IV pancreatic cancer, a statistically significant improvement in local control and median survival was seen in the patients who received IORT (20Gy) in addition to conventionally fractionated external beam radiation. This benefit was observed after excluding seven perioperative deaths [45]. Two treatment delivery techniques have been more commonly used. Intraoperative electron radiation treatment (IOERT) delivers a relative homogeneous dose throughout a tumor bed and high-dose-rate brachytherapy (HDR-IORT) which uses a flexible applicator, which can be shaped to conform to a tumor bed to deliver a more concentrated dose at the surface.

8.2.2 Neoadjuvant Treatment Strategies

Intraoperative surgical assessment and pathologic specimen examination has historically been used for evaluating resectability, estimating prognosis, and making adjuvant treatment recommendations. Neoadjuvant therapy offers some theoretical advantages, especially in patients with borderline resectable disease, but very few centers use this approach in patients deemed to have resectable disease at the time of diagnosis. There have been no prospective randomized studies reporting data comparing the efficacy of neoadjuvant therapy with adjuvant treatment in patients with resectable disease at the time of diagnosis, and there has been no clear advantage demonstrated favoring neoadjuvant treatment over adjuvant therapy in this setting. The largest retrospective study included 458 resectable pancreatic cancer patients from the Californian Cancer Surveillance Program, which demonstrated improved survival and a lower rate of lymph node involvement for the 8.5% who received neoadjuvant therapy [46, 47]. Another questionnaire-based study

demonstrated higher R0 resection rates in patients with resectable tumors who received neoadjuvant therapy compared to those who did not [48].

8.2.2.1 Neoadjuvant Chemotherapy (Without Radiation) for Resectable Disease

Early trials explored neoadjuvant chemotherapy without radiation to treat occult metastatic disease prior to surgery with attempt to avoid surgery in patients that would not likely benefit due to progressive disease. One single-arm phase II trial included 28 patients with resectable pancreatic cancer who received 4 cycles of twice weekly gemcitabine and cisplatin prior to surgery. Although most of the patients were able to undergo planned surgery and 71% underwent R0 resection, the median OS for the entire cohort was not substantially improved at 26.5 months [49]. A meta-analysis of 111 neoadjuvant studies including patients with initially resectable pancreatic cancer demonstrated improved response rates in patients treated with chemoradiation compared to chemotherapy alone, but resection rates did not differ when compared to an up-front surgery followed by adjuvant therapy approach [17]. Another meta-analysis including 20 prospective studies evaluated the benefit of modern neoadjuvant treatment regimens (gemcitabine-based) demonstrating only a marginal survival benefit in patients with initially resectable disease, regardless of whether they received radiation [50].

8.2.2.2 Neoadjuvant Chemoradiation for Resectable Disease

Results from phase II trials from MD Anderson Cancer Center (MDACC) have generated the most compelling data for neoadjuvant therapy in the setting of initially resectable disease, using a clear and consistent definition of resectability and surgical management across all studies [6, 12, 25, 51, 52]. These trials reported higher R0 resection rates in patients who completed neoadjuvant chemoradiation and were without radiographic evidence of progression compared to historical surgical data, and patients who underwent surgical resection demonstrated higher median and OS rates. A median OS of 21 months has been reported for patients using this aggressive neoadjuvant followed by surgery approach [53]. Other investigators have similarly reported lower recurrence, improved survival, and higher R0 resection rates for patients who received neoadjuvant chemoradiation compared to patients who received immediate surgery followed by adjuvant therapy [54].

8.2.2.3 Neoadjuvant Radiation Considerations

Similar to indications for adjuvant radiation, the use of modern radiation techniques including IMRT and VMAT are typically used in the neoadjuvant setting to reduce the rate of associated toxicity compared to conventional 3D CRT treatment. In addition, limiting radiation doses to surrounding normal tissues by using these highly conformal techniques potentially allows for the addition of more aggressive chemotherapy and selective radiation dose escalation, which may lead to improved local control, especially in those patients who are unlikely to undergo R0 resection. However, it is uncertain if intensifying treatment in the neoadjuvant setting leads to improved outcomes for resectable disease.

8.3 Borderline Resectable Disease

Borderline resectable pancreatic cancer is associated with a higher risk for positive resection margin due to tumor-vascular abutment, more complex surgical resection which may include vascular resection and reconstruction, and increased probability of occult distant metastases compared to initially resectable pancreatic cancer. Since R0 resection has been shown to be a significant factor predicting long-term survival in pancreatic cancer patients and positive margin following surgery yields prognosis similar to inoperable disease [2, 14, 55–58], neoadjuvant therapy with the intent of sterilizing the margin is often considered in the setting of borderline resectable disease with vascular involvement.

8.3.1 Neoadjuvant Treatment Strategies

8.3.1.1 Neoadjuvant Chemotherapy (Without Radiation) for Borderline Resectable Disease

Some investigators have tested treatment strategies utilizing aggressive neoadjuvant chemotherapy without concurrent radiation to maximize systemic therapy dosing, theoretically leading to more effective elimination of occult metastases and potentially improving survival. The NeoGemOx phase II study included 15 patients with borderline resectable tumors and 18 with unresectable tumors treated with neoadjuvant gemcitabine and oxaliplatin, resulting in a 39% resection rate, R0 resection rate of 69%, and median OS of 22 months for those who underwent resection compared to 12 months for those who did not [59]. The NeoGemTax study is a similar trial which treated a similar population of 12 borderline resectable and 13 unresectable patients resulting in a 32% resection rate, with 87% R0 resection rate, and a median OS of 16 months for those who underwent resection compared to 12 months for those who did not [60]. Retrospective studies have evaluated the use of neoadjuvant FOLFIRINOX, demonstrating resection rates from 33 to 42% and R0 resection rates from 55 to 92% [13, 61–65]. A recently published meta-analysis including 13 studies and 253 patients with initially resectable, borderline resectable, and unresectable disease reported similar resection and R0 resection rates overall (39% and 85%, respectively), with a 64% R0 resection rate for patients with borderline resectable tumors [65]. Despite inclusion of patients with locally advanced unresectable disease in these trials, the overall resection and R0 resection rates were high indicating that chemotherapy alone has a role in the neoadjuvant setting.

8.3.1.2 Neoadjuvant Chemoradiation for Borderline Resectable Disease

Several studies suggest that neoadjuvant chemoradiation may enhance R0 resection rates and improve local control [66–80]; however, most of these studies are limited by small sample size, lack of strict definition of borderline resectable disease, and inclusion of patients with unresectable tumors. Data from prospective

trials containing patients with borderline resectable disease demonstrate resection and R0 resection rates ranging from 24 to 64% and 87 to 100%, respectively [66–80]. One retrospective study reviewed data from 160 patients with borderline resectable tumors carefully selected with adequate staging studies and strict adherence to the definition of borderline resectable disease, who were treated with 2–4 months of neoadjuvant chemoradiation with 5-FU, gemcitabine, capecitabine, or paclitaxel. In this study, 78% completed the prescribed neoadjuvant regimen and restaging, 41% underwent surgical resection, with 27% requiring vascular resection/reconstruction, and 94% achieved R0 resections. Median OS was 40 months for patients who underwent surgery compared to 13 months for those who did not; however, 59% of the resected patients ultimately recurred, 45% of them systemically, 9% locally, and 11% regionally, with a median time to progression of 24 months [22].

As a result, the high rates of treatment failures observed in neoadjuvant studies for borderline resectable pancreatic cancer highlight the need to improve the efficacy of neoadjuvant strategies. In addition to utilization of more aggressive neoadjuvant systemic treatment regimens in an attempt to improve upon the distant failure rate, others have investigated the incorporation of highly targeted radiation delivery approaches in the neoadjuvant setting in an attempt to deliver more biologically effective doses of radiation while reducing toxicities of surrounding normal tissues.

8.3.1.3 Proton Therapy for Borderline Resectable Disease

The advantage of proton beam over conventional radiation is that the energy distribution of protons can be directed and deposited at the tumor site, taking advantage of the Bragg peak where the protons release most of its energy when they reach the end of their path at the tumor site, sparing adjacent normal tissues. Published dosimetric studies have reported an improved therapeutic index for pancreatic cancer treatment [37, 81–86]. Clinical trials have also explored the use of protons in the treatment of pancreatic cancer. One study included 22 patients with biopsy-proven pancreatic adenocarcinoma (5 resected; 5 borderline resectable; 12 locally advanced unresectable) treated with proton therapy (50.4 Gy (RBE) to 59.4 Gy (RBE)) and concurrent capecitabine, which resulted in only three cases of grade 2 and no grade 3 or higher gastrointestinal toxicities on follow-up [87]. More recently, intensity-modulated proton therapy (IPMT) using 3D passively scattered protons has been utilized in a preoperative short-course dose-escalation phase I/II study with capecitabine [88, 89]. Results from the phase I trial were compared to a similar study using the same hypofractionated dose schema, but delivered with photon radiation demonstrating less operative complications associated with proton therapy (27% vs. 63%, respectively) [90]. Despite these promising results, further evaluation of proton therapy in this setting is warranted as it is recognized that high-dose IMPT plans do not appear to be as conformal as high-dose IMRT plans, even though IMPT plans reduce low doses of radiation to surrounding gastrointestinal tissues, theoretically reducing low-grade acute toxicities. Nonetheless, the safety of patients with “resectable” pancreatic cancer treated with neoadjuvant proton therapy has

been established for treatment of pancreatic cancer [50] and additional studies will provide further data to examine the role of proton therapy in this setting.

8.3.1.4 Intraoperative Radiation Therapy (IORT) for Borderline Resectable Disease

A recently published retrospective study demonstrated the safety of IORT following intensive neoadjuvant therapy in patients with either borderline resectable or locally advanced pancreatic cancer who received induction chemotherapy (FOLFIRINOX, FOLFOX, or gemcitabine with nab-paclitaxel) and chemoradiation (50.4 Gy/28 fractions with concurrent capecitabine or infusional 5-FU), followed by exploratory laparotomy with attempted surgical resection with or without IORT for close (tumor <5 mm from resection margin) or positive margin on intraoperative frozen section. Ultimately, 60.3% of patients underwent surgical resection, with 26.5% found to have unresectable disease at the time of laparotomy, and 22 patients receiving IORT to resection bed with 1 cm margin (median dose 10Gy, range 8–13Gy; median energy 9 MeV electrons, range 6–18 MeV; median isodose line 80%, range 80%–90%) without impact on operative times or morbidity, but associated with increased hospital stay. R0 resection rates were similar for the no IORT cohort and IORT cohort, with 73% having close or positive margins in the latter group compared to 37% for the former. Local recurrence rates were not statistically significantly different for the two groups (32% no IORT vs. 27% IORT). Median OS was 35.1 months for patients who received IORT following resection and 24.5 months for patients who underwent resection alone [91]. These differences were not statistically significant likely due to small sample size and patient selection bias, but warrant further evaluation in larger prospective studies.

8.3.1.5 Stereotactic Body Radiation (SBRT) for Borderline Resectable Disease

SBRT allows precisely focused delivery of a few fractions of radiation in the ablative dose range using image guidance to ensure accurate radiation targeting. It utilizes a highly conformal radiation dose distribution with a steep gradient, making it possible to deliver high doses of radiation to the pancreas while limiting dose to surrounding normal tissue. Early phase I/II SBRT studies used 25 Gy in a single fraction resulting in excellent locoregional control of approximately 90%, but an unacceptable late grade 3 or higher toxicity rate (9%) consisting mainly of gastrointestinal ulceration and bleeding, and a modest 1-year OS of 21% due to early onset of distant metastasis [92]. To improve upon these results, a phase II multi-institutional study delivered SBRT using a fractionated approach (33 Gy in 5 fractions) to 49 patients after gemcitabine therapy, resulting in a lower rate of severe late gastrointestinal toxicity (6%), good local control (78%) and improved 1-year OS (59%) [93].

SBRT has been studied in the neoadjuvant setting for patients with borderline resectable pancreatic cancer, with the goal of downstaging the tumor to improve R0 resection rates and local-regional control. A retrospective study included patients with borderline resectable and locally advanced pancreatic cancer treated with

various systemic regimens followed by SBRT using a dose-painting technique to deliver 30 Gy in five fractions to the entire tumor while escalating dose to regions of vascular abutment/encasement to 40 Gy. Results of this study demonstrate that 56% of patients with borderline resectable tumors treated with this technique underwent surgery and 97% had R0 resections [94]. Another retrospective study suggests that the addition of SBRT to neoadjuvant chemotherapy may improve R0 resection rates [95]. While there are no randomized trials to compare neoadjuvant chemotherapy alone versus chemotherapy and SBRT for borderline resectable (or locally advanced) pancreatic cancer, SBRT following neoadjuvant systemic chemotherapy continues to be a subject of clinical investigation for patients with localized pancreatic cancer [47].

8.4 Treatment Planning

8.4.1 Patient Setup

Patients should be placed in a supine position, immobilized in a Vac-Lock (Civco Radiotherapy, Orange City, Iowa), Alpha Cradle (Smithers Medical Products Inc., North Canton, OH), or equivalent immobilization device with arms up.

8.4.2 Simulation

Patients should be scanned from the carina through the top of the pelvis using CT simulation (thin slices, 2–3 mm, through the pancreas or tumor bed and locoregional nodal basins).

- Imaging with oral contrast/water with and without IV contrast strongly recommended for improved delineation of the tumor or tumor bed and adjacent normal structures.
- If no IV contrast at the time of simulation, diagnostic CT with IV contrast should be fused with simulation CT to permit accurate identification of PV/CA/SMA.
- Ideal diagnostic imaging technique Spiral CT—ideally multisection CT:
  - Fast speed, thin-sections, optimal enhancement, and high spatial resolution.
  - Oral water as negative intraluminal contrast may be considered.
  - 120–150 mL of iodinated IV contrast administered at a rate of 3–4 mL/s.
  - Thin (2- to 3-mm) collimation during pancreatic parenchymal phase (at 25–35 s).
  - Liver phase obtained at 60–70 s.
- For proton treatments, a special table top may be used at the time of simulation or inserted into the CT images manually after data acquisition.
- Pancreatic position can vary depending on the amount of gastric distension, which should be accounted for during simulation and treatment. Patients should not eat or drink 2 h before simulation or treatment. Consider the use of

200–250 cc of oral contrast (simulation) or water (treatment) consumed immediately prior to treatment to ensure consistent filling.
- Consideration of four-dimensional CT (4D CT) or fluoroscopy to evaluate tumor motion.
  - Normal breathing, inspiratory, expiratory breath-hold CTs if fluoroscopy/4D CT not available.

8.4.3 Motion Evaluation

Both interfraction (mainly due to setup error) and intrafraction (motion from breathing or bowel/stomach distension not accounted for with pretreatment portal imaging) variations are important when considering margin expansions.

- 4D CT or fluoroscopy tumor motion data often used to define an internal target volume (ITV) expansion to ensure that tumor motion is incorporated into treatment planning for adequate dose coverage of target volumes.
  - 4D CT may underestimate motion compared to fluoroscopy as a result of technique or patient discomfort during the procedure.
- Known variations in tumor motion emphasize the need for individual patient assessment
  - Pancreatic tumor motion is variable ranging from 5 to 43 mm [96], indicating the need for individualized analysis for adequate treatment planning margins.
  - Motion of the pancreatic head, body, and tail appears to be different [97].
  - The surrounding vasculature (superior mesenteric and celiac arteries) typically move less than 5 mm [98].
- Real-time verification of positioning before and/or during treatment is ideal.
- Image-guided radiation therapy (IGRT) using daily pretreatment two- or three-dimensional imaging is often used to direct radiation therapy utilizing the imaging coordinates of the actual radiation treatment plan. The patient is placed in the same position as planned from the reference imaging dataset and precise target localization is accomplished using:
  - Cone beam computed tomography (CBCT) dataset compared with the planning computed tomography (CT) dataset.
  - Or by matching planar kilovoltage (kV) or megavoltage (MV) images with digital reconstructed radiographs (DRRs) generated from the planning CT.
- Fiducial markers placed in or around the tumor or surgical clips in the tumor bed may be used to enhance localization of target volume.

8.4.4 Motion Management for Optimized Treatment Delivery

- In general, if less than 3 mm motion is noted on fluoroscopic or 4D CT analysis, patients can be treated to an ITV while free-breathing, using the 0% and 50% phases of the respiratory cycle.

- If more than 3 mm motion is noted on fluoroscopic or 4D CT analysis, motion management techniques should be used rather than increasing planning margins to encompass a large ITV, which also increases radiation dose to surrounding normal tissues.
- Two approaches to motion management can be considered:
  - Immobilization using *reliable* abdominal compression devices, breath-hold techniques including active breath control (ABC), or self-held deep inspiration breath-hold (DIBH) techniques.
    Abdominal compression minimizes diaphragmatic excursion, but should be used with caution as bowel may be compressed into the target volume, increasing exposure to radiation dose.
    Active or passive breath-hold techniques eliminate breathing motion to ensure delivery of RT, while the breath is held within a previously selected tidal volume; however, patients typically are able to hold their breath over short periods.
  - Physiologically monitoring tumor motion for neoadjuvant treatment (tracking or gating).
    Tracking allows the radiation beam to follow tumor motion and requires fiducial markers to be placed. Phase- or amplitude-based gating is another alternative, choosing a respiratory phase/position interval for beam delivery, with the possibility of adjustments in the day of treatment based on fiducial positioning during fluoroscopy.
    Prior simulation 3 or more metallic fiducials are placed endoscopically (ideally) or percutaneously into the pancreatic tumor and adjacent tissues. CT simulation should be performed approximately 1 week later, as it is known that fiducial markers can migrate [99].
    Pancreatic stents have also been used to track pancreatic motion [100], but may migrate during the course of radiation [99] and have been associated with greater motion than GTV, which may result in a larger ITV expansion than necessary [101]. Hence, stents may not be reliable markers for daily IGRT.
- Real-time verification of positioning before and/or during treatment is ideal, especially if tight margins are used.

8.4.5 Dosimetric Treatment Planning

8.4.5.1 Target Volumes

- The quality of adjuvant radiation has been associated with improved survival in resected pancreatic cancer in a retrospective study analyzing the significance of adherence to standard guidelines and quality assurance with radiation delivery [102].
- To improve the quality of pancreatic cancer radiation, expert-defined target and normal tissue contouring guidelines have been developed (RTOG.org website), and emphasis on prospective peer review of treatment plans and detailed attention quality assurance measures before and during treatment has emerged as an important component of care [103].
- Contouring atlases are provided in Figs. 8.1 and 8.2.

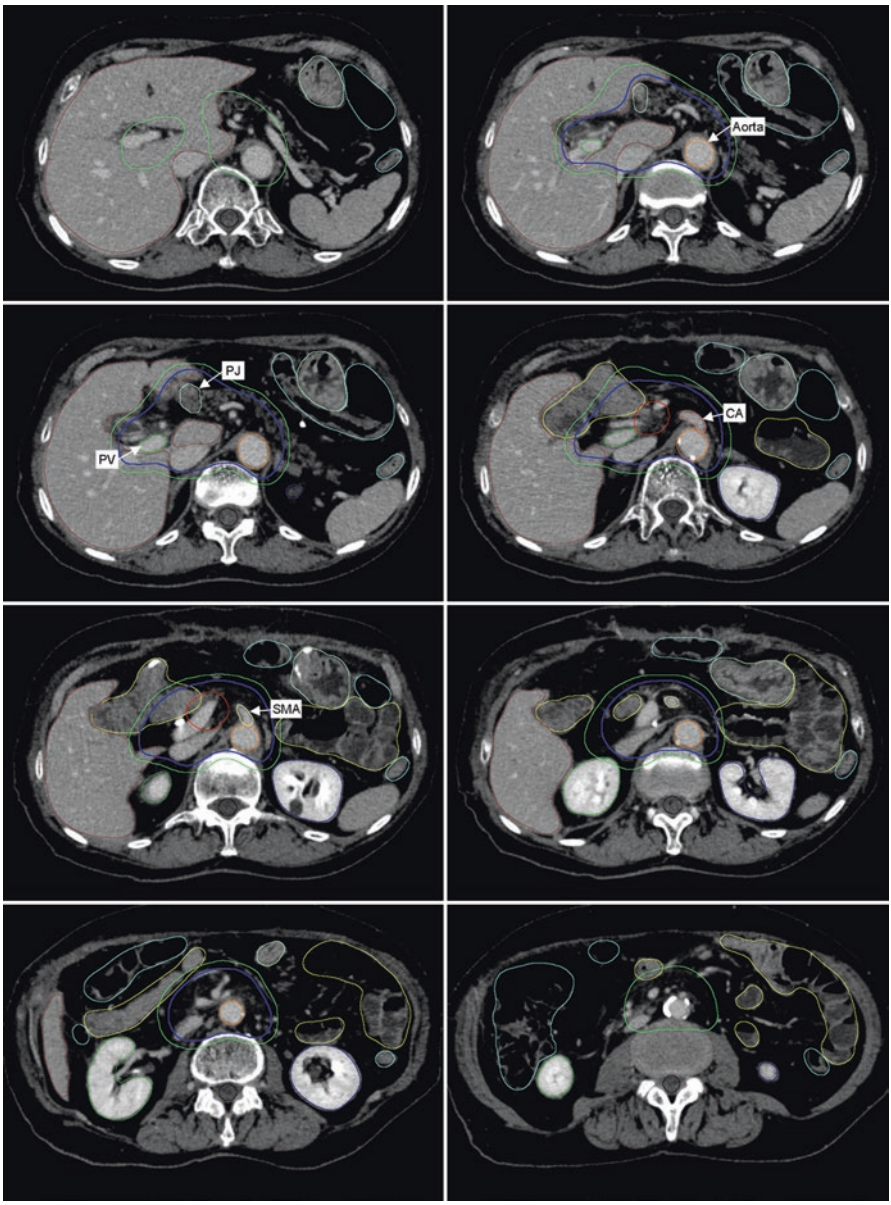

Fig. 8.1 Contouring atlas for target and normal tissue delineation used for ADJUVANT treatment in pancreatic cancer (an atlas of images illustrating target and normal tissue contouring for adjuvant radiation is also located at the RTOG.org website). *CA* celiac axis; *PJ* pancreaticojejunal anastomosis; *PV* portal vein; *SMA* superior mesenteric artery. Target volumes contours: in *Red* = preoperative GTV based on preoperative CT scan; in *Blue* = CTV encompassing the recommended nodal basins and areas at risk according to RTOG guideline for adjuvant irradiation, which includes expansions from aorta, SMA, PV, CA, PJ, and pre-op GTV; in *Green* = PTV, created by an expansion of 1 cm from the CTV. Normal tissue contours: in *Brown* = liver; *Yellow* = small bowel; *Cyan* = large bowel; *Light-green* = stomach; *Black* = spinal cord; *Dark-green* = right kidney; *Purple* = left kidney

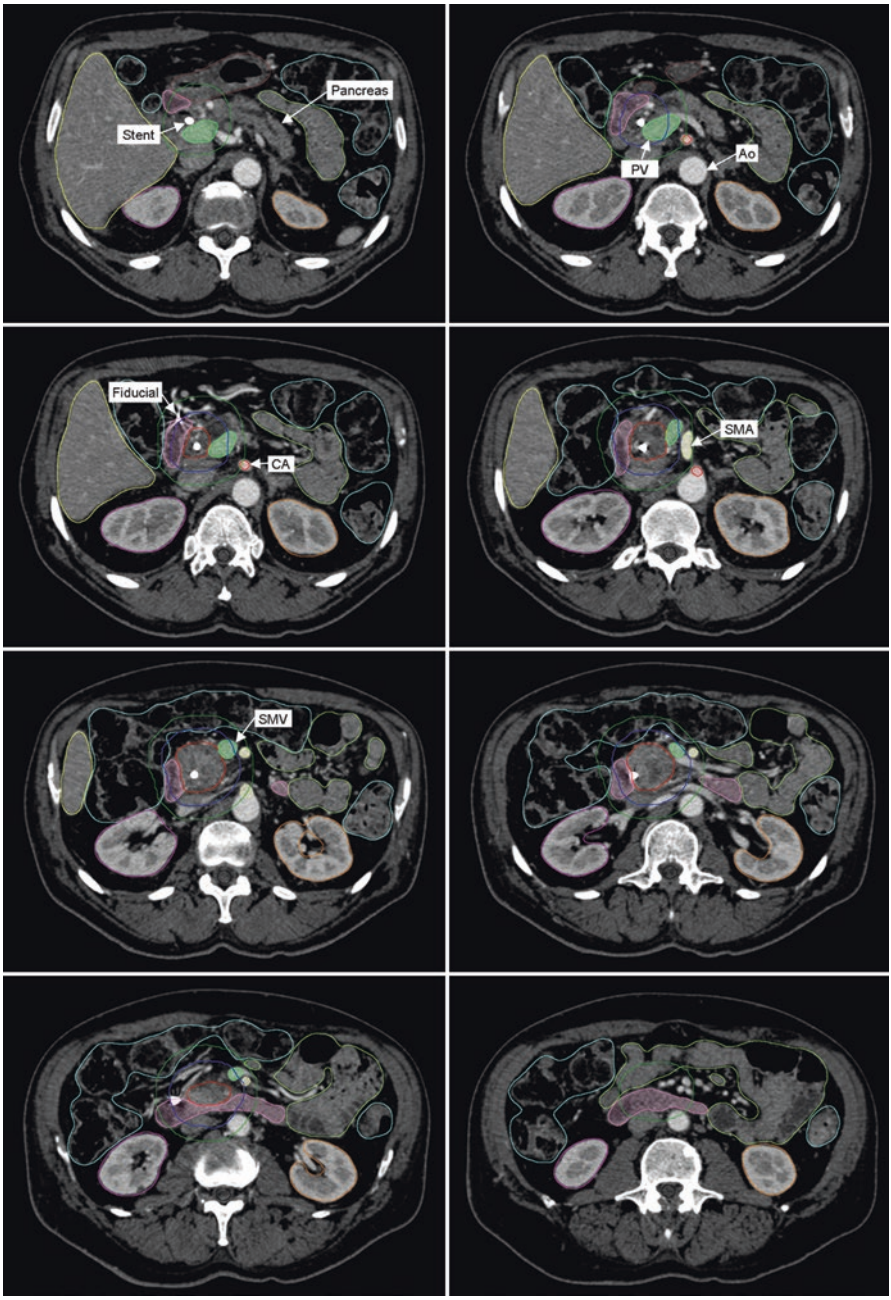

Fig. 8.2 Contouring atlas for target and normal tissue delineation used for NEOADJUVANT treatment in pancreatic cancer. *Ao* aorta; *CA* celiac axis; *PV* portal vein; *SMA* superior mesenteric artery; *SMV* superior mesenteric vein. Target volumes contours: in *Red* = GTV; in *Blue* = CTV, created by an expansion of 1 cm from the GTV; in *Green* = PTV, created by an expansion of 1 cm from the CTV. Normal tissue contours: in *Yellow* = liver; *Light-green* = small bowel; *Cyan* = large bowel; *Brown* = stomach; *Black* = spinal cord; *Magenta* = right kidney; *Orange* = left kidney

- Gross tumor volume (GTV) and pathologic nodes (defined as regional nodes measuring greater than1 cm on CT imaging) are contoured. Anatomical diagnostic CT and/or MR and functional imaging (PET-CT) may be co-registered with treatment planning imaging to assist in delineation of GTV.
- Clinical target volume (CTV) for ***neoadjuvant treatment*** for intact tumors includes the GTV with a 0.5-cm to 1.5-cm margin to target microscopic tumor extension. However, with SBRT, CTV margin is typically excluded.
- CTV for ***adjuvant treatment*** includes the postoperative tumor bed based on location of the initial tumor from preoperative imaging and pathology reports.
  - Elective nodal irradiation is commonly used for *adjuvant treatment,* but is controversial for neoadjuvant treatment. For adjuvant therapy, elective nodal irradiation includes abdominal nodal regions:
    - Peripancreatic;
    - Celiac;
    - Superior mesenteric;
    - Porta hepatis;
    - Para-aortic.
    - Nodal regions should include a 1–1.5 cm expansion around the:
      retropancreatic and pancreaticoduodenal space;
      proximal 1–1.5 cm of the celiac axis;
      proximal 2.5–3 cm of the superior mesenteric artery (SMA);
      portal vein segment that runs anteromedial to the inferior venal cava to the bifurcation at the liver hilum.
      Para-aortic node region should include asymmetric expansions around the aortic (contoured from the most cephalad contour of the celiac axis, portal vein, or pancreaticojejunostomy to the bottom of L2 or L3 if the GTV location is low) with the goal to cover paravertebral nodes laterally while avoiding kidneys as follows:
      2.5–3.0 cm to the right;
      1.0 cm to the left;
      2.0–2.5 cm anteriorly;
      0.2 cm posteriorly towards the anterior edge of the vertebral body (without covering more than 0.1 cm of the anterior vertebral body).
  - CTV includes the following surgical anastomoses for adjuvant treatment:
    - Pancreaticojejunostomy identified by following the pancreatic remnant medially and anteriorly until the junction with the jejunal loop, with expansion of 0.5–1.0 cm in all directions;
    - Choledochal or hepaticojunostomy with expansion of 0.5–1.0 cm in all directions;
    - Surgical clips with expansion of 0.5–1.0 cm in all directions.

- Planning target volume (PTV), defined per ICRU-62 guidelines, should be constructed based on the image guidance technique employed [104], typically 0.5–2.0 cm volume expansion from the CTV to account for tumor or breathing motion and patient setup errors. PTV for SBRT using fiducial markers is generated with a 0.2–0.5 cm expansion from the GTV.
- PTV expansion to ensure adequate target coverage may vary based on IGRT method used.
  - Portal imaging has been associated with a 5–6 mm setup uncertainty for radiation treatment.
  - CBCT is associated with 2.4 mm left-right, 2 mm anterior-posterior, and 3.2 mm cranio-caudal setup errors, in addition to 3.2 mm left-right, 1.8 mm anterior-posterior, and 3.6 mm cranio-caudal random errors [105].
- Motion analysis at the time of simulation can be used to generate an ITV which may be used to generate nonuniform PTVs based on individual measurements of tumor motion in three dimensions (as opposed to uniform PTV expansion).
- Placement of fiducial markers in or around the tumor, motion management techniques, and IGRT can result in improved PTV coverage with decreased dose to surrounding normal tissues.
- In addition to target volumes, the following normal tissues should be contoured on the treatment planning CT data set for treatment planning
  - Stomach;
  - Duodenum;
  - Jejunum;
  - Large Bowel;
  - Liver;
  - Right and Left Kidney;
  - Spinal Cord;
  - Celiac Axis (CA);
  - Superior Mesenteric Artery (SMA);
  - Superior Mesenteric Vein (SMV);
  - Portal Vein (PV).

8.4.6 Treatment Modalities

As previously described, there are a number of radiation treatment delivery methods that can be considered for the treatment of resectable pancreatic cancer. Table 8.2 describes the various radiation options and indications for the treatment of resectable pancreatic cancer.

Table 8.2 Radiation treatment approaches for resectable pancreatic cancer

Technique	Indication	Fractionation schedules	Beam arrangement	Appropriate chemotherapy
3D CRT[a]	Adjuvant therapy for initially resected tumors, especially for those with close or positive surgical margin	50.4 Gy; 1.8 Gy per fraction; 5 days per week	3 or 4 fields (APPA; right and left lateral)	Before radiation, and/or concurrent, and/or following radiation
	Neoadjuvant therapy for borderline resectable pancreatic cancer	50.4 Gy; 1.8 Gy per fraction; 5 days per week	4 fields (APPA; right and left lateral)	Induction and/or concurrent
IMRT and VMAT[a]	Adjuvant therapy for initially resected tumors, especially for those with close or positive surgical margin	50.4 Gy; 1.8 Gy per fraction; 5 days per week	IMRT: Multiple coplanar isocentric beams VMAT: Volumetrically modulated coplanar arcs	Before radiation, and/or concurrent, and/or following radiation
	Neoadjuvant therapy for borderline resectable pancreatic cancer	50.4 Gy; 1.8 Gy per fraction; 5 days per week or 30 Gy; 3 Gy per fraction; 5 days per week	IMRT: Multiple coplanar isocentric beams VMAT: Volumetrically modulated coplanar arcs	Induction and/or concurrent
IORT[b,c]	Delivered at the time of surgery for initially resectable or borderline resectable pancreatic cancer, especially in those patients who are not likely to achieve R0 resection determined at the time of surgery. May be used after neoadjuvant therapy.	10–15 Gy (microscopic) 15–20 Gy (gross residual)	En face electrons	No; Neoadjuvant or adjuvant chemotherapy or chemoradiation acceptable

Table 8.2 (continued)

Technique	Indication	Fractionation schedules	Beam arrangement	Appropriate chemotherapy
Proton Therapy[b,c]	Adjuvant therapy for initially resected tumors, especially for those with close or positive surgical margin	50.4 Gy (RBE); 1.8 Gy per fraction; 5 days per week	Typically, 3 fields (posterior Oblique: Right lateral oblique) with a 3-to-1 weighting to The posterior field to limit spinal cord dose	Before radiation, and/or concurrent, and/or following radiation
	Neoadjuvant therapy for borderline resectable pancreatic cancer IPMT only—neoadjuvant therapy for borderline resectable pancreatic cancer	50.4 Gy (RBE); 1.8 Gy per fraction; 5 days per week or 30 Gy (RBE); 3 Gy per fraction; 5 days per week	Typically, 3 fields (posterior Oblique: Right lateral oblique) with a 3-to-1 weighting to The posterior field to limit spinal cord dose	Induction and/or concurrent Concurrent capecitabine Concurrent capecitabine
SBRT[c]	Neoadjuvant therapy for borderline resectable pancreatic cancer	33 Gy; 6.6 Gy per fraction; Delivered over 1–2 weeks	Linac-based: IMRT: Multiple coplanar isocentric beams or VMAT: 1–3 volumetrically modulated coplanar arcs Cyberknife: Multiple noncoplanar nonisocentric beams	Induction or adjuvant following surgery

[a]High-energy photons (≥10 MV) preferred as lower energy may result in more gastrointestinal toxicity

[b]Treatment energy depending on depth of target volume

[c]May be appropriate for carefully selected patients

8.4.7 Treatment Plan Optimization

Regardless of the radiation modality utilized, treatment plans must be optimized for adequate target coverage and minimization of risks of treatment-related toxicity. Several strategies to treatment planning optimization are commonly utilized during the treatment planning process:

- Thoughtful choice of beam geometry and treatment energy selection to enhance dose homogeneity for the treatment volume and avoid concentration of radiation dose to normal tissue;
- Use of multiple coplanar and noncoplanar beams to improve dose homogeneity across the target and reduce high-dose regions within normal structures;
- Custom blocking and beam shaping using multileaf collimation to block normal tissue in the radiation beam;
- Use of treatment wedges and compensators to accommodate for irregularities of patient contour which may affect dose distribution;
- Use of off-axis normalization points to increase dose conformality to an irregular target while reducing dose to nearby tissue;
- Use of dose-sculpting techniques to achieve more conformal dose distributions using advance radiation technologies (IMRT, VMAT, SBRT, IMPT).

Each treatment plan is unique and must be optimized to accommodate patient and target-specific attributes. Normal tissue tolerances to radiation, however, have been the subject of investigation, and dose-volume relationships have been characterized for different dose fractionation regimens [106]. Modern era radiation treatment planning incorporates evaluation of dose to organs-at-risk to minimize radiation-induced complications. Tables 8.3 and 8.4 outline commonly used dose-volume relationships to be incorporated as treatment planning objectives for standard fractionation pancreatic radiotherapy and pancreatic SBRT. Figure 8.3 provides examples of optimized radiation treatment plans for various radiation modalities used to treat resectable and borderline resectable pancreatic cancer.

Table 8.3 Dose-volume considerations for treatment planning optimization of standard fractionation schedules for 3D CRT, IMRT, VMAT, and proton therapy (1.8 Gy × 28 fractions) [107]

Critical structure	Volume	Dose/volume	Toxicity rate	Toxicity endpoint
Liver	Mean	<30–32 Gy	<5%	RILD (in normal liver function)
Liver	Mean	<42 Gy	<50%	RILD (in normal liver function)
Liver	Mean	<28 Gy	<5%	RILD (in Child-Pugh A or HCC)
Liver	Mean	<36 Gy	<50%	RILD (in Child-Pugh A or HCC)
Kidney, bilateral	Mean	<15–18 Gy	<5%	Clinical dysfunction
Kidney, bilateral	Mean	<28 Gy	<50%	Clinical dysfunction
Kidney, bilateral	V12	<55%	<5%	Clinical dysfunction
Kidney, bilateral	V20	<32%	<5%	Clinical dysfunction
Kidney, bilateral	V23	<30%	<5%	Clinical dysfunction
Kidney, bilateral	V28	<20%	<5%	Clinical dysfunction
Stomach	D100	<45 Gy	<7%	Ulceration
Small bowel (individual loops)	V15	<120 cc	<10%	Grade 3+ toxicity
Small bowel (peritoneal cavity)	V45	<195 cc	<10%	Grade 3+ toxicity

Table 8.4 Dose-volume considerations for treatment planning optimization of pancreatic SBRT (6.6 Gy × 5 fractions) [79]

Objective	Dose (Gy)	Upper Limit
Pancreas GTV V25	25	99.99%
PTV V33	33	90%
PTV V42.9	42.9	1 cc
Proximal duodenum V15	15	9 cc
V20	20	3 cc
V33	33	1 cc
Proximal stomach V15	15	9 cc
V20	20	3 cc
V33	33	1 cc
Proximal jejunum V15	15	9 cc
V20	20	3 cc
V33	33	1 cc
Liver V12	12	50%
Combined kidney V12	12	25%
Right kidney V12	12	25%
Left kidney V12	12	25%
Stomach V12	12	50%
V33	33	1 cc
Spinal cord V8	8	1 cc

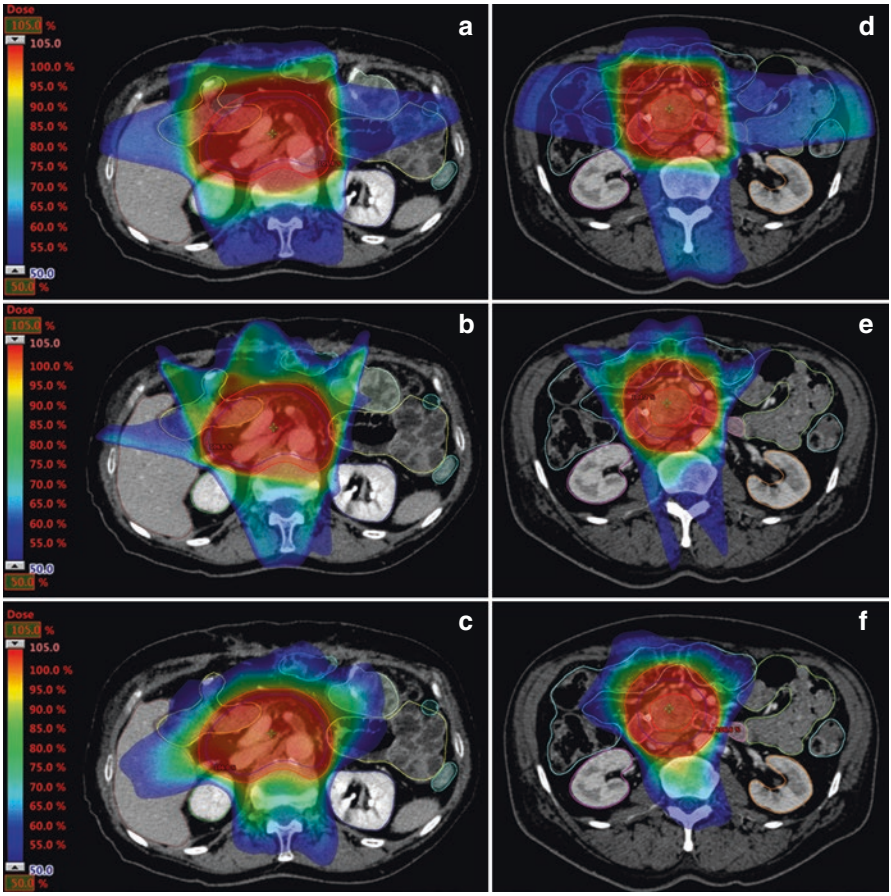

Fig. 8.3 Examples of optimized radiation treatment plans for various radiation modalities used to treat resectable and borderline resectable pancreatic cancer. Representative radiotherapy plans for adjuvant treatment (50.4 Gy in 28 fractions) of a resectable case using: (**a**) 3D–conformal radiotherapy (3D–CRT), (**b**) Intensity-modulated radiotherapy (IMRT), (**c**) Volumetric-modulated arc therapy (VMAT). Representative radiotherapy plans for neoadjuvant treatment (50.4 Gy in 28 fractions) of a borderline resectable case using (**d**) 3D–CRT, (**e**) IMRT, (**f**) VMAT, (**g**) Stereotactic body radiotherapy (SBRT) prescribed to 33 Gy in five fractions, and (**h**) proton therapy plan utilizing PA and LPO beams (50.4 Gy in 28 fractions). Target volumes contours: GTV in *Red* (when present), CTV in *Blue,* and PTV in *Red*

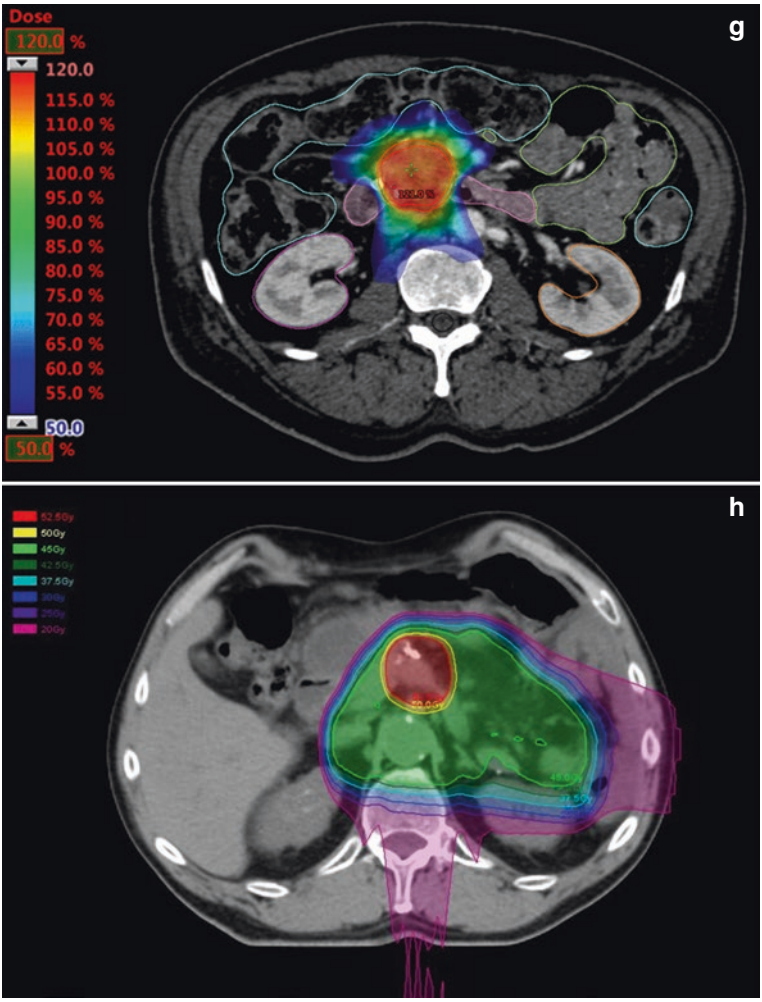

Fig. 8.3 (continued)

8.5 Treatment Management

8.5.1 Acute Side Effects

Treatment-related toxicity can include gastrointestinal toxicities (nausea, vomiting, diarrhea, and abdominal pain) and fatigue. As a result of the gastrointestinal effects of treatment, patients may lose weight from reduced calorie intake or develop dehydration from diarrhea or reduced oral intake. These side effects are managed with supportive care and medication. Acute side effects typically resolve in 4–6 weeks, but may take longer in some patients.

During treatment, patients should have vital signs monitored and be weighed at least weekly to evaluate for weight loss and/or dehydration, and if possible, be referred to a registered dietician for formal evaluation of nutritional status and dietary recommendations. In addition, since pancreatic exocrine insufficiency and diabetes is common in pancreatic cancer patients, specific attention and dietary/medication recommendations should be addressed.

- For weight loss:
  - High calorie nutrition supplementation or protein shakes.
- For dehydration:
  - Orthostatic vital signs to evaluate for dehydration;
  - Intravenous fluids;
  - Consider dose reduction or discontinuation of anti-hypertensive medication.
- For nausea and vomiting:
  - Antiemetic medications, as needed or scheduled for severe persistent nausea;
  - Low-dose dexamethasone as adjunct for nausea/vomiting uncontrolled with regular antiemetics;
  - Proton-pump inhibitor or H2 blocker;
  - Simethicone for gas pain.
- For diarrhea:
  - Low fiber/residue diet;
  - Over the counter loperamide to slow bowel transit time;
  - Prescription diphenoxylate/atropine for diarrhea refractory to loperamide;
  - Narcotic medication (prescribed for other symptoms) may also help slow bowel transit time.
- For fatigue:
  - Participation in regular routine with moderate exercise as tolerated;
  - Minimize daytime sleep in order to receive a full night's sleep;
  - Treat insomnia, if present.

8.5.2 Late Toxicities

Meticulous radiation treatment planning and delivery utilizing modern treatment techniques incorporating reproducible, optimized patient setup, motion evaluation and management, and accurate dose limitations to organs at risk (Table 8.3) can decrease risks of late effects from radiation.

- Small bowel fibrosis and/or adhesions are more common following surgery and abdominal radiation and can lead to bowel obstruction, which is typically managed non-surgically with bowel rest, pain control, and supportive care.
- Ulceration, perforation, or GI bleed are rare late effects of treatment, more common following SBRT hypofractionated radiation and often require urgent surgical or endoscopic intervention.

8.6 Summary

There are several therapeutic options for the treatment of resectable and borderline resectable pancreatic cancer. A treatment algorithm (Fig. 8.4) is included for consideration of various treatment modalities appropriate for different clinical scenarios in the setting of resectable pancreatic cancer. Even with potentially curative disease, there exists a high risk of systemic progression warranting consideration for neoadjuvant chemotherapy. Immediate surgery followed by adjuvant therapy remains an option for initially resectable disease. Although the role of adjuvant chemotherapy following resection has been established, it remains unclear whether adjuvant chemoradiation improves survival compared with chemotherapy alone. In general, radiation therapy including IORT should be considered in the multimodality treatment of pancreatic cancer in patients who have high-risk features following surgery and adjuvant chemotherapy (close R0, R1 and R2 surgical margins, or multiple nodes positive) or in patients with borderline resectable disease with favorable response or stable disease after initial chemotherapy. Local control following surgery appears to translate into a survival benefit in retrospective studies. However, the exact role of radiation in this setting is yet to be established. Results RTOG 0848 study may help to establish the role of adjuvant radiation in resectable pancreatic cancer.

Radiation therapy has been safely combined with newer chemotherapy regimens in clinical trials, but the optimal combination and sequencing has not been determined. Several radiation treatment modalities may be utilized when considering neoadjuvant or adjuvant treatment for localized pancreatic cancer. Newer technologies (IMRT, VMAT) that improve dose distribution to target volumes while minimizing radiation dose to organs at risk are superior to older radiation methods (3D CRT) and have reduced treatment toxicities. In addition, proton beam therapy appears to be useful in the treatment of localized pancreatic cancer as energy distribution can be directed and deposited at the tumor site, sparing adjacent normal tissues. Ongoing trials are investigating the safety of treatment regimens using IMRT or SBRT to escalate the dose of radiation in an attempt to improve local control in the setting of current more aggressive systemic treatments.

Careful attention to detail for radiation treatment planning and quality assurance is paramount to achieve best results from treatment. Reproducible patient set up, thin-sliced quality imaging during simulation preferably utilizing 4D CT or fluoroscopy for motion management and image-guidance during treatment delivery, adherence to standardized treatment volume definitions, and attention to published dose-volume limits are all important components in radiation treatment planning and delivery. Prospective peer-review and quality assurance also have been shown to improve radiation therapy for patients with pancreatic cancer.

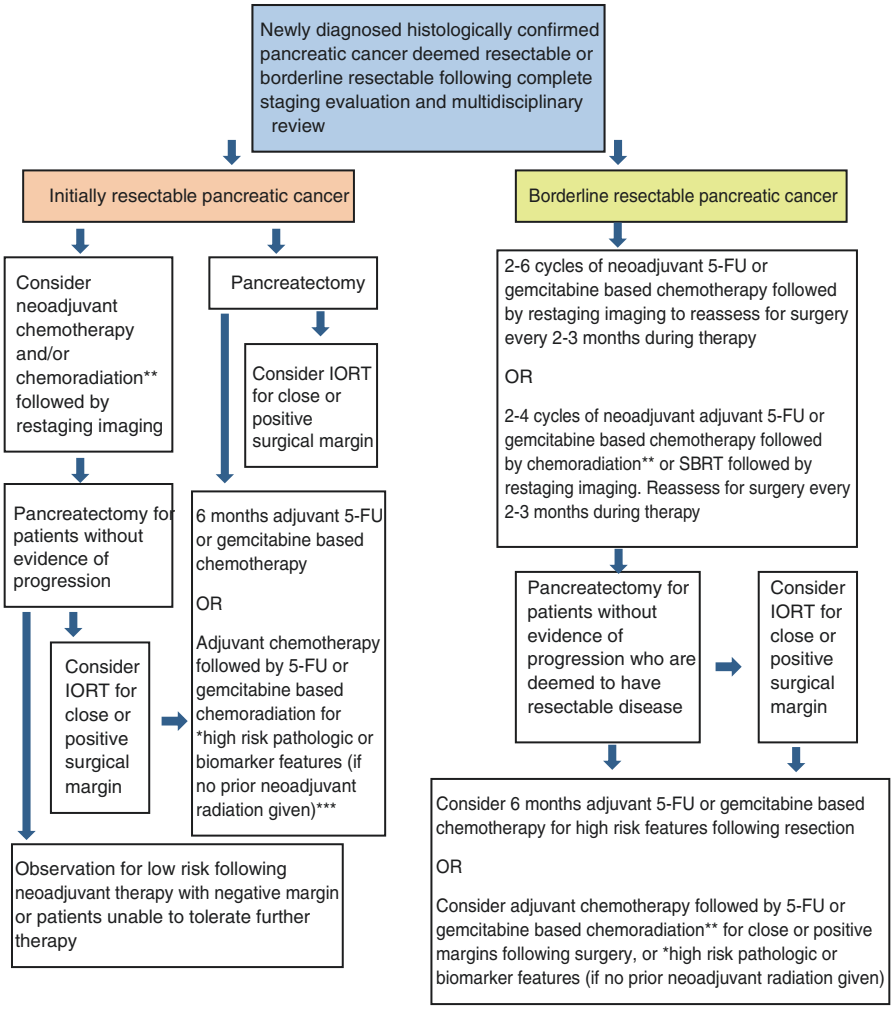

Fig. 8.4 This treatment algorithm is designed to help choose clinical scenarios appropriate for particular treatment modalities in the setting of resectable pancreatic cancer

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Locally Advanced/Unresectable Pancreatic Cancer

9

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Contents

9.1 Introduction

Patients with locally advanced pancreatic cancer (LAPC) have evidence of unresectable primary disease and no clinical/radiological evidence of distant metastatic disease. The criteria for resectability of pancreatic cancer were reviewed in the previous chapter and are largely related to the amount of arterial involvement of the tumor. The determination of resectability is made after obtaining anatomic information from a multiphase CT of the chest, abdomen, and pelvis and a full review from

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a multidisciplinary clinic with significant input from surgical oncology. Unfortunately, if a patient's lesion is deemed unresectable, there is no strong consensus for management and treatment planning. Many patients with LAPC eventually develop symptoms related to progression of their primary tumor, but also have a high likelihood of micrometastatic spread. Although systemic therapy will address micrometastatic spread, there is a constant dilemma with regard to best timing and management of local disease with radiation therapy. Local control of primary disease remains important as approximately 30% of patients with pancreatic cancer died from local disease without evidence of metastases [1]. Local progression can become symptomatic (biliary obstruction, pain, portal hypertension, and gastric outlet obstruction) and have impact on patient's quality of life.

9.2 Locally Advanced (Unresectable) Disease

LAPC portends a poor prognosis with a median overall survival of 9–11 months [2, 3]. Although definitive treatment utilizing concurrent conventional fractionated radiation and chemotherapy has been trialed, patient outcomes remain unsatisfactory. In an LAPC case, treatment plans need to be tailored to every patient's need and circumstances. Patient's symptoms (e.g., pain, abdominal discomfort, jaundice) should be addressed upfront. The aims of treatment in LAPC are: (1) Improve quality of life by achieving locoregional control; and (2) Prolong survival by preventing development of distant metastatic disease and local progression. It is important to discuss the goals of treatment with patients and involve palliative care services, where feasible, early in the course of treatment.

9.2.1 Treatment Strategies for Unresectable Disease

9.2.1.1 Chemotherapy (Without Radiation)

Initial systemic combination chemotherapy is recommended for most patients, given that 30–50% of patients with LAPC develop evidence of distant metastasis within 3 months. Recent studies have shown gemcitabine-based combination chemotherapy to be more effective in improving survival compared to best supportive care or gemcitabine alone. FOLFIRINOX has also been studied in the neoadjuvant setting. Both gemcitabine-based and FOLFIRINOX studies in the neoadjuvant setting had included patients with LAPC, and some patients, albeit a very small number, had demonstrated a remarkable response to chemotherapy with tumor downstaging, enabling them to proceed to surgery. The duration of chemotherapy remained unclear, but is typically given for at least 6 months, provided that no demonstrable disease progression (imaging and biochemical) and patient had tolerated the regimen well with no dramatic impact on his/her quality of life.

9.2.1.2 Chemoradiation

The role and timing of radiotherapy are frequently debated in LAPC cases. Local control of primary disease remains important as approximately 30% of patients with pancreatic cancer died from local disease, as evident by an autopsy study by Iacobuzio-Donahue et al. [1]. With regard to adding a radiosensitizing agent during radiotherapy, there is evidence that concurrent chemoradiotherapy is superior to radiotherapy alone. An early study by the Gastrointestinal Tumor Study Group (GITSG) established that concurrent chemoradiotherapy improved survival rates compared to radiotherapy alone (1-year overall survival 46% vs. 10% in 60 Gy arms) [4]. At the MD Anderson Cancer Center, our approach is to deliver definitive concurrent chemoradiotherapy after a period, typically 2–6 months, of chemotherapy. This approach will: (1) address the high risk of micrometastatic disease and development of distant disease will significantly impact survival, (2) reduce overtreatment of patients who will eventually develop distant disease and may only have marginal benefit from a long treatment course (5.5 weeks), and (3) potentially reduce toxicity from radiotherapy. The recent Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) LAP 07 randomized trial was aimed to investigate the role of chemoradiotherapy after chemotherapy in patients with LAPC [5]. This study demonstrated that there was no significant difference between the two groups in terms of overall survival, but those who received chemoradiotherapy had significantly improved local control (32% vs. 46%, $p = 0.03$). This study has its own limitations including that the chemotherapy regimen used was gemcitabine (±erlotinib) rather than FOLFIRINOX, and out of 88% available radiotherapy treatment plans available for quality assessment, 50% had minor deviations and 18% had major deviations [5]. Therefore, the results of this trial should be interpreted with caution.

9.2.1.3 Proton Therapy

Proton therapy may be utilized to deliver high doses of radiation with the aim of sterilizing the tumor in LAPC. The possible benefit and qualms of proton therapy were discussed in previous chapter. A dosimetry study comparing proton (double scattering and pencil beam scanning) with IMRT plans showed that proton therapy plans had significantly less low-dose scatter ($p < 0.01$) to organs at risk including small bowel, stomach, and duodenum than IMRT plans [6]. However, within the high-to-intermediate-dose regions, there were higher doses to the adjacent duodenum (<5%) and stomach (10%) than IMRT plans ($p < 0.01$) [6]. A phase I/II study on proton therapy (67.5 Gy/25 fractions) delivered with concurrent gemcitabine by Terashima et al. [7] found that the treatment was well-tolerated with ≤10% grade 3 toxicities and comparable 12-month progression-free, freedom from local progression, and overall survival rates of 64.3%, 81.7%, and 76.8%, respectively, to historical data. The majority of these patients had posttreatment endoscopy assessment. All patients received prophylactic lansoprazole and rebamipide pre- and during radiotherapy. Only 3% of patients exhibited grade ≥3 radiation-associated gastric and duodenal ulcers [8].

9.2.1.4 Stereotactic Body Radiation (SBRT)

SBRT enables the delivery of high doses of radiation delivered precisely to small area to achieve an ablative total dose to the tumor in only a few fractions (typically ≤7 fractions), while limiting dose to the surrounding organs at risk. A phase I dose escalation study by Koong et al. [9], which treated patients with LAPC with single fraction of 15 Gy, 20 Gy, or 25 Gy SBRT, found that the treatment was well-tolerated and provided good local control rate without any dose-limiting toxicity. Similar results were shown by Schellenberg et al. [10, 11] whereby patients treated with single fraction 25 Gy with sequential gemcitabine had 1- and 2-year survival of 50% and 20%, respectively. In terms of late toxicity, only 1 of 20 patients developed a duodenal perforation and three had ulcers (grade 2) that were managed medically [11]. Following these results, a multi-institutional trial investigating fractionated SBRT (33 Gy/5 fractions) with gemcitabine was performed and showed that fractionated SBRT was well-tolerated with low rates of acute and late ≥Grade 2 gastrointestinal toxicities (2% and 11%, respectively) which had 1-year overall survival of 59% [12].

9.3 Treatment Planning

Overall, patient setup, simulation, motion management, and treatment planning for LAPC are similar to resectable intact pancreatic cancer as described in the previous chapter. Here, we present specific treatment planning procedures for LAPC used at the MD Anderson Cancer Center, Houston, Texas, USA.

9.3.1 Pre-Simulation Instructions

Patients are instructed to fast at least 3 h prior to simulation and also for each fraction of radiation treatment to ensure reproducibility of stomach position and avoid daily variability in stomach filling (Fig. 9.1). The degree of stomach filling could potentially impact the tumor location and motion. Patients' allergies, particularly to iodine contrast, are clearly documented. Patients with allergy to iodine contrast should not be given intravenous (IV) contrast during simulation. For those who will receive IV contrast, a recent (usually within 2 weeks) renal function is obtained to ensure adequate renal function is documented prior to simulation. Intravenous contrast has the rare potential of causing contrast nephropathy complication.

For patients who will receive SBRT, treatment is given as per the radiation protocol on the ALLIANCE (discussed in the previous chapter). An endoscopy (gold standard) is performed to ensure there is no invasion of the duodenum which will preclude patient from SBRT. Previous studies have shown increased toxicity after invasion with direct duodenal invasion [12, 13]. Fiducial markers (preferably ≥3) are placed endoscopically at least 12 h prior to simulation and be placed within 1 cm and/or in the tumor. Although daily CT-on-rails imaging may be adequate for daily target alignment, the fiducial markers provide a second check/surrogate for daily target alignment during treatment with kV, cone-beam CT, or fluoroscopic image guidance.

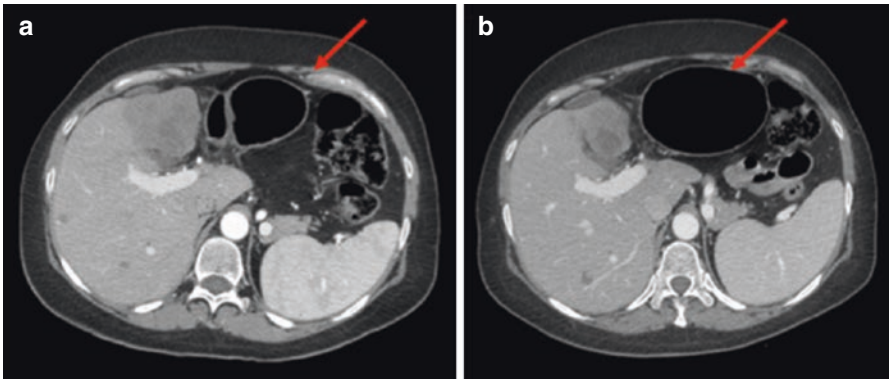


Fig. 9.1 These images depict the impact of stomach filling/bowel gas as depicted by the *red arrows* on movement of intra-abdominal organs

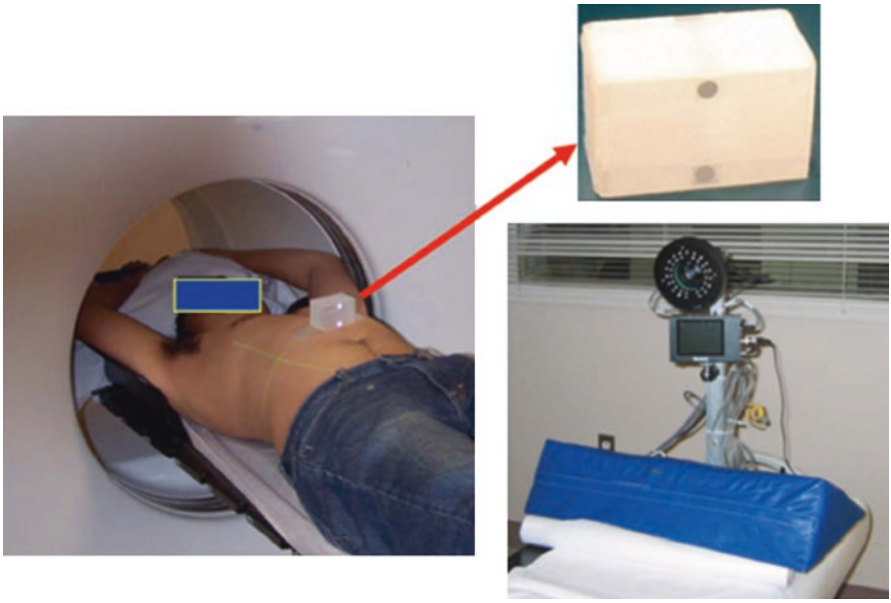


Fig. 9.2 Patient's position during simulation with RPM box taped on patient's abdomen. The RPM box has two dots which can be tracked by the RPM camera

9.3.2 Patient Setup

Patients are positioned supine, bilateral arms up, and immobilized with upper Vac-Lock (Civco Radiotherapy, Orange City, Iowa). A wingboard and Medtec leg holder (for photon treatment) or knee wedge (for proton treatment) are used for comfort and ensure reproducibility of treatment position. The Varian real-time patient monitoring (RPM) system is used to track respiration (Fig. 9.2). The RPM box is placed and taped onto the patient's abdomen in midline between the xiphoid process and

the umbilicus. The RPM camera is adjusted so that both dots on the RPM box are visible on the RPM computer and tracking is then commenced. The RPM box, positioned on the patient's abdomen, moves with patient's breathing, and therefore, is a surrogate marker used to track respiratory movement.

For conventional fractionated treatment (commonly 50.4 Gy/28 fractions), the RPM system will not be used. Free-breathing scans will be used for treatment planning. In other situations, it is acceptable and common to use respiratory gating to manage motion during conventionally fractionated therapy in an attempt to reduce normal tissue dose [14]. Our preference at UT MD Anderson is to plan on breath-hold scans, and this is explained in detail in the following sections.

9.3.3 Image Acquisition

Once the patient is comfortably positioned, an initial scout CT scan is performed and the scanning range is determined. Generally, scanning range extends from carina to iliac crests. Thin slices (2–3 mm) CT images were obtained.

Below is the workflow for image acquisition when breath-hold technique is implemented:

1. Perform scout CT
2. Determine scanning range (carina to iliac crest)
3. Perform free-breathing scan without contrast
4. Provide instructions and train patient to perform inspiration breath-hold. Each breath-hold should be comfortable and reproducible. It is not necessary and often not advisable to perform a "deep" inspiration hold, as this will often be challenging to reproduce during treatment. The aim of breath-hold is to reduce tumor motion, allowing reduction of planning target volume and dose to normal structures.
5. Once patient is comfortable with performing breath-hold, the breath-hold level is set in the RPM computer (between blue and orange bars). The bars should be set as narrow as feasible (Fig. 9.3).
6. Have practice runs with patient to ensure patient comfort, as well as consistency and reproducibility of breath-hold.
7. Perform 1–2 CT scans with breath-hold without contrast.
8. Perform breath-hold scans with contrast. We use 150 mL of iodine contrast (Optiray 320) at a rate of 5 mL/s. The first scan is performed at 30 s after commencement of IV contrast injection. Subsequent scans are performed at 30 s interval. Up to four scans are obtained.
9. The physician will select the optimal scan (best for tumor visualization and also considered to be most representative of all breath-hold scans) for treatment planning. The movement of the target between the various breath-hold scans gives a glimpse into patient compliance and the estimation of the variation that can occur even with breath-hold technique. This variation of target location during breathing should be accounted for as an ITV.
10. All CT images are exported to the treatment planning system.

If a patient is not able to perform breath-hold, a 4D-CT is performed.

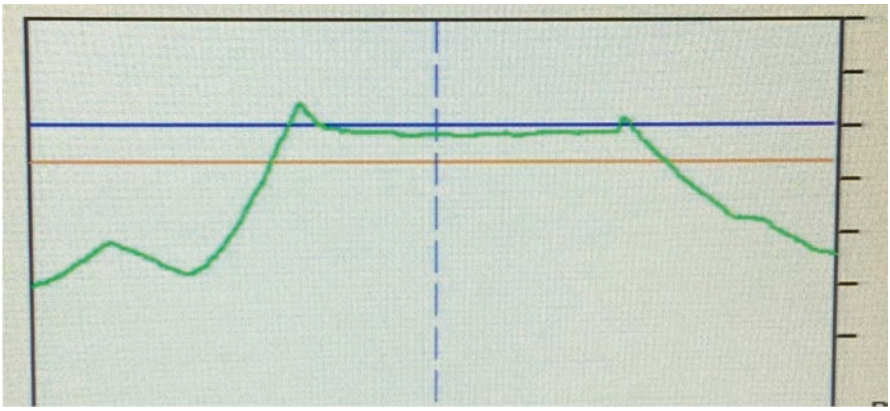


Fig. 9.3 Image showing the screen of RPM computer with the set level bars (*blue* and *orange* lines). The patient's respiratory movement is tracked and shown as the *green* line. Patient is instructed to try and maintain his/her breath-hold in between the *blue* and *orange* bars

9.3.4 Treatment Planning

9.3.4.1 Target Volumes for Conventional Dose/Fractionation (No Breath-Hold) Using Non-SBRT Techniques

- Figure 9.4 provides a contouring atlas for conventional dose/fractionation (50.4 Gy/28 fractions).
- Gross tumor volume (GTV) of the primary (GTVp) and pathological nodes (GTVn) are contoured.
- Contour:
  - Celiac artery (proximal 1–1.5 cm)
  - Superior mesenteric artery (SMA) (proximal 2.5–3 cm)
  - Porta hepatis (including the portal vein segment that runs anteromedial to the inferior venal cava to the bifurcation at the liver, and the liver hilum)
  - Duodenum (through the fourth portion)
  - Small bowel (particularly jejunum near the ligament of Treitz)
- Clinical target volume (CTV) = (GTV + celiac artery + SMA + porta hepatis) + 2 cm margin superiorly and inferiorly, and a 1 cm margin radially.
- Planning target volume (PTV) = CTV + institutional setup error (typically 0.5 cm margin).
- Dose/fractionation: 50.4 Gy in 28 fractions, 1.8 Gy per fraction, daily treatment 5 days per week over 5.5 weeks. This regimen is typically delivered with concurrent chemotherapy.

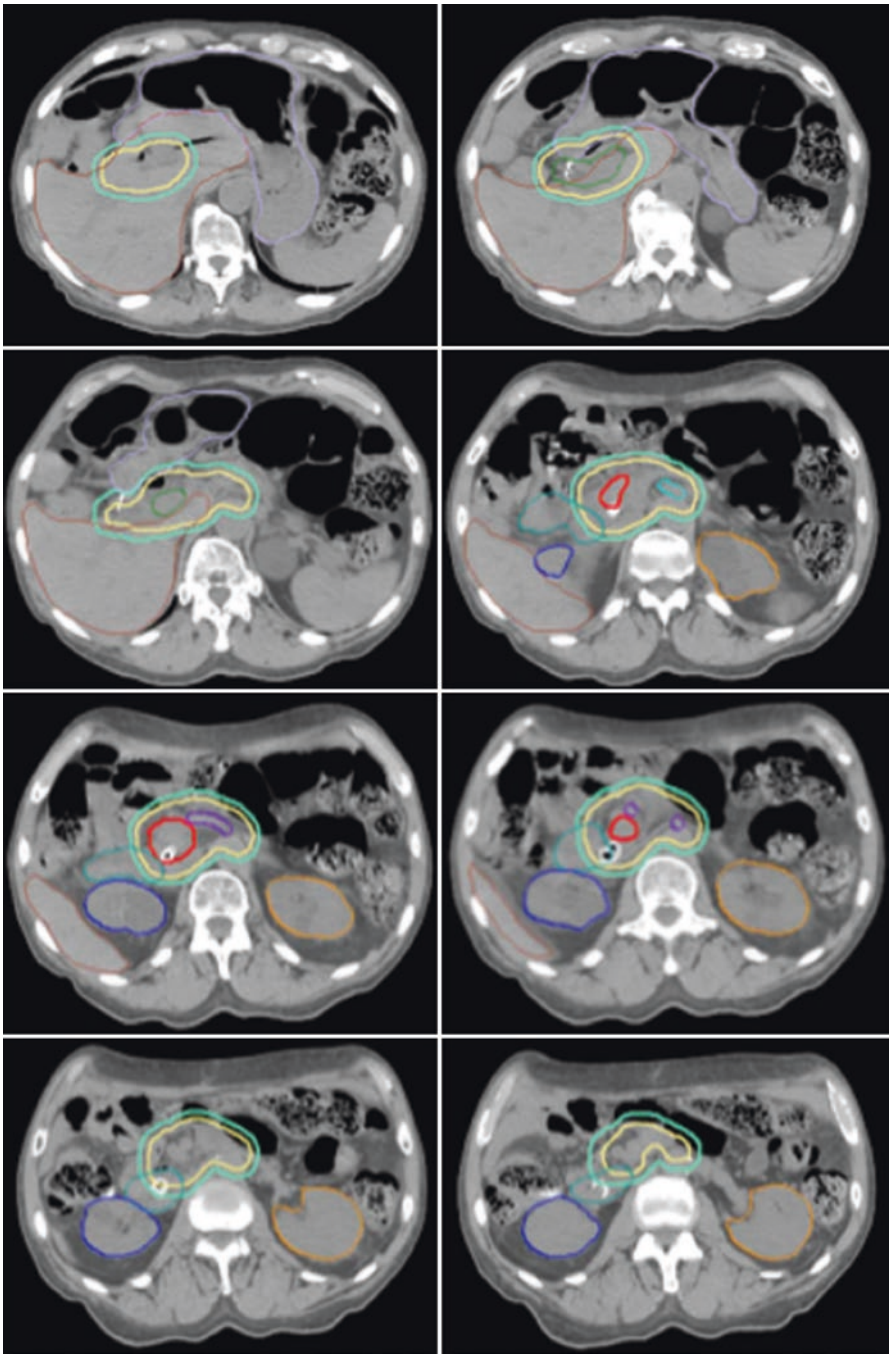


Fig. 9.4 Contouring atlas for conventional dose/fractionation (50.4 Gy/28 fractions). Target volumes: *Red*—GTV, *Yellow*—CTV, *Cyan*—PTV. Organs at risk: *Brown*—liver, *Green*—duodenum, *Blue*—right kidney, *Orange*—left kidney

9.3.4.2 Target Volumes and Dose/Fractionation for Non-SBRT Dose Escalation (Breath-Hold) Techniques

- Figure 9.5 provides a contouring atlas for dose-escalated regimens.
- GTV = primary tumor. Nodes are excluded from high dose treatment volumes.
- Internal target volume (I-GTV) = GTV expanded to encompass all GTV position seen on all breath-hold scans and combined to account for variable breath-hold positions and tumor motion.
- CTV is not generated in these cases
- Organs-at-risk are contoured and a planning organ at risk volume (PRV) is created for stomach, duodenum, and small bowel by adding a margin of 3 mm to these organs.
- PTV (high dose) = ITV + institutional setup error (typically 0.5 cm)—PRV
- A lower acceptable dose to the organs at risk is prescribed to the full PTV if the PTV extended into the PRV.
- Dose/fractionation
  - 60 Gy/15 fractions
  - 67.5 Gy/15 fractions
  - 70 Gy/28 fractions

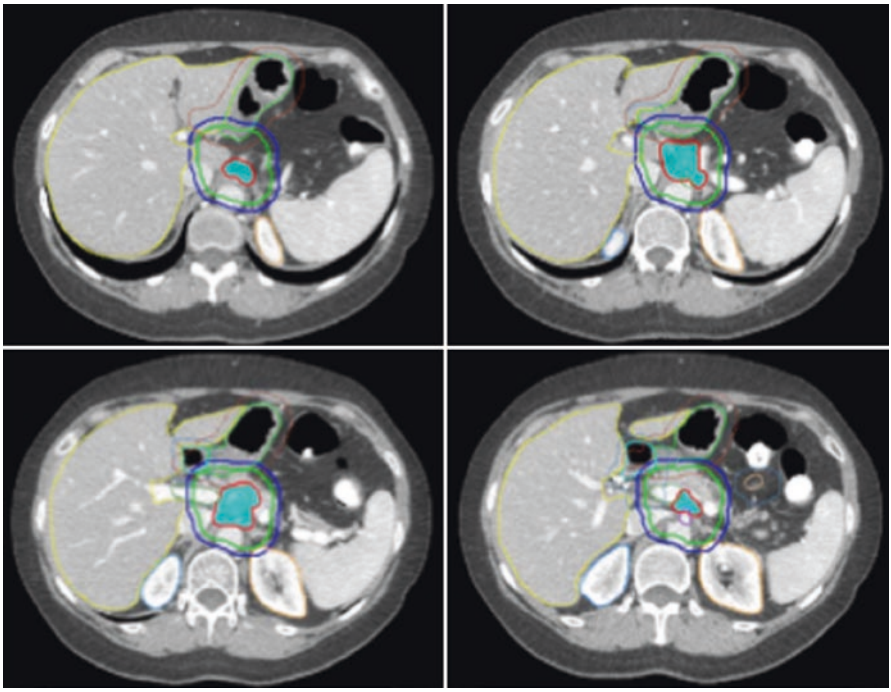


Fig. 9.5 Contouring atlas for dose-escalated regimens. Target volumes: *Red*—GTV, *Green*—CTV 37.5 Gy, *Dark blue*—PTV 37.5 Gy, *Cyan* filled—PTV 67.5 Gy. Organs at risk: *Yellow*—liver, *Light blue*—right kidney, *Orange*—left kidney, *Light green*—stomach, *Khaki*—small bowel, *Cyan* lined—duodenum

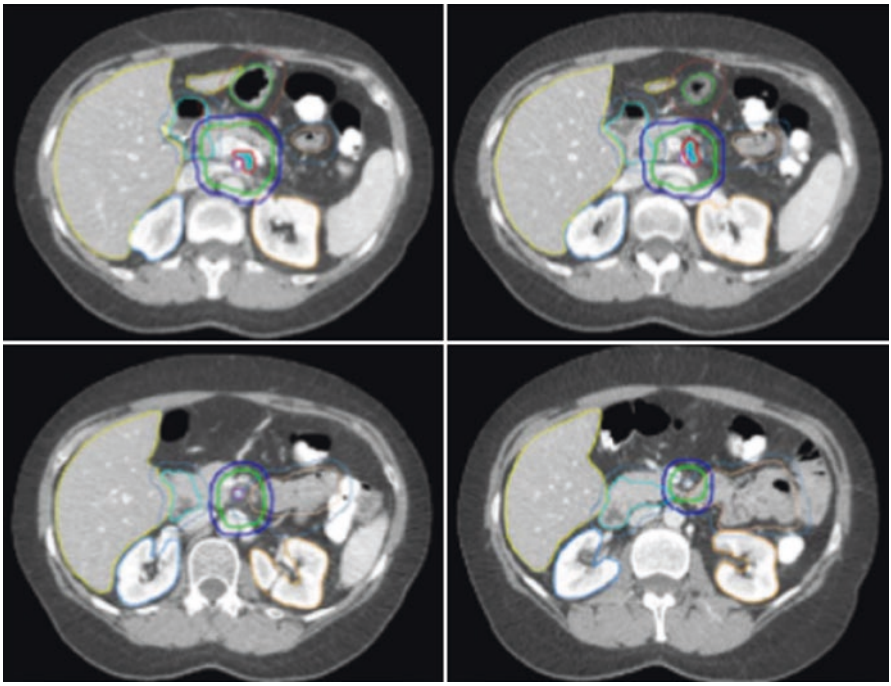


Fig. 9.5 (continued)

9.3.4.3 Target Volumes and Dose/Fractionation for SBRT Technique

We adopt the treatment planning procedures as the ALLIANCE study (NCT02839343).

- Figure 9.6 provides a contouring atlas for SBRT.
- GTV = primary tumor. Nodes are excluded from SBRT.
- I-GTV is generated to account for different breath-hold positions and tumor motion (see above).
- CTV is not generated for SBRT
- A tumor vessel interface (TVI) is contoured for each vessel (portal vein, SMA, common hepatic artery, celiac artery) separately that is in contact with the tumor (Fig. 9.7).
- Internal TVI (I-TVI) is generated by expanding the TVI to account for TVIs on all breath-hold scans.
- PRV is generated for stomach, duodenum, and small bowel by adding 3 mm margin to these organs. If possible, an ITV should first be generated from either 4DCT or multiple breath-hold scans. The duodenal and jejunal contours should be tightly adherent to the anatomy on CT and not a "bowel bag."
- Three PTVs are generated for different dose levels:
  - PTV1 = (I-GTV + I-TVI) + 3 mm to be treated to 25 Gy/5 fractions
  - PTV2 = PTV1—PRV to be treated to 33 Gy/5 fractions
  - PTV3 = (I-TVI + 3 mm)—PRV to be treated to 36 Gy/5 fractions
- Figures 9.7, 9.8, and 9.9 demonstrate SBRT planning target volumes with relation to adjacent normal structures.

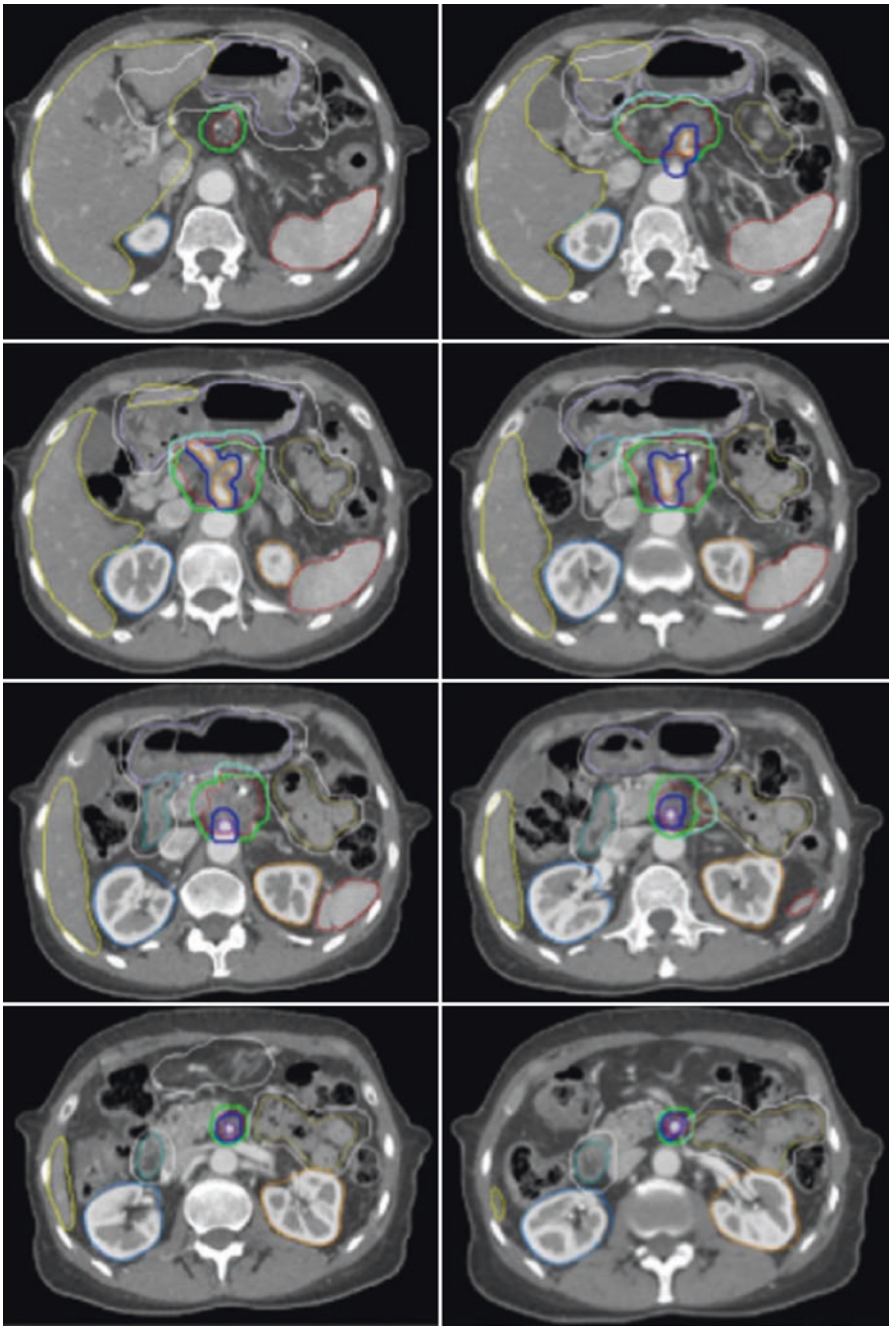


Fig. 9.6 Contouring atlas for SBRT. Target volumes: *Red*—GTV, *Cyan*—PTV1 (25 Gy), *Light green*—PTV2 (33 Gy), *Dark blue*—PTV3 (36–40 Gy). Organs at risk: *Yellow*—liver, *Dark green*—duodenum, *Purple*—stomach, *Orange*—Left kidney, *Light blue*—Right kidney, *Khaki*—Small bowel, *White*—PRV for stomach, duodenum, and small bowel

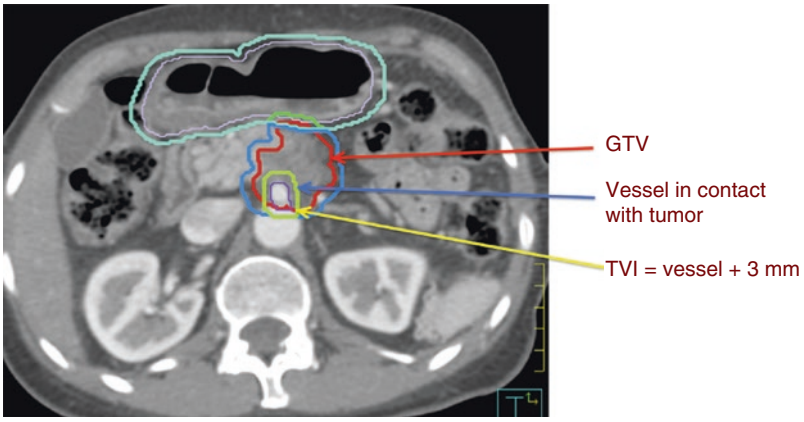


Fig. 9.7 SBRT treatment planning axial CT image illustrating the gross tumor volume (GTV in *red*) and tumor vessel interface (TVI in *neon green*) contours. The TVI will be treated to 36 Gy (maximum 40 Gy), the planning target volume (GTV plus margin, in *blue*) will be prescribed 33 Gy except for the region adjacent to the bowel (the region in *green* will be treated to 25 Gy)

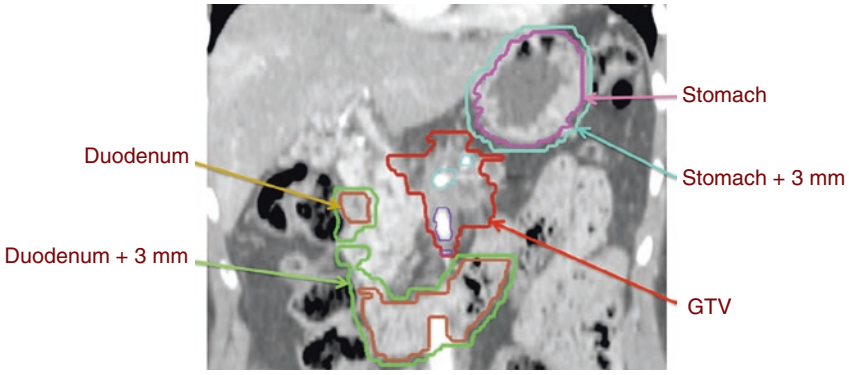


Fig. 9.8 SBRT treatment planning coronal CT image showing the planning organ-at-risk volume (PRV) generated by expanding the stomach (*purple*) and duodenum (*brown*) volumes by 3 mm

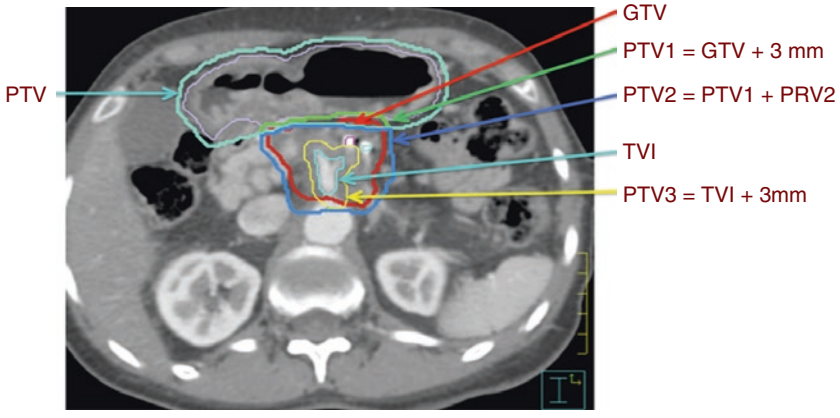


Fig. 9.9 Representative axial CT image depicting PTV1, PTV2, and PTV3 for SBRT treatment planning

9.3.4.4 Organs-at-Risk to be Contoured for Treatment Planning

- Duodenum
- Stomach
- Bowel bag (for conventional 50.4 Gy/28 fractions treatment)
- Small bowel loops (for dose escalation or SBRT). Make sure to account for jejunum near the ligament of Treitz.
- Large bowel loops (for dose escalation or SBRT)
- Liver
- Right and left kidneys
- Spinal cord
- Spleen
- Lungs
- Heart

9.3.5 Planning Aims and Dose Constraints

9.3.5.1 For Conventional Fractionation

Target coverage aims:

- PTV1: 50.4 Gy, V100% > 95%, V95% > 99%, V105% < 10%, Dmax < 120% (Table 9.1)

Table 9.1 Dose constraints for conventional fractionation

OAR	Constraints
Small bowel	Dmax < 50 Gy
Liver	Mean < 32 Gy, V20 < 60%, V30 < 33%
Combined kidneys	Mean < 18 Gy; V20 < 33% for each; if one exceeds, spare the other with V20 < 20%
Spinal cord	Dmax < 45 Gy
Spleen	Mean < 8Gy

9.3.5.2 For Dose-Escalated Regimens (67.5 Gy/15 Fractions)

Target coverage aims:

- For each PTV: V100% > 95%, V95% > 99%, V105% < 10%, Dmax < 120%

The priorities are first to meet dose constraints (ensuring that the treatment will be safe for the patient), secondly to optimize PTV coverage, and thirdly to try and delivery a high dose to the GTV/central core of tumor (accepting heterogeneity dose coverage) (Table 9.2).

Table 9.2 Dose constraints for 67.5 Gy/15 fractions (this will differ if a treatment dose/fractionation is used)

OAR	Constraints
Small bowel	Dmax < 40 Gy
Stomach Duodenum	Dmax < 45 Gy
Liver	Mean < 24 Gy
Common bile duct	Dmax < 60 Gy
Combined kidneys	Mean < 18 Gy; V20 < 33% for each; if one exceeds, spare the other with V20 < 20%
Spinal cord	Dmax < 30 Gy
Large bowel	Dmax < 50 Gy
Spleen	Mean < 6 Gy

9.3.5.3 For SBRT

Target coverage aims:

- PTV1: 25 Gy, Dmin >22.5 Gy
- PTV2: 33 Gy, Dmin >29.7 Gy
- PTV3: 36 Gy, Dmin > 32.4 Gy, Dmax 40 Gy

If the dose constraints cannot be met with the above target coverage, PTV1 will be reduced to 25 Gy/5 fractions with the aim of ≥90% PTV1 be covered by ≥95% of prescription dose and Dmax ≤ 110% of prescribed dose (Table 9.3).

Table 9.3 Dose constraints for SBRT

OAR	Constraints
Duodenum	V20 < 20 cc
	V35 < 1 cc
Small bowel (other)	V20 < 20 cc
	V35 < 1 cc
Stomach	V20 < 20 cc
	V35 < 1 cc
Liver	V12 < 50%
Combined kidneys	V12 < 25%
Spinal cord	V20 < 1 cc
Spleen	No constraint

9.3.6 Treatment Verification

For patients treated using conventional fractionation, daily kV-IGRT is used for treatment position verification.

For dose-escalated regimens and SBRT, patients are imaged daily using CT-on-rails (Fig. 9.10). CT-on-rails provides diagnostic high-quality on-board CT imaging which allow soft tissue to soft tissue matching with high accuracy. The ability to visualize soft tissue also allows dose escalation regimens to be delivered safely.

Workflow of CT-on-rails at the MD Anderson Cancer Center

1. Patient is brought into treatment suite, positioned, and set up on the treatment table with patient's head towards gantry (Fig. 9.10b).
2. Once setup has been established, the couch is rotated so that patient's head is towards the CT-on-rails (Fig. 9.10c).
3. Patient is imaged with CT-on-rails and the images are reviewed by the treating physician or trained therapists.
4. CT-on-rails images are compared to the planned CT images and contours (typically GTV) and isodose lines are displayed on both sets of images (Fig. 9.11).

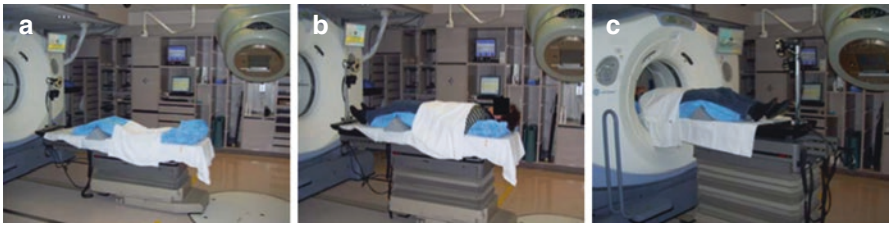


Fig. 9.10 Images depicting the CT-on-rails imaging process. (**a**)—setup before patient enters treatment room. (**b**)—patient positioned with head towards gantry. (**c**)—couch rotated 180° and patient positioned towards CT-on-rails

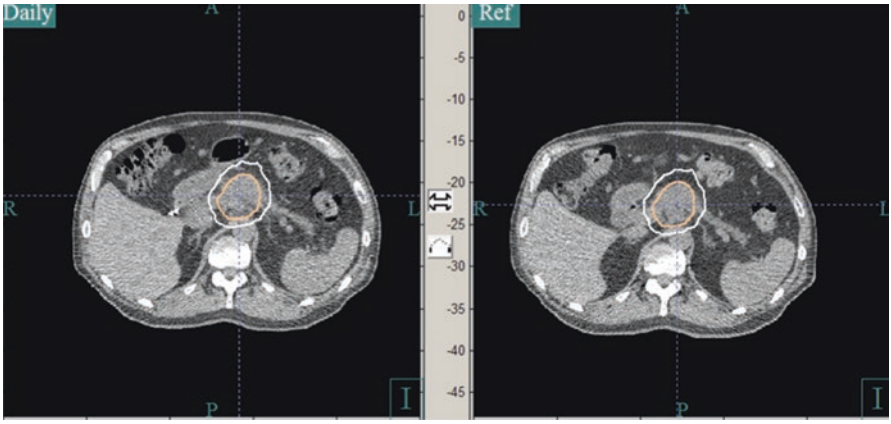


Fig. 9.11 Example of an image obtained from CT-on-rails ("Daily") compared to image obtained at simulation ("Ref"). *Khaki line*—GTV; *White line*—PTV

5. The CT-on-rails images are aligned to the planned images and couch shifts required are documented and made.
6. The couch is then rotated back so that patient's head is towards the gantry.
7. Treatment commenced.

During the whole process described above, patient is required to be in the treatment position.

9.3.7 Treatment Modalities

Table 9.4 describes the various radiation options and indications for the treatment of locally advanced pancreatic cancer (Figs. 9.12–9.15).

Table 9.4 Radiation treatment approaches for locally advanced pancreatic cancer

Technique	Indication	Fractionation schedules	Beam arrangement	Appropriate chemotherapy
3D CRT[a]	Definitive or consolidative therapy after chemotherapy	50.4 Gy; 1.8 Gy per fraction; 5 days per week	Three or four fields (APPA; right and left lateral)	Before radiation, and/or concurrent, and/or following radiation
IMRT VMAT[a]	Definitive or consolidative therapy before/after chemotherapy (IMRT/VMAT preferred over 3D CRT if available)	50.4 Gy; 1.8 Gy per fraction; 5 days per week	IMRT: Multiple coplanar isocentric beams VMAT: Volumetrically modulated coplanar arcs	Before radiation, and/or concurrent, and/or following radiation
Proton therapy[b]	Definitive or consolidative therapy before/after chemotherapy	50.4 Gy (RBE); 1.8 Gy per fraction; 5 days per week	Typically, three fields (posterior oblique: Right lateral oblique) with a 3-to-1 weighting to the posterior field to limit spinal cord dose	Before radiation, and/or concurrent, and/or following radiation
SBRT[b]	Consolidative therapy after chemotherapy	33 Gy; 6.6 Gy per fraction (or 25 Gy; 5 Gy per fraction if dose constraints not met with 33 Gy); Delivered over 5 days	Linac-based: IMRT: Multiple coplanar isocentric beams Cyberknife: Multiple noncoplanar nonisocentric beams	Before radiation, and/or following radiation

[a]High-energy photons (>10 MV) preferred as lower energy may result in more gastrointestinal toxicity
[b]May be appropriate for select cases

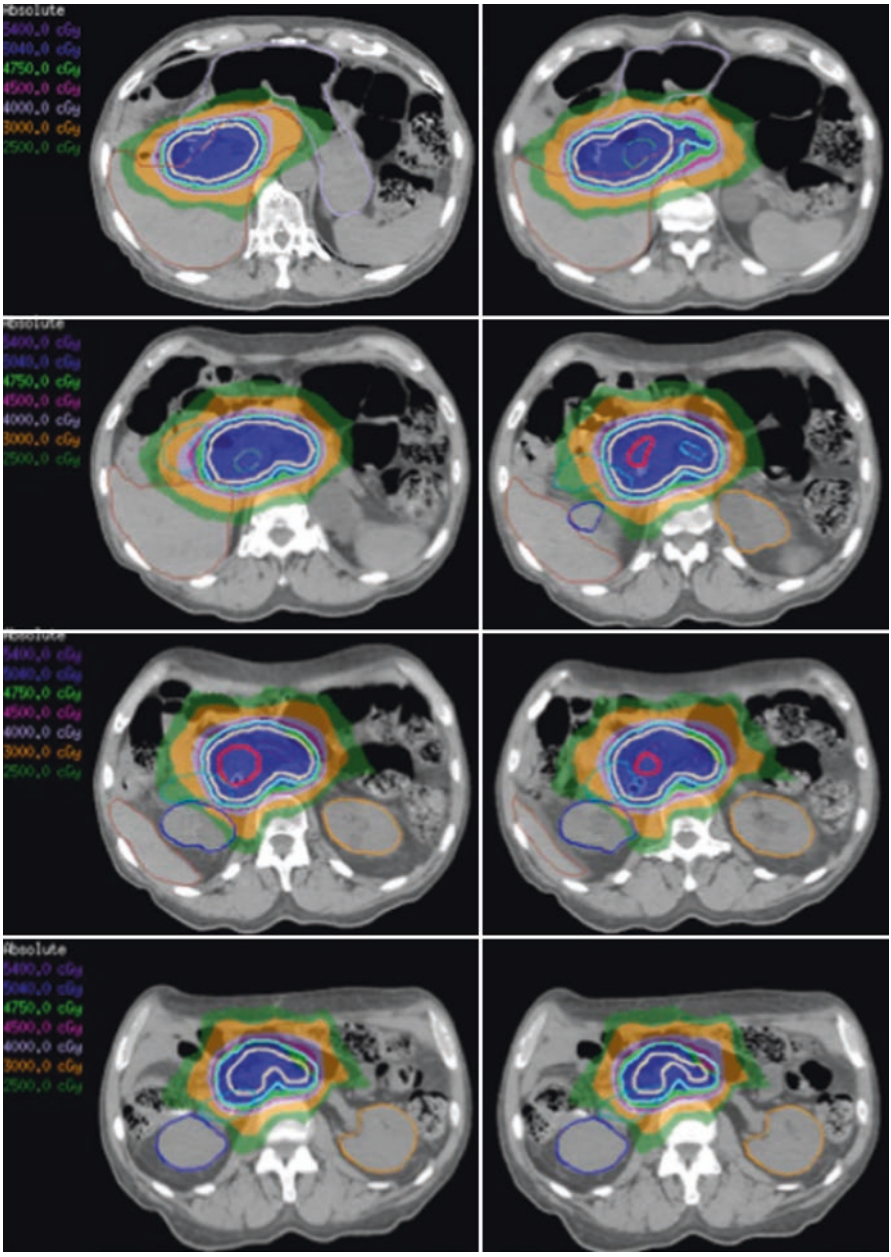


Fig. 9.12 Representative IMRT treatment plan for locally advanced, unresectable pancreatic cancer. Representative images of IMRT treatment plan and dose volume histogram (50.4 Gy/28 fractions). Dose volume histogram: *Cyan*—PTV, *Khaki*—CTV, *Purple*—Stomach, *Yellow*—Liver, *Dark blue*—Right kidney, *Red*—Spinal cord, *Orange*—Left kidney

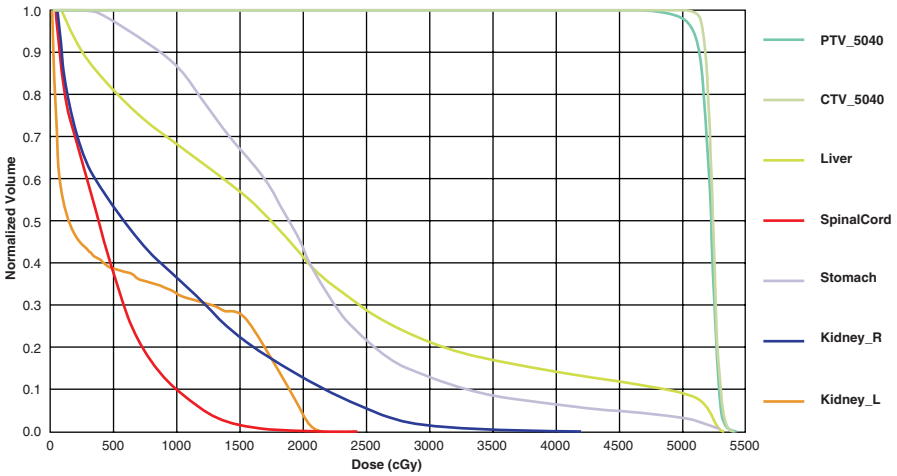


Fig. 9.12 (continued)

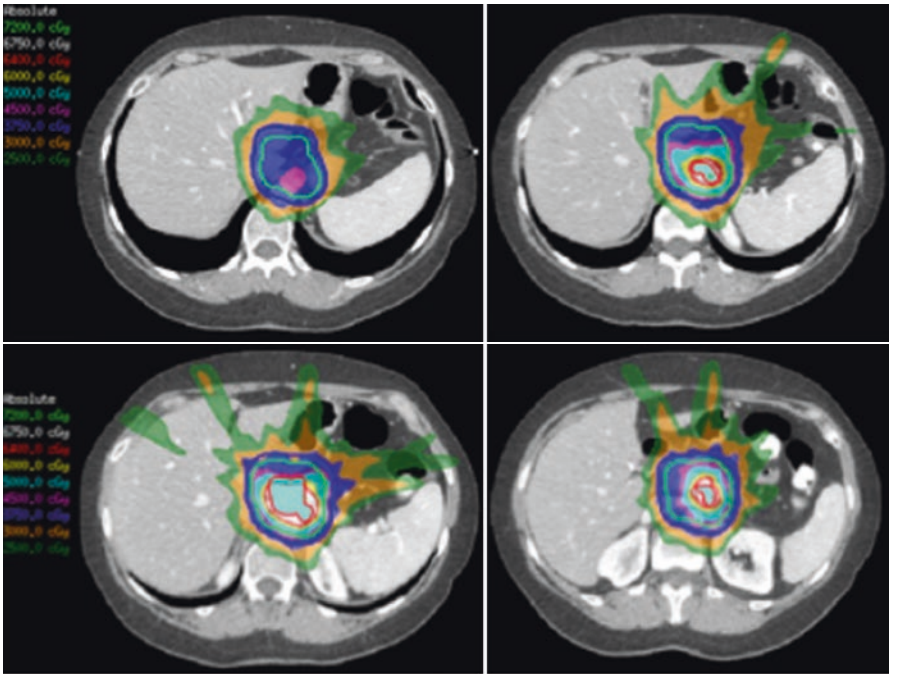
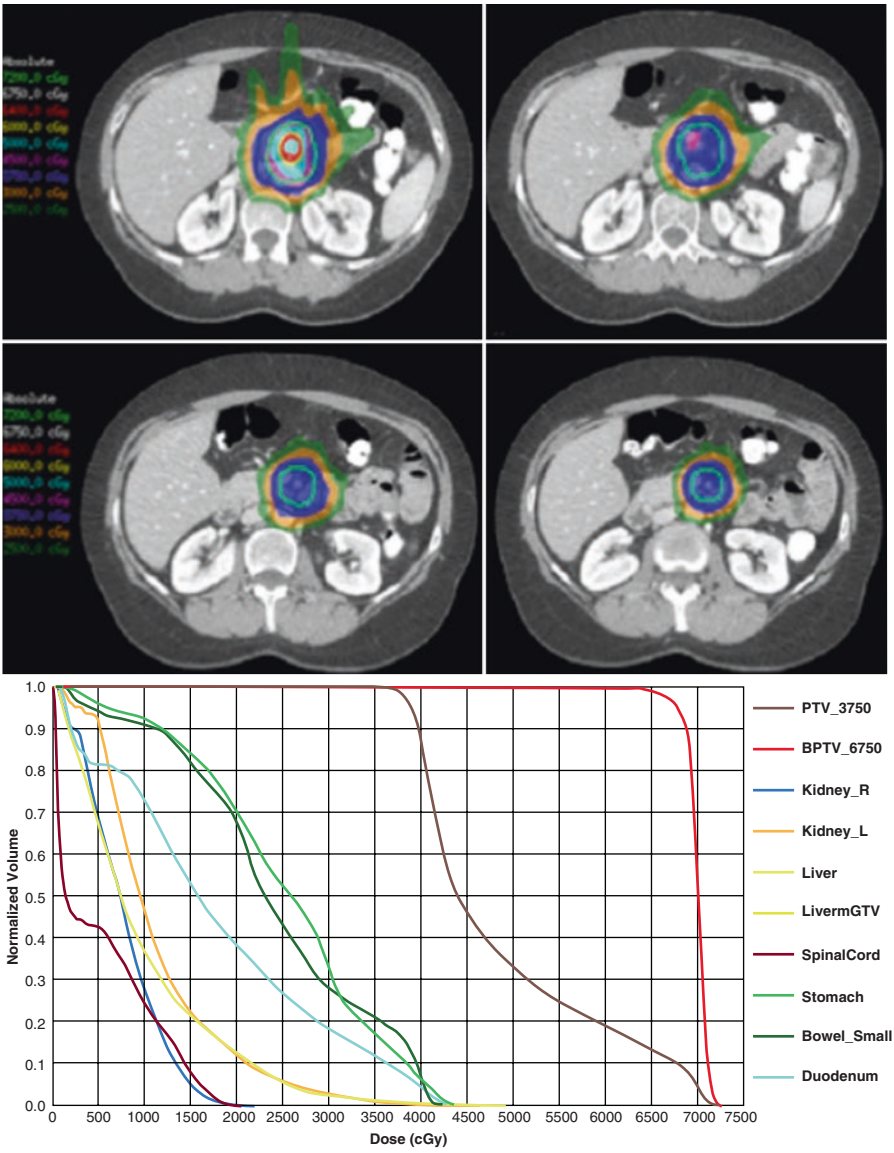


Fig. 9.13 Representative dose-escalated treatment plan for locally advanced, unresectable pancreatic cancer. Representative images of dose-escalated (in this case, 67.5 Gy/15 fractions) treatment plan and dose volume histogram. Dose volume histogram: *Red*—PTV 67.5 Gy, *Brown*—PTV 37.5 Gy, *Light green*—Stomach, *Dark green*—Small bowel, *Cyan*—Duodenum, *Orange*—Left kidney, *Yellow*–Liver, *Blue*—Right kidney, *Cherry red*—Spinal cord



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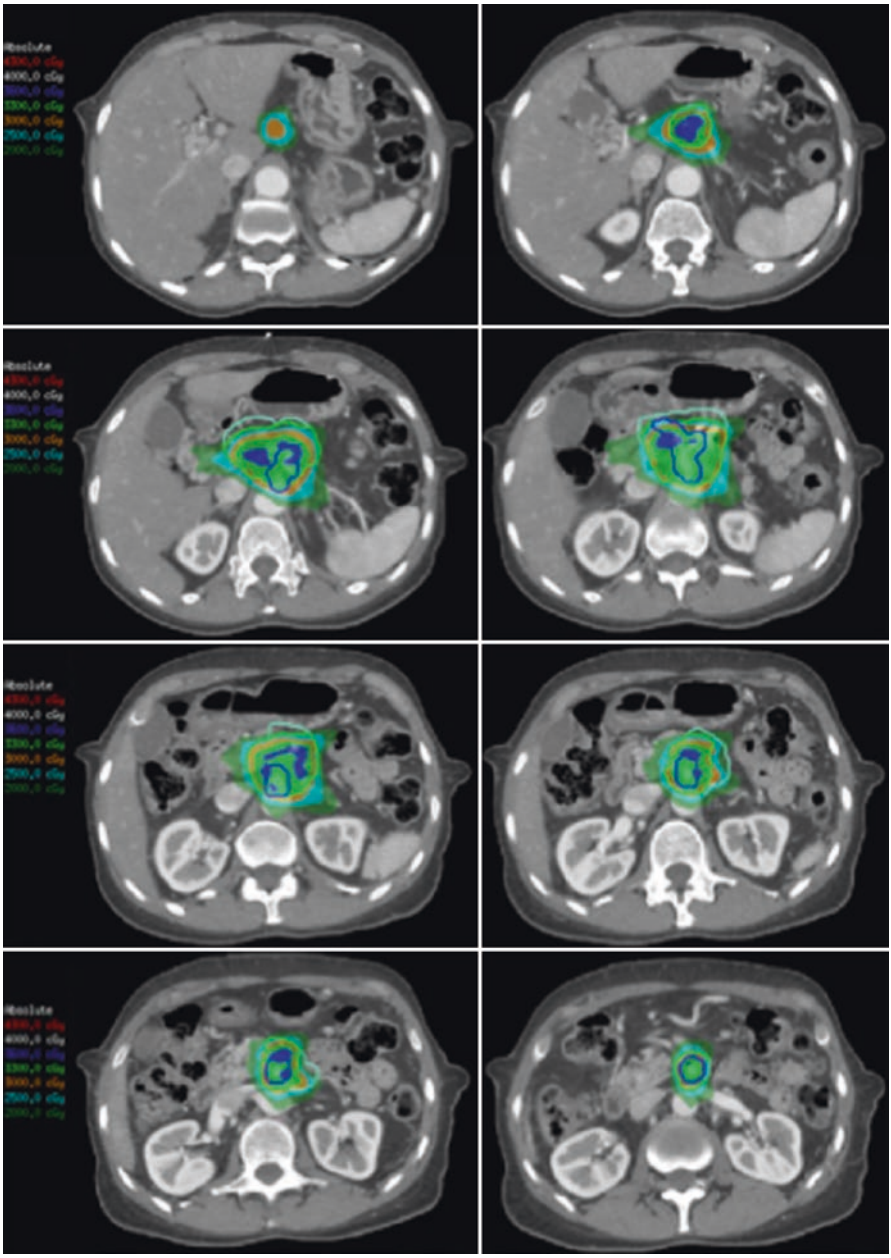

Fig. 9.14 Representative SBRT treatment plan for locally advanced, unresectable pancreatic cancer. Representative images of SBRT treatment plan (33 Gy/5 fractions) and dose volume histogram. Dose volume histogram: *Red*—PTV1 (25 Gy), *Brown*—PTV2 (33 Gy), *Blue*—PTV3 (36–40 Gy), *Light green*—Small bowel, *Cyan*—Right kidney, *Dark green*—Duodenum, *Orange*—Left kidney, *Yellow*—Liver, *Purple*—Stomach, *Khaki*—Spinal cord

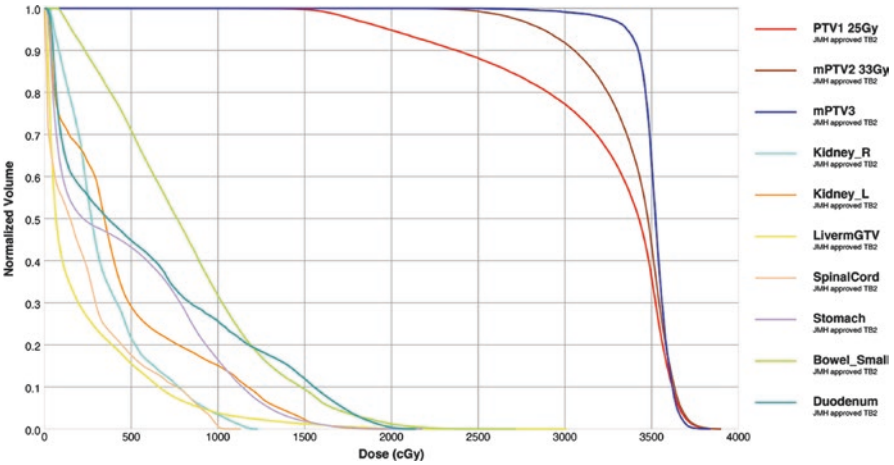

Fig. 9.14 (continued)

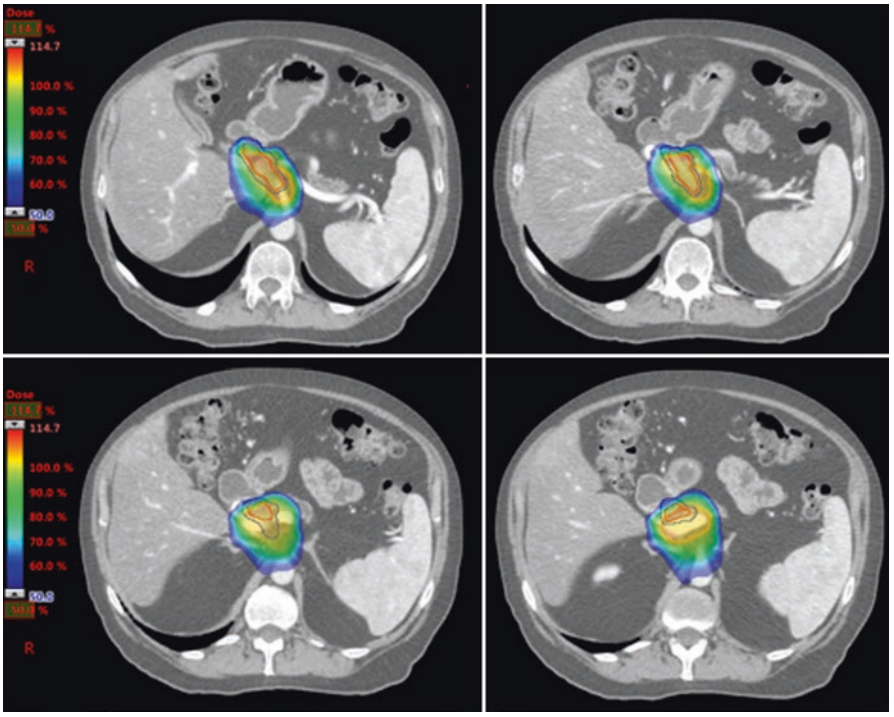

Fig. 9.15 Representative proton treatment plan for locally advanced, unresectable pancreatic cancer. Representative images of proton SBRT treatment plan (33 Gy/5 fractions) and dose volume histogram. Dose volume histogram: *Purple*—PTV1, *White*—PTV2, *Khaki*—PTV3, *Dark green*—Duodenum, *Yellow*—Liver, *Light green*—Small bowel, *Orange*—Left kidney, *Blue*—Right kidney, *Purple*—Stomach, *Red*—Spinal cord

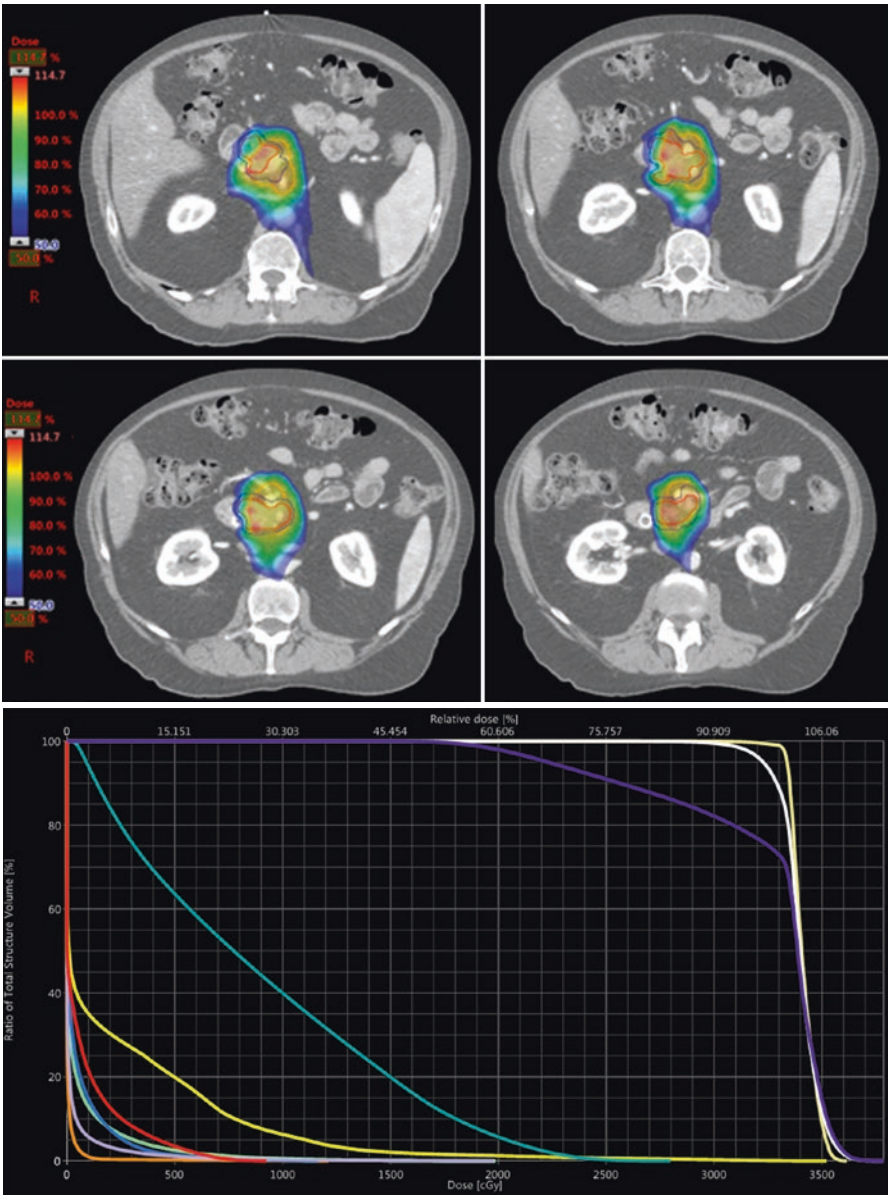

Fig. 9.15 (continued)

9.3.8 Treatment Plan Optimization and Special Considerations

To achieve satisfactory target coverage and dose to organs at risk, treatment plans must be optimized. Strategies to optimize treatment plans and special considerations for SBRT and proton therapy were described in detail in the previous chapter.

9.4 Summary

The optimal treatment and sequencing of chemotherapy and radiotherapy for locally advanced pancreatic cancer remained controversial. Without surgery, the prognosis in this group of patients is poor, and therefore, a frank discussion with patient with regard to goals of treatment upfront and an early referral to palliative care service, if feasible, is of importance. These patients have high risk of systemic progression warranting consideration of chemotherapy as first line of treatment. Achieving local control with radiation therapy following chemotherapy appears to translate into a survival benefit in some studies. However, the exact role and timing of radiation is yet to be established.

There are different radiation treatment modalities that can be considered when planning radiotherapy for patients with locally advanced pancreatic cancer. The choice of modality used will depend on the availability of equipment/technology, dose/fractionation, and dose to normal tissues. IMRT, VMAT, and proton therapy tend to have improved dose distribution to target volumes, while minimizing radiation dose to normal tissues than 3D CRT. SBRT can be considered in this group of patients, provided that patient has no invasion of the duodenum, and adequate respiratory/tumor motion management, immobilization, and on-board imaging are available (Fig. 9.16).

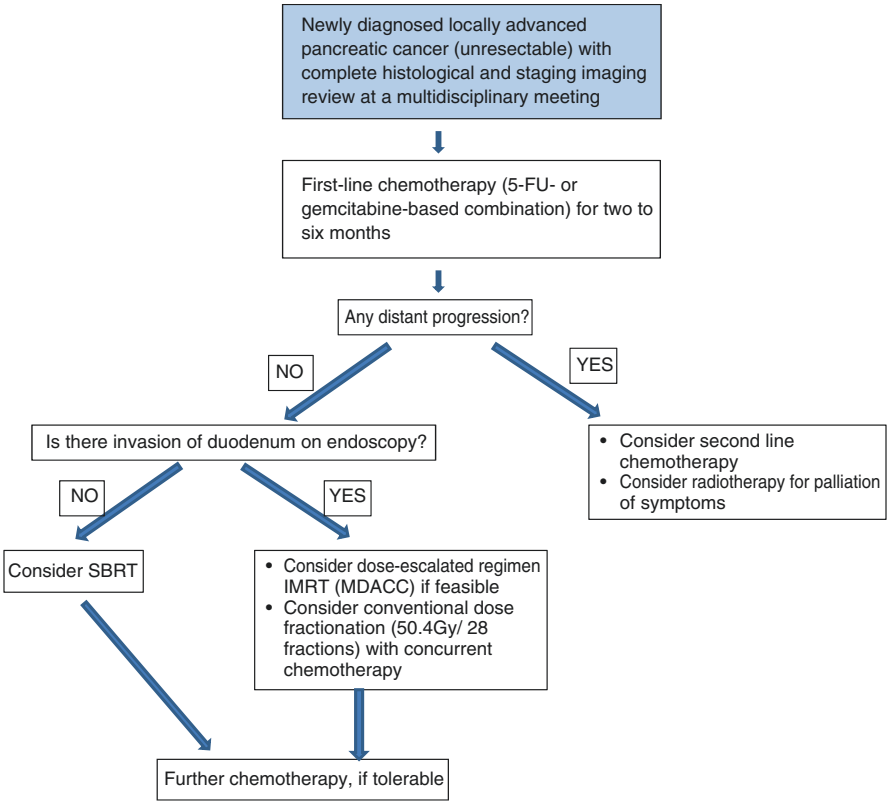

Fig. 9.16 Treatment algorithm designed to help choose clinical scenarios appropriate for particular treatment modalities in the setting of locally advanced pancreatic cancer

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Part V

Colorectal Cancer

Colon Cancer

10

Fumiko Chino, Christopher Willett, Manisha Palta, and Brian Czito

Contents

10.1 Introduction

Colon cancer remains a common cause of morbidity and mortality globally. Worldwide, approximately 1.4 million cases of colorectal cancer are diagnosed yearly with incidence varying by country [1]. In the United States, colon cancer is the third most commonly diagnosed cancer and the third leading cause of cancer

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death in both men and women [2]. In 2017, an estimated 95,500 cases are expected to be diagnosed with 50,000 deaths forecasted [2].

Anatomically, the colon consists of the cecum, ascending colon, transverse colon, descending colon, and sigmoid colon; colon cancers frequently present with differing symptoms depending on the region of origin in the colon and stage at presentation. Initial symptoms of colon cancer may include microcytic anemia due to occult blood loss, fatigue, unintentional weight loss, abdominal pain, change in bowel habits, and hematochezia/melena [3]. Early-stage tumors are more likely to be cured with initial treatment and to be treated with curative approaches at the time of recurrence [4]. Early/localized colon cancers are often asymptomatic at diagnosis; therefore, screening is essential to colon cancer's early detection and reducing colon cancer mortality [5, 6].

The US Preventative Services Task Force recommends screening for colon cancer for ages 50 through 75 years; screening decision from 76 to 85 years should be individualized based on patient factors [7]. Common screening options include yearly Fecal Occult Blood Test (FOBT), colonoscopy every 10 years or flexible sigmoidoscopy, or CT colonography every 5 years. Fecal Immunochemical Test (FIT) and FIT-DNA testing may be more accurate than FOBT, but may also have lower specificity, leading to increased endoscopies [8]. FIT-DNA is the preferred cancer detection test for patients who decline colonoscopy as recommended by the American College of Gastroenterology [9].

Colon cancer risk factors include increasing age, male sex, smoking, excess alcohol use, diet high in red meat, obesity, type II diabetes, inflammatory bowel disease, and family history of colorectal cancer, among others. Negative risk factors include regular exercise, diet high in fiber, vitamin consumption (folate, calcium), and regular NSAID/aspirin use [10–12]. Certain heritable and/or somatic mutations in mismatch repair genes (including MSH2, MSH3, MSH6, MLH1, PMS1, and PMS2) and adenomatous polyposis coli (APC) increase the risk of colon cancer significantly, as found in patients with Lynch Syndrome/HNPCC (Hereditary nonpolyposis colorectal cancer) and FAP/Familial Adenomatous Polyposis, respectively.

Overall, the incidence and mortality due to colorectal cancer is decreasing in the United States since at least 1985 [5, 13], with an observed mortality decline of 26% from 1975 to 2000. This is likely due to decrease in the incidence of risk factors (secondary to lifestyle changes in the general population including diet changes and lower rates of smoking), increases in screening (i.e., rising rates of screening colonoscopies), and improvements in disease treatment (including better surgical techniques and more effective adjuvant chemotherapies) [5, 14].

10.2 Treatment Overview

10.2.1 Surgery

Surgery is the primary, curative treatment approach for colon cancer. The optimal surgical technique, including approach (laparoscopic versus open) and extent of resection, can vary depending on clinical, tumor, and anatomical characteristics.

Laparoscopic and open surgical resection have similar reported efficacy in terms of overall survival and risk of recurrence; laparoscopic surgeries have the benefit of a shorter postoperative recovery time and hospital stay [15, 16]. Oncological resection should always include a longitudinal margin of normal colon as well as removal of lymphatic drainage basins at risk. This typically involves en bloc removal of adequate sections of proximal and distal bowel (typically 5 cm on each side of the tumor) [17] and mesenteric lymphatics; anatomically, this generally translates to right hemicolectomy, transverse colectomy, left hemicolectomy, and sigmoidectomy. Surgeons and hospitals with high volumes of colorectal surgeries have been associated with improved mortality following colon cancer surgery [18, 19]. This is likely due to improved preoperative, intraoperative, and postoperative decision making and care.

Extent of successful resection, including negative margins and sufficient lymph node retrieval, has been directly tied to colon cancer recurrence and survival [20]. En bloc resection, negative longitudinal and radial margins, and no residual lymph node disease are all required for "R0" resection [17]. Consensus for adequate lymph node resection is >12 lymph nodes based on database review and expert opinion [17, 21].

10.2.2 Intraoperative Radiation

Intraoperative radiation therapy (IORT) should be strongly considered for patients with anticipated high risk of residual disease (i.e., expected close or positive margins) at surgery. Anticipated use is primarily for patients with T4b (direct invasion or adherence to other organs or structure) tumors. The addition of 10–20 Gy IORT to locally advanced colon cancer (as part of multi-modality treatment) has been shown to improve both local control and other disease-related outcomes [22, 23]. IORT can also be considered for locally recurrent tumors with prior radiation treatment.

10.2.3 Adjuvant/Postoperative Chemotherapy

The role of postoperative chemotherapy to improve disease-free and overall survival for locally advanced/high-risk colorectal patients is well-established [24, 25]. The addition of oxaliplatin to fluorouracil (5-FU)/leucovorin [26–28] has been shown to improve both DFS and OS for patients under 70 years. The benefit of adjuvant systemic therapy is less clear for those over 70 years [29] and also for Stage II patients with adverse histologic features [30, 31]. The common substitution of capecitabine (an orally dosed 5-FU prodrug) has been shown to be as effective as traditional 5-FU/leucovorin bolus infusion [32].

10.2.4 Adjuvant/Postoperative Radiation

The indications for adjuvant external beam radiation therapy (EBRT) should be based on an increased risk of local recurrence following resection. Recurrence risk

increases with tumor invasion beyond the bowel wall (T4a/through the serosa), or direct invasion or adherence to other organs (T4b), involved lymph nodes [33], as well as patients with involved surgical margins. Recurrence is most likely to occur at the tumor bed/adjoining structures and less likely regional nodal basins [34]. In carefully selected, high-risk patients, adjuvant EBRT (usually in combination with fluoropyrimidine-based chemotherapy) has been shown to improve local control [35] and recurrence-free survival [36] in retrospective reviews. High-risk factors include T4 disease, gross residual disease/subtotal resection, involved margins and/or fistula, perforation, or abscess formation.

The Intergroup 0130 trial randomized patients to receive adjuvant chemoradiation followed by additional chemotherapy or adjuvant chemotherapy alone. Unfortunately, it closed due to slow accrual, with only 222/700 patients enrolled (187 analyzed). Study results showed no difference in disease-free or overall survival; however, outcomes have been limited due to broad inclusion criteria (including lower risk T3N1 patients) and lack of radiation localization guidance (dearth of localizing surgical clips or preoperative imaging). Additionally, standard assessment of the radial margin was not performed [37].

10.2.5 Neoadjuvant Treatment

Neoadjuvant chemotherapy or chemoradiation therapy can be considered for locally advanced or unresectable colon cancer. The FOxTROT pilot study showed that neoadjuvant chemotherapy for large T3 or T4 tumors was feasible with acceptable toxicity rates [38]; this study group has moved forward with a Phase 3 trial. Neoadjuvant chemoradiation has been shown in randomized trials to improve local control/disease-free survival in rectal cancer patients [39, 40]. However, there is no corresponding high-level evidence demonstrating its effectiveness in colon cancer patients. Retrospective data have shown high rates of R0 resection and local control with low toxicity rates with neoadjuvant chemoradiation for locally advanced colon cancer patients [41].

10.2.6 Unresectable or Metastatic Disease

Patients with unresectable tumors or metastatic disease at presentation are classically treated with palliative chemotherapy. An irinotecan-based (ex. FOLFIRI: irinotecan-fluorouracil-leucovorin) [42] or oxaliplatin-based (ex. FOLFOX: oxaliplatin-fluorouracil-leucovorin) regimen [43] with the addition of bevacizumab [44] or an EGFR inhibitor (ex. panitumumab or cetuximab) [45] (KRAS/NRAS

wild-type tumors) can prolong progression-free and potentially overall survival, among other regimens. Refractory disease may be treated with EGFR inhibitors [46] containing regimens (KRAS/NRAS wild-type tumors), PD-1 inhibitors like pembrolizumab [47] (MMR-deficient tumors), or oral multi-kinase inhibitors like regorafenib, or tipiracil/trifluridine. Additional targeted and immunotherapy agents are under evaluation.

Patients with near colonic obstruction may benefit from a diverting ostomy or stenting. Non-surgical candidates may benefit from palliative radiation to shrink a painful, near-obstructing, or bleeding mass.

10.2.7 Multi-modality Treatment Considerations

Additive treatments may lead to additive toxicities. Toxicity considerations should be made with the combination of any treatment modalities (surgery, chemotherapy, radiation). Intergroup 0130 showed that the adjuvant chemoradiation increased acute Grade 3 toxicity rates over chemotherapy alone [37], with statistically significant increases in hematologic toxicities (23% vs. 11%), although not nausea and diarrhea. Postsurgical bowel has impaired vascularity and lymphatic drainage and is already at increased risk of subsequent injury and obstruction; adjuvant treatment like radiation therapy may increase these risks even further [48, 49].

10.3 Radiation Treatment Techniques

The effective treatment of colon cancer ranges from a single treatment approach (curative surgery in early-stage disease) to true multi-modality treatment including combinations of surgery, chemotherapy, and radiation. Figure 10.1 shows a generalized treatment algorithm to guide decision making depending on clinical stage and surgical assessment. Radiation (either external beam or intraoperative) is typically reserved for locally advanced cases.

A number of different radiation treatment techniques can be used for treating colon cancer; their use is contingent on appropriate clinical and anatomical concerns. In general, however, 3D-CRT technique is used unless more compelling reasons exist to utilize IMRT or VMAT due to normal tissue tolerance concerns. IORT should be available and utilized during primary surgical resection for situations of expected residual disease/close or positive margins. 2D technique is often employed for simple palliative radiation approaches. Table 10.1 highlights the indications, advantages, and disadvantages of each radiation technique.

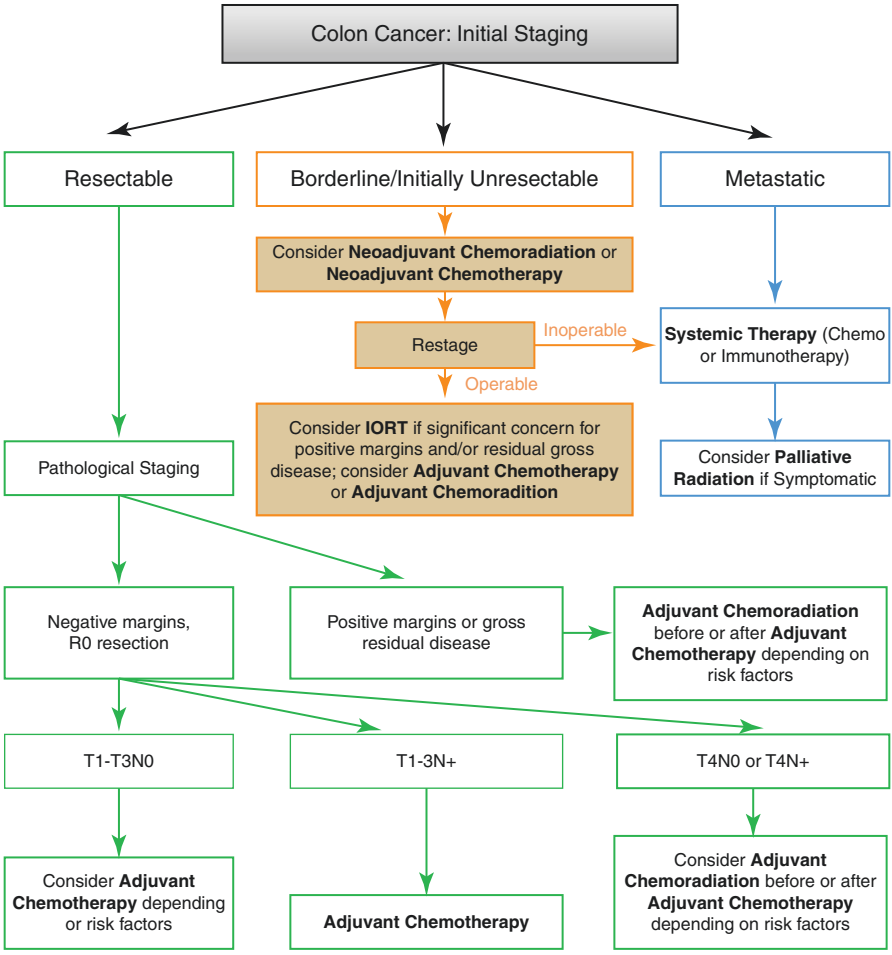

Fig. 10.1 Treatment algorithm; Indications for adjuvant therapy for colon cancer

Table 10.1 Radiation treatment modalities (with relative indications)

Modality	Indication	Advantages	Disadvantages
3D-CRT	Adjuvant or neoadjuvant radiation therapy for T4 disease, gross residual disease, positive margins, or other high risk of recurrence	Short treatment time Easy clinical setup Less complicated planning	Increased dose to neighboring tissues Potential dose inhomogeneity
IMRT (including VMAT)	Adjuvant or neoadjuvant radiation (as above), tumor bed near kidney or other organs at risk	Conformal treatment Decreased dose to organs at risk Potential for dose escalation where indicated	Long treatment time Required physics QA Increased imaging requirements More complicated planning Potential dose inhomogeneity
IORT	Close or involved margins at surgical resection, unresectable gross disease	Direct high-dose radiation to the areas of gross or microscopic disease Mobile organs at risk (bowel, bladder) can be moved out of field or directly shielded	Increased OR time (longer anesthesia, risk of infection, etc.) Risk of soft tissue/nerve damage for immediately adjacent tissue
2D	Palliative treatment	Short treatment time Easy clinical setup Less complicated planning	Limited dosimetric options to spare normal tissues

10.3.1 Treatment Timing

Adjuvant radiation treatment can be given either after surgery or after planned adjuvant chemotherapy course. Adjuvant radiation after surgery is typically initiated following sufficient recovery from primary resection. This is usually within 4–6 weeks of surgery. Wound dehiscence and/or active infection are generally considered contraindications to treatment start. Slow healing wounds, nutritional deficiency or decreased performance status after resection are relative contraindications and should be considered on a case-by-case basis. Adjuvant radiation after chemotherapy course is initiated after full cell count recovery, typically 2–3 weeks after the last chemotherapy cycle.

10.3.2 Simulation

Patients should undergo CT-based simulation to accurately establish three-dimensional anatomy. CT simulation position is dependent on tumor or tumor bed

site. Lower abdominal or pelvic tumors should often be simulated in prone position on a belly board in order to maximally displace small bowel out of the treatment field. Upper abdominal tumors should be simulated supine on a wing board for upper body immobilization. Left- and right-sided upper abdominal tumors may benefit from positioning in the decubitus position to similarly displace small bowel. Custom vac-lock bag or alpha cradle can be created for additional support for patients depending on their comfort and stability. Immobilization devices should be tailored to specific patient needs with the goal of a reproducible setup with minimal daily variation.

Both oral and IV contrast should be used during CT simulation unless there is a contraindication. IV contrast helps delineate both normal structures, including vasculature, and target tissues; oral contrast helps with accurate small bowel contours. Rectal tube with rectal contrast and anal verge marker may be helpful for some low lying colon cancers/tumor beds.

4D CT scans to assess respiratory motion should be considered depending on clinical concerns. They can be useful for neoadjuvant treatment of transverse colon tumors or in situations where tumor motion is expected to be a concern. In the postoperative setting, they are less commonly used as there is often no significant tumor bed movement; this is primarily due to tumor bed adhesions which fix the target area to the retroperitoneum, pelvis, or abdominal wall. Likewise, 4D CT scans are less helpful for ascending and descending colon tumors as these locations are generally considered to be fixed within the retroperitoneum.

Special patient instructions for CT simulation are dependent on treatment location and should be considered on a case by case basis. A full bladder can help displace small bowel out of the pelvis for sigmoid cancers. Fasting for 4 hours prior to scan can minimize gastric distention/irradiation in some cases of left-sided colon cancers. An empty bowel may help with rectal contrast delineation if it is being used for pelvic tumors. Instructions given to the patient at CT simulation should be considered carefully as they will need to be maintained throughout treatment; if patients cannot consistently maintain a full bladder for their daily treatments, for example, the total dose to the small bowel may be higher than initially expected.

Additional CT simulation variations or tests should be used to either ensure proper target coverage or protect organs at risk. A pretreatment renal scan can be helpful if a plan is expected to significantly treat one kidney; this is to ensure that the contralateral kidney has sufficient differential function should the ipsilateral kidney receive a nephron ablative dose. Simulation and treatment setup variations

include taping buttocks apart if simulated prone to avoid tissue "auto-bolus" effect and increased skin toxicity; similarly genitals for male patients should be displaced downwards (towards feet) away from anticipated treatment fields. Bolus should be considered at time of simulation if there is specific concern for tumor seeding of the surgical scars or gross tumor invasion to the level of the subcutaneous tissues. 1 cm of custom bolus can usually ensure proper dose delivery to these areas at risk.

10.3.3 Neoadjuvant Treatment Planning

Patients treated prior to surgery should have appropriate staging imaging studies fused to the CT simulation images to assist with treatment volume definition. If available, a PET/CT scan, in particular, can be very useful at delineating both extent of tumor spread and any involved lymph nodes. GTV is defined as all visualized gross disease including nodal spread. CTV is defined as areas at risk for microscopic spread of disease including at least a 2 cm margin on GTV (respecting anatomical boundaries); CTV may also include elective coverage of para-aortic nodal stations at risk for sub-clinical spread based on degree of clinical suspicion. PTV includes an expansion of CTV by 0.5–1 cm margin depending on setup uncertainty and frequency of verification imaging. Smaller margins can be used for cases with planned daily imaging, particularly if strategically placed surgical clips are available.

Organs at risk (OAR) should be contoured including small bowel (individual loops or a "bowel bag"), kidneys, liver, stomach, bladder, rectum, femoral heads, spinal cord, and uterus/ovaries (if appropriate). Treatment fields are designed to encompass the PTV, while minimizing excess dose to OAR. Table 10.2 lists generally accepted conservative dose tolerance and acute and/or chronic complications from treatment to each organ.

As previously stated, a 3D-CRT technique is typically utilized unless normal tissue tolerance constraints cannot be met. A 3- or 4- field technique (ex: PA with laterals or AP/PA with laterals, or combination of oblique beams) is preferable to 2-field technique, notably to respect small bowel tolerance [23, 48]. Figure 10.2 shows an example of neoadjuvant treatment for a cT4 sigmoid colon cancer (3D-CRT). Figure 10.3 shows an example of neoadjuvant treatment for a cT4 abdominal colon cancer (hybrid 3D-CRT). Dose is typically 45 Gy in 1.8 Gy fractions with optional up to 5.4 Gy boost to the gross disease plus margin.

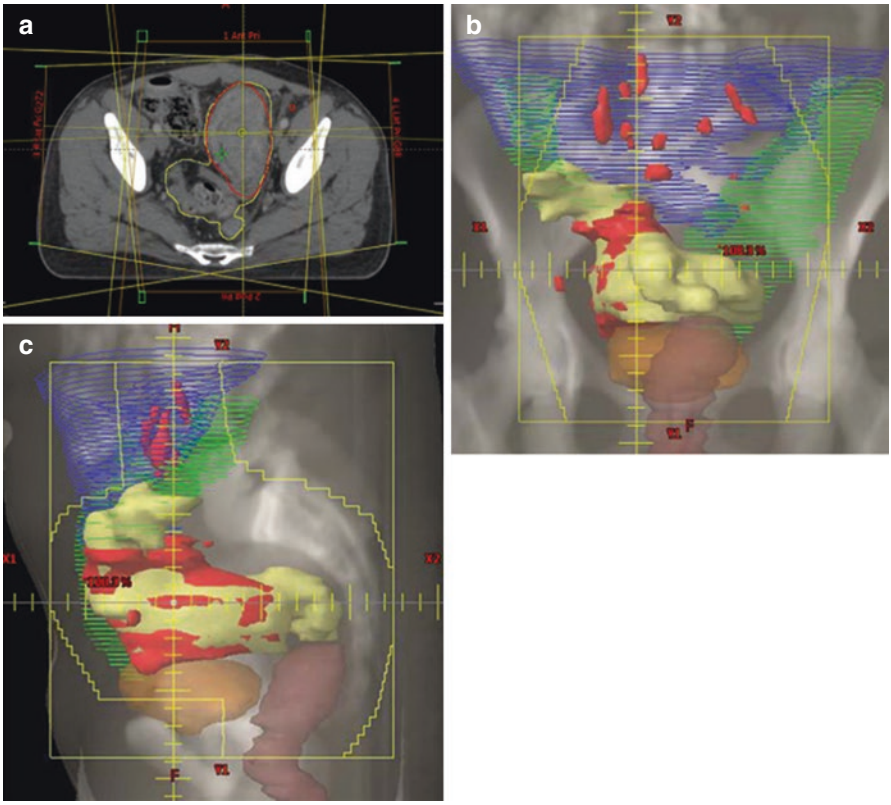

Fig. 10.2 Example of neoadjuvant chemoradiation 3D-CRT, pelvic treatment fields for a patient with cT4aN2 adenocarcinoma of the sigmoid colon treated to 48.6 Gy (45 Gy with reduced field boost 3.6 Gy) with concurrent Capecitabine over 5½ weeks. 3D-CRT with a 4-field technique (AP/PA with Opposed Laterals), 15 MV energy beams. Daily kV OBI (on board imaging) and a cone-beam CT (CBCT) on Day 1 and Day 6 performed. Daily treatment instructions include: full bladder, displace genitals toward feet. Patient ultimately underwent partial colectomy with pathology showing ypT3N1 disease with negative margins. (**a**): axial planning view with field placement; (**b**): anterior field; (**c**): left lateral field. *Red*: GTV (including nodes); *Yellow*: Sigmoid colon; *Brown*: Rectum; *Orange*: Bladder; *Green*: Large bowel; cursive Blue: Small bowel

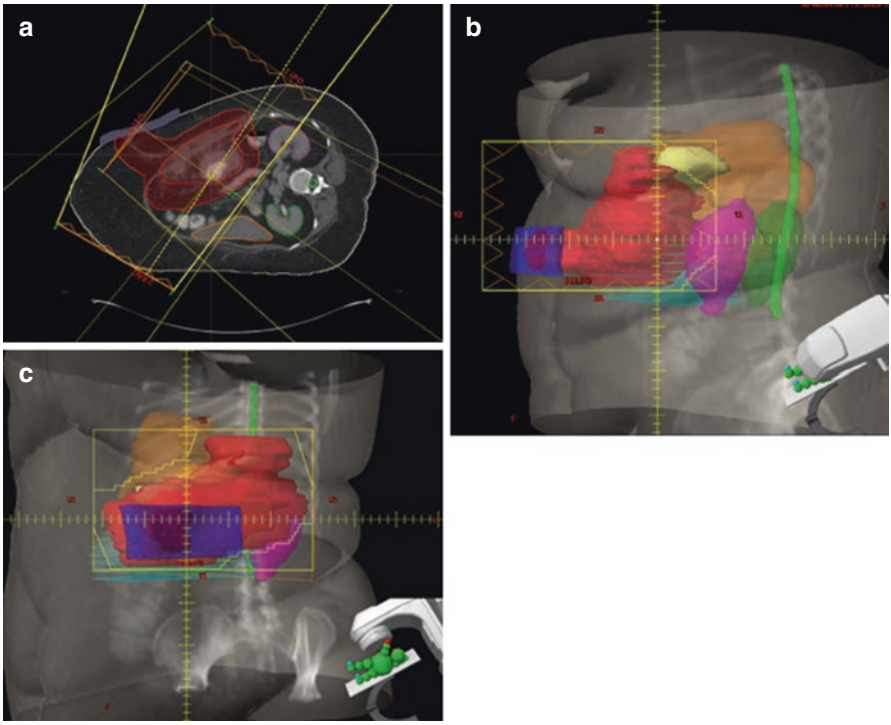

Fig. 10.3 Example of neoadjuvant chemoradiation 3D-CRT, abdomen treatment fields for a patient with cT4bN0 adenocarcinoma with signet ring features of the descending colon treated to 46.8 Gy with concurrent Capecitabine over 5 weeks. 3D-CRT hybrid with a 3-field technique (LAO with opposed RAO/LPO), 15 MV energy beams with electronic compensation and wedges. 1 cm of bolus applied daily to biopsy site. Daily kV OBI performed with weekly CBCT. Patient underwent partial colectomy with pathology showing ypT4aN0 disease, negative margins. (**a**): axial planning view with field placement (simulation, right lateral decubitus); (**b**): left anterior oblique field; (**c**): left posterior oblique field. *Red* (*small*): GTV; *Red* (*large*): PTV; *Dark Blue*: Bolus; *Orange*: Liver, *Light Blue*: Bowel; *Yellow*: Stomach; *Pink*: Left Kidney; *Dark Green*: Right Kidney; *Light Green*: Spinal Cord

10.3.4 IORT Treatment Planning

IORT requires significant advance planning prior to administration. OR requirements include after loader and shielded treatment room (for HDR delivery) or mobile linear accelerator. Department requirements include available advanced physics support. Radiation Oncology staff work closely with the surgical team to delineate the specific sites of residual disease, which are often confirmed on frozen section. Multi-channel applicator with custom dwell times or electron applicator is placed directly over the target site. Dose ranges from 10 to 20 Gy with higher doses delivered for known residual disease.

10.3.5 Adjuvant Treatment Planning

Patients treated following surgery should have appropriate pre-surgical imaging fused to the CT simulation to assist with treatment volumes. It is helpful to create a "pre-surgery" GTV including the initial extent of disease as a reference. GTV is otherwise defined as any areas of clinically visualized residual disease or positive margins at the time of surgical resection, which may be demarcated by clips. Thorough review of the operative report as well as discussion with the surgeon (including review of volumes if possible and significance of visualized clips) can be crucial in accurate delineation of appropriate target volume. CTV is defined as areas at risk for microscopic spread of disease including a 3–5 cm margin on the initial extent of disease ("pre-surgery GTV") to encompass areas within the expected surgical field; if present, strategically placed surgical clips can help define this volume. Elective nodal coverage of lymphatics is not typically required for adjuvant radiation with the exception of undissected nodal stations (ex. ileocolic vessels for right-sided tumors) or paraortic nodal coverage if known retroperitoneal extension or known residual adenopathy. PTV includes an expansion of CTV by 0.5–1 cm margin, depending on immobilization device and frequency of planned verification imaging as above.

Organs at risk should be contoured and dose limited as with a neoadjuvant treatment (Table 10.2); fields are designed to maximize PTV coverage while minimizing

Table 10.2 OAR, conservative organ tolerance, complications [50, 51]

Organ at risk	Organ tolerance	Complications
Small bowel	45 Gy (larger volume) 50.4 Gy (limited volume)	Acute: enteritis, nausea, vomiting Late: obstruction, GI bleed, fistula, perforation
Kidney	**Normal renal function:** V20 Gy < 70% (ipsilateral) V20 Gy < 30% (contralateral) **Impaired renal function:** V20 Gy < 50% (ipsilateral) V20 Gy < 30% (contralateral)	Chronic kidney disease including hypertension, elevated creatinine and end-stage renal disease
Bladder	50 Gy	Acute: cystitis, urgency, dysuria Late: fibrosis, hematuria, fistula
Stomach	45 Gy	Acute: gastritis, nausea, vomiting Late: ulceration, GI bleed, fistula, perforation
Large bowel and rectum	50 Gy	Acute: proctitis, tenesmus Late: obstruction, GI bleed, fistula, perforation
Spinal cord	45 Gy	Myelopathy
Liver	Mean < 28 Gy	Acute: transaminitis, nausea, vomiting Late: fibrosis, radiation-induced liver disease, liver failure
Femoral head	50 Gy	Avascular necrosis

dose to OAR to within acceptable range. Special considerations for postoperative plans include adhesions which may fix small bowel within the treatment field; this may limit the total dose. Figure 10.4 shows a sample adjuvant treatment for a pT4bN0 sigmoid colon cancer (3D-CRT with field in field technique). Figure 10.5 shows a sample adjuvant treatment for a pT4bN1 cecal cancer (3D-CRT). Dose is typically 45 Gy in 1.8 Gy fractions; boost to 50.4–54 Gy is used for areas at higher risk for harboring residual disease plus margin.

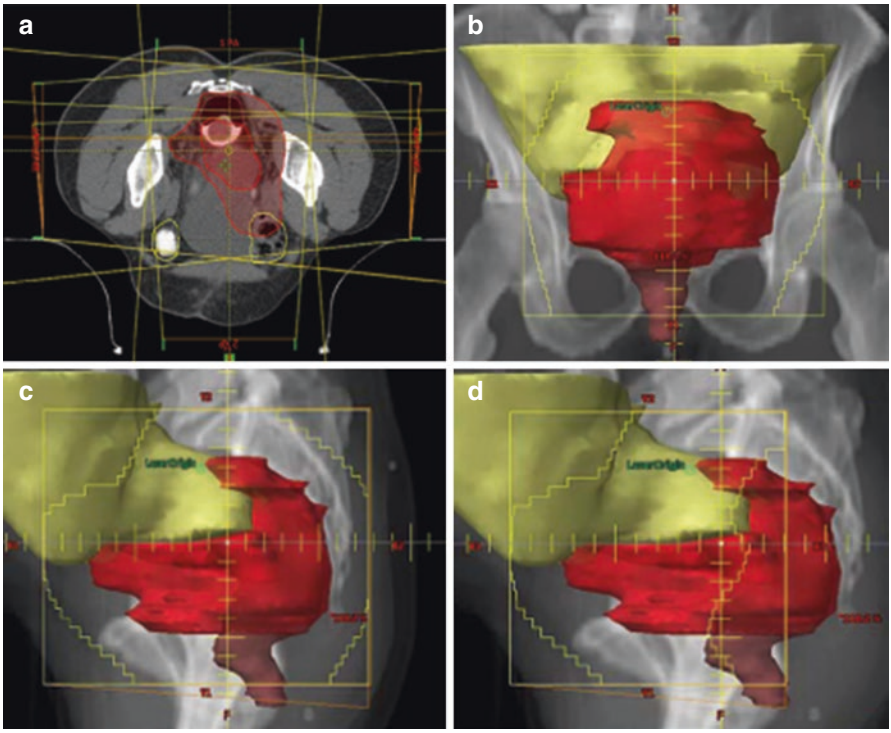

Fig. 10.4 Example of 3D-CRT, adjuvant pelvic treatment field for a patient with pT4bN0 (right vas deferens invasion) mucinous adenocarcinoma of the sigmoid colon treated to 45 Gy (no boost) with concurrent Capecitabine over 5 weeks. 3D-CRT with 4-field technique (AP/PA, Wedged Opposed Laterals with field in field to limit dose to rectum), 15 MV energy beams. Daily kV OBI for week 1 and then three times weekly thereafter with CBCT week 1. Special instructions for daily treatment: tape buttocks apart, full bladder, displace genitals toward feet. (**a**): axial planning view (prone on belly board); (**b**): anterior field; (**c**): left lateral wedged field; (**d**): left lateral wedged limited field. *Red*: CTV (postoperative; preoperative GTV in central *red*); *Yellow*: Bowel; *Brown*: Rectum

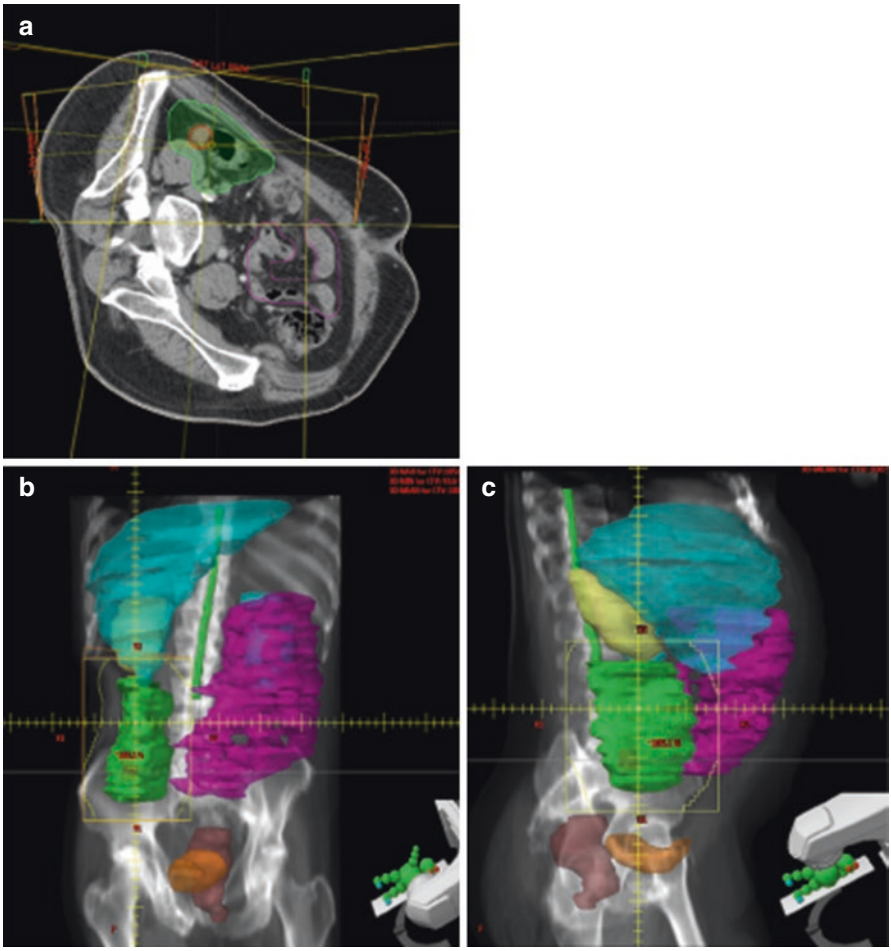

Fig. 10.5 Example of adjuvant 3D-CRT, abdominal treatment field for a patient with pT4bN1 (pelvic wall invasion) adenocarcinoma of the cecum, with positive margins treated to 54 Gy (45 Gy with reduced field boost 9 Gy) with concurrent Capecitabine over 6 weeks. 3D-CRT with 3-field technique (Lateral with Wedged AP/PA), 15 MV. Daily kV OBI for week 1 and then three times weekly thereafter; CBCT weekly. (**a**): axial planning view (simulation, *left* lateral decubitus); (**b**): posterior field; (**c**): right lateral field. *Red*: GTV; *Green*: CTV; *Light Blue*: Liver; *Pink*: Bowel; *Brown*: Rectum; *Orange*: Bladder; *Light Green*: Spinal Cord; *Light yellow*: Right Kidney

10.3.6 Dosimetry and Physics Considerations

Dosimetry and physics support is essential for proper plan optimization and quality assurance checks. This is particularly important for IMRT or VMAT plans. Dose inhomogeneity should be limited and special care should be taken to ensure that hot spots do not fall within small bowel or other critical organs. The addition of beam modifiers such as wedges or compensators can help correct for the irregular contours of patient anatomy.

10.3.7 On Treatment Imaging

Treatment delivery should be monitored with appropriate imaging to ensure accurate daily setup and treatment delivery to target volumes. Curative cases should be imaged with kV On Board Imaging (OBI) at a minimum of twice per week to insure proper patient alignment. Routine shifts greater than 1 cm should trigger a change to daily imaging. Contouring surgical clips is useful at the time of treatment for alignment and can help provide additional information than matching to bony anatomy.

Cone beam CT (CBCT) scans can give a more accurate assessment of target coverage, including internal rotational differences. They should be strongly considered on first day of treatment to ensure that devised plan translates accurately back onto a patient's three-dimensional anatomy. Consider repeat weekly CBCT for cases where high dose target is immediately adjacent to sensitive OAR or when there is concern for setup variability based on kV OBI shifts.

For IMRT plans, kV OBI should be checked daily and CBCT should be considered weekly. For palliative cases, kV OBI (or MV imaging) should be performed weekly.

10.3.8 Acute Side Effects and Management

Treatment-related toxicity is dependent on the treated region, but can include fatigue, dermatitis, nausea, vomiting, diarrhea, and abdominal cramping or pain. Patients may lose weight from reduced calorie intake or rapid transit time through the GI tract; they may also experience dehydration from diarrhea or reduced oral intake. Side effects can typically be managed with a combination of supportive care, including intravenous hydration, dietary modification, and prescription medications. Acute side effects are expected to resolve in the 4–6 weeks following treatment, although some patients can take months to return to baseline.

Patients should be weighed at least weekly during treatment to track weight loss. A registered dietician, if available, should meet with at-risk patients prior to starting treatment to optimize their nutritional status and provide specific dietary recommendations in the setting of diarrhea. Nutrition supplementation with either protein shakes and/or high calorie additives can also be useful.

Rapid weight loss of several pounds or more within 1 week is classically due to dehydration. Orthostatic vital signs can help determine if a patient is volume replete after IV fluids; some patients require multiple liters of fluids to return to their baseline. Often during treatment, patients will require reduced dose of their baseline anti-hypertensive medications; they may be able to stop some medications completely.

Nausea and vomiting can typically be controlled with a combination of antiemetic medications. Patients may require them on a regular schedule depending on their level of nausea. Low-dose dexamethasone can be an effective adjunct antiemetic for uncontrolled nausea or vomiting. An antacid medication including proton-pump inhibitor or H2 blocker can help reduce gastritis in upper colon tumors and simethicone can help with gas pain.

Diarrhea can be difficult to control at the end of treatment depending on the length of normal bowel being treated. Risk of radiation enteritis and colitis increases with both total dose and volume of bowel exposed. Over-the-counter medications like loperamide can help slow bowel transit time; prescription diphenoxylate/atropine may be required. Soluble fiber can work as a bulking agent to firm up loose stool and dietary modifications may lessen symptoms; narcotic usage for other symptoms may also help slow bowel transit time. Although some amount of diarrhea is expected when treating the bowel, there should be a relatively low threshold to test for *C. difficile* infection.

Fatigue or low energy can be difficult to combat during treatment. Patients should be encouraged to keep a regular routine and to minimize naps during the day in order to receive a full night's sleep. Insomnia should be treated if present. Moderate aerobic exercise should be encouraged, if feasible, as it can reduce fatigue levels during cancer treatment [52].

10.3.9 Late Toxicities

Modern treatment techniques (including accurate dose limitations to organs at risk as well as optimizing treatment position) can decrease risks of late effects from radiation. The biggest risk after combination of surgery and abdominal/pelvic radiation is small bowel fibrosis and/or adhesions leading to obstruction. Bowel obstruction is typically managed non-surgically with bowel rest, pain control, and fluid support. Chronic dysfunction of the large or small bowel leading to either chronic diarrhea or constipation is also possible for a small percent of patients. Ulceration, perforation, or GI bleed are rare late effects of treatment and often require more urgent surgical or endoscopic intervention. Spleen dysfunction (after radiation for a left-sided tumor) is also rare; pneumococcus vaccine and early antibiotics for fever are recommended given high risk of fulminant sepsis for those with functional asplenia.

10.4 Summary

Radiation therapy can be an effective component in the multi-modality treatment for locally advanced colon cancer. It should be considered in either the neoadjuvant, intraoperative, or adjuvant setting for high-risk patients with tumors invading into local structures, perforated tumors, or tumors with residual disease following maximal safe resection. Radiation therapy appears to improve local control and potentially disease-free survival; this is increasingly important as systemic therapies improve distant control rates. Abdominal or pelvic radiation is reasonably well-tolerated by patients when performed carefully, although some require significant supportive care to complete treatment.

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Rectal Cancer

11

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11.1 Introduction

Colorectal cancer (CRC) is the third most common cancer diagnosed in the United States in both men and women, excluding non-melanoma skin cancers. The American Cancer Society estimates that, for the year 2017, approximately 39,910 new cases of rectal cancer will be diagnosed in the United States. For men, the lifetime risk of CRC is approximately 1 in 21 (4.7%) and 1 in 23 (4.4%) for women. Other risk factors include age (>50 years), family history of adenomatous polyps (adenomas), family history of CRC in a first-degree relative (particularly if they were <45 years of age at diagnosis), inherited syndromes including familial adenomatous polyposis (FAP), Gardner, Turcot, Peutz-Jeghers, or Lynch (HNPCC) syndromes, personal history of inflammatory bowel disease, race (particularly African Americans and Ashkenazi Jews), type 2 diabetes, being overweight or obese, physical inactivity, diets high in red or processed meats, cooking meats at high temperatures, diets low in vegetables or whole grains, smoking, and heavy alcohol use (>2 drinks per day in men and >1 per day in women).

For the past several decades, the death rate from CRC has been declining in both men and women. This may be the result of enhanced detection techniques and improved treatment. Nonetheless, CRC continues to be the third leading cause of cancer-related deaths in women in the United States and second among men. It is estimated that CRC caused approximately 50,260 deaths in 2016 [1].

11.2 Treatment Overview

11.2.1 Operative Management of Localized Rectal Cancer

Despite ongoing investigation into improving the nonoperative management of rectal cancer, surgery is the mainstay of curative treatment. The most appropriate surgical approach depends on the location and extent of the primary tumor, as well as the presence or absence of lymph node metastases at diagnosis. Some very early-stage tumors can be managed with local excision alone. However, the majority of patients require a more extensive procedure, usually a low anterior resection (LAR) versus abdominoperineal resection (APR).

General oncologic surgical principles hold true in the rectum, as in other disease sites, where the goal of resection remains removal of all gross and microscopic disease with negative surgical margins. This includes an emphasis on the

circumferential margin. For those patients undergoing radical resection, this also includes removal of the adjacent mesorectum, known as a total mesorectal excision (TME), in an effort to remove all potential foci of disease. An adequate lymph node evaluation should include at least 12–15 perirectal and pelvic lymph nodes [2–5].

Several retrospective series have demonstrated a distal margin of 2 cm is acceptable based on the typical extent of intramural spread of disease. This allows for an increased likelihood of sphincter preservation based on surgical technique, allowing for more patients to undergo LAR [6–9]. Although a laparoscopic approach has some advantages to an open surgical procedure, for an experienced surgeon, the outcomes appear similar in several randomized trials [10–12].

11.2.2 Local Excision

The potential benefits of local excision in patients with early-stage rectal cancer include avoiding a major surgical procedure and colostomy. However, given the potential risk of lymph node spread in patients with T1 (5–10%) and T2 (20–35%) disease [13], patients undergoing local excision need to be carefully selected. To be considered an adequate excision, the tumor must be removed in an uninterrupted full thickness specimen with at least 1 cm proximal and distal margins. Based on the results of RTOG 89-02 and CALGB 8984, local excision appears to be a reasonable consideration for clinical T1 and some carefully selected favorable T2 lesions [14, 15]; however, the risk of locoregional (LR) recurrence may be unacceptably high for more advanced disease. General criteria for local excision include small lesions (<4 cm), moderately to well-differentiated tumors, tumors encompassing <40% of the circumference of the rectum, and those without lymphovascular invasion (LVI) [16–18]. Local excision is usually accomplished with techniques such as transanal excision or transanal endoscopic microsurgery (TEM).

11.2.3 Low Anterior Resection (LAR)

To be considered for LAR, the patient should have good sphincter function prior to surgery. Other important factors can include age, patient-specific anatomy, sex, and body habitus [19, 20]. Typically, tumors in the upper- and middle-third of the rectum can be considered for LAR. Advancements in surgical technique have also opened the door for pursuing LAR in appropriately selected patients with lesions in the lower third of the rectum [21]. LAR should not be performed if curative resection may be compromised or if adequate anorectal function cannot be preserved.

11.2.4 Abdominoperineal Resection (APR)

APR has long been considered a benchmark for resection in rectal cancer for distal lesions (those within 5 cm of the anal verge). Drawbacks of this approach include

permanent colostomy, slightly higher risk of morbidity and mortality, body image issues, and higher rates of positive surgical margins [22–25]. Several studies have shown similar rates of local and distant recurrence in LAR versus APR, for patients with negative surgical margins [22, 26].

11.2.5 Total Mesorectal Excision (TME)

Given the relatively high rates of LR recurrence following both APR and LAR in older surgical experiences, TME has become the established standard of care in order to reduce this risk of LR recurrence [27]. Some have postulated the blunt dissections used historically violated natural circumferential tissue planes, contributing to a high risk of local recurrence [28]. Some series have demonstrated that disease can spread not only laterally at the level of the tumor, but also more distally along the mesorectum [29]. TME involves sharp dissection along the pelvic fascia with a complete en bloc removal of the rectum [27]. On gross appearance, a TME specimen appears encapsulated and bi-lobed. Multiple reports have demonstrated improvement in LR control and overall survival (OS) for stage II and III disease managed with TME [28, 30–33]. However, there may be somewhat higher rates of anastomotic leak with this approach [27, 34, 35].

11.2.6 Other Surgical Considerations

For those patients who present with larger or more invasive lower rectal tumors, neoadjuvant radiation or chemoradiation can be considered to facilitate tumor shrinkage. For some patients, this may allow for sphincter preservation at the time of resection. For patients who present with locally advanced disease invading surrounding structures, extended resections, including pelvic exenteration, may be indicated.

11.2.7 Adjuvant Therapy

A number of historical trials have evaluated the role of adjuvant therapy compared to surgery alone in the treatment of rectal cancer. The NSABP R-02 trial showed an improvement in relapse-free survival (RFS) and disease-free survival (DFS), but no improvement in OS with 5-FU/leucovorin compared to MOF (5-FU, vincristine, semustine) in this setting. The addition of adjuvant radiation showed an improvement in LR control but not OS [36]. Although there was an increase in acute toxicity in the adjuvant combined modality arm receiving chemoradiation (CRT) in a trial by the GITSG, it was stopped early because of significant improvement in OS [37]. A Mayo-NCCTG trial compared adjuvant radiation alone to postoperative CRT and found decreased LR recurrence and improved 5-year OS in patients receiving adjuvant CRT [38].

Given the potential benefits of CRT, several subsequent trials further investigated optimal chemotherapy regimens. In the NCCTG 86-47-51 trial, adjuvant CRT with 5-FU was compared to 5-FU with semustine. This study also evaluated the method of 5-FU delivery, comparing bolus and continuous infusion. The 4-year OS was improved with continuous infusion 5-FU. Similarly, time to relapse and rate of distant metastasis (DM) were lower. Semustine did not appear to add additional benefit to 5-FU alone [39]. The Intergroup 0114 study evaluated radiation combined with four different chemotherapy regimens, including 5-FU alone. There was no difference in OS or DFS between the treatment arms [40].

The RTOG 89-02 study examined the role of adjuvant therapy in patients undergoing local excision. None of the patients with T1 lesions relapsed following local excision plus adjuvant CRT. However, a local recurrence rate of nearly 20% in patients with T2 and T3 disease suggests local excision followed by adjuvant therapy may represent an inferior approach for these patients.

11.2.8 T3N0 Rectal Cancer

For a select group of patients with favorable pathologic T3N0 disease, some investigators have suggested adjuvant chemotherapy alone with omission of adjuvant radiotherapy may be appropriate. A series from Memorial Sloan-Kettering evaluated patients with T3N0 rectal cancer treated with surgery alone. This study suggests a local recurrence rate of <10% in patients who receive a sharp mesorectal excision via APR or LAR with favorable T3 disease. The only histologic factor, which seemed to be associated with an increased risk of local recurrence, was LVI [41]. Similarly, in a retrospective review out of Massachusetts General Hospital, reasonable 10-year local control (95%) and relapse-free survival (87%) were seen in patients with favorable pathologic features including well or moderately differentiated tumors, invasion <2 mm into the perirectal fat, and absence of LVI [42]. A pooled analysis of five randomized controlled trials suggests the 5-year OS in patients with pT3N0 disease receiving surgery and adjuvant chemotherapy alone to be around 84% [43]. Despite this, there is currently insufficient randomized data to support omission of adjuvant radiotherapy for this group of patients.

11.2.9 Neoadjuvant Therapy

Despite the efficacy of adjuvant therapy, neoadjuvant treatment has become the standard of care for a majority of patients with rectal cancer. Neoadjuvant therapy has been associated with improvement in both local control and OS [31, 44]. The Swedish Rectal Cancer Trial included patients with Dukes A to C disease who were randomized to either short-course radiation followed by surgery 1 week later versus surgery alone (the specifics of short-course radiation therapy are discussed in detail below). The 5-year local relapse and OS rates were superior in the group receiving neoadjuvant radiation and this effect persisted with long-term follow-up [44, 45].

Several criticisms of this study include potential increase in late toxicity as a result of the fractionation schedule and insufficient time for treatment effect and tumor regression between radiation and surgical resection. This study was also conducted in the pre-TME era.

The French Lyon 90-01 study evaluated, in part, the effect of increasing the time to surgery following neoadjuvant radiation. Patients were randomized to undergo surgery either 2 or 6–8 weeks following neoadjuvant radiation. Although there was no significant difference in the rate of local control, there was an improvement in pathologic downstaging and pathologic complete response (pCR) rates in the delayed arm [46].

Given the emergence of TME [47], it was hypothesized that neoadjuvant treatment might be less critical with improvement in surgical resection techniques. However, a phase III Dutch trial in which patients were randomized to TME alone versus TME with short-course, neoadjuvant radiation demonstrated improvement in local recurrence at 2 years with preoperative radiation. There were similar rates of sphincter preservation in both groups. As one might expect, the risk of side effects was higher in those patients receiving radiation, including the risk of perineal complications [34, 48], sexual dysfunction, fecal incontinence, and worse quality of life scores [49, 50]. Several meta-analyses have demonstrated an improvement in rates of local recurrence, disease-specific survival [51, 52], and overall survival with neoadjuvant radiation therapy [52].

11.2.10 Neoadjuvant Radiation Versus Chemoradiation

In addition to evaluating the role of neoadjuvant radiotherapy, several groups have investigated the benefit of neoadjuvant CRT compared to neoadjuvant radiotherapy alone. The FFCD 9203 trial evaluated neoadjuvant radiation alone compared to radiation plus bolus 5-FU/leucovorin in patients with T3/4 disease. Patients in both treatment arms were treated to 45 Gy in 25 fractions, given over 5 weeks. Patients then went on to receive surgery followed by 4 cycles of adjuvant chemotherapy. The authors found improvement in pCR and local recurrence rates with neoadjuvant CRT, although there was no difference found in OS. The risk of high-grade toxicity (grades 3+) was higher with the addition of neoadjuvant chemotherapy [53].

Results of the EORTC 22921 study were similar to that of FFCD 9203. Patients in this study were also treated to 45 Gy in 25 fractions over 5 weeks. The investigators reported an improvement in downstaging and LR recurrence with neoadjuvant CRT, but no difference in OS. Again, there was an increase in acute toxicity with combined modality treatment. A subsequent meta-analysis confirmed improvement in pCR and local recurrence rates, but no difference in OS or DFS with neoadjuvant CRT [54].

Neoadjuvant CRT is currently preferred for patients with T3/4 primaries, node positive disease, distal tumors if tumor regression might allow for sphincter preservation, invasion of the mesorectal fascia, and/or to allow for a complete circumferential margin. In the landmark German Rectal Cancer Trial, advantages to a

neoadjuvant versus adjuvant approach include superior sphincter preservation rate, lower rate of anastomotic stenosis, and better local control with similar rates of OS [55]. Importantly, there seem to be reduced rates of both acute and late toxicity with preoperative treatment.

11.2.11 Short-Course Versus Long-Course Radiotherapy

Two treatment paradigms have emerged as standards of care in the neoadjuvant setting for rectal cancer. Short-course treatment with 5 Gy × 5 fractions is more popular in Northern Europe. Long-course CRT, utilizing 1.8–2 Gy fractions given with concurrent chemotherapy, is generally more popular in the United States and other parts of Europe. Despite four randomized trials comparing the two regimens, controversy remains regarding the optimal treatment approach in patients with rectal cancer.

11.2.12 Short-Course Radiotherapy

Several historical trials out of Sweden (briefly discussed above) included patients who were randomized to a short-course of neoadjuvant radiation versus surgery alone. Short-course RT consisted of 25 Gy delivered in five fractions. These studies noted decreased rates of LR recurrence [56–58], distant recurrence [56, 57], and improved OS with short-course RT. [58] On subset analysis, this held true for local recurrence in all stages of disease. This was not surprisingly at the expense of an increased side effect profile, including small bowel obstruction [59, 60]. A Dutch study examining the role of neoadjuvant radiation in the modern TME-era also demonstrated a benefit to short-course radiation in reducing local recurrence rates, despite improvement in surgical techniques [31].

Given concern for overtreatment in the era of TME and modern staging with endoscopic ultrasound (EUS) and/or magnetic resonance imaging (MRI), several groups including the Medical Research Council (MRC) and National Cancer Institute in Canada (NCIC) have evaluated preoperative RT with 25 Gy in five fractions versus selective adjuvant CRT in patients with involved circumferential resection margins. Patients who received short-course RT had lower rates of local recurrence and improved DFS but no difference in OS. Of note, only 12% of patients met criteria for adjuvant therapy [61]. In summary, all three trials of neoadjuvant short-course radiation demonstrated an improvement in local control, but concern remains that this regimen leads to an increased potential for late GI toxicity based on the long-term follow-up of the Dutch and Swedish trials.

11.2.13 Long-Course Radiotherapy

In the mid-1990s, several randomized trials were developed to further investigate long-course CRT. In the German Rectal Cancer Trial, patients received radiation to

50.4 Gy in 28 fractions. This represents a typical fractionation schedule for long-course CRT. The NSABP ran a similar trial, which closed early due to poor accrual. However, study results also found a similar effect on downstaging and a decrease in nodal positivity. DFS was improved with preoperative treatment, but no difference was noted in OS or local recurrence [62]. A single institution trial from Korea, similar in design but utilizing capecitabine instead of 5-FU, also demonstrated improvement in sphincter preservation, but no difference in OS, DFS, or local recurrence [63]. These trials utilizing long-course radiotherapy suggest improvement in downstaging and sphincter function in patients undergoing preoperative CRT.

The FFCD and EORTC have both evaluated preoperative long-course RT versus preoperative long-course RT plus chemotherapy. As noted previously, in the EORTC 22921 study, one of the randomizations included evaluation of long-course preoperative RT with or without bolus 5-FU. The addition of 5-FU in the neoadjuvant setting improved rates of pCR and downstaging, but no statistically significant difference was seen in OS, DFS, or DM [64]. Similarly, the FFCD 9203 trial evaluated preoperative long-course radiation compared to preoperative CRT in patients who went on to receive surgery and adjuvant chemotherapy. They similarly noted improvement in pCR and local recurrence rates, but no difference in survival [53].

Other studies have evaluated the role for alternative chemotherapy agents, besides infusional 5-FU, in combination with long-course RT. NSABP R-04 suggests similar outcomes with capecitabine compared to infusional 5-FU, suggesting this may also be considered a standard of care [65]. The exact role for combination chemotherapy with 5-FU and oxaliplatin remains unclear. The ACCORD 12/0405-PRODIGE2 trial found no improvement in DFS or OS, but preliminary results from CAO/ARO/AIO-04 suggest a DFS benefit with the addition of oxaliplatin at 3 years [66, 67].

11.2.14 Randomized Comparisons of Short-Course and Long-Course RT

The Polish I trial randomized patients with resectable T3/4 disease to 50.4 Gy with concurrent bolus 5-FU/leucovorin followed by TME after 4–6 weeks versus patients who underwent 25 Gy followed by TME after 1 week. Adjuvant chemotherapy was left to the discretion of the treating physician and was more commonly administered in the short-course arm (46% vs. 30%). The primary endpoint was sphincter preservation, which was not different between the arms. Similar to other studies, the patients receiving the long-course treatment had high rates of downstaging and pCR, but there was no apparent difference in local recurrence, 4-year DFS, 4-year OS, or high-grade late toxicity. There were lower rates of high-grade acute toxicities and better compliance in the short-course arm [68].

Similarly, the Polish II trial evaluated neoadjuvant short-course radiotherapy followed by consolidation chemotherapy versus long-course concurrent CRT. However, patients in this study had more advanced disease compared to those in the Polish I

study and were considered unresectable. Patients with fixed T3/4 tumors without evidence of distant metastatic disease were randomized to either 5 Gy × 5 followed by 3 cycles of consolidation FOLFOX4 or 50.4 Gy given in 28 fractions with concurrent bolus 5-FU, leucovorin, and oxaliplatin. Both groups then went on to surgery approximately 6 weeks after neoadjuvant treatment. The primary endpoint of this study was rate of R0 resection and was not different between the groups. There was also no difference noted in OS, DFS, or local failure, although there was a trend towards improvement in OS in the patients treated with short-course RT with consolidation chemotherapy ($p = 0.055$). Although there noted to be a higher rate of acute toxicity in the short-course arm, there was no difference in the rate of high-grade toxicities (grade 3+) [69].

The Trans Tasman Radiation Oncology Group (TROG) conducted a trial in which patients with clinical stage II and III disease were randomly assigned to 25 Gy in five fractions with surgery within a week versus long-course CRT to 50.4 Gy in 28 fractions with continuous infusion 5-FU and surgery in 4–6 weeks. All patients received TME followed by adjuvant chemotherapy with 5-FU. Both downstaging and pCR were improved in patients who received long-course CRT. There did not seem to be a difference in rate of patients requiring APR, 3-year local recurrence, 5-year DM, 5-year OS, or risk of late toxicity between the two regimens [70].

The precise timing of surgery after neoadjuvant therapy is unclear. The recently published Stockholm III trial evaluated both the optimal fractionation and timing of adjuvant radiation therapy. Patients with resectable rectal cancer were randomized to one of the following: (1) 5 Gy × 5 followed by surgery within 1 week, (2) 5 Gy × 5 followed by surgery after 4–8 weeks, and (3) 50 Gy in 25 fractions followed by surgery after 4–8 weeks. The primary endpoint was time to local recurrence. Outcomes were similar between all three treatment arms. Although there was noted to be an increase in radiation-related toxicities in the short-course RT arm with delay to surgery, there was a significant *decrease* in postoperative complications in these patients. The authors suggest that short-course RT with delay may be a useful alternative to conventional short-course RT followed by immediate surgery [71].

Commonly after neoadjuvant CRT, patients will undergo 4–6 months of adjuvant chemotherapy, often with an oxaliplatin-containing regimen like FOLFOX.

11.2.15 Neoadjuvant Chemotherapy Only

Given concern for potential long-term late effects of RT [72, 73], the PROSPECT trial was developed to evaluate the efficacy of neoadjuvant chemotherapy utilizing more modern chemotherapy regimens in hopes of permitting more selective use of RT. Inclusion criteria include those patients with cT2N1, T3N0, or T3N1 disease located in the upper or middle thirds of the rectum, who are without evidence of mesorectal fascial involvement. In the experimental arm, patients receive 6 cycles of FOLFOX with subsequent assessment of treatment response. If the tumor has

decreased in size by at least 20%, patients proceed directly to TME followed by 6 cycles of adjuvant FOLFOX. If the tumor has *not* decreased by at least 20%, patients receive neoadjuvant CRT (with 5-FU or capecitabine), TME, and then 2 cycles of adjuvant FOLFOX. This is being compared to standard long-course CRT (with 5-FU or capecitabine) followed by TME and 8 cycles of adjuvant FOLFOX. Primary endpoints include rate of pelvic R0 resection and time to local recurrence. Estimated primary completion date is July 2017 [74].

11.2.16 Neoadjuvant Chemotherapy and Radiation Therapy

A phase II trial from Spain (GCR-3) evaluated the role of induction chemotherapy in patients with rectal cancer. Patients with clinical stage T3/4 tumors or node positive disease with lesions in the distal or middle third of the rectum were randomly assigned to neoadjuvant CRT followed by surgery and adjuvant CAPOX versus 4 cycles of induction CAPOX followed by CRT then surgery. Local recurrence, DM, DFS, and OS were similar between the two groups at 5 years. There was improvement in compliance and lower rates of acute toxicity in patients undergoing induction chemotherapy. The authors advocated that this regimen deserves further evaluation in a phase III setting [75].

Non-randomized phase II data has examined the effect of adding additional cycles of mFOLFOX6 between neoadjuvant chemoradiation and surgery on pCR. All patients received CRT followed by TME 6–8 weeks later compared to 2, 4, or 6 cycles of mFOLFOX6 followed by TME. The addition of mFOLFOX6 improved the rate of pCR and this approach is currently being evaluated in a phase III setting [76]. However, delay to surgery in this trial may also have contributed to improvement in pCR.

An ongoing phase II multicenter randomized trial (NCI 13-213) is designed to evaluate 3-year DFS in patients with locally advanced rectal cancer randomizing patients to either induction or consolidation chemotherapy (FOLFOX or CapeOX) in conjunction with neoadjuvant CRT (5-FU or capecitabine). Patients then undergo restaging with clinical exam, endoscopy, and MRI. Those with significant clinical response will be managed nonoperatively. Those with inadequate clinical response will undergo TME [77].

11.2.17 Nonoperative Management (NOM)

Despite the oncologic benefits of TME in patients with rectal cancer, a variety of complications have been associated with this procedure including vascular injury [78], infection, wound complications, ureteral injury [79], and sexual dysfunction [80, 81]. Long-term complications include chronic bowel dysfunction [49, 59], urinary incontinence [82], and small bowel obstruction [60, 83]. Despite the risk

of morbidity and mortality associated with TME, the vast majority of patients with rectal cancer undergo surgical resection. However, some clinical scenarios have led to the pursuit of nonoperative management, particularly in patients with low lying rectal cancers requiring APR, in elderly patients, or those with significant medical comorbidities. Additionally, many patients experience significant impact on their quality of life following either LAR or APR procedures. Another potential rationale for NOM management comes from the rate of pCR observed in patients undergoing neoadjuvant therapy, particularly those who undergo long-course CRT.

Investigators from University of São Paulo School of Medicine evaluated NOM for patients with potentially resectable rectal cancer. The study included patients with T2-4 and N0-1 disease, who received neoadjuvant CRT to 50.4 Gy with concurrent 5-FU. Patients were reevaluated 8 weeks postoperatively. Response was assessed radiographically and pathologically via endoscopic biopsies. Patients with an incomplete response were sent immediately for resection. Those with clinical complete response (cCR) were followed closely with monthly physical exams, frequent proctoscopy with biopsies of any suspicious areas, serial CEA monitoring, and abdominal/pelvic CT scans every 6 months for the first year. Patients without evidence of disease for 1 year were considered to have a cCR [84]. Updated results have also been published with a larger cohort of patients [85]. The most recent report indicates that 31% of patients with an initial cCR went on to develop a local recurrence, the majority of which occurred in the first 12 months. Only 7% of these patients were not amenable to salvage surgery. Five-year cause-specific OS and DFS were 91% and 68%, respectively, with 14% of patients failing distantly [86].

Lim et al. published a series including medically inoperable patients or those who refused surgery from an Australian database. The majority of patients had distal T3 lesions and underwent CRT. Patients were followed clinically. Those patients who achieved a cCR had significantly longer PFS [87].

Maas et al. attempted to replicate the results of the São Paulo group with modern MRI staging techniques. In this study, there was a noticeably lower rate of cCR, likely the result of the strict imaging criteria that was used [88]. Memorial Sloan Kettering investigators compared the outcomes of 32 patients who had a cCR with NOM to a comparable group who had achieved a pCR with surgical resection. The local recurrence rate for patients undergoing NOM was 21% versus 0% in the pCR group after 28 months; however, all patients that failed locally were successfully salvaged with surgery. The clinical outcomes were otherwise similar between the groups [89]. This series has since been updated with OS and DFS remaining similar between the NOM and pCR groups [90].

Finally, a prospective trial from Denmark evaluated patients with resectable T2-3 primaries and N0-1 disease who were treated with high dose radiation to 60 Gy in 30 fractions with a 5 Gy endorectal brachytherapy boost and oral tegafur-uracil. Response was assessed via endoscopy and MRI/CT. If patients achieved a cCR,

they were followed closely with exams, endoscopy, and PET scans. Only 26% of patients had LR failure by 2 years and all patients were surgically salvaged [91].

Please see previous discussion of the ongoing phase II trial (NCI 13-213), which includes evaluation of NOM in patients with locally advanced rectal cancer.

11.2.18 Management of Recurrent Disease

Conceptually, recurrent rectal cancer is often treated in a similar fashion to T4 disease with a combination of neoadjuvant CRT, surgery, and adjuvant chemotherapy. Intraoperative radiation therapy (IORT) may also be considered. Common sites of local recurrence within the pelvis include the presacral space and pelvic sidewall. The 5-year OS for these patients is poor, approximately 20% for all comers. The rate of local control is higher in patients who have not previously undergone radiation therapy [92].

Several series have evaluated neoadjuvant treatment in this setting followed by surgery in patients who had not previously undergone radiation. One randomized trial compared neoadjuvant CRT to neoadjuvant radiotherapy alone prior to resection, including 25 patients with recurrent disease. They noted higher rates of R0 resection, local control, time to treatment failure, and cancer-specific survival in those patients who underwent CRT [93]. Another series included 123 patients with locally recurrent CRC who underwent radiation to 45–54 Gy, either neoadjuvantly or adjuvantly, followed by resection and IORT. Five-year OS was improved in patients who were able to get a gross total resection [94]. Another smaller series included patients who were not able to undergo surgical resection up front, but who went on to receive neoadjuvant CRT. Eighty percent of patients were ultimately able to undergo surgical resection [95].

Generally, patients who have not undergone prior radiation are treated with a course of neoadjuvant CRT to 50–54 Gy with concurrent 5-FU-based chemotherapy. These patients may also be considered for IORT.

11.2.19 Re-irradiation in Recurrent Disease

Re-irradiation can be considered in select patients who present with recurrent rectal cancer. A phase II series from Italy evaluated patients who had previously undergone pelvic radiation. Patients were treated with a hyperfractionated regimen to 30 Gy with a 10.8 Gy boost and concurrent 5-FU. Patients then proceeded to resection, if possible. Thirty-five percent of patients achieved an R0 resection and the OS at 5 years was 39%. The investigators noted low rates of acute and acceptable rates of late complications [96]. A retrospective series of patients with recurrent disease included 57 patients who had previously been irradiated and were retreated to a dose of 30.6 Gy. There was no apparent difference in late toxicity in those patients who were re-irradiated [97].

Another series included 103 patients with recurrent disease who had undergone neoadjuvant or adjuvant radiation therapy as part of their initial treatment (median initial dose 50.4 Gy). These patients were re-irradiated to 30 or 30.6 Gy with a 6–20 Gy boost to areas of gross tumor plus margin. Twenty-two patients experienced late toxicity following re-irradiation including persistent diarrhea, small bowel obstruction, fistula, and stricture [98]. MD Anderson investigators evaluated a hyperfractionated approach in this setting in an effort to reduce the incidence of late toxicity. Fifty patients who previously received radiation were treated to 30–39 Gy in 1.5 Gy BID fractions, most with concurrent chemotherapy. The rate of high-grade toxicity (grades 3+) at 3 years was 35% [99].

Based on these results, it is reasonable to consider a second course of treatment (30–39 Gy) in patients with recurrent disease, at the risk of late toxicity. Therefore, care should be taken to avoid normal structures, including small bowel, as much as reasonably possible.

11.2.20 Metastatic Disease

Important factors in patients who present with metastatic disease include whether or not the distant metastatic disease is resectable and whether the primary tumor is symptomatic. If both the primary tumor and metastatic disease are appropriate for resection, one option is short-course neoadjuvant radiotherapy followed by resection of both the primary and metastatic lesion(s). Other options include induction chemotherapy followed by short-course radiation, then surgery or neoadjuvant long-course CRT followed by surgery, either alone or following induction chemotherapy. Induction chemotherapy has the benefit of potential downstaging and allowing some time for the natural history of the patient's metastatic disease to manifest. Guidelines from expert groups in this setting differ. The NCCN recommends that any of the strategies mentioned above are reasonable. Conversely, the EMSO generally recommends against conventional long-course CRT in this setting. Whether or not the metastatic disease and the primary can be resected synchronously or in a staged fashion depends on the extent of the necessary resections themselves, the general condition of the patient, and the ability to achieve negative surgical margins at both sites.

For patients with unresectable metastatic disease, the approach depends on whether or not the primary lesion is symptomatic. For patients with symptomatic, obstructive, or near-obstructive disease, a diverting stoma, palliative resection, or palliative radiation can be considered for symptom relief and prevention of perforation. Intraluminal stents are another palliative option, but pose the risk of stent migration and intestinal erosion. If the lesion is non-obstructive, laser ablation or electrofulguration can be used. If the primary lesion is asymptomatic, the most appropriate treatment is systemic chemotherapy. Resection of the primary in this setting has not been shown to improve survival and is only recommended if the patient becomes symptomatic.

11.2.21 Brachytherapy and Intraoperative Radiotherapy (IORT)

Intraoperative radiation can be considered in the setting of locally advanced rectal cancer when the surgeon is concerned about a gross or microscopically positive margin. Some have suggested that patients with grossly positive margins benefit the most from the addition of IORT. The addition of IORT does not make up for poor surgical technique, however. IORT can also be considered in the setting of recurrent disease as noted above.

Currently, endorectal brachytherapy is not utilized as a typical component in the treatment of patients with rectal cancer. However, certain clinical situations might be the reason to consider brachytherapy including elderly patients with rectal cancer, those with significant medical comorbidities, and those who refuse APR. Brachytherapy may also be a reasonable option to provide palliation or local disease control for patients with extensive or recurrent disease, whose other treatment options are limited. Memorial Sloan Kettering investigators have opened a phase I dose-escalation study to evaluate the safety of endorectal brachytherapy with concurrent capecitabine or 5-FU in the management of locally recurrent or residual disease in patients who have previously undergone EBRT.

11.3 Radiation Treatment Approaches

The treatment of rectal cancer is dependent upon the stage of disease and can range from a local excision to tri-modality therapy. As discussed previously, surgery remains the mainstay of curative treatment for patients with rectal cancer. In patients with metastatic disease not amenable to resection, surgery is typically reserved for symptomatic patients.

The approach to radiation therapy depends on the patient's extent of disease and individual anatomy. The primary technique utilized in patients with rectal cancer is 3D-conformal radiation therapy (3D-CRT). Intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc treatment (VMAT) can be considered if appropriate normal tissue tolerance constraints cannot be met with a 3D approach. As discussed previously, IORT is usually reserved for patients with locally advanced rectal cancer with potentially compromised surgical margins. Table 11.1 summarizes the indications, advantages, and disadvantages of each approach.

Following neoadjuvant radiation, the time to surgery can range from as little as 1 week when combined with short-course radiation therapy, up to 8–12 weeks with long-course neoadjuvant CRT. A longer time interval between neoadjuvant therapy and surgery can increase the likelihood of downstaging and pCR. Adjuvant

Table 11.1 Summary of the various treatment modalities, including their indications, advantages, and disadvantages

Modality	Indication	Advantages	Disadvantages
3D-CRT	• Neoadjuvant treatment	•–Shorter treatment times	• Inhomogeneity
	• Adjuvant treatment	• Shorter treatment planning times	• Higher doses to surrounding normal structures
	• Primary modality used	• Easy clinical setup	
IMRT VMAT	• Neoadjuvant treatment	• Improved normal tissue sparing	• Longer treatment and treatment planning times
	• Adjuvant treatment	• Improved PTV coverage	• Increased verification imaging frequency
IORT	• Recurrent disease	• Sparing of surrounding normal tissues	• Requires significant physics and dosimetry support
	• Grossly positive resection margins	• Focused dose to known areas of gross disease	• Prolonged operating time
2D	• Palliative cases	• Shorter treatment times	• Increased risk of acute toxicity
		• Easy clinical setup	• Less sparing of normal tissues

radiation is typically performed 4–6 weeks after surgery, in order to give the patient adequate time to heal following their surgical resection.

11.3.1 Simulation

Reproducibility is paramount for patients undergoing CT simulation. Most patients with rectal cancer are simulated and treated in the prone position using techniques such as a belly board. The belly board allows for the small bowel to fall anteriorly and out of the pelvis, thereby minimizing the volume of small bowel within the treatment field [100]. A full bladder during simulation and treatment can also help to displace the small bowel up and out of the pelvis. Taping the patient's buttocks apart can minimize an auto-bolus effect and skin irritation within the gluteal fold. A marker should usually be placed at the anal verge. Intravenous, rectal, and small bowel contrast may be given at the time of simulation for better delineation of target and normal structures (unless a specific contraindication exists). Real-time fluoroscopic simulation with contrast can be considered for motion assessment.

11.3.2 Neoadjuvant Treatment Planning

Fusion of pretreatment staging studies, including PET scans, can aid in the process of accurate target delineation, in both the pre- and postoperative setting. GTV is defined as the areas of gross primary and nodal disease. CTV encompasses those areas at risk for microscopic spread, including a margin on gross disease, and areas at risk for regional nodal spread in the pelvis. CTV to PTV expansion accounts for daily setup variation. In this setting, the GTV to CTV expansion is at least 2 cm, respecting normal anatomic boundaries. CTV to PTV expansion is typically 0.5–1 cm, depending on the frequency of verification imaging and immobilization technique.

Generally, a 4-field (AP/PA/laterals) or a 3-field (PA/laterals) technique is used in the treatment of rectal cancer. The superior field edge should be placed at the L5/S1 interspace. The distal edge of each field depends on the tumor location (upper, middle, or lower third of the rectum), but should be approximately 3–5 cm below the GTV. The superior and inferior borders for the lateral treatment fields are the same as those for the AP/PA fields. Posteriorly, the lateral treatment fields should encompass the presacral space. Finally, to ensure coverage of the mesorectum, the anterior aspect of the lateral fields should extend approximately 4 cm anterior to the rectum. If the patient has extensive extrarectal disease, these general guidelines should be expanded to encompass the full extent of disease plus a reasonable margin.

If the desired normal tissue constraints cannot be met using a 3D-CRT approach, an IMRT/VMAT technique can be considered. In this setting, the GTV to CTV and CTV to PTV expansions used are similar to those used with a 3D-CRT approach (see above). If patients are planned for daily imaging, smaller margins can be considered.

Organs at risk (OAR) include small bowel, colon, bladder, femoral heads, genitalia, and uterus/ovaries (if present). Table 11.2 lists typical normal tissue tolerances and potential toxicities related to each OAR. As noted previously, a 3- or 4-field technique should be attempted first, with evaluation of an IMRT/VMAT plan if appropriate tissue constraints cannot be met.

Figure 11.1a, b show an example of a patient who received neoadjuvant treatment utilizing a 3D-CRT approach. Figure 11.2a–c show an example of a patient

Table 11.2 Organs at risk (OAR) when treating rectal cancer, normal tissue tolerances for each organ, and a summary of the more common toxicities for each OAR (both acute and late)

Organ at risk	Normal tissue tolerance	Acute and late toxicities
Small bowel	50.4 Gy (small volume)	*Acute*: nausea, vomiting, diarrhea, abdominal pain, cramping
	45 Gy (large volume)	*Late*: SBO, fistula, stenosis
Large bowel	50 Gy	*Acute*: nausea, vomiting, perforation, gas pain
		Late: fistula. GI bleed, stenosis
Bladder	50 Gy	*Acute*: cystitis, dysuria, urinary frequency
		Late: hematuria, fistula
Femoral heads	50 Gy	*Late*: avascular necrosis

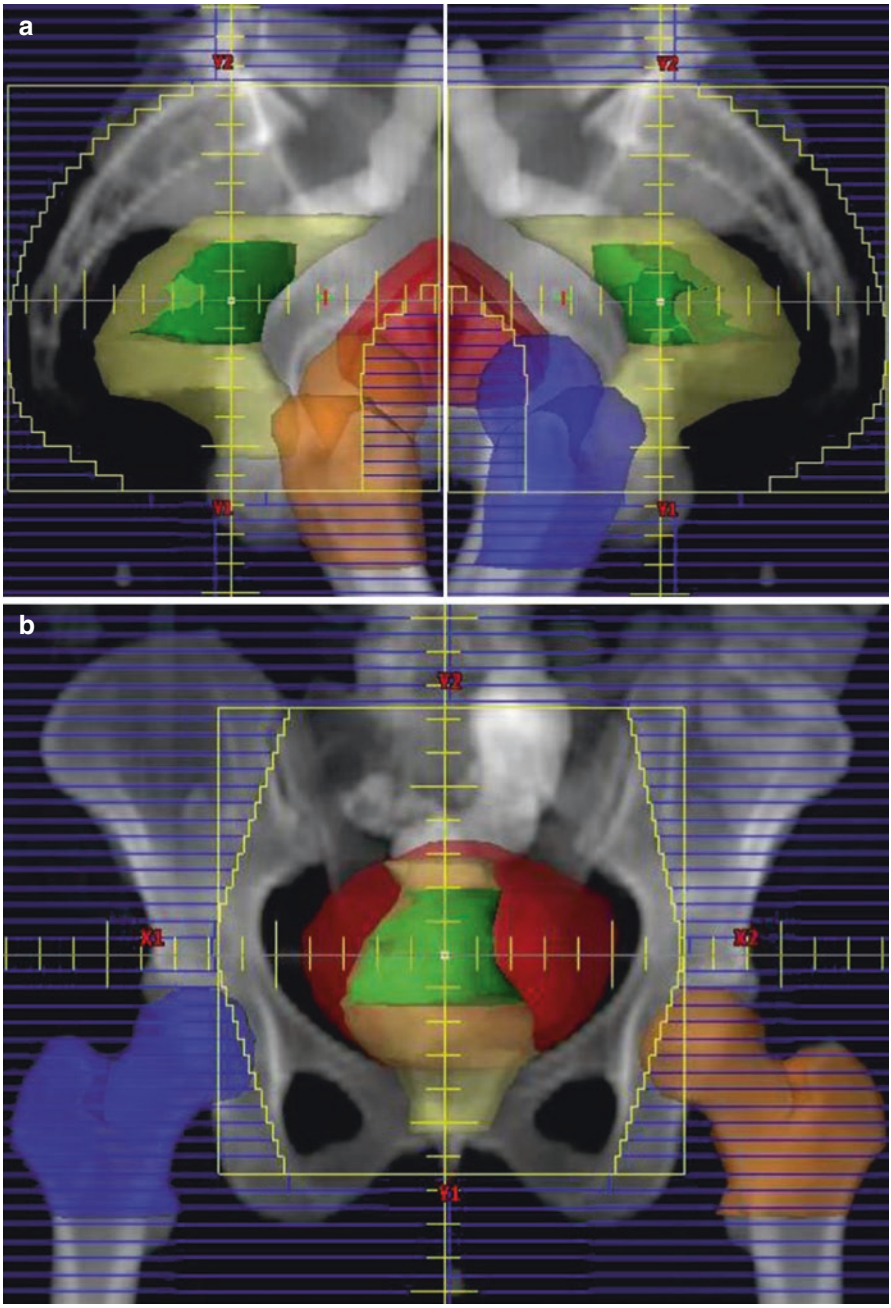


Fig. 11.1 (**a**) Lateral treatment fields for a 46-year-old patient with uT3N0 rectal cancer undergoing treatment in the neoadjuvant setting using a 3-field, 3D-CRT approach. *Green*: GTV. *Yellow*: rectum. *Red*: bladder. *Blue*: Left femoral head. *Orange*: Right femoral head. (**b**) PA treatment field for the same patient shown in (**a**)

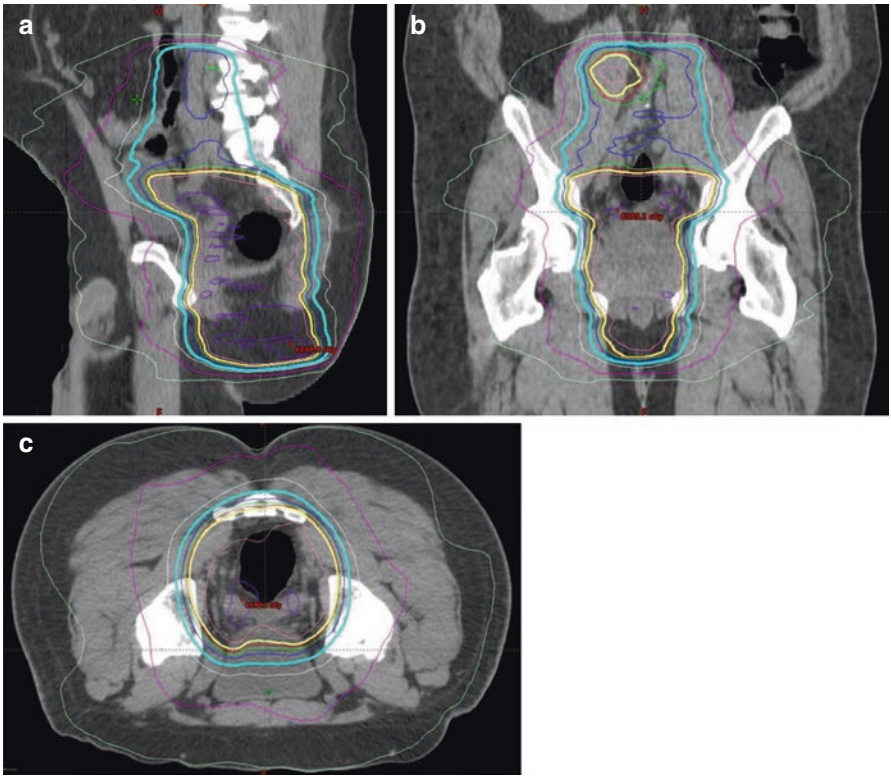


Fig. 11.2 (**a**) Sagittal view of the VMAT treatment plan for a 52-year-old patient with cT3N2 rectal cancer undergoing radiation therapy in the neoadjuvant setting. *Yellow* represents the 100% isodose line. This particular patient had an involved high retroperitoneal (RP) lymph node so a VMAT approach was chosen to allow for a boost to the RP node while respecting normal tissue tolerances. (**b**) Coronal view of the VMAT treatment plan for the patient in (**a**). (**c**) Axial view of the VMAT treatment plan for the patient in (**a**, **b**).

who received neoadjuvant treatment utilizing a VMAT approach. Figure 11.3 serves as a contouring atlas for elective CTV coverage in patients with rectal cancer based on the RTOG consensus guidelines [101]. The most commonly administered neoadjuvant dose is 45 Gy in 25 fractions, with an additional 5.4–9 Gy boost to the tumor bed via opposed lateral fields. To minimize the risk of acute and late toxicity, small bowel should be excluded from the field at doses above 50 Gy.

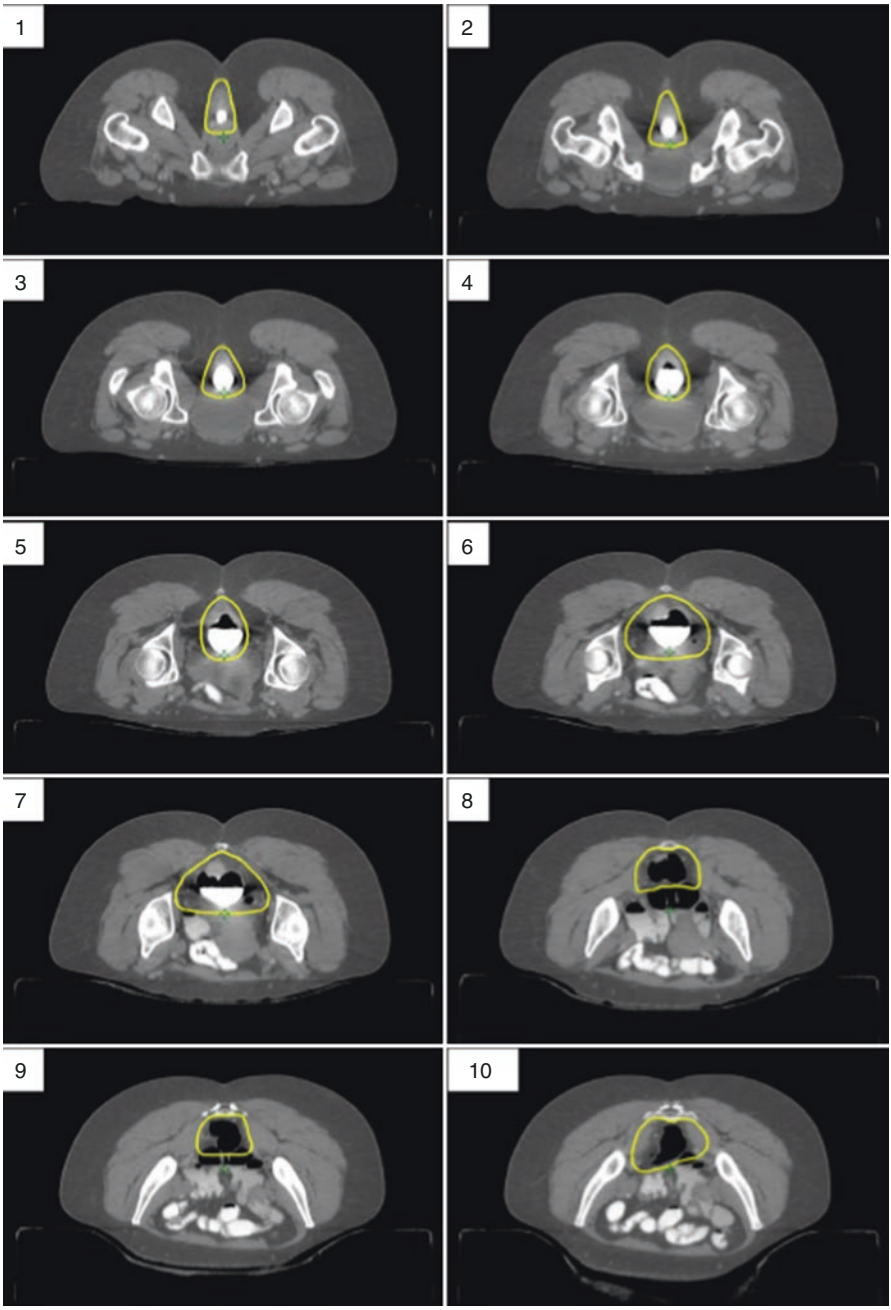


Fig. 11.3 Contouring atlas depicting the typical elective nodal coverage in patients with rectal cancer, including perirectal, presacral, and internal iliac coverage (based upon the RTOG consensus guidelines)

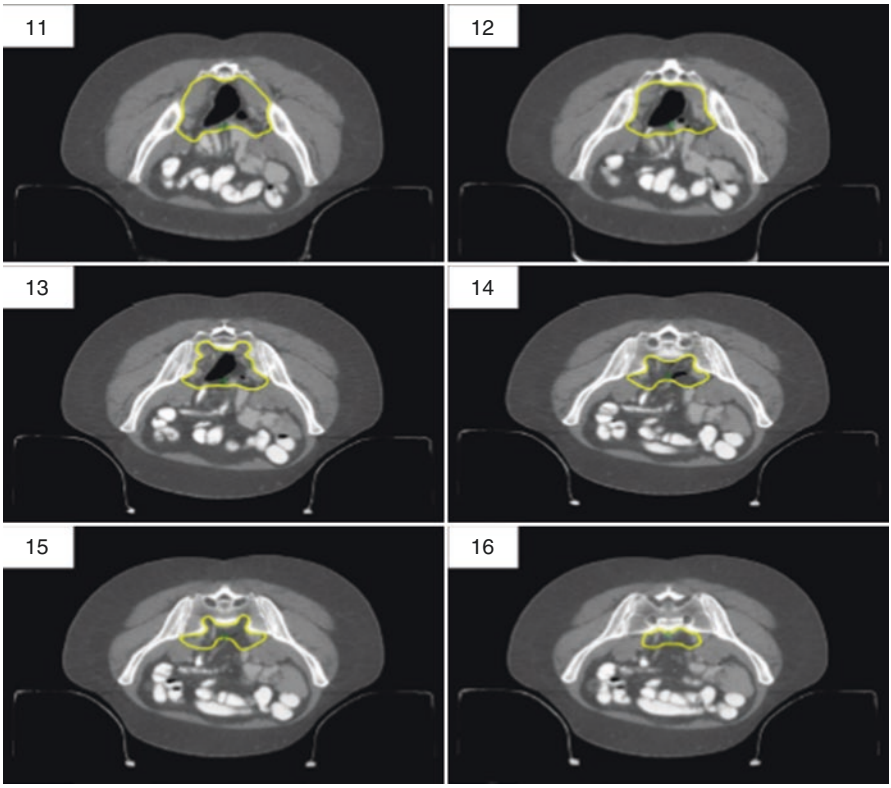


Fig. 11.3 (continued)

11.3.3 Adjuvant Treatment Planning

As noted above, fusion of preoperative staging studies, particularly PET scans, can be helpful in delineating target volumes by localizing areas that were high-risk prior to surgery. GTV in this setting represents any areas of residual disease or those with positive surgical margins, but this may be difficult to localize. The definitions of CTV and PTV are the same as those in the neoadjuvant setting (see above).

Utilizing a 3D-CRT approach, the distal field edge should be approximately 5 cm below the best estimate of the preoperative extent of disease. If the patient required an APR, the distal edge should be below the perineal scar. There should be an approximately 1.5 cm margin on the pelvic brim for the AP/PA fields. The lateral fields should be similar to those used in the neoadjuvant setting.

Again, if the desired normal tissue constraints cannot be met using 3D-CRT, an IMRT/VMAT technique can be considered. GTV to CTV expansion includes at least a 2 cm margin on the primary tumor and inclusion of areas at risk for regional nodal spread in the pelvis, respecting normal anatomic boundaries. Similar to the neoadjuvant setting, CTV to PTV expansion can range from 0.5 to 1 cm.

OAR and normal tissue constraints in this setting are similar to those in the neo-adjuvant setting (see Table 11.2). Figure 11.4a, b show an example of a patient who received adjuvant radiation utilizing a 3D-CRT approach. The total adjuvant dose is typically 45 Gy in 25 fractions. For patients with gross residual disease or involved margins, a boost can be given to 50.4 Gy to high-risk areas.

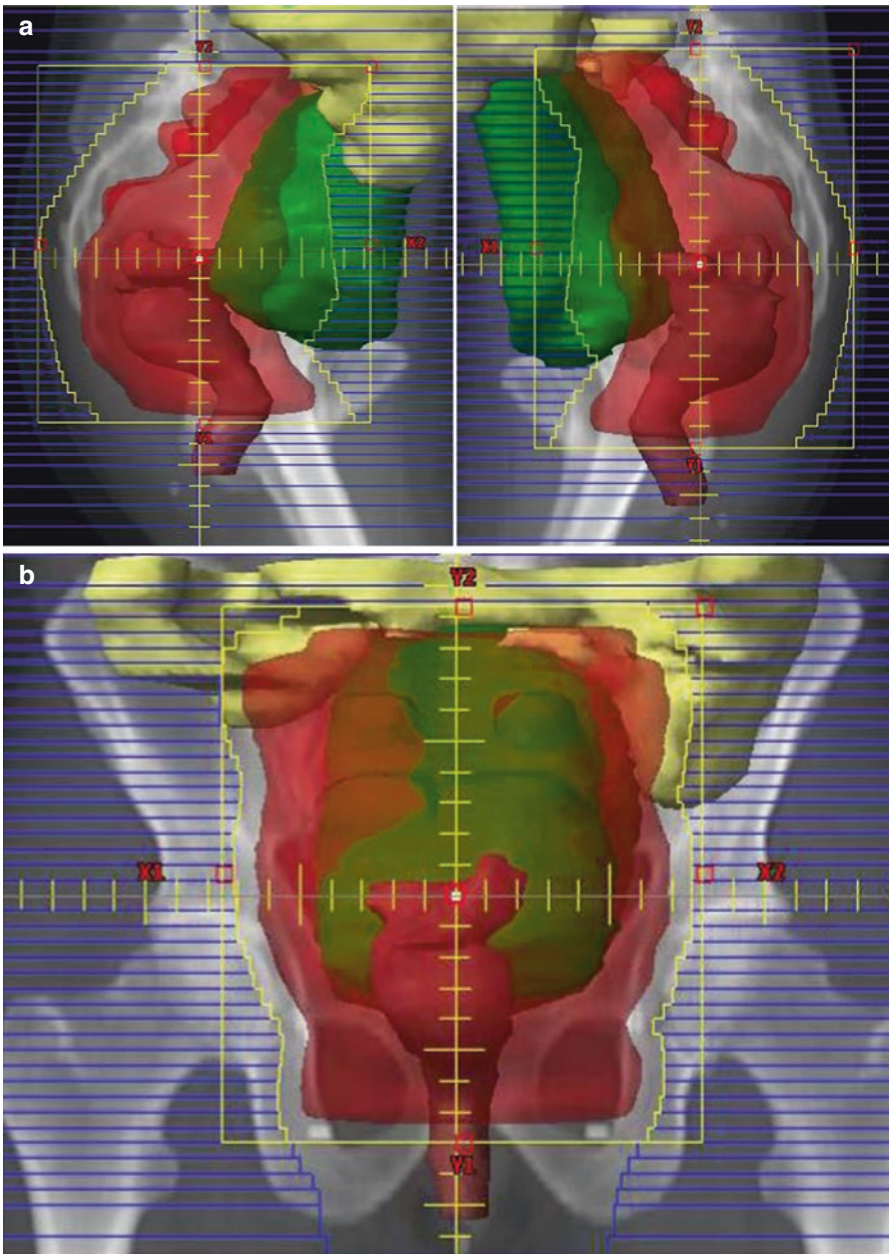


Fig. 11.4 (**a**) Lateral treatment fields for a 52-year-old patient undergoing treatment for rectal cancer with nodal involvement in the adjuvant setting using a 3-field, 3D-CRT approach. *Yellow*: small bowel. *Brown*: rectum. *Red*: PTV. *Green*: bladder. (**b**) PA treatment field for the same patient shown in (**a**)

11.3.4 Intraoperative Radiation and Brachytherapy Treatment Planning

Both of these technologies require adequate institutional and physics support. For IORT, a specially equipped operating room is required, which includes an afterloader and shielded treatment room or linear accelerator. A multi-channel applicator is necessary for brachytherapy. Both technologies require significant pretreatment planning. IORT should be an iterative process between the surgeon and the radiation oncologist to determine appropriate areas for treatment based on preoperative imaging, findings at the time of surgery, and frozen pathologic confirmation. Doses for IORT typically range from 10 to 20 Gy, depending on the extent of residual disease. The dose of brachytherapy depends on whether or not it is combined with EBRT, ranging from approximately 5–25 Gy.

11.3.5 On-Treatment Verification Imaging

Verification imaging is critical to monitor appropriate delivery of each patient's radiation therapy. For patients who undergo 3D-CRT, a typical approach would include a cone beam CT (CBCT) on day 1 and twice weekly kV On Board Imaging (OBI). For added soft tissue verification, weekly CBCTs can also be considered. If frequent shifts of at least 1 cm are required, the patient should be transitioned to daily imaging. In addition to anatomical landmarks, for patients who are being treated in the adjuvant setting, surgical clips can be used as additional information to ensure appropriate alignment. For IMRT/VMAT plans, kV OBI should be completed daily and CBCT scans should be obtained on day 1 and weekly thereafter. Finally, for patients undergoing palliative treatment, kV OBI performed weekly is generally considered sufficient.

11.3.6 Dosimetry and Physics Considerations

Quality assurance is highly dependent upon institutional support from dosimetry and physics, particularly when patients are treated with an IMRT/VMAT plan. Specialized physics support is also necessary in the case of IORT and brachytherapy. Care should be taken to prevent hot spots in the bowel in order to minimize the risk of short- and long-term side effects.

11.3.7 Acute Side Effects and Their Management

Side effects from treatment can typically be managed with a combination of best supportive care and prescription medications. The most bothersome symptoms for patients undergoing radiation for rectal cancer include weight loss, dehydration, enteritis, fatigue, skin reaction, and cystitis/dysuria.

Fatigue occurs frequently in patients being treated with radiation for rectal cancer, as it does in many disease sites. Adhering to a regular sleep routine, abiding by good sleep hygiene practices, and avoiding long naps during the day can be helpful. Some evidence also suggests that moderate aerobic exercise can help to reduce fatigue during cancer treatment [102].

Nausea and vomiting can typically be controlled with a combination of prescription anti-emetics including ondansetron, prochlorperazine, promethazine, and dexamethasone. These can be taken as needed or scheduled if necessary. Diarrhea is often the most bothersome symptom for patients and can lead to weight loss and dehydration. For patients with loose stools, soluble fiber supplements can sometimes help to bulk up the stool itself. For those patients struggling with diarrhea, loperamide may be helpful. Patients with inadequate or no response to these interventions may require a prescription for atropine/diphenoxylate. Simethicone can help to alleviate gas pains. Stool testing for *C. difficile* should be considered for persistent diarrhea based on clinical suspicion, duration, and severity of symptoms.

Cystitis/dysuria can occur given the proximity of the treatment fields to the bladder and urethra. UTI should first be ruled out. If there is no evidence of infection, symptoms can be treated by drinking more fluids, anti-inflammatories, or with a trial of phenazopyridine.

For patients who experience a skin reaction, a moisturizing cream can be applied to the affected areas. If the skin is pruritic, a topical steroid cream can be used as needed. If the pruritus is from the anal canal, steroid-based suppositories may be helpful. If the patient is experiencing a burning sensation of the skin, topical lidocaine as needed often provides relief.

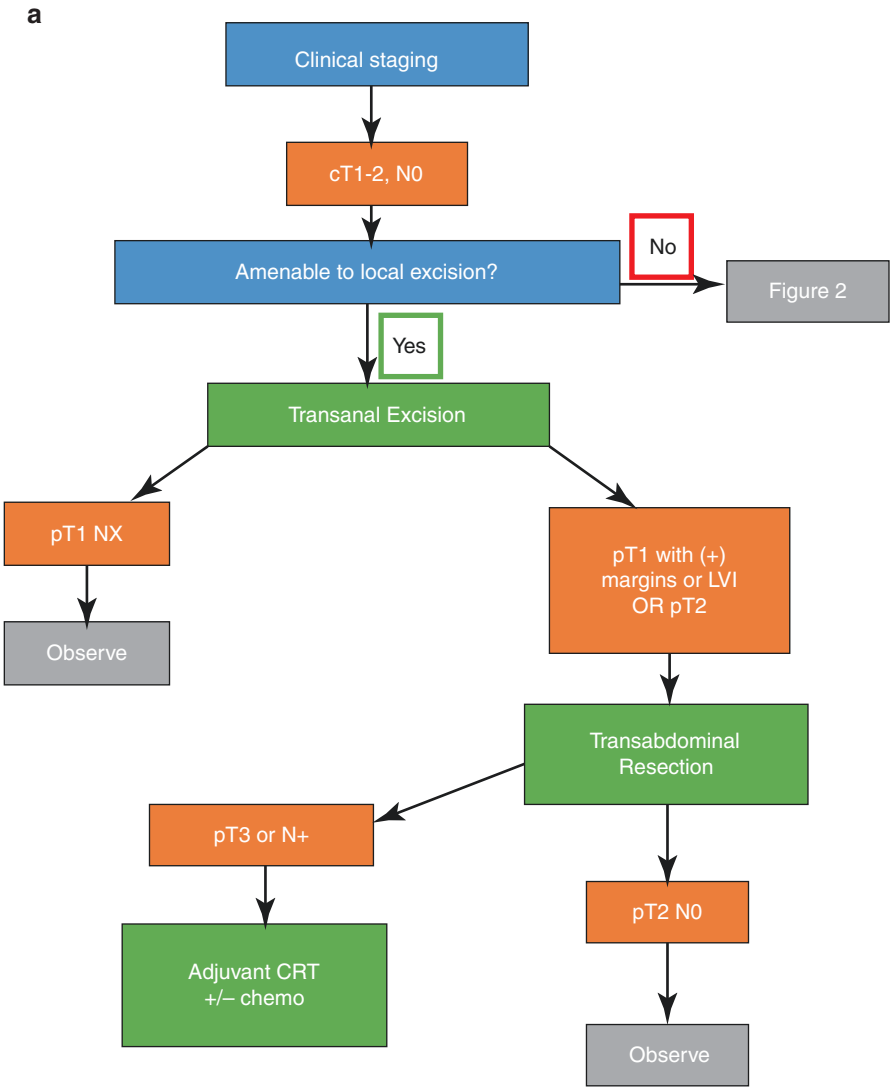
Patients should be weighed at least weekly during treatment, more often if they experience weight loss. Support from a clinical nutritionist can be very helpful. Patients with dehydration or significant diarrhea should be encouraged to increase their fluid intake and supported with intravenous fluids when necessary. Nutritional supplement shakes available over the counter can help to combat ongoing weight loss and protein calorie malnutrition. Enteral nutrition support can be considered in extreme cases.

11.3.8 Late Toxicities

One of the most common late toxicities following radiation and/or surgery in the management of rectal cancer includes the formation of bowel stenosis or intra-abdominal adhesions leading to bowel obstruction. This is most often managed conservatively. Patients can also have chronic bowel dysfunction if they undergo sphincter-sparing surgery including chronic diarrhea, constipation, GI bleeding, bowel urgency, fistula, and stool incontinence [49, 103]. Given the proximity to normal structures, patients can also experience reproductive, sexual [103–105], and urinary dysfunction [103, 106]. As with other disease sites, there is a risk of radiation-induced malignancy. Lastly, pelvic insufficiency fractures [107] and avascular necrosis [108] can occur in a small number of patients undergoing pelvic radiation. Persistent symptoms have been shown to negatively impact quality of life [109–111].

11.4 Summary

CRC remains one of the most commonly diagnosed cancers and one of the most common causes of cancer-related mortality in both men and women in the United States. Although surgery remains the gold standard for curative treatment of rectal cancer, the majority of patients will undergo neoadjuvant CRT as part of the management for their disease. Ongoing investigation is aimed at determining if neoadjuvant radiation can be omitted in carefully selected patients in order to minimize the risk of toxicity. Figure 11.5a–d summarize typical treatment approaches for patients with rectal cancer based on initial clinical staging. Radiation in patients with rectal cancer is reasonably tolerated, but often requires appropriate supportive care. Chronic side effects of treatment can negatively impact patient quality of life.



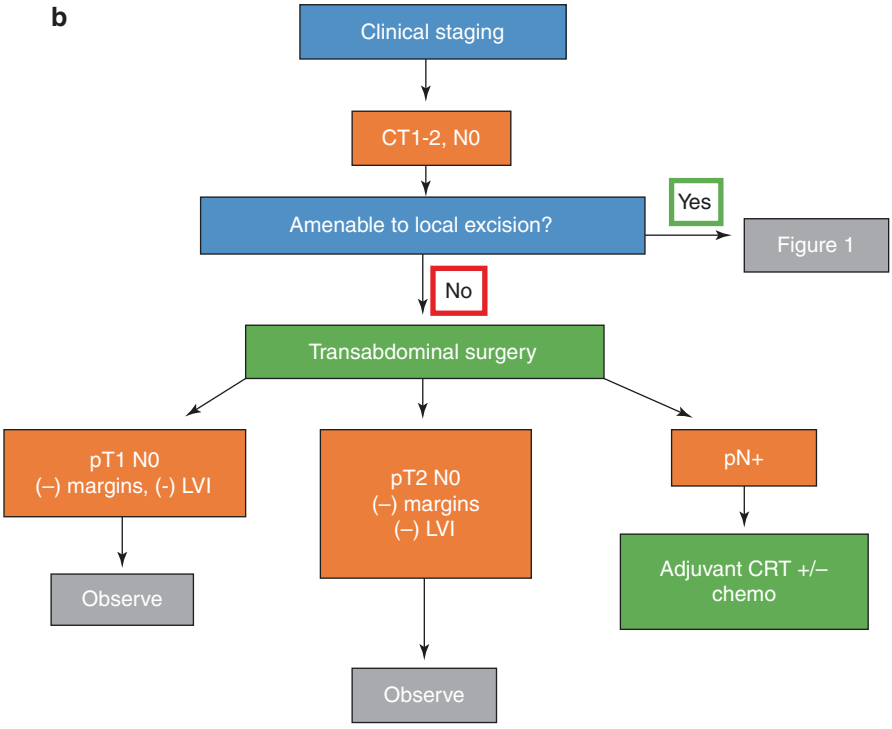


Fig. 11.5 (continued)

Fig. 11.5 (**a**) Basic treatment algorithm for early-stage rectal cancers (cT1-2 N0) in patients who are amenable to local excision. Clinical staging typically involves CT, MRI, and/or EUS. *CRT* chemoradiation, *LVI* lymphovascular invasion. (**b**) Basic treatment algorithm for patients with early-stage rectal cancer (cT1-2 N0) who are not candidates for local excision. Clinical staging typically involves CT, MRI, and/or EUS. *CRT* chemoradiation, *LVI* lymphovascular invasion. (**c**) Treatment algorithm for patients with cT2N0 rectal cancer, including management of patients who are pathologically upstaged to T3 disease at the time of resection. Clinical staging typically involves CT, MRI, and/or EUS. *CRT* chemoradiation, *LVI* lymphovascular invasion. *Neoadjuvant chemoradiation (CRT) or short-course RT can be considered in patients who are borderline for sphincter preservation, although this is somewhat controversial. (**d**) Basic treatment algorithm for patients with locally advanced rectal cancer, including cT4N2 disease. Clinical staging typically involves CT, MRI, and/or EUS. *CRT* chemoradiation

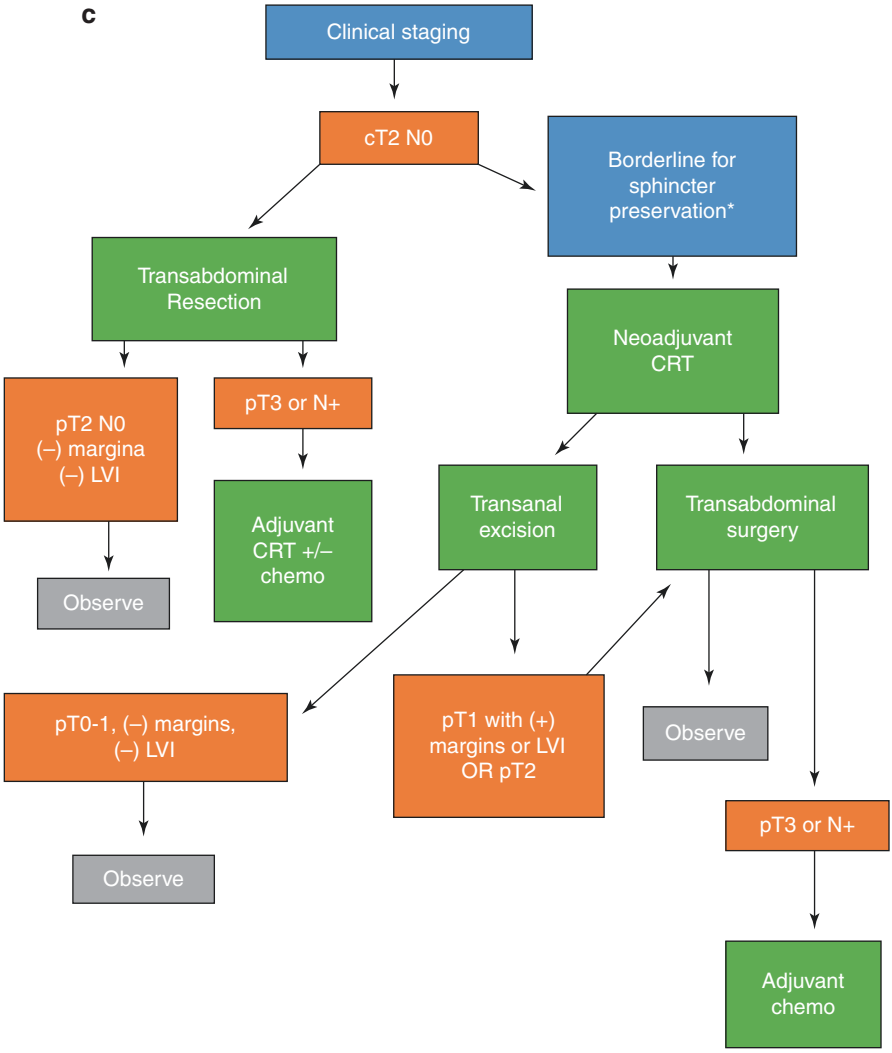


Fig. 11.5 (continued)

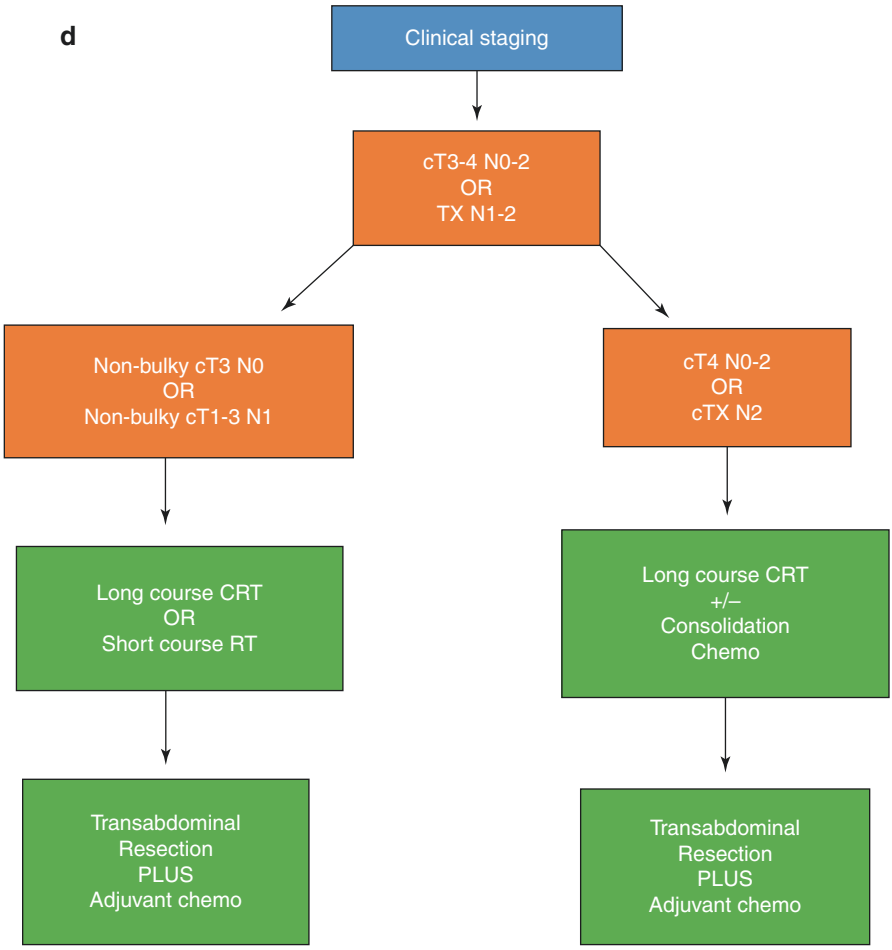


Fig. 11.5 (continued)

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Colorectal Cancer Liver Metastases

12

Jeffrey Meyer

Contents

12.1 Introduction

Management of patients with metastatic colorectal cancer, in particular those with liver metastases, involves the convergence of multiple medical specialties and treatment approaches. Both systemic and local-regional (liver-directed) therapies should be considered for each patient. In a broader context, treatment of patients with

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colorectal liver metastases has been an exemplary platform for multi-disciplinary care, discussions about the putative oligometastatic disease state, and the use of local-regional treatments for the potentially curative treatment of patients with metastatic disease.

12.2 Surgery

The liver is a common site for the development of metastatic lesions in patients with hematogenously spreading colon and rectal cancer. Approximately, 30–50% of patients with colon and rectal cancer will develop liver metastases, either in the synchronous or metachronous setting [1, 2]. Classical autopsy data indicate that the liver may be the only site harboring evident metastatic disease in a reasonable proportion of patients [1]. Thus, eradication of these metastases can be considered potentially curative [2, 3].

Surgery has been the primary local therapy for colorectal cancer liver metastases (CRLM) for decades. Despite lack of high-level evidence in the form of randomized trials, resection of CRLM in selected patients is a largely accepted clinical practice. Part of this acceptance comes from publication of long-term follow-up from institutional series, which indicate the potential for long-term survival in selected patients. Fong and colleagues reported on survival outcomes for 1001 patients with CRLM who underwent resection [4]. For all patients, actuarial survival at 5 years was 37%. A number of variables were independently associated with survival, including the number of liver metastases, the presence of extrahepatic disease, and disease-free interval (from the time of the primary tumor to the development of metastatic disease). In a review of 1600 patients treated at Memorial Sloan-Kettering Cancer Center, 5-year *recurrence-free* survival ranged from 27 to 33% depending on the era of treatment [5]. Across large resection series, 5-year survival has been on the order of 35–58% [reviewed in [2]].

Surgery can take the form of anatomic resections, with removal of defined segments of the liver, or non-anatomic procedures such as wedge resections. Surgery affords the opportunity to both directly examine the liver and use intraoperative ultrasound for the detection of small lesions which may have been unappreciated on preoperative cross-sectional imaging [6].

Proponents of surgery argue that the reported clinical results are superior to what would be obtained with no treatment or systemic therapy alone. However, it is the issue of selection bias that is the foundation for much of the residual controversy over the use of surgery (and, by extension, any local therapy) for patients with CRLM [7].

Patient selection factors for surgery have changed over time, with the focus shifting away from the extent of tumor removed and toward the extent of normal liver left behind following the surgery [8]. This is the subtle but important principle of the organ's "critical volume," which is also a useful consideration in other, non-surgical, local treatments for liver tumors, including radiation therapy [9, 10]. In the context of surgery and ablative therapies, the critical volume is the minimum volume of

liver parenchyma and biliary and vascular supply that can meet the patient's physiologic and metabolic demands. A future liver remnant (FLR) volume of 20% is considered sufficient in otherwise healthy livers, and higher percentage volumes are required in the setting of prior extended exposure to chemotherapy or with underlying liver disease such as cirrhosis [reviewed in [2]]. Redundancy of function in the organ is the basis of this principle. In the terminology of classical radiobiology, the liver harbors a substantial reservoir of subunits, in anatomical-functional parallel arrangement [9]. Elimination of these subunits by surgery or ablative treatments does not necessarily render the organ as a whole non-functional, so long as a critical amount of subunits remain in the postsurgical FLR. In patients for whom the predicted FLR following surgery is insufficient, portal vein embolization (PVE) can be considered. With this procedure, the left or right branch of the portal vein is embolized, leading to atrophy of the treated hemi-liver and hypertrophy of the contralateral hemi-liver [reviewed in [2]]. This hypertrophy may increase the FLR volume (in the range of 10%) to an adequate level to allow for extended liver resections for patients with large and/or multi-focal tumors [[11], and reviewed in [2]]. PVE can also be combined with a two-stage resection approach [12]. This is performed when there is concern about rapid growth of disease within the FLR. Metastases in the FLR are resected or ablated first, followed by PVE to the contralateral hemi-liver, followed by the planned extended resection.

The main limitations of surgery include the need for the patient to be medically operable, i.e., able to tolerate a major operation, taking into account comorbidities including baseline underlying liver disease; the need to leave a critical volume of liver/sufficient FLR, again taking into account the functionality of the remnant organ; as well as anatomical considerations, such as location of the tumor with respect to critical structures such as inferior vena cava, which may increase the risk of a margin-positive resection [13].

Some patients will present with synchronous tumors—an intact primary colon or rectal cancer and liver metastasis/es. This situation raises a host of questions relating to sequencing of surgery for the primary tumor and the liver metastases, the role and timing of systemic therapies, and in the case of rectal cancer, the role and timing of radiation therapy. There is no clear consensus as to the appropriate sequencing of therapies [14]. However, there is general agreement that all sites of gross disease must ultimately be addressed with local therapies if the intent of the treatment course is for cure.

12.3 Embolization and Thermal Ablation

A wide variety of non-surgical liver-directed treatments exist for the treatment of CRLM and other liver tumors. These include arterial embolization therapies, thermal ablation treatments, and radiation therapy. The use of embolization is predicated on the dual blood supply to the liver—the normal liver parenchyma is primarily perfused by the portal vein and its branches, whereas tumors in the liver are exclusively or almost exclusively supplied by branches of the hepatic artery [15].

Embolization with particles occludes blood supply to liver tumors and can be combined with chemotherapeutic agents (chemoembolization), including drug-eluting beads, or radiation, such as yttrium-90 radionuclides associated with glass spheres or resins [16, 17]. Thermal ablation treatments typically take the form of percutaneous probe-based treatments, including radiofrequency and microwave ablation (RFA/MWA) (extreme heat) and cryoablation (extreme cold) [Reviewed in [18]]. These treatments can also be used during open or laparoscopic liver resections as well, potentially as part of a combination approach with resection. Radiofrequency ablation results for patients with colorectal liver metastases are available and show results which rival those of surgical series in highly selected cohorts of patients. Oshowo and colleagues compared the results of surgery and RFA for the management of solitary CRLM [19]. Survival at 3 years was over 50% and nearly identical in the two groups. RFA or MWA are not widely accepted, however, as alternatives to resection in CRLM patients who are medically operable. This is due to a number of reasons, including fundamental limitations of thermal ablation (discussed below) and lack of randomized comparison [20].

The main limiting factors for the success of thermal ablation include tumor size; technical approach, with the percutaneous approach potentially leading to inferior outcomes relative to intraoperative use; and abutment of high-caliber vessels which may lead to inadequate heating by a cooling/heat-sink effect (more problematic for RFA relative to MWA) [21–23].

12.4 Radiation Therapy

The routine consideration of radiation therapy for the management of CRLM and other liver tumors is a relatively recent development in clinical oncology. Historically, there has been concern for the induction of (classical) radiation-induced liver disease (RILD), a potentially fatal syndrome classically seen in patients who have undergone irradiation of the whole liver or a large volume of it [24, 25]. The dose associated with development of RILD (around 30 Gy delivered with a conventionally fractionated treatment course) is well below that needed for eradication of CRLM. In modern times, risk of RILD is of particular concern for patients receiving radiation therapy for colorectal liver metastases as most of these patients have been heavily treated with multiple chemotherapy regimens, which has been associated with chemotherapy-associated steatohepatitis (CASH). However, a number of developments have changed the perception of liver irradiation in recent years. These include (1) an appreciation of volume effects in the liver, predicated on its generally parallel anatomical-functional arrangement and exemplified in the promising results of three-dimensional conformal partial liver irradiation, and (2) continued improvements in technology and treatment planning, which have allowed for substantial dose escalation to liver tumors while limiting irradiation of non-targeted liver tissue. Details of these technological improvements and practical means of implementing them in the treatment of CRLMs are discussed later in this chapter.

Pioneering work from investigators at the University of Michigan demonstrated the ability to escalate dose to focal intrahepatic tumors, while keeping the risk of classical

RILD and non-classical RILD low [26]. These studies made use of three dimensional conformal radiation treatment planning. Subsequently, in the 1990s and 2000s the field of extracranial radiosurgery evolved [27]. This approach took inspiration from stereotactic intracranial radiosurgery. Safely delivering radiosurgery requires extreme treatment precision and accuracy and a steep gradient of dose outside of the targeted lesion. The latter is achieved through the use of radiation delivered by a multitude of beam directions, including non-axial and non-coplanar arrangements.

Herfarth and colleagues reported on a phase I study of single-fraction liver irradiation, making use of a stereotactic body frame, for patients with liver tumors [28]. Other phase I studies of single-fraction treatments have also been reported [29, 30]. Rusthoven and colleagues conducted a phase II study of 3-fraction liver SBRT, with excellent local control results through 18 months median follow-up [31]. Other phase II and institutional studies, including studies specifically evaluating the treatment of CRLMs, also have demonstrated promising local control results in selected patients [32–34]. Recently, using a prescription dose of 25 Gy × 3 fractions, Scorsetti et al. demonstrated a 91% local control rate at 2 years for colorectal liver metastases [34].

Given the challenges associated with delivering tumoricidal radiation doses in the setting of the radiosensitive liver, there is interest in alternatives to external photon beam irradiation. These include the use of particle therapies such as proton and carbon ion beams; interstitial brachytherapy; and radioembolization. Ion beam therapy carries the physical advantage of the Bragg peak, with overall reduced energy deposition in organs at risk relative to photon irradiation. Carbon ion beams also have potential biological advantages relative to protons and photons [35]. Facility costs have limited the number of particle facilities available, but the number of centers is increasing. High dose-rate (HDR) interstitial brachytherapy is not widely used, but has an advantage relating to its steep dose gradients [36].

Radioembolization, also known as selective internal radiation therapy, involves the intra-arterial delivery of radionuclides (yttrium-90) bound to glass or resin spheres. The main promise of radioembolization is concentrated delivery of yttrium-90, which undergoes β decay with limited path length, to tumors by virtue of the blood supply [37]. Large volume or more focal radioembolization (radiation segmentectomy) treatments can be delivered [38]. The SIRFLOX trial randomized patients with liver-only or predominant metastatic colorectal cancer to treatment with systemic therapy or systemic therapy and radioembolization [39]. The primary endpoint of the trial was progression-free survival (at any site, including the liver). The difference between the two groups was not statistically significant. However, time to progression in the liver was substantially prolonged in the patients treated with radioembolization.

12.5 Systemic Therapy

Systemic therapies for the treatment of metastatic colorectal cancer have undergone substantial evolution in recent years. Treatment with 5-Fluorouracil remains a key component of systemic regimens, but a number of additional agents have been introduced and found effective in combination regimens, including classical cytotoxic drugs such as oxaliplatin and irinotecan [reviewed in [40]]. Drug agents which

target vascular endothelial growth factor (VEGF) and other components of angiogenesis as well as the epidermal growth factor receptor (EGFR) have also found utility in the treatment of metastatic colorectal cancer [reviewed in [41]]. More recently, immunomodulating drugs have been under study, with evidence of efficacy in selected patients [42].

Chemotherapy can be delivered by the conventional intravenous route or by hepatic arterial infusion (HAI) [reviewed in [43]]. The latter approach seeks to take advantage of the arterial-based perfusion of liver metastases as well as pharmacologic benefits of high liver extraction of certain chemotherapy drugs. Although generally associated with high response rates, HAI carries the risk of biliary toxicity, and its value in the setting of modern systemic regimens is uncertain. Increased response rates may convert patients with initially unresectable disease to resectable status, but this is also a controversial issue.

Although widely used in the treatment of patients with metastatic colorectal cancer, the value of systemic therapy in patients with *resectable* metastatic disease is controversial [44]. Systemic therapy may have special value in the setting of CRLM where the lesions are considered borderline resectable because of volume of disease or association with critical vascular structures, in which case cytoreduction may render the metastases resectable [45, 46]. The value of systemic therapy in patients for whom radiation is planned as the primary curative-intent liver-directed treatment is also uncertain. Cytoreduction with systemic therapy may be of additive value in this situation. In the setting of very bulky liver metastases, for whom radiation therapy is planned, treatment with up-front systemic therapy may lead to substantial cytoreduction and a reduction in the target volume for the radiation course. However, systemic therapies used to treat metastatic metastatic colorectal cancer can injure the liver through a variety of mechanisms, making subsequent surgical or ablative treatments (including SBRT) more risky. Sinusoidal obstruction, the histopathological basis of liver veno-occlusive disease, is one of the risks associated with chemotherapy, in particular oxaliplatin [47]. Of note, a similar histopathological picture is the underlying basis of classical RILD [24]. Careful assessment of liver function, through laboratory studies and possibly specialized imaging, prior to planned liver-directed therapy is critical [48]. The radiation oncologist must also be aware that therapies which target angiogenesis have also been associated with significant normal tissue toxicity, in particular bowel toxicity, when delivered around the time of abdominal irradiation [reviewed in [49]]. Strict guidelines as to the sequencing of these treatments are not yet available, but potentially serious interactions between these treatments must be considered, especially when bowel is close to the liver target volume.

12.6 A Multi-Disciplinary Approach: Patient Selection

The patient with CRLM can thus be seen to have both systemic and liver-directed therapies as treatment options, the latter to include a multitude of different approaches ranging from open surgery to more minimally invasive therapies. The

judicious use of local therapies in the patient with metastatic disease is perhaps one of the most important and challenging decisions to be made during the treatment course for patients with metastatic colon or rectal cancer. This question may in fact arise several times during a given patient's course, usually in the context of ongoing effective systemic therapy.

A number of variables need to be addressed when considering liver-directed therapies for patients with CRLMs. Chief among these, and perhaps the most difficult consideration, is an assessment of the biological behavior of the tumor. Surrogates for aggressive behavior, including the presence of "widespread" extrahepatic metastases, should be considered. It is generally accepted that local therapies for liver metastases in this setting are unlikely to meaningfully impact survival metrics. Moreover, in this situation, complications from local therapies may delay the use of systemic therapies, and thus, lead to worse survival outcomes. In the future, molecular studies, such as miRNA analysis, may indicate which patients with metastatic disease truly fit into the category of "oligometastatic" cancer, and thus, would be most likely to benefit from the use of local treatments [50]. Also of note, some patients with "polymetastatic" cancer may indeed be treated with local therapies if there is the goal of synergizing with systemic therapies, such as immunomodulating systemic treatments [51]. This is an active area of clinical research interest [52].

For the reasons discussed above, surgery is usually considered the "gold standard" approach to patients who indeed have resectable liver metastases and who are otherwise considered good candidates for liver-directed treatments. Non-surgical therapies such as thermal ablation and radiation therapy may be considered in patients who are not surgical candidates because of medical comorbidities, anatomical constraints, or patient choice. To the best of the author's knowledge, there are no randomized data comparing thermal ablation with radiation therapy for the treatment of liver metastases. The RAS01 study was a randomized comparison of RFA and stereotactic body radiation therapy (SBRT) for the treatment of patients with CRLMs. However, this study closed because of inadequate accrual (information available at: https://clinicaltrials.gov/ct2/show/NCT01233544?term=RAS01&rank=1).

Tumor size and location may be of help in deciding between percutaneous thermal ablation and high-dose hypofractionated radiation therapy. Large tumor size and abutment of large-caliber blood vessels limit the efficacy of RFA. Lesions near the hilum of the liver or near the dome may be difficult to access with a percutaneous approach and/or place the patient at significant risk for biliary, bowel, or pulmonary complications from the procedure; treatment of hilar lesions may also be challenging for radiation due to the proximity of large bile ducts and bowel, which may limit the amount of radiation that can be delivered depending on the exact location. In special circumstances, "spacer" material may be placed before ablations or radiation therapy to put space between critical organs and intrahepatic targets [53, 54].

Data from the University of Michigan, in patients with hepatocellular carcinoma (HCC), showed improved freedom from local progression with the use of SBRT as opposed to RFA for larger (>2 cm) tumors [55]. The strict applicability of these data to patients with CRLM or other types of metastases, however, is of course uncertain. Stintzing and colleagues compared CyberKnife radiosurgery (27 Gy in one

fraction) with RFA for patients with CRLMs [56]. Patients were matched for clinical features. One-year local control rates were similar between the two groups (85% for radiation and 65% for RFA).

Microwave ablation and new techniques such as irreversible electroporation, which may provide greater efficacy and safety compared to RFA depending on the context, will also need to be considered in comparison with SBRT [reviewed in [57]].

Table 12.1 outlines potential treatment options for colorectal liver metastases during different clinical scenarios.

Table 12.1 Potential treatment options for colorectal liver metastases

Local treatment modality	Appropriate clinical scenario
Surgery[a]	Complete resection must be feasible based on anatomy and extent of disease, with appropriate future liver remnant taking into account the patient's baseline liver function[b] Patients presenting with synchronous disease—resectable metastatic disease and an intact primary tumor—should be planned for resection of all sites of gross disease if the treatment intent is curative When insufficient liver volume is initially present, preoperative portal vein embolization with or without staged liver resection can be considered to increase the future liver remnant size Re-resection can be considered in selected patients in the setting of otherwise controlled systemic disease and adequate hepatic function
Ablation[a]	Ablative therapies, including RFA, microwave ablation, and cryoablation, are reasonable treatment options for non-surgical patients. These techniques may be limited by anatomical considerations such as proximity to vasculature and baseline hepatic function
Hepatic arterial infusion (HAI)	Placement of a hepatic arterial port or implantable pump during surgery with chemotherapy infusion directed to arterially perfused liver metastases may be considered as a regional treatment option in the setting of unresectable liver metastases; this approach may also convert unresectable disease to resectable status. Biliary toxicity is a concern. HAI should only be considered selectively at institutions with extensive medical and surgical oncology experience with this procedure
Arterial-directed embolic therapy (TACE)	Trans-arterial embolization of liver metastases, with local delivery of chemotherapy as part of the procedure, often with the use of drug-eluting beads, alone or in combination with systemic therapy, may be an option in selected patients
Radioembolization	Arterially directed catheter therapy using yttrium 90 microspheres, selective internal radiation is an option in selected patients with predominant liver metastases. Unlike other ablative techniques, there is less limitation due to anatomical considerations and extent of disease, but hepatic function should be considered
3D CRT/IMRT/ SBRT radiotherapy	Highly conformal external beam radiation therapy may be considered in selected cases. As with ablation therapies, radiotherapy is not used in place of surgery in medically and antomically operable patients

[a]Ablative techniques may be considered alone in conjunction with resection as long as all original sites of disease are amenable to resection or ablation

[b]When considering local therapies for colorectal liver metastases, primary tumor should ideally have undergone R0 resection (plan for debulking < R0 resection not recommended) and there should be no evidence of uncontrolled extrahepatic disease

12.7 Radiation Therapy: Clinical and Planning Considerations

Once the key issue of patient selection has been addressed in multi-disciplinary discussion and a plan to move forward with radiation therapy is made, the radiation oncologist must consider multiple treatment planning problems. In this section, we consider these issues individually and present solutions when indicated. (Note that the issue of fiducial placement, which must precede simulation, is discussed in Sect. 12.7.7).

The reader is also referred to the AAPM Task Group 101 report on recommendations for SBRT planning [58].

12.7.1 Motion Management

Situated under the diaphragm, the liver is often highly mobile throughout the respiratory cycle. The internal target volume (ITV) is the envelope of space which encompasses the motion of the gross tumor volume (GTV). Treating GTVs which are very mobile, and thus have large ITVs, results in exposure of a higher volume of normal tissue to radiation.

A number of strategies are in common clinical use to mitigate this problem. These include: (1) Respiratory gating, in which the target is irradiated only during a certain portion of the respiratory cycle, often around end-expiration because of the relative stability of the target volume during this time period, with, in essence, a truncated ITV (relative to the non-gated, free-breathing situation); (2) Treatment in breath-hold, which can be considered an extreme form of gating, as the target is (nearly) motionless near end-inspiration or end-expiration; (3) Abdominal compression, which uses a physical device to limit diaphragmatic motion and thus limit liver excursion; and (4) Tracking, such as used with the CyberKnife Synchrony (Accuray, Sunnvale, CA) system, which uses external surrogates to follow internal tumor motion [59–62]. All of these approaches have value and their specific use depends on physician and institutional preference as well as patient tolerance.

At the author's institution, abdominal compression and breath-hold techniques are used for patients with mobile liver metastases.

Abdominal compression as practiced at our institution involves the use of a plastic plate placed inferior to the xyphoid and ribs [63]. A compression screw is used to apply pressure to the plate. Fluroscopy is used to determine the decrement in upper abdomen/diaphragm motion, and pressure gradually and iteratively applied to limit motion to <1 cm, and preferably <5 mm. Coaching of the patient throughout the process is critical to ensure a stable breathing pattern.

For the breath-hold simulations and treatments at our institution, the Active Breathing Coordinator (ABC) (Elekta, Stockholm) is used. With this device, the patient's respiratory cycle is monitored. At a selected threshold, inflow of air is sealed and the breath-hold begins. The device works as a spirometer, with the

threshold set as a volume of gas that is inhaled beyond the patient's functional residual capacity. Patient should be coached to adopt a steady breathing rhythm [64]. The treating physician should be aware of intra-fractional differences in tumor position that may occur during the treatment process with each repeated breath-hold [65, 66]. These differences can be assessed at the time of simulation by performing multiple CT scans in breath-hold or by imaging with fluoroscopy and measuring differences in position of a surrogate structure (such as the diaphragm) relative to some fixed anatomy (such as the spine). These intra-fractional positional differences need to be considered in the design of the planning target volume (PTV).

12.7.2 Simulation: Immobilization

Strict but tolerable immobilization is essential to limit unexpected patient and tumor motion during the radiation treatment delivery. A variety of means of achieving this goal are widely used in radiation oncology clinics. At the author's institution, we use a stereotactic body frame (Elekta, Stockholm) with a custom-fit vacuum pillow placed inside the body frame. This approach has proved very useful, with results from a report by Foster et al. showing minimal intra-fractional motion for multiple treatment sites [63, 67].

12.7.3 Simulation: Use of Contrast for Target Delineation

Identification of the tumor targets within the liver is one of the most critical, and challenging, parts of the treatment preparation process. As previously discussed, the liver receives dual blood supply, from the hepatic artery and the portal vein, with arterial supply the main source of perfusion to liver tumors [15]. Moreover, colorectal liver metastases tend to be poorly vascularized tumors [68]. Thus, they are often best appreciated during the portal venous phase of a CT scan with contrast. In this phase, the metastatic lesion will appear hypodense relative to the enhancing normal liver tissue. It is often helpful to evaluate available diagnostic CT studies prior to CT simulation to determine which phase(s) will be most helpful to obtain during the simulation.

Once the phases of interest are identified, the timing of imaging relative to the start of the contrast injection needs to be established. Bolus tracking is one feature which may allow for good timing of the arterial phase. If bolus tracking is not available, the scans need to be timed properly to achieve the desired phase. Also of importance are the type of contrast (specifically, the concentration of iodine) and the rate of contrast injection.

At the author's institution, the following scan parameters are used. Isovue (iopamidol) 300 or Isovue 370 iodinated contrast is used and injected at a rate of 3–4 mL/s. For this dose rate, a 20 gauge IV catheter is used. For smaller-bore catheters, an infusion rate of 2 mL/s is used. For late arterial-phase imaging, the scan is timed so that the liver is imaged about 40 s after the contrast infusion is started. For portal venous-phase imaging, the timing is 65 s, and for delayed-phase imaging, the timing is about 3 min. The author also typically obtains a non-contrasted study at the beginning.

12.7.4 Target and Normal Tissue Delineation

For CRLM treatment planning, usually the non-contrast and portal venous-phase scans are fused on the basis of spine matching. In the author's practice, the non-contrast scan is used for treatment planning. When the ABC system is used, the GTV is identified. Typically, no margin is added to the GTV to create a clinical target volume (CTV); hence, the CTV equals the GTV. In the setting of treatment of recurrent disease following prior liver resection, in which the recurrence is close to the original resection site, margin can be considered over concern for meaningful extension of microscopic tumor beyond the edges of what is radiographically visible.

When the abdominal compression system is used, an ITV is generated based on delineation of the GTV on the various respiratory phases (at the least, the 0 and 50 phases). For hypodense targets, the reconstructed minimum intensity projection (MinIP) set may be of use in identifying the ITV.

Expansions from the CTV/GTV and the ITV (in the case of abdominal compression) to the PTV depend on a number of factors. These include the robustness of immobilization, the use of image-guidance to make adjustments prior to treatment, and concerns about any residual motion not addressed by the ITV. Typically, in the author's practice an expansion of 0.5–1 cm is made, isotropically.

A variety of normal structures are at risk when using radiation to treat targets in the upper abdomen. Many of these structures are hollow organs which behave as serial structures, such as the intestines, stomach, and spinal cord/cauda equina, in which high doses to even low volumes may cause serious consequences. In many situations, it will be the (uninvolved) liver itself which may be dose-limiting. Various liver toxicities can be seen clinically, including RILD, characterized by ascites and anicteric liver enlargement, with a substantial increase in alkaline phosphatase levels [25]. "Nonclassic" RILD has been defined as significant increases in hepatic enzymes without features of classic RILD [25].

Also as discussed above, the liver parenchyma has parallel functional-anatomical arrangement. For such organs, high doses to limited volumes are not expected to

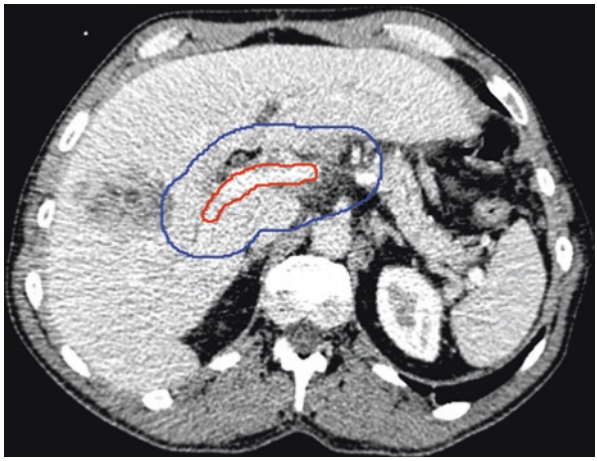

Fig. 12.1 The central liver zone (*blue contour*) has been defined as a 2 cm isotropic expansion surrounding the path of the portal vein (*red contour*) to its bifurcation point(s) within the liver. Note the hypodense liver metastasis immediately lateral to the central liver zone in this portal venous phase scan

generate clinically relevant toxicity. It should be noted, however, that near the hilum of the liver, with the coalescing biliary system as well as the portal vein and hepatic artery, the liver should be considered to have more of a serial structure. Damage to these structures can have substantial consequences to the remaining liver parenchyma. Such a transition is similar to the central lung structures. Distinct biliary toxicity has been reported in cases of central liver SBRT [69]. At our institution, we used a "central liver zone" in a phase I dose-escalation study to exclude patients from getting very high single-fraction doses of radiation [30]. This zone was defined as the course of the portal vein to its bifurcation within the liver, expanded by 2 cm, analogous to the central lung zone considered in lung SBRT [70]. Of note, Eriguchi and colleagues used a similar approach to define the central liver and found that a prescription dose of 40 Gy in five fractions was tolerable with respect to biliary complications [71]. An example of central liver zone target volume is represented in Fig. 12.1.

Suggested liver constraints are shown in Table 12.2. The radiation oncologist should assess baseline liver function by evaluation of the liver's synthetic function (albumin and coagulation study results) as well as the bilirubin and hepatic enzyme levels. The liver constraints shown in the table refer to patients without significant underlying liver disease. More conservative measures must be considered in the setting of cirrhosis or other liver disease [72]. It should be emphasized that this Table is simply a guide with general recommendations and that many of the constraints are not rooted in a large body of supportive clinical data. Please refer to the table and its legend for more details. Future clinical results should help refine these constraints.

Table 12.2 Normal tissue constraints for liver SBRT[a]

	1 Fraction	3 Fractions	5 Fractions	Other references
Liver[b]	700 cc gets <9.1 Gy	700 cc gets <15.1 Gy	700 cc gets <21.5 Gy	
Stomach[a]	Maximum point: 12 Gy	Maximum point: 24 Gy	Maximum point: 30 Gy	
Small intestine and colon[a]	Maximum point: 12 Gy	Maximum point: 24 Gy	Maximum point: 30 Gy	[73, 74]
Spinal cord	Maximum point: 14 Gy <0.35 cc gets >10 Gy	Maximum point: 22.5 Gy <0.35 cc gets >15.9 Gy	Maximum point: 28 Gy <0.35 cc gets >22 Gy	
Skin	Maximum point: 27.5 Gy <10 cc gets >25.5 Gy	Maximum point: 33 Gy <10 cc gets >31 Gy	Maximum point: 38.5 Gy <10 cc gets >36.5 Gy	
Esophagus	Maximum point: 16 Gy <5 cc gets >11.9 Gy	Maximum point: 27 Gy <5 cc gets >17.7 Gy	Maximum point: 52.5Gy <5 cc gets >27.5 Gy	Adapted from RTOG 06-31
Heart	Maximum point: 22 Gy <15 cc gets >16 Gy	Maximum point: 30 Gy	Maximum point: 52.5Gy <15 cc gets >32 Gy	Adapted from RTOG 06-31

[a]These are institutional (University of Texas Southwestern Medical Center) constraints, authored by Robert Timmerman, MD. The stomach and duodenum constraints are those used specifically by the author of this chapter (J. M.) "Point" volumes are defined as 0.035 cc or less. The "Other References" column gives references to various published literature which analyze clinical data regarding dose constraints. The issue of dose constraints for bile ducts is discussed in the text

[b]For the liver, the greater of 700 cc **or** 1/3 of the organ's volume (preceding resection or other means of liver volume reduction) is chosen as the constraint. As an example, if the patient's liver is 2400 cc, then the volume constraint is 800 cc (= 1/3 of 2400 cc), **not** 700 cc. Conversely, the reader will note that the 700 cc constraint may be considered overly restrictive for patients with smaller livers (livers less than 2000 cc in volume). The radiation oncologist must consider the reason for the small liver volume—for example, if it is in the setting of cirrhosis. In that setting, maintaining a requirement for more strict liver sparing, such as 700 cc, is appropriately more conservative than allowing for 1/3 of a volume much less than 2000 cc

12.7.5 Dose Selection

As previously discussed, a number of dose-fractionation prescriptions have been studied and reported. SBRT courses are delivered in 1–5 fractions. In the author's practice, dose selection is based on the ability to meet the OAR dose constraints, taking into account underlying liver function, as well as location of the tumor within the liver (see discussion above). Common dose prescriptions are shown in Table 12.3. Typical dose requirements are the following: dose is prescribed to PTV coverage, with the D95 for the PTV set at the prescription dose; the minimum dose in the PTV should be 90% of the prescription. This latter objective allows for some degree of "underdosing" of the PTV when it expands into critical structures.

Table 12.3 Liver SBRT dose prescriptions[a]

1, 3, and 5 fraction regimens	Tumors in the central liver zone[b]	Tumors outside of the central liver zone[b]
1 Fraction	–	30 Gy × 1 fraction [29] 35 Gy × 1 fraction [30] 40 Gy × 1 fraction [30]
3 Fractions	–	18 Gy × 3 fractions = 54 Gy
5 Fractions	10 Gy × 5 fractions	12 Gy × 5 fractions [75]

[a]Common prescriptions used in the author's practice, with supporting references as noted
[b]Central liver zone is defined as the course of the portal vein to its bifurcation within the liver expanded by 2 cm

Chang and colleagues evaluated local control results from three institutions and concluded that, for a 3-fraction SBRT course, a total dose of about 48 Gy would be needed for 90% likelihood of local control at 1 year for colorectal liver metastases [76]. Interestingly, in their analysis, although dose was associated with local control outcomes, tumor (GTV) volume was not.

It should be noted that the "stereotactic approach" to treatment planning can be applied to any dose-fractionation scheme, including more modestly hypofractionated treatment approaches. The therapeutic ratio for the treatment of very bulky tumors, or tumors abutting critical structures, may benefit from more and more protracted treatment course (while still hypofractionated relative to conventional radiation therapy) as opposed to lowering the dose-per-fraction for a 5-fraction course. Dose to the areas of abutment can be limited while still delivering a high dose to the bulk of the tumor. Tao and colleagues demonstrated the advantages to this approach in a large series of patients with cholangiocarcinoma [77]. The same principle can be applied to the treatment of select CRLMs.

12.7.6 Treatment Planning

As previously discussed, treatment planning principles for extracranial SBRT are inspired by intracranial radiosurgery practice. Traditional 2-, 3-, and 4-field treatment plans are not compatible with liver SBRT. A variety of treatment approaches can achieve the goal of high focal dose with sharp gradient. A single dynamic conformal arc can provide excellent coverage and OAR sparing, especially for spherical targets (Fig. 12.2). Another approach includes multiple conformal beams, including the use of non-axial and non-coplanar beams, similar to the "beam bouquets" previously described [78, 79]. For both of these 3D approaches to treatment planning, block

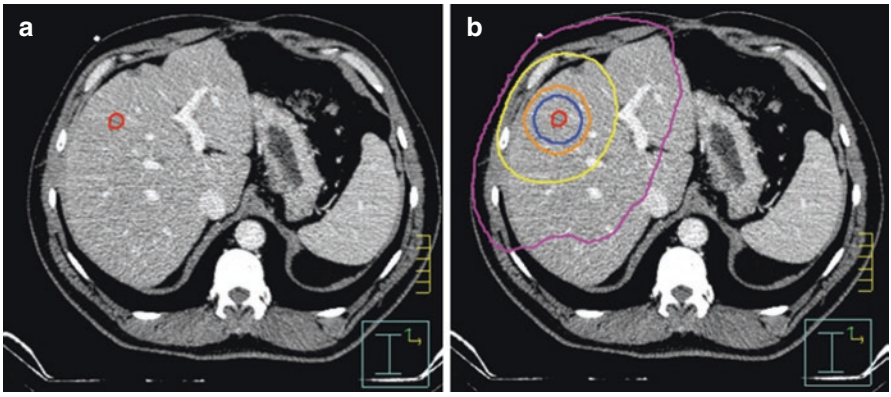

Fig. 12.2 A 50-year-old patient with known history of metastatic colon cancer presented with a growing lesion in segment V of the liver. The patient had undergone prior resection of multiple hepatic metastases. To treat the growing lesion in segment V, a course of SBRT was arranged. In (**a**), the hypodense lesion as detected on the portal venous phase of the CT simulation scans is outlined in *red* (GTV). Window/level are adjusted to maximize the conspicuity of the lesion. A portion of the stereotactic body frame is seen in this cropped image as well. In (**b**) the treatment plan with isodose line distribution is shown, planned on the preceding non-contrast scan and overlaid on this portal venous phase image. A dose of 30 Gy in one fraction was prescribed to the periphery of the PTV. A single dynamic conformal arc was used for dose delivery. *Red* interior circle is the GTV, *blue line* = 30 Gy, *orange line* = 20 Gy, *yellow line* = 10 Gy, *purple line* = 5 Gy. (Note: PTV not shown). (Treatment plan: Jonathan Dougherty, CMD)

margins around the target projection must be considered. Zero or even negative block margins, with prescription to a low isodose line, may provide the sharpest dose gradients surrounding the target, simultaneously leading to extreme hot spots within the target, replicating what is achieved with Gamma Knife radiosurgery [80]. This heterogeneity within the target may not be desirable if the target surrounds a critical structure.

Intensity modulation methods may also be of value, in particular for highly complex target shapes with concavities. Volumetric modulated arc treatments (VMAT) are another option (Fig. 12.3). When intensity modulation is used to treat a mobile target, consequences of the leaf interplay effect must be considered, especially for hypofractionated courses [81, 82]. IMRT/VMAT can be used to keep the dose within the target homogenous, if desired. Conversely, relaxing constraints on hot spots within the target can improve dose gradients outside of the tumor [83].

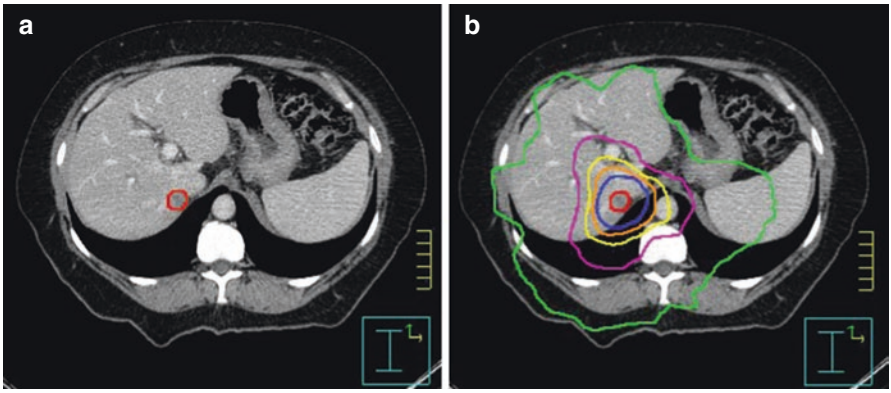

Fig. 12.3 A 52-year-old patient with known history of metastatic colon cancer presented with a lesion in segment VII of the liver, near the vena cava. The patient had undergone prior chemotherapy with reduction in size of the mass, but it persisted on imaging. In (**a**), the hypodense lesion as detected on the portal venous phase of the CT simulation scans is outlined in *red* (GTV). Window/level are adjusted to maximize the conspicuity of the lesion. A portion of the stereotactic body frame is seen in this cropped image as well. In (**b**) the treatment plan with isodose line distribution is shown, planned on the preceding non-contrast scan and overlaid on this portal venous phase image. A dose of 50 Gy in five fractions of 10 Gy per fraction was prescribed to the periphery of the PTV. This dose was based on the location of the tumor relative to the central liver zone. A volumetric modulated arc therapy plan was chosen based on the location of the tumor. *Red* interior circle is the GTV, *blue line* = 50 Gy, *orange line* = 40 Gy, *yellow line* = 30 Gy, *purple line* = 20 Gy, *green line* = 10 Gy. (Note: PTV not shown). (Treatment plan: Jonathan Dougherty, CMD)

12.7.7 Treatment Delivery

Image guidance is a critical component of SBRT delivery. At our institution, we use cone beam CT (CBCT) imaging for target localization prior to treatment. Final adjustments in patient positioning are made by couch adjustments. Other methods, such as tracking techniques used by the CyberKnife, are also available.

Intrahepatic tumors are typically not visible on CBCT imaging. Fiducial markers may play a role in helping to localize the area of interest prior to treatment. The decision to place fiducials must of course be made prior to the simulation. Without fiducial placement, the treating physician must rely on the liver, or region of target location within the liver, as a fiducial of sorts. Other anatomical structures may also provide guidance, as can clips or similar materials from prior surgeries. Although implanted fiducials have obvious advantages for localization, the risks of implanting them, including hemorrhage and fiducial migration, must be considered as well. There are little clinical data to support or refute the need for implant fiducials when treating liver tumors. Data from the University of Michigan show a potential benefit for their use in a series of patients treated for HCC, but the difference compared to patients treated without fiducials did not reach statistical significance [55].

12.8 Summary

Management of liver metastases presents a wide variety of challenges. Patient selection is the most critical and perhaps the most challenging step and demands multidisciplinary communication. For patients with CRLMs, the question of utilizing local therapies may be raised multiple times during a patient's clinical course. The application of local therapies to treat patients with metastatic disease, beyond palliation, is likely to increase as systemic therapies improve. Indeed, a number of clinical trials are evaluating this potential shift in tradition.

Radiation therapy has grown from a treatment with marginal applications for patients with liver metastases to become an important and viable alternative to surgery and non-surgical ablation options. Results with hypofractionated treatment courses have shown great promise with respect to tumor control and safety.

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Part VI

Anal Cancer

Carcinoma of the Anal Canal

13

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Contents

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13.1 Introduction

There will be an estimated 8200 cases of anal canal cancer in 2017 with an estimated 1100 deaths from the disease [1]. Although uncommon, the relative incidence of anal cancer has been increasing over the last 20 years, largely due to infection by the human papillomavirus (HPV) [2]. Historically, the treatment of squamous cell carcinoma of the anal canal has been surgery with abdominoperineal resection (APR). This produced overall survival rates of approximately 50%, but resulted in a permanent colostomy and high locoregional recurrence [3, 4]. In an effort to improve these results, Nigro and colleagues, over three decades ago, pioneered a preoperative regimen combining pelvic radiation therapy and chemotherapy with 5-fluorouracil (5-FU, 25 mg/kg continuous infusion [CI]) and mitomycin (MMC, 0.5 mg/kg bolus) [5]. Radiation was prescribed to 30 Gy in 15 fractions and calculated at the central axis mid-plane. Treatment was delivered using anterior and posterior opposed fields to the true pelvis and inguinal lymphatics. Surgery followed chemoradiation 4–6 weeks later. In a report of their first 28 patients treated with this combined modality approach, 26 patients underwent either APR or local excision following chemoradiation [6]. Eighty percent of patients were found to have pathologic complete response. In a subsequent series of 38 patients treated with chemoradiation alone as definitive therapy, an 84% clinical complete response rate was achieved [5]. Following these promising results, randomized clinical trials have sought to validate sphincter-preserving chemoradiation as the primary treatment for anal cancer.

13.1.1 Combined Modality Therapy

The Nigro regimen was empirically derived. As such, subsequent clinical trials have critically examined components of this regimen. The question of the relative benefit of chemoradiation compared to radiation alone was assessed in two separate studies: the European Organization for Research and Treatment of Cancer (EORTC) 22861 trial and the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) ACT I trial [7, 8]. In the EORTC trial, 110 patients from 1987–1994 were randomized between radiation alone or radiation with 5-FU (750 mg/m^2 CI days 1–5 and days 29–33) and MMC (15 mg/m^2 bolus on day 1). Inclusion criteria encompassed T3-T4 primary or any tumor stage with node-positive disease. Pelvic radiation was delivered using a 3 or 4 field technique to 45 Gy in 25 fractions followed by a 6-week rest period. Patients then underwent a boost of 15 Gy if achieving a complete clinical response or 20 Gy if achieving a partial response, which was delivered by electrons, photons, or iridium 192 implant. Compared to radiation alone, combined modality treatment led to an improvement in clinical complete response (80% vs. 54%), 5-year local control (68% vs. 50%, $P = 0.02$), and 5-year colostomy-free survival (72% vs. 40%, $P = 0.02$) [8]. The overall survival for the entire cohort was 56% with no difference between the two arms, likely due to patients undergoing successful salvage APR.

In a similar design, the UK ACT I trial accrued 585 patients (51% clinical T3 disease, 20% positive nodes) between 1987 and 1994 to radiation alone or radiation with 5-FU (750–1000 mg/m^2 CI days 1–5 and days 29–33) and MMC (12 mg/m^2 bolus on day 1). Radiation was prescribed to 45 Gy using anterior (AP) and posterior (PA) opposed fields followed by a 6-week rest period. Patients with less than a 50% clinical response underwent surgical resection. Patients with more than a 50% clinical response received a boost of 15–25 Gy delivered by electrons, photons, or an iridium implant [8]. Six weeks after completion of the primary radiation treatment, there were comparable rates of patients with greater than 50% response (92% in both arms). Early morbidity, including hematologic, skin, gastrointestinal, and genitourinary toxicity, was significantly worse with the addition of chemotherapy (48%) vs. radiation alone (39%), $P = 0.03$. With a median follow-up of 13 years, patients in the combined modality arm had lower rates of local failure (32% vs. 57%, $P < 0.001$) without improvements in overall survival (53% vs. 58%, $P = 0.12$). However, there was an increased rate of anal cancer-specific survival in patients receiving combined modality therapy compared to radiation alone (70% vs. 58%, $P = 0.004$). Late morbidity did not differ between concurrent therapy and radiation alone (42% vs. 38%, $P = 0.39$).

13.1.2 Evaluating the Benefit of Mitomycin and Additional Chemotherapy

Despite the benefits of combined modality therapy observed in the UK ACT I and EORTC trials, the acute toxicity was significant. In the UK ACT I trial, six patients died of chemotherapy-related hematologic toxicity [7]. The U.S. Intergroup (Radiation Therapy Oncology Group [RTOG] 8704/Eastern Cooperative Oncology Group [ECOG] 1289) trial directly evaluated whether MMC was an essential component of combined modality therapy [9]. Between 1988 and 1991, 310 patients were randomized to radiation therapy with 5-FU (1000 mg/m^2 CI days 1–4 and days 28–31) or radiation with 5-FU (same regimen) and MMC (10 mg/m^2 bolus on days 1 and 28). Any tumor or nodal stage was allowed to enroll, with 85% of patients having T2-T4 disease and 17% clinically node-positive. Radiation was delivered using large anterior and posterior opposed fields to 45 Gy in 25 fractions with shrinking AP-PA fields after 30.6 Gy. Patients received an additional 5.4 Gy boost for persistently palpable tumor. At 4 years, patients receiving 5-FU and MMC experienced a lower colostomy rate (9% vs. 22%, $P = 0.002$) and higher disease-free survival (73% vs. 51%, $P = 0.0003$). There was no statistical difference in overall survival in the 5-FU/MMC arm compared to 5-FU alone (76% vs. 67%, $P = 0.31$). Despite improvements in disease-specific outcomes, toxicity was increased in the MMC arm with 23% of patients experiencing a grade 4 or 5 toxicity compared to 7% of patients receiving 5-FU alone ($P < 0.001$).

The RTOG 9811 trial also evaluated whether MMC could be eliminated from the standard chemoradiation backbone. Rather than a direct substitution of MMC, the trial evaluated whether two cycles of induction cisplatin/5-FU followed by

cisplatin/5-FU-based chemoradiation would offer improved disease-free survival compared to the standard regimen of chemoradiation with mitomycin/5-FU [10, 11]. From 1998–2005, 682 patients were randomized among the two arms. Inclusion criteria comprised T2-T4 primaries of any nodal status, with 35% having T3-T4 primary disease and 26% being node-positive. The control arm was treated akin to the 5-FU and MMC arm from RTOG 8704. The experimental arm included two cycles of induction chemotherapy using CI 5-FU 1000 mg/m^2/day days 1–4, 29–32, 57–60, and 85–88 with bolus cisplatin 75 mg/m^2 on days 1, 29, 57, and 84, and then a substitution of bolus cisplatin instead of MMC during chemoradiation. For both arms, radiation was administered as 45 Gy in 25 fractions with AP-PA or multiple field techniques. The initial fields encompassed the pelvis (mesorectum/iliacs), anus, presacral region, and inguinal nodes with the superior border at L5-S1 and inferiorly 2.5 cm below the anus and tumor. After 30.6 Gy, the superior border was reduced to the bottom of the sacroiliac joints and the pelvis was boosted to 45 Gy. For patients with T3-T4 primaries, positive inguinal nodes, or T2 with residual disease, an additional radiation boost of 10–14 Gy at 2 Gy/fraction was delivered. In contrast to the prior randomized trials discussed, there was no planned radiation break between the pelvic 45 Gy and the tumor boost. Although the initial report observed no difference in the primary endpoint of disease-free survival, three-year colostomy rates were significantly worse with cisplatin (10% vs. 16%, $P = 0.02$) [11]. There was also no difference in acute grade 3–4 non-hematologic side effects between the arms (74% for both arms), although acute grade 3–4 hematologic toxicity was significantly worse with MMC (62% vs. 42%, $P < 0.001$). In the 5-year update, cisplatin was found to be detrimental in terms disease-free survival (68% vs. 58%, $P = 0.006$), overall survival (78% vs. 71%, $P = 0.026$), and colostomy-free survival (72% vs. 65%, $P = 0.05$) [10]. Differences in locoregional failure (20% vs. 26%, $P = 0.087$) and colostomy rates (12% vs. 17%, $P = 0.074$) did not reach statistical significance. Late grade 3 and 4 side effect rates were comparable over time (13% MMC vs. 11% cisplatin, $P = 0.35$). As such, chemoradiation with concurrent 5-FU and MMC remains the standard of care in the United States.

The UK ACT II trial evaluated a more direct comparison of whether MMC could be substituted for cisplatin during chemoradiation with a primary endpoint of clinical complete response at 26 weeks, as well as whether maintenance chemotherapy with cisplatin would improve progression-free survival beyond chemoradiation alone [12]. Between 2001-2008, 940 patients were randomized to radiation with 5-FU (1000 mg/m^2/day CI days 1–4 and 29–32) and MMC (12 mg/m^2 bolus on day 1), or radiation with 5-FU and cisplatin (60 mg/m^2 bolus on days 1 and 29). In a 2 × 2 factorial design, a second randomization evaluated the benefit of adjuvant 5-FU/cisplatin chemotherapy (an additional two cycles of 5-FU days 71–74 and 92–95 and cisplatin days 71 and 92). T3-T4 primaries made up 46% of patients and 32% had involved nodes. Radiation was prescribed to 50.4 Gy using an AP/PA filed design, with a field reduction at 30.6 Gy. Treatment was given continuously without a planned break, in contrast to the UK ACT I trial. The cisplatin and MMC arms demonstrated similar rates of clinical complete response at 26 weeks (89.6% vs. 90.5%, $P = 0.64$). With a median follow-up of 5 years, there also was no difference

in progression-free survival by maintenance (74%) vs. no maintenance (73%), $P = 0.7$. The rates of any grade 3 or 4 toxicities were similar in both the MMC and cisplatin arms (72 vs 73%), but the MMC arm had higher rates of grade 3 or 4 hematologic toxicity (26% vs. 16%, $P < 0.001$). The authors concluded that 5-FU/MMC-based chemoradiation remains the standard of care due to fewer cycles of chemotherapy, similar toxic effects, fewer non-chemotherapy drugs, less infusion time, and lower costs. However, cisplatin-based chemotherapy may be considered as an alternative regimen in patients who would not tolerate the hematologic toxicity associated with MMC.

In contrast to RTOG 9811, the UK ACT II trial did not include induction chemotherapy within the cisplatin containing arm. One hypothesis regarding the inferiority of the cisplatin regimen in RTOG 9811 is that the overall treatment time was extended in this arm, potentially leading to accelerated repopulation and inferior oncologic outcomes. In a pooled analysis from RTOG 8704 and RTOG 9811, the overall treatment time had a detrimental effect on local failure and colostomy-free survival. Patients with overall treatment times greater than 53 days had nearly a two times higher risk of local failure compared to patients with treatment times less than 53 days (HR = 1.86, 95% CI 1.31–2.64, $P = 0.0006$) [13]. Retrospective studies have also observed similar detrimental effects from prolonged treatment time [12, 14].

13.2 Radiation Treatment Approaches

The existing randomized controlled trial data previously discussed all utilized older 2-dimensional or 3-dimensional conformal RT (3D-CRT) techniques. In either approach, orthogonal beams of radiation covering the gross tumor and pelvic and inguinal nodal regions generally use an AP/PA field arrangement that indiscriminately delivers homogeneous high doses of radiation to large volumes of normal surrounding bowel, bone, bladder, genitalia, and skin, leading to treatment-associated morbidity. In 2D planning, the design of the radiation field borders and blocking of normal organs are based on known correlations between bony anatomy and the tumor and nodal targets. The surrounding adjacent normal tissues cannot be spared, limiting the radiation dose that can be safely administered. 3D-CRT techniques utilize an initial CT simulation of the patient in the treatment position (discussed later in this chapter); yet, the degree of planning can vary widely. For example, some radiation oncologists use a 3D approach to have confidence that the tumor volume is accurately covered by the radiation fields. Gross tumor volume is contoured on each CT slice, but the fields and blocks may still be based on bony landmarks akin to the 2D technique. However, with a more optimal 3D approach, one could also contour the clinical target volume (gross tumor volume and draining nodal regions) and the normal organs on each CT slice. Radiation dose is prescribed to the target volume, and dose constraints are placed on normal tissues. Treatment accuracy, delivery, and dose quantification with a highly conformal 3D-CRT approach are superior to the 2D technique, but even with an excellent 3D plan,

adjacent normal tissues cannot be adequately spared, as these techniques use uniform, static fields for radiation therapy delivery.

Since there is inherent difficulty in sparing the critical surrounding tissue with 2D or 3D radiation delivery techniques, chemoradiation is associated with significant acute toxicity including hematologic, dermatologic, and gastrointestinal. In RTOG 9811, the rate of acute non-hematologic grade 3 or 4 toxicity was 74% in both the MMC and cisplatin groups, with a rate of grade 3 or 4 hematologic toxicity of 62% in the standard 5-FU/MMC arm [11]. In the UK ACT II trial, rates of grade 3 or 4 non-hematologic toxicity were 62% in the 5-FU/MMC arm, with a rate of grade 3 or 4 hematologic toxicity of 26% (of note, only one dose of MMC day 1 is administered in the UK in contrast to two doses given days 1 and 28 in the US) [12].

13.2.1 3D-CRT Technique

3D-CRT uses a sequential cone down technique with an AP/PA or 4-field arrangement [11]. Initial pelvic fields are treated to 30.6 Gy at 1.8 Gy per fraction from the L5/S1 interspace to at least 2.5 cm inferior to the anal tumor or bottom of the anal canal. The lateral borders of the AP fields include the inguinal lymph nodal compartments. At 30.6 Gy, the superior border is reduced to the greater sciatic notch for an additional 14.4 Gy to a total dose of 45 Gy at 1.8 Gy per fraction. Subsequently, the primary tumor is treated with a 2–2.5 cm margin for the final boost to a total of 54–59 Gy. Grossly involved pelvic lymph nodes are also included in the final boost phase if small bowel could be sufficiently avoided. For a 4-field technique, the inguinal lymph nodes are included in the AP and lateral fields, but not the PA field to allow femoral head sparing. Anterior electron fields matched to the exit of the PA fields provide additional dose to supplement the inguinal lymph node targets. For involved inguinal lymph nodes, the entire inguinal space is treated to 45 Gy with a boost to 54–59 Gy to the gross disease. Representative 3D-Conformal fields are illustrated in Fig. 13.1.

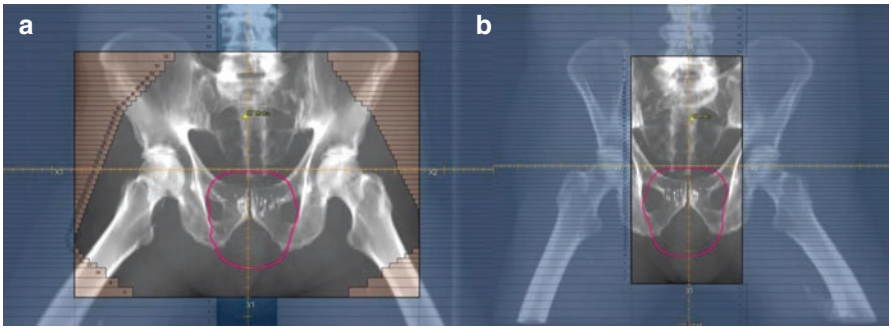

Fig. 13.1 3D-Conformal technique using AP (**a**) and PA (**b**) fields. The PA field is reduced laterally to spare the femoral heads. Additional dose is provided to the inguinal lymph nodes with electrons

13.2.2 The Potential of Intensity-Modulated Radiation Therapy

Intensity-modulated radiotherapy (IMRT) is a form of advanced, photon-based therapy that uses inverse planning with a computer-optimized algorithm to create radiation-beam characteristics to meet stringent tumor and target volume coverage directives and normal tissue constraints. The IMRT plan conforms the radiation dose to the tumor and target volumes with a steep dose gradient, allowing for decreased radiation dose to the surrounding normal organs. Thus, IMRT has the potential to reduce the acute and late toxicities from 5-FU/MMC chemoradiation for anal canal cancer. In turn, the use of IMRT may also reduce treatment breaks that negatively influence outcomes and allow for radiation dose escalation in trials for high-risk, locally advanced patients. In contrast to the 2–4 fields used for 2D or 3D-CRT radiation delivery, IMRT allows for the modulation of radiation intensity and often relies on nine or more radiation fields. IMRT can be dynamic, in which collimating leaves move across an active radiation field, or step-and-shoot, in which leaves sculpt the field shape while the beam is off. More recently, volumetric-modulated arc therapy (VMAT) has been utilized, in which intensity-modulated techniques are performed in the setting of continuous gantry rotation.

13.2.3 Clinical Experience Using Intensity-Modulated Radiation Therapy

Retrospective dosimetric comparative studies assessing 3D-CRT compared to IMRT have all demonstrated a reduction in radiation dose to the normal organs at risk. Compared to traditional techniques, IMRT reduces dose to the small bowel, genitalia, and bladder [14, 15]. Early experiences with IMRT appear to achieve similar local control and improved toxicity compared to historical experiences [15, 16]. In the first multicenter trial assessing the use of IMRT for anal cancer, Salama and colleagues reported their retrospective experience of 53 patients who underwent IMRT with concurrent 5-FU and MMC [15]. Patients treated at the University of Chicago received 45 Gy in 1.8 Gy fractions to nodal regions at risk and to gross disease followed by a sequential IMRT boost plan to 54 Gy to gross disease. A separate cohort from the Mayo Clinic was treated using a simultaneous integrated boost technique to three different target dose levels (50 Gy, 45 Gy, and 41.25 Gy) in 25 fractions. The rate of grade 3 or higher gastrointestinal (GI) and dermatologic toxicity was 15% and 38%, respectively. Eighteen-month colostomy-free survival, overall survival, and freedom from local failure were 84%, 93%, and 84%, respectively. These data suggested improved treatment tolerance with IMRT and similar efficacy when compared to the 5-FU and MMC arm of RTOG 9811.

Kachnic et al. reported their results of 43 patients treated with a single phase dose-painting static IMRT technique [16]. In this multi-institutional retrospective review, the prescription dose varied depending on the stage of the disease. In patients with T2N0 cancer, the primary tumor received 50.4 Gy in 1.8 Gy per

fraction, and the elective nodal planning target volume (PTV) was treated to 42 Gy in 1.5 Gy per fraction. For patients with T3/T4 N0-3 disease, the primary tumor received 54 Gy in 1.8 Gy per fraction, and the elective nodal PTV received 45 Gy in 1.5 Gy per fraction. IMRT was delivered with 8–10 static fields. Grade 3 or higher skin toxicity was observed in 10% of patients, while grade 3 or higher GI toxicity was noted in 7% of patients. These toxicity rates compared favorably to those observed in the standard 5-FU/MMC arm of RTOG 9811 (49% grade 3 or higher dermatologic events and 36% grade 3 or higher GI toxicity). Two-year local control, overall survival, colostomy-free survival, and metastasis-free survival were 95%, 94%, 90%, and 92%, respectively. The proportion of patients requiring a treatment break was 40%, which was similar to the IMRT series by Salama and colleagues in which 42% of patients required a treatment break. Both IMRT studies observed reduced rates of treatment breaks compared to the 62% of patients who required a break in the standard 5-FU/MMC arm of RTOG 9811 [11, 15, 16].

RTOG 0529 is the only prospective trial for the use of IMRT in patients with squamous cell carcinoma of the anal canal [17]. The rationale for this phase II trial was to evaluate whether reduced dose to the organs at risk with IMRT could result in a reduction in acute toxicity. The primary end point of the study was grade 2 or higher GI or genitourinary (GU) events as compared to historical controls on the standard arm of RTOG 9811. A total of 52 patients were evaluable on the trial. Eligible patients included patients with T2-T4 disease with any N category. Treatment was provided using a dose-painting technique with differential prescriptions based on the tumor stage. Similar to the series by Kachnic and colleagues above, patients with T2N0 disease received 50.4 Gy to the primary tumor and 42 Gy to the elective nodal volumes in 28 fractions. Patients with T3/T4N0-3 disease received 54 Gy to the primary site and 45 Gy to the elective nodal volume in 30 fractions. Involved lymph nodes were treated to 54 Gy if greater than 3 cm or 50.4 Gy if less than or equal to 3 cm in 30 fractions. All patients received 5-FU (1000 mg/m^2/day, 96 h CI) and MMC (10 mg/m^2 IV bolus) days 1 and 29. Compared to the historical control arm from RTOG 9811, there were no differences in grade 2 or higher GI/GU morbidity (77% vs. 77%, $P = 0.50$). However, in the patients treated with IMRT, there was a significant reduction in combined grade 3 or higher GI events (21% vs. 36%, $P = 0.0052$), grade 3 or higher dermatologic toxicity (23% vs. 49%, $P = 0.0052$), and grade 2 or higher hematologic events (73% vs. 85%, $P = 0.032$). In addition, treatment breaks due to toxicity were needed in 49% of IMRT-treated patients compared with 62% on the 5-FU/MMC arm of 9811 ($P = 0.09$), with a median duration of radiotherapy of 42.5 days (range: 32–59) using IMRT, compared with 49 days (range: 0–102) on RTOG 9811 ($P < 0.0001$). A recent update of this study showed that this IMRT approach

Table 13.1 Grade 3+ acute toxicity sparing with IMRT

Series	Patient #	Hematologic (%)	Dermatologic (%)	Gastrointestinal (%)	Genitourinary
RTOG 9811 [11] 5-FU/MMC	325	62	4	36	3%
RTOG 0529 [17]	52	58	23	21	2%
Salama [15]	53	59	38	15	0%
Defoe [18]	78	13	29	18	NR
Kachnic [16]	43	51	10	7	7%
Chuong [19]	52	29	12	10	0%
Han [20]	58	41	46	9	0%
Franco [21]	54	17	13	8	2%
Call [22]	152	41	20	11	0%

also yielded similar 2-year disease-related outcomes compared with the 5-FU/MMC arm of RTOG 9811 [22]. Table 13.1 reviews the grade 3 and higher acute toxicity rates of the 5-FU/MMC arm of RTOG 9811 [11] as compared to several IMRT series [15, 16, 18–22] and RTOG 0529 [17]. Collectively, with the reduction in GI and dermatologic acute adverse events, improved treatment tolerance, and similar outcomes, IMRT-based chemoradiation has become the standard of care in the definitive treatment of anal cancer [23].

13.2.4 Proton Therapy

There is emerging interest in the use of intensity-modulated proton therapy (IMPT) for treatment of anal cancer. Dosimetric studies have shown reduced dose to bowel, bladder, genitalia, and bone marrow with IMPT as compared to IMRT, with preserved PTV coverage [34, 35]. With use of IMPT, a common approach is a 3-field Multi Field Optimized (MFO) split target technique. A posterior field is used to cover the primary tumor and posterior pelvic lymph nodes. Two anterior oblique fields are used to cover the inguinal lymph nodes and anterior pelvic lymph nodes. Given the limited number of beam paths and reduced exit dose with proton therapy, this technique allows for sparing of the anterior structures (bowel/bladder) and lateral pelvic bone structures without compromise in the PTV coverage. Representative IMPT and IMRT plans are shown in Fig. 13.2. The feasibility of pencil beam scanning proton therapy techniques for anal cancer is the subject of ongoing trials (NCT03018418, NCT01858025).

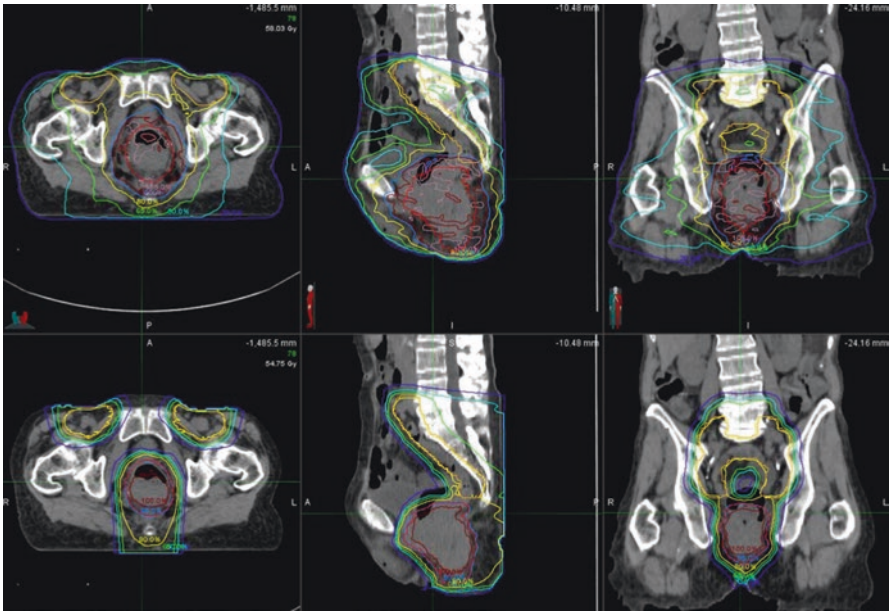

Fig. 13.2 Representative comparison plans and isodose distributions for IMRT (*top*) and IMPT (*bottom*)

13.3 IMRT Planning

13.3.1 Considerations in Work-Up Prior to Planning

It is important to consider the cause of the anal cancer. Order HIV testing (in patients with established risk factors) and obtain p16 expression on anal pathology (if an HPV panel was not already performed). If the patient does have a history of high-risk HPV infection in the anus, it is important to then consider evaluation of the cervix, vulva, or penis to rule out any synchronous disease before proceeding with standard IMRT contouring. Local extent of disease is evaluated with physical examination, which typically includes anoscopy for enhanced visualization and histological confirmation. Evaluation for distant metastatic disease and locoregional inguinal and pelvic lymph node involvement require radiographic imaging. Contrasted CT imaging is routinely used for this purpose, but is considered inferior to physical examination for evaluation of primary anal tumors. MRI may be useful in certain cases for further characterization of primary tumors, especially when local invasion is suspected, but in general has not been demonstrated

Table 13.2 AJCC nodal staging for anal cancer, eighth edition (2016)

Regional LYMPH nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastasis in external iliac with any N1a nodes

additional benefit over the use of CT for routine staging of anal cancer. Positron emission tomography (PET) and PET-CT are now routinely integrated into the staging algorithm for patients. PET-CT appears to have a higher sensitivity than conventional imaging (CT and/or magnetic resonance imaging [MRI]) for detecting regional lymph node metastases, and as such, has been found to change IMRT dose-painting design [24].

It is also important to note that there are changes to the new 2016 edition of the American Joint Commission on Cancer (AJCC) staging system. The major change in this Eighth Edition is a revision of the nodal staging [25]. Based on the recent analysis of the impact of TN category of disease on the outcomes of RTOG 9811, there were no notable outcome differences beyond nodal positivity [26]. The location or amount of lymph node disease was not prognostic. Thus, patients should now be staged as N0 or N1, and the N1 category is further subdivided by the nodal regions involved, Table 13.2.

Lastly, although wide local excision is not considered standard in the treatment of anal canal cancer, it is sometimes performed in the initial evaluation or management of early stage small tumors without evidence of anal sphincter or nodal involvement. Even with adequate staging, the risk of recurrence remains high enough following local excision to warrant definitive chemoradiation, which is considered the standard of care for the treatment of carcinoma of the anal canal.

13.3.2 CT Simulation Techniques

Patients may undergo CT simulation in a supine/frog leg position or a prone position on a bowel displacement device (“belly board”). Advantages of supine position include allowing for a frog leg position and direct visualization of the inguinal lymph node targets. Prone position with use of a belly board may be particularly advantageous for patients with a larger body habitus to improve small bowel sparing

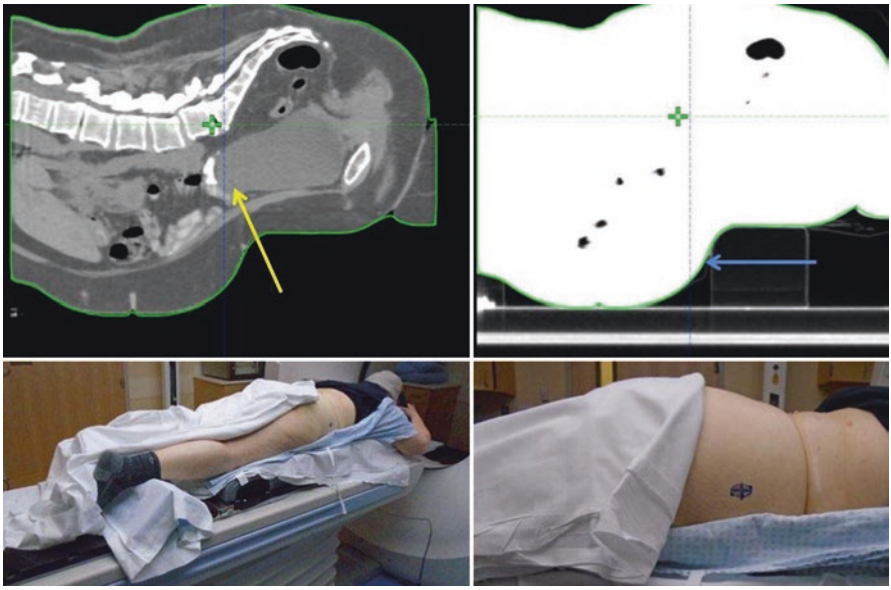

Fig. 13.3 Prone CT simulation using a belly board. *Blue arrow* delineates the gap in the prone belly board that allows for geometric displacement of small bowel. *Yellow arrow* shows that bladder filling may provide additional small bowel displacement

(Fig. 13.3). At the time of simulation, visible disease should be noted and marked with a radiopaque wire to ensure adequate dose coverage (Fig. 13.4). Placement of a radiopaque anal marker may also be useful to determine the distance of the disease from the verge for contouring purposes. Use of bolus may be required to achieve adequate dose coverage for patients with superficial tumors extending outside of the verge (Fig. 13.4). Oral contrast is given approximately 30 min prior to simulation for better small bowel visualization. Intravenous contrast may be useful in visualizing and contouring the elective nodal vessels, particularly in patients who are thin; however, more commonly, these authors utilize fusion with the patient's CT with contrast staging study if needed. For additional small bowel sparing, bladder filling may also be utilized, but remember to reproduce filling prior to each treatment (Fig. 13.3). Once the patient is appropriately positioned, CT images at 3 mm intervals from the upper lumbar spine to the mid-femur) should be obtained.

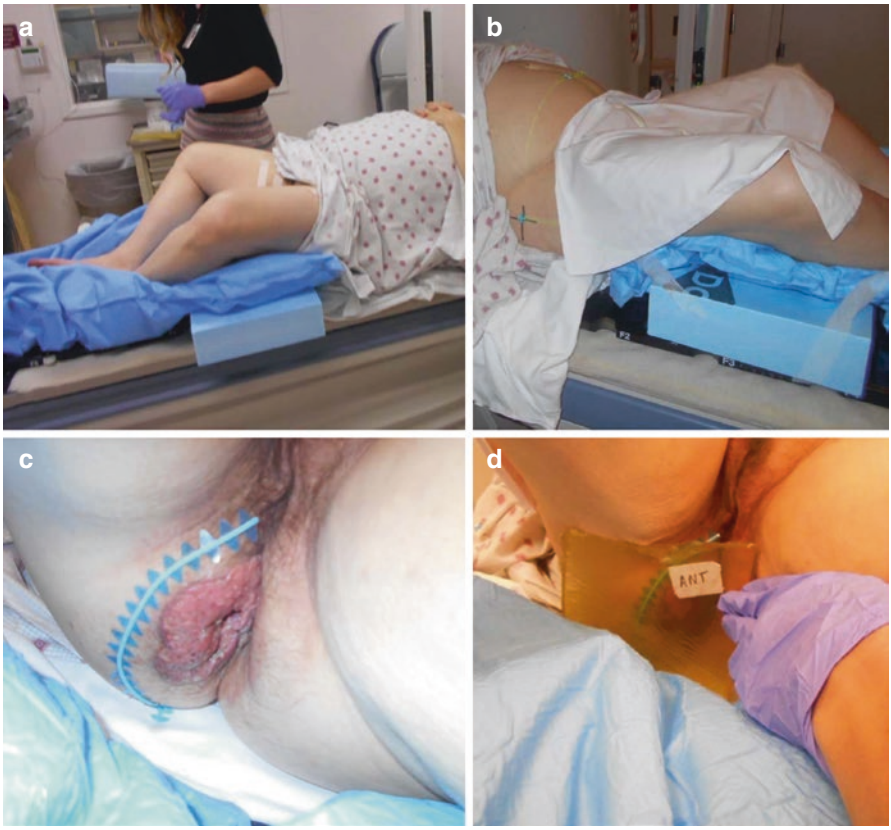

Fig. 13.4 Supine CT simulation for a patient with extension of the anal canal tumor outside of the verge onto skin. The patient underwent simulation in the frog leg position. The gross tumor outside of the verge was marked with a wire (2c), and bolus was applied (2d) for daily treatments

13.3.3 Importance of Accurate Target Delineation

Careful attention to target delineation (including gross disease, elective nodal volume, and normal structures) is essential for conformal treatment of anal cancer, respective of the treatment technique employed. The RTOG 0529 trial of IMRT included prospective radiation planning quality assurance as a component of the trial. A review of the quality assurance data revealed that 81% of cases required plan revisions prior to treatment; 46% required multiple revisions, and four plans did not pass. Reasons for not passing included incorrect contouring of gross tumor (21%), miscontouring of elective nodal volumes (mesorectum 55%, presacrum 43%, inguinal fossa 33%, iliac nodal groups 31%), and/or misidentification of normal structures (small bowel 60%, large bowel 45%) [21].

13.3.4 Target Volumes

According to the International Commission on Radiological Units 50 guidelines, all target and normal tissue structures are contoured on the planning CT slices. Multiple consensus atlases now exist from the RTOG, [27] Australasian Gastrointestinal Trial Group [28], and the United Kingdom [29] which illustrate target definitions with representative case examples. A detailed comparison of these atlases is reviewed in Table 13.3. For IMRT planning and delivery, the most common approach is the use of a dose-painting IMRT technique (as demonstrated in RTOG 0529) with simultaneous differential daily doses to the gross target volume (GTV) and the elective nodal volume. The total dose to the primary tumor as well as gross lymphadenopathy is determined by the maximum size of each respective target. The total elective nodal dose will vary depending on the prescription dose to the primary tumor using a simultaneous integrated boost technique. While we will review this dose-painted approach that is widely used in the Unites States, an initial IMRT comprehensive field followed by a sequential IMRT boost is also acceptable.

When contouring the GTV, one should use all available clinical and radiographic information including radiopaque wires/markers at the time of simulation. Endoscopy reports may also be helpful. Contouring of the GTV may be aided by registration of the diagnostic PET, PET-CT, or MRI in the treatment planning system. An MRI (T2-weighted sequences) may be particularly useful in patients with advanced disease with invasion of nearby organs (Fig. 13.5). Gross lymphadenopathy should be contoured and noted as separate structures when using an IMRT simultaneous integrated boost technique.

Construction of the clinical target volume (CTV) of the primary tumor is performed by an isotropic expansion of 1.5–2 cm from the GTV. The primary tumor CTV should include the entire GTV as well as the entire anal canal and anal sphincter muscles. This structure should be modified to account for the natural barriers of bone and muscle if the tumor does not involve these structures. An elective dose volume should be constructed that includes the primary and nodal CTVs as well as the entire mesorectum, internal iliac, external iliac, presacral, and bilateral inguinal lymph node regions. Common errors in contouring the elective nodal volume include failure to correctly contour the entire extent of the mesorectum as well as insufficient inguinal lymph node delineation. When contouring the inguinal lymph node region, a 5–7 mm isotropic expansion around the femoral vessels will *not* adequately cover the inguinal lymphatics at risk [30]. Instead, the entire inguinal compartment bounded by musculature should be contoured. Table 13.3 depicts the gross tumor and elective target delineations and prescription doses depicted in the three published IMRT atlases. Of note, these authors have slightly modified the RTOG 0529 anal primary CTV recommendations, and now use a 1.5–2.0 cm isotropic expansion with a 5 mm expansion for the PTV (provided that daily image guidance is used). Excellent definitions of elective nodal volume contouring may be found in the Australasian Gastrointestinal Trial Group [28]. In contouring of the normal pelvic organs at risk (OARs), the small bowel, left femoral head, right

Table 13.3 Target definitions and dose prescriptions from contemporary anal cancer atlases

	RTOG 0529/NRG oncology atlas [27]	Australasian gastrointestinal trials group atlas [28]	United Kingdom atlas [29]
Primary tumor GTV; GTVp Node-positive GTV; GTVn+	Use all clinical and imaging information; contoured separately	Use all clinical and imaging information	Use all clinical and imaging information
Primary tumor CTV; CTVp	2.5 cm isotropic expansion around anal primary GTV, modified to avoid overlap into natural barriers to tumor infiltration (non-target muscles or bone); includes the entire anal canal	Includes the GTV, entire anal canal from the anorectal junction to the anal verge, and the anal sphincters and an additional 2 cm isotropic expansion modified for anatomic boundaries	1.5 cm isotropic expansion of around anal primary GTV; manually enlarge to include anal canal from anorectal junction (4 cm from anal verge marker); include sphincters and exclude bone and muscle if free from tumor
Primary tumor PTV, PTVp	1.0 cm isotropic CTV expansion	1.0 cm isotropic CTV expansion 0.5–0.7 cm if daily image guidance	1.0 cm isotropic CTV expansion with daily image guidance
Primary tumor dose	Tumors > 5 cm (T3, T4) or any T, N positive—54 Gy at 1.8 Gy per fraction; PTVp_5400 Tumors < 5 cm (T2) and N negative—50.4 Gy at 1.8 per fraction; PTVp_5040	54 Gy at 1.8 Gy per fraction for most tumors; consider 50.4 Gy at 1.8 Gy per fraction for T1 or non-bulky T2 tumors	Tumors > 5 cm (T3, T4) or any T, N positive—53.2 Gy at 1.9 Gy per fraction Tumors < 5 cm (T1, T2) and N negative—50.4 Gy at 1.8 Gy per fraction
Gross nodal CTV; CTVn+	Gross lymph node +1 cm CTV avoiding non-target muscle/bone	Gross lymph node +1–2 cm CTV avoiding non-target muscle/bone	Gross lymph node +0.5 cm CTV avoiding non-target muscle/bone
Gross nodal PTV; PTVn+	1.0 cm isotropic CTV expansion	1.0 cm isotropic CTV expansion; 0.5–0.7 cm with daily image guidance	0.5 cm isotropic CTV expansion with daily image guidance
Gross nodal dose	50.4 Gy at 1.8 Gy per fraction if ≤3 cm; PTVn+_5040 54 Gy at 1.8 Gy per fraction if >3 cm; PTVn+_5400	50.4–54 Gy depending on size at 1.8 Gy per fraction	50.4 Gy at 1.8 Gy per fraction
Elective nodal dose	T2 N0: 42 Gy at 1.5 Gy per fraction; PTVn_4200 T3/T4 or N+: 45 Gy at 1.5 Gy per fraction; PTVn_4500	42 Gy at 1.5 Gy per fraction if primary dose is 50.4 Gy in 28 fractions 45 Gy at 1.5 Gy per fraction if primary dose is 54 Gy in 30 fractions	40 Gy at 1.43 Gy per fraction (28 fractions) for all patients

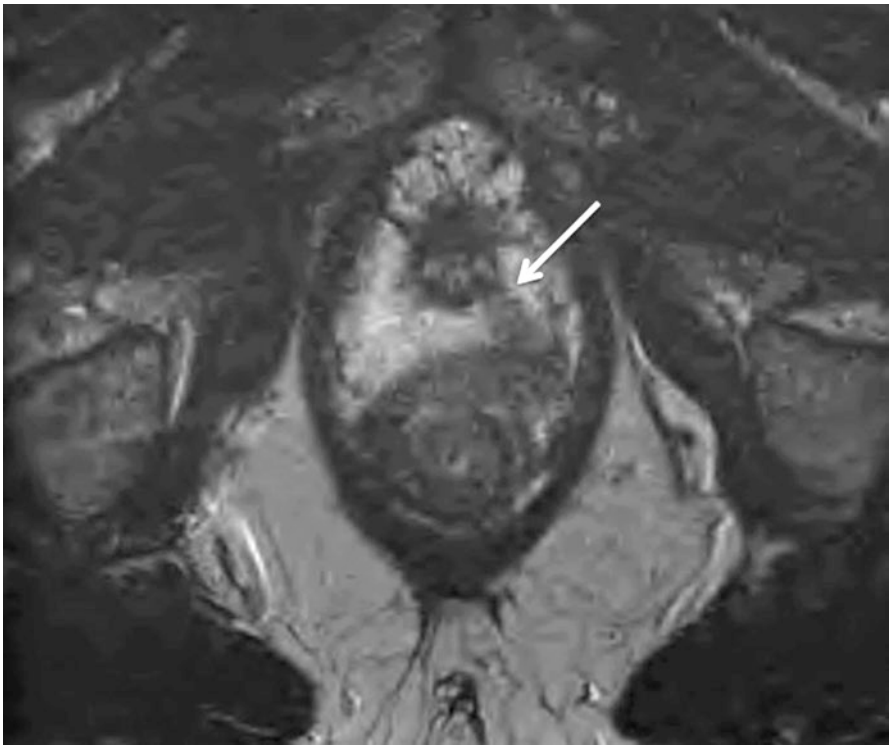

Fig. 13.5 Axial T2-weighted MRI image showing invasion of the anal canal cancer into the prostate with abutment of the urethra (*white arrow*) indicating T4 disease

femoral head, genitalia, bladder, pelvic bones, large bowel, and skin should all be outlined on each axial CT slice. The external contours of all pelvic bones, including iliacs, lumbosacral spine, and lower pelvic bones, should be contoured together as a surrogate for pelvic bone marrow. Bowel should be drawn as individual loops without the intertwining mesentery or as a bowel bag delineated from L4-5 down. The tissue within the skin surface and outside all other critical normal structures and PTVs is designated as unspecified tissue. The RTOG atlas for normal pelvic tissues may be useful for contouring normal organs [31]. A representative IMRT plan and radiation targets are shown in Fig. 13.6.

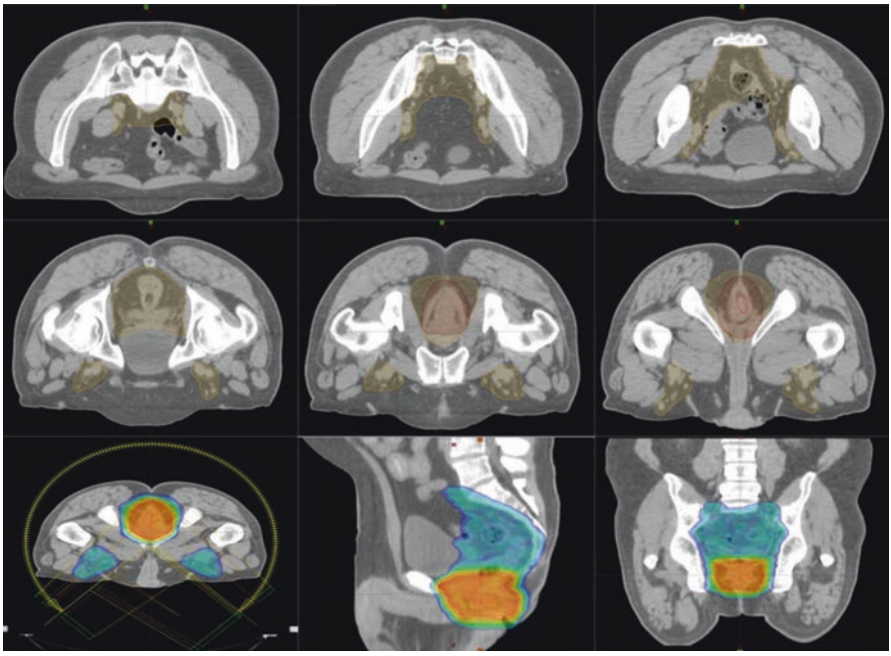

Fig. 13.6 Representative IMRT CTV contouring axial slices (GTVp_5040 in *red*; CTVn_4200 in *orange*) and treatment plan for a male patient with Stage II—T2N0M0 anal cancer. The patient was positioned prone on a bowel displacement device and treated with an IMRT plan using Volumetric Arc Therapy (VMAT). This VMAT plan utilized 10 MV beams and 270° arcs with gantry start/stop angles similar to those used with a 7-field IMRT technique in order to cover the anterior elective nodal volume and spare entrance dose to anterior organs at risk. The primary PTV (PTVp_5040) received 50.4 Gy (*Red*) and the elective nodal PTV (PTVn_4200) received 42 Gy (*blue*) in 28 fractions

13.3.5 IMRT Dosimetric Planning and Delivery

IMRT planning allows for differential doses to the gross disease, elective nodal regions, and the OARs. The OARs used in optimization typically include the small bowel, femoral heads, genitalia, bladder, pelvic bones, and large bowel. In addition, all PTVs should spare non-target skin surfaces manually or automatically trimmed by 3–5 mm (unless there is skin involvement). For bone marrow sparing, pelvic bones including the iliac crests, lumbosacral spine, and lower pelvic bones should be contoured together as a surrogate for pelvic bone marrow. Representative dose constraints based on RTOG 0529 and the UK NICE guidance for IMRT are outlined in Table 13.4. For IMRT optimization in patients enrolled on RTOG 0529, major violations included greater than 5 cc small bowel receiving more than 50 Gy, any point dose small bowel higher than 54 Gy, and greater than 5% femoral heads receiving more than 44 Gy [17]. All other dose constraint deviations were considered minor violations, but were acceptable for treatment.

Table 13.4 Normal organs at risk treatment planning parameters for anal cancer IMRT

Organ at risk	Representative constraints (RTOG 0529 [31] and UK NICE guidance for IMRT [33])
Small bowel	V45Gy < 20 cc V35Gy < 150 cc V30Gy < 200 cc
Femoral heads (L&R)	V44Gy [%] ≤ 5 V40Gy [%] ≤ 35 V30Gy [%] ≤ 50
Bladder	V50Gy [%] ≤ 5 V40Gy [%] ≤ 35 V35Gy [%] ≤ 50
Genitalia	V40Gy [%] ≤ 5 V30Gy [%] ≤ 35 V20Gy [%] ≤ 50
Large bowel	V45Gy < 20 cc V35Gy < 150 cc V30Gy < 200 cc
Bone marrow	V50Gy [%] ≤ 5 V40Gy [%] ≤ 35 V30Gy [%] ≤ 50

Treatment planning priorities should be considered in order of decreasing importance:

1. PTVp—covering 95% of the PTV.
2. PTVn+—covering 95% of the PTV.
3. PTVn (elective nodes)—covering 95% of the PTV.
4. Small bowel.
5. Femoral heads.
6. External genitalia.
7. Bladder.
8. Pelvic bone marrow.
9. Large bowel.

For IMRT plans, patient-specific quality assurance (QA) is highly recommended. QA is performed by delivering the plan onto a phantom or portal imager to measure the 2D/3D dose. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 4% dose difference and 3 mm distance to agreement. The pass rate should be at least 90% measured for the entire plan.

Patients should receive daily KV images for setup and treatment verification. Bone should be used as the surrogate. Corrections should be made for shifts of 1 mm or greater and recorded. Cone beam CT images, if available, may also be helpful to evaluate the relationship of the CTV to the bladder/rectum, to verify male genitalia position, and to evaluate weight loss or tumor volume reduction that may necessitate adaptive re-planning.

For IMRT systems where isocenter is not defined (e.g., tomotherapy), setup verification images may consist of a series of axial CT images (megavoltage or kilovoltage) obtained over at least 5 cm length, to be compared with simulation CT images. It is recommended that there be an option to display target structures on the simulation images. It is also recommended that the setup verification images be obtained at levels where cephalocaudad positioning, as well as transverse positioning, can be verified. Appropriate levels would include either around the mid to upper sacrum or around the upper border of the acetabulae.

13.3.6 Radiation Dose Considerations

The dose required for locally advanced lesions remains an area of active investigation. An analysis of locoregional failures by T and N stage was performed for patients enrolled in RTOG 9811 [30]. In patients treated with 5-FU and MMC, the three-year colostomy failure rates were 9% (T2N0), 12% (T3N0), 20% (T4N0), 4%(T2N1-3), 19% (T3N1-3), and 28% (T4N1-3). Higher failure rates in high-risk patients raise the question of whether the radiation dose should be escalated. The intended dose for T3, T4, or node-positive patients enrolled on RTOG 9811 was 45 Gy followed by a boost to 55–59 Gy in 30–32 fractions administered over 5.5–6.5 weeks.

Dose escalation was assessed in a randomized design in the French Action Clinique Coordonnées en Cancérologie Digestive (ACCORD-03) trial [32]. In this 2 × 2 factorial study, the roles of two cycles of cisplatin/5-FU induction chemotherapy and dose-escalated radiation were both evaluated. Radiation was delivered using conventional AP/PA or 4-field box techniques to 45 Gy followed by a 3-week break for primary tumor assessment. Patients in the standard boost arms received an additional 15 Gy (60 Gy total dose) using external beam or low dose-rate brachytherapy. Patients in the high-dose boost arms received an additional 25 Gy (total 70 Gy) if there was less than an 80% response at the primary tumor and 20 Gy (total 65 Gy) if there was greater than an 80% response. Patients with no change or progression were recommended to undergo abdominoperineal resection. After a median follow-up of 50 months, there was no advantage in the high-dose boost arms in regard to local control or colostomy-free survival. The addition of induction chemotherapy (which was also found to have no improvement on outcomes) and the inclusion of a three-week treatment gap between external beam radiation and the boost phase may have confounded the interpretation of dose escalation utility in this trial.

Radiation dose will be evaluated in the international PLATO trial (Personalizing Radiotherapy Dose in Anal Cancer) using dose-painted IMRT [33]. This umbrella trial will assess radiation dose intensification in high-risk patients and dose de-escalation in favorable patients. Patients with T1/T2N0 tumors $\leq$ 4 cm will be enrolled on the phase II ACT IV trial and will be randomized to 50.4 Gy in 28 fractions or 41.4 Gy in 23 fractions. Enrollment is planned at 162 patients with a 2:1 randomization. Patients with tumors that are greater than 4 cm or node-positive

will be randomized on the Phase II/III ACT V trial to 53.2 Gy in 28 fractions, 58.8 Gy in 28 fractions, or 61.6 Gy in 28 fractions with standard chemotherapy. Only one of the dose-escalated arms (58.8 Gy or 61.6 Gy) will be evaluated for the phase III component. The primary endpoint for each trial is three-year locoregional failure.

13.4 Toxicity Management

Definitive chemoradiation for anal canal cancer may be one of the most difficult treatments for patients to complete. Acute side effects of chemoradiation may result in treatment breaks, which can compromise the local control of the disease [13]. Table 13.5 summarizes the acute and late side effects of chemoradiation for patients with anal cancer. Patients with anal cancer require close multidisciplinary care. Attention in weekly management visits is warranted with frequent skin exams and query of the patient's GI, genitourinary, nutritional, and overall status. Patients should also have close hematologic monitoring. Those with cytopenias must be counseled for neutropenic fever, which may necessitate inpatient admission for IV antibiotics. In patients with severe acute mucosal toxicity (skin or GI) that occurs early in the course of therapy, the treating physician should consider

Table 13.5 Acute and late toxicities associated with chemoradiation for anal cancer

Organ system	Acute effects	Late effects
Skin	Dermatitis Skin desquamation	Telangectasias Hyperpigmentation Skin dryness
Bone marrow	Neutropenia Lymphopenia Thrombocytopenia Anemia Neutropenic sepsis	Not applicable
Gastrointestinal	Nausea/anorexia Diarrhea Frequent bowel movements Fecal leakage Fecal urgency Tenesmus	Radiation enteropathy Chronic anorectal dysfunction Chronic urgency/leakage Chronic diarrhea/alternating constipation Small bowel obstruction Rectal bleeding Rectovaginal fistula
Genitourinary	Urinary frequency Dysuria	Hematuria
Sexual/reproductive	Vaginal pain	Vaginal stenosis Vaginal dryness Infertility Erectile dysfunction in men
Musculoskeletal	Not applicable	Decreased bone density Insufficiency fractures of the sacrum or femoral heads

dihydropyrimidine dehydrogenase (DPD) deficiency. DPD-deficient patients hypometabolize 5-FU or capecitabine chemotherapy, which may result in effective overdosing of the drug with heightened toxicity. This likely will necessitate a dose reduction or discontinuation of any additional fluoropyrimidine-based chemotherapy.

13.4.1 Dermatitis

The perianal and inguinal skin should be evaluated at least weekly as patients progress through therapy. Even with highly conformal techniques, perianal skin reactions are often seen due to close proximity to the high-dose PTV. Limiting the PTV to 3–5 mm from the uninvolved skin surface may reduce skin effects with modern IMRT techniques. This may be particularly beneficial in the region of elective nodal coverage. Early during treatment, barrier creams should be instructed for skin lubrication and comfort. Barrier creams may be particularly useful in patients with frequent or loose bowel movements to avoid direct contact of stool to the affected skin. Sitz baths may also provide symptomatic relief throughout treatment. As patients develop desquamation of the skin, topical lidocaine ointments and silver sulfadiazine creams can provide symptom relief and healing. Application of Domeboro-soaked gauze may also be useful in patients with moist desquamation by helping to cleanse the skin of exudative debris. Following gauze removal, patients can then apply a topical silvadene and lidocaine mixture to the clean surface. This may be repeated 2–3 times per day.

13.4.2 Hematologic Toxicity

Bone marrow suppression following chemoradiation with 5-FU and MMC-based chemotherapy continues to be a challenge. The rate of grade 3 or 4 hematologic toxicity was 61% in the standard arm of RTOG 9811, which used concurrent 5-FU/MMC and 3D-conformal techniques [11]. In the RTOG 0529 trial using an IMRT technique, hematologic toxicity rate of grade 3 or higher was 58% [17]. The concept of bone marrow sparing using IMRT or IMPT is an area of active investigation. Bazan and colleagues have described a normal tissue complication probability model (NCTP) in anal cancer patients undergoing chemoradiation [36]. This model suggests that, despite the cytotoxic effects of 5-FU/MMC, a dose-response relationship exists between radiation dose to the pelvic bone marrow and hematologic toxicity. Based on this data, the authors conclude that reductions in mean bone marrow dose <22.5 Gy and <25 Gy can reduce rates of grade 3 or higher hematologic toxicity to <5% and <10%, respectively.

Much like the liver, bone marrow is a synthetic organ with functional subunits arranged in parallel. An absolute volume of liver has been found to be a useful treatment planning parameter in liver SBRT [37]. Similar volume-based parameters may also predict for hematologic toxicity. Investigators recently evaluated this concept

in a cohort of 57 patients with anal cancer receiving chemoradiation [38]. In patients with >700 cc of pelvic bone spared 30 Gy, the incidence of grade 3 or higher hematologic events was 5% during chemoradiation compared to 54% if the volume of marrow spared 30 Gy was less than 700 cc ($P < 0.01$). There is also emerging interest in identifying metabolically active regions of pelvic bone marrow using FDG-PET imaging, which may preferentially be spared during treatment planning [39, 40]. The optimal treatment planning parameters for sparing hematologic toxicity remains an active area of investigation.

13.4.3 Gastrointestinal Toxicity

Patients with anal cancer often have bowel symptoms that can be quite challenging to manage during and after therapy. Avoidance of organs at risk during treatment planning is the primary preventative strategy. This may be assisted with prone treatment position, bladder filling, and IMRT. Several studies have evaluated dosimetric predictors of acute GI toxicity during chemoradiation for anal cancer. Investigators from the University of Pittsburgh reviewed 58 patients undergoing IMRT [41]. Bowel was contoured using the bowel bag technique that extends from the anterior abdominal wall to include the entire peritoneum. The volume of bowel receiving 30 Gy and 40 Gy were significant predictors of grade 3 or higher GI toxicity. In patients with V30 Gy > 310 cc, the rate of toxicity was 39% compared to 9% if the V30 Gy < 310 cc ($P = 0.016$). In patients with V40 Gy < 70 cc, the rate of toxicity was 6% compared to 36% if the V40 Gy > 70 cc ($P = 0.045$). In a similar analysis that also included grade 2 adverse events, a V30 Gy of >450 cc resulted in grade 2 or higher GI toxicity in 33% compared to 8% of patients with a V30 Gy < 450 cc ($P = 0.003$) [42].

During treatment, loose and frequent bowel movements may exacerbate perineal skin reactions. Dietary modification is a useful first step in management and prevention. Patients should adhere to a low-fat, lactose-free, and low-residue diet. Consultation with a dietician should be arranged for a detailed review of potential trigger food and meal planning. Antidiarrheal agents will often be required for refractory, frequent, and loose stools despite dietary modification. A common approach is to start medical therapy with loperamide, which is readily available over the counter. This may be given as needed if symptoms are infrequent. For persistent symptoms, a second agent such as atropine/diphenoxylate may be added to the regimen. The etiology of diarrhea in patients undergoing radiation therapy may also be in part due to bile acid malabsorption [43, 44]. For that reason, bile acid binders such as cholestyramine powder may also aid in symptom relief.

Potential late GI toxicities include rectal bleeding and fecal incontinence. Rectal bleeding, often a result of RT-induced telangiectasia development, is initially

managed with endoscopic evaluation followed by bowel habit optimization and medical therapy including sucralfate enemas and oral metronidazole with or without concurrent formalin [45, 46]. Fecal incontinence is generally managed with pelvic floor exercises, bulking agents, dietary modification, antidiarrheal medications, biofeedback techniques, surgical sphincter repair, and sacral nerve stimulation [44, 46].

13.4.4 Genitourinary Toxicity

Urinary symptoms, which may include urinary frequency and dysuria, are often problematic for patients undergoing definitive treatment for anal cancer. Dosimetric parameters for urinary toxicity mitigation in patients with anal cancer are less defined compared to other organs at risk. It is important to illicit a detailed history regarding the urinary symptoms. Signs of infection, especially early in treatment, should prompt a urinalysis with appropriate use of antibiotics as indicated. Patients with dysuria that occur early on in the urinary stream may be related to periurethral irritation. The physical exam may also reveal periurethral acute reactions. In these patients, a peri-bottle may provide symptom relief. The patient should be instructed to use the bottle to cleanse the skin during and after the urinary stream. Suprapubic pain at the end of the urinary stream, often described as cramping, may imply cystitis. Anti-spasmodics or phenazopyridine may offer symptomatic relief. The risk of late effects has not been well-reported likely due to total mean dose being relatively low as compared to radiation for prostate cancer.

13.4.5 Sexual and Bone Late Effects

Following completion of treatment, patients should be counseled on sexual function and the potential late effects of radiotherapy. Data from quality of life series have demonstrated high rates of long-term sexual toxicity with over 50% of patients reporting decreased interest, dyspareunia, erectile dysfunction, and loss of feeling attractive [47]. For women, vaginal stenosis is common after chemoradiation for anal cancer, causing grade 2 or higher stenosis in over 60% of patients [48]. Young age at diagnosis, treatment during an earlier era, and higher dose to the primary tumor were all associated with higher grades of vaginal stenosis. Efforts to both prevent and treat these symptoms center on combination usage of vaginal dilators, topical estrogen, moisturizers/lubricants, and sexual health counseling [49]. Female patients should be instructed on vaginal dilator use to mitigate vaginal stenosis. No randomized data exist that clearly demonstrate reduction in vaginal stenosis with dilator use. However, a prospective study assessing vaginal dilator use in patients

with rectal or anal cancer noted that patients with less than 40% compliance had higher rates of vaginal stenosis [50]. A typical recommendation for dilator use is 10 min at least three times per week. For men, phosphodiesterase inhibitors are typically used to improve sexual function.

Other late effects of treatment include insufficiency fractures of the sacrum or femoral heads. In a cohort of 492 rectal cancer patients undergoing pelvic radiation therapy, the incidence of sacral insufficiency fracture was 7%. Increasing age, osteoporosis, and female sex were found to be independent predictors of sacral insufficiency fracture [51]. The incidence of insufficiency fractures in anal cancer patients is less well-described. In a cohort of 24 anal cancer patients receiving IMRT, nine (37%) were noted to have pelvic insufficiency fractures at a median time of 15 months following completion of treatment [52]. For patients who develop insufficiency fractures, consider consultation with orthopedics and therapy with anti-inflammatories, vitamin D, and calcium supplements.

13.5 Follow-Up Recommendations

Immediately following completion of chemoradiation, patients should be observed closely to evaluate for resolution of acute toxicities with aggressive supportive care measures as needed. A clinical response assessment should be made monthly following completion of treatment. If residual tumor remains, the patient should be followed closely to evaluate regression. It may take up to 6 months for a complete clinical response to be observed. In the UK ACT II trial, 90% of patients ultimately obtained a complete response at 6 months in the 5-FU/MMC arm [12].

Additionally, the authors generally recommend anoscopy and PET to evaluate for complete response at approximately 3 months post-completion of chemoradiation. A complete metabolic response on a posttreatment PET scan has been observed to be prognostic following chemoradiation for anal cancer [53]. In a series of 53 patients with pretreatment and posttreatment PET scans (median 2 months), the two-year cause-specific survival was 94% in patients with a complete metabolic response compared to 39% in patients with a partial metabolic response [53]. Biopsies should not be performed routinely prior to 6 months due to the risk of radionecrosis, unless there is concern for tumor progression. Once a complete response has been obtained, a regular follow-up regimen should be established that includes digital rectal exam and inguinal lymph node evaluation every 3–6 months for 5 years, anoscopy evaluation every 6–12 months for 3 years, and CT imaging at least annually for high-risk patients (lymph node involvement, T3/T4). Patients with biopsy-proven local recurrence should be referred for abdominoperineal resection (Fig. 13.7).

13.6 Summary

Radiation therapy with 5-flourouracil and mitomycin remains the standard of care for squamous cell carcinoma of the anal canal. This approach highlights an early success in organ-preserving therapy. Despite this success, toxicity remains high in these patients. Conformal radiation planning and delivery with IMRT has been useful in reducing morbidity. However, careful adherence to standardized treatment volume definitions, attention to published dose-volume limits, quality assurance, and image guidance during treatment delivery are all important components in optimizing IMRT outcomes. Ongoing trials are investigating the safety of treatment regimens using IMRT to escalate the dose of radiation for high-risk patients in an attempt to improve local control.

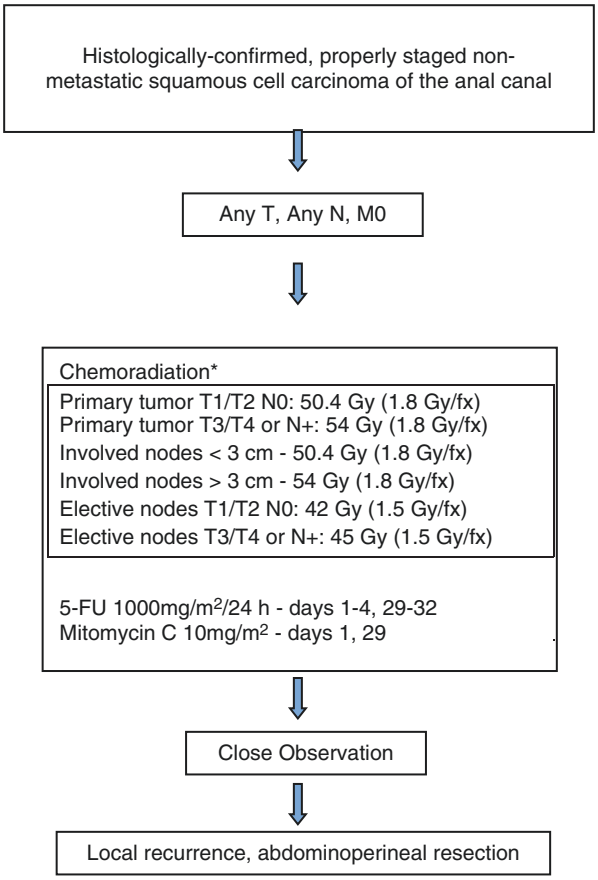

Fig. 13.7 Treatment algorithm. *IMRT radiation is preferred; 3D-CRT is considered an option; proton therapy is under investigation

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Part VII

General Considerations

Dosimetry and Physics Quality Assurance

14

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Contents

14.1 Quality Assurance Considerations for 3D CRT and IMRT/VMAT

To improve the quality of cancer radiation, the routine use of expert-defined target and normal tissue contouring guidelines developed (RTOG.org website) is encouraged, and emphasis on prospective peer-review of treatment plans and detailed attention quality assurance measures before and during treatment has emerged as an important component of care [1]. ICRU Reports 50, 62, and 83 on prescribing, recording, and reporting photon-beam therapy provide guidance for both 3D CRT and IMRT delivery systems.

Specific recommendations from an expert panel outline specific quality assurance (QA), infrastructure, and personnel requirements and technical process

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requirements for safe radiation practice are detailed in "Safety is No Accident: A Framework for Quality Radiation Oncology and Care" available at the ASTRO.org website. Modality-specific recommendations continue to emerge [2–4]. The American Association of Physicists in Medicine (AAPM) has published the Task Group reports outlining recommendations on quality assurance processes for photon-based 3D CRT, IMRT/VMAT, SBRT.

For 3D CRT, it is recommended to perform secondary Monitor Unit (MU) calculation based on Task Group 71 formalism with the discrepancy tolerance thresholds specified by Task Group 114 [5, 6]. Although AAPM recommendations did not venture past secondary MU calculations to a point, a few commercially available systems can perform three-dimentional secondary dose calculations with DVH comparison.

IMRT/VMAT commissioning, planning, and delivery is guided by Task Groups 82 and 120 [7, 8]. Phantom-based verification measurements of calculated dose distributions are an essential part of IMRT/VMAT quality assurance and should be performed prior to the first patient treatment. As image-guidance plays a crucial role in targeting, all components need to be comprehensively tested for accuracy [9]. In many gastrointestinal malignancy cases, motion management is an additional consideration, and depending on the approach and technique utilized, specific QA and tolerances need to be applied per published protocols [10].

14.2 Special Treatment Planning Considerations for SBRT with Motion Tracking Using Implantable Fiducial Markers

SBRT can be delivered using gantry-based delivery systems. Characteristics of SBRT include:

- Secure robust immobilization avoiding patient movement for the typical long treatment sessions
  - Body frames
  - Vacuum pillows
  - Thermoplastic devices
- Accurate repositioning from simulation to treatment
- Rigorous accounting of organ motion
  - Generic PTV expansion
  - 4D CT (Internal Target Volume)
  - Three phase CT (free breathing, deep expiration, and deep inspiration)
  - Motion dampening using abdominal compression or active breath control
  - Motion gating
- Minimization of normal tissue exposure attained by using multiple (e.g., ten or more) or large-angle arcing small aperture fields
- Stereotactic registration (i.e., via fiducial markers or surrogates) of tumor targets and normal tissue avoidance structures to the treatment delivery machine

- Ablative dose fractionation delivered to the patient with subcentimeter accuracy

In contrast to gating and breath-holding techniques on gantry-based delivery platforms, the robotic arm-based platform CyberKnife® (Accuray Incorporated, Sunnyvale, CA) is the only system capable of moving the radiation beam with the motion of the tumor (Synchrony™) with patient breathing freely during treatment. First, fiducial markers are implanted inside or in close proximity to tumor. During simulation, 4DCT is acquired to examine the location of the markers and their pattern of motion. Fiducial markers that move nonrigidly relative to the tumor are usually considered inadequate surrogates for tracking tumor motion and are discarded during treatment.

Treatment planning with CyberKnife® involves inverse planning with non-isocentric non-coplanar pencil beams shaped by either conical collimators, IRIS collimator (a 12-sided polygon), or InCise™ MLC. As with inverse planning on gantry-based linear accelerators, planning for CyberKnife® is an iterative optimization process based on meeting a list of set priorities of target coverage, conformality, and sparing surrounding normal tissue. With a demonstrated accuracy of better than 1.5 mm, the need to add larger PTV margins is eliminated, thus allowing to create sharper dose gradients between the target and adjacent critical organs [11]. The Synchrony™ tracking system relies on orthogonal X-ray images of target area with internal fiducials acquired every 10–30 s. Since the X-ray imaging cannot be acquired fast enough to keep up with respiratory motion, external infrared transmitting diodes taped to patient abdomen are used to predict position of the internal markers based on a correlation model. This predictive model is continuously updated with a new pair of X-rays taken every 90 s during the treatment delivery process. Since Synchrony™ heavily relies on reproducible position of internal fiducial markers, it is prudent to ensure that the markers are in expected positions and have not migrated before proceeding with treatment delivery.

14.3 Quality Assurance Considerations for 3D SBRT

Due to the high fraction doses to the target and sharp dose falloff to the surrounding tissue, the practice of SBRT requires a high level of confidence in the accuracy of the entire treatment delivery process from treatment simulation and planning to treatment delivery. This imperative need for accuracy requires special considerations when designing SBRT programs including acceptance, commissioning, and quality assurance tests. For instance, it is paramount to verify that the radiation isocenter coincides with the mechanical isocenter of gantry, collimator, and couch on the linear accelerator and coincides with the imaging isocenter [12].

Non-isocentric modalities such as CyberKnife® have a similar test which can verify the overall geometric accuracy of treatment delivery [13]. Even if errors contributed by individual components of the SBRT delivery process (imaging, motion management, treatment) are small, cumulative system accuracy for the procedure can be significant and needs to be characterized through an end-to-end test using

phantoms with dosimetric detectors that undergo the SBRT treatment starting from setup, imaging, positioning, gating, and finishing with treatment delivery. Particularly for abdominal SBRT, the best way to accomplish end-to-end test is to use a moving phantom with the internal fiducial markers and compare the planned and delivered doses. The large dose per fraction and short treatment course might not allow for correction of errors and can lead to significant harm to a patient. Thus, Task Group 101 recommends a qualified medical physicist to be present during SBRT delivery in order to verify patient immobilization, setup, imaging, and gating parameters [14].

14.4 Special Treatment Planning Considerations for Proton Therapy

14.4.1 Proton Delivery Techniques

By taking advantage of the Bragg peak, protons are inherently capable of delivering higher dose conformity and lower integral dose to the body than photons, but the method of delivery is an important consideration.

1. Passive Spreading—the proton beam is spread by placing scattering material into the path of the protons.
   (a) Uniform scanning (US)—single scattering broadens the beam sufficiently for small treatment fields.
   (b) Double scattering (DS)—a second scatterer is needed to ensure a uniform dose profile for larger fields. This is accomplished with a combination of custom-made collimators and compensators conform the dose to the target volume, and a set of range modulator wheels or ridge filters inside the nozzle of the delivery system results in a "spread out Bragg peak" covering the treatment target
   • Individualized patient-specific beam-modification devices (collimators or compensators) to conform the dose to the treatment volume are utilized in scattering proton delivery systems.
   – beam-modification devices may be manufactured in-house or outsourced
   – protons lose energy and penetrating power when interacting with scattering material, resulting in reduction of the maximum depth of the Bragg peak and limiting use for treatment of deep tumors
   – some unnecessary dose is deposited in tissues close to the treatment volume when using compensators because the spread of the Bragg peak is constant across the treated depth. Multiple fields can be used to improve target conformality, but requires increased time for treatment due to switching of compensators and apertures
   – Beam scattering can accommodate slightly for daily variations in tumor location and organ motion, because of the smearing effect of the broadened beam

  - beam-modification devices become radioactive from exposure to protons, requiring storage after use in a dedicated storage area
  - generation of neutrons occurs when the proton beam hits scatterers and beam-modifying devices resulting in undesirable secondary radiation which increases the integral radiation dose to the patient
2. Active Spreading (Beam Scanning)—computer-controlled magnets deflect and steer a monoenergetic proton beam and "paints" the treatment volume over individual voxels in successive layers. The depth of the Bragg Peak is adjusted by varying the energy of the beam before entering the nozzle.
   (a) Pencil beam scanning (PBS) enables protons to penetrate deeper than scattering, allowing treatment of deep tumor locations.
   - does not require any collimators, compensators, or other beam-modifying devices and produces fewer neutrons.
   - enhanced ability to paint dose conformally increases the risk of target misses due to daily organ motion.
   - Beam scanning requires increased complexity in planning, computation, and equipment than beam scattering.

14.4.2 IMPT

Intensity-modulated proton therapy provides the ability to vary the dose distribution throughout the treatment volume and decreases integral dose.

- Beam Scattering—multiple fields can deposit dose from different directions, but requires switching compensators and apertures, increasing treatment time.
- Beam Scanning—varies proton-beam intensity and/or the speed of the scan to vary the dose distribution over individual voxels and "paints" a nonuniform dose over an area to provide an overall uniform target dose, improve dose conformity, and reduce integral dose.

Proton radiotherapy treatment planning requires precise and accurate information used to calculate the stopping power properties of the tissues in a patient's body obtained from CT images using a reliable calibration curve to convert Hounsfield units into relative proton stopping power values. Proton therapy poses the same requirements for accurate, repeatable patient positioning, and setup as does IMRT. Detailed attention to a reproducible daily setup with reliable motion management is an important component of an optimized treatment plan. Tumor motion may be accounted for by either passive or active methods.

Treatment planning must incorporate attention to detail to minimize treatment setup variations, careful evaluation of setup and range uncertainties, and focus on uncertainty mitigation to generate robust treatment plans to improve dose conformity and homogeneity. Treatment planning techniques using volumetric imaging in proton therapy must also take into account patient setup and immobilization devices

(Alpha cradle and special proton treatment table top, which may be used at the time of simulation or inserted into the CT images manually after data acquisition).

In addition, evaluation of the effects of motion resulting in significant differences in doses to the target (variable relative biological effectiveness) and critical structures (toxicity risks) emphasizes the importance of accurate proton dose computation methods. Each institution must define metrics to define a robustness database of acceptable parameters specific to the proton delivery method available, which is incorporated in the analysis of individual treatment plans. In addition, high- and low-density structures moving in and out of the beam due to patient motion or tumor shrinkage alter the range of the Bragg peak. Hence, it is essential to verify daily that the target volume and surrounding normal structures correlate with locations during treatment planning prior to treatment using image-guidance techniques. System-specific and patient-specific quality assurance measures are equally important.

14.5 Special Quality Assurance Considerations for Proton Therapy

Proton therapy provides unique quality assurance challenges: the complexity and associated uncertainties require careful consideration and customized techniques to assure accurate plan delivery. The overall structure of a proton therapy system QA program might look similar to a photon linear accelerator one, and thus, follow AAPM Task Group 142, but the specific recommendations will not be applicable. Customized tests and frequencies need to be designed to encompass both the equipment and the treatment techniques used in a facility. ICRU Report 78 on prescribing, recording, and reporting proton-beam therapy provides some QA guidance for both passive and scanning beam delivery systems. Patient-specific QA usually includes 2D dose verification measurements where the patient plan, with its specific accessories and range shifting, is delivered on a planar array detector at different depths. As thorough as these types of tests are, they do not capture the full complexity of doses delivered inside a patient, in particular where motion is a concern such as gastrointestinal malignancy cases. QA needs then to go beyond these static and limited pretreatment testing scenarios to encompass the daily treatment challenges.

Daily imaging is an essential component of assuring the precise delivery of the intended dose distribution. Volumetric imaging is becoming the tool of choice as one can confirm that both the target and the surrounding normal tissue are in an acceptable position, particularly in conjunction with a six degrees-of-freedom patient support system. Gated volumetric imaging, such as 4D–CBCT, provides both anatomy and motion management information.

Standard motion mitigation approaches can be used such as breath hold and gating, tools which require their own standard QA. Of particular interest is motion mitigation in spot scanning techniques, which offer the greatest challenge due to intrafractional motion, but also the most desirable dose distribution. Currently, spot scanning is restricted at most centers to static tumors, but options are being developed: “rescanning” where the same dose distribution is delivered multiple times,

phase-controlled scanning where the respiratory cycle is considered in beam delivery, or using larger spot sizes to increase delivery speed [15, 16]. To adequately monitor such a dynamic scenario, new verification techniques that not only image anatomy but also provide dosimetric information need to be developed as new proton therapy facilities are rapidly adopting active scanning. In-vivo dosimetry is desirable and actively researched. Beyond the standard detector systems used in external beam therapy (diodes, MOSFETs, TLDs, OSLDs), PET and prompt gamma ray imaging are showing promise [17, 18]. The advances in motion management, daily imaging, and daily dose verification promise to adequately assure quality in challenging proton therapy treatment scenarios.

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